publiziert bei: AWMF online
Das Portal der wissenschaftlichen Medizin

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose

Leitlinienreport

2. Auflage – 03. März 2020
AWMF-Registernummer: 004-028

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und Ina Kopp für die Steuergruppe

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2.1 Allgemeine Informationen zum Leitlinienreport

Dieser Leitlinienreport bezieht sich auf das erste Update der Leitlinie (Version 2.0). Der Leitlinienreport zur Version 1.0 ist diesem Report angehängt (Anlage 9.8). Strukturell orientiert sich der Leitlinienreport am *"Leitfaden zur Erstellung des Leitlinienreports für Autoren von S2k, S2e und S3-Leitlinien"* der AWMF vom 05.12.2016. Im Leitlinienreport sowie der Leitlinie selbst wird aus Gründen der besseren Lesbarkeit ausschließlich die männliche Form verwendet. Sie bezieht sich ausdrücklich auf Personen aller Geschlechter (m/w/d). Sollten sich Texte ausschließlich auf ein Geschlecht beziehen, ist dies gesondert vermerkt.

2.1.1 Autoren des Leitlinienreports

Hans-Henning Eckstein, Andreas Kühnl, Helge Knüttel, Frederik Wein, Martin Storck, Ina Kopp

2.1.2 Federführende Fachgesellschaft

Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG)

2.1.3 Finanzierung der Leitlinien

Das Update der Leitlinie wurde durch die Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG), die Deutsche Gesellschaft für Neurologie (DGN), die deutsche Gesellschaft für Neuroradiologie (DGNR), die deutsche Gesellschaft für Angiologie (DGA), die deutsche Diabetes Gesellschaft (DDG), die deutsche Gesellschaft für Neurochirurgie (DGNC) und die Deutsche Schlaganfallgesellschaft (DSG) finanziell unterstützt. Ebenso erfolgte eine indirekte finanzielle Unterstützung durch alle entsendenden Fachgesellschaften und Verbände (u.a. Übernahme von Reisekosten der Mandatsträger). Die Finanzierung durch die Fachgesellschaften führte zu keiner inhaltlichen Beeinflussung der Leitlinienarbeit.

2.1.4 Kontakt Leitliniensekretariat

Klinikum rechts der Isar
Klinik für Vaskuläre und Endovaskuläre Chirurgie
Univ.-Prof. H.-H. Eckstein
Ismaninger Str. 22
81675 München
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Fax.: 089/4140-4861

2.1.5 Zitierweise des Leitlinienreports

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose: Leitlinienreport, Version 2.0, 2019, AWMF-Registernummer 004–028. [abgerufen am: TT.MM.JJJJ]

2.2 Begründung für die Auswahl des Leitlinienthemas

Epidemiologische Untersuchungen zeigen, dass bei 1-3% aller Erwachsenen arteriosklerotisch bedingte extracranielle Carotisstenosen mit einem Stenosegrad von >50% vorliegen. Ab dem 65. Lebensjahr steigt die Prävalenz auf 6-15% an. Dies bedeutet, dass in Deutschland ca. 1 Mio. Menschen mit einer >50%igen Carotisstenose leben. Das Risiko eines carotis-assoziierten, ischämischen Schlaganfalls beträgt bei klinisch asymptomatischen >50%igen Stenosen 1-5%/Jahr, bei >50%igen symptomatischen Stenosen 10-30%/Jahr.
Ca. 80% aller Schlaganfälle werden durch eine zerebrale Ischämie verursacht, hiervon 15-20% durch Stenosen oder Verschlüsse der extracraniellen, hirnversorgenden Gefäße. Bei einer Gesamtzahl von ca. 280.000 Schlaganfällen (Statistisches Bundesamt 2007) errechnet sich daraus für Deutschland eine Inzidenz von bis zu 40.000 carotis-assoziierten Schlaganfällen/Jahr. In Anbetracht der o.g. Prävalenz von Carotisstenosen sowie der hohen Inzidenz carotis-assoziierter Schlaganfälle kommt einer effektiven Primär- und Sekundärprävention carotis-bedingter Schlaganfälle große Bedeutung zu. Aufgrund des enormen Wissenszuwachs in den Themengebieten Schlaganfallprävention, Carotisstenose und Atherosklerose, der aus einer Vielzahl randomisierter Studien, internationaler Leitlinien und Empfehlungen hervorging, erschien die Erstellung einer deutsch-österreichischen, interdisziplinären, evidenzbasierten Leitlinie zur Diagnostik und Therapie extracranieller Carotisstenosen zwingend geboten.

2.3 Zielorientierung der Leitlinie

Zielsetzung der Leitlinie ist die Sicherstellung einer evidenzbasierten, flächendeckenden, optimalen Versorgung von Patienten mit extracraniellen Carotisstenosen in Deutschland. Sie soll entsprechend der Definition von Leitlinien zur Entscheidungsfindung für Arzt und Patient bei diagnostischen und therapeutischen Maßnahmen dienen. Die Leitlinie nimmt insbesondere zu folgenden Fragen und Themenkreisen Stellung:

- Epidemiologie, Risikofaktoren und Co-Morbidität
- Symptome und Diagnostik
- Konservative, operative und endovaskuläre Therapieverfahren
- Nachsorge, Rezidivtherapie und Lebensqualität
- Gesundheitsökonomische Aspekte

Die Leitlinienempfehlungen verstehen sich als Orientierungshilfe im Sinne von Handlungs- und Entscheidungskorridoren, von denen in begründeten Fällen natürlich abgewichen werden kann. Sämtliche Leitlinien der wissenschaftlichen medizinischen Fachgesellschaften sind für Ärzte rechtlich nicht bindend und haben daher weder haftungsbegründende noch haftungsbefreiende Wirkung. Was im juristischen Sinne den ärztlichen Standard in der konkreten Behandlung eines Patienten darstellt, kann nur im Einzelfall entschieden werden. Auch die vorliegende Leitlinie entbindet den Arzt nicht von seiner Verpflichtung, individuell unter Würdigung der Gesamtsituation des Patienten, die adäquate Vorgehensweise zu prüfen. Die vorliegende Leitlinie hat zum Ziel, dem Leser die für die Behandlung der extracraniellen Carotisstenose wichtigsten Erkenntnisse und Informationen aus den

verschiedenen Spezialgebieten zusammenzutragen, um so eine Handlungshilfe im praktischen und klinischen Alltag zu geben.
Der Entwicklung der ersten Version der S3 Leitlinie ging die Verabschiedung einer S1 Leitlinie zur extracraniellen Carotisstenose der Deutschen Gesellschaft für Gefäßchirurgie (DGG) im Jahre 1998, eine S1 Leitlinie der Deutschen Gesellschaft für Neurologie (DGN) und Deutschen Schlaganfall-Gesellschaft (DSG) zur Primär- und Sekundärprävention der zerebralen Ischämie (zuletzt aktualisiert 2008) sowie eine S1 Leitlinie zur Diagnostik zerebrovaskulärer Erkrankungen voraus. Verbindungen zu anderen aktuellen Leitlinien im Register der AWMF sind bei der Erstellung und Aktualisierung der vorliegenden Leitlinie berücksichtigt worden. Aufgrund neuer wissenschaftlicher Analysen, der Publikation von Langzeitergebnissen randomisierter kontrollierter Studien sowie den Regularien der AWMF war eine Aktualisierung der 2012 publizierte ersten Version der S3-Leitlinie nun geboten.

2.4 Patientenzielgruppe

Die Leitlinie bezieht sich auf erwachsene Patienten jeglichen Alters mit nachgewiesener Stenose der extracraniellen A. carotis communis oder A. carotis interna. Sie gilt auch für Patienten, bei denen ein deutlich erhöhtes Risiko einer extracraniellen Carotisstenose besteht (z.B. Arteriosklerosepatienten mit KHK oder PAVK). Sie gilt nicht für Kinder. Die Behandlung nicht-atheromatöser Ursachen extracranieller Carotisstenosen (Vaskulitis, Dissektion, Riesenzellarteriitis, Fibromuskuläre Dysplasie [FMD], postradiogene Stenosen) wird in jeweiliger Abgrenzung zu arteriosklerotischen Stenosen diskutiert, steht aber nicht im Focus dieser Leitlinie.

2.5 Versorgungsbereich

Sie deckt alle Bereiche der Epidemiologie, Diagnostik, Therapie und Nachsorge von Patienten mit Carotisstenose sowie gesundheitsökonomische Aspekte im ambulanten und stationären Versorgungsbereich sowie im Bereich der Rehabilitationsmedizin ab.

2.6 Anwenderzielgruppe / Adressaten

Die Leitlinie richtet sich an alle, die mit der Betreuung und Behandlung von Patienten mit extracranieller Carotisstenose befasst sind. Zum primären Adressatenkreis der Leitlinie gehören alle Ärzte und nicht-ärztlichen Mitarbeiter aus dem ambulanten und stationären Versorgungsbereich, sowie aus dem Bereich der Rehabilitationsmedizin, die Patienten mit extracraniellen Carotisstenosen betreuen oder behandeln und die durch die ihre Interessen vertretenden Fachgesellschaften oder Organisationen, welche an der Erstellung dieser Leitlinie aktiv mitgewirkt haben (siehe Punkt 3). Die Leitlinie soll auch eine Informationsquelle für alle im Gesundheitswesen tätige Institutionen sein. Die Leitlinie richtet sich aber auch an interessierte Patienten und deren Angehörige mit dem Ziel, den Kenntnisstand über das Krankheitsbild sowie die verschiedenen diagnostischen und therapeutischen Optionen zu verbessern und den Betroffenen eine partizipative Entscheidungsfindung zu ermöglichen. Dies soll durch eine laienverständliche Version (Patientenversion) unterstützt werden.

3 Beteiligung von Interessensgruppen

3.1 Initiierung und Organisation

Im Auftrag des Vorstands der Deutschen Gesellschaft für Gefäßchirurgie (DGG) wurde im Jahr 2003 die Entwicklung einer interdisziplinären S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose unter der Federführung von Prof. Dr. H.-H. Eckstein initiiert. Die konstituierende Sitzung der interdisziplinären Steuergruppe fand am 12.7.2004 in Heidelberg statt. Die weitere Absprache der Steuergruppe erfolgte über zahlreiche Telefon-Konferenzen. Ein erstes Konsensus-Treffen fand am 13.9.2005 in Frankfurt unter der Moderation von Fr. Prof. Dr. I. Kopp (AWMF) statt. Für die fünf verschiedenen Themenbereiche (Epidemiologie, Diagnostik, Therapie, Nachsorge, Ökonomie) wurden im Rahmen der Konsensus-Konferenz und eines anschließenden DELPHI-Verfahrens insgesamt 68 Schlüsselfragen konsentiert. Diese Fragen wurden in den Arbeitsgruppen schrittweise bearbeitet und im August 2009 in einer zweiten Konsensuskonferenz (Leitung Prof. Kopp) diskutiert und konsentiert.

Erstes Update: Vor Ablauf der regulären Gültigkeitsdauer der ersten Version der Leitlinie wurde gemäß AWMF Regelwerk eine Aktualisierung der Leitlinie durch die Steuergruppe initiiert.

3.2 Mitglieder der Steuergruppe:

Name	Gebiet	Arbeitgeber
Prof. Dr. H.-H. Eckstein	Gefäßchirurgie	Klinikum rechts der Isar der TU München
Prof. Dr. A. Dörfler	Neuroradiologie	Universitätsklinikum Erlangen
Fr. Prof. Dr. I. Kopp	Leitlinienmethodik	AWMF-Institut für Medizinisches Wissensmanagment
Prof. Dr. D. Sander	Neurologie	Benedictus Krankenhaus Tutzing
PD Dr. P. Ringleb	Neurologie	Neurologische Klinik, Univ.-Klinikum Heidelberg
Prof. Dr. M. Storck	Gefäßchirurgie	Städtisches Klinikum Karlsruhe
Dr. R. Langhoff	Angiologie	Evangelisches Krankenhaus Königin Elisabeth Herzberge, Berlin (seit 2007)
Dr. H. Lawall	Angiologie	Klinikum Karlsbad-Langensteinbach
Prof. Dr. R. Diel	Gesundheitsökonomie	Gesundheitsamt Hamburg-Harburg
Prof. Dr. A. Kühnl	Sekretär seit 1.4.2008	Klinikum rechts der Isar der TU München
Prof. Dr. K. L. Schulte	*Angiologie*	*Evangelisches Krankenhaus Königin Elisabeth Herzberge, Berlin (bis 2006)*
Dr. M. Hanke	*Sekretär bis 31.3.2008*	*Klinikum rechts der Isar der TU München*

3.3 Repräsentativität der Leitliniengruppe: Beteiligte Berufsgruppen

Von Ende 2004 bis Anfang 2005 wurden insgesamt 25 medizinische Fachgesellschaften und Organisationen sowie drei Selbsthilfegruppen schriftlich eingeladen, sich an der Erstellung der Leitlinie zu beteiligen. Insgesamt haben 22 Fachgesellschaften/Organisationen eigene Vertreter benannt und 6 Organisationen (inkl. aller Selbsthilfegruppen) kein Interesse an einer Mitarbeit bekundet.

August 2009 wurden erneut die Vorstände aller beteiligten Fachgesellschaften, Organisationen und Selbsthilfegruppen angeschrieben und um offizielle Bestätigung bzw. Neubesetzung der Mandatsträger gebeten. Bis zum 27.09.2009 haben insgesamt 16 Fachgesellschaften/Organisationen geantwortet, die alle ihr Interesse an einer weiteren Mitarbeit signalisierten.

Erstes Update: Im Rahmen der ersten Aktualisierung der Leitlinie wurden im September und Dezember 2015 sowie im April 2019 erneut die Vorstände, Geschäftsstellen und, wenn vorhanden, die Leitlinienbeauftragten der in untenstehender Tabelle aufgelisteten Fachgesellschaften, Organisationen und Selbsthilfegruppen angeschrieben und um offizielle Bestätigung bzw. Neubesetzung der Mandatsträger gebeten. In nachstehender Tabelle sind alle offiziell bestätigten Mandatsträger aufgelistet:

Fachgesellschaft Organisation	**Vertreter 2009 (initiale S3 LL-Version)**	**Mandatsträger 2019 (erstes Update)**
Deutsche Gesellschaft für Gefäßchirurgie	Prof. Dr. H.H. Eckstein, München Prof. Dr. M. Storck, Karlsruhe Prof. Dr. W. Lang, Erlangen Dr. M. Hanke, München, bis 2007 Prof. Dr. A. Kühnl, München, ab 2008	Prof. H.H. Eckstein, München
Deutsche Gesellschaft für Neurologie	PD Dr. P. Ringleb, Heidelberg, Prof. Dr. D. Sander, Loipl Prof. Dr. M. Hennerici, Mannheim	Prof. P. Ringleb, Heidelberg Prof. D. Sander, Tutzing
Deutsche Gesellschaft für Neurologische Rehabilitation	PD Dr. S. Hesse, Berlin Prof. Dr. D. Steube, Neustadt/Saale	Kein Mandatsträger benannt, aktive Absage
Deutsche Schlaganfallgesellschaft	Prof. Dr. D. G. Nabavi, Berlin PD Dr. R. Stingele, Kiel PD Dr. P. Ringleb, Heidelberg	Prof. P. Ringleb, Heidelberg Prof. Dr. D. G. Nabavi, Berlin
Deutsche Gesellschaft für Ultraschall in der Medizin	Prof. Dr. C. Arning, Hamburg-Wandsbek PD Dr. M.W. Görtler, Magdeburg	Prof. M. Köhrmann, Essen Prof. P. Ringleb, Heidelberg
Deutsche Gesellschaft für Neuroradiologie	Prof. Dr. A. Dörfler, Erlangen Prof. Dr. J. Berkefeld, Frankfurt Prof. Dr. Brückmann, München Prof. Dr. O. Jansen, Kiel PD Dr. M. Hartmann, Heidelberg	Prof. J. Berkefeld, Frankfurt Prof. A. Dörfler, Erlangen
Deutsche Röntgen-Gesellschaft	Prof. Dr. med. W. Gross-Fengels, Harburg Prof. Dr. D. Vorwerk, Ingolstadt Prof. Dr. P. Huppert, Darmstadt	Prof. W. Gross-Fengels, Harburg
Deutsche Gesellschaft für Interventionelle Radiologie und minimalinvasive Therapie	Prof. Dr. T. Helmberger, München Prof. Dr. A. Bücker, Homburg Prof. Dr. S. Müller-Hülsbeck, Flensburg	Prof. P. Huppert, Darmstadt

Deutsche Gesellschaft für Angiologie Gesellschaft für Gefäßmedizin	Dr. H. Lawall, Langensteinbach Prof. Dr. K.L. Schulte, Berlin (bis 2007) Dr. R. Langhoff, Berlin (seit 2008) Dr. J. Ranft, Bottrop Prof. Dr. U. Hoffmann, München	Dr. H. Lawall, Langensteinbach Dr. R. Langhoff, Berlin
Deutsche Gesellschaft für Kardiologie	Prof. Dr. Sievert, Frankfurt Prof. Dr. Mudra, München Prof. Dr. Silber, München	Prof. H. Mudra, München Prof. Th. Zeller, Bad Krozingen
Deutsche Diabetes Gesellschaft	Prof. Dr. Schnell, München-Neuherberg	Prof. O. Schnell, München PD Dr. K. Rittig, Frankfurt (Oder)
Deutsche Gesellschaft für Geriatrie	Dr. C. Ploenes, Düsseldorf	Dr. C. Ploenes, Düsseldorf Dr. H. Görtz, Lingen
Österreichischer Verband für Gefäßmedizin	Prof. Dr. G. Fraedrich, Innsbruck PD Dr. A. Assadian, Wien	Prof. G. Fraedrich, Innsbruck Prof. B. Rantner, München
Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie	Prof. Dr. G. Walterbusch, Dortmund Dr. M. Siggelkow, Kiel Dr. G. Walluschek, Kiel	Prof. M. Czerny, Freiburg
Deutsche Gesellschaft für Neurochirurgie	Prof. Dr. Antonianidis, Ulm PD Dr. Deinsberger, Gießen Prof. Dr. K. Schwerdtfeger	Prof. K. Schwerdtfeger, Homburg
Deutsche Gesellschaft für Chirurgie	Prof. Dr. E. Neugebauer, Köln	Prof. M. Storck, Karlsruhe Prof. M. Steinbauer, Regensburg
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin	Dr. R. Litz, Univ.Klinikum Dresden	Dr. R. Litz, Augsburg Prof. K. Engelhard, Mainz
Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin	Kein Vertreter benannt (aktive Absage)	Kein Mandatsträger benannt, aktive Absage.
Deutsche Gesellschaft für Prävention und Rehabilitation von Herz-Kreislauferkrankungen	Prof. Dr. T. Brandt, Heidelberg	Kein Mandatsträger benannt, keine Rückmeldung
Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften	Prof. Dr. I. Kopp, Marburg	Prof. I. Kopp, Marburg
Deutsche Gefäßliga e.V.	Prof. Dr. C. Diehm, Langensteinbach	Dr. S. Schulte, Köln
Deutscher Verband für Physiotherapie	A. Fründ, Bad Oeynhausen	A. Fründ, Bad Oeynhausen
Deutscher Verband der Ergotherapeuten	Frau Sabine George, Karlsbad Herr Andreas Hörstgen, Karlsbad	A. Hörstgen, Karslbad C. Lüdeking, Minden
Deutscher Pflegerat	Kein Vertreter benannt	R. Schamberger, Regensburg J. Hanl, Friedrichshafen

3.4 Repräsentativität der Leitliniengruppe: Beteiligung von Patienten

Folgende Patienten- und Selbsthilfegruppen wurden sowohl im Rahmen der Ersterstellung der Leitlinie sowie im Rahmen des Aktualisierungsprozesses angeschrieben.

Patienten- und Selbsthilfegruppen	Vertreter 2009 (initiale S3 LL-Version)	Mandatsträger 2019 (1. Update)
Deutsche Arbeitsgemeinschaft Selbsthilfegruppen e.V.	Kein Vertreter benannt	Kein Mandatsträger benannt, keine Rückmeldung.
Bayerischer Verband Schlaganfall-Betroffener München	Kein Vertreter benannt	Kein Mandatsträger benannt, keine Rückmeldung.
Deutsche Schlaganfallhilfe	siehe Vertreter der Deutschen Schlaganfallgesellschaft	Prof. Dr. D. G. Nabavi, Berlin Prof. Dr. R. Stingele, Berlin

3.5 Beteiligung weiterer Gruppen:

Folgende Fachgesellschaften und Organisationen wurden im Rahmen der Ersterstellung der Leitlinie über das Vorhaben informiert:

- Deutsche Gesellschaft für Innere Medizin (vertreten durch die Deutsche Gesellschaft für Angiologie)
- Bundesgeschäftsstelle Qualitätssicherung BQS, Düsseldorf (erste Version der Leitlinie) bzw. für das erste Update das Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG)[1]
- Ärztliches Zentrum für Qualität in der Medizin ÄZQ
- Wissenschaftliches Institut der AOK WIDO
- Deutscher Physiotherapeutenverband

Für den Bereich Studienbewertung:

- Regina Hollweck Institut für Medizinische Statistik und Epidemiologie, Technische Universität München
- Dr. M. Hennig, Institut für Medizische Statistik und Epidemiologie, Technische Universität München

Für den Bereich Gesundheitsökonomie/Public Health:

- Prof. Dr. O. Schöffski, Lehrstuhl Gesundheitsmanagement, Universität Erlangen
- PD Dr. R. Diel, Leiter des Gesundheitsamts Hamburg-Harburg,
- Prof. Dr. Max Geraedts, Universität Marburg

[1] Die Information erfolgte über Prof. Martin Stork und Prof. Joachim Berkefeld, Mitglieder der Bundesfachgruppe QS Modul 10/2 sowie der Steuergruppe der vorliegenden S3-Leitlinie

4 Methodologische Exaktheit

4.1 Recherche, Auswahl und Bewertung wissenschaftlicher Belege (Evidenzbasierung)

4.1.1 Formulierung von Schlüsselfragen

Das erste Konsensus-Treffen von insgesamt 28 Vertretern der teilnehmenden Fachgesellschaften und Organisationen fand unter der Moderation von Fr. Prof. Dr. I. Kopp (AWMF) am 13.9.2005 in Frankfurt statt. Hier wurde zunächst mit 22/28 Stimmen der Titel der S3 Leitlinie konsentiert: „Diagnostik, Therapie und Nachsorge der extrakraniellen Karotisstenose“. Für die von der Steuergruppe festgelegten Arbeitsgruppen wurden Schlüsselfragen diskutiert und konsentiert. Für die Gruppen 3-5 (Therapie, Nachsorge, Ökonomie) erfolgte die Abstimmung über die Schlüsselfragen schriftlich anhand eines Fragebogens (Delphi-Verfahren). Die insgesamt 68 Schlüsselfragen und die Ergebnisse der Abstimmung sind im Leitlinienreport zur ersten Version hinterlegt.

4.1.2 Feststellung des Überarbeitungsbedarfs

Im Juni 2015 wurde die Planung des Updates der Leitlinie (Version 2.0) durch die Steuergruppe initiiert. In einem strukturierten Verfahren wurde zunächst innerhalb der Steuergruppe der Überarbeitungsbedarf kapitelweise festgestellt, konsentiert und im April 2016 der gesamten Leitliniengruppe zur Kommentierung und Ergänzung vorgelegt.

Nach Eingang aller Rückmeldungen wurde im August 2016 durch die Steuergruppe entschieden, aufgrund der umfangreichen Ergänzungs- und Änderungsbedarfe eine komplette Überarbeitung des Leitlinientextes vorzunehmen und die systematische Literaturrecherche dementsprechend zu planen. Im April 2017 wurden nach umfangreichen Vorarbeiten der Steuergruppe die Autoren der einzelnen Kapitel angeschrieben mit der Bitte, ihre jeweiligen Kapitel gemäß den Beschlüssen der Steuergruppe (u.a. in einer Telefonkonferenz im November 2016) zu überarbeiten und mit den Ko-Autoren abzustimmen. Im Februar 2019 wurde im Rahmen eines Arbeitstreffens der Steuergruppe eine teilweise Restrukturierung, redaktionelle Kürzung und Zusammenfassung thematisch ähnlicher Kapitel der Leitlinie vorgenommen, um die Lesbarkeit und Verständlichkeit zu verbessern. Einzelne Schüsselfragen wurden auf Wunsch der Steuergruppe hinzugefügt. Die neue Gliederung der Schlüsselfragen und der Hintergrundtexte ist in nachfolgender Tabelle abgebildet.

Kap.	Schlüsselfrage
6	**Epidemiologie von extracraniellen Carotisläsionen**
6.1	Wie hoch ist die Prävalenz extracranieller Carotisstenosen in Deutschland?
6.2	Wie hoch sind Prävalenz und Inzidenz der carotis-assoziierten zerebralen Ischämie in Deutschland?
6.3	Welche klinischen und morphologischen Faktoren beeinflussen das Auftreten einer carotis-bedingten zerebralen Ischämie bei bislang asymptomatischer Carotisstenose?
6.4	Welche klinischen und morphologischen Faktoren beeinflussen das Auftreten und die Prognose einer zerebralen Ischämie bei symptomatischer Carotisstenose
6.5	Wie häufig kommt es zu einem Verschluss der extracraniellen A. carotis interna und wie hoch ist das Schlaganfallrisiko eines akuten und eines chronischen Carotisverschluss?

Kap.	Schlüsselfrage
7	**Symptome und Diagnostik von extracraniellen Carotisläsionen**
7.1	Definition der asymptomatischen und symptomatischen Carotisstenose
7.2	Welche Skalen sind zur Beurteilung des Schweregrades einer zerebralen Ischämie notwendig, geeignet und zu empfehlen?
7.3	Welche Untersuchungsverfahren sind valide zur Diagnostik und Verlaufsbebachtung einer extracraniellen Carotisstenose?
7.4	Welche Diagnostik ist notwendig vor geplanter OP oder Intervention?
7.5	Sind Screening Untersuchungen (von Risikogruppen) sinnvoll?
8	**Therapieverfahren - Indikationen und Patientenperspektive**
8.1	Wer soll die Indikation auf der Basis welcher klinischen und apparativen Befunde zu den einzelnen Therapieverfahren stellen?
8.2	Wann und zu welchem Zeitpunkt besteht die Indikation zur OP oder zur endovaskulären Therapie einer asymptomatischen Carotisstenose), inkl. Subgruppen, die eher von einer operativen, endovaskulären oder konservativen Therapie profitieren?
8.3	Wann und zu welchem Zeitpunkt besteht die Indikation zur OP oder zur endovaskulären Therapie einer symptomatischen Carotisstenose (einschließlich Notfallindikation), inkl. Subgruppen, die eher von einer operativen, endovaskulären oder konservativen Therapie profitieren?
8.4	Wie soll beim Vorliegen einer behandlungsbedürftigen Carotisstenose und einer behandlungsbedürftigen KHK vorgegangen werden? Operativ, endovaskulär oder konservativ?
8.5	Wie sehen Patienten die Alternative CEA oder CAS?
8.6	Wie sind die klinischen und/oder morphologischen Langzeitergebnisse nach CEA und CAS?
9	**Operative Therapie**
9.1	Unterscheiden sich die konventionelle TEA (mit oder ohne Patch) und die Eversions TEA hinsichtlich Erfolgs-, Komplikations-, und Rezidivstenoseraten?
9.2	Bei welchen Patienten sollte intraoperativ obligat oder selektiv ein Shunt eingelegt werden?
9.3	Verbessert ein intraoperatives Monitoring bei OP in Allgemeinanästhesie das outcome? Wenn ja, wie ist der Stellenwert der einzelnen Monitoringverfahren?
9.4	NEU: Verbessert der Einsatz intraoperativer Kontrollverfahren das outcome? Wenn ja, wie ist der Stellenwert der einzelnen Kontrollverfahren?
9.5	Welches Anästhesieverfahren ist bei der operativen Therapie zu bevorzugen?
9.6	NEU: Risikoeinschätzung CEA - welche klinischen und morphologischen Faktoren sind mit einem erhöhten Behandlungsrisiko assoziiert? Z.T. alt Kap 8.6, aber jetzt ohne CAS!
9.7	NEU: Perioperatives medikamentöses und nicht-medikamentöses Management
9.8	Wie sieht das optimale Management von operationsspezifischen prozeduralen Komplikationen aus?

Kap.	Schlüsselfrage
10	**Endovaskuläre Therapie**
10.1	Ist bei Patienten mit einer hochgradigen extracraniellen Carotisstenose die alleinige PTA im Vergleich zur PTA mit Stent unterschiedlich hohen Erfolgs-, Komplikations- und Rezidivraten assoziiert?
10.2	Welche Materialien (Katheter, Stents, Protektionssysteme) sind bei CAS zu bevorzugen?
10.3	Risikoeinschätzung CAS - welche klinischen und morphologischen Faktoren sind mit einem erhöhten Behandlungsrisiko assoziiert?
10.4	Was ist zu beachten für ein optimales medikamentöses periinterventionelles Management?
10.5	Wie sieht das optimale Management periinterventioneller Komplikationen aus?
11	**Versorgungsstruktur**
11.1	Ist eine ambulante Therapie der Carotisstenose mittels CEA oder CAS möglich und sinnvoll? (Storck)
11.2	Welche Anforderungen an Weiterbildung und Strukturqualität ist an Einrichtungen zu stellen, in denen operative/endovaskuläre Revaskularisationen der A. carotis durchgeführt werden? (Sto, Berkefeld, Dörf)
11.3	Gibt es einen Zusammenhang zwischen Qualifikation, Volume (individuell, Klinik) und Outcome für die operative oder endovaskuläre Therapie? (Eck, Berkefeld, Dörf)
12	**Nachsorge, Rezidivtherapie und Lebensqualität**
12.1	Welche Patienten profitieren nach einer Carotis-Revaskularisation von einer Rehabilitationsmaßnahme bzw. Anschlussheilbehandlung (AHB)? (Lawall et al.)
12.2	Welche medikamentösen und nicht-medikamentösen Maßnahmen sollten wie lange zur Rezidivprophylaxe einer zerebrovaskulären Ischämie und/oder einer Carotisstenose eingesetzt werden und in welchen Intervallen ist eine Nachuntersuchung angezeigt? Lawall et al.)
12.3	Wie wird ein Therapieversagen bzw. ein Rezidiv klinisch und morphologisch definiert und wie muss dann diagnostisch und therapeutisch vorgegangen werden? Lawall et al.)
12.4	Gibt es eine Einschränkung der Lebensqualität nach operativer oder endovaskulärer Therapie einer Carotisstenose und wie wird diese erfasst? Lawall et al.)
12.5	Wie oft treten im ersten Jahr nach operativer oder endovaskulärer Therapie von Carotisstenosen schwere kardiovaskuläre Ereignisse auf? Lawall et al.)

4.1.3 Systematische Literaturrecherche

Die systematische Literaturrecherche wurde für die erste Version der Leitlinie sowie für das Update Ende 2016 und im Mai/Juni 2019 durch Herrn Dr. rer. nat. Helge Knüttel von der Universitätsbibliothek Regensburg durchgeführt. Die Suche erfolgte über das DIMDI und umfasste für die initiale Version der Leitlinie den Zeitraum 01.01.1990 bis 30.06.2009.

Details zur initialen Literaturrecherche finden sich im Leitlinienreport zur Initialen Version der Leitlinie von 2012.

Für das Update beschränkte sich die Suche auf Empfehlung der AWMF (Prof. I. Kopp) und nach umfangreicher Diskussion in der Steuergruppe auf den Zeitraum ab Publikationsjahr 2011

sowie auf Leitlinien, systematische Reviews und Meta-Analysen. Ergebnisse anderer Studientypen (z.B. RCT, Kohortenstudien, Fall-Kontroll-Studien) wurden nach Abstimmung in der Steuergruppe ebenfalls berücksichtigt, sofern sie über die zuvor genannten Studien hinaus entscheidungsrelevante Informationen lieferten oder keine (methodisch guten) Leitlinien bzw. systematische Reviews zur Beantwortung der Schlüsselfragen vorlagen. Die Syntax, das Protokoll sowie die Ergebnisübersicht der Datenbankrecherche finden sich in Anhang 9.1.

4.1.4 Auswahl der Evidenz

Die Auswahl der zu verwendenden Evidenz erfolgte anhand eines zuvor festgelegten Screeningschemas (siehe Anlage 9.2). Gemäß Empfehlungen der AWMF (Prof. I. Kopp) erfolgte die Beantwortung der einzelnen Schlüsselfragen auf Basis der jeweils besten verfügbaren Evidenz in folgender, absteigender Reihenfolge:

1. Leitlinien
2. Systematische Reviews
3. Meta-Analysen
4. Einzelne RCT
5. Sonstige Studien (Kohortenstudien, Fall-Kontroll Studien)

4.1.5 Bewertung der Evidenz

Die Bewertung der im ersten Update eingeschlossenen Leitlinien erfolgte durch Prof. H.-H. Eckstein und Prof. P. Ringleb unter Verwendung des Deutschen Leitlinien-Bewertungs-Instruments (DELBI), Domäne 3. Die Einzelbewertungen finden sich in Anhang 9.3.1.
Die Bewertung der eingeschlossenen systematischen Reviews und Meta-Analysen erfolgte nach Diskussion und Übereinkunft in der Steuergruppe durch die externe Organisation KSR (Kleijnen Systematic Reviews Ltd., York, UK). Eine Ergebnisübersicht findet sich in Anhang 9.3.2, die detaillierten Bewertungen in Anhang 9.3.3.
Für die Bewertung einzelner RCTs wurde das Cochrane Risk of Bias Tool verwendet.

4.1.6 Verwendung existierender Leitlinien zum Thema

Die in der initialen Version der Leitlinie vorhandenen Leitlinientabellen wurden im Rahmen des ersten Updates durch neu publizierte Leitlinien erweitert bzw. ergänzt. Die Leitlinientabellen finden sich in Anhang 9.4.1.

4.1.7 Erstellung von Evidenztabellen

Die in der initialen Version der Leitlinie vorhandenen Evidenztabellen wurden auf Basis der gefundenen neuen Studien erweitert bzw. ergänzt. Die Evidenztabellen zu existierenden systematischen Reviews und Meta-Analysen finden sich zusammen mit dem Bias-Assessment in Anhang 9.3.3, die von Einzel-RCTs finden sich in Anhang 9.4.3.

4.2 Formulierung der Empfehlungen und strukturierte Konsensfindung

4.2.1 Formale Konsensfindung: Verfahren und Durchführung

Der Ablauf der Konsensfindung auf der Konsensuskonferenz erfolgte jeweils in mehreren Schritten:

- Stille Durchsicht des zuvor versandten Leitlinienmanuskripts (Gesamtentwurf)
- Schriftliche oder mündliche Stellungnahmen der einzelnen Fachvertreter zu den Kernaussagen, Schlüsselempfehlungen und der vorgeschlagenen Graduierung
- Registrierung der Stellungnahmen und Alternativvorschläge aller Teilnehmer zu allen Aussagen und Empfehlungen im Einzelumlaufverfahren durch die Moderatorin. Rednerbeiträge dienten dabei nur zur Klarstellung. Die Projektion der Texte, Alternativvorschläge und der TED-Abstimmung erfolgte per Beamer.
- Vorabstimmung aller Empfehlungen und Empfehlungsgrade und der genannten Alternativen
- Diskussion der Punkte, für die im ersten Durchgang kein Konsens erzielt werden konnte
- Endgültige Abstimmung

Alle Empfehlungen und Texte, die während der Konsensuskonferenzen vor Ort nicht final abgestimmt werden konnten, wurden im Nachgang im Rahmen von mehreren DELPHI Runden konsentiert.

4.2.1.1 Konsensfindung 2005:

Eine erste Fassung der vorliegenden Leitlinie wurde im Rahmen eines ersten formalen Konsensusverfahrens[2] im September 2005 diskutiert.

Aufgrund laufender randomisierter Studien zum Vergleich der CEA mit der endovaskulären Therapie (CAS) und der Notwendigkeit der umfassenden Sichtung internationaler Leitlinien, Reviews und Originalia wurden die Arbeitsgruppen zunächst beauftragt, schrittweise die Schlüsselfragen zu beantworten.

4.2.1.2 Konsensfindung 2009:

Nach Fertigstellung des Fließtextes und der einzelnen Evidenztabellen erfolgte die Verabschiedung der Kernaussagen und Empfehlungen durch die Leitliniengruppe in einem zweiten Konsensusverfahren im August 2009 (Konsensuskonferenz in München), gefolgt von mehreren DELPHI-Runden im Nachgang der Konferenz. Die meisten Empfehlungen wurden im "starken Konsens" (Zustimmung von > 95% der Teilnehmer) oder im Konsens (Zustimmung von > 75% der Teilnehmer) verabschiedet. Für Empfehlungen, für die kein Konsens erzielt werden konnte, sind die unterschiedlichen Positionen im Kapiteltext dargelegt.

Die Abstimmungs- und Ergebnisprotokolle der Sitzungen können über das Leitliniensekretariat angefordert und eingesehen werden

[2] Nominaler Gruppenprozess nach Black N et al. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy 1999; 4: 236-48.61

4.2.1.3 Konsensfindung 2019:

Nach Einbeziehung der aktualisierten Rechercheergebnisse und Überarbeitung der Empfehlungen und Hintergrundtexte erfolgte im Februar und April 2019 zunächst eine Konsentierung innerhalb der Steuergruppe. Die final überarbeiteten Dokumente (Gesamtentwurf) wurden am 19.–20.Mai 2019 den offiziell benannten Mandatsträgern zugesandt. Den zu diesem Datum noch nicht bekannten Mandatsträgern wurde der Leitlinientext unmittelbar nach Benennung bzw. Bestätigung durch ihre Fachgesellschaften elektronisch zugesandt.

Die formale Abstimmung erfolgte auf einer Konsensuskonferenz am 25.–26.Juni 2019 gemäß dem üblichen, oben dargestellten Verfahren zur Konsensfindung. Die aus zeitlichen oder inhaltlichen Gründen nicht abschließend auf der Konsensuskonferenz bearbeitbaren Empfehlungen wurden im Nachgang im Rahmen eines DELPHI Verfahrens konsentiert. Das DELPHI-Verfahren umfasste 3 Runden und dauerte vom 09.07.2019 bis 12.09.2019. Das finale Ergebnis der DELPHI-Abstimmungen ist in Anlage 9.5 angegeben.

4.2.2 Berücksichtigung von Nutzen, Nebenwirkungen-relevanten Outcomes

Die Relevanz der Endpunkte wurde getrennt nach Sicherheitsendpunkten (0–30 Tage nach CEA oder CAS bzw. nach Randomisierung) und Effektivitätsendpunkten (Safety + Follow-up und Follow-up allein) von jedem Mitglied der Steuergruppe auf einer Skala von 1="irrelevant" bis 9="zwingend einzuschließen" gewichtet. Die folgenden Tabellen zeigen die Mittelwerte:

Sicherheitsendpunkte	Anzahl	Mittelwert
Jeder Schlaganfall oder Tod	6	9,0
Jeder schwere Schlaganfall (mRS>2) oder Tod	6	9,0
Tod	6	9,0
Jeder Schlaganfall	6	9,0
Jeder ipsilaterale Schlaganfall	6	9,0
Myokardinfarkt (jeglicher)	6	8,0
Myokardinfarkt (STEMI)	6	9,0
Hirnnervenläsion	6	6,3
Quality of Life (QoL, z.B. SF36)	6	2,3
Lokale Komplikationen (Nachblutung, Wundinfektion)	6	8,0
Vorschlag JB: Reperfusionssyndrom, Blutungskomplikationen	1	8,0

Effektivitätsendpunkte	Anzahl	Mittelwert
Jeder Schlaganfall oder Tod	6	9,0
jeder schwere Schlaganfall (mRS>2) oder Tod	6	9,0
Tod	6	9,0
Jeder Schlaganfall (bzw. schlaganfallfreies Überleben)	6	9,0
jeder ipsilaterale Schlaganfall (bzw. ipsilateral schlaganfallfreies Überleben)	6	9,0
Myokardinfarkt (jeglicher)	6	5,7
Myokardinfarkt (STEMI)	6	7,0
Persistierende Hirnnervenläsionen (>30 Tage und > 6 Monate)	6	9,0
Quality of Life (QoL, z.B. SF36)	6	7,3
Lokale Komplikationen (Nachblutung, Wundinfektion)	6	3,5
Vorschlag DS: Komb. Endpunkt (Schlaganfall, MI, vaskulärer Tod)	1	7,0

4.2.3 Formulierung der Empfehlungen und Vergabe von Evidenz- / Empfehlungsgraden

Der Text der Leitlinie wurde auf der Basis der Synopse internationaler Leitlinienempfehlungen und der Ergebnisse der eigenen Literaturrecherche und -bewertung erstellt. Bei der Darstellung der Inhalte wurde zwischen Kernaussagen/Schlüsselempfehlungen (fett geschrieben, im Textkasten), deren Herleitung (Fließtext, Quellenangaben) und der Darstellung der Primärliteratur (Evidenztabellen) unterschieden. Bei den Empfehlungen wird zwischen drei Empfehlungsgraden unterschieden, deren unterschiedliche Qualität bzw. Härte durch die Formulierung ("soll", "sollte", "kann") und Pfeilsymbole ausgedrückt wird. Empfehlungen *gegen* eine Intervention werden entsprechend sprachlich ausgedrückt bei Verwendung der gleichen Symbole. In der Regel bestimmt die Qualität der Evidenz (Evidenzstärke, siehe Anlage 9.5) den Empfehlungsgrad. D.h. eine Empfehlung auf Basis einer mittleren Evidenzstärke ist in der Regel mit einem mittleren Empfehlungsgrad verknüpft. Folgende Tabelle stellt die Graduierung der Evidenz- und Empfehlungsstärke dar.

Studienqualität	Evidenzstärke	Empfehlung	Beschreibung	Symbol
Systematische Übersichtsarbeit (Meta- Analyse) oder RCT (Therapie) oder Kohortenstudien (Risikofaktoren, Diagnostik) von hoher Qualität	hoch	„soll“	Starke Empfehlung	↑↑
RCT oder Kohortenstudien von eingeschränkter Qualität	mäßig	„sollte“	Empfehlung	↑
RCT oder Kohortenstudien von schlechter Qualität, alle anderen Studiendesigns, Expertenmeinung	schwach	„kann“	Empfehlung offen	↔

Die aufgeführten Empfehlungen richten sich nach der jeweils verfügbaren Evidenz. Bei fehlenden oder lückenhaften Daten sind die Konsensusempfehlungen (**EK = Expertenkonsens**) als Ergebnis der interdisziplinären Diskussionen aufgeführt.

Die Empfehlungsgrade orientieren sich an den Vorgaben der AWMF[3] (siehe Abbildung 1). Bei der Festlegung dieser Empfehlungsgrade im formalen Konsensusverfahren wurden neben der Güte der zugrundeliegenden Evidenz auch die Direktheit/externe Validität und Homogenität der Gesamtevidenz, die Nutzen-Risiko-Abwägung, die klinische Relevanz der Effektivitätsmaße der Studien, die Umsetzbarkeit in der Versorgungsrealität und ethische Verpflichtungen mitbetrachtet. Somit repräsentiert die vorliegende Textfassung der S3-Leitlinie Carotisstenose die Ansicht aller beteiligten Fachgesellschaften.

Auf Grund der genannten Aspekte wurde in Einzelfällen eine Auf- oder Abwertung des Empfehlungsgrades gegenüber der Evidenzstärke vorgenommen. Die jeweiligen Begründungen für solche Abweichungen sind dem Hintergrundtext zu den Empfehlungen zu entnehmen.

[3] https://www.awmf.org/leitlinien/awmf-regelwerk/ll-entwicklung/awmf-regelwerk-03-leitlinienentwicklung/ll-entwicklung-graduierung-der-empfehlungen.html

Abbildung 1: Evidenzstärke und Empfehlungsgrade

4.2.4 Konsensusstärke

Zur Feststellung der Konsensusstärke wurde bei allen Konsensuskonferenzen ein TED-System eingesetzt. Es wurde jeweils die absolute Anzahl der Ja-Stimmen, der Nein-Stimmen und der Enthaltungen anonym dokumentiert. Der Grad der Zustimmung wurde als prozentualer Anteil der Ja-Stimmen an allen Ja- und Nein-Stimmen berechnet. Die Konsensusstärke wurde gemäß folgender Tabelle klassifiziert:

Konsensusstärke	Anteil der Zustimmung
Starker Konsens	> 95%
Konsens	> 75% – 95%
Mehrheitliche Zustimmung	> 50% – 75%
Kein Konsens	≤ 50%

Wurde kein Konsensus erreicht bestand die Möglichkeit der Formulierung von Sondervoten, falls eine oder mehrere Fachgesellschaften einer der Empfehlungen trotz formal erreichten Konsens nicht zustimmten. Alle Empfehlungen wurden mit starkem Konsens oder Konsens angenommen, Sondervoten wurden nicht eingereicht.

5 Externe Begutachtung und Verabschiedung

5.1 Pilottestung

Zur Steigerung der Akzeptanz einer Leitlinie wird empfohlen (siehe DELBI Domäne 7) vor einer umfassenden Implementierung der Leitlinie eine Pilotstudie innerhalb der Anwendergruppe oder mindestens eines repräsentativen Teils der Anwendergruppe durchzuführen. Aufgrund des erheblichen personellen und finanziellen Ausmaßes einer derartigen Implementierungsstudie war eine Testung vor Verabschiedung nicht möglich. Es wird jedoch angestrebt, die Umsetzung von Leitlinienempfehlungen im Alltag, z.B. unter Nutzung von Routinedaten zu evaluieren.

5.2 Externe Begutachtung

Eine externe Begutachtung gemäß DELBI-Kriterium 13 erfolgt wie folgt:

- Vor der Veröffentlichung der Langversion auf den Internetseiten der AWMF erfolgte eine formale Prüfung und Freigabe durch alle beteiligten Fachgesellschaften.
- Vor der geplanten Publikation im Deutschen Ärzteblatt erfolgt routinemäßig eine formale Begutachtung durch externe Experten (Peer-Review Prozess)

5.3 Verabschiedung durch die Vorstände beteiligten Organisationen

5.3.1 Initiale Version der Leitlinie (2012)

Die endgültige Abstimmung des Gesamtmanuskripts durch die Leitliniengruppe erfolgte im Rahmen eines zweistufigen Delphiverfahrens. Im Rahmen der ersten Delphirunde wurden strukturierte Fragebögen versandt und die Rückmeldungen quantitativ ausgewertet. Empfehlungen, die starken Konsens oder Konsens erzielten und Qualitätsindikatoren mit einer Bewertung im Median >7 wurden in den präfinalen Leitlinienentwurf aufgenommen. Die Beschlussfassung über die Berücksichtigung begründeter Änderungswünsche erfolgte im Rahmen einer Telefonkonferenz der Steuergruppe. Die Beschlussfassung über die Berücksichtigung der Kommentare aus dieser zweiten Delphirunde erfolgte in einer abschließenden Sitzung der Steuergruppe. Im Falle von Zurückweisungen wurden entsprechende Begründungen dokumentiert. Das Protokoll dieses schriftlichen Verfahrens kann ebenfalls über das Leitliniensekretariat eingesehen werden. Abschließend wurde die Leitlinie formal durch die Vorstände der mitherausgebenden Fachgesellschaften bzw. Organisationen verabschiedet und autorisiert.

5.3.2 Erstes Update der Leitlinie (2019)

Die Konsentierung der Leitlinienempfehlungen erfolgte auf einer Konsensuskonferenz Ende Juni 2019. Nicht konsentierte Empfehlungen wurden in einem anschließenden Delphi-Verfahren iterativ bearbeitet. Die finale Version der Leitlinie inklusive der eingearbeiteten Kommentare des Delphiverfahrens wurde den Mitgliedern der Leitliniengruppe im Oktober 2019 zugesandt und bis Dezember 2019 formal durch alle Vorstände der mitherausgebenden Fachgesellschaften bzw. Organisationen verabschiedet.

6 Redaktionelle Unabhängigkeit

6.1 Finanzierung der Leitlinie

6.1.1 Initiale Version der S3-Leitlinie

Die anfallenden Kosten der Leitlinienerstellung übernahm die Deutsche Gesellschaft für Gefäßchirurgie (DGG). Es bestehen keine finanziellen Unterstützungen außerhalb der DGG. Insbesondere gab es keine Unterstützung durch andere Fachgesellschaften oder Berufsverbände, durch die Industrie oder durch Kostenträger. Reisekosten für Mandatsträger wurden von den beteiligten Fachgesellschaften übernommen. Den Autoren und Teilnehmern am Konsensusverfahren gilt großer Dank für ihre ausschließlich ehrenamtliche Arbeit.

6.1.2 Erste Aktualisierung der Leitlinie

Die anfallenden Kosten der Leitlinienerstellung übernahm erneut primär die Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG). Von Seiten folgender Fachgesellschaften erfolgte eine finanzielle Unterstützung, deren Höhe im Leitliniensekretariat angefragt werden kann:

- Deutsche Diabetes Gesellschaft
- Deutsche Gesellschaft für Angiologie
- Deutsche Gesellschaft für Gefäßchirurgie
- Deutsche Gesellschaft für Neurochirurgie
- Deutsche Gesellschaft für Neurologie
- Deutsche Gesellschaft für Neuroradiologie

Die finanzierenden Organisationen haben keinen Einfluss auf Inhalte der Leitlinie genommen.

6.2 Darlegung von und Umgang mit Interessenkonflikten

Im Verlauf der Erstellung der initialen Version der Leitlinie legten alle Mitglieder der Leitliniengruppe potentielle Interessen schriftlich offen.

Aufgrund geänderter Vorgaben der AWMF in Bezug auf die Darlegung von Interessen und den Umgang mit Interessenkonflikten (Conflicts of Interest, COI) wurden im April 2019 alle Mandatsträger aufgefordert, die von der AWMF offiziell bereitgestellten CoI-Formblätter (siehe Anhang 9.7.1) auszufüllen und dem CoI-Beauftragten der Steuergruppe (Prof. Dr. P. Ringleb) vertraulich zuzusenden. Die Bewertung der CoI von Prof. Ringleb erfolgte durch Prof. Kühnl. Der Umgang mit Interessenkonflikten erfolgte gemäß den zum Zeitpunkt der Anmeldung des Updates gültigen Regeln der AWMF. Unter der Voraussetzung, dass ein thematischer Bezug zur aktuellen Leitlinie bestand, wurden Interessenkonflikte durch Studienteilnahmen und Vorträge als gering eingeschätzt und Mitgliedschaften in Advisory Boards als hoch; Industrie- und Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz) kamen nicht vor. Die aggregierten Daten der Auswertung sind in Anhang 9.7.2 aufgelistet.

7 Verbreitung und Implementierung

7.1 Konzept zur Verbreitung und Implementierung

Die überarbeitete S3-Leitlinie „Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose“ wird als Langversion einschließlich Methodenreport kostenfrei über die Internetseite der AWMF zur Verfügung gestellt werden. Darüber hinaus wird sie in folgenden Formaten publiziert:

- Langversion einer Zeitschrift mit Peer-review-Verfahren (Gefässchirurgie)
- Kurzversion im Deutschen Ärzteblatt
- Deutschsprachige und englische Kurzversion fachspezifisch in den entsprechenden nationalen und internationalen Organen der Fachgesellschaften
- Kurzversion in englischer Sprache im Internet (Guidelines International Network, www.g-i-n.net)
- Geplant ist die Publikation einer kurzgefassten Patientenversion

7.2 Unterstützende Materialien für die Anwendung der Leitlinie

Die geplanten Publikationen sind Bestandteil der Implementierungsstrategie. Es wird explizit angeregt, die Leitlinie unter Bezugnahme auf die genannten Publikationen in die Praxis zu überführen. Vor allem wird empfohlen:

- Einbindung der Leitlinienempfehlungen in einrichtungsinterne Behandlungspfade
- Berücksichtigung der Leitlinie in lokalen Patienteninformationen/Broschüren

Die Verbreitung und Implementierung wird von der Leitliniensteuergruppe aktiv unterstützt durch:

- Pressemeldung an den Informationsdienst Wissenschaft (idw-online.de)
- Vorstellung der Leitlinie im Rahmen von Fachkongressen der beteiligten Gesellschaften und Organisationen

Unterstützung der Erstellung von Materialien für die kontinuierliche Fort- und Weiterbildung (CME-Beiträge entsprechend der Anforderungen der Landesärztekammern)

7.3 Diskussion möglicher organisatorischer und/oder finanzieller Barrieren gegenüber der Anwendung der Leitlinienempfehlungen

Gemäß DELBI-Kriterium 19 können Leitlinien durch ihre Empfehlungen Veränderungen der üblichen Organisation der Gesundheitsversorgung in einer Einrichtung auf struktureller Ebene oder im Verhalten der medizinischen Leistungserbringer, notwendig machen. Diese potenziellen Veränderungen können die Umsetzung der Empfehlungen be- oder verhindern. Gemäß DELBI-Kriterium 20 wird durch die Umsetzung von Leitlinien in der Regel eine rationellere Ressourcenverwendung erwartet. Nicht selten jedoch können für die Realisierung der Empfehlungen u. U. zusätzliche Ressourcen erforderlich sein.

Es wird angestrebt, die Änderungen im Hinblick auf personelle, materielle und finanzielle Ressourcen, welche für die Realisierung der Umsetzung der Empfehlungen notwendig sind, systematisch in einer separaten Publikation zu analysieren und zu diskutieren.

7.4 Messgrößen für das Monitoring: Qualitätsziele, Qualitätsindikatoren

Mit diesen Empfehlungen wird eine Verknüpfung der Leitlinie mit zertifizierten Fortbildungsmaßnahmen und Qualitätsmanagementsystemen angestrebt. Die begleitende Evaluierung der Leitlinienimplementierung ist ein wichtiges Anliegen. Insbesondere für die Implementierung der Qualitätsziele und die Evaluation der Versorgungswirklichkeit wird eine enge Abstimmung mit Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG) sowie dem Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) sowie den Qualitätssicherungsorganen der regionalen Ärztekammern angestrebt.

8 Gültigkeitsdauer und Aktualisierungsverfahren

8.1 Datum der letzten inhaltlichen Überarbeitung und Status

Die letzte inhaltliche Überarbeitung erfolgte am 15.01.2020.

8.2 Aktualisierungsverfahren

Die Leitlinie soll regelmäßig, vorzugsweise mindestens alle 3-5 Jahre aktualisiert werden. Verantwortlich für das Aktualisierungsverfahren sind die Koordinatoren. Neu erscheinende wissenschaftliche Erkenntnisse werden von der Leitliniengruppe beobachtet und sich hieraus ergebende relevante Neuerungen bzw. Korrekturen als Addendum publiziert (Internetversion, Fachzeitschriften). Gültig ist nur die jeweils neueste Version gemäß AWMF-Register. Kommentierungen und Hinweise für den Aktualisierungsprozess aus der Praxis sind ausdrücklich erwünscht und können an das Leitliniensekretariat (a.kuehnl@tum.de) gerichtet werden.

9 Anhänge - Übersicht

9.1 Literaturrecherche 2015/16 und 2019 (Syntax, Protokoll, Ergebnisübersicht)

9.2 Flowchart: Screening der Literatur-Rechercheergebnisse

9.3 Systematische Bewertung der Evidenz

9.3.1 Bewertungen der Leitlinien (DELBI Domäne 3)
9.3.2 Bewertungen der systematischen Reviews durch KSR: Übersicht
9.3.3 Bewertungen der systematischen Reviews durch KSR: Einzelbewertungen inkl. Zusammenfassung der Ergebnisse

9.4 Zusammenfassung der Evidenz

9.4.1 Leitlinientabellen
9.4.2 Ergebnisse systematischer Reviews und Metaanalysen siehe 9.3.3
9.4.3 Evidenztabellen (RCTs)

9.5 Endergebnis des Delphi-Verfahrens 2019

9.6 Schema der Evidenzgraduierung nach Oxford: CEBM 2009

9.7 Erklärung von Interessenkonflikten (CoI)

9.7.1 Interessenkonflikterklärungen: AWMF Conflict of Interest Erhebungsbogen
9.7.2 Interessenkonflikterklärungen: CoI-Übersichttabelle

9.8 Leitlinienreport Version 1.0 zur ersten Version der Leitlinie

Erstveröffentlichung	08/2012
Überarbeitung von	02/2020
Nächste Überprüfung geplant	02/2025

Autorisiert für elektronische Publikation

AWMF online

Dokumentation einer Systematischen Literatursuche

Versionen dieses Dokuments

Version	Datum	Bemerkung
1	22.09.2016	Suche in Leitliniendatenbanken
2	11.10.2016	Suche nach Leitlinien in bibliographischen Datenbanken
3	15.12.2016	Suche nach Systematic Reviews und Metaanalysen beim DIMDI

Auftraggeber

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Thema

Update der S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose
AWMF-Registernummer der bestehenden Leitlinie: 004-028

Durchführung

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Einschränkungen der Suche

Einschränkungen bei der Suche auf Wunsche des Auftraggebers:

- Datum: ab Publikationsjahr 2011
- Sprachen:
  - keine Einschränkungen bei der Leitliniensuche
  - Publikationssprache Deutsch und Englisch bei der Suche nach Systematic Reviews und Metaanalysen

Hinweise
Diese Dokumentation beinhaltet alle mir möglichen Angaben für ein Reporting nach den Empfehlungen in [1–3].

Suche in Leitlinien-Datenbanken

Wie in [4] empfohlen wird zuerst in Leitlinien-Datenbanken recherchiert.

AWMF

An der Aktualisierung dieser S3-Leitlinie unter dem Dach der AWMF sind insgesamt 20 Fachgesellschaften beteiligt. Auf eine separate Suche nach relevanten AWMF-Leitlinien wird verzichtet, da diese bekannt vorausgesetzt werden können.

leitlinien.de (Portal des ÄZQ)

Suche am 21.09.2016.

Liste mit 12 Nationalen VersorgungsLeitlinien (NVL), von denen keine thematisch relevant ist:
http://www.leitlinien.de/nvl

Leitlinien der Bundesärztekammer

Suche am 21.09.2016.

Liste mit 15 Leitlinien, von denen keine thematisch relevant ist:
http://www.bundesaerztekammer.de/richtlinien/leitlinien/

Leitliniengruppe Hessen

Suche am 21.09.2016.

Liste mit 16 Leitlinien (Zielgruppe Hausärzte), von denen keine thematisch relevant ist:
http://www.pmvforschungsgruppe.de/content/03_publikationen/03_d_leitlinien.htm

Arztbibliothek.de

Suche am 21.09.2016.

Die in [4] für die Recherche empfohlene Website http://www.arztbibliothek.de/ wird auf http://www.aezq.de/aezq/arztbibliothek umgeleitet. Dort gibt es die Info, dass die Arztbibliothek des ÄZQ nur bis 2015 existierte.

Guidelines International Network (G-I-N): International Guideline Library

Suche am 21.09.2016
http://www.g-i-n.net/library/international-guidelines-library

Angepasst an die Suchoberfläche wurden breite und teilweise redundante Suchterme (mit und ohne Trunkierung) für die einfache Suche gewählt. Die Suche mit MESH-Termen bot nur eine kleine Auswahl breiter Terme.

Suchterm (Simple Search)	**Treffer**
carotid	3
carotis	0
caroti*	3
karoti*	1
endarterectomy	1
endarterectom*	1
angioplasty	8
angioplast*	8
Advanced Search: Suche nach MESH-Term „Arterial Occlusive Diseases“	32

Nach Deduplikation bleiben insgesamt 39 Treffer. Diese sind in der Datei „kuehnl_2685_Treffer_GIN_2016-09-21.xlsx“ gespeichert.
Relevante Treffer können beim GIN wieder gesucht werden, um dann die Details einzusehen.

National Guideline Clearinghouse (NGC)

Suche am 22.09.2016
http://www.guideline.gov/

Angepasst an die Suchoberfläche wurden breite und teilweise redundante Suchterme (mit und ohne Trunkierung) für die einfache Suche gewählt.

Suchterm	**Treffer**
carotid OR carotis OR caroti* OR karoti* OR endarterectomy OR endarterectom* OR angioplasty OR angioplast*	103

Diese Treffer sind in der Datei „kuehnl_2685_NGC_2016-09-22.pdf“ gespeichert.
Relevante Treffer können beim NGC wieder gesucht werden, um dann die Details einzusehen.

SIGN Scottish Intercollegiate Guidelines Network

Suche am 22.09.2016
http://www.sign.ac.uk/guidelines/index.html

Dort sind ca. 150 Leitlinien (incl. ungültiger) gelistet, u.a. auch zur Carotisstenose. Die Liste ist gespeichert in der Datei „kuehnl_2685_SIGN_2016-09-22.pdf“.

National Institute for Health and Care Excellence (NICE)

Suche am 22.09.2016
https://www.nice.org.uk/guidance

Angepasst an die Suchoberfläche wurden breite und teilweise redundante Suchterme (mit und ohne Trunkierung) für die einfache Suche gewählt.

Suchterm	**Treffer**
carotid OR carotis OR caroti* OR endarterectomy OR endarterectom* OR angioplasty OR angioplast*	111

Diese Treffer sind in der Datei „kuehnl_2685_NICE_2016-09-22.pdf" gespeichert.
Relevante Treffer können beim NGC wieder gesucht werden, um dann die Details einzusehen:
https://www.nice.org.uk/Search?ps=150&q=carotid+or+carotis+or+caroti*+or+endarterectomy+or+endarterectom*+or+angioplasty+or+angioplast*&sp=off

11.10.2016: Suche nach Leitlinien in bibliographischen Datenbanken beim DIMDI

Wie in [4] empfohlen wird nach bestehenden Leitlinien gesucht, hier in bibliographischen Datenbanken.
Es gibt ein aktuelles Systematic Review der Leitlinien zum Thema [5].
Die Suche beinhaltet nur Treffer ab dem Publikationsjahr 2011.

Fragestellungen

Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose.
Suche nach bestehenden Leitlinien in bibliographischen Datenbanken beim Host DIMDI.

Dies ergibt die folgenden Konzepte:
A: Carotisstenose
B: Leitlinien

Suche:
A AND B

Die publizierten Suchstrategien aktueller Cochrane-Reviews für das Konzept „Carotisstenose" unterscheiden sich, auch wegen der unterschiedlichen Themen, deutlich [6–8]. Die hier verwendete Suchstrategie ist auf hohe Sensitivität ausgerichtet und beinhaltet Elemente dieser drei Cochrane-Reviews sowie der Suchstrategie der Vorgängerversionen der hier zu aktualisierenden AWMF-Leitlinie. Diese Suchstrategie ist bezüglich der Suchterme umfassender, als die der Vorgängerversionen.
Das Konzept „Leitlinien" beruht auf den „Suchfiltern für Leitlinien" in [4].
Bei beiden Konzepten wurden bei übernommenen Suchtermen notwendige Anpassungen an die Syntax der DIMDI-ClassicSearch und bzgl. der verwendeten Datenbanken vorgenommen.

Datenbankauswahl

Suche im beim DIMDI (Deutsche Institut für Medizinische Dokumentation und Information) gehosteten Datenbanken. Siehe http://www.dimdi.de/
Die Anzahl der beim DIMDI verfügbaren Datenbanken nahm in den vergangenen Jahren stark ab. Hier wurde daraus eine Auswahl von Datenbanken getroffen, bei denen relevante Leitlinien erwartet wurden.

Recherchedatum: 11.10.2016

Jeweils Angabe von Kürzel, Name und Hersteller der Datenbanken:

```
5 database(s) with 33012436 documents selected
ME10   MEDLINE                        NLM
       New MeSH 2016 and Class-Maintained Database
EM10   EMBASE                         2016 Elsevier B.V.
BA10   BIOSIS Previews                Thomson Reuters
EA08   EMBASE Alert                   2015 Elsevier B.V.
IS10   SciSearch                      Thomson Reuters
```

Updatestatus und Dokumentenzahlen der Datenbanken siehe Datei „DIMDI_Updatestatus_2016-10-11.pdf".

Suchprofil

Die Suche erfolgte mit der Kommandosprache „DIMDI ClassicSearch“. Dokumentation siehe http://www.dimdi.de/static/de/db/open/benutzerhandbuch.pdf.

Suchschritte

Jeweils Angabe von Nummer des Suchschritts, Anzahl der Treffer, Suchbegriff:

```
? t cont

      NO             HITS    SEARCH EXPRESSION

C=     1         33012436    ME10; EM10; BA10; EA08; IS10
S=     2            15010    CT=CAROTID STENOSIS
       3             7475    CT = CAROTID ARTERY DISEASES
       4             6693    CT = CAROTID ARTERY DISEASE
       5              990    CT = CAROTID ARTERY THROMBOSIS
       6            11963    CT D CAROTID ARTERY OBSTRUCTION
       7              144    (CT D CAROTID ARTERIES) AND (CT =
                             CONSTRICTION, PATHOLOGIC)
       8               55    (CT D CAROTID ARTERY) AND (CT = ARTERY
                             CONSTRICTION)
       9            54520    CAROTI# # # # # #,
                             (STENO?;NARROW?;OBSTRUCT?;OCCLU?;PLAQUE;THROMB
                             O?;BRUIT?;ATHERO?;ARTERIOSCLERO?;DISSECT?).
      10             8134    CT = ENDARTERECTOMY, CAROTID
      11             9265    CT = CAROTID ENDARTERECTOMY
      12             8945    CT D CAROTID ARTERY SURGERY
      13            22516    CAROTI# # # # # #,
                             (ANGIOPLAST?;STENT?;ENDARTERECT?;THROMB###ARTE
                             RECT?;ENDOVASC?).
      14             3191    CAROTI# # # # # #,
                             (CATHETER?;ENDOLUM?;TRANSLUM?;REPAIR;DILAT?).
      15            68900    2 - 14
      16             7270    DT=PRACTICE GUIDELINE
      17             1052    DT = GUIDELINE
      18             3581    CONSENSUS DEVELOPMENT CONFERENCE
      19             9391    CONSENSUS STATEMENT
      20           166054    CT D PRACTICE GUIDELINE
      21           138782    CT = GUIDELINES AS TOPIC
      22           167014    CT = PRACTICE GUIDELINES AS TOPIC
      23            25950    CT = HEALTH PLANNING GUIDELINES
      24           185603    ?GUIDELINE?/CT
      25             8202    CT D CONSENSUS DEVELOPMENT CONFERENCES AS
                             TOPIC
      26              105    DT = CONSENSUS DEVELOPMENT CONFERENCE, NIH
      27             3191    DT = CONSENSUS DEVELOPMENT CONFERENCE
      28            92801    GUIDELINE?/TI
      29             3142    PRACTICE # # #, PARAMETER?
      30            33786    CT = CLINICAL PROTOCOLS
      31           161504    GUIDANCE/(TI;AB)
      32             6645    CARE PATHWAY?/(TI;AB)
      33             5361    CT = CRITICAL PATHWAYS
      34            10039    CLINICAL # # #, PATHWAY*/(TI;AB)
      35           212285    CT = ALGORITHMS
      36           689332    16 - 35
      37             1928    15 AND 36
      38             1652    37 AND PY>=2011
      39             1525    38 NOT SU=MEDLINE
      40             1246    check duplicates: unique in s=39
*** END OF TAB ***
```

Verteilung der Treffer auf die verschiedenen Datenbanken im Suchergebnis

Vor (Suchschritt 38) und nach Dublettencheck (Suchschritt 40), jeweils Angabe von Nummer des Suchschritts, Anzahl der Treffer im Suchschritt gesamt, Suchbegriff, Datenbank und Treffer in den einzelnen Datenbanken:

```
? t cont;detail;s=38;39;40

      NO             HITS    SEARCH EXPRESSION

      38             1652    37 AND PY>=2011
                             ME10: 463
                             EM10: 1002
                             BA10: 45
                             EA08: 2
                             IS10: 140
      39             1525    38 NOT SU=MEDLINE
                             ME10: 463
                             EM10: 875
                             BA10: 45
                             EA08: 2
                             IS10: 140
      40             1246    check duplicates: unique in s=39
                             ME10: 463
                             EM10: 732
                             BA10: 8
                             EA08: 1
                             IS10: 42
*** END OF TAB ***
```

Trefferausgabe

Konzept A: Carotisstenose = Suchschritt 15 (68900 Treffer)
Konzept B: Leitlinien = Suchschritt 36 (689332 Treffer)

A AND B = Suchschritt 37 (1928 Treffer)
Einschränkung Publikationsjahr >= 2011 = Suchschritt 38 (1652 Treffer)

Gesamtergebnis vor Dublettenentfernung in Suchschritt 38: 1652Treffer
Gesamtergebnis nach Dublettenentfernung in Suchschritt 40: 1246 Treffer

Um Kosten zu sparen wurde die Gesamttreffermenge von Suchschritt 40 für die Ausgabe unterteilt und separat ausgegeben:

Treffer-anzahl	Datei	Bemerkung
463	kuehnl_2685_2016-10-11_PubMed_MEDLINE.txt	Treffer aus Medline zum Import in Lit.-verwaltungssoft ware mit dem PubMed/MEDLIN E-Textfilter
1246	kuehnl_2685_2016-10-11_Trefferauswahl.xlsx	Alle Treffer. Zur Auswahl anhand des Titels. Enthält insb. die kostenpflichtigen Datenbanken.

Die Treffer aus MEDLINE konnte ich bereits separat kostenlos aus PubMed mit den bibliographischen Angaben und Abstracts ausgeben.
In der Excel-Datei „kuehnl_2685_2016-10-11_Trefferauswahl.xlsx" sind die beim DIMDI kostenlos ausgegebenen Titel aller Treffer enthalten. Anhand der Titel kann eine Vorauswahl stattfinden. Bitte gewünschte Treffer in der ersten Spalte „Auswahl" mit einem „x" kennzeichnen. Für die markierten Treffer kann ich dann die bibliographischen Angaben incl. evtl. Abstracts zum jeweils angegebenen Dokumentenpreis ausgeben. Das Exportformat ist RIS, das problemlos von Endnote und anderer Literaturverwaltungssoftware importiert werden kann.
Die Treffer der Datenbank „SciSearch" stammen aus dem Web of Science, das Sie vmtl. auch an der TU München abonniert haben. Sie können hier ggf. die Artikeltitel im Feld „Title" suchen und sich damit die teure Ausgabe beim DIMDI ersparen.

12.12.2016: Suche nach Systematic Reviews und Metaanalysen beim DIMDI

Es wurde in bibliographischen Datenbanken nach den Studiendesigns Systematische Reviews (SR) sowie Metaanalysen zum Konzept „Carotisstenose“ gesucht.

Nach Möglichkeit wurden publizierte und validierte Suchfilter für die Studiendesigns (Methodenfilter) verwendet. Die Auswahl erfolgte aus den bei [9] gelisteten Filtern.

Einschränkung bei der Recherche:

- Publikationsdatum: ab 2011
- Publikationssprache Deutsch und Englisch

Fragestellungen

Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose. Methodenfilter für die ausgewählten Studiendesigns.
Suche in bibliographischen Datenbanken beim Host DIMDI.

Dies ergibt die folgenden Konzepte:
A: Carotisstenose
Das Konzept „Carotisstenose“ wird mit derselben Suchstrategie gesucht, wie bei der vorangegangenen Suche nach Leitlinien in bibliographischen Datenbanken.

B: Systematische Reviews (SR) und Metaanalysen
SR-/HTA-Datenbanken: Alle Treffer.
MEDLINE: “Top strategy minimising the difference between sensitivity and specificity” aus [10] (Table 2).
Embase: Filter "best optimization of sensitivity and specificity" aus [11] (Table 2)

Suche:
A AND B

Datenbankauswahl

Suche im beim DIMDI (Deutsche Institut für Medizinische Dokumentation und Information) gehosteten Datenbanken. Siehe http://www.dimdi.de/

Recherchedatum: 12.12.2016

Jeweils Angabe von Kürzel, Name und Hersteller der Datenbanken:

CDSR93	Cochrane Database of Systematic Reviews	The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
CDAR94	Database of Abstracts of Reviews of Effects	2015 University of York. Published by John Wiley & Sons, Ltd.
DAHTA	DAHTA-Datenbank	Deutsches Institut fuer Medizinische Dokumentation und Information
INAHTA	Health Technology Assessment Database	2016 University of York. Published by John Wiley & Sons, Ltd.
CCTR93	Cochrane Central Register of Controlled Trials	The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
ME10	MEDLINE New MeSH 2016 and Class-Maintained Database	NLM
EM10	EMBASE	2016 Elsevier B.V.
EA08	EMBASE Alert	2015 Elsevier B.V.

Die Datenbank CCTR93 Cochrane Central Register of Controlled Trials wurde zwar für die Suche selektiert, beim Konzept „B: Systematische Reviews (SR) und Metaanalysen“ aber nicht mit eingeschlossen. Im Endergebnis sind daher keine Treffer aus CCTR93 enthalten.

Suchprofil

Die Suche erfolgte mit der Kommandosprache „DIMDI ClassicSearch“. Dokumentation siehe http://www.dimdi.de/static/de/db/open/benutzerhandbuch.pdf.

Suchschritte

Jeweils Angabe von Nummer des Suchschritts, Anzahl der Treffer, Suchbegriff:

```
? t cont

      NO             HITS    SEARCH EXPRESSION

C=     1         17713244    CDSR93; CDAR94; DAHTA; INAHTA; CCTR93; ME10;
                             EM10; EA08
S=     2            14693    CT=CAROTID STENOSIS
       3             6936    CT = CAROTID ARTERY DISEASES
       4             6982    CT = CAROTID ARTERY DISEASE
       5              943    CT = CAROTID ARTERY THROMBOSIS
       6            12456    CT D CAROTID ARTERY OBSTRUCTION
       7              154    (CT D CAROTID ARTERIES) AND (CT =
                             CONSTRICTION, PATHOLOGIC)
       8               56    (CT D CAROTID ARTERY) AND (CT = ARTERY
                             CONSTRICTION)
       9            38776    CAROTI# # # # # #,
                             (STENO?;NARROW?;OBSTRUCT?;OCCLU?;PLAQUE;THROMB
                             O?;BRUIT?;ATHERO?;ARTERIOSCLERO?;DISSECT?).
      10             8784    CT = ENDARTERECTOMY, CAROTID
      11             8990    CT = CAROTID ENDARTERECTOMY
      12             9195    CT D CAROTID ARTERY SURGERY
      13            17108    CAROTI# # # # # #,
                             (ANGIOPLAST?;STENT?;ENDARTEREC T?;THROMB###ARTE
                             RECT?;ENDOVASC?).
      14             2296    CAROTI# # # # # #,
                             (CATHETER?;ENDOLUM?;TRANSLUM?;REPAIR;DILAT?).
      15            49717    2 - 14
      16              219    15 AND BASE=(CDSR93;CDAR94;DAHTA;INAHTA)
      17               10    META-ANALYSIS(TI;AB;CT;DT)
      18          1394567    DT=REVIEW
      19                4    SEARCH?(TI;AB)
      20          1394577    17 - 19
      21           661723    20 AND BASE=ME10
      22           230101    META-ANALYS?/(TI;AB;CT)
      23                4    SEARCH?(TI;AB)
      24          1394567    DT=REVIEW
      25          1555354    22 - 24
      26           823188    25 AND BASE=(EM10;EA08)
      27          1485130    16;21;26
      28             4300    15 AND 27
      29             3942    28 AND LA=(GERM;ENGL)
      30             3281    29 AND PY >= 2011
      31             3068    30 NOT SU=MEDLINE
      32             2539    check duplicates: unique in s=31
*** END OF TAB ***
```

Verteilung der Treffer auf die verschiedenen Datenbanken im Suchergebnis

Vor (Suchschritt 30) und nach Dublettencheck (Suchschritt 32), jeweils Angabe von Nummer des Suchschritts, Anzahl der Treffer im Suchschritt gesamt, Suchbegriff, Datenbank und Treffer in der einzelnen Datenbank:

```
? t cont;detail;s=30;31;32

      NO             HITS    SEARCH EXPRESSION

      30             3281    29 AND PY >= 2011
                             CDSR93: 10
                             CDAR94: 57
                             INAHTA: 8
                             ME10: 1026
                             EM10: 2157
                             EA08: 23
      31             3068    30 NOT SU=MEDLINE
                             CDSR93: 10
                             CDAR94: 57
                             INAHTA: 8
                             ME10: 1026
                             EM10: 1944
                             EA08: 23
      32             2539    check duplicates: unique in s=31
                             CDSR93: 10
                             CDAR94: 57
                             INAHTA: 7
                             ME10: 1017
                             EM10: 1442
                             EA08: 6
*** END OF TAB ***
```

Trefferausgabe

Konzept A: Carotisstenose = Suchschritt 15 (49717 Treffer)
Konzept B: Systematische Reviews (SR) und Metaanalysen = Suchschritt 27 (1485130 Treffer)

A AND B = Suchschritt 28 (4300 Treffer)
Einschränkung Sprachen = Suchschritt 29 (3942 Treffer)
Einschränkung Publikationsjahr >= 2011 = Suchschritt 30 (3281Treffer)

Gesamtergebnis vor Dublettenentfernung in Suchschritt 30: 3281 Treffer
Gesamtergebnis nach Dublettenentfernung in Suchschritt 32: 2539 Treffer

Aus dem Gesamtergebnis in Suchschritt 32 wurden vor der Trefferausgabe weiterhin die **Dubletten zur vorangegangenen Leitliniensuche beim DIMDI entfernt**. Diese sind in einer Liste aller Treffer markiert (Datei „kuehnl_2685_2016-12-12_Trefferliste.xlsx").

Um Kosten zu sparen wurde die Gesamttreffermenge für die Ausgabe unterteilt und separat ausgegeben. Beachte: Die Trefferzahlen sind wegen der Entfernung der Dubletten zur Leitliniensuche geringer als bei den oben dokumentierten Suchschritten.

Treffer-anzahl	Datei	Bemerkung
74	kuehnl_2685_2016-12-12_kostenlose.ris	Kostenlose Treffer aus Cochrane-Datenbanken & DAHTA zum Import in Lit.-verwaltungssoftware mit dem RIS-Textfilter
929	kuehnl_2685_2016-12-12_PubMed_MEDLINE.txt	Treffer aus Medline zum Import in Lit.-verwaltungssoftware mit dem PubMed/MEDLINE-Textfilter
1311	kuehnl_2685_2016-12-12_Embase.ris	Treffer aus Embase & Embase Alert zum Import in Lit.-verwaltungssoftware mit dem RIS-Textfilter
2539	kuehnl_2685_2016-12-12_Trefferliste.xlsx	Alle Treffer. Dubletten zur LL-Suche markiert. Alle Treffer wurden bereits ausgegeben. Daher keine Auswahl nur anhand des Titels mehr notwendig.

Dateien in der Anlage

Folgende Dateien gehören zu dieser Dokumentation:

- kuehnl_2685_Treffer_GIN_2016-09-21.xlsx
- kuehnl_2685_NGC_2016-09-22.pdf
- kuehnl_2685_SIGN_2016-09-22.pdf
- DIMDI_Updatestatus_2016-10-11.pdf
- kuehnl_2685_2016-10-11_PubMed_MEDLINE.txt
- kuehnl_2685_2016-10-11_Trefferauswahl.xlsx
- kuehnl_2685_2016-12-12_kostenlose.ris
- kuehnl_2685_2016-12-12_PubMed_MEDLINE.txt
- kuehnl_2685_2016-12-12_Embase.ris
- kuehnl_2685_2016-12-12_Trefferliste.xlsx

Verwendete Literatur

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Dokumentation einer Systematischen Literaturrecherche

Suchauftrag: 2746_kuehnl

Versionen dieses Dokuments

Version	Datum	Bemerkung
1	07.06.2019	Suchen vom 05.-07.06.2019

Auftraggeber
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Thema
Update der Literatursuche zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose
AWMF-Registernummer der bestehenden Leitlinie: 004-028

Durchführung der Recherche und Dokumentation
Dr. Helge Knüttel, Universitätsbibliothek Regensburg

Hinweise
Es existiert eine Reihe aktueller Empfehlungen für das Reporting von Literatursuchen im Rahmen von Systematic Reviews (1–6) bzw. der Leitlinienentwicklung (7). Diese Empfehlungen weisen große Übereinstimmungen auf, im Detail aber auch Unterschiede, v. a. bzgl. des Umfangs. Diese Dokumentation der Literatursuche beinhaltet alle mir möglichen Angaben für ein Reporting nach den Übereinstimmungen in den Empfehlungen. Neben internen Angaben für die praktische Durchführung sind insb. alle Angaben enthalten, um die Literatursuche in einer Publikation gemäß den aktuellen Anforderungen an Transparenz und Reproduzierbarkeit darstellen zu können.

Manche Aufgaben bei der Suche (bspw. Durchsicht von Literaturverzeichnissen und Webseiten) sind im Allgemeinen vom Auftraggeber durchzuführen. Dieser ist dann verantwortlich, die Dokumentation dieser Schritte zu ergänzen. In der Dokumentation sind bereits entsprechenden Stellen im Abschnitt „Manuelle Suche“ ausgewiesen.

In Publikationen, die auf dieser Recherche basieren, bitte ich um einen Hinweis auf meine Unterstützung bei der Literatursuche (z.B. Material und Methoden, Danksagung). Insbesondere bei Dissertationen ist dies eine in Ihrem Interesse liegende Notwendigkeit, da gemäß den Promotionsordnungen die Offenlegung aller Quellen und Hilfsmittel erklärt werden muss.
Bei substanziellen Beiträgen meinerseits bin ich ggf. auch an einer Co-Autorenschaft interessiert. Bitte fragen Sie mich.

Übersetzung der Forschungsfrage in Suchanfragen / Translating the research question into a search question

Umfang der Suchstrategie / Sampling strategy

Breit angelegte Recherche, die auch zahlreiche nicht relevante Treffer bringen kann (Recall maximiert), um systematische Fehler bei der Literaturauswahl zu minimieren.

Gewählte Einschränkungen bei der Suche

Einschränkungen bei der Suche auf Wunsch des Auftraggebers:

- Publikationsdatum: ab 2016
- Sprachen: deutsch, englisch
- Methodische Filter: Leitlinien, Systematic Reviews, Meta-Analysen

Komponenten der Suche

In der Fragestellung wurden für die Suche die folgenden Komponenten identifiziert. Diese bilden die Basis für die Suche in den einzelnen Informationsquellen.

Suchkomponente „Patient“	Carotisstenose
Suchkomponente „Studiendesign“	Leitlinien, Systematische Reviews (SR) und Metaanalysen
Suchkomponente „Publikationsdatum“	>=2016
Suchkomponente „Sprache“	Deutsch, englisch

Aus den Treffermengen der Suchkomponenten wird mit dem Booleschen Operator AND die Schnittmenge gebildet.
Nicht bei jeder der Datenbanken/Webseiten war die Verwendung aller Komponenten sinnvoll oder möglich.

Identifizierung von Synonymen

Wie wurden Synonyme identifiziert?
Die Suchterme wurden gemeinsam von einem medizinischen Bibliothekar mit Erfahrung in umfangreichen, systematischen Suchen und einem Domänenspezialisten festgelegt. Bei Datenbanken mit kontrolliertem Vokabular/Thesaurus wurden passende Schlagworte ermittelt.

Update der Suchen von 2016

Dies ist ein Update der früheren Suchen für die Leitlinie, zuletzt 2016.
Aufgrund Veränderungen bei den Datenbankanbietern (u. a. stellten DIMDI und National Guideline Clearinghouse das Angebot ein) und neueren Empfehlungen zur Literatursuche konnten die Recherchen von 2016 jedoch nicht unverändert wiederholt werden, sondern mussten fallweise angepasst werden.
Diese Recherche orientiert sich insb. an den aktuellen Empfehlungen in (7).
Die Suchstrategien basierten auf den von 2016. Schlagworte/Thesauri wurden auf zwischenzeitliche Änderungen überprüft.
Die 2016 recherchierte Datenbank BIOSIS stand nicht mehr zur Verfügung.
Der Science Citation Index Expanded (Web of Science; 2016 beim DIMDI: SciSearch) wird in (7) nicht als Recherchequelle für die hier gewünschten Dokumententypen (Leitlinien, Systematische Reviews (SR) und Metaanalysen) empfohlen. Es konnten zudem keine passenden Suchfilter ermittelt werden. Daher wurde auf die Recherche im Web of Science verzichtet.
Zusätzlich wurden insb. PROSPERO, TRIP und Epistemonikos als Datenquellen aufgenommen.

Suche in Leitlinien-Datenbanken und bei Leitlinien-Erstellern

Wie in (7) empfohlen wurde zuerst in den dort genannten Leitlinien-Datenbanken sowie auf Internetseiten von Leitlinien-Erstellern recherchiert.

AWMF

An der Aktualisierung dieser S3-Leitlinie unter dem Dach der AWMF sind insgesamt ca. 20 Fachgesellschaften beteiligt. Auf eine separate Suche nach relevanten AWMF-Leitlinien wurde verzichtet, da diese bekannt vorausgesetzt werden konnten.

Guidelines International Network (G-I-N): International Guideline Library

Suche am 05.06.2019
https://www.g-i-n.net/library/international-guidelines-library

Angepasst an die Suchoberfläche wurden breite und teilweise redundante Suchterme (mit und ohne Trunkierung) für die einfache Suche gewählt.
In der erweiterten Suche gab es zwei Optionen mit MeSH-Schlagworten zu suchen: „MeSH Terms“ bot nur eine kleine Auswahl breiter Terme, „MeSH 2015“ sehr viel mehr der Schlagworte für eine gezieltere Suche.

Suchterm (Simple Search)	**Treffer**
carotid	4
carotis	0
caroti*	4
karoti*	1
endarterectomy	1
endarterectom*	1
angioplasty	9
angioplast*	9
Advanced Search: Suche in “MeSH TermS” nach „Arterial Occlusive Diseases“	32
Advanced Search: Suche in „MeSH 2015“ einzeln nach: Carotid Stenosis (C14.907.137.230) Carotid Stenosis (C14.907.253.123.360) Carotid Stenosis (C10.228.140.300.200.360)	0

Nach Deduplikation blieben insgesamt 41 Treffer. Diese wurden in der Datei „kuehnl_2746_GIN.xlsx“ gespeichert. Aus dem angegeben Datum wurde das Jahr extrahiert. 6 der Treffer fallen in den relevanten Zeitraum ab 2016 bzw. sind ohne Datumsangabe. Relevante Treffer können beim GIN wieder gesucht werden. Die Details sind erst nach Registrierung einzusehen.

TRIP

Suche am 05.06.2019
https://www.tripdatabase.com/
Einfache Suche
Suchstring: "carotid stenosis" OR endarterectomy OR (angioplast* AND caroti*) from:2016
Ingesamt 1416 Treffer, mit Filter “Guidelines” 62 Treffer

Diese 62 Treffer wurden exportiert die die Datei „kuehnl_2746_tripexport.ris“ (RIS-Format). Diese wurde in die Endnote-Datenbank importiert.

Bemerkung: Die bibliographischen Angaben in dieser RIS-Datei sind unvollständig. Allerdings haben alle Einträge eine URL zum Volltext. Viele der Einträge haben eine DOI, die allerdings nicht immer korrekt zu sein scheint und nicht mit der URL zum Volltext übereinstimmt.

Portal des ÄZQ (leitlinien.de)

Suche am 06.06.2019
https://www.leitlinien.de/nvl/
Liste der 8 Nationalen VersorgungsLeitlinien (NVL), von denen keine thematisch relevant ist.

SIGN Scottish Intercollegiate Guidelines Network

Suche am 06.06.2019

Liste der aktuellen Leitlinien: https://www.sign.ac.uk/our-guidelines.html
Die insgesamt 51 aktuellen Leitlinien auf der Webseite wurden in eine Excel-Datei „kuehnl_2746_SIGN_current-guidelines.xlsx“ gespeichert. 13 der 51 Leitlinien fallen in den Zeitraum 2016-2019.
Links vom Titel der Leitlinie führen auf die Webseite mit den jeweiligen Leitlinien-Dokumenten.

Liste mit vorgeschlagenen Leitlinien: https://www.sign.ac.uk/current-proposals.html
Diese Liste ließ sich nicht in Excel speichern. Darum wurde eine pdf-Version der Webseite abgespeichert: „kuehnl_2746_SIGN_guideline-proposals.pdf“.

National Institute for Health and Care Excellence (NICE)

Suche am 06.06.2019

Die Suche im Bereich „NICE Guidance“ (https://www.nice.org.uk/guidance/published) funktioniert nicht gut.
Daher wurde in der allgemeinen Suche der NICE-Webseite (https://www.nice.org.uk/) gesucht und das Suchergebnis dann über Filter eingeschränkt:

Suchstring: caroti* OR endarterectom* OR angioplast*
Filter “Evidence type” = “Guidance”
Filter “Date” = “01/01/2016 - 31/12/2019”

Diese Suche kann mit folgendem Link wieder aufgerufen werden:
https://www.evidence.nhs.uk/search?from=01%2F01%2F2016&to=31%2F12%2F2019&om=%5B%7B%22ety%22%3A%5B%22Guidance%22%5D%7D%5D&pa=1&ps=250&q=caroti*+OR+endarterectom*+OR+angioplast*&sp=on

Das Ergebnis sind 137 Treffer. Diese wurden in der Datei “kuehnl_2746_NICE.ris” gespeichert. Diese wurde in die Endnote-Datenbank importiert.

Bemerkung: Die bibliographischen Angaben in dieser RIS-Datei sind unvollständig. Allerdings haben alle Einträge eine URL zum Volltext.

KCE Reports des Belgian Health Care Knowledge Centre

Suche am 06.06.2019
https://kce.fgov.be/

Die Suchmöglichkeiten sind sehr eingeschränkt. Daher wurde in getrennten Suchen mit Einzeltermen gesucht. Eine Filterung nach einem Datumsbereich war nicht möglich, nur eine Eingrenzung auf einzelne Jahre. Daher wurden die Ergebnisse nach Datum absteigend sortiert und in pdf-Dateien ausgegeben, so dass der relevante Bereich 2016-2019 abgedeckt wurde. Die Suchen sind mit folgenden URLs wieder aufzurufen.

Suchterm: caroti*
URL: https://kce.fgov.be/en/all-reports?search=caroti%2A
Anzahl Treffer 2016-2019: 4
pdf-Datei: kuehnl_2746_KCE_caroti.pdf

Suchterm: endarterectom*
URL: https://kce.fgov.be/en/all-reports?search=endarterectom%2A
pdf-Datei: -
Anzahl Treffer 2016-2019: 0

Suchterm: angioplast*
URL: https://kce.fgov.be/en/all-reports?search=angioplast%2A
Anzahl Treffer 2016-2019: 4
pdf-Datei: kuehnl_2746_KCE_angioplast.pdf

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)

Wie in (7) empfohlen wird auf folgender Webseite nach Leitliniensynopsen des IQWiG gesucht.
Suche am 2019-06-06
https://www.iqwig.de/de/projekte-ergebnisse/projekte.1057.html

Die Stichwortsuche funktionierte nicht wie erwartet, weshalb nur eine Einschränkung der Projekte nach den angebotenen Filtern erfolgte:
Anwendungsgebiet: DMP und Leitlinien
Jahr: 2016-2019

Die Suche kann über folgenden Link wieder aufgerufen werden:
https://www.iqwig.de/de/projekte-ergebnisse/projekte.1057.html?application=DMP+und+Leitlinien&year[]=2019&year[]=2018&year[]=2017&year[]=2016

Ergebnis: 16 Treffer

Die Treffer wurden in der Excel-Datei „kuehnl_2746_IQWiG.xlsx“ gespeichert. Die Ergebnisseite wurde zusätzlich in die pdf-Datei „kuehnl_2746_IQWiG.pdf“ ausgegeben.

Suche in bibliographischen Datenbanken

Es wurde in bibliographischen Datenbanken nach Leitlinien, Systematischen Reviews (SR) sowie Metaanalysen zum Konzept „Carotisstenose“ gesucht.

Die Suchstrategie wurde an die jeweiligen Datenbanken und Rechercheoberflächen insb. bezüglich Schlagworten, Syntax und enthaltenen Dokumenten angepasst.

Nach Möglichkeit wurden publizierte und validierte Suchfilter für die Leitlinien bzw. Studiendesigns (Methodenfilter) verwendet.

Liste der Datenbanken

Name of Database	Provider / Interface	Time period covered
PROSPERO	University of York	?–current
Epistemonikos	Epistemonikos Foundation	?–current
EMBASE	Ovid	1974–current
MEDLINE	Ovid	1946–current
Cochrane Library:		
CDRS (Cochrane Database of Systematic Reviews)	Wiley Online Library	1995–current

Es folgt eine Dokumentation für jede der verwendeten Datenbanken.

Dabei bedeutet:

Vorbereitete Suchstrategie

Diese Strategie wurde vorbereitet und ist in einer Form, die ggf. leichter weiterentwickelt werden kann, als die von der Such-Plattform exportierte Suchhistorie.

Suchhistorie

Die eingegebenen Suchausdrücke und Suchterme werden ggf. von der Such-Plattform verändert. Hier ist die von der Plattform exportierte Version dokumentiert.

PROSPERO

Datenbank	
PROSPERO International prospective register of systematic reviews	
Plattform (ggf. incl. Version)	
https://www.crd.york.ac.uk/prospero/	
Zeitliche Abdeckung der Datenbank	
2011–current	
Zeitliche Einschränkung	
Keine Einschränkung möglich/sinnvoll	
Standard-Suchfilter	
Keine Suchfilter	
Sonstige Limits	
Keine Limits	
Datum der Suche	
06-06-2019	
Suche durchgeführt von	
Helge Knüttel	
Überprüfung der Suchstrategie (Peer Review)	
nein	
Anzahl der Treffer (vor Dublettenentfernung)	
212	
Exportformat der Treffer	
PROSPERO-Export-Format	
Datei(en) mit exportierten Treffern	
kuehnl_2746_PROSPERO_export.txt (Für Endnote-PROSPERO-Filter) kuehnl_2746_PROSPERO.ris Die txt-Datei wurde in die Endnote-Datenbank importiert.	
Datei(en) der vorbereiteten Suchstrategie	
kuehnl_2746_cmds.txt	
Datei(en) mit von der Suchplattform exportierten Suchstrategie/Suchhistorie	
kuehnl_2746_PROSPERO_search-history.txt (Copy/Paste in Textdatei)	
Name der auf der Plattform gespeicherten Suchstrategie. Die Suche kann damit ggf. dort wiederholt werden.	
-	
Notizen zur Suche	
Keine Besonderheiten.	

Suchhistorie

Line	Search for	Hits
#1	caroti*	209
#2	MeSH DESCRIPTOR Carotid Stenosis EXPLODE ALL TREES	23
#3	MeSH DESCRIPTOR Carotid Artery Diseases EXPLODE ALL TREES	39
#4	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES	0
#5	MeSH DESCRIPTOR Carotid Arteries EXPLODE ALL TREES	27
#6	MeSH DESCRIPTOR Endarterectomy, Carotid EXPLODE ALL TREES	17
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	212

Epistemonikos

Datenbank	
Epistemonikos	
Plattform (ggf. incl. Version)	
https://www.epistemonikos.org/	
Zeitliche Abdeckung der Datenbank	
?–current	
Zeitliche Einschränkung	
Publication year from 2016 to 2019	
Standard-Suchfilter	
Keine Suchfilter	
Sonstige Limits	
Publication type: • Broad Synthesis • Structured Summary • Systematic Review	
Datum der Suche	
2019-06-07	
Suche durchgeführt von	
Helge Knüttel	
Überprüfung der Suchstrategie (Peer Review)	
nein	
Anzahl der Treffer (vor Dublettenentfernung)	
Broad Synthesis: 3 Structured Summary: 2 Systematic Review: 381	
Exportformat der Treffer	
RIS	
Datei(en) mit exportierten Treffern	
kuehnl_2746_Epistemonikos_broad_synthesis.ris kuehnl_2746_Epistemonikos_structured_summary.ris kuehnl_2746_Epistemonikos_systematic_review.ris Die RIS-Dateien wurde in die Endnote-Datenbank importiert.	
Datei(en) der vorbereiteten Suchstrategie	
kuehnl_2746_cmds.txt	
Datei(en) mit von der Suchplattform exportierten Suchstrategie/Suchhistorie	
Screenshot: kuehnl_2746_Epistemonikos_search-history.PNG Die unten dokumentierte Suchhistorie wurde aus der Weboberfläche kopiert.	
Name der auf der Plattform gespeicherten Suchstrategie. Die Suche kann damit ggf. dort wiederholt werden.	

kuehnl_2746	
Notizen zur Suche	

Die Suchstrategie wird an verschiedenen Stellen der Suchoberfläche angezeigt. Dabei werden teilweise unterschiedliche Suchstrings angezeigt (vgl. Screenshot in Datei „kuehnl_2746_Epistemonikos_search-history.PNG“). Auch die beim Download der Suchstrategie erhaltene Version entspricht nicht der Eingabe. Hier dokumentierte ich den eingegebenen Suchstring sowie die Version, die in der tabellarischen Suchhistorie angezeigt wurde. Diese Suchstrings stimmen überein und passen zu den resultierenden URLs, die hier ebenfalls dokumentiert wurden.

Treffer in Exportdateien überprüft:

Die Treffer wurden separat nach dem Filter „Publication type“ exportiert. Es ist jeweils die erwarte Anzahl Treffer in den Exportdateien:

```
$ for file in `find . -name 'kuehnl_2746_Epistemonikos_*\.ris' -print` ;
do echo $file;  grep "^ER  - " $file | wc -l ; done
./kuehnl_2746_Epistemonikos_broad_synthesis.ris
3
./kuehnl_2746_Epistemonikos_structured_summary.ris
2
./kuehnl_2746_Epistemonikos_systematic_review.ris
381
```

Suchhistorie

Advanced search
https://www.epistemonikos.org/en/advanced_search

Eingegebener Suchstring:

title:(caroti* AND (steno* OR narrow* OR obstruct* OR occlu* OR plaque OR thrombo* OR bruit* OR athero* OR arteriosclero* OR dissect* OR angioplast* OR stent* OR endarterect* OR thrombarterect* OR thrombendarterect* OR endovasc* OR catheter* OR endolum* OR translum* OR repair OR dilat*)) OR abstract:(caroti* AND (steno* OR narrow* OR obstruct* OR occlu* OR plaque OR thrombo* OR bruit* OR athero* OR arteriosclero* OR dissect* OR angioplast* OR stent* OR endarterect* OR thrombarterect* OR thrombendarterect* OR endovasc* OR catheter* OR endolum* OR translum* OR repair OR dilat*))

Suchstring in tabellarischer Suchhistorie:

title:(caroti* AND (steno* OR narrow* OR obstruct* OR occlu* OR plaque OR thrombo* OR bruit* OR athero* OR arteriosclero* OR dissect* OR angioplast* OR stent* OR endarterect* OR thrombarterect* OR thrombendarterect* OR endovasc* OR catheter* OR endolum* OR translum* OR repair OR dilat*)) OR abstract:(caroti* AND (steno* OR narrow* OR obstruct* OR occlu* OR plaque OR thrombo* OR bruit* OR athero* OR arteriosclero* OR dissect* OR angioplast* OR stent* OR endarterect* OR thrombarterect* OR thrombendarterect* OR endovasc* OR catheter* OR endolum* OR translum* OR repair OR dilat*))

Anschließende Filterung nach „Publication year“ = „from 2016 to 2019“ und einzeln nach „Publication type”. Über die resultierenden URLs können die Suchen wieder aufgerufen werden:

Broad Synthesis:
https://www.epistemonikos.org/advanced_search?q=title:(caroti*%20AND%20(steno*%20OR%20narrow*%20OR%20obstruct*%20OR%20occlu*%20OR%20plaque%20OR%20thrombo*%20OR%20bruit*%20OR%20athero*%20OR%20arteriosclero*%20OR%20dissect*%20OR%20angioplast*%20OR%20stent*%20OR%20endarterect*%20OR%20thrombarterect*%20OR%20thrombendarterect*%20OR%20endovasc*%20OR%20catheter*%20OR%20endolum*%20OR%20translum*%20OR%20repair%20OR%20dilat*))%20OR%20abstract:(caroti*%20AND%20(steno*%20OR%20narrow*%20OR%20obstruct*%20OR%20occlu*%20OR%20plaque%20OR%20thrombo*%20OR%20bruit*%20OR%20athero*%20OR%20arteriosclero*%20OR%20dissect*%20OR%20angioplast*%20OR%20stent*%20OR%20endarterect*%20OR%20thrombarterect*%20OR%20thrombendarterect*%20OR%20endovasc*%20OR%20catheter*%20OR%20endolum*%20OR%20translum*%20OR%20repair%20OR%20dilat*))&protocol=no&classification=broad-synthesis&min_year=2016&max_year=2019
Structured Summary:
https://www.epistemonikos.org/advanced_search?q=title:(caroti*%20AND%20(steno*%20OR%20narrow*%20OR%20obstruct*%20OR%20occlu*%20OR%20plaque%20OR%20thrombo*%20OR%20bruit*%20OR%20athero*%20OR%20arteriosclero*%20OR%20dissect*%20OR%20angioplast*%20OR%20stent*%20OR%20endarterect*%20OR%20thrombarterect*%20OR%20thrombendarterect*%20OR%20endovasc*%20OR%20catheter*%20OR%20endolum*%20OR%20translum*%20OR%20repair%20OR%20dilat*))%20OR%20abstract:(caroti*%20AND%20(steno*%20OR%20narrow*%20OR%20obstruct*%20OR%20occlu*%20OR%20plaque%20OR%20thrombo*%20OR%20bruit*%20OR%20athero*%20OR%20arteriosclero*%20OR%20dissect*%20OR%20angioplast*%20OR%20stent*%20OR%20endarterect*%20OR%20thrombarterect*%20OR%20thrombendarterect*%20OR%20endovasc*%20OR%20catheter*%20OR%20endolum*%20OR%20translum*%20OR%20repair%20OR%20dilat*))&protocol=no&classification=structured-summary-of-systematic-review&min_year=2016&max_year=2019
Systematic Review:
https://www.epistemonikos.org/advanced_search?q=title:(caroti*%20AND%20(steno*%20OR%20narrow*%20OR%20obstruct*%20OR%20occlu*%20OR%20plaque%20OR%20thrombo*%20OR%20bruit*%20OR%20athero*%20OR%20arteriosclero*%20OR%20dissect*%20OR%20angioplast*%20OR%20stent*%20OR%20endarterect*%20OR%20thrombarterect*%20OR%20thrombendarterect*%20OR%20endovasc*%20OR%20catheter*%20OR%20endolum*%20OR%20translum*%20OR%20repair%20OR%20dilat*))%20OR%20abstract:(caroti*%20AND%20(steno*%20OR%20narrow*%20OR%20obstruct*%20OR%20occlu*%20OR%20plaque%20OR%20thrombo*%20OR%20bruit*%20OR%20athero*%20OR%20arteriosclero*%20OR%20dissect*%20OR%20angioplast*%20OR%20stent*%20OR%20endarterect*%20OR%20thrombarterect*%20OR%20thrombendarterect*%20OR%20endovasc*%20OR%20catheter*%20OR%20endolum*%20OR%20translum*%20OR%20repair%20OR%20dilat*))&protocol=no&classification=systematic-review&min_year=2016&max_year=2019#

EMBASE

Datenbank	
Embase 1974 to 2019 June 05 (oemezd)	
Plattform (ggf. incl. Version)	
Ovid	
Zeitliche Abdeckung der Datenbank	
1974–current	
Zeitliche Einschränkung	
2016-current	
Standard-Suchfilter	
• CADTH Search Filter for Guidelines - OVID Medline, Embase, PsycINFO aus (8) • CADTH Search Filter for Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase aus (8)	
Sonstige Limits	
Sprache deutsch, englisch	
Datum der Suche	
2019-06-06	
Suche durchgeführt von	
Helge Knüttel	
Überprüfung der Suchstrategie (Peer Review)	
nein	
Anzahl der Treffer (vor Dublettenentfernung)	
1297	
Exportformat der Treffer	
OvidSP für Citavi (Citavi-Importfilter: OvidSP)	
Datei(en) mit exportierten Treffern	
kuehnl_2746_EMBASE_endnote_r*-*.cgi kuehnl_2746_EMBASE_r*-*.ris Die CGI-Dateien wurde in die Endnote-Datenbank importiert.	
Datei(en) der vorbereiteten Suchstrategie	
kuehnl_2746_cmds.txt	
Datei(en) mit von der Suchplattform exportierten Suchstrategie/Suchhistorie	
kuehnl_2746_EMBASE_search-history.txt	
Name der auf der Plattform gespeicherten Suchstrategie. Die Suche kann damit ggf. dort wiederholt werden.	
kuehnl_2746_embase	
Notizen zur Suche	
Treffer in Exportdateien überprüfen:	

Die 1297 Treffer wurden komplett in Portionen zu den maximal zulässigen 1000 Treffern exportiert:

```
$ for file in `find . -name 'kuehnl_2746_EMBASE_r*\.ris'
 -print` ; do echo $file;  grep "^ER  - " $file | wc -l ; done
./kuehnl_2746_EMBASE_r0001-1000.ris
1000
./kuehnl_2746_EMBASE_r1001-1297.ris
297
```

Suchhistorie

Statement identifier	Search statement	Record count	Annotation
1	exp carotid artery obstruction/ or carotid artery disease/ or carotid artery bruit/ or exp carotid artery obstruction/ or (exp carotid artery/ and artery constriction/) or exp carotid artery surgery/ or (caroti* adj6 (steno* or narrow* or obstruct* or occlu* or plaque or thrombo* or bruit* or athero* or arteriosclero* or dissect*)).ti,ab,kw. or (caroti* adj6 (angioplast* or stent* or endarterect* or thrombarterect* or thrombendarterect* or endovasc*)).ti,ab,kw. or (caroti* adj6 (catheter* or endolum* or translum* or repair or dilat*)).ti,ab,kw.	82647	carotid stenosis
2	exp clinical pathway/ or exp clinical protocol/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or exp treatment guidelines/ or (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. or (standards or guideline or guidelines).ti,kf,kw. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf,kw.	762235	
3	consensus*.ab. /freq=2	29910	
4	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. or recommendat*.ti,kf,kw. or (care adj2 (standard or path or paths or pathway or pathways or map or	185765	

	maps or plan or plans)).ti,ab,kf,kw. or (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw. or (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.		
5	or/2-4	917329	CADTH Search Filter for Guidelines - OVID Medline, Embase, PsycINFO
6	meta-analysis.pt. or (meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/) or ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. or ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. or ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. or (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. or (handsearch* or hand search*).ti,ab,kf,kw. or (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. or (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw. or (meta regression* or metaregression*).ti,ab,kf,kw. or (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. or (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. or (cochrane or (health adj2 technology assessment) or evidence report).jw. or (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. or (outcomes research or relative effectiveness).ti,ab,kf,kw. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	606662	CADTH Search Filter for Systematic Reviews/Meta-Analysis/Health Technology Assessment - OVID Medline, Embase

7	1 and 5	2688	carotid stenosis AND guidelines filter
8	1 and 6	2447	carotid stenosis AND SR filter
9	7 or 8	4834	carotid stenosis AND (guidelines OR SR)
10	limit 9 to (english or german)	4591	language limit
11	limit 10 to yr="2016 -Current"	1297	date limit

MEDLINE

Datenbank	
Ovid MEDLINE(R) ALL 1946 to June 04, 2019 (medall)	
Plattform (ggf. incl. Version)	
Ovid	
Zeitliche Abdeckung der Datenbank	
ca. 1946– current	
Zeitliche Einschränkung	
2016-current	
Standard-Suchfilter	
• CADTH Search Filter for Guidelines - OVID Medline, Embase, PsycINFO aus (8) • CADTH Search Filter for Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase aus (8)	
Sonstige Limits	
Sprache deutsch, englisch	
Datum der Suche	
2019-06-06	
Suche durchgeführt von	
Helge Knüttel	
Überprüfung der Suchstrategie (Peer Review)	
nein	
Anzahl der Treffer (vor Dublettenentfernung)	
508	
Exportformat der Treffer	
OvidSP für Citavi (Citavi-Importfilter: OvidSP)	
Datei(en) mit exportierten Treffern	
kuehnl_2746_MEDLINE.cgi kuehnl_2746_MEDLINE.ris Die CGI-Datei wurde in die Endnote-Datenbank importiert.	
Datei(en) der vorbereiteten Suchstrategie	
kuehnl_2746_cmds.txt	
Datei(en) mit von der Suchplattform exportierten Suchstrategie/Suchhistorie	
kuehnl_2746_MEDLINE_search-history.txt	
Name der auf der Plattform gespeicherten Suchstrategie. Die Suche kann damit ggf. dort wiederholt werden.	
kuehnl_2746_medline	
Notizen zur Suche	
Treffer in Exportdateien überprüfen:	

Die 508 Treffer wurden komplett exportiert:

```
$ for file in `find . -name 'kuehnl_2746_MEDLINE*\.ris'
-print` ; do echo $file;  grep "^ER  - " $file | wc -l ; done
./kuehnl_2746_MEDLINE.ris
508
```

Suchhistorie

Statement identifier	Search statement	Record count	Annotation
1	Carotid Stenosis/ or Carotid Artery Diseases/ or Carotid Artery Thrombosis/ or (exp Carotid Arteries/ and (Constriction, Pathologic/ or su.fs.)) or Endarterectomy, Carotid/ or (caroti* adj6 (steno* or narrow* or obstruct* or occlu* or plaque or thrombo* or bruit* or athero* or arteriosclero* or dissect*)).ti,ab,kw. or (caroti* adj6 (angioplast* or stent* or endarterect* or thrombarterect* or thrombendarterect* or endovasc*)).ti,ab,kw. or (caroti* adj6 (catheter* or endolum* or translum* or repair or dilat*)).ti,ab,kw.	68664	carotid stenosis
2	exp clinical pathway/ or exp clinical protocol/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or exp treatment guidelines/ or (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. or (standards or guideline or guidelines).ti,kf,kw. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf,kw.	464619	
3	consensus*.ab. /freq=2	22752	
4	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. or recommendat*.ti,kf,kw. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw. or (algorithm* adj2 (screening or examination or test or tested or	121716	

	testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw. or (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.		
5	or/2-4	570223	CADTH Search Filter for Guidelines - OVID Medline, Embase, PsycINFO
6	meta-analysis.pt. or (meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/) or ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. or ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. or ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. or (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. or (handsearch* or hand search*).ti,ab,kf,kw. or (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. or (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw. or (meta regression* or metaregression*).ti,ab,kf,kw. or (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. or (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. or (cochrane or (health adj2 technology assessment) or evidence report).jw. or (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. or (outcomes research or relative effectiveness).ti,ab,kf,kw. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	412618	CADTH Search Filter for Systematic Reviews/Meta-Analysis/Health Technology Assessment â€“ OVID Medline, Embase

7	1 and 5	1128	carotid stenosis AND guidelines filter
8	1 and 6	1310	carotid stenosis AND SR filter
9	7 or 8	2355	carotid stenosis AND (guidelines OR SR)
10	limit 9 to (english or german)	2236	language limit
11	limit 10 to yr="2016 -Current"	508	date limit

Cochrane Library

Datenbank	
Cochrane Library: • CDRS (Cochrane Database of Systematic Reviews)	
Plattform (ggf. incl. Version)	
Wiley Online Library	
Zeitliche Abdeckung der Datenbank	
• CDRS (Cochrane Database of Systematic Reviews): 1993–current	
Zeitliche Einschränkung	
Cochrane Library publication date Between Jan 2016 and Dec 2019	
Standard-Suchfilter	
Keine Suchfilter	
Sonstige Limits	
Keine Limits	
Datum der Suche	
2019-06-06	
Suche durchgeführt von	
Helge Knüttel	
Überprüfung der Suchstrategie (Peer Review)	
nein	
Anzahl der Treffer (vor Dublettenentfernung)	
5	
Exportformat der Treffer	
PC mit Abstract (Citavi-Importfilter: Cochrane Library)	
Datei(en) mit exportierten Treffern	
kuehnl_2746_Cochrane_CDSR.ris Die RIS-Datei wurde in die Endnote-Datenbank importiert.	
Datei(en) der vorbereiteten Suchstrategie	
kuehnl_2746_cmds.txt	
Datei(en) mit von der Suchplattform exportierten Suchstrategie/Suchhistorie	
kuehnl_2746_Cochrane_search-history.txt	
Name der auf der Plattform gespeicherten Suchstrategie. Die Suche kann damit ggf. dort wiederholt werden.	
kuehnl_2746	
Notizen zur Suche	
Nur Cochrane Reviews (CDRS = Cochrane Database of Systematic Reviews) gesucht!	

Suchhistorie

ID	Search	Hits
#1	(caroti* NEAR/5 (steno* or narrow* or obstruct* or occlu* or plaque or thrombo* or bruit* or athero* or arteriosclero* or dissect*)):ti,ab,kw	3146
#2	(caroti* NEAR/5 (angioplast* or stent* or endarterect* or thrombarterect* or thrombendarterect* or endovasc*)):ti,ab,kw	2066
#3	(caroti* NEAR/5 (catheter* or endolum* or translum* or repair or dilat*)):ti,ab,kw	191
#4	#1 OR #2 OR #3 with Cochrane Library publication date Between Jan 2016 and Dec 2019, in Cochrane Reviews	5

Weiterverarbeitung der Treffer und Deduplizierung

Die der Suchen in Datenbanken wurden soweit importfähige Formate vorlagen wie oben jeweils angegeben in eine Endnote-Datenbank importiert (insgesamt 2607 Einträge):

kuehnl_2746.enl

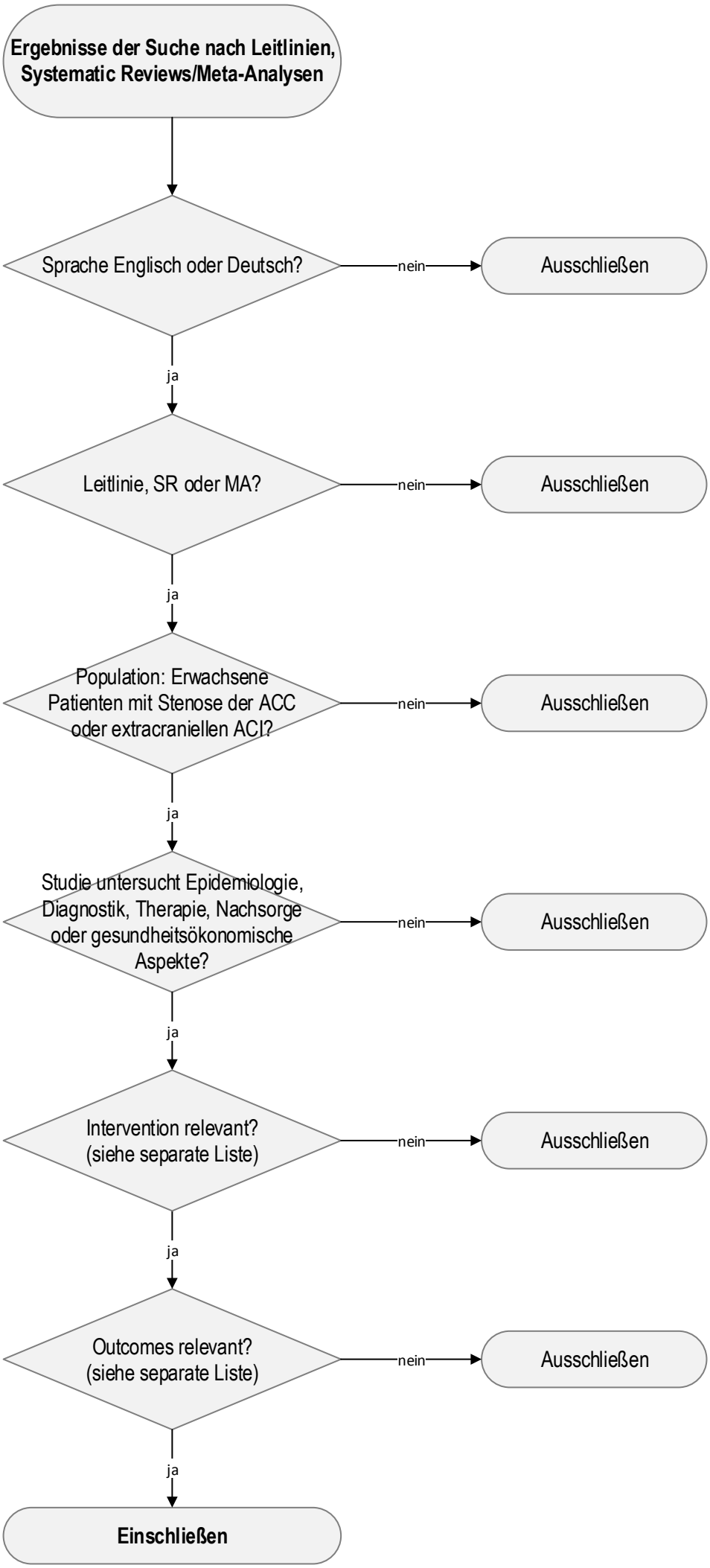
Die Treffer sind dort per Kategorie Ihrer Herkunft zugeordnet. Die Treffer sollten im Sinne der Reproduzierbarkeit immer in der jeweiligen Herkunfts-Kategorie belassen bleiben.

Die Deduplizierung der Treffer wird durch die Auftraggeber in Endnote erfolgen.

Alle Treffer wurden in die Gruppe „1 Screening von Titel und Abstract > 1.1 noch nicht beurteilt“ kopiert. Aus dieser Gruppe können sie nach Bearbeitungsstand in entsprechende Gruppen verschoben werden.

Zitierte Literatur

1. McGowan J, Sampson M, Lefebvre C. An Evidence Based Checklist for the Peer Review of Electronic Search Strategies (PRESS EBC). EBLIP 2010; 5(1):149–54. Available from: URL: http://ejournals.library.ualberta.ca/index.php/EBLIP/article/view/7402.
2. Atkinson KM, Koenka AC, Sanchez CE, Moshontz H, Cooper H. Reporting standards for literature searches and report inclusion criteria: making research syntheses more transparent and easy to replicate. Res. Syn. Meth. 2015; 6(1):87–95.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009 [cited 2013 Feb 22]; 6(7):e1000097.
4. Rader T, Mann M, Stansfield C, Cooper C, Sampson M. Methods for documenting systematic review searches: a discussion of common issues. Res Synth Methods 2014; 5(2):98–115.
5. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017; 358:j4008.
6. Niederstadt C, Droste S. Reporting and presenting information retrieval processes: the need for optimizing common practice in health technology assessment. Int J Technol Assess Health Care 2010; 26(4):450–7.
7. Cochrane Deutschland Stiftung, Institut für Evidenz in der Medizin, Institut für Medizinische Biometrie und Statistik, Freiburg, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften- Institut für Medizinisches Wissensmanagement, Ärztliches Zentrum für Qualität in der Medizin. Manual systematische Recherche für Evidenzsynthesen und Leitlinien; 2019 Apr 1. Available from: URL: https://freidok.uni-freiburg.de/data/149324.
8. Canadian Agency for Drugs and Technologies in Health (CADTH). Strings Attached: CADTH's Database Search Filters; 2016 [cited 2019 Jun 6]. Available from: URL: https://www.cadth.ca/resources/finding-evidence.


Ergebnisse der Suche nach Leitlinien, Systematic Reviews/Meta-Analysen
Sprache Englisch oder Deutsch?
nein
Ausschließen
ja
Leitlinie, SR oder MA?
nein
Ausschließen
ja
Population: Erwachsene Patienten mit Stenose der ACC oder extracraniellen ACI?
nein
Ausschließen
ja
Studie untersucht Epidemiologie, Diagnostik, Therapie, Nachsorge oder gesundheitsökonomische Aspekte?
nein
Ausschließen
ja
Intervention relevant? (siehe separate Liste)
nein
Ausschließen
ja
Outcomes relevant? (siehe separate Liste)
nein
Ausschließen
ja
Einschließen

Nr	Guideline (PDF Name) Bewertung Hans-Henning Eckstein (HHE)	Jahr	D3.8	D3.9	D3.10	D3.11	D3.12	D3.13	D3.14	Summe
1	AHA/ASA Secondary prevention of stroke STROKE	2014	3	3	3	2	4	1	4	20
2	AHA/ASA Primary prevention of stroke STROKE	2014	4	3	3	2	4	4	1	21
3	AHA/ASA Stroke prevention in women STROKE	2014	3	3	3	3	4	3	1	20
4	Canadian GLs sec stroke prev WORLD STROKE ORGANIZATION	2014	3	3	3	3	4	4	1	21
5	GL Diabetes in adults INST CLIN SYST IMPROVEMENT	2014	2	1	2	3	3	3	4	18
6	ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management	2014	3	3	4	4	4	4	0	22
7	DGN, Akuttherapie des ischämischen Schlaganfalls (Ergänzung) – Rekanalisierende Therapie	2015	4	1	3	3	1	3	4	19
8	DGN und DSG, S3-LL zur Sekundärprophylaxe ischämischer Schlaganfall und TIA, Teil 1	2015	4	4	4	4	4	4	4	28
9	enning Eckstein (HHE)	2016	3	3	4	4	4	4	0	22
10	UK National GL for stroke 5th edition	2016	4	4	4	4	4	4	4	28
11	ESVS: Recommendations on the management of Carotid Artery Disease	2017	3	3	2	2	4	4	4	22
12	ESC GL on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the ESVS	2017	3	3	4	4	4	4	4	26
13	Update on Italian Stroke Organization guidelines on CEA and CAS	2017	2	1	4	2	3	2	0	14
14	Australian clinical guidelines for stroke management	2017	4	4	4	4	4	4	0	24
15	AHA Guidelines for the early management of patients with acute ischemic stroke	2018	2	2	3	4	4	4	0	19
16	SVS practice guidelines on follow-up after vascular surgery	2018	2	2	3	4	4	0	0	15
17	ESC/ESH Guidelines for the management of arterial hypertension	2018	3	3	4	4	4	4	1	23
18	ESO and ESMINT guidelines on mechanical thrombectomy in acute ischaemic stroke	2019	4	4	4	4	4	4	0	24

Nr	Guideline (PDF Name) Bewertung Peter Ringleb (PR)	Jahr	D3.8	D3.9	D3.10	D3.11	D3.12	D3.13	D3.14	Summe	Delta HHE-PR	Summe [HHE+PR]	Mean	≥14 Pkt	≥20 Pkt
1	AHA/ASA Secondary prevention of stroke STROKE	2014	2	2	3	2	4	1	4	18	2	38	19	ja	nein
2	AHA/ASA Primary prevention of stroke STROKE	2014	2	1	1	2	4	4	1	15	6	36	18	ja	nein
3	AHA/ASA Stroke prevention in women STROKE	2014	2	1	2	2	4	2	1	14	6	34	17	ja	nein
4	Canadian GLs sec stroke prev WORLD STROKE ORGANIZATION	2014	2	2	3	3	4	2	2	18	3	39	19	ja	nein
5	GL Diabetes in adults INST CLIN SYST IMPROVEMENT	2014	2	1	2	3	4	3	4	19	1	37	18	ja	nein
6	ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management	2014	1	2	1	2	4	3	1	14	8	36	18	ja	nein
7	DGN, Akuttherapie des ischämischen Schlaganfalls (Ergänzung) – Rekanalisierende Therapie	2015	1	1	4	4	1	2	4	17	2	36	18	ja	nein
8	DGN und DSG, S3-LL zur Sekundärprophylaxe ischämischer Schlaganfall und TIA, Teil 1	2015	4	4	4	4	2	3	3	24	4	52	26	ja	ja
9	ESC/EAS Guidelines for the Management of Dyslipiaemias	2016	1	2	1	2	4	3	1	14	12	36	18	ja	nein
10	UK National GL for stroke 5th edition	2016	3	4	4	4	4	4	3	26	2	54	27	ja	ja
11	ESVS: Recommendations on the management of Carotid Artery Disease	2017	3	1	4	4	4	4	1	21	3	43	21	ja	ja
12	ESC GL on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the ESVS	2017	1	2	1	2	4	3	1	14	12	40	20	ja	ja
13	Update on Italian Stroke Organization guidelines on CEA and CAS	2017	2	2	3	2	2	2	1	14	0	28	14	ja	nein
14	Australian clinical guidelines for stroke management	2017	2	2	4	3	4	1	1	17	7	41	20	ja	ja
15	AHA Guidelines for the early management of patients with acute ischemic stroke	2018	2	2	3	4	4	2	1	18	1	37	18	ja	nein
16	SVS practice guidelines on follow-up after vascular surgery	2018	2	3	4	4	3	2	1	19	4	34	17	ja	nein
17	ESC/ESH Guidelines for the management of arterial hypertension	2018	1	2	1	2	4	3	4	17	12	40	20	ja	ja
18	ESO and ESMINT guidelines on mechanical thrombectomy in acute ischaemic stroke	2019	3	4	4	4	4	2	1	22	2	46	23	ja	ja

Bias Assessment: Domain 1 (D1), Study Eligibility Criteria Domain 2 (D2), Identification and Selection of Studies Domain 3 (D3), Data Collection and Study Appraisal Domain 4 (D4), Synthesis and Findings	Low Risk
	Unclear
	Not Analyzed, Meta-Analysis only
	High Risk

S3 LL Carotisstenose Juni 2019

Methodische Bewertung aller verwendeten Systematischen Reviews/Metanalasen seit 2014

KSR Nr.	Jahr	Autoren	Titel	D1	D2	D3	D4
KSRA84832	2019	Aber A, et al.	Impact of Carotid Artery Stenosis on Quality of Life: A Systematic Review				
KSRA42331	2017	Abreu P, et al.	Intracerebral hemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization: systematic review and meta-analysis				
KSRA101554	2014	Antoniou GA, et al.	Meta-analysis of retrojugular versus antejugular approach for carotid endarterectomy				
KSRA34602	2017	Baradaran H, et al.	Hemispheric Differences in Leukoaraiosis in Patients with Carotid Artery Stenosis: A Systematic Review				
KSRA35119	2016	Baradaran H, et al.	White Matter Diffusion Abnormalities in Carotid Artery Disease: A Systematic Review and Meta-Analysis				
KSRA49253	2017	Baradaran H, et al.	Association between Carotid Plaque Features on CTA and Cerebrovascular Ischemia: A Systematic Review and Meta-Analysis				
KSRA66075	2018	Barkat M, et al.	Systematic review and network meta-analysis of treatment strategies for asymptomatic carotid disease				
KSRA34611	2017	Barkat M, et al.	Systematic Review and Meta-analysis of Dual Versus Single Antiplatelet Therapy in Carotid Interventions				
KSRA50865	2016	Best LM, et al.	Transcranial Doppler Ultrasound Detection of Microemboli as a Predictor of Cerebral Events in Patients with Symptomatic and Asymptomatic Carotid Disease: A Systematic Review and Meta-Analysis				
KSRA484	2015	Boulanger M, et al.	Periprocedural Myocardial Infarction After Carotid Endarterectomy and Stenting: Systematic Review and Meta-Analysis				
KSRA34866	2017	Brinjikji W, et al.	The effects of statin therapy on carotid plaque composition and volume: A systematic review and meta-analysis				
KSRA6866	2015	Brinjikji W, et al.	Ultrasound characteristics of symptomatic carotid plaques: A systematic review and meta-analysis				
KSRA67129	2018	Cho, Y. D, et al.	Protected versus unprotected carotid artery stenting: meta-analysis of the current literature				

Bias Assessment: Domain 1 (D1), Study Eligibility Criteria Domain 2 (D2), Identification and Selection of Studies Domain 3 (D3), Data Collection and Study Appraisal Domain 4 (D4), Synthesis and Findings	Low Risk
	Unclear
	Not Analyzed, Meta-Analysis only
	High Risk

KSR Nr.	Jahr	Autoren	Titel	D1	D2	D3	D4
KSRA101551	2014	Chongruksut W, et al.	Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting)				
KSRA61818	2018	Cui L, et al.	Safety of Stenting and Endarterectomy for Asymptomatic Carotid Artery Stenosis: A Meta-Analysis of Randomised Controlled Trials				
KSRA10772	2015	De Rango P, et al.	Summary of Evidence on Early Carotid Intervention for Recently Symptomatic Stenosis Based on Meta-Analysis of Current Risks				
KSRA26722	2017	Demirel S, et al.	Systematic review and meta-analysis of postcarotid endarterectomy hypertension after eversion versus conventional carotid endarterectomy				
KSRA59106	2018	Essat M, et al.	Patient-Reported Outcome Measures in Carotid Artery Revascularization: Systematic Review and Psychometric Analysis				
KSRA26271	2017	Finn C, et al.	The Association between Carotid Artery Atherosclerosis and Silent Brain Infarction: A Systematic Review and Meta-analysis				
KSRA1674	2015	Fokkema M, et al.	Stenting versus endarterectomy for restenosis following prior ipsilateral carotid endarterectomy: An individual patient data meta-analysis				
KSRA39370	2017	Galyfos G, et al.	Cerebral hyperperfusion syndrome and intracranial hemorrhage after carotid endarterectomy or carotid stenting: A meta-analysis				
KSRA75861	2018	Galyfos G, et al.	Carotid endarterectomy versus carotid stenting or best medical treatment in asymptomatic patients with significant carotid stenosis: A meta-analysis				
KSRA9964	2015	Gargiulo G, et al.	New cerebral lesions at magnetic resonance imaging after carotid artery stenting versus endarterectomy: An updated meta-analysis				
KSRA2058	2015	Giannopoulos A, et al.	Long-term Mortality in Patients with Asymptomatic Carotid Stenosis: Implications for Statin Therapy				
KSRA20197	2016	Goyal M, et al.	Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials				
KSRA101552	2013	Guay J, et al.	Cerebral monitors versus regional anesthesia to detect cerebral ischemia in patients undergoing carotid endarterectomy: A meta-analysis				
KSRA20249	2016	Guirguis-Blake JM, et al.	Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force				
KSRA2193	2015	Gupta A, et al.	Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis				

Bias Assessment: Domain 1 (D1), Study Eligibility Criteria Domain 2 (D2), Identification and Selection of Studies Domain 3 (D3), Data Collection and Study Appraisal Domain 4 (D4), Synthesis and Findings	Low Risk
	Unclear
	Not Analyzed, Meta-Analysis only
	High Risk

KSR Nr.	Jahr	Autoren	Titel	D1	D2	D3	D4
KSRA20493	2016	Hackam DG	Prognosis of Asymptomatic Carotid Artery Occlusion: Systematic Review and Meta-Analysis				
KSRA101545	2014	Hadar N, et al.	Asymptomatic carotid artery stenosis treated with medical therapy alone: temporal trends and implications for risk assessment and the design of future studies				
KSRA93423	2007	Holt PJ, et al.	Meta-analysis and systematic review of the relationship between hospital volume and outcome following carotid endarterectomy				
KSRA20704	2016	Howard G, et al.	Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: A meta-analysis of pooled patient data from four randomised trials				
KSRA10329	2015	Jaffer U, et al.	Pre-operative methods to predict need for shunting during carotid endarterectomy				
KSRA101547	2014	Jonas DE, et al.	Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the U.S. Preventive Services Task Force				
KSRA100760	2019	Judge C, et al.	Lipid Lowering Therapy, Low-Density Lipoprotein Level and Risk of Intracerebral Hemorrhage - A Meta-Analysis				
KSRA20948	2016	Kakisis JD, et al.	Protamine Reduces Bleeding Complications without Increasing the Risk of Stroke after Carotid Endarterectomy: A Meta-analysis				
KSRA26995	2017	Kakisis JD, et al.	Cranial Nerve Injury After Carotid Endarterectomy: Incidence, Risk Factors, and Time Trends				
KSRA32002	2017	Kakkos SK, et al.	Endarterectomy achieves lower stroke and death rates compared with stenting in patients with asymptomatic carotid stenosis				
KSRA93424	2007	Killeen SD, et al.	Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures				
KSRA27237	2017	Kumar R, et al.	Restenosis after Carotid Interventions and Its Relationship with Recurrent Ipsilateral Stroke: A Systematic Review and Meta-analysis				
KSRA37945	2017	Li Y, et al.	Long-term efficacy and safety of carotid artery stenting versus endarterectomy: A meta-analysis of randomized controlled trials				
KSRA18353	2015	Liao SQ, et al.	The association between leukoaraiosis and carotid atherosclerosis: a systematic review and meta-analysis				
KSRA50263	2018	Lokuge K, et al.	Meta-analysis of the procedural risks of carotid endarterectomy and carotid artery stenting over time				
KSRA3248	2015	Luebke T, et al.	Meta- analysis and meta-regression analysis of the associations between sex and the operative outcomes of carotid endarterectomy				

Bias Assessment: Domain 1 (D1), Study Eligibility Criteria Domain 2 (D2), Identification and Selection of Studies Domain 3 (D3), Data Collection and Study Appraisal Domain 4 (D4), Synthesis and Findings	Low Risk
	Unclear
	Not Analyzed, Meta-Analysis only
	High Risk

KSR Nr.	Jahr	Autoren	Titel	D1	D2	D3	D4
KSRA94088	2019	Mahmoud AN, et al.	Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials				
KSRA76783	2018	Milgrom D, et al.	Editor's Choice - Systematic Review and Meta-Analysis of Very Urgent Carotid Intervention for Symptomatic Carotid Disease				
KSRA44793	2017	Moresoli P, et al.	Carotid Stenting Versus Endarterectomy for Asymptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis				
KSRA86922	2019	Murphy SJX, et al.	Optimal antiplatelet therapy in moderate to severe asymptomatic and symptomatic carotid stenosis: a comprehensive review of the literature				
KSRA11948	2016	Newhall KA, et al.	Use of Protamine for Anticoagulation During Carotid Endarterectomy: A Meta-analysis				
KSRA5510	2015	Nwachuku EL, et al.	Diagnostic value of somatosensory evoked potential changes during carotid endarterectomy: a systematic review and meta-analysis				
KSRA34066	2017	Orrapin S, et al.	Carotid endarterectomy for symptomatic carotid stenosis				
KSRA8880	2015	Ouyang YA, et al.	Efficacy and safety of stenting for elderly patients with severe and symptomatic carotid artery stenosis: A critical meta-analysis of randomized controlled trials				
KSRA19071	2016	Pandit AK, et al.	High-dose statin therapy and risk of intracerebral hemorrhage: a meta-analysis				
KSRA27462	2017	Paraskevas KI, et al.	Carotid Stenting Prior to Coronary Bypass Surgery: An Updated Systematic Review and Meta-Analysis				
KSRA59948	2018	Paraskevas KI, et al.	An Updated Systematic Review and Meta-analysis of Outcomes Following Eversion vs. Conventional Carotid Endarterectomy in Randomised Controlled Trials and Observational Studies				
KSRA32480	2017	Phillips P, et al.	Systematic review of carotid artery procedures and the volume-outcome relationship in Europe				
KSRA52445	2017	Pini R, et al.	The fate of asymptomatic severe carotid stenosis in the era of best medical therapy				
KSRA77299	2018	Poorthuis MHF, et al.	High Operator and Hospital Volume are Associated With a Decreased Risk of Death and Stroke Following Carotid Revascularization: A Systematic Review and Meta-analysis				
KSRA101546	2013	Raman G, et al.	Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis				

Bias Assessment: Domain 1 (D1), Study Eligibility Criteria Domain 2 (D2), Identification and Selection of Studies Domain 3 (D3), Data Collection and Study Appraisal Domain 4 (D4), Synthesis and Findings	Low Risk
	Unclear
	Not Analyzed, Meta-Analysis only
	High Risk

KSR Nr.	Jahr	Autoren	Titel	D1	D2	D3	D4
KSRA101549	2017	Rantner B, et al.	Early Endarterectomy Carries a Lower Procedural Risk Than Early Stenting in Patients With Symptomatic Stenosis of the Internal Carotid Artery: Results From 4 Randomized Controlled Trials				
KSRA101550	2013	Ren S, et al.	Systematic Review of Randomized Controlled Trials of Different Types of Patch Materials during Carotid Endarterectomy				
KSRA104783	2018	Rothwell PM, et al.	Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials				
KSRA4703	2015	Shan L, et al.	Quality of life and functional status after carotid revascularisation: a systematic review and meta-analysis				
KSRA101548	2013	Taylor F, et al.	Statins for the primary prevention of cardiovascular disease				
KSRA64940	2018	Texakalidis P, et al.	Carotid Artery Endarterectomy versus Carotid Artery Stenting for Restenosis After Carotid Artery Endarterectomy: A Systematic Review and Meta-Analysis				
KSRA83276	2018	Texakalidis P, et al.	A meta-analysis of randomized trials comparing bovine pericardium and other patch materials for carotid endarterectomy				
KSRA72932	2018	Texakalidis P, et al.	Outcome of Carotid Artery Endarterectomy in Statin Users versus Statin-Naive Patients: A Systematic Review and Meta-Analysis				
KSRA72933	2018	Texakalidis P, et al.	Effect of Open- vs Closed-Cell Stent Design on Periprocedural Outcomes and Restenosis After Carotid Artery Stenting: A Systematic Review and Comprehensive Meta-analysis				
KSRA56918	2018	Texakalidis P, et al.	Proximal embolic protection versus distal filter protection versus combined protection in carotid artery stenting: A systematic review and meta-analysis				
KSRA60338	2018	Texakalidis, P. et al.	Revascularization of radiation-induced carotid artery stenosis with carotid endarterectomy vs. carotid artery stenting: A systematic review and meta-analysis				
KSRA101143	2019	Texakalidis P, et al.	Carotid revascularization in older adults: a systematic review and meta-analysis				
KSRA15775	2016	Thirumala PD, et al.	Diagnostic accuracy of EEG changes during carotid endarterectomy in predicting perioperative strokes				
KSRA4518	2015	Tu J, et al.	Repeated carotid endarterectomy versus carotid artery stenting for patients with carotid restenosis after carotid endarterectomy: Systematic review and meta-analysisKSRA42331				
KSRA45255	2017	Udesh R, et al.	Transcranial Doppler Monitoring in Carotid Endarterectomy: A Systematic Review and Meta-analysis				

Bias Assessment: Domain 1 (D1), Study Eligibility Criteria Domain 2 (D2), Identification and Selection of Studies Domain 3 (D3), Data Collection and Study Appraisal Domain 4 (D4), Synthesis and Findings	Low Risk
	Unclear
	Not Analyzed, Meta-Analysis only
	High Risk

KSR Nr.	Jahr	Autoren	Titel	D1	D2	D3	D4
KSRA101553	2013	Vaniyapong T, et al.	Local versus general anaesthesia for carotid endarterectomy				
KSRA16952	2015	Vincent S, et al.	Meta-analysis of randomized controlled trials comparing the long-term outcomes of carotid artery stenting versus endarterectomy				
KSRA78784	2018	Wodarg F, et al.	Influence of stent design and use of protection devices on outcome of carotid artery stenting: a pooled analysis of individual patient data				
KSRA65499	2018	Yuan G, et al.	Carotid Artery Stenting Versus Carotid Endarterectomy for Treatment of Asymptomatic Carotid Artery Stenosis				

KSRA84832 2019 Aber A, et al. Impact of Carotid Artery Stenosis on Quality of Life: A Systematic Review

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 4 **Number of participants** 62 **Last search date** September 2018 **Review type** Prognostic/Predictive ObjectiveTo identify the impact of carotid artery stenosis and its treatment on quality of life. **Population** Patients (≥16 years of age) diagnosed with carotid artery stenosis (CAS), have had or are undergoing surgical treatment. Participants undergoing treatment for stroke or transient ischaemic attack (TIA) secondary to a diagnosis of CAS. Any studies with undefined population were excluded. Outcome Health-related quality of life (HRQoL) based on patient-reported outcome measures. Five domains of the themes were anxiety, impact on personal roles and activities, the effect on independence, psychological impact and symptoms. **Study design** Semi-structured interviews, descriptions, focus groups either as stand-alone studies or embedded in a quantitative study **PP factor** Carotid artery stenosis and its treatment.	Overall, five domains were identified that impacted the health-related quality of life (HRQoL) of patients with carotid artery stenosis (CAS) throughout their care pathway: anxiety, impact on personal roles and activities, the effect on independence, psychological impact and symptoms. One study reported that patients with successful revascularisation reported improved psychological wellbeing and felt that they could move on with their lives compared to the time prior to their procedure. Another study found that patients also suggested that the symptomatic CAS causing transient ischaemic attack (TIA) dramatically changed their perception about their physical health. Three studies observed that patients who had the operation and did not experience any complications reported that they felt happier emotionally having dealt with a potentially significant disease that made them feel unhappy. Another study demonstrated that patients experiencing TIA reported classical symptoms including loss of sensation, weakness, temporary loss of the ability to speak and loss of vision. The best-fit generic and disease-specific patient-reported outcome measures (PROMs) were the Medical Outcomes Study 36-Item Short Form (SF-36) and the Carotid Stenosis Specific Outcome Measure (CSSOM), respectively. None of the included PROMs covered all the themes identified in the qualitative systematic review.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. Only English language studies were considered for inclusion in the review.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching CINAHL via EBSCO, Medline and Medline in Process via Ovid, Embase via Ovid, PsycINFO via Ovid, Social Science Citation Index/Science Citation Index via Web of Science (Thomson Reuters) and Proquest dissertations and theses. Additional efforts were made in addition to a database search to identify relevant studies. The search strategy was reported in full and appeared confused with several duplicated lines and apparent restriction to 2015-2017; probably the wrong strategy was attached to the paper. No restrictions were reported based on date, publication format, or language. Two reviewers were independently involved in study selection and disagreements were resolved by discussion.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and risk of bias assessment. Discrepancies were resolved by discussion with a third reviewer. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was assessed using the CASP tools.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. A narrative synthesis was performed to summarise the findings. The quality of the individual studies was considered in the synthesis.** **Overall summary** **Only English language studies were considered for inclusion in the review. The search strategy attached to the paper appeared to be the wrong one.**

Bottom line: The current evidence suggests that the review identified important themes that affect patients with carotid stenosis disease in five main domains: anxiety, impact on personal roles and activities, effect on independence, psychological impact, and symptoms. None of the included patient-reported outcome measures covered all the themes identified in the qualitative systematic review. However, the proposed themes can be used to develop new disease-specific patient-reported outcome measures to measure the health-related quality of life. The inclusion of only English language studies means some of the relevant studies may have been missed.

KSRA42331 2017 Abreu P, et al. Intracerebral hemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization: systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 41 **Number of participants** 28956 Last search date January 2016 **Review type** Incidence, risk factors and outcomes. **Objective** To estimate the frequency of intracerebral haemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization and its case fatality. **Population** Patients with carotid occlusive disease undergoing carotid revascularization (carotid angioplasty with stenting [CAS] or carotid endarterectomy [CEA]). Studies with CEA/CAS performed for other specific conditions were excluded. **Interventions** NA **Comparator** NA Outcome Intracerebral haemorrhage frequency and case fatality. **Study design** Observational studies. Case reports and animal studies were excluded. **Reference standard** NA Exposure Cerebral hyperperfusion syndrome (CHS) after carotid revascularization. Studies in which the definition and frequency of intracerebral haemorrhage related CHS were not described were excluded. **PP factor** NA	The pooled analysis reported that frequency and case fatality of intracerebral haemorrhage (ICH) in the context of cerebral hyperperfusion syndrome (CHS) was found to be 38% (95% confidence interval [CI] 26% to 51%, 24 studies) and 51% (95% CI 32% to 71%, 17 studies), respectively. Moreover, 21 studies reported that the mortality from ICH related to CHS ranged from 0% to 100%, while the mortality in large studies was ≥ 50% in more than half of the studies (17 studies). The post-procedural ICH in the context of CHS was less frequent in carotid endarterectomy (CEA) (range: 0% to 3.57%, 25 studies) when compared to carotid angioplasty with stenting (CAS) (range: 0% to 4.54%, 21 studies) and the ICH was found in only 4 studies in asymptomatic patients. The most frequent risk factors for ICH were periprocedural hypertension (4 studies) followed by severe ipsilateral stenosis (3 studies). The ICH to CHS proportion was higher after CAS than CES where 63.6% of CAS studies (range: 0 to 100%) and 41.6% of CES studies (range: 0 to 80%) had 50% or more hemorrhagic CHS (range 0 to 100%).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Inclusion criteria were not explicitly defined with regard to the study design. No restrictions were imposed based on study characteristics. Only full-text English written publications were included.** **Domain 2: Identification and Selection of Studies** **PubMed and other databases accessed via EBSCOhost including MEDLINE, ScienceDirect, academic one file, J-stage, general one file, OAIster, expanded academic ASAP, China/Asia on demand, SciELO, Scitech connect MedicLatina and Korean studies information study system were searched for relevant studies. EMBASE was not searched. No additional attempts were made to locate further studies. Only search terms were provided, full details of search strategy were not reported. The searches were restricted to studies published between 1986 and January 2016 and found to be appropriate. Two reviewers were independently involved in the study selection process and any disagreements between them were resolved by consensus.** **Domain 3: Data Collection and Study Appraisal** **Two investigators were independently involved in the data extraction and any discrepancies between them were resolved by consensus. Insufficient study characteristics appear to have been extracted to allow interpretation of results. Details of the confounders adjusted for were not provided. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the criteria from National Institutes of Health tools. Two investigators were independently involved in the risk of bias assessment. Discrepancies were resolved by discussion and consensus achieved.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was a significant evidence of heterogeneity among the studies. No appropriate attempts were made to explore the possible sources of heterogeneity. Robustness of the findings was not addressed. The quality of individual studies was considered in the synthesis.** **Overall summary** **Inclusion criteria were not explicitly defined with regard to the study design. Restriction to English language studies, limited range of database search, lack of search strategy and no additional attempts to locate further studies means some eligible studies may have been missed. Details of the confounders adjusted for were not provided. No appropriate attempts were made to explore possible sources of heterogeneity. Robustness of the findings was not addressed.**

Bottom line: The evidence suggests that intracerebral haemorrhage is a rare manifestation of cerebral hyperperfusion syndrome after carotid revascularization despite its association with high case-fatality rates, while the most common risk factors are periprocedural hypertension and ipsilateral severe stenosis. The review had significant methodological weaknesses in all the domains, so the findings should be interpreted with caution. Further studies are needed to determine the role of other risk factors for intracerebral haemorrhage.

KSRA101554 2014 Antoniou GA, et al. Meta-analysis of retrojugular versus antejugular approach for carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 6 **Number of participants** 740 **Last search date** NR **Review type** Intervention Objective To identify studies comparing the outcomes of carotid endarterectomy performed with the retrojugular and antejugular approach. **Population** Patients with the symptomatic or asymptomatic carotid disease treated with the conventional (primary or patch closure) or eversion carotid endarterectomy technique under regional or general anaesthesia were considered. **Interventions** Carotid endarterectomy performed with the retrojugular approach. Comparator Carotid endarterectomy performed with the antejugular approach. **Outcome** Damage of specific cranial nerves (laryngeal, hypoglossal, accessory nerve) and early postoperative adverse cerebrovascular events. **Study design** Randomised control studies, retrospective, correspondence and prospective non-randomised.	The pooled analysis reported that retrojugular approach was associated with a higher incidence of laryngeal nerve damage (odds ratio [OR] 3.21, 95% confidence interval [CI] 1.46 to 7.07) compared to the antejugular approach group. However there were no statistically significant differences between the two groups in terms of the incidence of hypoglossal nerve damage (OR 1.09, 95% CI 0.31 to 3.80) accessory nerve damage (OR 11.51, 95% CI 0.59 to 225.43), cranial nerve damage (OR 2.96, 95% CI: 0.79 to 11.13), perioperative stroke (OR 1.26, 95% CI 0.31 to 5.21) and mortality rates (OR 1.28, 95% CI 0.25 to 6.50).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were applied in eligibility criteria based on study characteristics and sources of information. The in- and exclusion criteria were not clearly stated.** **Domain 2: Identification and Selection of Studies** **Relevant studies were identified from MEDLINE via PubMed. Further efforts were made to manually search reference lists of included studies to identify additional articles. Search terms were provided and appear very limited, a full search strategy was not reported. It was unclear whether the searches were restricted to date, publication format, or language. Study selection was performed independently by two authors.** **Domain 3: Data Collection and Study Appraisal** **Study selection and data extraction were performed independently by two authors. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was assessed. No information was provided on the number of reviewers involved in the risk of bias assessment. However, like all other stages of the review were performed in duplicate and it is likely that this stage also involved two reviewers.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. The method of analysis was explained and appeared inappropriate as different study designs were pooled together. No significant heterogeneity was found between the studies. The likelihood of publication bias was reported as low however, this was not appropriate as the number of trials included in the review was small (< 10). Bias in primary studies was addressed while interpreting findings.** **Overall summary** **Embase was not searched. Search terms were provided but a full search strategy was not reported. The method of analysis appeared inappropriate as different study designs were pooled together. The likelihood of publication bias was reported as low however, this was not appropriate as the number of trials included in the review was small (< 10).**

Bottom line: Currently, there is inconclusive evidence to suggest one approach over the other for carotid endarterectomy. However, the findings need cautious interpretation as the review had a number of shortcomings. Further high-quality trials are required.

KSRA34602 2017 Baradaran H, et al. Hemispheric Differences in Leukoaraiosis in Patients with Carotid Artery Stenosis: A Systematic Review

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 5 **Number of participants** 776 **Last search date** September 2013 **Review type** Prognostic/Predictive **Objective** To determine the relationship between carotid disease and leukoaraiosis. **Population** Patients with unilateral extracranial carotid artery stenosis of at least 30% determined by any imaging modality including ultrasound (US), magnetic resonance angiography (MRA), digital subtraction angiography (DSA), or computed tomography angiography (CTA) according to North American Symptomatic Carotid Stenosis Endarterectomy Trial (NASCET) criteria. **Interventions** NA **Comparator** NA **Outcome** Leukoaraiosis **Study design** Prospective or retrospective studies. **Reference standard** NA **Exposure** Carotid artery disease **PP factor** Carotid artery disease.	Four studies reported no association between carotid artery stenosis and degree of white matter hyperintensities. One study observed significantly increased white matter disease as determined by the Fazekas grading scale ipsilateral to carotid artery stenosis.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. Studies with at least 10 patients and published between 1990 and September 2013 were included and found to be appropriate. Only English language studies were considered for inclusion in the review.** **Domain 2: Identification and Selection of Studies:** **Ovid MEDLINE, Ovid EMBASE, Scopus, and the Cochrane library databases were searched for relevant studies. Additionally, records were identified with the related articles featured in Pubmed and the cite reference search in ISI Web of Science. Search terms were provided, but a full search strategy was not reported. There was no information whether searches were restricted by publication format or language. One reviewer involved in title/abstract screening and two independent reviewers were involved in full-text screening and this was found to be inappropriate.** **Domain 3: Data Collection and Study Appraisal:** **Three reviewers were involved in the data extraction process. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. There was no formal assessment of the methodological quality of included studies, but some quality indicators were discussed.** **Domain 4: Synthesis and Findings:** **The synthesis included all relevant studies and was appropriate. Meta-analysis was not performed due to considerable heterogeneity between the studies. A narrative synthesis was performed to summarise the findings of the review. The quality of the individual studies was not considered in the synthesis.** **Overall summary: High risk of bias in the review** **Only English language studies were considered for inclusion in the review. Search terms were provided but a full search strategy was not reported. Only one reviewer was involved in title/abstract screening. There was no formal assessment of the methodological quality of included studies.**

Bottom line: The evidence suggests no definite relationship could be observed between carotid artery atherosclerosis and white matter disease detectable on magnetic resonance imaging. There were some limitations with the review methods such as restriction to the English language, the lack of full search strategy, no appropriate efforts to minimise errors in study selection and no assessment of study quality. Further studies with separate asymptomatic and symptomatic cohorts are needed to focus on understanding the relationship between large vessel atherosclerosis and white matter disease in patients with unilateral carotid artery stenosis.

KSRA35119 2016 Baradaran H, et al. White Matter Diffusion Abnormalities in Carotid Artery Disease: A Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 6 **Number of participants** 230 **Last search date** November 2013 **Review type** Aetiological ObjectiveTo evaluate the association between unilateral carotid steno-occlusion and ipsilateral apparent diffusion coefficient, fractional anisotropy, and mean diffusivity abnormality. **Population** Patients with unilateral extracranial or intracranial carotid stenosis of at least 70% as determined by any imaging modality including ultra-sound, MRA, DSA, or CTA defined by North American Symptomatic Carotid Endarterectomy Trial criteria **Outcome** White matter quantification both ipsilateral and contralateral to carotid artery disease site assessing either apparent diffusion coefficient, fractional anisotropy, and mean diffusivity abnormality which was determined by brain magnetic resonance imaging on 1.5T or 3T magnet field strength. **Study design** Prospective and retrospective studies. Duplicate cohorts were excluded. Exposure Unilateral carotid steno-occlusion.	Pooled analysis of the included studies reported higher and lower values of apparent diffusion coefficient [ADC] (Standardized mean difference [SMD] = 1.13, 95% Confidence interval [CI] 0.79 to 1.47; 2 studies) and fractional anisotropy [FA] (SMD = -0.42, 95% CI -0.62 to -0.21; 5 studies) respectively to the ipsilateral cerebral hemisphere of the carotid artery disease site when compared to the contralateral cerebral hemisphere. Summary estimates from 2 studies reported no significant differences (SMD = 0.23, 95% CI -0.32 to 0.77) between the two hemispheres in case of mean diffusivity [MD]. Subgroup analysis reported significant ADC values in case of b-values (greater than 1300: SMD = 1.414, 95% CI 0.881 to 1.947; 1 study, n = 34 patients; less than 1300: SMD = 0.937, 95% CI 0.5 to 1.374; 3 studies, n = 72 patients), symptomatic status (asymptomatic: SMD = 0.750, 95% CI 0.138 to 1.362; 1 study, n = 22 patients; symptomatic: SMD = 1.131, 95% CI 0.507 to 1.756; 1 study, n = 23 patients; both: SMD = 1.414, 95% CI 0.881 to 1.947; 2 studies, n = 61 patients), and disease site (ICA: SMD = 0.937, 95% CI 0.5 to 1.374; 3 studies, n = 72 patients; MCA: SMD = 1.414, 95% CI 0.881 to 1.947; 1 study, n = 34 patients). Subgroup analysis reported non-significant values for FA studies with ICA disease and asymptomatic patients and for all MD related subgroups.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and the eligibility criteria were well defined. No restrictions were reported based on the study characteristics. Studies were restricted to the English language.** **Domain 2: Identification and Selection of Studies:** **Literature searches were conducted in Ovid Medline, Ovid Embase, Scopus, and the Cochrane Library. Additional attempts to identify further studies were made by featuring related articles in PubMed and the Cited Reference Search in ISI Web of Science. Search terms and search strategy were not reported. Searches were restricted to studies published from 1990 to September 2013 which was appropriate. All abstracts were screened by one reviewer and potentially relevant articles were identified through full-text review by two reviewers.** **Domain 3: Data Collection and Study Appraisal:** **At least three authors were involved in the data extraction process. Sufficient study characteristics appear to have been extracted for the interpretation of the results. Details of the confounders were not provided. Relevant study results appear to have been extracted. There was no methodological quality assessment of the included studies.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all the relevant studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity among all studies. Publication bias could not be assessed due to the low number of studies included in the review. The quality of the individual studies was not assessed in the synthesis. There were errors in the presentation of the results where a minus sign was used before 0.77.** **Overall summary: High risk of bias in the review** **Studies were restricted to the English language. Search terms and search strategy were not reported. Only one reviewer was involved in the study selection. The quality of the individual studies was not assessed in the synthesis.**

Bottom line: The available evidence suggests a positive association between unilateral carotid steno-occlusion and abnormalities of the apparent diffusion coefficient and fractional anisotropy. Restriction of studies to the English language means that some relevant studies may have been missed.The full search strategy was not provided so it was difficult to judge whether or not as many studies as possible were likely to be retrieved. Only one author was involved in the study selection process which not appropriate. Bias in primary studies was not considered in the synthesis. Further prospective cohort studies are needed to manifest the suitability of these imaging metrics as risk stratification tools.

KSRA49253 2017 Baradaran H, et al. Association between Carotid Plaque Features on CTA and Cerebrovascular Ischemia: A Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 16 **Number of participants** 2861 **Last search date** March 9, 2016 **Review type** Prognostic/Predictive **Objective** To evaluate the association between specific carotid plaque features on CTA and ipsilateral cerebrovascular ischemia. **Population** Patients with a plaque in the extracranial internal carotid artery. **Outcome** Ischemic events, defined as ipsilateral ischemic stroke or transient ischemic attack in the vascular territory supplied by the index carotid artery. **Study design** Prospective and retrospective, cross-sectional studies. **Reference standard** NR **Exposure** CTA-detected carotid plaque features. **PP factor** Plaque features on CTA imaging.	The meta analysis showed positive association between soft or low-attenuation plaque, plaque ulceration, and increased common carotid artery wall thickness and the presence of recent ipsilateral stroke or TIA, with pooled ORs of 2.92 (95% CI, 1.41–6.04; P = .004), 2.20 (95% CI,1.43–3.40; P < .001), and 6.19 (95% CI, 2.47–15.55; P < .001), respectively. Similarly, pooling to investigate the association of the presence of a calcified plaque and downstream cerebrovascular ischemic symptoms and found a negative association with a pooled OR of 0.536 (95% CI, 0.384 –0.749;P <. 001).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Inclusion criteria were not explicitly defined with regard to the study design. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Ovid MEDLINE, Ovid Embase, Scopus, and the Cochrane Library were searched for relevant studies. Only database searching was employed to identify studies, additional methods were not made to retrieve further studies. Authors attempted to contact the corresponding authors for additional details when necessary. The search strategy was reported in full and appeared adequate. The searches were not restricted by date, publication format, or language. Two authors were independently involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Data extraction was performed by two authors independently and disagreements were resolved by a third reader. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using the appropriate criteria. Three authors were involved in the assessment of the risk of bias.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The methodological analysis section of the review was sufficiently elucidated. There was significant evidence of heterogeneity for the outcome association between plaque ulceration and prior ipsilateral ischemic events. Appropriate attempts were not made to explore the possible sources of heterogeneity. Funnel plots asymmetry revealed significant publication bias, but was hampered by a limited number of studies. The quality of all the included studies was not considered in the synthesis.** **Overall summary** **Inclusion criteria were not explicitly defined with regard to the study design. No additional attempts were made to locate further studies. There was significant evidence of heterogeneity for the outcome association between plaque ulceration and prior ipsilateral ischemic events. Funnel plots asymmetry revealed significant publication bias. The quality of all the included studies was not considered in the synthesis.**
Bottom line: Evidence suggests that soft plaque, plaque ulceration, and increased common carotid artery wall thickness on CTA imaging are associated with ipsilateral cerebrovascular ischemia, while calcified plaque is negatively associated with downstream ischemic events. There were limitations with the review methods such as the lack of details with regards to eligibility criteria for the study design, presence of heterogeneity and publication bias and no assessment of study quality for all included studies.		

KSRA66075 2018 Barkat M, et al.Systematic review and network meta-analysis of treatment strategies for asymptomatic carotid disease

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** 8,954 **Last search date** October 2016 **Review type** Intervention **Objective** To investigate the outcomes of treatment strategies for asymptomatic carotid disease. **Population** Any patients (no age or gender restriction) with an asymptomatic carotid disease (diagnosed with carotid stenosis >50% without any neurological symptoms indicating a cerebrovascular event during the 180 days preceding initiation of treatment for the carotid disease). **Interventions** Carotid endarterectomy (CEA) (any technique of CEA was considered including conventional endarterectomy with direct or patch closure or the eversion technique); carotid stenting (CAS) (CAS could have been performed with or without a cerebral protective device, any type of stent including a closed or open cell design); and best medical therapy (mainly consisted of optimal antiplatelet therapy according to clinical practice at the participating centres, cholesterol-lowering agents (e.g. statin), antihypertensive medication and targeted risk factor modifcation). **Comparator** with one of the interventions. **Outcome** Primary outcomes: Stroke and death occurring within 30 days of treatment or during the hospital stay for the index procedure (CEA or CAS) and during follow up. Secondary outcomes: Myocardial infarction and transient ischemic attack occurring in the perioperative period (within 30 days or during the hospital stay) and during follow up. **Study design** Randomised controlled trials (RCTs). Systematic reviews, registries, or non-RCTs were excluded.	The pooled analysis of five randomised controlled trials (RCTs) (n=5610) reported that the best medical therapy (BMT) significantly reduced the incidence of ipsilateral stroke (risk difference [RD] 0.01, 95% confidence interval [CI] 0.01 to 0.02) and mortality (RD 0.01, 95% CI 0.00 to 0.01) occurring within 30 days of treatment compared to carotid endarterectomy (CEA) in patients with asymptomatic carotid disease. However, BMT significantly increased the incidence of myocardial infarction (MI) occurring within 30 days of treatment compared to CEA (OR 12.07, 95% CI 2.82 to 51.6, 3 RCTs, n=3635). No significant difference was observed between BMT and CEA for transient ischemic attack (TIA) occurring within 30 days of treatment (odds ratio [OR] 1.63, 95% CI 0.81 to 3.27, 3 RCTs, n=3635). In contrast, CEA significantly reduced the incidence rates of ipsilateral stroke (OR 0.59, 95% CI 0.49 to 0.7, 4 RCTs, n=5278), mortality (OR 0.75, 95% CI 0.59 to 0.96, 3 RCTs, n=4834) and TIA (OR 0.27, 95% CI 0.12 to 0.59, 2 RCTs, n=515) during the follow up period compared to BMT. However, no significant difference was observed between BMT and CEA for MI during follow up (OR 0.57, 95% CI 0.1 to 3.38, 2 RCTs, n=126). No significant differences were found between CEA and carotid stenting (CAS) in terms of ipsilateral stroke (RD -0.01, 95% CI -0.01 to 0.00, 5 RCTs, n=3255), mortality (RD -0.00, 95% CI -0.01 to 0.00, 5 RCTs, n=3255), TIA (RD -0.01, 95% CI -0.02 to 0.01, 3 RCTs, n=1674) and MI (RD 0.01, 95% CI -0.00 to 0.02, 3 RCTs, n=2770) occurring within 30 days of treatment. Similarly, no significant differences were found between CEA and CAS in terms of ipsilateral stroke (OR 1.05, 95% CI 0.59 to 1.87, 2 RCTs, n=1690), mortality (OR 0.79, 95% CI 0.55 to 1.15, 2 RCTs, n=1589) and TIA (OR 0.33, 95% CI 0.01 to 8.21, 1 RCT, n=136) during follow up. None of the identified trials provided direct evidence between CAS and BMT. Overall, the network meta-analyses observed that BMT was ranked superior to CEA and CAS in terms of perioperative stroke risk and mortality occurring within 30 days of treatment for patients with asymptomatic carotid disease; whereas CEA was ranked as the best treatment option for long-term mortality and ipsilateral stroke.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were applied to eligibility criteria based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **MEDLINE, EMBASE, CINAHL and CENTRAL were searched for relevant studies. Additional records were identified through trials registries (World Health Organization International Clinical Trials Registry and the ISRCTN Register), a manual search of the references lists and other sources. The search strategy was reported in full and appeared adequate. Searches were not restricted to date, publication format or language. Two review authors were independently involved in study selection and disagreements were resolved by consulting the third review author.** **Domain 3: Data Collection and Study Appraisal** **One review author extracted the data from the selected studies and a second review author cross-checked the collected data. Disagreements were resolved by discussion between the authors. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The quality was assessed using the Cochrane tool for the assessment of the risk of bias of the selected trials. No information was provided on the number of reviewers involved in the risk of bias assessment. However, like all other stages of the review were performed in duplicate and it is likely that this stage also involved two reviewers.** **Domain 4: Synthesis and Findings** **Results of the studies included in meta-analyses appear relatively similar. While the review authors appear to have investigated heterogeneity and clinical factors, results are not reported. Sensitivity analyses were conducted and funnel plots were used to test for publication bias.** **Overall summary** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate. There was evidence of significant methodological as well as statistical heterogeneity among studies. The pair-wise meta-analysis had variation in follow up period together with significant heterogeneity in BMT within and between the studies. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.**

Bottom line: Current evidence suggests that best medical therapy (BMT) seems to be superior to carotid endarterectomy (CEA) and carotid stenting (CAS) in terms of perioperative stroke risk and mortality for patients with asymptomatic carotid disease; whereas CEA appears to be the best treatment method to reduce the long-term risk of ipsilateral stroke and mortality compared to BMT, but there is probably no difference between CEA and CAS. The result should be interpreted with caution given the evident heterogeneity among the studies.

KSRA34611 2017 Barkat M, et al.Systematic Review and Meta-analysis of Dual Versus Single Antiplatelet Therapy in Carotid Interventions

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 10 **Number of participants** 37031 **Last search date** June 2016 **Review type** Intervention **Objective** To determine the effects of dual antiplatelet therapy in carotid endarterectomy and stenting. **Population** Patients of any age and gender diagnosed with symptomatic or asymptomatic carotid disease undergoing carotid endarterectomy (CEA) or stenting (CAS). Patients undergoing carotid intervention within 14 days following thrombolysis for acute ischaemic stroke were excluded. **Interventions** Dual antiplatelet therapy, for example, aspirin 75 mg and clopidogrel 75 mg. **Comparator** Single antiplatelet therapy. **Outcome** Primary outcomes: Mortality and stroke within 30 days. Secondary outcomes: Transient ischaemic attack (TIA), major bleeding, groin or neck haematoma, and myocardial infarction (MI). **Study design** Randomised controlled trials (RCTs) and observational studies.	The pooled analysis reported no significant differences between single and dual antiplatelet therapy regarding thirty-day mortality (risk difference [RD] -0.00, 95% confidence interval [CI] -0.00 to 0.00, 5 studies, n=30021), stroke (RD -0.00, 95% CI -0.00 to 0.00, 7 studies, n=35170) and transient ischaemic attack (TIA) (RD -0.00, 95% CI -0.00 to 0.00, 5 studies, n=30385) in carotid endarterectomy (CEA). Five studies reported that the myocardial infarction (MI) rate was higher in the dual therapy group (1.11%) than the single therapy group (0.73%) (RD 0.00, 95% CI 0.00 to 0.01, 5 studies, n=30021) in CEA. Major bleeding (RD 0.00, 95% CI, 0.00 to 0.01, 7 studies, n=35856) and neck haematoma (RD, 0.04, 95% CI 0.01 to 0.06, 6 studies, n=2495) risk were higher with dual therapy than single therapy in CEA. In carotid stenting (CAS) no significant differences were observed in major bleeding (RD 0.00, 95% CI -0.04 to 0.04, 2 studies, n=150) or haematoma formation (RD -0.04, 95% CI -0.11 to 0.03, 2 studies, n=150) between the two groups. However, TIA was significantly higher with single therapy than dual therapy group (RD -0.13, 95% CI -0.22 to -0.05, 2 studies, n=150).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching United States National Library of Medicine's database (MEDLINE), Excerpta Medica database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, bibliographies of included studies, the World Health Organisation (WHO) International Clinical Trials Registry http://apps.who.int/trialsearch/, ClinicalTrials.gov http://clinicaltrials.gov/, and ISRCTN Register http://www. isrctn.com/ for ongoing clinical trials were searched for additional findings. The search strategy was reported in full and appeared adequate. There were no restrictions imposed based on date, publication format, or language. Two reviewers were independently involved in study selection process, disagreement between these two review authors was resolved by a third review author.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and disagreements were resolved by discussion with the third reviewer. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of observational studies was assessed using the Newcastle-Ottawa Quality Assessment Scale and RCTs using the Cochrane Risk of Bias Tool. Two reviewers were independently involved in risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. Analyses pre-defined in the methodology section were performed appropriately. Pooling can be challenged as not being appropriate as it includes both observational studies and one RCT pooled together, which may lead to bias. However, it concerned only one very small RCT, and much larger observational studies. No significant heterogeneity was found between the studies. Publication bias was assessed using Egger's test. Sensitivity analysis was performed to check the robustness of study results. The quality of the individual studies was considered in the synthesis.** **Overall summary** **Generally a good systematic review.**

Bottom line: The current evidence suggests that dual antiplatelet therapy may be more effective than single antiplatelet therapy in carotid stenting, However, dual antiplatelet therapy was associated with increased risk of bleeding complications in carotid endarterectomy.

KSRA50865 2016 Best LM, et al. Transcranial Doppler Ultrasound Detection of Microemboli as a Predictor of Cerebral Events in Patients with Symptomatic and Asymptomatic Carotid Disease: A Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 28 **Number of participants** 5004 **Last search date** September 2015 **Review type** Prognostic/Predictive **Objective** (i)To evaluate the prognostic use of microembolic signals recorded by transcranial Doppler ultrasound (TCD) ultrasound to detect stroke risk in patients with the carotid atherogenic disease and (ii) to quantifying the temporal bone window availability in studies selected for the primary objective there by to judge feasibility of TCD ultrasound in patients with carotid disease. **Population** Patients with carotid atherosclerosis. Outcome Detection of stroke and/or transient ischemic attack of microembolic signals. Feasibility of TCD ultrasound in patients with carotid disease. **Study design** Prospective studies. **Reference standard** NA **PP factor** The use of transcranial Doppler ultrasound (TCD), Temporal bone window availability. Studies lacking TCD scan results or information of patient cerebrovascular events were excluded.	Twenty-two (n = 3720 patients) out of 28 included studies reported that the sensitivity and specificity were 79.87 (95% confidence interval [CI] 63.39 to 90.09) and 67.07 (95% CI 56.56 to 76.11), respectively for the detection of stroke or transient ischemic attack (TIA) with the use of transcranial Doppler ultrasound (TCD). The positive and negative likelihood ratios were 2.43 (95% CI 1.85 to 3.18) and 0.30 (95% CI 0.16 to 0.55), respectively. The median pre-test probability for these studies was 6.7%, while the corresponding positive and negative post-test probabilities were 14.8% (95% CI 11.7 to 18.6) and 2.1% (95% CI 1.2 to 3.8), respectively. Subgroup analysis reported that the sensitivity and specificity were 68.73 (95% CI 50 to 82.85) and 79.96 (95% CI 72.24 to 85.95), respectively, for the pre-operative group and 89.61 (95% CI 70.8 to 96.84) and 46.38 (95% CI 35.27 to 57.85), respectively, for the peri- and post-operative group. At the median pre-test probability of 6.7%, the post-test probabilities of positive and negative tests were 19.8% (95% CI 14.8 to 25.9) and 2.7% (95% CI 1.6 to 4.5), respectively, for the pre-operative group and 10.7% (95% CI 8.8 to 13) and 1.6% (95% CI 0.5 to 4.6), respectively, for the peri- and post-operative group. Nineteen studies (n = 5,570 patients) reported stroke as an outcome along with data for TCD recording of microembolic signals. The sensitivity and specificity were 73.14 (95% CI 48.16 to 88.86) and 70.27 (95% CI 58.61 to 79.78), respectively. The positive and negative likelihood ratios were 2.46 (95% CI 1.69 to 3.59) and 0.38 (95% CI 0.18 to 0.81), respectively. At the median pre-test probability of stroke of 3.0%, the post-test probabilities of a positive and negative TCD were 7.1% (95% CI 5 to 10.1) and 1.2% (95% CI 0.6 to 2.5), respectively. Subgroup analysis reported that for the pre-operative group the sensitivity and specificity were 71.27 (95% CI 41.49 to 89.67) and 83.72 (95% CI 76.61 to 88.98), respectively, while for the peri- and post-operative group the sensitivity and specificity were 78.86 (95% CI 44.75 to 94.5) and 47.43 (95% CI 35.69 to 59.46), respectively. Eight studies (n = 1,414 patients) reported stroke or TIA as an outcome along with data for TCD recording of microembolic signals (MES) with high MES counts defined as positive. The sensitivity and specificity were 52.38 (95% CI 30.59 to 73.29) and 90.07 (95% CI 83.72 to 94.12), respectively. The positive and negative likelihood ratios were 5.27 (95% CI 2.73 to 10.17) and 0.53 (95% CI 0.33 to 0.85), respectively. At the median pre-test probability of 3.1%, the post-test probabilities of a positive and negative TCD were 14.4% (95% CI 8 to 24.5) and 1.7% (95% CI 1.0 to 2.7), respectively. Thirteen studies (n = 2,400 patients) reported that an average of 89.0% of patients had a thin enough temporal bone for scanning.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Medline (PubMed), Embase, and the Cochrane Databases were searched for relevant studies. The reference lists of all included studies and previously published reviews were hand-searched to identify additional studies. Search terms and search strategy were reported and appeared to be limited. There was no information as to whether searches were restricted by publication format or language. Two authors were independently involved in the study selection process. Any disagreements were resolved by discussion.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of authors involved in the data extraction process. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using the QUADAS-2 tool. No information was provided regarding the number of authors involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The methodological analysis section of the review was sufficiently elucidated. No measure of statistical heterogeneity was reported. Funnel plots, sensitivity analysis or any test to measure the findings robustness was not performed. The quality of individual studies was considered in the synthesis.** **Overall summary** **Search terms and search strategy were reported and appeared to be limited. There was no information as to whether searches were restricted by publication format or language. No information was provided regarding the number of authors involved in the data extraction and the risk of bias assessment. No measure of statistical heterogeneity was reported. Funnel plots, sensitivity analysis or any measure of data robustness were not performed.**

Bottom line: A weak level of evidence indicates that transcranial Doppler (TCD) ultrasound provides clinically useful information about stroke risk for patients with the carotid disease and is technically feasible in most patients. There were some limitations with the review methods such as the lack of full search strategy, no information on limitation in the literature search regarding the publication year, status or language, lack of information on the number of authors involved in the data extraction and the risk of bias assessment, lack of measure of statistical heterogeneity and no assessment of the robustness of the findings. Further high quality studies are required to establish TCD as an effective adjunct indicator of stroke along with carotid stenosis.

KSRA484 2015 Boulanger M, et al. Periprocedural Myocardial Infarction After Carotid Endarterectomy and Stenting: Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 273 references **Number of participants** Unclear, but many thousands **Last search date** June 2014 **Review type** Intervention **Objective** To evaluate the periprocedural risk of myocardial infarction and death after carotid endarterectomy and carotid angioplasty and stenting. To identify whether risk factors for these outcomes differ between the 2 interventions. **Population** Patients with symptomatic or asymptomatic stenosis in the region of the carotid bifurcation, treated by carotid angioplasty and stenting or carotid endarterectomy. Studies on specific populations (e.g., postradiation stenosis, restenosis after carotid endarterectomy, and patients treated under emergency) and case reports were excluded. **Interventions** Carotid angioplasty and stenting (CAS). **Comparator** Carotid endarterectomy (CEA). Outcome Risk of myocardial infarction (MI), death due to stroke and MI. **Study design** Randomised trials and observational studies.	The pooled analysis of the studies reported a non-significant difference in terms of 30-day absolute risk of myocardial infarction (MI) between carotid endarterectomy (CEA) (0.87%, 95% confidence interval [CI] 0.69 to 1.07) and carotid angioplasty and stenting (CAS) (0.70%, 95% CI 0.54 to 0.88). Ninety-nine independent studies reported the 30-day risk of death in patients who underwent CEA (Risk ratio [RR]= 0.92%, 95% CI 0.79 to 1.08, n = 274765 patients) and those who underwent CAS (RR= 1.03%, 95% CI 0.83 to 1.26, 83 studies, n = 39184 participants).Thirty-five independent studies (n = 24690) demonstrated that the proportion of 30-day death due to stroke and MI was found to be 35% (95% CI 25 to 46) and 24% (95% CI 17 to 31), respectively, after CEA. Similarly, 21 studies (n = 7321) reported that death due to stroke and MI was 42% (95% CI 25 to 60) and 18% (95% CI 8 to 29), respectively, after CAS. An increased risk of MI was associated with age, history of coronary artery disease, peripheral artery disease, and restenosis. Moreover, men demonstrated a lower risk of MI than women after CAS, however, no such difference was observed between men and women after CEA.	**Domain 1: Study Eligibility Criteria** **Eligibility criteria were well described and appeared appropriate to address the present review question. No restriction was reported based on the study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Medline, Embase, and Cochrane Library database were searched to retrieve eligible studies. The reference lists of all included studies and any relevant reviews were hand-searched and authors were contacted to identify additional relevant studies. Additionally, books of abstracts from recent conferences that were available online, the US Food and Drug Administration and the European Medicines Agency databases were searched for relevant information. A search strategy was provided, which did not appear adequate to identify all articles relevant to this review. No restrictions based on the date, publication format or language were reported. No information was provided regarding the number of reviewers involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of reviewers involved in the data extraction process. Insufficient study characteristics were presented for the interpretation of the results. There was no formal assessment of the methodological quality of the included studies.** **Domain 4: Synthesis and Findings** **All studies included in the review contributed to the synthesis. Analyses were explained specifically in the methods section and results reported for defined outcomes. Appropriate methods were used to analyse the data. However various high I-squared values were reported, indicating substantial heterogeneity. Robustness of the findings was not demonstrated. Bias in primary trials was not addressed while interpreting the findings.** **Overall summary** **No information was provided regarding the number of reviewers involved in the study selection and data extraction process. Sufficient study characteristics were not available for the interpretation of the results. The methodological quality of the included studies was not considered in the synthesis of the findings. Robustness of the findings was not demonstrated.**

Bottom line: Available evidence suggests no significant difference in the risk of myocardial infarction after carotid endarterectomy and carotid angioplasty and stenting. The risk of myocardial infarction was lower in men after carotid angioplasty and stenting, but this was not observed after carotid endarterectomy. The authors did not state whether study selection and data extraction were undertaken in duplicate, hence, reviewer error and bias could not be ruled out. Insufficient study characteristics were available for the interpretation of the results. The methodological quality of the included studies was not considered in the synthesis of the findings. Robustness of the findings was not demonstrated.

KSRA34866 2017 Brinjikji W, et al. The effects of statin therapy on carotid plaque composition and volume: A systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 7 **Number of participants** 361 **Last search date** 31st December 2015 **Review type** Intervention **Objective** To determine the effects of statin therapy on carotid plaque composition as seen on serial high-resolution carotid plaque MRI. **Population** All patients on statin therapy. **Interventions** Statin therapy. **Comparator** NA. **Outcome** At least one of the following outcomes: change in lipid-rich-necrotic core over time, change in wall volume over time, and change in lumen volume over time; each measured by serial carotid plaque MRI with a dedicated surface coil and a minimum field strength of 1.5 T at all time points. **Study design** Prospective studies including a minimum of 10 patients with a minimum follow-up duration of at least three months.	In terms of the change in lipid-rich necrotic core (LRNC) volume over time, the pooled analysis reported a significant reduction in LRNC volume at >12 months (weighted mean difference [WMD] -9.9 mm, 95% confidence interval [CI] -18.9 to -0.8, four studies, n=243 participants) and at last follow-up (WMD -10.6, 95% CI -18.9 to -2.3, five studies, n=269 participants). However, no significant differences were reported to be observed in LRNC volume at one to six months (WMD -7.9, 95% CI -56.9 to -41.1) and at seven to 12 months (WMD -38.0, 95% CI -86.9 to 10.7) following initiation of statin therapy. In terms of the change in wall volume over time, the pooled analysis of seven studies reported no significant differences in wall volume at any time point following initiation of statin therapy (one to six months: WMD -10.2, 95% CI -109.5 to 89.1); seven to 12 months (WMD -4.9, 95% CI -17.8 to -8.1); >12 months (WMD -19.0, 95% CI -49.2 to 11.3) and last follow-up (WMD -15.9, 95% CI -42.9 to 11.1). In terms of the change in lumen volume over time, the pooled analysis of five studies reported no significant differences in lumen volume at any time point following initiation of statin therapy (one to six months: not reported; seven to 12 months WMD -10.0, 95% CI -130.6 to 110.6); >12 months (WMD -12.2, 95% CI -32.5 to 8.0) and last follow-up (WMD -12.2, 95% CI -32.5 to 8.0).	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. The eligibility criteria were broad, but well defined and appeared to be appropriate for the review question. Studies were restricted based on sample size (studies with less than 10 patients were excluded); however, this restriction was found to be appropriate. No restrictions based on sources of information were reported.** **Domain 2: Identification and Selection of Studies** **Literature searches were conducted in MEDLINE, EMBASE and Web of Science. The reference lists from key articles were handsearched to identify additional studies, and clinical trials.gov was manually searched to identify relevant completed trials. The full search strategy was provided, and appeared to be unnecessarily restrictive. The studies were restricted based on language (only English studies were included), year (searches were stated to be performed from 1st January 2000; although the full search strategy reports 2005 as the lower date limit) and publication format (abstracts were excluded). No information was provided on the number of reviewers involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal:** **No information was provided on the number of reviewers involved in the data extraction process or the risk of bias assessment. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality was assessed using the Newcastle-Ottawa Quality Assessment Scale.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. Analyses explained in the methodology section were performed appropriately. Significant heterogeneity was found for some outcomes (LRNC and wall volumes). While the authors planned to assess publication bias using funnel plots and asymmetry testing, this could not be performed due to the low number of studies (<20). Quality of the individual studies was considered in the synthesis.** **Overall summary** **The full search strategy was provided and appeared to be unnecessarily restrictive, and studies were restricted based on language, year and publication format, meaning relevant studies may have been missed. No information was provided on the number of reviewers involved in the study selection, data extraction or risk of bias assessment, meaning error and bias cannot be ruled out. Significant heterogeneity was found for some outcomes.**

Bottom line: The current evidence suggests that statin therapy may be associated with significant reductions in lipid-rich necrotic core volume in the long-term (>12 months following statin therapy). However, no significant changes in carotid wall volume or carotid lumen volume were reported. These results must be interpreted with caution, since several issues mean that relevant studies may have been missed and error and bias cannot be ruled out. Using MRI to achieve high-resolution plaque imaging may represent an important non-invasive way to track patient responses to other lipid-lowering therapies and atherosclerotic treatments.

KSRA6866 2015 Brinjikji W, et al. Ultrasound characteristics of symptomatic carotid plaques: A systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 23 **Number of participants** Unclear **Last search date** April 2014 **Review type** Unclear **Objective** To better define the risk of stroke based on the sonographic characteristics of carotid plaques. **Population** Patients (18 years of age and older) with symptomatic (those with a history of ipsilateral stroke, transient ischaemic attacks [TIA] [transient cerebral symptoms or amaurosis fugax] within 30 days of the carotid ultrasound) and asymptomatic plaques (those with no history of ipsilateral stroke or TIA). Patients with ischaemic events occurring more than 30 days prior to imaging were considered asymptomatic. **Interventions** Carotid ultrasound techniques. **Comparator** Not relevant. **Outcome** Heterogenous echotexture, intraplaque motion, irregular surface, plaque echolucency, plaque neovascularity, and plaque ulceration. Outcomes were assessed for symptomatic and asymptomatic plaques. **Study design** Case-control studies and cohort studies. Reference standard NA. **Exposure** Not relevant. **PP factor** Not relevant.	The pooled analyses reported that individuals with symptomatic carotid artery stenosis showed higher prevalence of plaque neovascularity (odds ratio [OR] = 19.68, 95% confidence interval [CI] = 3.14 to 123.16), complex plaque (OR = 5.12, 95% CI = 3.42 to 7.67), plaque ulceration (OR = 3.58, 95% CI = 1.66 to 7.71), plaque echolucency (OR = 3.99, 95% CI = 3.06 to 5.19) and intraplaque motion (OR = 1.57, 95% CI = 1.02 to 2.41), compared to findings in individuals with asymptomatic carotid artery stenosis, as determined by ultrasound plaque characteristics. Heterogenous echotexture (OR = 2.68, 95% CI = 0.56 to 12.80) and surface irregularity without ulceration (OR = 2.38, 95% CI = 0.70 to 8.11) did not seem to be associated with symptom status, as determined by ultrasound plaque characteristics.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate eligibility criteria were defined. Only published studies in English were included in the review.** **Domain 2: Identification and Selection of Studies** **MEDLINE and EMBASE databases were searched for relevant literature. The reference lists of studies included were searched for additional articles. Only search terms were provided, hence in the absence of a complete search strategy, it was not possible to conclude if all relevant studies were included in this review. One reviewer reviewed the abstracts of studies identified in the literature search to determine whether the studies met the inclusion criteria.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of reviewers involved in the data collection process. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. The study results were appropriately collected for the synthesis. The Newcastle-Ottawa scale was used to assess the risk of bias in the individual studies. No information was provided regarding the number of reviewers involved in the risk of bias assessment process.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant studies and was appropriate. All predefined analyses were explained in the methodology section. The method used to pool the data was appropriate. Heterogeneity among the included studies was assessed and found to be high. Sensitivity analyses were performed to assess robustness of the findings. No evidence of publication bias was observed based on Egger's test and the funnel plot. Quality of the individual studies was taken into account for the synthesis of the findings.** **Overall summary** **Only studies published in English were included in the review, which means eligible studies in other languages may have been missed. Only one reviewer was involved in the study selection, which was not appropriate. Heterogeneity among included studies was found to be high and proper efforts were not made to address it. It was unclear if two reviewers were independently involved in the data collection and quality assessment process, making it difficult to rule out reviewer error and bias.**

Bottom line: The current evidence indicates that complex carotid plaques i.e. with plaque neovascularity, plaque ulceration, plaque echolucency, and intraplaque motion are significantly associated with symptomatic events, as determined by ultrasound plaque characteristics. However, surface irregularity without ulceration and heterogeneous echotexture were not associated with symptomatic events. Only studies published in English were included in the review, which means eligible studies either unpublished and/or in other languages may have been missed. Only one reviewer was involved in the study selection, which was not appropriate. Heterogeneity among included studies was found to be high and proper efforts were not made to address it. It was unclear if two reviewers were independently involved in the data collection and quality assessment process, making it difficult to rule out reviewer error and bias. Further prospective trials are needed to provide inferential evidence of a stroke risk marker.

KSRA67129 2018 Cho, Y.D, et al. Protected versus unprotected carotid artery stenting: meta-analysis of the current literature

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 25 **Number of participants** Unclear **Last search date** October 2016 **Review type** Intervention **Objective** To compare peri-operative any symptomatic stroke after carotid angioplasty and stenting, based on the application or absence of a cerebral protection device. **Population** Patients with symptomatic and / or asymptomatic stenosis in the internal carotid artery or carotid bifurcation. **Interventions** Protected (through common femoral artery) carotid artery stenting (CAS). Procedures which were performed due to carotid dissection or aneurysm, or the use of covered stents or conducted in an emergency or other procedural approaches, other than common femoral artery were excluded. **Comparator** Unprotected CAS. **Outcome** Primary endpoint: peri-operative any symptomatic stroke within 30 days after the procedure and the number of peri-procedural complications such as stroke, death or myocardial infarction within 30 days. Stroke was defined as any sudden neurologic deficits due to cerebral infarction including bilateral involvement. Asymptomatic signal change on brain magnetic resonance imaging. **Study design** Randomised controlled trials and non-randomised studies (cohort studies, retrospective or prospective case series). Non-comparative studies, commentary, review articles, case reports or letters were excluded.	The pooled analysis reported that the number of stroke events was 326 (2.0%) in protected carotid artery stenting (CAS) and 142 (3.4%) in unprotected CAS. The use of cerebral protection device significantly decreased stroke after CAS compared to the use of unprotected CAS (odds ratio [OR] 0.633, 95% confidence interval [CI] 0.479 to 0.837, 25 studies, n=20,670 events). Moreover, in subgroup analysis regarding symptomatic patients (4 studies, 539 CAS procedures), the number of strokes was 6 (1.7%) in protected CAS and 11 (5.7%) in unprotected CAS. However, no significant difference was observed between protected and unprotected CAS with respect to perioperative stroke events in symptomatic patients (OR 0.455, 95% CI 0.151 to 1.366, 4 studies, n=539).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. Date limitations appeared appropriate. No restriction was reported based on sources of information.** **Domain 2: Identification and Selection of Studies** **PubMed, Embase and the Cochrane Central were searched for relevant studies. No further efforts were made to perform searches additional to a database search. Search terms were provided, but a full search strategy was not reported. There was no information as to whether searches were restricted by date, publication format or language. Two review authors were involved in the study selection process and disagreements were resolved by discussion or by consulting the third review author.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of authors involved in the data extraction and risk of bias assessment. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The quality of the included studies was assessed using the Cochrane risk of bias for randomised controlled trials and Newcastle-Ottawa scale for non-randomised studies.** **Domain 4: Synthesis and Findings** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate, however different types of observational studies appear to have been included in a single meta-analysis. There was no evidence of significant heterogeneity for symptomatic stroke after carotid artery stenting. No evidence of significant publication bias was found using Egger's regression test. The quality of individual studies was considered in the synthesis.** **Overall summary** **No further efforts were made to perform searches additional to a database search. Search terms were provided, but a full search strategy was not reported. There was no information as to whether searches were restricted by date, publication format or language. No information was provided regarding the number of authors involved in the data extraction and risk of bias assessment.**

Bottom line: The available evidence suggests that the use of a protection device significantly decreased any symptomatic stroke after carotid artery stenting (CAS). However, its efficacy is not demonstrated in symptomatic patients. Therefore, routine use of protection device during CAS should be critically assessed before mandatory use. The review had some methodological weaknesses, so the findings should be interpreted with caution. Further, randomised controlled trials on perioperative complications according to the symptomaticity and risk stratification, and adverse events in long-term observation are needed to support the current findings.

KSRA101551 2014 Chongruksut W, et al. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting)

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 6 **Number of participants** 1270 **Last search date** August 2013 **Review type** Intervention **Objective** To assess the effect of routine versus selective or no shunting during carotid endarterectomy and to assess the best method for selecting people for shunting. **Population** People undergoing carotid endarterectomy. **Interventions** Routine shunting. **Comparator** No shunting or selective shunting. **Outcome** All strokes (ischaemic and haemorrhagic) that occurred during the operation within 24 hours of surgery, within 30 days of surgery, and during the whole of follow-up, all ipsilateral strokes, death from any cause within 30 days of surgery and during follow-up, other complications within 30 days of surgery, long-term arterial complications and cognitive function at the end of follow-up. **Study design** Randomised and quasi-randomised trials.	The pooled analysis reported no significant differences between routine and no shunting with respect to outcomes all stroke (odds ratio [OR] 0.42, 95% confidence interval [CI] 0.16 to 1.07, 3 studies, 655 participants), ipsilateral stroke (OR 0.42, 95% CI 0.17 to 1.08, 3 studies, 737 participants) and death up to 30 days after surgery (OR 0.45, 95% CI 0.13 to 1.59, 3 studies, 655 participants). Similarly, no significant difference was found between the groups in terms of the postoperative neurological deficit between selective shunting with and without near-infrared refractory spectroscopy monitoring. Also, no significant difference between the risk of ipsilateral stroke in participants selected for shunting with the combination of electroencephalographic and carotid pressure assessment compared with pressure assessment alone.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching the Cochrane Stroke Group Trials Register (last searched August 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2013, Issue 8), MEDLINE (1966 to August 2013), EMBASE (1980 to August 2013) and Index to Scientific and Technical Proceedings (1980 to August 2013). In addition, the authors handsearched journals and conference proceedings, checked reference lists and contacted experts in the field for relevant articles. The search strategy was reported in full and appeared adequate. No restrictions were reported based on date, publication format, or language. Three reviewers were independently involved in study selection and disagreements were resolved by discussion.** **Domain 3: Data Collection and Study Appraisal** **At least two reviewers were independently involved in the data extraction process and risk of bias assessment. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all the relevant studies. The method of analysis was explained and appeared appropriate. Low to high heterogeneity was present between studies. Subgroup analyses were performed to address the between-study heterogeneity. Sensitivity analysis was planned to check the robustness of the study results. The quality of the individual studies was considered in the synthesis.** **Overall summary** **All domains were considered at low concern.**
Bottom line: The current evidence is limited/insufficient to draw conclusions regarding the use of routine or selective shunting in carotid endarterectomy. Further, well-designed randomised controlled trials are needed to support these findings.		

KSRA61818 2018 Cui L, et al. Safety of Stenting and Endarterectomy for Asymptomatic Carotid Artery Stenosis: A Meta-Analysis of Randomised Controlled Trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 40 articles (5 RCTs) **Number of participants** 3901 **Last search date** 31 May 2017 **Review type** Intervention Objective To determine the safety of carotid artery stenting versus carotid endarterectomy for asymptomatic carotid stenosis with average risk. **Population** Adult patients (aged ≥ 18 years) with asymptomatic extracranial carotid stenosis. **Interventions** Carotid artery stenting (CAS). **Comparator** Carotid endarterectomy (CEA). **Outcome** Composite of ipsilateral stroke, any stroke, major stroke, minor stroke, myocardial infarction (MI) and death during the post-procedural period. **Study design** Randomised controlled trials (RCTs). Observational or retrospective studies were excluded.	The pooled analysis reported that the risk of any stroke during the peri-procedural period was significantly lower in patients who underwent carotid endarterectomy (CEA) than carotid artery stenting (CAS) (odds ratio [OR] 0.53, 95% confidence interval [CI] 0.29 to 0.96, 5 studies, 2915 participants). However, no significant differences were found between the CEA and CAS groups with respect to outcomes the risk of peri-procedural death (OR 1.49, 95% CI 0.26 to 8.68, 4 studies, 1734 participants), major stroke (OR 0.69, 95% CI 0.20 to 2.35, 4 studies, 2779 participants), minor stroke (OR 0.50, 95% CI 0.25 to 1.00, 4 studies, 2779 participants) ipsilateral stroke (OR 0.63, 95% CI 0.27 to 1.47, 4 studies, 1734 participants) and myocardial infarction (MI) (OR 1.75, 95% CI 0.84 to 3.65, 5 studies, 2915 participants). Most of the included trials reported that the mid- to long-term outcomes were similar between stenting and endarterectomy. The mid- to long-term follow-up duration ranged from 4 to 10 years. Further sensitivity analyses supported the above findings.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. Conference abstracts were excluded.** **Domain 2: Identification and Selection of Studies** **High** **Studies were identified by searching MEDLINE, Embase and Cochrane Library databases. In addition, the references of previous reviews and related original studies were searched to retrieve potential RCTs that were not included in the electronic search. Search terms were provided but a full search strategy was not reported. The search was restricted to English language studies.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and disagreements were resolved by discussion with the third reviewer. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Three reviewers evaluated the quality and applicability of each study using the Cochrane Collaboration's tool.** **Domain 4: Synthesis and Findings** **Low** **The synthesis appeared to have included all the relevant studies. The method of analysis was explained and appeared appropriate. A narrative synthesis was performed where meta-analysis was not possible. No significant heterogeneity was found between the studies in the pooled analysis. A pooled subgroup analysis of detailed information could not be conducted because of inadequacies in the reported data. Sensitivity analysis was performed to check the robustness of the study results. The quality of the individual studies was considered in the synthesis.** **Overall summary** **Conference abstracts were excluded. Search terms were provided but a full search strategy was not reported. The search was restricted to English language studies.**

Bottom line: The current evidence suggests that carotid artery stenting is associated with a higher rate of any peri-procedural stroke and peri-procedural minor stroke than carotid endarterectomy for asymptomatic carotid stenosis. However, no significant differences were found between the carotid artery stenting and carotid endarterectomy regarding the composite of peri-procedural death, periprocedural ipsilateral stroke, major stroke and myocardial infarction. The inclusion of only English language studies and exclusion of conference abstracts means some of the relevant studies may have been missed.

KSRA10772 2015 De Rango P, et al. Summary of Evidence on Early Carotid Intervention for Recently Symptomatic Stenosis Based on Meta-Analysis of Current Risks

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 47 studies (50 reports) **Number of participants** Unclear **Last search date** March 2015 **Review type** Intervention **Objective** To evaluate the evidence on the periprocedural (<30 days) risks of carotid intervention in relation to the timing of procedure in patients with recently symptomatic carotid stenosis. **Population** Patients with symptomatic carotid stenosis. Studies focused on intracranial and total occlusion were excluded. Interventions Carotid endarterectomy (CEA) and carotid stenting (CAS) (performed within zero to 48 hours, zero to seven days and zero to 15 days). Studies of early intervention after thrombolysis for acute stroke were included if CAS or CEA were performed within 15 days from symptom onset, and periprocedural risks within 30 days of intervention were detailed. Studies reporting results of carotid surgery or stenting for carotid dissection, non-atherosclerotic disease, and total carotid occlusion and studies reporting on acute stroke surgery or stenting for intracranial disease or tandem disease and urgent synchronous carotid and coronary interventions were excluded. **Comparator** NA. **Outcome** Risk of strokes and deaths and periprocedural (30 days) risks. Studies with unclear reporting of periprocedural events stratified by timing (within 15 days) were excluded if no clarification was obtained after personal contact with authors. **Study design** Case series. Review articles and case reports were excluded.	The pooled estimates from studies reported that risk of stroke was found to be 3.4% (95% CI 2.6 to 4.3; 40 studies) within 30 days of CEA performed ≤15 days from index event. Subgroup analysis based on index event reported that risk of perioperative stroke after CEA within zero to 15 days was 1.6% (95% CI 0.7 to 2.9; 14 studies) and 5.0% (95% CI 3.6 to 6.6; 24 studies) for the subgroup of patients with TIA as index and for the subgroup of patients with stroke as index event respectively. … The pooled risk of periprocedural (30 days) stroke and the stroke/death rate were found to be 3.9% (95% CI, 1.9 to 6.5; nine studies) and 3.86% (95% CI 1.89 to 6.511; nine studies) after carotid revascularisation procedures those performed within 15 days from symptom onset in patients with thrombolysis.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. Studies with <five cases were not considered in the eligibility criteria and this was found to be appropriate. Only English language studies were included. To focus on current data and avoid overlapping with previous systematic reviews published on this topic in 2009, the search was restricted to articles published (between August 2008 and March 2015).** **Domain 2: Identification and Selection of Studies** **MEDLINE and EMBASE databases were searched for relevant studies. The reference lists of identified articles were also searched to identify additional studies. The search terms were provided, but a full search strategy was not reported. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of authors involved in the data extraction and risk of bias assessment. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Cochrane risk of bias assessment tool, which is not appropriate for case series.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity among the studies. Residual heterogeneity existed even after performing the subgroup analysis. Robustness of the findings or publication bias was not assessed. The quality of individual studies was considered in the synthesis.** **Overall summary** **Only English language studies were included. The search terms were provided, but a full search strategy was not reported. No information was provided regarding the number of authors involved in the study selection, data extraction and risk of bias assessment. Residual heterogeneity existed even after performing the subgroup analysis. Robustness of the findings or publication bias was not assessed.**

Bottom line: The evidence suggests that the risk of perioperative stroke is <3.5% in those carotid endarterectomies (CEA) performed within 15 days from stroke/transient ischaemic attack. The risk of stroke is 4.8% within the same period with carotid stenting (CAS). Similar perioperative risks are observed after CEA and CAS performed earlier within zero to seven days. Caution should be taken while interpreting the findings due to significant heterogeneity among the studies. There were some limitations with the review methods such as a restriction to the English language, the lack of a full search strategy and no assessment of robustness or publication bias. It is unclear whether the study selection, data extraction and quality assessment were undertaken in duplicate, which means that possible reviewer-induced error and subsequent bias should not be eliminated.

KSRA26722 2017 Demirel S, et al. Systematic review and meta-analysis of postcarotid endarterectomy hypertension after eversion versus conventional carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 7 **Number of participants** 1,275 **Last search date** June 2016 **Review type** Intervention **Objective** To determine whether eversion-carotid endarterectomy is associated with post-carotid endarterectomy hypertension in the early postoperative period of surgery. **Population** Patients suffering from asymptomatic or symptomatic internal carotid artery stenosis requiring carotid endarterectomy (CEA) for stroke prevention. Patients with other diseases of the internal carotid artery such as aneurysms or vasculitis were excluded. **Interventions** Eversion carotid endarterectomy (E-CEA). Studies with sinus nerve-preserving E-CEA, or with the Chevalier technique of CEA were excluded. **Comparator** Conventional-CEA with or without patch plasty. **Outcome** Primary outcome: incidence of a postoperative need for vasodilator therapy. Secondary outcomes: intergroup mean difference of the mean within-group changes of postoperative (24 hours) to baseline systolic blood pressure, incidence of postoperative hypotension requiring vasopressor therapy, and major postoperative complications (myocardial infarction, stroke, neck haematoma, and death). **Study design** Prospective, retrospective comparative cohort studies and randomised controlled trials. Letters/comments/editorials were excluded.	The pooled analyses of seven studies reported the increased rates of post-carotid endarterectomy hypertension requiring vasodilator therapy with E-CEA compared to conventional carotid endarterectomy (C-CEA) (odds ratio [OR] 2.75, 95% CI 1.82 to 4.16). The pooled effect of five studies reported postoperative blood pressure was in favour of C-CEA when compared to E-CEA (mean difference 12.92 mmHg, 95% CI 8.06 to 17.78). The pooled analyses of three studies reported odds of hypotensive events were larger after C-CEA when compared to E-CEA (OR 11.37, 95% CI, 1.95 to 66.46). The pooled analyses reported no significant difference in terms of myocardial infarction (OR 1.57, 95% CI 0.44 to 5.72, four studies), stroke (OR 1.03, 95% CI 0.36 to 2.94, five studies), neck haematoma (OR 0.97, 95% CI 0.45 to 2.12, four studies) and death (OR 1.61, 95% CI 0.23 to 11.52, two studies) between E-CEA and C-CEA.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. The eligibility criteria were well described and appeared appropriate to address the present review question. No restriction was reported based on study characteristics. Meeting abstracts were excluded.** **Domain 2: Identification and Selection of Studies** **Only MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched for relevant studies. The reference lists of retrieved articles were handsearched for additional relevant studies. The search strategy was reported and appeared to be adequate. Searches were not restricted to the date, publication format or language. Two review authors were independently involved in the study selection and any disagreements were resolved by consensus.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process and any disagreements were resolved by consensus. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) assessment tool, but it was inappropriate as included one randomised controlled trial. Two reviewers independently assessed quality of the included studies and any disagreements were resolved by consensus.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared inappropriate due to pooling of different study designs (retrospective/prospective cohort and randomised controlled trial) into a single estimate. There was significant evidence of heterogeneity for secondary outcomes (postoperative BP). Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary** **Meeting abstracts were not considered. The search did not include EMBASE which for this topic means relevant trials are likely to have been missed. The tool used to assess the methodological quality of included studies was inappropriate for the one included randomised control trial. Pooling of different study designs (retrospective/prospective cohort and randomised controlled trial) into a single estimate was inappropriate. Appropriate attempts were not made to explore the possible sources of heterogeneity.**

Bottom line: The current evidence suggests that eversion carotid endarterectomy may be associated with an increase in the risk for post-carotid endarterectomy hypertension, whereas conventional carotid endarterectomy is associated with hypotension. Postoperative monitoring of blood pressure at least during the early postoperative days after carotid endarterectomy especially when eversion technique is used. The results must be interpreted cautiously due to the presence of heterogeneity. A restriction to the publication format and a limited database search means that some relevant studies may have been missed. The tool used to assess the methodological quality of included studies was inappropriate for the one included randomised control trial. Pooling of different study designs into a single estimate was inappropriate. Further randomised controlled trials are required to support the current findings.

KSRA59106 2018 Essat M, et al. Patient-Reported Outcome Measures in Carotid Artery Revascularization: Systematic Review and Psychometric Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 5 **Number of participants** 3095 **Last search date** February 2017 **Review type** Unclear **Objective** To identify patient-reported outcome measures that have been developed and/or validated in patients with carotid artery stenosis undergoing revascularization and to assess their psychometric properties and examine suitability for research and clinical use. Population Patients with a confirmed diagnosis of symptomatic and/ or asymptomatic carotid artery stenosis (CAS) (using ultrasonography, computed tomography, magnetic resonance imaging, or conventional angiography) who need, have had, or are undergoing revascularization. Patients not diagnosed with CAS were excluded. **Interventions** Any surgical treatment indicated for CAS that is, carotid endarterectomy, carotid artery stenting and angioplasty. Non-surgical interventions for CAS were excluded. **Comparator** NA **Outcome** Patient-reported outcome measures (PROMs) (including generic, disease-specific, preference-based, functional and symptoms i.e. 36-Item Short Form Health Survey, Euro-QoL-5-Dimension Scale, Hospital Anxiety and Depression Scale, Dizziness Handicap Inventory, quality of life [QoL] for carotid artery disease scale, and a disease-specific PROM for CAS) and psychometric properties. Outcome measures of patient satisfaction or experience in the relevant population PROMs from proxy were excluded. **Study design** Any study design. Reviews, editorial and opinion pieces were excluded. **Reference standard** NA **Exposure** NA **PP factor** NA	The narrative analysis of five studies reported six patient-reported outcome measures (PROMs) for carotid artery stenosis (CAS) i.e. 36-Item Short Form Health Survey (SF-36), Euro-QoL-5-Dimension Scale (EQ-5D), Hospital Anxiety and Depression Scale, Dizziness Handicap Inventory, quality of life [QoL] for carotid artery disease scale, and a disease-specific PROM. Evidence for acceptability for the use of SF-36 (2 studies), EQ-5D (1 study) and the disease-specific PROM (2 studies) was rated good in most studies. Only one study reported the evidence for internal consistency using SF-36 with a Cronbach's alpha score >0.70. None of the identified studies reported evidence on construct validity and test-retest reliability. Overall, the psychometric evaluation of all included PROMs was rated as poor within the CAS population undergoing revascularisation.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were applied to eligibility criteria based on study characteristics. Only English language studies published in peer-reviewed journals were included.** **Domain 2: Identification and Selection of Studies** **MEDLINE (Ovid), MEDLINE in Process, EMBASE, the Cochrane Library, CINAHL, PROQOLID, PsycINFO, and Web of Science were searched for relevant studies. Supplementary citation searching, hand-searching reference lists of included studies were also undertaken and contacted with experts in the field for additional relevant studies. The search strategy was reported in full and appeared adequate. Searches were not restricted to date, publication format or language. At least two review authors were involved in study selection and disagreements were resolved by discussion or by consulting the third review author.** **Domain 3: Data Collection and Study Appraisal** **One reviewer extracted data while a second reviewer checked it; any disagreements were resolved by discussion and when needed with the involvement of a third reviewer. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Two review authors were independently involved in the assessment of the methodological quality of included studies using the consensus-based standards for the selection of health measurement instruments and Oxford criteria, any disagreements between the two reviewers were resolved with discussion.** **Domain 4: Synthesis and Findings** **The synthesis included all of the relevant studies. A narrative synthesis was performed to summarise the findings due to the heterogeneity of the type of carotid artery stenosis, the stage of the disease and treatment pathway. The quality of individual studies was considered in the synthesis.** **Overall summary** **The author acknowledged possibly missing of studies due to the restriction of English language studies. Only peer-reviewed journals were included.**

Bottom line: The available review highlights a lack of evidence for valid, reliable, responsive and acceptable patient-reported outcome measures (PROMs) for patients undergoing carotid artery revascularisation. Therefore, the development and validation of a new PROM for this patient population is warranted to provide data which can supplement traditional clinical outcomes and capture changes in health status and quality of life to help inform treatment decisions. Restriction to English language studies published in peer-reviewed journals means some relevant data may have been missed.

KSRA26271 2017 Finn C, et al. The Association between Carotid Artery Atherosclerosis and Silent Brain Infarction: A Systematic Review and Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 16 **Number of participants** 18918 **Last search date** May 12, 2016 **Review type** Aetiological **Objective** To evaluate the relationship between silent brain infarction and carotid atherosclerotic disease, focusing on the 2 distinct entities of intima-media thickening and plaque-causing luminal stenosis. **Population** Carotid atherosclerosis (intima-media thickening and plaque-causing luminal stenosis) patients with and without silent brain infarction **Outcome** Risk of silent brain infarction. **Study design** Cross-sectional non-prospective, cross-sectional analysis of prospective cohort, prospective cohort studies, retrospective cohort studies and case control studies. **Exposure** Carotid atherosclerosis (intima-media thickening and plaque-causing luminal stenosis).	The pooled analyses of seven studies reported that the subjects with silent brain infarction (SBI) had a larger mean intima-media thickening (IMT) than subjects without SBI (Standardised mean difference [SMD] 0.37, 95% Confidence interval [CI] 0.23 to 0.51). Similarly, the pooled effect of eleven studies reported a significant positive relationship between carotid atherosclerosis and SBI (Odds ratio [OR] 2.78, 95% CI 2,19 to 3.52). The prevalence of SBI among subjects with carotid stenosis was higher (30.4%) than subjects lacking carotid atherosclerosis (17.4%). One study reported increased SBI ipsilateral to sites of carotid stenosis. Another study reported no difference in the prevalence of carotid stenosis contralateral and ipsilateral to SBI in a population of subjects with unilateral SBI. The higher prevalence of SBI in the vascular distribution of the stenotic artery was reported in the subjects with asymptomatic, unilateral internal carotid artery stenosis (one study).	**Domain 1: Study Eligibility Criteria: High** **The research objective was clearly stated. Inclusion criteria were not explicitly defined with regard to study design. No restrictions were reported based on study characteristics. Only English language studies were included.** **Domain 2: Identification and Selection of Studies: High** **Ovid MEDLINE, Ovid Embase, and the Cochrane Library were searched for relevant studies. The references and citing articles of each selected article using the "View References" and "Cited by" tools in Scopus were searched for additional studies. The search strategy was reported and appeared adequate. Searches were not restricted to date, publication format or language. A single researcher screened the titles and abstracts of all relevant articles (increased risk of errors). Two independent readers assessed whether the articles met inclusion and exclusion criteria and evaluated the full text of selected articles.** **Domain 3: Data Collection and Study Appraisal: Low** **Two review authors were independently involved in the data extraction and any discrepancies were resolved by consensus. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the appropriate criteria. Two reviewers assessed the quality of the included studies and any disagreements were resolved by consensus.** **Domain 4: Synthesis and Findings: High** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was a significant evidence of heterogeneity for the two main outcomes (association between IMT and SBI and association between Carotid Atherosclerosis and SBI). Residual heterogeneity existed even after performing the subgroup analyses. The quality of individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **Eligibility criteria were not explicitly defined with regard to study design. Restriction to the English language studies was reported in the inclusion. The author has acknowledged the presence of heterogeneity in the limitation section.**

Bottom line: Current evidence suggests that silent brain infarction is strongly associated with the two forms of carotid atherosclerosis, elevated intima-media thickening and luminal stenosis. The prevalence of silent brain infarction was higher among subjects with carotid stenosis compared to subjects lacking carotid atherosclerosis. The results must be interpreted cautiously due to the presence of heterogeneity. Eligibility criteria were not explicitly defined in terms of study design. Restriction to the English language studies means some relevant studies may have been missed. Further research is still needed to add power to these findings.

KSRA1674 2015 Fokkema M, et al. Stenting versus endarterectomy for restenosis following prior ipsilateral carotid endarterectomy: An individual patient data meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 13 **Number of participants** 1,132 **Last search date** July 2013 **Review type** Intervention **Objective** To compare outcomes after carotid artery stenting and carotid endarterectomy for restenosis after prior ipsilateral carotid endarterectomy in an individual patient data meta analysis. **Population** Patients who underwent carotid endarterectomy (CEA) or carotid artery stenting (CAS) for restenosis after prior ipsilateral CEA. **Interventions** Carotid artery stenting. **Comparator** Carotid endarterectomy. **Outcome** Primary endpoint: perioperative stroke or death. Secondary endpoint: restenosis greater than 50% during follow-up. Other procedural complications such as cranial nerve injury, neck haematoma, wound infection, bradycardia/ arrhythmia during the procedure, residual stenosis (>30%), technical failure, and access site complications were also examined. **Study design** NR.	No difference in perioperative stroke or death rate between carotid artery stenting and carotid endarterectomy was reported (n=1,132, odds ratio [OR] 0.8, 95% confidence interval [CI] 0.4 to 1.8), and the effect was not changed after propensity score adjustment, myocardial infarction, any stroke, and mortality adjustment. Perioperative stroke or death rate was not differed between symptomatic and asymptomatic patients. No statistically significant difference was observed between the CEA and CAS groups in patients treated for early restenosis (adjusted OR 0.3, 95% CI 0.04 to 1.8) and in patients with with late restenosis (adjusted OR 1.6, 95% CI 0.3 to 7.8). Restenosis greater than 50% occurred in 34 patients (8.5%), and greater than 70% occurred in 16 patients (4.0%) in the CAS group. These numbers were 23 (7.3%) and 24 (7.7%), respectively in the CEA group. Restenosis greater than 50% or 70% (including occlusions) was not significantly differed between CAS and CEA patients in the adjusted analysis and the 50% cutoff was not differed between symptomatic and asymptomatic patients in the adjusted analysis. Technical failure rate, residual stenosis, access site complications and bradycardia or arrhythmia during the procedure occurred in 1.3%, 0.3%, 1.9%, and in 1.4% of cases after CAS. Cranial nerve injury, bleeding and wound infections were observed in 5.5%, 2.7% and in 0.2% of subjects after CEA.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated, but the review methods did not prespecify the study design. Publications in English, Dutch, German, French, or Spanish in full text were included. Studies with less than five patients were excluded.** **Domain 2: Identification and Selection of Studies** **A search was performed in the databases PubMed and EMBASE. References of relevant articles were searched for additional studies. The search strategy was reported and appeared inadequate. The search strategy was not restricted to the date, publication type or any language. Two reviewers independently assessed the studies for inclusion.** **Domain 3: Data Collection and Study Appraisal** **No information was mentioned regarding the number of authors involved in the data extraction. Sufficient study characteristics have not been extracted to allow interpretation of the results. The study results were not appropriately collected for the synthesis. No information was reported on the methodological quality assessment of included studies.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant studies and was appropriate. Predefined analysis was explained in the methodology section. Individual patient data analysis was performed. Sufficient study characteristics were not given, so it was unclear whether the pooling was appropriate or not. A sensitivity analyses was performed for assessing robustness of the outcomes. Risk of bias was not addressed in the synthesis.** **Overall summary** **The eligibility criteria were not well described with respect to study design. Publications in English, Dutch, German, French, or Spanish in full text were included. The search strategy was reported and appeared inadequate. No information was mentioned regarding the number of authors involved in the data extraction. Sufficient study characteristics have not been extracted to allow interpretation of the results. The study results were not appropriately collected for the synthesis. No information was reported on the methodological quality assessment of included studies. Sufficient study characteristics were not given, so it was unclear whether the pooling was appropriate or not. Risk of bias was not addressed in the synthesis.**

Bottom line: The current evidence suggests that carotid artery stenting and carotid endarterectomy are equally effective for patients with an indication for the intervention for recurrent stenosis, but are associated with the risk of cranial nerve injury and other procedure-related complications. The eligibility criteria were not well described with respect to study design. A language restriction was imposed and the search strategy was inappropriate, which means that some eligible studies may have been missed. Individual study characteristics and results were not mentioned and the quality was not considered, so the findings should be interpreted with caution. It was unclear if two reviewers were independently involved in the data extraction stage, making it difficult to rule out reviewer error and bias.

KSRA39370 2017 Galyfos G, et al. Cerebral hyperperfusion syndrome and intracranial hemorrhage after carotid endarterectomy or carotid stenting: A meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 6 **Number of participants** Unclear (236537 procedures) **Last search date** February 2017 **Review type** Intervention **Objective** To compare cerebral hyperperfusion syndrome and intracranial haemorrhage risk between carotid endarterectomy and carotid angioplasty with stenting. **Population** Patients undergoing carotid revascularisation. **Interventions** Carotid endarterectomy (CEA). **Comparator** Carotid angioplasty with stenting (CAS). **Outcome** Primary outcomes: Cerebral hyperperfusion syndrome (CHS) and intracranial haemorrhage (ICH). Secondary outcomes: Stroke and death due to ICH. **Study design** Clinical studies (prospective, retrospective, randomised). Reviews, letters, meta-analyses, case reports/series (< 10 patients) or editorials were excluded.	The pooled analysis reported a higher risk of cerebral hyperperfusion syndrome (CHS) with carotid endarterectomy (CEA) (3.4%) compared to carotid angioplasty with stenting (CAS) (2.2%) (pooled odds ratio [OR] 1.432, 95% confidence interval [CI] 1.078 to 1.901, 5 studies). Four studies found no difference regarding intracranial haemorrhage (ICH) incidence between the two groups (OR 0.544, 95% CI 0.111 to 2.658). No significant difference was found between CEA and CAS regarding the incidence of stroke (OR 0.964, 95% CI 0.741 to 1.252, 4 studies, 253 patients). However, the death rate was significantly higher among patients with ICH (60/361) compared to patients without ICH (97/233,205) (OR 386.977, 95% CI 246.746 to 606.906, 4 studies). Stratified analysis according to the year of publication reported that CEA was found to be associated with a higher CHS risk (OR 1.79, 95% CI 1.088 to 2.957) compared to CAS in studies published prior to 2012 (10 to 5 years ago).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching Pubmed, Embase, Scopus and the Cochrane Library databases. In addition, reference lists of all included studies, meta-analyses and reviews were manually evaluated, including unpublished data. Search terms were provided but a full search strategy was not reported. Three authors were involved in study selection procedure and disagreements were resolved by discussion with the senior reviewer.** **Domain 3: Data Collection and Study Appraisal** **Three reviewers were independently involved in data extraction process and risk of bias assessment. Discrepancies were resolved by discussion. Relevant study results appear to have been extracted. The quality of each study was assessed using criteria for non-randomised studies, which may not be appropriate for the included randomised controlled trial. Only overall assessments of quality were reported, not the results for each item.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. Analyses pre-defined in the methodology section were performed appropriately. There seems to be some discrepancy between the values reported in the figure and full text. Significant heterogeneity was found between the studies. Publication bias was assessed using funnel plots and Egger's regression test and this appeared inappropriate given the less number of included studies. The quality of the individual studies was not considered in the analyses.** **Overall summary** **Search terms were provided but a full search strategy was not reported. The quality of each study was assessed using criteria for non-randomised studies, which may not be appropriate for the included randomised controlled trial. Significant heterogeneity was found between the studies. Publication bias was assessed using funnel plots and Egger's regression test and this appeared inappropriate given the low number of included studies. The quality of the individual studies was not considered in the analyses.**
Bottom line: This review suggests that carotid endarterectomy is associated with a higher risk for cerebral hyperperfusion syndrome compared to carotid angioplasty with stenting although this difference seems to be generated mainly from older studies. However, no difference is observed in case of intracranial haemorrhage risk between the two methods. The review had significant methodological weaknesses, so the findings should be interpreted with caution.		

KSRA75861 2018 Galyfos G, et al. Carotid endarterectomy versus carotid stenting or best medical treatment in asymptomatic patients with significant carotid stenosis: A meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 10 **Number of participants** 10,764 **Last search date** July 2017 **Review type** Intervention **Objective** To compare outcomes among asymptomatic patients with significant carotid stenosis undergoing carotid endarterectomy versus carotid stenting or best medical treatment. **Population** Patients with significant asymptomatic carotid stenosis. Patients with symptomatic carotid stenosis were excluded. **Interventions** Carotid endarterectomy. **Comparator** Carotid stenting or best medical treatment. **Outcome** Early outcomes: Rates of all stroke, death, myocardial infarction (MI), all stroke/death and all stroke/death/MI occurring during the first 30 postoperative days; Late outcomes: Rates of ipsilateral stroke, death due to stroke occurring during follow-up or after the first 30-day postoperative period. **Study design** Randomised trials. Non-randomised clinical studies, case reports/series (<10 patients), editorials, letters, reviews, meta-analyses or conferences were excluded.	The pooled analysis reported that carotid endarterectomy (CEA) had a significantly lower risk of 30-day all stroke compared to carotid stenting (CAS) in patients with significant asymptomatic carotid stenosis (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.312 to 0.989, 6 trials, n=3131). However, no significant differences were observed between CEA and CAS for other early and late outcomes. Moreover, CEA had a significantly higher risk of 30-day all stroke (OR 3.43, 95% CI 1.810 to 6.510, 4 trials, n=5483), death (OR 4.75, 95%CI 1.548 to 14.581, 4 trials, n=5515) and myocardial infarction (MI) (OR 9.18, 95% CI 1.668 to 50.524, 3 trials, n=5208) compared to best medical treatment (BMT). CEA had a significantly higher risk of 30-day all stroke/death (OR 3.94, 95% CI 2.278 to 6.809, 4 trials, n=5459) and all stroke/death/MI (OR 4.85, 95% CI 2.817 to 8.355, 3 trials, n=5132) compared to BMT. CEA had a significantly lower risk of long-term ipsilateral stroke risk compared to BMT (OR 0.46, 95% CI 0.361 to 0.596, 3 trials, n=4922), although no significant difference was found between CEA and BMT for long-term death due to stroke risk (OR 0.57, 95% CI 0.223 to 1.457, 2 trials, n=2083). None of the identified trials compared CAS to BMT.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. Restrictions on sample size fewer than 50 patients were reported. Only English language studies published in full-text were included.** **Domain 2: Identification and Selection of Studies:** **Pubmed, Embase, Scopus and Cochrane Library databases were searched for relevant studies. The reference lists of all included studies, meta-analyses, reviews, eligible articles or textbooks were manually searched for unpublished data. Search terms were provided and appeared very limited; a full search strategy was not reported. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal:** **Three review authors were independently involved in the data extraction process and risk of bias assessment and any disagreements were resolved by discussion or by consulting the third review author. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The criteria used to assess the methodological quality of the included studies were unclear, and their results were not reported in detail.** **Domain 4: Synthesis and Findings:** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate. There was evidence of heterogeneity. Appropriate attempts were not made to explore the possible sources of heterogeneity. No evidence of significant publication bias was found using Harbord-Egger tests for all analyses except for the long-term death due to stroke risk, but this was not appropriate as the number of included studies for each comparison was small (< 10). The quality of individual studies was considered in the synthesis.** **Overall summary. High risk of bias in the review** **There was restriction to English language studies and heterogeneity between the studies was present. Restrictions on sample size fewer than 50 patients were reported. Only full-texts were included. Search terms appeared limited and a full search strategy was not reported. No information was provided regarding the number of authors involved in the study selection process.**

Bottom line: Current evidence suggests that carotid endarterectomy (CEA) seems to be associated with a lower early all stroke risk compared to carotid stenting. Other early or late outcomes did not show any difference between the two methods in patients with significant asymptomatic carotid stenosis. Moreover, CEA appears to have a benefit over best medical treatment against long-term ipsilateral stroke, although early outcomes are worse after CEA. The review had significant methodological weaknesses, so the findings should be interpreted with caution.

KSRA9964 2015 Gargiulo G, et al. New cerebral lesions at magnetic resonance imaging after carotid artery stenting versus endarterectomy: An updated meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 20 **Number of participants** 2,104 **Last search date** March 2015 **Review type** Intervention **Objective** To provide updated evidence on the incidence of new brain lesions after carotid artery stenting compared with carotid endarterectomy as detected by diffusion-weighted magnetic resonance imaging. **Population** Patients who underwent either carotid artery stenting or carotid endarterectomy. **Interventions** Carotid artery stenting (CAS). **Comparator** Carotid endarterectomy (CEA). **Outcome** Primary outcome: the incidence of new brain lesions detected by diffusion-weighted magnetic resonance imaging after carotid endarterectomy (CEA) or carotid artery stenting (CAS). Secondary outcomes: stroke and stroke of transient ischaemic attack. Studies were included if the studies were reported on both the criteria such as presence of comparison between CAS versus CEA and presence of postoperative incidence of cerebral lesions detected by diffusion-weighted magnetic resonance imaging in both groups. Studies in which the outcome of interest was not clearly reported or could not be derived from the published results were excluded. **Study design** Randomised controlled trials, non-randomised studies. Duplicate publications were excluded. Exposure Carotid artery stenting or carotid endarterectomy	The pooled analysis of 20 studies reported that the incidence of new diffusion-weighted imaging (DWI) lesions significantly increased approximately five times with CAS compared with CEA (40.3% [399 of 989] versus 12.2% [136 of 1,115]; odds ratio [OR] 5.17, 95% confidence interval [CI] 3.31 to 8.06, n = 2,104 patients). Similarly, the subgroup analysis also reported a significant association within both randomised (OR 3.94, 95% CI 2.40 to 6.46, two studies, n = 381 patients) and non-randomised studies (OR 5.65, 95% CI 3.30 to 9.65, 18 studies, n = 1,723 patients); however, the difference was non-significant between these two subgroups. The summary estimates reported that CAS significantly increased the incidence of post-procedural stroke (OR 2.01, 95% CI 1.14 to 3.55, 17 studies, n = 1,833 patients) and stroke or transient ischaemic attack (TIA) (OR 2.40, 95% CI 1.42 to 4.08, 17 studies, n = 1,833 patients) when compared with CEA. No significant difference was found between CAS and CEA in the risk difference for stroke (risk difference [RD] 0.02, 95% CI 0.00 to 0.03, 17 studies, n = 1,833 patients) and a slight difference was found in the stroke or TIA (RD 0.03, 95% CI 0.01 to 0.04, 17 studies, n = 1,833 patients). Subgroup analysis based on the stent type used in CAS reported no significant difference between CAS and CEA in the incidence of stroke in the subgroup of closed cell stents (OR 1.82, 95% CI 0.60 to 5.55, seven studies, n = 626 patients) and both open and closed cell stents (OR 2.18, 95% CI 0.94 to 5.05, seven studies, n = 880 patients). Similarly, no significant difference was found in the incidence of stroke or TIA with closed cell stents (OR 1.69, 95% CI 0.59 to 4.78, seven studies, n = 626 patients) and open cell stents (OR 5.86, 95% CI 0.29 to 120.11, one study, n = 47 patients), whereas a higher incidence was found in both stents in the CAS (OR 2.70, 95% CI 1.22 to 6.00, seven studies, n = 880 patients).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate eligibility criteria were defined. Restrictions were reported based on study characteristics, but these appeared to be appropriate to the review question. No restrictions were imposed based on the sources of information.** **Domain 2: Identification and Selection of Studies** **Literature searches were conducted in MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases. The full texts and bibliography of all retrieved articles were also searched for additional studies. Only keywords were provided, full details of the search strategy were not reported. There were no restrictions imposed based on the language. Two reviewers were independently involved in the study selection process and discrepancies were resolved by consensus.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of authors involved in the data extraction process. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. However, details of the confounders adjusted were not provided. Relevant study results appear to have been extracted. There was no formal assessment of the methodological quality of included studies.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared inappropriate due to pooling of different study designs (non-randomised studies and randomised controlled trials) into a single estimate; however separate subgroup analyses according to study design were provided. There was significant evidence of heterogeneity for the outcome incidence of new brain lesions. However, meta-regression analysis was used to assess the impact of age, male sex, hypertension, diabetes, dyslipidemia, smoke, coronary artery disease, symptoms and year of publication on the incidence of new brain lesions, stroke and stroke or TIA. No significant evidence of publication bias was found using the funnel plots, Egger's test and trim and fill method. Sensitivity analysis was performed to test the robustness of findings. Biases in the individual studies were not taken into account for the synthesis of findings.** **Overall summary** **The search strategy was not reported. No information was provided regarding the number of authors involved in the data extraction process. The pooling of different study designs was inappropriate. The quality of individual studies was not considered in the synthesis. The authors have acknowledged the presence of heterogeneity and no adjustment of the baseline characteristics of patients undergoing CAS or CEA.**

Bottom line: The available evidence suggests that carotid artery stenting is significantly associated with an increased incidence of new brain lesions, stroke and stroke or transient ischaemic attack after surgery when compared to carotid endarterectomy. However, the results must be interpreted with caution due to the presence of heterogeneity. There were some limitations with the review methods such as limited database searches, lack of a search strategy, lack of information on the number of authors involved in the data extraction, no adjustment of confounders, inappropriate pooling and no assessment of the quality of individual studies.

KSRA2058 2015 Giannopoulos A, et al. Long-term Mortality in Patients with Asymptomatic Carotid Stenosis: Implications for Statin Therapy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 29 **Number of participants** 15463 **Last search date** October 2014 **Review type** Intervention **Objective** To determine (a) the long-term all-cause and cardiac-related mortality in patients with asymptomatic carotid stenosis greater than fifty percent. (b) whether there has been a decrease in mortality in recent years, (c) the available methods of mortality risk stratification, and (d) whether the latest ACC/AHA guidelines on the treatment of serum lipids can be applied to this group of patients. **Population** Patients with medically or surgically treated asymptomatic carotid stenosis > 50%. Patients with an asymptomatic carotid stenosis after treatment of a contralateral symptomatic side were excluded. **Interventions** Medical or surgical treatment. **Comparator** NA Outcome All-cause and cardiac-related mortality at 5 or 10 years. **Study design** Any clinical studies.	The weighted average cumulative all-cause mortality was 23.6% (17 studies, n=11391, 95% confidence interval [CI] 20.5% to 26.80%) at 5-years and cardiac mortality in studies with follow-up >2 years was 62.8% (12 studies, n=4072, 95% CI 58.8% to 66.9%). The weighted average cumulative all-cause mortalities were 52.4% (95% CI 50.65 to 54.08) and 25.8% (95% CI 24.35 to 27.36) at 10 and 5-year respectively in seven studies (n=3297) reporting both 5- and 10-year cumulative mortality. Diabetes, abnormal electrocardiogram results, and intermittent claudication, coronary bypass within 6 months, congestive heart failure, chronic obstructive pulmonary disease, creatinine >=2.0 mg/dL (>=176.8 mmol/L), contralateral carotid occlusion, and age >80 years are some of the risk factors associated with mortality.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restriction was reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **A search was performed in the databases PubMed, EuroPubMed, and the Cochrane Library. Reference lists of identified studies were searched for relevant articles. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. No restrictions based on date, publication format, or language were reported. Two reviewers independently performed the study selection and any disagreement was resolved by discussion.** **Domain 3: Data Collection and Study Appraisal** **No information was mentioned regarding the number of authors involved in data extraction. Insufficient study characteristics have been presented to allow interpretation of results. There was no formal methodological quality assessment of included studies.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant studies and was appropriate. Predefined analyses were explained in the methodology section. The methods used to pool data were appropriate. Heterogeneity was assessed and varied from low to high. Sources of heterogeneity were not explored. Robustness of outcomes was not assessed. Risk of bias was not addressed in the synthesis.** **Overall summary** **A limited range of databases was searched. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. No information was given regarding the number of authors involved in data extraction. Insufficient study characteristics were presented to allow interpretation of results. There was no formal methodological quality assessment of included studies. Sources of heterogeneity were not explored. Robustness of outcomes was not assessed. Risk of bias was not addressed in the synthesis.**

Bottom line: Current evidence indicates high all-cause and cardiac mortality in asymptomatic carotid stenosis patients. Aggressive statin therapy is indicated if the new ACC/AHA guidelines on serum lipids are to be adhered to. The literature searches were limited means that some eligible studies may have been missed. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. It was unclear if two reviewers were independently involved in data extraction stage, making it difficult to rule out reviewer error and bias. Robustness of outcomes was not assessed, quality was not considered and heterogeneity among the studies was not appropriately addressed, so the findings should be interpreted with caution. Future prospective cohort studies and randomised trials are required to address this review question.

KSRA20197 2016 Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 5 **Number of participants** 1287 **Last search date** December 23, 2014 **Review type** Intervention **Objective** To evaluate the effect of endovascular thrombectomy after large-vessel ischaemic stroke. **Population** Patients with anterior circulation ischaemic stroke. **Interventions** Endovascular neurothrombectomy treatment plus usual care. **Comparator** Usual care alone. **Outcome** Primary outcome: The degree of disability on the modified Rankin Scale at 90 days. Secondary outcomes: the proportion of patients with functional independence at 90 days, stroke severity as measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 h after stroke onset; the proportion of patients with NIHSS score 0-2 at 24 h; the proportion of patients with major early neurological recovery at 24 h, proportion of patients with symptomatic intracranial haemorrhage, neuroradiological parenchymal haematoma type 2. **Study design** Randomised trials.	The pooled data reported reduced chance of disability at 90 days in patients assigned to thrombectomy compared to those assigned to control (Adjusted common odds ratios [cOR] 2.49, 95% Confidence interval [CI] 1.76 to 3.53). The proportion of patients with an mRS score 0 to 2 at 90 days was higher in the endovascular thrombectomy population than in the control population. National Institutes of Health Stroke Scale score was significantly higher after 24 h and reported more improvement between baseline and 24 h after treatment in patients assigned to thrombectomy. No difference was reported in the mortality at 90 days and risk of parenchymal haematoma type 2 and symptomatic intracranial haemorrhage between the intervention group and control group. Subgroup analysis based on age reported patients older than 80 years assigned to thrombectomy had a slightly reduced risk of death compared to the control (adjusted rate ratio 0.60, 95% CI 0.36 to 0.99).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appropriate to address present review question. No restrictions were reported based on study characteristics. No restrictions were reported based on sources of information.** **Domain 2: Identification and Selection of Studies** **Medline and PubMed were searched for relevant studies. There were no additional attempts made to locate further studies. Search terms were provided, but a full search strategy was not reported. Searches were restricted to studies published between Jan 1, 2010, and Dec 23, 2015. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process. There were insufficient study details available to allow the reader to interpret the results. Relevant study results were extracted. There was no formal assessment of the methodological quality of included studies.** **Domain 4: Synthesis and Findings** **The synthesis included all eligible studies. The method of analysis was explained and appropriate. There was no evidence of significant heterogeneity. The quality of individual studies was not considered in the synthesis.** **Overall summary** **Limited databases were searched for relevant studies. No further efforts were made to perform searches additional to the database search. Search terms were provided, but a full search strategy was not reported. Information regarding the number of authors involved in the study selection process was not provided. Methodological quality of the included studies was not assessed.**

Bottom line: Evidence suggests that endovascular thrombectomy may benefit to most patients with the acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. The review had a number of methodological weaknesses.

KSRA101552 2013 Guay J, et al. Cerebral monitors versus regional anesthesia to detect cerebral ischemia in patients undergoing carotid endarterectomy: A meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 29 **Number of participants** Unclear Last search date May 2012 **Review type** Diagnostic **Objective** To compare the ability of different types of brain monitoring systems vs clinical monitoring of the brain function to detect cerebral ischemia during cross-clamping of the carotid artery under regional anaesthesia. **Population** Patients undergoing carotid endarterectomy performed under regional anaesthesia. **Interventions** Cerebral/brain monitoring systems include transcranial Doppler (TCD), electroencephalography (EEG), cerebral saturation (CS), evoked potentials (EP) and others. **Comparator** Clinical brain monitoring systems. **Outcome** Sensitivity, specificity, diagnostic odds ratio (DOR), area under the curve (AUC) and likelihood ratios. **Study design** Prospective trials **Reference standard** Not specified	The pooled sensitivity (Se) and specificity (Sp) were Se 0.70 (95% confidence interval [CI] 0.58 to 0.80) and Sp 0.96 (95% CI 0.94 to 0.97) for electroencephalography (EEG), Se 0.81 (95% CI 0.69 to 0.91) and Sp 0.92 (95% CI 0.89 to 0.94) for transcranial Doppler (TCD), Se 0.84 (95% CI 0.66 to 0.95) and Sp 0.78 (95% CI 0.69 to 0.86) for evoked potentials (EP), Se 0.74 (95% CI 0.54 to 0.89) and Sp 0.82 (95% CI 0.76 to 0.88) for cerebral saturation (CS) and Se 0.75 (95% CI 0.69 to 0.81) and Sp 0.88 (95% CI 0.86 to 0.89) for stump pressure, respectively. The pooled diagnostic odds ratios (DOR) for EEG, TCD, stump pressure, evoked potentials and cerebral saturation were DOR 65.3 (95% CI 20.5 to 207.7), DOR 58.1 (95% CI 23.0 to 146.3), DOR 27.8 (95% CI 13.4 to 57.9), DOR 17.2 (95% CI 2.4 to 123.9) and DOR 12.1 (95% CI 3.5 to 41.2), respectively. Sequential testing with stump pressure 25 mmHg followed by either TCD or EEG delivered the best post-test probabilities. For EEG, the DOR increases with the number of channels used (P = 0.03). The classical fail-safe numbers (i.e., number of negative studies required to render the DOR non-statistically significant) were 99 for TCD, 153 for EEG and 15 for cerebral saturation.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were not explicitly defined with regard to the reference standard. Only prospective trials with 20 patients or more were included. No restrictions based on sources of information have been reported.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching PubMed (from January 1950), Cochrane Central Register of Controlled Trials (April 2012), Cochrane Database of Systematic Reviews (2005 to April 2012), EMBASE (1988 to 2012 Week 18) and Ovid MEDLINE (1945 to May Week 1 2012). In addition, reference lists of included studies were searched for additional findings. Search terms and search strategy was reported, and appeared to be limited. The search was restricted to English language studies. No information was provided on the number of reviewers involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was assessed using the Cochrane Collaboration's tool for assessing the quality of diagnostic studies. No information was provided on the number of reviewers involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all the relevant studies. The method of analysis was explained and appeared appropriate. No significant (high) heterogeneity was found between the studies in the pooled analysis. Also, a meta-regression analysis was performed. The summary receiver operating characteristics (SROC) curve was constructed. The quality of the individual studies was considered in the synthesis.** **Overall summary** **The authors acknowledged English language restrictions in the limitations. Eligibility criteria were not explicitly defined with regard to the reference standard. Only prospective trials with 20 patients or more were included. No information was provided on the number of reviewers involved in the study selection process and risk of bias assessment.**
Bottom line: The current evidence suggests that a combination of stump pressure and either transcranial Doppler or electroencephalography appears to give the best results. However, no single monitor can reproduce the detection of brain ischemia achievable with regional anaesthesia. The inclusion of only English language studies, and only prospective trials with 20 patients or more means some of the relevant studies may have been missed. Further, well-designed randomised controlled trials are needed before any firm conclusion of these findings.		

KSRA20249 2016 Guirguis-Blake JM, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** 118445 **Last search date** January 2015 **Review type** Intervention **Objective** To update a systematic review about the benefits of aspirin for the primary prevention of cardiovascular events in adults aged 40 years or older and to evaluate effect modification in subpopulations. **Population** Adults (aged 40 years or older). **Interventions** Oral aspirin (a minimum of 75 mg every other day for 1 year or more). Studies on interventions that included nonaspirin antithrombotic medications or aspirin as cotreatment with another active intervention were excluded. **Comparator** Placebo or no treatment. **Outcome** Primary outcomes: Non-fatal myocardial infarction (MI); non-fatal stroke (all types); cardiovascular disease (CVD) mortality defined as a composite of death due to MI, stroke, and CVD; and all-cause mortality. **Study design** Randomised controlled trials (RCTs) and controlled clinical trials.	In pooled analyses of all doses, aspirin significantly reduced the risk for nonfatal myocardial infarction (MI) (relative risk [RR] 0.78, 95% confidence interval [CI] 0.71 to 0.87, 10 trials) compared to control, while no significant difference was found between aspirin and control groups in terms of nonfatal stroke (RR 0.95, 95% CI 0.85 to 1.06, 10 trials), all-cause mortality (RR 0.94, 95% CI 0.89 to 0.99, 11 trials) or composite cardiovascular mortality (RR 0.94, 95% CI 0.86 to 1.03, 11 trials). In trials with aspirin doses of 100 mg or less per day, the reduction in nonfatal MI benefit persisted (RR 0.83, 95% CI 0.74 to 0.94, 8 trials) and a 14% reduction in nonfatal stroke benefit was noted (RR 0.86, 95% CI 0.76 to 0.98, 7 trials), but no benefit was found for all-cause mortality (RR 0.95, 95% CI 0.89 to 1.01, 8 trials) or cardiovascular mortality (RR 0.97, 95% CI 0.85 to 1.10, 8 trials). Nine trials reported time-to-event data for various outcomes and that any cardiovascular disease (CVD) benefits began within the first 5 years. Older adults achieved greater relative MI reduction (3 trials), but not age-specific stroke events. There were conflicting findings for composite cardiovascular outcomes (6 trials). For total MI, one trial reported a beneficial effect in men, but not women, in unadjusted analyses (RR for men: 0.58, 95% CI 0.41 to 0.81; RR for women 0.81, 95% CI 0.49 to 1.31). In adjusted analysis, one study reported a trend toward reduction of total MI in men and harm in women, while, the Early Treatment Diabetic Retinopathy study reported a greater although a not significant reduction in total MI in men but not women. Risk reductions of stroke were greater but not significant in women in 2 of 3 trials. Seven trials reported no statistical difference in aspirin's effect on total MI by diabetes status, while 3 trials reported no statistically significant stroke difference. Across the range of baseline event rates, for each 1000 person-years of low-dose aspirin use, absolute benefits were modest for nonfatal MIs and nonfatal strokes prevented (0.15 to 1.43 person-years, 8 trials and 0.17 to 0.68 person-years, 7 trials, respectively); for all risk levels (low, medium and high-risk levels), these nonfatal events were prevented. Aspirin did not clearly prevent all-cause mortality (8 trials) or CVD death (8 trials) for any risk level.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies:** **MEDLINE, PubMed, Cochrane Central Register of Controlled Trials were searched for relevant studies. Embase was not searched. Reference lists from systematic reviews were also searched to identify additional studies. A full search strategy was reported in citation 18. Searches were limited to studies in English and published from January 2008 to January 2015, these restrictions were considered inappropriate. Two authors were independently involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal:** **One reviewer extracted data and a second checked data accuracy. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using appropriate criteria. Two authors were independently involved in the assessment of the risk of bias. Disagreements were resolved by a third author.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared appropriate. There was evidence of heterogeneity for one outcome (nonfatal MI). However, it was reduced after performing a subgroup analysis. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary:** **The search did not include Embase. Searches were limited to studies published in English from January 2008 to January 2015.**

Bottom line: Evidence suggests that aspirin does provide a modest benefit in reducing nonfatal myocardial infarction (MI) at doses of 100 mg or less per day without any effect on nonfatal stroke events, cardiovascular disease mortality or all-cause mortality. Older adults seem to achieve a greater relative MI benefit. There were some limitations with the review methods such as the limited database search, and restriction to studies reported in English and published between from January 2008 to January 2015.

KSRA2193 2015 Gupta A, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 8 **Number of participants** 7934 **Last search date** March 2014 **Review type** Prognostic/Predictive **Objective** To evaluate the association between carotid plaque echolucency and future stroke in asymptomatic patients. **Population** Asymptomatic patients without histories of prior ipsilateral stroke or transient ischemic attack at the time of imaging. **Outcome** The risk of future ipsilateral stroke. **Study design** Prospective, longitudinal non-randomised observational studies. Exposure Carotid artery plaque echolucency **PP factor** Carotid plaque echolucency.	The pooled analysis of five studies demonstrated a significant positive relationship between ultrasound-determined plaque echolucency and future ipsilateral stroke in patients with ≥50% stenosis (relative risk [RR] 2.61 , 95% confidence interval [CI] 1.47 to 4.63).Similarly, pooled effect of seven studies reported a positive significant association between ultrasound-determined plaque echolucency and the risk of future ipsilateral stroke (RR = 2.31, 95% CI 1.58 to 3.39).	**Domain 1: Study Eligibility Criteria.** **A clear research objective was reported and appropriate inclusion criteria were defined. Restriction with sample size of ≥30 participants was imposed, which was found to be appropriate. Only studies published in English language were included.** **Domain 2: Identification and Selection of Studies:** **Ovid MEDLINE, Ovid Embase, the Cochrane Library, and Clinicaltrials.gov were searched to retrieve all relevant studies. Additional records were identified by employing the Related Citations feature in PubMed and the Cited Reference Search in Web of Science. The search strategy was reported in full and appeared adequate. No restrictions based on date, publication format, or language were reported. Single review authors screened the title and abstract and full text were assessed by two review authors for inclusion and any disagreements were resolved by consulting third review author.** **Domain 3: Data Collection and Study Appraisal:** **Two review authors involved in the data extraction process and disagreements in data extraction were resolved by consulting third review author. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Study results were appropriately collected for the synthesis. The methodological quality of the included studies was assessed by using appropriate criteria.** **Domain 4: Synthesis and Findings:** **The synthesis included all eligible studies. Method of analysis was explained and appeared appropriate. Heterogeneity was assessed and found to be non significant. Subgroup analyses were performed to address heterogeneity. Sensitivity analyses were performed to test the robustness of findings. Publication bias was assessed by using Begg's test. Quality of the individual studies was considered in the synthesis of findings.** **Overall summary: High risk of bias in the review** **Restriction to English language was applied. Only one review author was involved in the title and abstract screening, so reviewer error and bias could not be ruled out.**

Bottom line: The current evidence indicates a positive relationship between ultrasound-determined carotid plaque echolucency and future ipsilateral stroke in patients with extracranial carotid stenosis. Restriction to English language, and involvement of single reviewer in study selection process means that some relevant studies may have been missed. Further well-designed studies on risk from plaque echolucency are needed to address the present review question.

KSRA20493 2016 Hackam DG Prognosis of Asymptomatic Carotid Artery Occlusion: Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 13 **Number of participants** 718 **Last search date** NR **Review type** Prognostic/Predictive **Objective raman** To explore the risk of ipsilateral stroke in patients with asymptomatic carotid artery occlusion. **Population** Patients with asymptomatic carotid artery occlusion. **Outcome** Primary outcome: Risk of ipsilateral ischemic stroke. **Study design** Prospective and retrospective observational studies **Reference standard** NA **PP factor** Asymptomatic carotid artery occlusion. Studies enrolling patients who underwent carotid revascularization were excluded as revascularization may alter the natural history of carotid occlusion.	The annual ipsilateral stroke rate, two and 5-year rates of stroke were 1.3% (95% CI 0.4 to 2.1%; 13 studies), 2.5% and 6.3% respectively. The annual total stroke and the annual rate of ipsilateral transient ischemic attack (TIA) were reported to be 2.0% (95% CI 0.9 to 3.0%; 12 studies) and 1.0% (95% CI 0.3 to 1.8%; 11 studies) respectively. Annual total TIA and the annual rate of death was 3.0% (95% CI 1.9 to 4.1; 9 studies) and 7.7% (95% CI 4.3 to 11.2; 7 studies) respectively. The annual rate of stroke-related death and cardiac death were found to be 1.1% (95% CI 0.07 to 2.1; 6 studies) and 3.3% per year (95% CI 1.2 to 5.4; 6 studies) respectively.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were imposed based on study characteristics. Only English language studies published as full-text were included.** **Domain 2: Identification and Selection of Studies:** **OVID MEDLINE (from 1946) and EMBASE (from 1947) databases included MEDLINE, OLDMEDLINE, MEDLINE In-Process & Other Non-indexed Citations, MEDLINE Daily, EMBASE Classic was searched for relevant studies. The reference lists of relevant studies were reviewed (snowballing) to obtain additional eligible studies. Limited search terms were provided, but a full search strategy was not reported. There was no information as to whether searches were restricted by publication date, format or language. No information was provided regarding the number of authors involved in the study selection process (but the paper has only one author).** **Domain 3: Data Collection and Study Appraisal:** **No information was provided regarding the number of authors involved in the data extraction and risk of bias assessment. There were insufficient study details available to allow the reader to interpret the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was a substantial heterogeneity for most of the measures. Meta-regression analyses were used to assess the impact of variables such as sample size, publication year, study design (prospective versus retrospective), mean age, sex female, (%), mean length of follow-up, and Newcastle Ottawa scale on outcomes. Subgroup analysis based on studies published on or after the year 2000 to examine the rate of ipsilateral stroke. Evidence of significant publication bias was found using funnel plot and it was adjusted using Duval and Tweedie trim-and-fill analysis. The quality of individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **Only English language studies published as full-text were included. Limited search terms were provided, but a full search strategy was not reported. There was no information as to whether searches were restricted by publication format or language. No information was provided regarding the number of authors involved in the study selection, data extraction and risk of bias assessment (but the paper has only one author). There were insufficient study details available to allow the reader to interpret the results.**

Bottom line: The evidence suggests that risk of stroke is rare but mortality rates are high in patients with asymptomatic carotid artery occlusion. Hence, the intensive medical therapy could be recommended for patients with asymptomatic carotid artery occlusion. There were some limitations with the review methods such as restriction to the English language studies published as full-text, the lack of full search strategy, no information on limitation in the literature search regarding the publication year, status or language and insufficient study details. It is unclear whether study selection, data extraction and quality assessment were undertaken in duplicate meaning that possible reviewer-induced error and subsequent bias should not be eliminated.

KSRA101545 2014 Hadar N, et al. Asymptomatic carotid artery stenosis treated with medical therapy alone: temporal trends and implications for risk assessment and the design of future studies

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 41 **Number of participants** 16,178 **Last search date** 31 December 2012 **Review type** Epidemiological study **Objective** To investigate temporal changes in the incidence rate of clinical outcomes among patients with asymptomatic carotid stenosis receiving medical therapy alone. **Population** Adults (≥18 years) with asymptomatic carotid stenosis receiving medical therapy alone (use of antiplatelets, anticoagulants, antihypertensives, lipid-lowering drugs, control of diabetes, and lifestyle modification [e.g., smoking cessation, exercise, and dietary changes]) (50-99% atherosclerotic narrowing of the carotid bifurcation lumen or extracranial part of the internal carotid artery) without ipsilateral carotid territory symptoms in the previous 6 months Studies that compared different types of medical treatments and studies that utilized comparisons of interventions with historical controls were excluded **Interventions** NA **Comparator** NA **Outcome** Incidence of ipsilateral stroke, any stroke, cardiovascular death, death, and myocardial infarction **Study design** Prospective cohort studies and single arm of randomised controlled trials Retrospective medical cohort studies were excluded **Reference standard** NA **Exposure** NA **PP factor** NA	The pooled analysis reported that the incidence rates of ipsilateral carotid territory stroke (25 studies), any territory stroke (17 studies), cardiovascular death (6 studies), death (13 studies) and myocardial infarction (5 studies) were 1.7, 2.7, 4.1, 4.6, and 1.8 per 100 person-years, respectively for patients with asymptomatic carotid stenosis treated with medical therapy alone. Moreover, the summary incidence rate of ipsilateral stroke was significantly lower in recent studies (last recruitment year between 2000 and 2010) when compared with the studies completing recruitment earlier (1.0 versus 2.3 events per 100 person-years). Subgroup analysis by degree of stenosis showed that the incidence rate of ipsilateral stroke did not differ significantly between populations with more than 70% carotid stenosis and those with 50-70% stenosis.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. Restrictions on sample size fewer than 30 patients were reported and found to be appropriate. No restriction was reported based on sources of information.** **Domain 2: Identification and Selection of Studies:** **MEDLINE, the Cochrane Central Register of Controlled Trials and US Food and Drug Administration documents were searched for relevant studies. In addition, bibliographies and the reference lists of retrieved articles were searched for additional relevant studies and contacted the corresponding authors of eligible studies for unpublished data. The search strategy was reported in full and did not include any terms for medical therapies. Searches were restricted to the English language publications. One review author was involved in the screening process while a second reviewer checked it; any disagreements were resolved by consulting the third review author.** **Domain 3: Data Collection and Study Appraisal:** **One reviewer extracted data while a second reviewer checked it. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Appropriate criteria were used to assess the methodological quality of the included studies. Two reviewers assessed the risk of bias and any and discrepancies were resolved by consensus involving a third reviewer.** **Domain 4: Synthesis and Findings:** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate. There was evidence of heterogeneity. Subgroup analysis and meta-regression analysis were performed to address the heterogeneity between the studies. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **The author acknowledged the presence of significant heterogeneity between the studies. Only MEDLINE, the Cochrane Central Register of Controlled Trials and US Food and Drug Administration documents were searched for relevant studies. Searches were restricted to the English language publications. The search strategy did not include any terms for medical therapies.**

Bottom line: The available evidence suggests that the prognosis of patients with asymptomatic carotid stenosis receiving medical treatment alone seems to be improved over time, with the rates of ipsilateral stroke are significantly lower in recent studies. Searches restricted to the English language publications and limited databases searched, and inadequate search strategies means some relevant data may have been missed. Future comparative studies will need to enroll large numbers of patients to assess treatment effectiveness.

KSRA93423 2007 Holt PJ, et al. Meta-analysis and systematic review of the relationship between hospital volume and outcome following carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 25 **Number of participants** 936436 **Last search date** Not reported **Review type** Prognostic/Predictive **Objective** To assess the relationship between annual hospital volume and the outcomes in carotid endarterectomy and to define a critical volume threshold for the procedure. **Population** Patients undergoing carotid endarterectomy. **Outcome** Post-operative mortality, post-operative stroke rates. **Study design** Not reported **Reference standard** N/A **PP factor** Annual hospital volume of carotid endarterectomy.	Mean death rate in included studies was 1.6% (ranging from 0.3% to 5.2%) while the mean disabling stroke rate was 2.7% (range 0.23% to 6.1%). For post-operative death, the odds ratio (OR) was 0.77 (95% confidence interval (CI) 0.74 to 0.81, 15 studies) in favour of higher volume hospitals with a critical volume threshold of 81 cases per year per hospital. The results for post-operative stroke (OR 0.84, 95% CI 0.79 to 0.88, critical volume threshold of 72, n=9) and post-operative death and stroke combined (OR 0.73, 95% CI 0.68 to 0.78, critical volume threshold of 84, n=9) are also statistically significant. Four identified studies could not be included in the meta-analyses. Two of these found significant improvements in outcomes with volumes while the other two studies did not (no further details reported).	**Domain 1: Study Eligibility Criteria** **Limited details on the inclusion and exclusion criteria have been reported, however, these appear appropriate and it seems as if the review adhered to these.** **Domain 2: Identification and Selection of Studies** **Searches were conducted in PubMed, EMBASE and the Cochrane Library, search dates not reported. Included references were checked for further relevant references but no additional attempts on identifying further studies were made. The search strategy does not include MeSH terms and is likely to have missed potentially relevant references. It is unclear how many reviewers were involved in selecting the studies. However, as only one reviewer appears to have been involved in data extraction, it can be assumed that screening was conducted by a single researcher.** **Domain 3: Data Collection and Study Appraisal** **Data were extracted by only one reviewer. Insufficient details are reported for the included studies. The review mentions that some quality assessment was done. However, no further details, e.g. on the tool or the number of assessors, are given.** **Domain 4: Synthesis and Findings** **Results of the studies included in meta-analyses appear relatively similar. While the review authors appear to have investigated heterogeneity and clinical factors, results are not reported. Sensitivity analyses were conducted and funnel plots were used to test for publication bias.** **Overall summary** **The search methods appear insufficient, relevant studies might have been missed. Details reported for the key stages of the systematic review process, e.g. inclusion screening, data extraction and risk of bias assessment, indicate some limitations.**

Bottom line: The systematic review found statistically significant evidence in favour of higher volume hospitals (threshold approx. 70-80 cases per year and hospital) regarding post-operative death and stroke when treating patients following carotid endarterectomy. However, given some shortcomings in the review process, e.g. regarding searches and data extraction, relevant information might have been missed. Furthermore, the quality of included studies was not considered, i.e. it is unclear how trustworthy these findings are. Subsequent systematic reviews should follow state-of-the-art methods to confirm or reject these findings.

KSRA20704 2016 Howard G, et al. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: A meta-analysis of pooled patient data from four randomised trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 4 **Number of participants** 4754 **Last search date** NR **Review type** Prognostic/Predictive **Objective** To describe the differential treatment effect by providing age-specific estimates of the risk of stroke and death within narrow (5-year) age groups for patients treated with carotid artery stenting and carotid endarterectomy and the compare the carotid artery stenting and carotid endarterectomy treatment difference. **Population** Patients with symptomatic stenosis treated with carotid artery stenting and carotid endarterectomy. **Outcome** Primary outcome: Any of stroke or death during the periprocedural period (defined for this study as time of randomisation to 120 days after randomisation) and ipsilateral stroke events during the postprocedural period (after 120 days). **Study design** Data from 4 randomised controlled trials. **Reference standard** NA **PP factor** Age group (<60 years, 60 to 64 years, 65 to 69 years, 70 to 74 years, 75 to 79 years, and ≥80 years).	For patients assigned to carotid artery stenting (CAS), the periprocedural hazard ratio of stroke and death in patients aged 65 to 69 years was found to be 2·16 (95% confidence interval [CI] 1·13 to 4·13; n = 462 patients) compared with patients younger than 60 years. The HRs was 4·01 (95% CI 2·19 to 7·32; n = 480 patients) for patients aged 70 years or older. However, the increased risk of stroke or death was not observed by age group in patients assigned to carotid endarterectomy (CEA) group. The increased risk for stroke or death was not significant in patients assigned to CAS relative to those assigned to CEA, the hazard ratio (HR) of stroke or death was 0·62 (95% CI 0·31 to 1·23; n = 814 patients), 1·07, (95% CI 0·56 to 2·01; n = 692 patients), and 1·61 (95% CI 0·90 to 2·88; n = 884 patients) for patients younger than 60 years, 60 to 64 years and 65 to 69 years respectively. But, at age 70 years or older, the risk of stroke or death was significantly high among all age groups in patients with CAS than for those treated with CEA. 4289 patients were followed for a median of 2·7 years (2·0 to 4·5) after the periprocedural period and 98 patients (2·3% out of 4289) had a stroke during this postprocedural period. No evidence showed that the postprocedural risk for ipsilateral stroke differed across the age range of patients assigned to either CEA or CAS. The HRs for patients treated with CEA was not reduced for age groups younger than 80 years compared with the reference age group of those younger than 60 years (HRs ranging from 0·55 to 0·94), and postprocedural risk for ipsilateral stroke was not significantly higher for those aged 80 years and older (HR 1·44, 95% CI 0·59 to 3·46; n = 270 patients). The risk of stroke and death was not increased compared with the youngest age group (HRs between 1·01 and 2·05), for patients of any age treated with CAS. Similarly, there was no evidence reported the treatment effect of CAS and CEA differed across the age range during the postprocedural period with CAS-versus-CEA HRs ranged from 0·60 to 2·06.	**Domain 1: Study Eligibility Criteria** **NA, Meta-analysis only** **Not applicable. This article describes the results of a meta-analysis of 4 randomised trials but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 2: Identification and Selection of Studies** **NA, Meta-analysis only** **Not applicable. This article describes the results of a meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 3: Data Collection and Study Appraisal** **NA, Meta-analysis only** **Not applicable. This article describes the results of a meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 4: Synthesis and Findings** **All included studies were randomised, placebo-controlled trials, measuring the risk of stroke and death. This article describes the results where individual participants in all studies were combined, i.e. the 4 studies. Estimated risk of stroke and death rates were presented for different age groups (within narrow 5-year) for patients treated with carotid artery stenting and carotid endarterectomy and reported the treatment differences of carotid artery stenting and carotid endarterectomy. The methodological quality of the primary studies was not considered.** **Overall summary** **High risk of bias in the review**

Bottom line: The evidence suggests that carotid endarterectomy is superior to that of carotid artery stenting in reducing the risk of periprocedural stroke in patients aged 70 to 74 years and older. The increased risk in carotid artery stenting patients but not carotid endarterectomy patients supports a nearly monotonic increase in the carotid artery stenting patients-versus carotid endarterectomy risk with increased age. The effect of age on carotid endarterectomy periprocedural risk or on postprocedural risk seems to be low after either procedure. This was an individual patient data meta-analysis of 4 studies. Data from other studies were not included. Bias in primary studies was not addressed while interpreting findings.

KSRA10329 2015 Jaffer U, et al. Pre-operative methods to predict need for shunting during carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 20 **Number of participants** Unclear **Last search date** 2015 **Review type** Prognostic/Predictive **Objective** To determine whether preoperative investigations are able to predict cerebral tolerance to carotid cross-clamping during carotid endarterectomy (CEA). **Population** Not specified - patients undergoing carotid endarterectomy may have been included. **Outcome** Not specified - cerebral tolerance to carotid cross-clamping, sensitivity, specificity, positive predictive value and negative predictive value of preoperative investigations. **Study design** Not specified - observational studies, prospective and retrospective studies may have been included. **Reference standard** NR. PP factor Preoperative investigations such as angiogram with electroencephalogram monitoring, magnetic resonance angiography, etc.	One study (n = 30 patients) reported that 16 patients required shunting predicted by preoperative angiograms of all patients. A sensitivity of 74%, specificity of 57% and positive predictive value (PPV) of 79% were found in another study (n = 67 patients) with angiograms of all patients who underwent carotid endarterectomy (CEA) under general anaesthesia (GA) with intraoperative electroencephalogram (EEG) monitoring. Out of 87 patients on angiography with somatosensory evoked potential, 51 patients with adequate cross-filling were not shunted and only nine patients without cross-filling from the contralateral internal carotid artery required shunting, while the sensitivity, specificity, PPV and negative predictive values of this procedure were 100%, 65%, 25% and 100%. The probability of need for a shunt was 60% when the assessment of relative perfusion was compared to the contralateral vessel during hypercapnia or carotid compression testing (one study, n = 178 patients). An asymmetry in peak systolic and mean velocities of the MCA were significantly higher in patients requiring shunts in one study, while the cerebrovascular reactivity was significantly higher in patients without shunts than in patients with shunts (one study).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. However, the eligibility criteria were not predefined in terms of participants, study design and outcomes. No restrictions were imposed based on the sources of information.** **Domain 2: Identification and Selection of Studies** **MEDLINE database was searched for relevant studies. Manual cross-referencing of the retrieved studies was done to identify additional studies. The search terms and search strategy were reported and appeared to be limited. Studies published (from 1950 to 2015) were searched. One reviewer was involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding the number of authors involved in the data extraction process. Sufficient study characteristics do not appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. There was no formal assessment of the methodological quality of included studies.** **Domain 4: Synthesis and Findings** **A narrative synthesis was performed to summarise the findings. Biases in the individual studies were not taken into account for the synthesis of findings.** **Overall summary** **The eligibility criteria were not predefined in terms of participants, study design and outcomes. Only MEDLINE database was searched for the study selection purpose and a limited search strategy means that some relevant studies may have been missed. Only one author was involved in the study selection and the authors did not state whether the data extraction was undertaken in duplicate, so reviewer error and bias could not be ruled out. Study characteristics were not reported for included studies. The number of studies included in the synthesis was unclear. The quality of individual studies was not considered in the synthesis.**

Bottom line: The available evidence suggests that preoperative imaging investigations are able to predict the need for shunting or cerebral tolerance to carotid cross-clamping during carotid endarterectomy. The review had significant methodological weaknesses in all the domains, so the findings should be interpreted with caution. Because of the limited available evidence, more studies are needed to support the review findings.

KSRA101547 2014 Jonas DE, et al. Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the U.S. Preventive Services Task Force

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 56 **Number of participants** Unclear **Last search date** 31 March 2014 **Review type** Intervention **Objective** To evaluate whether screening asymptomatic adults for carotid artery stenosis reduces the risk for ipsilateral stroke and on harms associated with screening and interventions for carotid artery stenosis. **Population** Asymptomatic adults with carotid artery stenosis. **Interventions** Carotid endarterectomy. **Comparator** Medical therapy. **Outcome** Ipsilateral Stroke, perioperative stroke/death or subsequent ipsilateral stroke, all-cause mortality. **Study design** Randomised controlled trials and cohort studies.	No trials compared screening with no screening or stenting with medical therapy or assessed intensification of medical therapy, and no externally validated, reliable risk-stratification tools were found. The pooled analyses reported perioperative stroke/death or any ipsilateral stroke (Risk difference [RD] -0.02, 95% Confidence interval [CI] -0.03 to -0.01, 3 studies), perioperative stroke/death or any stroke (RD -0.03, 95% CI -0.05 to -0.02, 3 studies), any stroke or death (RD -0.03, 95% CI -0.05 to -0.00, 3 studies), Ipsilateral stroke (nonperioperative) (RD -0.04, 95% CI -0.05 to -0.03, 3 studies), any nonperioperative stroke (RD -0.05, 95% CI -0.07 to -0.04, 3 studies) was in favor of the carotid endarterectomy (CEA) compared to the medical therapy. The pooled analyses reported no significant difference in the all-cause mortality between CEA and medical therapy (RD 0.01, 95% CI -0.02 to 0.03, 3 studies). The pooled analyses reported more participants had perioperative (30-day) stroke or death with CEA compared to the medical therapy (RD 1.9%, 95% CI 1.2% to 2.6%). The 30-day rates of stroke or death after CEA in trials and cohort studies were 2.4% (CI, 1.7% to 3.1%; 6 trials; 3435 participants) and 3.3% (CI, 2.7% to 3.9%; 7 studies; 17 474 participants), respectively.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were reported based on study characteristics. No restrictions were reported based on sources of information.** **Domain 2: Identification and Selection of Studies:** **MEDLINE, the Cochrane Library, and EMBASE were searched for relevant studies. The reference lists of identified articles were reviewed to identify other relevant articles. The search strategy was reported and appeared appropriate. Searches were restricted to English language studies. Two review authors were independently involved in study selection.** **Domain 3: Data Collection and Study Appraisal:** **One review author extracted the data from the included studies and another investigator reviewed extractions for completeness and accuracy. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Two reviewers were independently assessed the quality of the included studies and any disagreements were resolved by discussion.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity for all outcomes. Robustness of the findings was not assessed likely due to small numbers of studies per meta analysis. The quality of individual studies was considered in the synthesis.** **Overall summary:** **There was restriction to English language studies.**

Bottom line: No trials compared screening with no screening or stenting with medical therapy or assessed intensification of medical therapy, and no externally validated, reliable risk-stratification tools were found. There is no evidence to establish superior overall benefits of the intervention (carotid endarterectomy) beyond current standard medical therapy. Potential for overall benefit is limited by low prevalence and harms. Restriction to the English language means some relevant studies may have been missed.

KSRA100760 2019 Judge C, et al. Lipid Lowering Therapy, Low-Density Lipoprotein Level and Risk of Intracerebral Hemorrhage - A Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 39 **Number of participants** 287,651 **Last search date** May 2018 **Review type** Intervention **Objective** To examine whether lipid-lowering therapy increased the risk of intracerebral haemorrhage overall, and within prespecified subgroups of participants (those with lower baseline low-density lipoprotein cholesterol level, a larger magnitude of low-density lipoprotein reduction and prior cardiovascular disease). **Population** Subjects aged >18 years. **Interventions** Lipid-lowering therapy. **Comparator** Not specified, "control group". **Outcome** Intracerebral haemorrhage, ischemic stroke and all-cause mortality. **Study design** Randomised controlled trials.	The meta-analysis reported that lipid-lowering therapy was not significantly associated with an increased risk of overall intracerebral haemorrhage (ICH) (odds ratio [OR] 1.12, 95% confidence interval [CI] 0.98 to 1.28; 39 studies) compared to the control group. The pooled analysis reported that lipid-lowering therapy was significantly associated with an increased risk for intracerebral haemorrhage (ICH) compared to control group in secondary prevention trials (OR 1.18, 95% CI 1.00 to 1.38; 22 studies). However, lipid-lowering therapy was not significantly associated with an increased risk for ICH compared to control group in primary prevention trials (OR 1.01, 95% CI 0.78 to 1.30; 17 studies). The summary estimates reported a significantly decreased ischemic stroke (OR 0.82, 95% CI 0.76 to 0.88; 37 studies) and all-cause mortality (OR 0.94, 95% CI 0.90 to 0.98) with lipid-lowering therapy compared with the control group.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. However, the nature of the control groups was not described. No restrictions were imposed based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Only the PUBMED database was searched for relevant studies. The reference list of similar review articles and earlier published meta-analyses were searched for additional studies. Search terms and full search strategy was not reported. Searches were restricted to published, peer-reviewed studies in English. Searches were restricted studies published between January 2012 to May 2018 and found to be appropriate. Four reviewers were independently involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **At least two reviewers were independently involved in the data extraction process. Sufficient study characteristics appear to have not been extracted to allow interpretation of results. Relevant study results appear to have been extracted. There was no formal assessment of the methodological quality of the included studies.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity for all outcomes. Meta-regression analyses were used to assess the impact of variables, such as low-density lipoprotein cholesterol level on outcomes. Robustness of the findings was not assessed. The quality of individual studies was not considered in the synthesis.** **Overall summary** **Only the Pubmed database was searched for the study selection process. Search terms and full search strategy was not reported. Searches were restricted to published, peer-reviewed studies in English. Sufficient study characteristics appear to have not been extracted to allow interpretation of results. There was no formal assessment of the methodological quality of the included studies. Robustness of the findings was not assessed.**

Bottom line:
The evidence suggests that lipid-lowering therapy is not significantly associated increased risk of overall intracerebral haemorrhage compared to control group. However, lipid-lowering therapy is significantly associated with decreased ischemic stroke and all-cause mortality compared to the control group. There were a range of limitations with the review methods including a limited database search, restriction to published, peer-reviewed studies in English, the lack of full search strategy, no sufficient study characteristics presentation, and no assessment of study quality.

KSRA20948 2016 Kakisis JD, et al. Protamine Reduces Bleeding Complications without Increasing the Risk of Stroke after Carotid Endarterectomy: A Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 7 **Number of participants** 9,887 **Last search date** September 2015 **Review type** Intervention **Objective** To evaluate the safety and efficacy of heparin reversal with protamine after completion of carotid endarterectomy. **Population** Patients with carotid stenosis that underwent carotid endarterectomy with or without reversal with protamine after heparin anticoagulation. **Interventions** Protamine. **Comparator** No protamine. Outcome Stroke and wound haematoma rates. **Study design** Randomised and non-randomised studies, editorials, systematic reviews, meta-analyses, short papers, letters to the editor, personal views and special communications.	The pooled analyses of seven studies showed a significant reduction in wound haematoma after heparin reversal with the use of protamine when compared to no protamine for patients undergoing carotid endarterectomy (CEA) (odds ratio [OR] 0.36, 95% confidence interval [CI] 0.21 to 0.63). The summary estimate of seven studies showed a statistically significant reduction in wound haematoma requiring re-operation after heparin reversal with protamine when compared to no protamine in patients undergoing CEA (OR 0.42, 95% CI 0.22 to 0.80). The pooled analyses of seven studies showed no significant difference in stroke rates between protamine for reversal of heparin and no protamine (OR 0.71, 95% CI 0.49 to 1.03).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. The eligibility criteria were well described and appeared appropriate to address the review question. No restriction was reported based on study characteristics. Studies published (between January 1974 until September 2015) were included, which was considered appropriate.** **Domain 2: Identification and Selection of Studies** **MEDLINE, EMBASE, Scopus, Google Scholar, Ovid, and the Cochrane Library were searched for relevant studies. All reference lists were searched for additional relevant studies. A detailed search strategy was not reported. The search strategy was not restricted to the date, publication type or any language. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process and any disagreements were resolved by discussion and consensus, after applying the kappa calculation. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. There was no formal assessment of the methodological quality of randomised controlled studies. Two reviewers independently assessed the quality of included studies.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared inappropriate due to pooling of different study designs (prospective case-control and randomised controlled trials) into a single estimate. There was moderate heterogeneity for the occurrence of wound haematoma outcome, therefore pooling may not have been appropriate. No evidence of significant publication bias was found using Egger's test and funnel plots, but this may be due to the low number of included studies for each comparison (< 10). The quality of individual studies was not considered in the synthesis for randomised control trials.** **Overall summary** **A limited search strategy was reported. It is likely that other terms could have been used and therefore relevant articles may have been missed. Information regarding the number of authors involved in the study selection process was not provided. There was no formal assessment of the methodological quality of randomised controlled studies. The method of analysis was explained and may have been inappropriate due to pooling of different study designs into a single estimate. Although publication bias was assessed using Egger's test and funnel plots, this may not have been appropriate as the number of studies included in the review was small (< 10).**

Bottom line: The current evidence suggests that heparin reversal with protamine may reduce the relative risk of wound haematoma and the relative risk of wound haematoma requiring re-operation, without increasing the risk of procedural stroke in patients undergoing carotid endarterectomy. This review had a number of limitations. Further studies are needed to add power to these findings.

KSRA26995 2017 Kakisis JD, et al. Cranial Nerve Injury After Carotid Endarterectomy: Incidence, Risk Factors, and Time Trends

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 26 **Number of participants** Unclear **Last search date** December 2015 **Review type** Epidemiology **Objective** To evaluate the incidence of post-carotid endarterectomy cranial nerve injury as well as the risk factors associated with increased cranial nerve injury risk, and to examine whether the incidence of cranial nerve injury has changed over the past few decades. **Population** Patients with cranial nerve injury after primary carotid endarterectomy. **Interventions** NA. **Comparator** NA. **Outcome** Incidence of post- carotid endarterectomy cranial nerve injury, risk of cranial nerve injury. **Study design** Retrospective and prospective studies, randomised controlled trial. **Reference standard** NA. **Exposure** NA. **PP factor** Urgent carotid endarterectomy, local anaesthesia, use of the patch, redo operation, return to the operating room for a neurological event or bleeding, and use of shunt on cranial nerve injury during carotid endarterectomy.	The pooled analyses of 22 studies reported that the nerve injury rate for the facial nerve was 1.97% (95% confidence interval [CI] 1.37 to 2.66, 16,077 participants). Similarly, the pooled effect reported that the nerve injury rate for vagus nerve (X) was observed to be 3.99% (95% CI 2.56 to 5.70, 22 studies, 14,510 participants) and hypoglossal nerve (XII) injury rate was found to be 3.79% (95% CI 2.73 to 4.99, 24 studies, 16,248 participants). The pooled analyses of two studies reported that the urgent procedures (odds ratio [OR] 1.59, 95% CI 1.21 to 2.10, 10,640 participants) and return to the operating room for a neurological event or bleeding (OR 2.21, 95% CI 1.35 to 3.61, two studies, 8,029 participants) were associated with the increased risk of cranial nerve injury, whereas no statistically significant association was found between cranial nerve injuries and the type of anaesthesia, the use of a patch, redo operation, and the use of a shunt. The injury rate was decreased from about 8% to 2% and 1%, respectively, over the last 35 years.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. The inclusion criteria were not explicitly defined with regard to study design. No restriction was reported based on study characteristics. No restriction was reported based on sources of information.** **Domain 2: Identification and Selection of Studies** **MEDLINE, Scopus, EMBASE, Google Scholar, Ovid, and the Cochrane Library were searched for relevant studies. The reference lists of eligible articles were followed to retrieve additional articles. A detailed search strategy was not reported. Searches were restricted to studies published (between January 1970 and December 2015), which was considered appropriate. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **No information was mentioned regarding the number of authors involved in data extraction. Insufficient study characteristics have been presented to allow interpretation of results. There was no formal methodological quality assessment of included studies.** **Domain 4: Synthesis and Findings** **Two review authors were independently involved in the data extraction process and the final decision was reached by consensus. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using the Newcastle-Ottawa scale for cohort studies, which was inappropriate for the randomised controlled trials. At least two authors assessed quality of the included studies.** **Overall summary** **The eligibility criteria were not explicitly defined with regard to study design. A detailed search strategy was not reported. Information regarding the number of authors involved in the study selection process was not provided. The quality of included studies was assessed using an inappropriate tool. Pooling of different study designs into a single estimate was inappropriate. The authors have acknowledged the presence of publication bias.**

Bottom line: The current evidence suggests that vagus nerve may be the most frequently injured cranial nerve after carotid endarterectomy, followed by the hypoglossal nerve. Urgent procedures and return to the operating room for a neurological event or bleeding are associated with an increased risk of cranial nerve injury. There are some limitations with the review methods such as the eligibility criteria not being explicitly defined with regard to study design, the lack of a detailed search strategy, no information on whether the study selection was undertaken in duplicate, the presence of publication bias and addressing the bias in primary studies using inappropriate criteria.

KSRA32002 2017 Kakkos SK, et al. Endarterectomy achieves lower stroke and death rates compared with stenting in patients with asymptomatic carotid stenosis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 9 (8 in meta-analysis) **Number of participants** 3,709 **Last search date** 17 March 2017 **Review type** Intervention **Objective** To compare carotid artery stenting with carotid endarterectomy for patients with significant asymptomatic stenosis. **Population** Patients with significant asymptomatic stenosis. **Interventions** Carotid endarterectomy (CEA). **Comparator** Carotid artery stenting (CAS). **Outcome** Primary safety outcome: stroke or death rate at 30 days. Primary efficacy outcome: ipsilateral stroke at one year (including ipsilateral stroke and death rate at 30 days). Secondary outcomes: perioperative stroke, ipsilateral stroke, myocardial infarction (MI), and cranial nerve injury (CNI). **Study design** Randomised controlled trials.	The pooled analysis reported that stroke or death rate at 30 days was significantly higher with CAS compared to CEA (odds ratio [OR] 1.57, 95% confidence interval [CI] 1.01 to 2.44, eight trials, n=3,607). Similarly, stroke rate at 30 days was significantly higher with CAS compared to CEA (OR 1.63, 95% CI 1.04 to 2.54, eight trials, n=3,607). No difference was detected between the standard surgical risk and high surgical risk subgroups. No significant difference was found in ipsilateral stroke rate at 30 days between CAS and CEA (OR 1.56, 95% CI 0.71 to 3.43, four trials, n=1,737). Myocardial infarction (MI) at 30 days (OR 0.53, 95% CI 0.24 to 1.14, five trials, n=2,885) and cranial nerve injury (CNI) at 30 days (OR 0.13, 95% CI 0.07 to 0.26, four trials, n=2,855) were lower for CAS than for CEA. Long-term outcome of stroke or death rate at 30 days and ipsilateral stroke during follow-up was significantly higher for CAS than for CEA (OR 1.51, 95% CI 1.02 to 2.24, eight trials, n=3,603).	**Domain 1: Study Eligibility Criteria: High** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. Only English language studies were considered for inclusion in the review.** **Domain 2: Identification and Selection of Studies: High** **Studies were identified by searching MEDLINE, the Cochrane Central Register of Controlled Trials and Scopus databases. Scopus covers EMBASE journals, but does not allow extensive searching as in EMBASE. In addition, reference lists of included studies were manually searched for additional findings. The search terms were provided, but a full search strategy was not reported. There was no information on whether searches were restricted by publication format or language. Two reviewers were independently involved in the study selection and disagreements were resolved by discussion.** **Domain 3: Data Collection and Study Appraisal: Low** **Two reviewers were independently involved in the data extraction process and risk of bias assessment. Discrepancies were resolved by discussion. Sufficient study characteristics have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using appropriate criteria.** **Domain 4: Synthesis and Findings: Low** **The synthesis appeared to have included all relevant studies. Analyses predefined in the methodology section were performed appropriately. No significant heterogeneity was found between the studies. Sensitivity analysis was planned in case heterogeneity was present, but this was not required. In addition, the relatively small number of trials included in the present meta-analysis did not allow assessment of publication bias. Quality of the individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **Only English language studies were considered for inclusion in the review. A limited range of databases were searched for the study selection process. The search terms were provided, but a full search strategy was not reported. There was no information on whether searches were restricted by publication format or language.**

Bottom line: The current evidence suggests that carotid artery stenting shows higher 30 day stroke or death rates compared with carotid endarterectomy. A restriction to English language studies and a limited range of databases searched means that some relevant studies may have been missed. The search terms were provided, but a full search strategy was not reported, therefore it is not possible to judge if all relevant studies have been retrieved. Furthermore, a large number of high-quality trials are needed to support these findings.

KSRA93424 2007 Killeen SD, et al. Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 54 **Number of participants** 1240998 **Last search date** 2005 **Review type** Prognostic/Predictive **Objective** Systematic review of the relationship between provider volume and outcome for a number of key vascular procedures, focusing on the relative roles of operator case load, hospital volume, and surgeon training. **Population** Community-based or population-based sample, following abdominal aortic aneurysm repair, carotid endarterectomy, or lower limb vascular procedures. **Outcome** Mortality, morbidity, stroke, cardiac complications, neurological complications Studies reporting a composite of death and complications were excluded. **Study design** Database studies, registry data, surveys, cross-sectional studies. Study quality score > 4 (tool not specified) and published after 1980. Single institution studies and case series as well as multiple publications on the same database were excluded. **Reference standard** Not applicable **PP factor** Volume of cardiovascular procedures in hospital, surgeon training and experience.	There was some heterogeneity in the included studies, e.g. with regards to definition of surgeon (high-volume definition of between >10 and >26 aneurysm repairs per year or between >10 or >50 carotid endarterectomies (CEAs) per year) and hospital caseload (high-volume defined as >10 to >80 abdominal aortic aneurysm (AAA) repairs per year or >20 to >164 CEAs). Due to the diversity of studies, no meta-analyses were conducted. Included studies (n=25) suggested an inverse relationship between provider volume and outcome for elective AAA repair. The absolute reductions in risk-adjusted mortality rates (RAMR) typically ranged from 3.1% to 7% for high-volume hospitals and 2.3% to 11% for high-volume surgeons. Seven studies assessed hospital and surgeon caseload in the same study. There was no consensus on the relative contributions of operator and institutional volume to the aforementioned relationship. There was an association between surgeon specialty training and improved outcomes (RAMR 2.5%, 4.4%, and 7.3% for vascular, cardiac, and general surgeons, respectively). High-volume hospitals were associated with a decreased relative risk of complications, including pulmonary failure, reintubation, pneumonia, cardiac complications and shock (n=2). Most of the 25 studies included for CEA showed an inverse relationship between provider volume and mortality as well as morbidity. Four studies not showing a relationship were smaller while no study showed a converse correlation. Absolute reduction in RAMR ranged from 0.4% to 0.9% and 0.2% to 1.1% for high-volume hospitals and surgeons, respectively. Of nine studies reporting surgeon and hospital volume in the same study, seven found a significant relationship for surgeon volume, suggesting this to be the main factor (data not included). Eight studies assessed the relationship between surgeon specialty and outcomes, only one did not find a positive correlation. Studies assessing lower limb vascular procedures were smaller and more ambiguous. Seven studies demonstrated an inverse relationship between provider volume and mortality. Two studies did not show a relationship while no study showed a converse relationship. According to the review, vascular surgery training was linked to reduced RAMR (1.2%) and fewer amputations (rate 2.3%).	**Domain 1: Study Eligibility Criteria** **Inclusion criteria are reported and appear appropriate for the review question. However, there is some ambiguity, e.g. only studies of a certain quality were included but the tool used for the quality assessment was not specified. Study inclusion was further restricted to studies published 1980 or later that were published in English.** **Domain 2: Identification and Selection of Studies** **The review searched Medline, EMBASE, and the Cochrane library. Results were evaluated for sensitivity and specificity (no further details reported). Furthermore, the trial register of the relevant Cochrane group was consulted and bibliographies of included studies searched. The search strategy is reported, however, it is likely that relevant studies might have been missed as does not seem comprehensive (no flow chart has been reported to explore this further). Three reviewers screened references for inclusion.** **Domain 3: Data Collection and Study Appraisal** **Three reviewers were involved in the screening for relevant studies, i.e. it can be assumed these were also involved in data extraction and risk of bias assessment of included studies. However, it is unclear which tool was used to assess the risk of bias of included studies.** **Domain 4: Synthesis and Findings** **Due to the heterogeneity of included studies, no meta-analyses were conducted and results presented narratively. Robustness of findings and biases of the primary studies were not explored.** **Overall summary** **The inclusion criteria were restricted to studies published in English after 1980. Furthermore, the search strategy is limited so relevant studies might have been missed. It is unclear which tool was used to assess the risk of bias of included studies and robustness of findings as well as risk of bias was not explored.**

Bottom line: The results of this systematic review confirm that higher volumes of cases for both, hospitals and surgeons, are associated with better outcomes (mortality, morbidity and complications) for patients undergoing abdominal aortic aneurysm repair, carotid endarterectomy, or lower limb vascular procedures. However, only English studies published after 1980 were included. Due to this and the limited search strategy, relevant studies might have been missed. Furthermore, the risk of bias of included studies was not discussed, i.e. findings should be interpreted with some caution. Further studies should report comparable outcome measures and use similar definitions of caseloads. Future systematic reviews should not restrict inclusion by year or language of publication and should be clearly reported.

KSRA27237 2017 Kumar R, et al. Restenosis after Carotid Interventions and Its Relationship with Recurrent Ipsilateral Stroke: A Systematic Review and Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** NR **Last search date** July 2016 **Review type** Epidemiological **Objective** To explore the prevalence of restenosis >70% and/or occlusion in patients with primary atherosclerotic disease undergoing carotid endarterectomy and carotid artery stenting and also to evaluate the association between untreated asymptomatic restenoses >70% and risk of late ipsilateral stroke than patients with no significant restenoses. **Population** Patients with primary atherosclerotic disease undergoing carotid endarterectomy and carotid artery stenting. **Interventions** NA. **Comparator** NA. **Outcome** Prevalence of restenosis >70% and/or occlusion and late ipsilateral stroke. **Study design** Randomised controlled trials. **Reference standard** NA. Exposure Asymptomatic restenoses >70% or without restenoses. PP factor NA.	The pooled analysis of 11 randomised controlled trials (RCTs) reported that the prevalence of restenosis >70% (or occlusion) to be 5.8% (95% confidence interval [CI] 4.1 to 8.2; n = 4,249 patients) in patients undergoing any type of carotid endarterectomy [CEA] (eversion, traditional, patched, primarily closed) over a mean follow-up of 47 months. The pooled estimates reported that the prevalence of restenosis rates >70% or occlusion following patched CEA was 4.1% (95% CI 2.0 to 8.4; five RCTs, n = 1,078 patients) over a mean follow-up of 32 months. The summary estimates reported that the prevalence of restenosis >70% (or occlusion) to be 10.3% (95% CI 6.0 to 16.4; six RCTs, n = 2,916 patients) in patients undergoing any sort of endovascular intervention (carotid artery stenting [CAS], balloon angioplasty) over a mean follow-up of 60 months. The pooled analysis reported that the prevalence of restenosis rates >70% or occlusion was 10.0% (95% CI 6.0 to 16.3; five RCTs, n = 2,716 patients) in patients undergoing CAS over a mean follow-up of 62 months. The summary estimates reported that late ipsilateral stroke was observed in one of 125 (0.8%) with restenosis >70% (or occlusion) after CAS (i.e. not including balloon angioplasty) over a mean follow-up of 50 months compared with 37 of 1,839 (2.0%) in CAS patients with no significant restenosis (OR = 0.87; 95% CI 0.24 to 3.21; four RCTs, n = 1,964 patients). Similarly, a late ipsilateral stroke was observed in 13 out of 141 (9.2%) with restenosis >70% (or occlusion) after any type of CEA (eversion/traditional; primary/patched) over a mean follow-up of 37 months compared with 33 out of 2,669 (1.2%) in patients with no significant restenoses (OR = 9.02; 95% CI 4.70 to 17.28; seven RCTs, n = 2,810 patients). Late ipsilateral stroke was observed in seven out of 135 patients (5.2%) with a previously asymptomatic, untreated restenosis >70% (or occlusion) compared with 40 out 2,704 (1.5%) in CEA patients with no significant restenosis prior to stroke onset (OR 4.77; 95% CI 2.29 to 9.92; eight RCTs).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria appear to have been defined. No restrictions were imposed based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **PubMed/MEDLINE, EMBASE and the Cochrane databases were searched for relevant studies. Manual searches were performed for additional studies in journals such as Stroke, the European Journal of Vascular and Endovascular Surgery, the Journal of Vascular Surgery, and the Annals of Vascular Surgery. The search terms and search strategy were not reported. Searches were restricted to studies published (between January 1990 and July 2016), but was found to be appropriate. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Two investigators were independently involved in the data extraction process and any disagreements between them were resolved by a consensus discussion or referral to a third party. Sufficient study characteristics have not been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Jadad scale which was found to be inappropriate. No information was provided regarding the number of authors involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was evidence of significant heterogeneity among the studies. No appropriate attempts were made to explore the possible sources of heterogeneity. Robustness of the findings or publication bias was not assessed. The quality of individual studies was considered in the synthesis using inappropriate criteria.** **Overall summary** **The search terms and search strategy were not reported. No information was provided regarding the number of authors involved in the study selection and risk of bias assessment. Sufficient study characteristics appear to have not been extracted to allow interpretation of the results. Appropriate attempts were not made to explore the possible sources of heterogeneity. Robustness of the findings or publication bias was not assessed. The quality of individual studies was considered in the synthesis using inappropriate criteria.**

Bottom line: The evidence suggests that the rate of late ipsilateral stroke is low in carotid artery stenting patients with untreated asymptomatic >70% restenosis and significantly higher in carotid endarterectomy patients with untreated, asymptomatic >70% restenosis compared with patients with no restenosis. There were a number of limitations with the review methods such as the lack of a full search strategy, insufficient study details, addressing of risk of bias using inappropriate criteria and no assessment of robustness or publication bias. The authors did not state whether the study selection and quality assessment were undertaken in duplicate, so reviewer error and bias could not be ruled out. Therefore, the results should be interpreted with caution.

KSRA37945 2017 Li Y, et al. Long-term efficacy and safety of carotid artery stenting versus endarterectomy: A meta-analysis of randomized controlled trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 8 **Number of participants** 7,015 **Last search date** 6th May 2016 **Review type** Intervention Objective To determine the long-term comparative efficacy and safety of carotid artery stenting versus endarterectomy in patients with carotid artery stenosis. **Population** Patients with carotid artery stenosis (regardless of whether they were symptomatic or asymptomatic or a mixed population). **Interventions** Carotid artery stenting (CAS). **Comparator** Carotid endarterectomy (CEA). Outcome Periprocedural outcomes (defined as an endpoint that occurred during the 30 days following the intervention or 36 days after the randomisation if the procedure was not performed within 30 days after the randomisation), including stroke, death, myocardial infarction, cranial nerve palsy and haematoma. Postprocedural outcomes (defined as events that occurred from the beginning of the periprocedural period to the last time of follow-up), including death, stroke and restenosis. Outcomes had to be reported with a median follow-up of at least four years. **Study design** Randomised controlled trials that contained at least 20 patients. Non-randomised prospective trials, retrospective trials, observational trials, systemic reviews and meta-analyses were excluded.	In terms of periprocedural outcomes, the pooled analysis reported that CAS was associated with a lower risk of periprocedural myocardial infarction (odds ratio [OR] 0.52, 95% confidence interval [CI] 0.33 to 0.81, five studies, n=5,409 participants) and a higher incidence of the composite outcome of death or stroke (OR 1.76, 95% CI 1.38 to 2.25, eight studies, n=6,863 participants) and minor stroke (OR 2.19, 95% CI 1.59 to 3.01, eight studies, n=6,863 participants) compared to CEA. No differences were reported between CAS and CEA in terms of the incidence of periprocedural death (OR 1.68, 95% CI: 0.82 to 3.44, eight studies, 4,361 participants) or major stroke (OR 1.41, 95% CI 0.95 to 2.09, eight studies, n=6,863 participants). In terms of postprocedural outcomes, the pooled analysis reported that CAS was associated with a higher risk of stroke (OR 1.45, 95% CI 1.22 to 1.73, seven studies, n=6,799 participants) and a higher risk of the composite outcome of death, ipsilateral stroke or periprocedural stroke compared to CEA (OR 1.25, 95% CI 1.05 to 1.48, eight studies, n=7,005 participants). No differences were reported between CAS and CEA in terms of all-cause mortality (OR 1.09, 95% CI 0.95 to 1.26, six studies, n=4,405 participants), ipsilateral stroke rate (OR 1.04, 95% CI 0.79 to 1.37, six studies, n=6,715 participants) and restenosis (OR 1.48, 95% CI 0.93 to 2.35, six studies, n=4,752 participants). Sensitivity analyses were reported to confirm the consistency of the main findings and meta-regression analysis was reported to show that the two study-level variables, patient type or use of an embolic protection device did not have an effect on either stroke or the composite endpoint between the two groups.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Some eligibility criteria (including mixed patient populations) may not have been appropriate for the review question. The studies were restricted based on language (only English language studies were included), study design (only studies with at least 20 patients were included) and publication format (only full text studies were included).** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching EMBASE, the Cochrane Library Central Register of Controlled Trials (CENTRAL) and PubMed databases. The reference lists of included studies and relevant reviews were searched to identify additional studies. The search strategy was reported in full and appeared to be adequate. The searches were restricted by language (only English language studies were included). Two reviewers were independently involved in the study selection and any discrepancies were resolved by consensus with a third reviewer.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process, and any discrepancies were resolved by discussion with a third reviewer. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was performed using the Cochrane risk of bias tool. Two reviewers were independently involved in the risk of bias assessment, and any discrepancies were resolved by discussion with a third reviewer.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. Analyses predefined in the methodology section were performed appropriately. No evidence of significant heterogeneity was found in any of the analyses. Meta-regression and sensitivity analyses were performed. Publication bias was evaluated using funnel plots, Begg and Egger tests. Quality of the individual studies was considered in the synthesis.** **Overall summary** **Some eligibility criteria (including mixed patient populations) may not have been appropriate for the review question. The studies were restricted based on language (only English language studies were included), study design (only studies with at least 20 patients were included) and publication format (only full text studies were included).**

Bottom line: The current evidence suggests that carotid endarterectomy may be more effective than stenting in terms of short-term and long-term outcomes, but also appears to be associated with a higher risk of periprocedural myocardial infarction. These results should be interpreted with caution, since some relevant studies may have been missed and the inclusion of mixed patient populations may make the interpretation of these results more challenging. Further well-designed studies focused on the comparative efficacy and safety of both these techniques are needed to fully address this review question, especially since rapid progress is being made in the development of new devices and treatment approaches.

KSRA18353 2015 Liao SQ, et al. The association between leukoaraiosis and carotid atherosclerosis: a systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 32 **Number of participants** 17,721 **Last search date** February 2014 **Review type** Aetiological **Objective** To determine the association between leukoaraiosis and carotid atherosclerosis manifested as atherosclerotic stenosis, plaques and increased intima-media thickness. **Population** Patients of case group who suffered from leukoaraiosis (also known as white matter lesions, white matter hyperintensity, white matter ischaemia) and all the patients underwent effective imaging diagnosis such as magnetic resonance angiography, digital subtraction angiography, computed tomography angiography, carotid duplex ultrasound. Studies reporting on white matter changes resulting from multiple sclerosis, history of acute anoxia, radiation and other known non-vascular causes were excluded. **Outcome** Leukoaraiosis. **Study design** Case-control studies, cohort studies or cross-sectional studies. **Reference standard** NA **Exposure** Carotid atherosclerosis (atherosclerosis including diameter stenosis demonstrated by digital subtraction angiography [DSA], magnetic resonance angiography [MRA], and computed tomography angiography [CTA], plaque or plaque composition demonstrated by MRA, CTA, and carotid duplex ultrasound (CDUS), even endarterectomy specimen increased intima-media thickness demonstrated by CDUS). **PP factor** Leukoaraiosis Papers in which the relationship between LA and carotid atherosclerosis was unclear or could not be determined were excluded	Out of 32 studies, 18 studies reported an association between leukoaraiosis (LA) and carotid atherosclerosis (including diameter stenosis, plaque and intima-media thickness [IMT]). Moreover, LA was significantly associated with IMT (nine studies), CAWT (similar to the role of the IMT) (one study), carotid plaque (11 [79%] out of 14 studies) including presence of plaque (seven out of 14 studies) and unstable/fatty plaques (four out of seven studies) and carotid stenosis (seven studies). However, 16 studies reported no significant association between LA and carotid stenosis and neither with the degree of carotid stenosis (11 studies) nor with severe stenosis (≥50%) (five studies). The pooled analysis reported no significant association between carotid atherosclerosis and LA (odds ratio [OR] 1.10, 95% confidence interval [CI] 0.61 to 1.98, 10 studies, n = 6,931 patients). The subgroup analysis reported that LA was significantly associated with carotid plaque (OR 3.53, 95% CI 1.83 to 6.79, four studies, n = 1,283 patients) and carotid IMT (mean difference [MD] 0.11, 95% CI 0.01 to 0.22, four studies, n = 1,100 patients). In contrast, carotid stenosis was reported as a protective factor for LA (OR 0.53, 95% CI 0.32 to 0.87, six studies, n = 5,648 patients).	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies:** **Literature searches were conducted in PubMed, EMBASE and Web of Science. The reference lists of included articles were manual searched for relevant studies. Only search terms were provided, full details of the search strategy were not reported in the review. The search was restricted to English language studies. Two investigators were independently involved in the study selection process and disagreements were resolved by discussion.** **Domain 3: Data Collection and Study Appraisal:** **Data extraction was performed by two authors independently and any disagreements were resolved by consensus with another author. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. However, details of the confounders adjusted were not provided. Relevant study results appear to have been extracted. There was no formal assessment of the methodological quality of included studies.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared appropriate. A narrative synthesis was performed where meta-analysis was not possible. There was significant evidence of heterogeneity among the studies. Residual heterogeneity existed even after performing subgroup analysis. No evidence of significant publication bias was found using funnel plot symmetry. Sensitivity analysis was performed to test robustness of the findings. Biases in the individual studies were not taken into account for the synthesis of findings.** **Overall summary: High risk of bias in the review** **The authors have acknowledged the presence of clinical heterogeneity in the techniques for the assessment of LA and carotid atherosclerosis. The complete search strategy was not reported. The search was restricted to** **English language studies. Details of the confounders adjusted were not provided. The quality of individual studies was not considered in the synthesis.**
Bottom line: The authors have acknowledged the presence of clinical heterogeneity in the techniques for the assessment of LA and carotid atherosclerosis. The complete search strategy was not reported. The search was restricted to English language studies. Details of the confounders adjusted were not provided. The quality of individual studies was not considered in the synthesis.		

KSRA50263 2018 Lokuge K, et al. Meta-analysis of the procedural risks of carotid endarterectomy and carotid artery stenting over time

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 51 **Number of participants** 296274 **Last search date** 20th May 2016 **Review type** Intervention **Objective** To investigate whether the procedural stroke/death risks from carotid endarterectomy and carotid artery stenting have changed over time. **Population** Patients diagnosed with carotid stenosis. **Interventions** Carotid endarterectomy or carotid artery stenting. **Comparator** NA **Outcome** Primary outcomes: Stroke or death events occurring within 30 days from the procedure. Secondary outcomes: Death, stroke, MI, stroke/death/MI, major stroke (modified Rankin score at least 3) and minor stroke (modified Rankin score less than 3). **Study design** Observational cohort studies. Comment, editorial, letter or notes were excluded.	The procedural stroke/death risk following carotid endarterectomy (CEA) was 3·44 (95% confidence interval [CI] 2·70 to 4·23) per cent in symptomatic patients and 2·00 (95% CI 1·49 to 2·58) per cent in asymptomatic patients across 24 studies. Risks were substantially lower in studies completing recruitment in 2005 or later, both in symptomatic (5·11 per cent [95% CI 3·48 to 7·06] before 2005 versus 2·68 per cent [95% CI 2·12 to 3·31] from 2005 onwards) and asymptomatic (3·17 per cent [95% CI 2·39 to 4·06] before 2005 versus 1·50 per cent [95% CI 1·01 to 2·07] from 2005 onwards) patients. The meta-regression analysis assessing annual trends over time indicated a 6·1 (95% CI 3·0 to 9·2) and 6·9 (95% CI 3·0 to 10·5) per cent per annum reduction in CEA procedural stroke/death rate in symptomatic and asymptomatic patients, respectively. When considered separately, the rates of procedural deaths and strokes were lower in later studies but only the reduction in death rate in asymptomatic patients was statistically significant. There was no statistically significant difference between rates of procedural myocardial infarction (MI) in studies completing recruitment before 2005 and later studies in symptomatic patients (overall risk: 0·96, 95% CI 0·71 to 1·25) per cent and asymptomatic patients (overall risk: 1·06, 95% CI 0·77 to 1·40) per cent. The procedural stroke/death risk following carotid artery stenting (CAS) was 4.77 (95% CI 3.67 to 5.99) per cent in symptomatic patients and 2·59 (95% CI 1·77 to 3.56) per cent in asymptomatic patients across the 13 studies. In the meta-regression analysis, there was a non-significant per cent per annum reduction in CAS procedural stroke/death rate in symptomatic patients (2·7%, 95% CI -3·4 to 8·4) and asymptomatic patients (1·8%, 95% CI 8·1 to 10·9). There were no differences between the rates of procedural death and stroke, separately, before 2005 and from 2005 onwards in both symptomatic and asymptomatic patients. The ratio between rates of procedural major to minor strokes was about 2:3 in symptomatic (1·54 versus 2·38 per cent) and asymptomatic (0·87 versus 1·46 per cent) patients. The combined rate of procedural MI across five contributing studies, all completing recruitment in 2005 or later was 0·92 (95% CI 0·44 to 1·54) per cent in symptomatic patients and 0·56 (0·25 to 0·97) per cent in asymptomatic patients.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. Studies with a population of ≤ 1000 were excluded. Conference abstracts and studies written language other than English were excluded.** **Domain 2: Identification and Selection of Studies** **MEDLINE and Embase were searched for relevant studies. Other recent systematic reviews were also searched to identify additional studies. The search strategy was reported in full and appeared to have shortcomings as no MeSH or Emtree terms seem to have been used. The searches were not restricted by date, publication format, or language. One author reviewed all citations. A second author screened a random sample of 20 per cent of the citations by title and abstract, and then by full text.** **Domain 3: Data Collection and Study Appraisal** **Data extraction was performed by one author. The second reviewer extracted data from 20 per cent of the included studies. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using the Newcastle quality assessment scale. One reviewer was involved in the assessment of the risk of bias. The second reviewer also assessed the risk of bias from 20 per cent of the included studies.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The methodological analysis section of the review was sufficiently elucidated. There was significant evidence of heterogeneity among the studies. Appropriate attempts were not made to explore the possible sources of heterogeneity. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary** **There were some limitations with the review methods such as the restriction to studies with a population of > 1000; in the English language, excluding conference abstracts; and the involvement of only one author in the complete study selection, data extraction and risk of bias assessment; and presence of heterogeneity.**

Bottom line:
Evidence suggests that risks of procedural stroke/death following carotid endarterectomy appear to have decreased substantially in both symptomatic and asymptomatic patients in recent years. However, the procedural risks of carotid artery stenting appear to have remained stable over time. The review had significant methodological weaknesses in all the domains, so the findings should be interpreted with caution.

KSRA3248 2015 Luebke T, et al. Meta- analysis and meta-regression analysis of the associations between sex and the operative outcomes of carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 58 **Number of participants** Unclear **Last search date** January 2015 **Review type** Prognostic/Predictive **Objective** To investigate the association between gender and procedural risk of stroke and/or death following carotid endarterectomy. **Population** Patients undergoing carotid endarterectomy for symptomatic or asymptomatic stenosis. Outcome Peri-operative risk of stroke and/or death. **Study design** Randomised control trials, case series, and databases. **Reference standard** NA Exposure Patient sex. **PP factor** Patient gender.	In the overall meta-analysis, the incidence of stroke and death in the male and female groups differed significantly (OR, 1,162; 95 % CI, 1.067-1.266), revealing a worse outcome for female patients. In sensitivity analyses the meta-analysis of case series with gender aspects as a secondary outcome showed a significantly increased risk for 30-day stroke and death in women compared to men (OR, 1.390; 95 % CI, 1.148-1.684), In contrast, meta-analysis of databases (OR, 1.025; 95 % CI, 0.958-1.097) and case series with gender related outcomes as a primary aim (OR, 1.202; 95 % CI, 0.925-1.561) demonstrated no increase in operative risk of stroke and death in women compared to men.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were applied in eligibility criteria based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **PubMed, EMBASE and Cochrane Central Register of Controlled Trials were searched for articles to be included in the review. Further efforts were made to manually search reference lists of included studies to identify additional articles. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. There were no restrictions based on date, publication format, or language. Number of reviewers involved in study selection was unclear.** **Domain 3: Data Collection and Study Appraisal** **No information was provided regarding number of authors involved in the data extraction and quality assessment process. Sufficient study characteristics were collected and documented in the review. All the results of individual studies were explained and detailed appropriately in the synthesis. Study quality was assessed with the Newcastle-Ottawa Scale for case-control observational studies (but no case-control studies were included), and the Jadad scale used for randomised control trials is outdated.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant studies. Meta-regression models were used to explore potential heterogeneity as a result of potential risk factors or confounders on outcomes. Sensitivity analyses were undertaken to evaluate the potential effect of key assumptions and study-level factors on the overall results, in addition publication bias was reported to be assessed using funnel plots but the data was not shown.** **Overall summary** **Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. Number of reviewers involved in study selection, data extraction and quality assessment process were unclear. Assessment of the quality of included studies was done using inappropriate criteria.**

Bottom line: Meta-analyses of case series and databases dealing with CEA reveal inconsistent results regarding gender differences related to CEA-procedure and should not be transferred into clinical practice. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. The authors did not state whether study selection, data extraction and quality assessment were undertaken in duplicate, so reviewer error and bias could not be ruled out. As methodological quality assessment of included studies was inappropriately performed, one may question the reliability of the findings.

KSRA94088 2019 Mahmoud AN, et al. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** 157248 **Last search date** 25 September 2018 **Review type** Intervention **Objective** To examine the efficacy and safety of aspirin among patients without a prior known history of atherosclerotic cardiovascular disease. **Population** Adult patients without prior history of atherosclerosis (including peripheral arterial disease, coronary artery disease, prior myocardial infarction, prior stroke or transient ischaemic attack, prior percutaneous coronary intervention, prior coronary artery bypass grafting). Trials that were conducted exclusively in patients with diabetes were included in the final cohort, as long as they had no known history of atherosclerosis. **Interventions** Aspirin. **Comparator** Placebo or no aspirin control. **Outcome** Primary outcome: All-cause mortality and major bleeding. Secondary outcome: Cardiovascular mortality, fatal and non-fatal myocardial infarction, and fatal, non-fatal ischaemic stroke and intracranial haemorrhage. **Study design** Randomised controlled trials.	The pooled analysis reported no significant difference between aspirin and placebo in terms of incidence of all-cause mortality (RR 0.98, 95% CI 0.93 to 1.02; 11 trials; n = 157248 participants), incidence of cardiovascular mortality (RR 0.92, 95% CI 0.83 to 1.01; 11 trials; n = 157248 participants) and ischaemic stroke (RR 0.94, 95% CI 0.86 to 1.02; 11 trials; n = 157248 participants). The summary estimates reported that the incidence of myocardial infarction (RR 0.82, 95% CI 0.71 to 0.94; 11 trials; n = 157248 participants) was significantly lower in the aspirin group compared to placebo. However, the incidence of major bleeding (RR 1.47, 95% CI 1.31 to 1.65; 11 trials; n = 157248 participants) and the risk of intracranial haemorrhage (RR 1.33, 95% CI 1.13 to 1.58; 11 trials; n = 157248 participants) was significantly higher in the aspirin group compared to placebo.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. Studies with a sample size of 500 or more patients were included and found to be appropriate. No restrictions were imposed based on sources of information.** **Domain 2: Identification and Selection of Studies** **Pubmed, MEDLINE, Web of Science, and Embase were searched for relevant studies. The bibliographies of the included studies and prior meta-analyses on the same topic were also searched for additional studies. Search terms were provided but full search strategy was not reported, therefore it cannot be assessed how efficient it was. Searches were not restricted to language. Two authors were involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Two authors were involved in the data extraction process. A third author crosschecked the data for any errors during data extraction and any disagreements between them were resolved by consensus. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of the included studies was assessed using the Cochrane risk of bias assessment tool. No information was provided regarding the number of authors involved in the risk of bias assessment. However, as all other stages of the review were performed by two reviewers, it is likely that this stage also involved two reviewers.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity for any outcomes. Subgroup analysis were also performed based on aspirin daily dose (≤100mg/day versus >100 mg/day), diabetes status (diabetes only trials versus other trials), mid-enrolment year (before 2000 versus 2000 and after), for trials with low risk of bias and high risk of bias and 10-year major adverse cardiovascular events. Meta-regression analyses were used to assess the impact of variables such as mid-enrolment year, mean age, percentage of females, hypertension, and smoking on the incidence of all-cause mortality major bleeding. No evidence of significant publication bias was found using Begg's test for the incidence of all-cause mortality. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary** **Search terms were provided but full search strategy was not reported, therefore it cannot be assessed how efficient it was.**

Bottom line: The evidence suggests that aspirin is significantly associated with a lower incidence of myocardial infarction, higher incidence of major bleeding and greater risk of intracranial haemorrhage compared with the control group among adult patients without prior history of atherosclerosis. However, the difference in all-cause mortality, incidence of cardiovascular mortality and ischaemic stroke is not significant between the groups. The routine use of aspirin for primary prevention needs to be reviewed. The lack of a search strategy means some eligible studies may have been missed.

KSRA76783 2018 Milgrom D, et al. Editor's Choice - Systematic Review and Meta-Analysis of Very Urgent Carotid Intervention for Symptomatic Carotid Disease

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 13 **Number of participants** 5751 **Last search date** September 2017 **Review type** Intervention **Objective** To investigate outcomes of very urgent (< 48 h from neurological event) in comparison to urgent (≥ 48 h from neurological event) carotid intervention for symptomatic carotid disease. **Population** Subjects undergoing carotid endarterectomies (CEAs) or carotid artery stenting (CAS) procedures. Men or women of any age presenting with a recent (over the preceding 90 days) cerebrovascular episode (stroke, transient ischaemic attack [TIA], or amaurosis fugax) that was presumed to have been caused by extracranial carotid disease. **Interventions** Very urgent (< 48 h from neurological event) need of carotid intervention. **Comparator** Urgent (≥ 48 h from neurological event) need of carotid intervention. **Outcome** Peri-procedural outcomes of carotid intervention. Primary outcomes: ipsilateral stroke and death. Secondary outcomes: transient ischaemic attack (TIA) and myocardial infarction (MI). **Study design** Randomised control trials (RCTs) and observational studies.	Overall pooled analysis of 5751 patients demonstrated that compared to the urgent group, the very urgent carotid intervention was associated with a significantly higher risk of stroke (odds ratio [OR] 2.19, 95% confidence interval [CI] 1.46 to 3.26). Twelve studies involving 5586 patients reported that the difference in mortality between the groups was not significant (OR 1.55, 95% CI 0.81 to 2.96). Pooled analysis of 5 studies involving 1088 patients found no significant difference in transient ischaemic attack (TIA) between the groups (OR 1.33, 95% CI 0.55 to 3.19). Four studies with 912 patients reported no significant difference in myocardial infarction between the very urgent and urgent carotid intervention (OR 1.33, 95% CI 0.41 to 4.33).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The search strategy was presented, and judged to have used a limited set of keywords. Additionally, the bibliographic lists of the included articles and relevant review articles meeting the inclusion criteria that were identified during the electronic searches were interrogated for relevant studies. Two reviewers were independently involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **One reviewer performed data extraction and checked by another reviewer. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was assessed using the Cochrane risk-of-bias assessment tool for RCTs and the Newcastle-Ottawa Scale for the assessment of observational cohort studies. Two reviewers were independently involved in risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. The method of analysis was explained and appeared appropriate. No significant heterogeneity was found between the studies in the pooled analysis. Potential reporting bias was assessed using the Egger test and represented graphically with Begg funnel plots. Sensitivity analysis was performed to check the robustness of the study results. The quality of the individual studies was considered in the synthesis.** **Overall summary** **All domains were considered at low or unclear concern.**

Bottom line: Current evidence suggests that very urgent carotid intervention is significantly associated with increased risk of stroke. Whether in the crucial acute period, the risk is significantly higher than the risk of recurrent stroke without surgery should be established and high quality multicentre prospective longitudinal studies or randomised controlled trials are warranted.

KSRA44793 2017 Moresoli P, et al. Carotid Stenting Versus Endarterectomy for Asymptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 5 RCTs (11 reports) **Number of participants** 3019 **Last search date** April 29, 2016 **Review type** Intervention **Objective** To compare the efficacy and safety of carotid artery stenting with that of carotid endarterectomy in patients with asymptomatic carotid stenosis with respect to stroke, myocardial infarction, cranial nerve palsy, hematoma, death, and combinations of these events in the periprocedural period and thereafter. **Population** Patients with asymptomatic carotid stenosis. **Interventions** Carotid artery stenting. Randomised controlled trials in which the randomised groups did not have an equal opportunity to receive anticoagulation or antiplatelet therapies in the post-operative period were excluded. **Comparator** Carotid endarterectomy. **Outcome** Periprocedural or long-term outcomes: Any stroke (whether disabling, major, non-disabling, or minor), myocardial infarction, cranial nerve palsy, hematoma, or death. **Study design** Randomised controlled trials. Case reports, case series, observational studies (e.g., case-control, cross-sectional, and cohort studies), systematic reviews and meta-analyses, letters to the editor, reviews, editorials, commentaries, studies on animal models, and basic science studies were excluded.	The pooled estimates reported that the risk of any periprocedural stroke (Risk ratio [RR] = 1.84, 95% confidence interval [CI] 0.99 to 3.40; 4 trials, n = 2749 patients), any periprocedural stroke or death (RR = 1.72, 95% CI 0.95 to 3.11; 4 trials, n = 2749 patients) and peri-procedural non-disabling stroke (RR = 1.95, 95% CI 0.98 to 3.89; 4 trials, n = 2749 patients) tend to increase with carotid artery stenting (CAS) compared to carotid artery endarterectomy (CEA). However, the risk of periprocedural cranial nerve palsy was significantly lower among patients in the CAS group (RR = 0.07, 95% CI 0.02 to 0.25; 3 trials) compared to CEA group. The summary estimates reported that no significant difference was found between CAS and CEA groups in terms of risk of periprocedural disabling stroke (RR = 1.41, 95% CI 0.41 to 4.84; 4 trials), periprocedural myocardial infarction (RR = 0.55, 95% CI 0.26 to 1.16; 3 trials), any periprocedural or long-term stroke (RR = 1.24, 95% CI 0.76 to 2.03; 3 trials) and the composite outcome of periprocedural stroke, death or myocardial infarction, or long-term ipsilateral stroke (RR = 0.92, 95% CI 0.70 to 1.21; 3 trials).	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. Only randomised controlled trials randomising ≥50 patients were included and found to be appropriate. Conference abstracts were not considered for inclusion. Only English or French language studies were included.** **Domain 2: Identification and Selection of Studies:** **EMBASE (via Ovid), PubMed, MEDLINE (via Ovid), and the Cochrane Library of Controlled Trials were searched for relevant studies. There were no additional attempts made to locate further studies. Search terms were provided, but a full search strategy was not reported. Searches were restricted to studies published in the English or French language, found to be inappropriate. Two reviewers were independently involved in the study selection process and any disagreements between them were resolved by consensus.** **Domain 3: Data Collection and Study Appraisal:** **Two reviewers were independently involved in the data extraction process and any disagreements between them were resolved by consensus or by a third reviewer if required. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Cochrane risk of bias assessment tool. Two reviewers were independently involved in the risk of bias assessment and any disagreements between them were resolved by consensus or by a third reviewer if required.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity for all outcomes. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **The authors acknowledged possible missing of studies due to English or French language restriction in the limitations. Conference abstracts were not considered for inclusion. There were no additional attempts made to locate further studies. Search terms were provided, but a full search strategy was not reported.**

Bottom line: The evidence suggests that any periprocedural stroke, periprocedural non-disabling stroke, and any periprocedural stroke or death seems to be increased with carotid artery stenting compared to carotid endarterectomy in patients with asymptomatic carotid stenosis. Hence, the carotid endarterectomy appears to be the safer and more efficacious treatment for asymptomatic carotid artery stenosis. However, there were some concerns about the review methods and relevant data may have been missed. More randomised controlled trials are needed to address the present review question.

KSRA86922 2017 Murphy SJX, et al. Optimal antiplatelet therapy in moderate to severe asymptomatic and symptomatic carotid stenosis: a comprehensive review of the literature

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 25 **Number of participants** 24,272 **Last search date** 8 July 2018 **Review type** Intervention **Objective** To systematically review the evidence from relevant randomised trials in patients with extracranial moderate to severe asymptomatic and symptomatic carotid stenosis who were treated with antiplatelet therapy. **Population** Male or female patients (aged ≥18 years) with moderate to severe asymptomatic and symptomatic carotid stenosis Interventions Antiplatelet therapy, carotid endarterectomy. **Comparator** Best medical therapy alone. **Outcome** Not specified in the methods section. Reported outcomes include: incidence of ipsilateral neurological events, annual rate of all ischaemic events and death from any cause, cumulative incidence of stroke, death or myocardial infarction within 30 days after the procedure, or death or ipsilateral stroke between 31 days and 1 year, perioperative mortality and morbidity (death or stroke within 30 days) and non-perioperative stroke, cumulative rate of death/any stroke within 30 days etc., ipsilateral stroke alone, all strokes, ipsilateral transient ischemic attack, stroke or any perioperative stroke or death, vascular events only, primary endpoint plus ipsilateral stroke or death between 1 and 3 years, a composite measure of complications, freedom from reintervention or restenosis etc. **Study design** Randomised controlled trials.	One randomised controlled trial reported no significant difference between aspirin and placebo groups in terms of the annual incidence of all ischaemic events (transient ischaemic attack [TIA], ischaemic stroke, unstable angina, myocardial infarction (MI), and death from any cause in patients with asymptomatic carotid stenosis. Six studies reported that primary trial outcomes were observed in 1.5 to 20.1% of asymptomatic > 50% stenosis patients treated by carotid endarterectomy (CEA). Six studies reported that primary trial outcomes were observed in 1.5 to 12% of endovascular treatment (EVT) treated patients over 1 to 120 months. Three studies reported that primary outcomes were observed in 19.4 to 26% of symptomatic patients treated with best medical therapy (BMT) only (predominantly aspirin) over 12 to 36 months follow-up. Overall, various primary outcomes occurred in 1.96 to 14.2% of symptomatic patients after CEA who were mainly treated with aspirin alone (3 studies) or in combination with other antiplatelet regimens (3 studies) over a 6 to 120 month follow up period. Three studies reported that primary outcomes were observed in 1.88 to 14.3% of symptomatic patients after EVT who were mainly treated with initial aspirin-clopidogrel combination therapy, usually for one month after the procedure with longer-term antiplatelet therapy left to the discretion of treating physicians.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. Inclusion criteria were not explicitly defined with regard to outcomes. No restrictions were imposed based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies:** **Medline, Ovid, Embase, Web of Science/Web of Knowledge, and Google Scholar were searched for relevant studies. The reference lists of selected studies and reviews were manually screened for additional relevant articles. Search terms were provided but full search strategy was not reported, therefore it cannot be assessed how efficient it was. Searches were restricted to studies published in the English language between January 1988 and July 2018. The first author was involved in the screening of titles and abstracts. If the abstract suggested the article met the inclusion criteria, the full-text article was obtained and reviewed by the first author and independently by the supervising author. Any discrepancies between them were resolved by consensus.** **Domain 3: Data Collection and Study Appraisal:** **No information was provided regarding the number of authors involved in the data extraction process. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. There was no formal assessment of the methodological quality of the included studies.** **Domain 4: Synthesis and Findings:** **The synthesis included all eligible studies. A narrative synthesis was performed to summarise the findings due to heterogeneity among the studies. The quality of individual studies was not considered in the synthesis.** **Overall summary: High risk of bias in the review** **Inclusion criteria were not explicitly defined with regard to outcomes. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. Searches were restricted to studies published in the English language between January 1988 and July 2018. Appropriate efforts were not made to minimise errors in the study selection process. No information was provided regarding the number of authors involved in the data extraction process. There was no formal assessment of the methodological quality of the included studies.**

Bottom line: The evidence is not sufficient to guide the choice of optimal antiplatelet therapy in patients with carotid stenosis. The review had significant methodological weaknesses, so the findings should be interpreted with caution. Further, randomised controlled trials with comprehensive reporting of recurrent cerebrovascular events are needed to evaluate the relative efficacy and safety of different antiplatelet regimens to optimise peri-procedural and long-term preventive treatment in asymptomatic and symptomatic carotid stenosis patients.

KSRA11948 2016 Newhall KA, et al. Use of Protamine for Anticoagulation During Carotid Endarterectomy: A Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 12 **Number of participants** 10,621 **Last search date** November 2014 **Review type** Intervention Objective To determine whether protamine use is associated with increased rates of thrombotic complications and lower rates of bleeding after carotid endarterectomy. **Population** Adult patients undergoing any carotid procedures who were therapeutically anticoagulated with heparin. **Interventions** Protamine sulfate to reverse heparin at the end of the procedure. **Comparator** No reversal of heparin. **Outcome** Primary outcome: incidence of any type or severity of stroke during hospitalisation. Secondary outcomes: thromboembolic complications (death, myocardial infarction, and transient ischaemic attack) and postoperative bleeding (defined as re-operation for bleeding) events. **Study design** Randomised clinical trial, retrospective or prospective cohort, nested case-control, before-and-after study, or secondary analysis of a randomised trial.	The pooled analysis reported no significant difference between patients who received protamine and those who did not in the risk of stroke (risk ratio [RR] 0.84, 95% confidence interval [CI] 0.55 to 1.29, nine studies, n = 9,932 patients), myocardial infarction (RR 0.89, 95% CI 0.53 to 1.51, three studies, n = 8,189 patients) or death (RR 0.9, 95% CI 0.62 to 1.29, seven studies, n = 9,391 patients). However, the rates of perioperative stroke (1.59% versus 2.02%), the risk of major bleeding (1.7% versus 3.5%) and all-cause mortality (1.2% versus 1.7%) were lower in patients who received protamine when compared to those who did not. The pooled estimates reported that the risk of major bleeding complications requiring re-operation were significantly lower in patients who received protamine (RR 0.57, 95% CI 0.39 to 0.84, 10 studies, n = 10,112 patients) when compared to those who did not receive protamine. The subgroup analysis reported that protamine use was not significantly associated with an increased risk for stroke in the patch closure (RR 1.00, 95% CI 0.06 to 17.59, three studies, n = 381 patients), primary closure (RR 4.95, 95% CI 0.92 to 26.48, three studies, n = 393 patients), no shunt (RR 1.99, 95% CI 0.24 to 16.56, three studies, n = 310 patients) or shunt subgroups (RR 1.46, 95% CI 0.29 to 7.37, four studies, n = 1,206 patients).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate eligibility criteria were defined. Restrictions were reported based on study characteristics, but these appeared to be appropriate to the review question. No restrictions were imposed based on the sources of information.** **Domain 2: Identification and Selection of Studies** **Literature searches were conducted in MEDLINE, EMBASE and Cochrane Library. In addition, clinical trial registries World Health Organisation International Clinical Trials Registry and clinicaltrials.gov, annual proceedings from the annual meetings of the Society for Vascular Surgery and the American Heart Association Scientific Sessions and references of included articles were handsearched to identify unpublished, incomplete or ongoing clinical trials and any further studies. The search terms and search strategy were reported and appeared to be adequate. There were no restrictions imposed based on the language. Two reviewers were independently involved in the study selection process and discrepancies were resolved by consensus.** **Domain 3: Data Collection and Study Appraisal** **At least two reviewers were independently involved in the data extraction process and all discrepancies were resolved by consensus. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using a modified version of the Newcastle-Ottawa scale for both observational studies and randomised trials, which was found to be appropriate. Two reviewers were independently involved in the risk of bias assessment and discrepancies were resolved by consensus.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared inappropriate due to pooling of different study designs (observational studies and randomised controlled trials) into a single estimate. There was no evidence of significant heterogeneity among the studies. Residual moderate heterogeneity decreased after performing sensitivity analysis. Subgroup analysis was also performed. Robustness of the findings was addressed. The quality of individual studies was considered in the synthesis using inappropriate criteria for randomised controlled trials.** **Overall summary** **The method of pooling was inappropriate and the quality of individual studies was considered in the synthesis using inappropriate criteria for randomised controlled trials.**

Bottom line: The evidence suggests that the use of protamine decreases the risk of bleeding complications requiring re-operation after carotid endarterectomy; however, it does not affect the risk of stroke, myocardial infarction or death. The method of pooling and criteria used to assess the quality of randomised controlled trials were inappropriate. Further research is needed to support the review findings across all types of carotid revascularisation.

KSRA5510 2015 Nwachuku EL, et al. Diagnostic value of somatosensory evoked potential changes during carotid endarterectomy: a systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 15 **Number of participants** 4,557 **Last search date** January 2013 **Review type** Diagnostic **Objective** To determine whether changes in somatosensory evoked potential during carotid endarterectomy are diagnostic of perioperative stroke in patients with symptomatic carotid stenosis. **Population** Adults (≥18 years of age) with symptomatic carotid stenosis undergoing carotid endarterectomy. **Interventions** Index test: intraoperative somatosensory evoked potential. **Comparator** NA. **Outcome** Sensitivity, specificity, diagnostic odds ratio, and area under receiver operating characteristic curves of somatosensory evoked potential (SSEP) predicting postoperative neurological outcome. **Study design** Inclusion criteria focused on randomised clinical trials and prospective or retrospective cohort studies, but only prospective and retrospective cohort studies were included. **Reference standard** Postoperative neurological outcome.	The pooled estimates from studies reported a change in SSEP with a strong mean specificity, but with a weaker mean sensitivity of 91% (95% confidence interval [CI] 86 to 94; 15 studies) and 58% (95% CI 49 to 68; 15 studies) respectively in patients with symptomatic carotid stenosis undergoing carotid endarterectomy. Individual studies of patients with a neurological deficit reported that a diagnostic odds ratio for changes in SSEPs was found to be 14.39 (95% CI 8.34 to 24.82), which was 14 times higher than in individuals without a neurologic deficit.	**Domain 1: Study Eligibility Criteria** **High** **The research objective was clearly stated. The inclusion criteria were not explicitly defined with regard to the reference standard. Studies with a sample size of at least 50 patients were included and found to be appropriate. Only English language studies were included.** **Domain 2: Identification and Selection of Studies** **High** **Only PubMed database was searched for relevant studies. The World Science Database for reference lists of retrieved reports and/or experiments was searched for relevant studies. The search terms were provided, but a full search strategy was not reported. Searches were restricted to studies published (between January 1950 and January 2013) and was found to be appropriate. The authors were independently involved in the study selection process and disagreements between them were resolved through discussion.** **Domain 3: Data Collection and Study Appraisal** **Unclear** **No information was provided regarding the number of authors involved in the data extraction and risk of bias assessment. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the QUADAS-2 tool; however, the results of QUADAS-2 assessments are not reported.** **Domain 4: Synthesis and Findings** **Unclear** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity for one outcome (specificity). Meta-regression analyses were used to assess the impact of variables such as rate of the shunt and SSEP reversibility on outcomes. Sensitivity analysis was performed to test the robustness of findings. No evidence of significant publication bias was found using the Deeks funnel plot test. The quality of individual studies does not seem to have been considered in the synthesis.** **Overall summary** **The inclusion criteria were not explicitly defined with regard to the reference standard. Only English language studies were included. A limited range of databases were searched for the study selection process. The search terms were provided, but a full search strategy was not reported; therefore it was not possible to judge if all relevant studies have been retrieved. No information was provided regarding the number of authors involved in the data extraction and risk of bias assessment.**

Bottom line: The evidence suggests that the specificity of intraoperative somatosensory evoked potential is high, but with a low sensitivity in patients with symptomatic carotid stenosis undergoing carotid endarterectomy. Hence, the change in somatosensory evoked potential could be useful in predicting the neurological outcome in those treated with carotid endarterectomy. The change in somatosensory evoked potential is 14 times greater in patients with perioperative neurological deficits than patients without neurological deficits during carotid endarterectomy. There were some limitations with the review methods such as the lack of details with regards to eligibility criteria for the reference standard, a restriction to the English language, a limited database search and the lack of a search strategy. It is unclear whether data extraction and quality assessment were undertaken in duplicate, which means that possible reviewer-induced error and subsequent bias should not be eliminated. Further studies are needed for better understanding the etiologies of perioperative strokes and also to focus on the use of somatosensory evoked potential to design prevention strategies in reducing perioperative cerebral infarctions during carotid endarterectomy.

KSRA34066 2017 Orrapin S, et al. Carotid endarterectomy for symptomatic carotid stenosis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 3 **Number of participants** 6343 **Last search date** July 2016 **Review type** Intervention **Objective** To determine the balance of benefit versus risk of endarterectomy plus best medical management compared with best medical management alone, in people with a recent symptomatic carotid stenosis (i.e. transient ischaemic attack or non-disabling stroke). **Population** People with carotid stenosis and recent transient ischaemic attacks (TIA) or minor ischaemic strokes in the territory of that artery. **Interventions** Carotid surgery (i.e. best medical therapy plus surgery). Surgery was defined as the first carotid endarterectomy performed in participants who were randomised to surgery. **Comparator** No carotid surgery (i.e. best medical therapy alone). **Outcome** Primary outcomes: Five-year cumulative any stroke or operative death (includes all deaths within 30 days of trial surgery); five-year cumulative ipsilateral ischaemic stroke (described as insufficient blood flow to the cerebral hemisphere secondary to the same side occlusion, or severe stenosis of the internal carotid artery in participants), or operative stroke, or operative death Secondary outcomes: Five-year cumulative disabling or fatal ipsilateral ischaemic, or operative stroke, and operative death **Study design** Randomised controlled trials.	The pooled analysis reported that the surgery endarterectomy plus best medical management significantly reduced the risk of any stroke or operative death in patients with carotid stenosis of 70 to 99% (Risk ratio [RR] 0.53, 95% confidence interval [CI] 0.42 to 0.67, 3 randomised controlled trials [RCTs], n = 1095 patients) and 50 to 69% (RR 0.77, 95% CI 0.63 to 0.94, 3 RCTs, n = 1549 patients) when compared to medical management alone, whereas, no significant difference was found between endarterectomy plus best medical management and best medical management alone in patients with near occlusion (RR 0.95, 95% CI 0.59 to 1.53, 2 RCTs, n = 271 patients), carotid stenosis of 30 to 49% (RR 0.97, 95% CI 0.79 to 1.19, 2 RCTs, n = 1429 patients) and <30% (RR 1.25, 95% CI 0.99 to 1.56, 2 RCTs, n = 1746 patients). The summary estimates reported no significant difference between surgery and no surgery groups in the risk of ipsilateral ischemic stroke and any operative stroke or death (Near occlusions: RR 1.03, 95% CI 0.57 to 1.84, 2 RCTs, n = 271 patients; carotid stenosis of 50 to 69%: RR 0.84, 95% CI 0.60 to 1.18, 3 RCTs, n = 1549 patients; 30 to 49%: RR 0.93, 95% CI 0.62 to 1.38, 2 RCTs, n = 1429 patients; <30%: RR 1.27, 95% CI 0.80 to 2.01, 2 RCTs, n = 1746 patients) and also in the risk of disabling or fatal ipsilateral ischemic or operative stroke and death (Near occlusions: RR 1.29, 95% CI 0.51 to 3.27, 2 RCTs, n = 271 patients; carotid stenosis of 50 to 69%: RR 0.73, 95% CI 0.46 to 1.15, 2 RCTs, n = 1502 patients; 30 to 49%: RR 0.96, 95% CI 0.60 to 1.54, 2 RCTs, n = 1429 patients; <30%: RR 1.72, 95% CI 0.99 to 2.96, 2 RCTs, n = 1746 patients). The pooled estimates from 3 trials (n = 1095 patients) reported that the surgery significantly reduced the risk of ipsilateral ischemic stroke and any operative stroke or death (RR 0.47, 95% CI 0.25 to 0.88) and disabling or fatal ipsilateral ischemic or operative stroke and death (RR 0.40, 95% CI 0.26 to 0.64) in patients with carotid stenosis of 70 to 99%. The subgroup analysis of 2 RCTs reported that a significant reduction in the risk of 5-year cumulative risk of ipsilateral carotid ischaemic stroke, and any stroke or death within 30 days after surgery in men (Risk difference [RD] -0.10, 95% CI -0.13 to -0.06, n = 1886 patients), in all age groups such as <65 years (RD -0.05, 95% CI -0.09 to -0.01, n = 1281 patients), 64 to 74 years (RD -0.07, 95% CI -0.12 to -0.03, n = 1143 patients) and >75 groups (RD -0.17, 95% CI -0.26 to -0.09, n = 294 patients), in <2 weeks since last event, 2 to 4 weeks and 4 to 12 weeks since last event. However, no significant reduction was found in women and in >12 weeks since last event.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies:** **Literature searches were conducted in the Cochrane Stroke Group Trials Register, CENTRAL, MEDLINE, Embase, Web of Science Core Collection, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform portal. Reference lists of all relevant studies and journals such as Annals of Surgery, Annals of Vascular Surgery, Cardiovascular Surgery, European Journal of Vascular Surgery, Journal of Vascular Surgery, Stroke were hand-searched for further published, unpublished and ongoing trials. The search strategy was reported in full and appeared adequate. The searches were not restricted to any language. Two review authors were independently involved in the study selection process and disagreements were resolved through discussion.** **Domain 3: Data Collection and Study Appraisal:** **Data extraction was performed by two review authors independently and disagreements were resolved through discussion. Sufficient study characteristics were extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool. One review author assessed the risk of bias and another review author independently reviewed these decisions. Disagreements between the authors were resolved through discussion.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity among the studies. Subgroup analysis was performed to explore any sources of heterogeneity. Sensitivity analysis was planned to test the robustness of the findings. However, it was not feasible due to a low number of included studies. The quality of individual studies was considered in the synthesis.** **Overall summary** **All domains were considered at low concern suggesting no limitations regarding the review process.**

Bottom line: The available evidence suggests that the endarterectomy has some benefit for participants with 50% to 69% of symptomatic stenosis, and more beneficial for those with 70% to 99% of stenosis without near-occlusion, especially in men when compared to medical management alone. The evidence also suggests that the effectiveness of surgery decreases with increasing delay of time since the last event. These findings are likely to be reliable given that this review was assessed as having low risk of bias. Secondary research in this area remains pertinent.

KSRA8880 2015 Ouyang YA, et al. Efficacy and safety of stenting for elderly patients with severe and symptomatic carotid artery stenosis: A critical meta-analysis of randomized controlled trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 9 **Number of participants** 6,984 **Last search date** May 2015 **Review type** Intervention **Objective** To estimate short-term and long-term therapeutic efficacy and safety of carotid artery stenting and carotid artery endarterectomy for elderly patients with severe and symptomatic carotid artery stenosis. **Population** Elderly patients (>60 years of age) with severe and symptomatic carotid artery stenosis >50% of the luminal diameter or asymptomatic patients with a >60% stenosis. **Interventions** Carotid artery stenting (CAS). Preoperative aspirin was begun at least 72 hours before CAS or CEA and was continued indefinitely in both groups. **Comparator** Carotid artery endarterectomy (CEA). Preoperative aspirin was begun at least 72 hours before CAS or CEA and was continued indefinitely in both groups. **Outcome** Primary outcomes: stroke, death, or both of them. Secondary outcomes: complications (transient ischaemic attack, cranial nerve palsy, haematoma, restenosis, infection, and artery thrombosis) and hospital stay. **Study design** Randomised controlled trials (RCTs). Reviews, non-RCTs and meeting abstracts were excluded.	The pooled analysis reported no significant difference for mortality between CAS and CEA during periprocedural 30 days (risk ratio [RR] 1.22, 95% confidence interval [CI] 0.69 to 2.14, six studies, n=3,160), postprocedural 24 months (RR 0.99, 95% CI 0.71 to 1.37, two studies, n=1,530), 48 months (RR 1.07, 95% CI 0.89 to 1.29, four studies, n=3,867) and >48 months (RR 1.23, 95% CI 1.00 to 1.52, three studies, n=1,970). A higher incidence of stroke was associated with CAS during periprocedural 30 days (RR 1.62, 95% CI 1.31 to 2.00, seven studies, n=6,749), 48 months (RR 1.37, 95% CI 1.11 to 1.70, four studies, n=3,867) and >48 months (RR 1.76, 95% CI 1.34 to 2.31, three studies, n=1,967) compared to CEA, whereas there was no significant difference between the groups during postprocedural 24 months (RR 1.08, 95% CI 0.80 to 1.47, three studies, n=1,617). Compared with CEA, CAS showed a decreased incidence of periprocedural myocardial infarction (MI) at 30 days (RR 0.44, 95% CI 0.26 to 0.75, four studies, n=3,860), haematoma (RR 0.31, 95% CI 0.14 to 0.68, four studies, n=1,215) and cranial nerve palsy (RR 0.09, 95% CI 0.04 to 0.22, five studies, n=1,549) and increased risk of bradycardia or hypotension (RR 8.45, 95% CI 2.91 to 24.58, two studies, n=624). No significant difference was observed between CAS and CEA with respect to hospital stay (mean difference [MD] -2.08, 95% CI -4.47 to -0.32, three trials).	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. Meeting abstracts and non-English published papers were excluded.** **Domain 2: Identification and Selection of Studies:** **Literature searches were conducted in PubMed, EMBASE, the Cochrane Library, Clinical Trials Register Centres and Google Scholar. Additionally, related articles, references of relevant trials, and reviews were also screened to identify potential publications. The search terms were provided, but a full search strategy was not reported. There was no information on whether searches were restricted by publication format or language. No information was provided on the number of reviewers involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal:** **Two reviewers were independently involved in the data extraction process and risk of bias assessment. Discrepancies were resolved by discussion with a third reviewer. Sufficient study characteristics have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was performed by using the Cochrane risk of bias tool.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to have included all relevant studies. Analyses predefined in the methodology section were performed appropriately. No significant heterogeneity was found between the studies. Publication bias was assessed using funnel plots and found no evidence of bias. Quality of the individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **Only English language studies were considered for inclusion in the review. A limited range of databases were searched for the study selection process. The search terms were provided, but a full search strategy was not reported. There was no information on whether searches were restricted by publication format or language.**

Bottom line: The current evidence suggests that carotid artery stenting is associated with a higher risk of non-disabling stroke of both short-term and long-term periods in elderly patients with severe and symptomatic carotid stenosis. However, carotid artery stenting reduces the risk of haematoma, periprocedural myocardial infarction and cranial nerve palsy. The exclusion of meeting abstracts and non-English published papers and the lack of a complete search strategy means that some relevant studies may have been missed. It was unclear if two reviewers were independently involved in the study selection, making it difficult to rule out reviewer error and bias.

KSRA19071 2016 Pandit AK, et al. High-dose statin therapy and risk of intracerebral hemorrhage: a meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 7 **Number of participants** 62204 **Last search date** June 10, 2015 **Review type** Intervention **Objective** To assess the association between higher dose of various statins and risk of intracerebral hemorrhage among patients with cardiovascular disease. **Population** Adults patients (age ≥18 years) with cardiovascular disease. **Interventions** High dose of statins (atorvastatin 80 mg, simvastatin 80 mg, pravastatin 40 mg, rosuvastatin 20 mg per day). **Comparator** Placebo. Outcome Intracerebral hemorrhage. **Study design** Randomised controlled trials.	The pooled analyses reported a high dose of statin was significantly associated with the risk of intracerebral hemorrhage compared to the control group (Risk ratio [RR] 1.53, 95% Confidence interval [CI]: 1.16 to 2.01, 7 trials, n= 62204 patients). The pooled analyses reported no significant difference in the all-cause mortality between the high dose of statin and control groups (RR 0.95, 95% CI: 0.86 to 1.06, 7 trials, n= 62204 patients).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were reported based on study characteristics. No restrictions were reported based on sources of information.** **Domain 2: Identification and Selection of Studies** **PubMed, EMBASE, and Google Scholar were searched for relevant studies. Other sources were searched for additional studies. A detailed search strategy was not reported. Searches were not restricted to date, publication format or language. Two review authors were involved in study selection and disagreements were resolved by discussion among all the authors until consensus was obtained.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process and any disagreements were resolved by discussion among all the authors until consensus was obtained. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of the included studies was assessed using the Jadad score, which is outdated. Two reviewers were independently assessed the quality of the included studies and any disagreements were resolved by discussion among all the authors, and subsequent agreement was reached.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity for all-cause mortality. Appropriate attempts were not made to explore the possible sources of heterogeneity. No evidence of significant publication bias was found using Begg's funnel plot, but this was not appropriate as the number of included studies for each comparison was small (< 10). The quality of individual studies was considered in the synthesis.** **Overall summary** **A detailed search strategy was not reported. Appropriate attempts were not made to explore the possible sources of heterogeneity.**

Bottom line: Evidence indicates that a higher dose of statins may be associated with the risk of intracerebral hemorrhage in patients with cardiovascular disease. There was no difference in all-cause mortality between the high dose of statin and control groups. The results must be interpreted cautiously due to the presence of heterogeneity, and methodological weaknesses of the review. Future studies are needed to confirm the current findings.

KSRA27462 2017 Paraskevas KI, et al. Carotid Stenting Prior to Coronary Bypass Surgery: An Updated Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 31 **Number of participants** 2,727 **Last search date** 31 October 2015 **Review type** Intervention **Objective** To determine 30 day outcomes in patients with concurrent carotid and cardiac disease who underwent carotid artery stenting followed by coronary artery bypass grafting. Secondary endpoints included similar analyses in specified subgroups of: 'same-day' versus staged carotid artery stenting plus coronary artery bypass grafting, neurologically asymptomatic versus symptomatic patients and outcomes (including bleeding complications) stratified for the choice of perioperative antiplatelet strategy. **Population** Patients with preoperative neurological status (asymptomatic or symptomatic, past history of transient ischaemic attack, stroke, or amaurosis fugax) with unilateral or bilateral carotid stenoses and cardiac disease. Interventions Carotid artery stenting plus coronary artery bypass grafting. **Comparator** NA. **Outcome** Prevalence of death, any stroke, myocardial infarction, death/stroke, and death/stroke/myocardial infarction and postoperative bleeding complications. **Study design** Non-randomised cohort studies. Case reports, reviews, letters, editorials and animal studies were excluded. Reference standard NA Exposure NA **PP factor** Timing of the CAS and CABG procedures and type of antiplatelet strategy	The pooled analysis of 31 studies (n = 2,727 patients) reported that the prevalence of 30 day mortality or death, any stroke, myocardial infarction (MI), death/any stroke and 30 day death/stroke/MI was found to be 4.3% (95% confidence interval [CI] 3.6 to 5.3), 5.2% (95% CI 4.4 to 6.2), 2.3% (95% CI 1.6 to 3.3), 7.9% (95% CI 6.9 to 9.2) and 8.8% (95% CI 7.3 to 10.5) respectively in patients undergoing carotid artery stenting (CAS) plus coronary artery bypass grafting (CABG) Subgroup analysis reported that patients (from 20 studies, n = 2,196 patients) received staged CAS then CABG procedures were associated a mortality rate of 4.8% (95% CI 3.3 to 6.8), perioperative stroke rate of 5.4% (95% CI 4.5 to 6.5) and MI rate of 4.2% (95% CI 3.2 to 5.6). Subgroup analysis reported that patients (from 12 studies, n = 531 patients) who received same-day CAS plus CABG procedures were associated with a mortality rate of 4.5% (95% CI 2.9 to 7.0), perioperative stroke rate of 3.4% (95% CI 2.0 to 5.9) and MI rate of 1.8% (95% CI 0.9 to 3.7). The summary estimates from five studies in purely asymptomatic patients (n = 441 patients) reported a mortality rate of 3.7% (95% CI 2.3 to 6.0), perioperative stroke rate of 3.2% (95% CI 1.9 to 5.4) and MI rate of 2.2% (95% CI 1.2 to 4.1). Five antiplatelet (APRx) strategies were identified in the review: 1. No APRx (death 1.4%; stroke 3%; MI 1.7%; no data on bleeding complications). 2. Single APRx before CAS and CABG, then dual APRx after CABG (death 5.1%; stroke 2%; MI 1.6%; 7.3% bleeding complications). 3. Dual APRx pre-CAS down to one APRx pre-CABG (death 5%; stroke 5.2%; MI 2.7%; 2.8% bleeding complications). 4. Dual APRx pre-CAS, both stopped pre-CABG (death 8.1%; stroke 6.3%; MI 1.9%; insufficient data on bleeding). 5. Dual APRx pre-CAS and continued through CABG (death 6.1%; stroke 7.3%; MI 4%; insufficient data on bleeding complications).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated, however the inclusion criteria were not clearly defined. No restrictions were imposed based on study characteristics. Only English language studies were included.** **Domain 2: Identification and Selection of Studies** **The PubMed/MEDLINE, EMBASE and the Cochrane databases were searched for relevant studies. There were no additional attempts made to locate further studies. A full search strategy was not reported, the authors reported that searching was around 'CAS plus CABG'. The searches were restricted to studies published (between January 1997 and October 2015) and found to be inappropriate. Two investigators were involved in the study selection process and any disagreements between them were resolved either by consensus discussion or by consulting a third party.** **Domain 3: Data Collection and Study Appraisal** **Two investigators were independently involved in the data extraction and any disagreements between them were resolved through discussion. Insufficient study characteristics were provided, making it difficult for the reader to interpret the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Newcastle-Ottawa scale. No information was provided regarding the number of authors involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity for any outcome. Evidence of significant publication bias was found by means of a funnel plot, adjusted using trim and fill method. The quality of individual studies was considered in the synthesis.** **Overall summary** **High risk of bias in the review**

Bottom line: The evidence suggests that 7.9% risk of death/stroke and an 8.8% risk of death/stroke/myocardial infarction following carotid artery stenting (CAS) plus coronary artery bypass grafting (CABG) is higher than the risk of death/stroke in patients who received isolated CABG. Hence, a safety advantage with prophylactic CAS is not beneficial over isolated CABG in this type of patient. Moreover, overall 30 day outcomes after CAS plus CABG are similar to those found after CEA plus CABG, except in patients with a history of transient ischaemic attack/ stroke, where staged or same-day carotid endarterectomy plus CABG is apparently the better option. However, there were several limitations in the review methods and relevant data may have been missed.

KSRA59948 2018 Paraskevas KI, et al. An Updated Systematic Review and Meta-analysis of Outcomes Following Eversion vs. Conventional Carotid Endarterectomy in Randomised Controlled Trials and Observational Studies

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 25 **Number of participants** 49,500 **Last search date** 1 February 2017 **Review type** Intervention **Objective** To establish whether eversion carotid endarterectomy confers significant benefit over conventional carotid endarterectomy. **Population** Patients undergoing eversion (eCEA) or conventional (cCEA) carotid endarterectomy. **Interventions** Eversion carotid endarterectomy (CEA). Other interventions were excluded. **Comparator** Conventional CEA or patched CEA. **Outcome** Peri-operative outcomes (30-day stroke, death, myocardial infarction [MI], stroke/death, stroke/death/MI, neck haematoma, cranial nerve injury) and late (>50%) restenosis. **Study design** Randomised controlled trials and observational studies. Case reports, reviews, letters or editorials were excluded.	The pooled analysis of randomised controlled trials (RCTs) reported no significant differences between eversion carotid endarterectomy (eCEA) and conventional CEA (cCEA) in terms of 30-day stroke (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.31 to 1.04, n=2406), 30-day death (OR 0.75, 95% CI 0.34 to 1.70, n=2406), 30-day death/stroke (OR 0.37, 95% CI 0.11 to 1.28, n=2406), 30-day myocardial infarction (MI) (OR 1.13, 95% CI 0.39 to 3.25, n=2270), 30-day death/stroke/MI (OR 0.51, 95% CI 0.18 to 1.46, n=2270), cranial nerve injury (CNI) (OR 0.68, 95% CI 0.45 to 1.01, n=2406) and neck haematoma (OR 0.69, 95% CI 0.27 to 1.77, n=2005). However, eCEA was associated with a significant reduction in late >50% restenosis compared to cCEA (OR 0.40, 95% CI 0.23 to 0.69, n=1890). The pooled analysis of observational studies (OSs) observed that eCEA was associated with significant reductions in 30-day ipsilateral stroke (OR 0.58, 95% CI 0.49 to 0.71, n=20,270), 30-day death (OR 0.46, 95% CI 0.32 to 0.67, n=20,270), 30-day death/ stroke (OR 0.52, 95% CI 0.44 to 0.61, n=20,270), 30-day death/stroke/MI (OR 0.50, 95% CI 0.38 to 0.67, n=7718) and late >50% restenosis (OR 0.49, 95% CI 0.25 to 0.94, n=8008) compared to cCEA. However, no significant differences was found between eCEA and cCEA in terms of 30 day MI (OR 1.01, 95% CI 0.71 to 1.44, n=7718), CNI (OR 0.76, 95% CI 0.37 to 1.56, n=19111) or neck haematoma (OR 1.25, 95% CI 0.82 to 1.90, n=7398). The combined results of RCTs and OSs reported that eCEA was associated with significant reductions in 30-day ipsilateral stroke (OR 0.63, 95% CI 0.46 to 0.86, n=44449), 30-day death (OR 0.55, 95% CI 0.43 to 0.72, n=25,489), 30-day death/stroke (OR 0.58, 95% CI 0.50 to 0.67, n=24,929), neck haematoma (OR 1.27, 95% CI 1.01 to 1.58, n=30,166) and late >50% restenosis (OR 0.45, 95% CI 0.26 to 0.78, n=11,465) compared to cCEA. There were no differences in 30 day MI (OR 1.04, 95% CI 0.75 to 1.45, n=29,328), 30 day death/stroke/MI (OR 0.68, 95% CI 0.45 to 1.02, n=9808), or CNI (OR 0.69, 95% CI 0.40 to 1.22, n=41,720). Similarly, the combined results of RCTs and OSs observed no significant differences between eCEA and patched CEA (pCEA) in terms of 30-day stroke (OR 0.71, 95% CI 0.37 to 1.36, n=16,149), 30-day death (OR 0.64, 95% CI 0.35 to 1.18, n=16,709), 30-day MI (OR 0.98, 95% CI 0.17 to 5.69, n=736), 30-day death/stroke (OR 0.64, 95% CI 0.35 to 1.18, n=16,149), CNI (OR 0.50, 95% CI 0.20 to 1.28, n=13,299), or late >50 restenosis (OR 0.68, 95% CI 0.24 to 1.95, n=2488). However, eCEA was associated with significantly lower rates of neck haematoma compared to pCEA (OR 0.53, 95% CI 0.30 to 0.95, n=1895).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. Date limitations appeared appropriate. Only English language studies were included.** **Domain 2: Identification and Selection of Studies** **PubMed/Medline, Embase and the Cochrane databases were searched for relevant studies. No further efforts were made to perform searches additional to a database search. Search terms were provided, but a full search strategy was not reported. The search strategy excluded non-English language studies, however, the risk of bias rating for this domain remains low because the exclusion of non-English language studies has been accounted for in domain 1.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process and any disagreements were resolved by discussion. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The quality of the included studies was assessed using the Cochrane risk of bias assessment tool for randomised controlled trials the Newcastle-Ottawa score for observational studies. No information was provided regarding the number of authors involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate. There was evidence of significant heterogeneity. Sensitivity analysis was performed to address the heterogeneity and robustness of the findings. The quality of individual studies was considered in the synthesis.** **Overall summary** **Restriction to English language studies was reported. No further efforts were made to perform searches additional to a database search. Search terms were provided, but a full search strategy was not reported. No information was provided regarding the number of authors involved in the risk of bias assessment.**

Bottom line: The available evidence suggests that eversion carotid endarterectomy (eCEA) seems to be superior to conventional CEA regarding peri-operative outcomes (stroke, death, death/stroke) and late restenosis but appears to be similar to patched CEA in both early and late outcomes. Restriction to English language studies, no attempts on methods additional to database searching and lack of search strategy means some relevant studies may have been missed. The authors did not state whether the risk of bias assessment was undertaken in duplicate, so reviewer error and bias could not be ruled out.

KSRA32480 2017 Phillips P, et al. Systematic review of carotid artery procedures and the volume-outcome relationship in Europe

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** 233,411 **Last search date** June 2016 **Review type** Aetiological **Objective** To evaluate the relationship between the volume of carotid procedures and outcomes, including mortality and stroke. **Population** Patients undergoing extracranial carotid procedures in Europe. **Outcome** Mortality, stroke, length of hospital stay and complications. **Study design** Observational studies (retrospective). Exposure Volume of carotid procedures.	Two large studies reported an inverse relationship between hospital volume and mortality and combined mortality and stroke, following carotid endarterectomy (CEA). However, three smaller studies found no statistically significant evidence of a relationship. One study reported no evidence of a relationship between the hospital volume of elective or emergency CEAs undertaken and complication rates (renal, respiratory, infection, shock, local complications, thrombotic or embolic events, cardiac and disseminated intravascular coagulation or transfusion reactions). One study found evidence of a statistically significant association between increased hospital volume of CEA and reduced length of hospital stay. No clear convincing evidence of an association was found following carotid artery stenting (CAS) regarding mortality and combined mortality and stroke. One study reported no significant evidence of a relationship between hospital CAS volume and stroke, or between hospital CAS volume and acute myocardial infarction. Additionally, no clinically relevant volume-related trends were identified regarding the length of hospital stay and CAS.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. No information was provided about the restrictions related to sources of information.** **Domain 2: Identification and Selection of Studies** **Literature searches were conducted in MEDLINE, EMBASE, the Cochrane Library, Science Citation Index and CINAHL. In addition, subsequent handsearches of key journals, conference proceedings, citation and reference list searches (of included studies and relevant systematic reviews) were conducted. The search strategy was reported in full and appeared to be adequate. There were no restrictions reported based on the date, publication format or language. Two authors independently screened titles, abstracts and full texts to assess the study eligibility.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and risk of bias assessment. Sufficient study characteristics have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using appropriate criteria.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant studies and was appropriate. Due to the high risk of bias and the methodological and clinical heterogeneity among the included studies, meta-analysis was considered inappropriate. A narrative synthesis was performed to summarise the findings of the review. Quality of the individual studies was considered in the synthesis.** **Overall summary** **The authors acknowledged that the quality of the review is also potentially affected by the restriction to English language papers as a result of available resources for translation and interpretation in the limitations.**
Bottom line: The current review suggests the existence of a relationship between the hospital volume of elective carotid endarterectomy and mortality in European populations and thereby supports the centralisation of carotid endarterectomy. Further larger reviews incorporating studies from the rest of the world is needed.		

KSRA52445 2017 Pini R, et al. The fate of asymptomatic severe carotid stenosis in the era of best medical therapy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** 2185 **Last search date** January 2016 **Review type** Prognostic/Predictive **Objective** To assess the ipsilateral transient ischemic attack (TIA) stroke and annual risk of stroke in patients with ACAS ≥70%, thereby also evaluating the adherence to best medical therapy. Population Patients with asymptomatic carotid artery stenosis (ACAS) ≥70%. **Interventions** NA **Comparator** NA **Outcome** Ipsilateral transient ischemic attack-stroke and annual risk of stroke. **Study design** No limitations or restrictions for the study design were used **Reference standard** NA **Exposure** NA **PP factor** Time; outcomes per year were reported.	The pooled risk was 3.4%/year for ipsilateral transient ischemic attack (TIA)-stroke and 1.6%/year for stroke. Five studies, published from 2014, had best medical therapy adherence, for a total of 1665 patients/year. The pooled risk was 3.5%/year for ipsilateral TIA-stroke and for stroke.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were applied in eligibility criteria based on study characteristics. Case reports, non-English language publications, unpublished data or data reported only in the abstract form were excluded.** **Domain 2: Identification and Selection of Studies:** **Relevant trials were identified from the PubMed and Scopus. References of included studies were screened in order to identify additional relevant studies. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. The searches were restricted to date, publication format, and language. Two reviewers independently judged study eligibility. The final inclusion of the studies was based on an agreement between all the authors of the study.** **Domain 3: Data Collection and Study Appraisal:** **Two review authors independently extracted the data. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was performed using the Newcastle–Ottawa Scale for observational studies. However, no quality assessment tool was used for the included randomised controlled trial.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to have included all relevant studies. The method of analysis was explained and appeared appropriate. No significant heterogeneity was found. Robustness of the findings was not demonstrated. Bias in primary studies was addressed while interpreting findings.** **Overall summary: High risk of bias in the review** **Non-English language publications, unpublished data or data reported only in the abstract form were excluded.** **No full search strategy was reported.**

Bottom line: Current evidence suggests that severe asymptomatic carotid artery stenosis has a fairly high-risk rate of progression towards symptoms, even when treated with contemporary best medical therapy. The review had a number of shortcomings, including a limitation to English language publications. Unpublished data or data reported only in the abstract form were excluded.

KSRA77299 2018 Poorthuis MHF, et al. High Operator and Hospital Volume are Associated With a Decreased Risk of Death and Stroke Following Carotid Revascularization: A Systematic Review and Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 87 **Number of participants** >4,547,992 **Last search date** 21 August 2017 **Review type** Prognostic/Predictive **Objective** To examine the association between operator or hospital volume and procedural outcomes of carotid revascularisation. **Population** Patients undergoing either carotid endarterectomy (CEA) or carotid artery stenting (CAS) for asymptomatic or symptomatic carotid stenosis. **Outcome** Primary Outcomes: Composite outcomes of procedural death or stroke (within 30-days). Secondary Outcomes: Procedural death; procedural stroke; procedural myocardial infarction; procedural death, stroke or myocardial infarction; cranial nerve injury following carotid endarterectomy (CEA) (defined as any temporary palsy of a cranial nerve at the operative side without an underlying stroke or transient ischaemic attack). **Study design** Observational studies and randomised clinical trials. Learning curve studies were excluded. **Reference standard** NA **PP factor** Hospital volume (defined as the number of carotid procedures performed per hospital within a certain timeframe) or operator volume (defined as the number of carotid procedures performed per operator within a certain timeframe). In-trial volumes were excluded, since they can differ widely from annual volumes.	For patients undergoing carotid endarterectomy (CEA): In terms of the operator volume for patients undergoing CEA, pooled analysis reported that a high operator volume was associated with lower odds of procedural death or stroke (odds ratio [OR] 0.50, 95% confidence interval [CI] 0.28 to 0.87; 3 studies) and lower risk of procedural death or stroke (relative risk [RR] 0.59, 95% confidence interval [CI] 0.42 to 0.83; 9 studies) compared to low operator volume. … For patients undergoing carotid artery stenting (CAS): In terms of the operator volume for patients undergoing CAS, a single study reported that a high operator volume was associated with lower odds of procedural death or stroke (OR 0.43, 95% CI 0.20 to 0.95; 1 study) and lower risk of procedural death or stroke (RR 0.43, 95% CI 0.26 to 0.74; 1 study) compared to low operator volume. … In terms of the hospital volume for patients undergoing CAS, a single study reported that a high hospital volume was associated with no difference in the hazard of procedural death, stroke or myocardial infarction (hazard ratio [HR] 1.10, 95% CI 0.75 to 1.63; 1 study) or the risk of procedural death, stroke or myocardial infarction (RR 0.94, 95% CI 0.44 to 2.00; 1 study) compared to low hospital volume.	**Domain 1: Study Eligibility Criteria** **Eligibility criteria were well described, and appeared to be suitable to address the review question. Studies were restricted based on publication format (only full-text articles published in peer-reviewed journals were included) and language (only articles written in English, German, French, Spanish or Dutch were included).** **Domain 2: Identification and Selection of Studies** **Pubmed and EMBASE databases were searched to identify relevant articles. Grey literature was excluded; however, the reference lists of included articles and identified reviews were checked to identify additional studies. The search strategies were reported in full, and appeared to be adequate. Study selection was performed independently by two authors, and disagreements were resolved through consensus involving three authors.** **Domain 3: Data Collection and Study Appraisal** **Two authors were independently involved in data extraction. Sufficient study characteristics appear to have been extracted to enable interpretation of the results. All relevant studies appear to have been included. Risk of bias was assessed using an adapted version of the Newcastle-Ottawa Scale (NOS); this was considered appropriate. No information was provided on the number of reviewers involved in risk of bias assessment.** **Domain 4: Synthesis and Findings** **All relevant studies appear to be included in the synthesis. All pre-defined analyses appear to be presented; although there are some minor deviations in which outcomes will be presented in the full paper vs. the PROSPERO record. The synthesis is generally appropriate. Heterogeneity was assessed, and found to be substantial (>50%) for some outcomes. Sensitivity analyses were performed and did not appear to impact the outcome, suggesting the data was robust; however, since I2 values were not provided, it was not clear what impact these analyses had on heterogeneity. Publication bias was assessed using funnel plots and Egger's regression, and found to be significant for some outcomes. The quality of the studies was considered in the synthesis.** **Overall summary** **Studies were restricted based on publication format (only full-text articles published in peer-reviewed journals were included) and language (only articles written in English, German, French, Spanish or Dutch were included), meaning relevant studies may have been missed. No information was provided on the number of reviewers involved in risk of bias assessment, meaning reviewer error and bias may have been present. Publication bias was assessed using funnel plots and Egger's regression, and found to be significant for some outcomes.**

Bottom line: Current evidence suggests that patients undergoing carotid revascularisation procedures (such as carotid endarterectomy or carotid artery stenting) under a surgical team or in a hospital that performs a high volume of surgeries per year are less likely to experience death or stroke as a result of their surgery. However, these conclusions must be interpreted with some caution, since relevant studies may have been missed, and reviewer error and bias may have been present. Future studies that focus on carotid artery stenting (an underresearched indication) and that assess a more extensive range of outcomes (such as myocardial infarction and cranial nerve injury) are needed to provide additional evidence to inform the review question.

KSRA101546 2013 Raman G, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 47 (56 publications) **Number of participants** Unclear **Last search date** 31 December 2012 **Review type** Intervention **Objective** To compare management strategies for adults with asymptomatic carotid artery stenosis and the incidence of ipsilateral stroke with medical therapy alone. **Population** Adults (aged 18 years or older) who had asymptomatic atherosclerotic narrowing of the lumen of the carotid bifurcation or the extracranial part of the internal carotid artery between 50% and 99%, but had no ipsilateral carotid territory symptoms within the preceding 6 months **Interventions** Carotid artery stenting (CAS) plus medical therapy, carotid endarterectomy (CEA) plus medical therapy. **Comparator** Medical therapy alone, CEA plus medical therapy. **Outcome** Periprocedural and 30-Day outcomes, long-term outcome, rate of ipsilaterai Stroke. **Study design** Randomised, controlled trials and prospective or retrospective nonrandomised, comparative studies.	The pooled analyses reported statistically significant differences the risk for fatal stroke, death from any cause, or death from cardiovascular causes between the carotid endarterectomy (CEA) and medical therapy (RR 0.93, 95% Confidence interval [CI] 0.14 to 6.24, 3 nonrandomised comparative studies). The pooled analyses reported ipsilateral stroke, including any stroke within 30 days was in favor of the CEA group compared to the medical therapy (RR 0.72, 95% CI 0.58 to 0.90, 3 Randomised controlled trials). The pooled analyses of twenty-six studies reported the incidence rate of ipsilateral stroke was 1.68% per year of follow-up. Studies reported the rate of the periprocedural composite outcome of stroke or death was greater in the carotid artery stenting (CAS) group compared to the CEA. Studies reported the rate of periprocedural myocardial infarction was greater with CEA compared to the CAS. Studies reported no significant difference in the risk for outcomes of ipsilateral stroke (including the periprocedural composite outcome of stroke or death), any stroke (including periprocedural death), or a composite endpoint including ipsilateral stroke between patients treated with CAS or CEA. One trial reported greater incidences of postprocedural ipsilateral stroke (including any periprocedural stroke) in the CAS than in the CEA group. Two trials reported an increased risk for periprocedural stroke, death, and myocardial infarction with CEA and medical therapy compared to medical therapy alone. Trials reported statistically significantly lower ipsilateral stroke and any stroke with CEA than with medical therapy alone.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. Comparative studies with at least 30 patients per intervention group were included which was considered appropriate. No restrictions were reported based on sources of information.** **Domain 2: Identification and Selection of Studies:** **MEDLINE and the Cochrane Central Register of Controlled Trials were searched for relevant studies. Hand-searched bibliographies of systematic and narrative reviews searched the U.S. Food and Drug Administration Web site and contacted corresponding authors of eligible studies for unpublished data. The search strategy was reported and appeared appropriate. Searches were restricted to English language studies. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal:** **One review author extracted the data from the included studies and reviewed by a second reviewer for completeness and accuracy. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using appropriate criteria. At least two reviewers assessed the quality of the included studies.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity. Due to the small number of studies in each comparison subgroup analysis was not performed. The quality of individual studies was considered in the synthesis.** **Overall summary: High risk of bias in the review** **The search did not include EMBASE which for this topic means relevant studies are likely to have been missed. There was restriction to English language studies. Information regarding the number of authors involved in the study selection process was not provided.**

Bottom line: Evidence indicates that event rates in patients treated with medical therapy have decreased over time. This review emphasises the uncertainty that remains in this area. The results must be interpreted cautiously due to the presence of heterogeneity. The review had significant methodological weaknesses. Future randomised controlled trials of asymptomatic carotid stenosis should focus not only on whether carotid artery stenting is equal or superior to carotid endarterectomy but also on whether these invasive interventional procedures provide incremental benefits over best-available medical therapy.

KSRA101549 2017 Rantner B, et al. Early Endarterectomy Carries a Lower Procedural Risk Than Early Stenting in Patients With Symptomatic Stenosis of the Internal Carotid Artery: Results From 4 Randomized Controlled Trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 4 **Number of participants** 4754 **Last search date** NR **Review type** Intervention **Objective** To investigate associations between periprocedural outcome and timing of treatment for early endarterectomy and early stenting. **Population** Patients with symptomatic moderate-to-severe carotid stenosis (≥50% stenosis measured according to NASCET criteria and patients with transient ischemic attack, amaurosis fugax, and minor nondisabling ischemic stroke. Interventions Carotid endarterectomy. **Comparator** Carotid artery stenting. Outcome Primary outcome: The combination of any stroke or death occurring within 30 days after treatment. Secondary outcome: Any stroke and fatal or disabling stroke happening within the same time period. **Study design** Randomised clinical trials.	This patient-level pooled analysis included data from 4754 randomised patients, in four randomised clinical trials. The pooled analyses reported a significantly higher risk of any stroke or death within 30 days after treatment with the carotid artery stenting (CAS) compared with the carotid endarterectomy (CEA) group (Risk ratio [RR] 2.29, 95% confidence interval [CI] 1.71 to 3.08). The pooled analyses reported a significantly higher risk of any stroke or death in the crude with the CAS compared to the CEA (RR 6.51, 95% CI 2.00 to 21.21). The pooled analyses reported a significantly higher risk of stroke and death in the CAS group compared to the CEA group in the later treatment (RR 2.00, 95% CI, 1.49 to 2.67). The pooled analyses reported significantly higher fatal or disabling stroke outcome at 30 days with the CAS group compared to the CEA group within 7 days (RR 8.29, 95% CI 1.07 to 64.28) and after 7 days (RR 1.77, 95% CI 1.10 to 2.85). There were fewer strokes and deaths in the CAS group in patients treated after 7 days compared with those treated within 7 days. There was no statistically significant interaction for fatal or disabling stroke between the CAS and CEA.	**Domain 1: Study Eligibility Criteria** **This article describes the results of a meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 2: Identification and Selection of Studies** **This article describes the results of a meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 3: Data Collection and Study Appraisal** **This article describes the results of a meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 4: Synthesis and Findings** **Low** **The article presents the results of an IPD meta-analysis of four randomised clinical trials. To obtain a combined estimate (risk ratio [RR] with 95% confidence intervals [CIs]), logistic mixed models were applied with the source study as random variable using a log link. The first model was unadjusted, whereas the second model accounted for age at treatment, sex, and type of qualifying event (retinal ischemia, transient ischemic attack, or stroke). Age at treatment was log-transformed based on the natural logarithm (ln) in the mixed-model analysis. A P-value of <0.10 for interaction terms was considered statistically significant. For all other statistical analyses, a P-value of <0.05 was considered to indicate statistical significance.** **Overall summary** **This article reports a well conducted individual patient data meta-analysis.**

Bottom line: Evidence indicates that carotid artery stenting may be associated with a substantially higher periprocedural risk during the first 7 days after the onset of symptoms. Early surgery is safer than stenting for preventing a future stroke. A randomised trial on the timing of treatment would be mandatory in the near future.

KSRA101550 2013 Ren S, et al. Systematic Review of Randomized Controlled Trials of Different Types of Patch Materials during Carotid Endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 13 **Number of participants** 2561 **Last search date** November 2012 **Review type** Intervention **Objective** To evaluate the effect of angioplasty using venous patch versus synthetic patch material, and Dacron patch versus polytetrafluoroethylene (PTFE) patch material during CEA. **Population** Patients undergoing carotid endarterectomy. Interventions Carotid patch angioplasty with autologous venous patch. **Comparator** Synthetic patch material, or different types of the synthetic patch such as polytetrafluoroethylene (PTFE) patch material. **Outcome** Hemostasis time, mortality rate, stroke rate, restenosis, the incidence of reoperation for wound hematoma, wound infection and operative time, and intraoperative suture line bleeding with bovine pericardium. **Study design** Randomised controlled trials (RCTs). Non-RCTs, abstracts or unpublished reports, case reports, and reviews were excluded.	The pooled analysis of randomised controlled trials (RCTs) reported no significant difference between carotid endarterectomy (CEA) with venous patch versus synthetic patch material in the incidence of mortality (risk ratio [RR] 1.23, 95% confidence interval [CI] 0.79 to 1.89, 11 RCTs, n = 1944), any stroke events (RR 0.77, 95% CI 0.54 to 1.10, 10 RCTs, n = 1939), or restenosis of carotid artery (RR 1.26, 95% CI 0.93 to 1.70, 12 RCTs, n = 2208), respectively. Similarly, no significant difference was observed between the two groups was observed in terms of incidence of postoperative wound infection (RR 1.97, 95% CI 0.70 to 5.51, 3 RCTs, n = 578), incidence of reoperation for wound hematoma (RR 0.67, 95% CI 0.34 to 1.32, 4 RCTs, n = 834). However, the mean operative time (Mean difference [MD] 20.45, 95% CI 25.44 to 23.57, 5 RCTs, n = 882), and the hemostasis time (MD 218.53, 95% CI 220.87 to 216.19, 2 RCTs, n = 424) in the synthetic patch group was found to be significantly longer than in venous patch group. The summary estimate of RCTs reported that the incidence of transient ischemic attack and stroke (RR 4.45, 95% CI 1.79 to 11.06, 2 RCTs, n = 600), 50% restenosis to occlusion of carotid artery (RR 12.27, 95% CI 5.26 to 28.64, 2 RCTs, n = 600), and carotid thrombosis (RR 8.00, 95% CI 1.01 to 63.38, 2 RCTs, n = 400) after CEA were found to be significantly higher in the Dacron patch group than in polytetrafluoroethylene patch group. However, the incidence of mortality rate did not differ significantly (RR 5.00, 95% CI 0.24 to 102.85). In addition, the hemostasis time in the polytetrafluoroethylene patch group was found to be significantly longer than in Dacron patch cohort (MD -2.71, 95% CI -3.78 to -1.64, 2 RCTs, n = 400), even though the operative times between both groups were found to be similar (MD -3.23, 95% CI -7.87 to 1.41; P = 0.17, 2 RCTs, n = 400). Moreover, single RCT reported that the incidence of suture line bleeding at 3 minutes in the bovine pericardium group and Dacron group was found to be 14% (7/51) and 55% (24/44), respectively.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Cochrane Library, Pubmed, Ovid, EMBASE and Google Scholar were searched to retrieve all relevant studies. In addition, the reference lists of reviews and retrieved papers were searched manually. Search terms were reported, but full details of the search strategy were not reported. The language was not restricted in the literature search. Two review authors independently involved in the study selection process and any disagreements were resolved through discussion.** **Domain 3: Data Collection and Study Appraisal** **Sufficient study characteristics appear to have been extracted to allow interpretation of results. Study results were appropriately collected for the synthesis. The methodological quality of the included trials was assessed using the Jadad checklist.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant trials and was appropriate. The predefined analysis was explained in the methodology section. Heterogeneity was assessed and found to be low in the eight comparisons, moderate in one comparison and high in three comparisons. Appropriate attempts were not made to explore the possible sources of heterogeneity. No evidence of publication bias was found using funnel plots. The quality of the individual trials was not considered in the synthesis of findings.** **Overall summary** **Search terms were reported, but full details of the search strategy were not reported. Information regarding the number of authors involved in the risk of the bias assessment process was not provided. The authors cautioned the readers regarding the presence of high heterogeneity between the trials in the limitation section.**

Bottom line: Evidence indicates that the hemostasis time with polytetrafluoroethylene (PTFE) patch seems to be longer than with venous patch or Dacron patch in patients undergoing carotid endarterectomy. Moreover, the mortality rate, stroke rate, restenosis, and operative time are appeared to be similar when using venous patch versus synthetic patch, or using Dacron patch versus PTFE patch. However, some of the existing data should be cautiously interpreted because of heterogeneity. Lack of full details of the search strategy means that some relevant studies might have been missed. The authors did not state whether quality assessment was undertaken in duplicate, so reviewer error and bias could not be ruled out. Further trials on the optimal patch materials and the priority of autologous venous patch versus synthetic patch are warranted.

KSRA104783 2018 Rothwell PM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 10 **Number of participants** 117279 **Last search date** NR **Review type** Intervention ObjectiveTo investigate the modifying effects of weight, height, body mass index, and other measures of body size on the effectiveness of low and higher doses of aspirin in primary prevention of vascular events, with validation in trials in secondary prevention of stroke and to investigate the effect of aspirin on long-term risk of colorectal cancer, and on short-term, in-trial risk of any cancer, affected by weight and height. **Population** Subjects with stroke or other cardiovascular events. Individual patient data on age, sex, weight, height, and vascular risk factors (including smoking status and diabetes status) at baseline. **Interventions** Aspirin. **Comparator** Placebo, no aspirin and others. **Outcome** Risks of vascular events. These included all major vascular events (including stroke [ischaemic, intracerebral, or subarachnoid haemorrhage], myocardial infarction, vascular death, other coronary death, and other major ischaemic vascular events, excluding unstable angina and transient ischaemic attack), major bleeds (intracerebral haemorrhage and extracranial bleeds that were fatal or required blood transfusion or hospital admission), cancers (first cancer, excluding non-melanoma skin cancer, diagnosed after randomisation), and deaths that occurred during follow-up. **Study design** Randomised controlled trials (RCTs). Trials of short-term (≤90 days) treatment were excluded.	The ability of 75-100 mg aspirin to reduce cardiovascular events decreased with increasing weight with benefit seen in people weighing 50 to 69 kg (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.65 to 0.85) but not for vascular death in those weighing 70 kg (HR 0.95, 95% CI 0.86 to 1.04) or more (HR 1.09, 95% CI 0.93 to 1.29). Moreover, the case fatality of a first cardiovascular event was increased by low-dose aspirin in people weighing 70 kg or more (odds ratio [OR] 1.33, 95% CI 1.08 to 1.64). Cardiovascular events were reduced in participants weighing 70 kg or more (HR 0.79, 95% CI 0.70 to 0.90) with 300 to 325 mg aspirin and in those weighing 90 kg or more (HR 0.45, 95% CI 0.26 to 0.79) with 500 mg or more indicating an opposite interaction with bodyweight. Similar findings were observed in men and women, in people with diabetes, in trials of aspirin in secondary prevention, and in relation to height. Aspirin-mediated reductions in long-term risk of colorectal cancer were also weight dependent. Stratification by body size showed that the risk of sudden death was increased by aspirin in people at low weight and risk of all-cause death was increased in people weighing less than 50 kg who were receiving 75 to 100 mg aspirin (HR 1.52, 95% CI 1.04 to 2.21). In participants aged 70 years or older, the 3-year risk of cancer was also increased by aspirin (HR 1.20, 95% CI 1.03 to 1.47), especially in those weighing less than 70 kg (1.31, 95% CI 1.07 to 1.61) and consequently in women (1.44, 95% CI 1.11 to 1.87).	**Domain 1: Study Eligibility Criteria** **Not applicable. This article describes the results of a individual patient data meta-analysis, but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 2: Identification and Selection of Studies** **Not applicable. This article describes the results of a individual patient data meta-analysis, but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 3: Data Collection and Study Appraisal** **Not applicable. This article describes the results of a individual patient data meta-analysis, but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. The method of analysis was explained and appeared appropriate. Analyses of the effects of aspirin were done by intention to treat based on randomised allocation, unless otherwise specified. Kaplan-Meier curves were also generated for time to event and dichotomised by bodyweight (<70 kg vs ≥70 kg), with significance established by use of the log-rank test stratified by trial. The risk of bias of the individual studies was not considered in the synthesis.** **Overall summary** **The risk of bias of the individual studies was not considered in the synthesis.**

Bottom line: Current evidence suggests that the optimal dose of aspirin to prevent cardiovascular events depends on body weight, especially lean body mass and height than by body-mass index. In people weighing 70 kg or more, particularly those who smoked or were treated with enteric-coated formulations, low dose (75 to 100 mg) aspirin once a day is ineffective, whereas higher doses are effective with increasing weight. The substantial reductions in cardiovascular events and death at optimal doses for weight highlight the potential to improve effectiveness and encourage a more tailored dosing strategy instead of the one-dose-fits-all strategy. The methodological quality of the individual studies was not considered in the review.

KSRA4703 2015 Shan L, et al. Quality of life and functional status after carotid revascularisation: a systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 12 **Number of participants** 4,224 **Last search date** June 2014 **Review type** Intervention **Objective** To estimate the quality of life and functional status after carotid revascularisation. **Population** Patients (18 years of age) with asymptomatic or symptomatic carotid stenosis. **Interventions** Ipsilateral carotid revascularisation by endarterectomy (CEA) or carotid revascularisation by stenting (CAS) recorded on postoperative quality of life (QoL). **Comparator** Preoperative QoL, reference populations, or other interventions. **Outcome** Medical Outcomes Short Form 36 (SF-36), Sickness Impact Profile, Hospital Anxiety and Depression Scale, Katz Index of Independence in Activities of Daily Living, European Quality of Life EQ-5D Questionnaire, and the Multidimensional Index of Life Quality Questionnaire. **Study design** Prospective, retrospective, and randomised control trials.	No significant difference between the post and pre-treatment was observed in the studies that assessed the SF-36 scores after carotid endarterectomy among the patients with asymptomatic or symptomatic carotid stenosis of the physical function (standard mean difference (SMD) 0.04, 95% confidence interval (CI) -0.02 to 0.09, three studies, n=2,328 post-op and 2,762 pre-op), bodily pain (SMD 0.03, 95% CI -0.02 to 0.09, three studies, n=2,328 post-op and 2,762 pre-op) and social function (SMD 0.10, 95% CI -0.13 to 0.33, two studies, n=2,227 post-op and 2,611 pre-op) for six to 12 month follow-up period. Significant effect of the postoperative treatment as compared to preoperative treatment was observed in the studies that assessed the SF-36 scores after carotid endarterectomy for the role physical (SMD 0.12, 95% CI 0.07 to 0.18, three studies, n=2,328 post-op and 2,762 pre-op), vitality (SMD 0.14, 95% CI 0.08 to 0.19, three studies, n=2,328 post-op and 2,762 pre-op), general health (SMD 0.09, 95% CI 0.04 to 0.15, three studies, n=2,328 post-op and 2,762 pre-op), role emotional (SMD 0.19, 95% CI 0.14 to 0.25, two studies) and mental health (SMD 0.19, 95% CI 0.14 to 0.25, two studies, n=2,227 post-op and 2,611 pre-op) for six to 12 month follow-up period. Of the 12 studies, eight studies reported the perioperative mortality rate 0.0% to 2.0% and the stroke rate 2.3% to 8.0% after CEA and after CAS (five studies) the perioperative mortality rate was 0.0% to 0.7% and the stroke rate was found to be 2.1% to 4.1%. Five studies reported the perioperative myocardial infarction among the CEA was 0.8% to 6.6% and in CAS was 0.0% to 1.9%.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were imposed based on the study characteristics. Only the original research published in the English language were included in the study, which meant that some relevant studies may have been missed.** **Domain 2: Identification and Selection of Studies** **PubMed was searched to identify the relevant literature. In addition, hand searches of OVID (MEDLINE) and EBSCOhost (EMBASE) as well as reference lists of all included studies were screened to find other relevant studies missed. Details of the search strategy were reported and showed a lack of synonyms, spelling variants and use of alternative free text searching terms, resulting in few articles being found and possibly relevant studies being missed. Inclusion was limited to studies published in English after January 1990. Two investigators independently screened the search results and screened the titles and abstracts, and subsequently the full-text reports of all the potentially relevant studies.** **Domain 3: Data Collection and Study Appraisal** **Two independent investigators extracted data from the included studies. Sufficient study characteristics were available for interpretation of the results. The relevant study results were appropriately collected for the synthesis. Methodological quality assessment of the included studies was performed by a qualitative review based on study quality. The number of authors involved in the quality assessment process was not clearly reported; however, this appeared to have been performed as part of the data extraction, which was performed by two authors.** **Domain 4: Synthesis and Findings** **All studies included in the review contributed to the synthesis. Analyses were explained specifically in the methods section and results were reported for defined outcomes. Appropriate methods were used to analyse the data. No significant heterogeneity was found except the studies that assessed social function with significant heterogeneity, no possible steps were taken to minimise the heterogeneity. Sensitivity analysis and publication bias of the included studies was not performed. Bias of the included studies was considered.** **Overall summary** **Only the original research published in the English language were included in the study, which meant that some relevant studies may have been missed. Only search terms were given, hence in the absence of a complete search strategy, it was not possible to judge if all relevant studies had been included in this review. No information was reported regarding the number of authors involved in the quality assessment process. Studies that assessed social function with significant heterogeneity, no possible steps were taken to minimise the heterogeneity. Sensitivity analysis and publication bias of the included studies was not performed.**

Bottom line: The evidence indicated that revascularisation by endarterectomy or carotid revascularisation by stenting maintained preoperative quality of life. A restriction to the English language and lack of a complete search strategy, meant that some relevant studies may have been missed. No information was imposed regarding the number of authors involved in the quality assessment process. Significant heterogeneity was observed in the studies that assessed social function, no possible steps were taken to minimise the heterogeneity. Sensitivity analysis and publication bias of the included studies was not performed, bias may exist in the review.

KSRA101548 2013 Taylor F, et al. Statins for the primary prevention of cardiovascular disease

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 18 **Number of participants** 56934 **Last search date** January 2012 **Review type** Intervention **Objective** To assess the effects, both harms, and benefits, of statins in people with no history of cardiovascular disease. **Population** Men and women (aged 18 or more) with no restrictions on the total, low or high-density lipoprotein cholesterol levels. **Interventions** Statins (HMG CoA reductase inhibitors). **Comparator** Placebo or usual care. Outcome Death from all causes, fatal and non-fatal coronary heart disease [CHD], cardiovascular disease and stroke events, combined endpoint (fatal and non-fatal CHD, CHD and stroke events), change in blood total and low-density lipoprotein, revascularisation, adverse events, quality of life and costs. **Study design** Randomised controlled trials.	The pooled analyses reported reduced all-cause mortality (OR 0.86, 95% CI 0.79 to 0.94, 13 trials, n= 48060 patients) as was combined fatal and non-fatal cardiovascular disease (RR 0.75, 95% CI 0.70 to 0.81, 9 trials, n= 23805 patients), combined fatal and non-fatal coronary heart disease events (RR 0.73, 95% CI 0.67 to 0.80, 14 trials, n= 48049 patients) and combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.68 to 0.89, 10 trials, n= 40295 patients) with the statin compared to the placebo. The pooled analyses reported significantly reduced combined fatal and non-fatal coronary heart disease, cardiovascular disease and stroke events (RR 0.65, 95% CI 0.58 to 0.73, 4 trials, n= 35254 patients) with the statins compared to the placebo. The pooled analyses reported reduced revascularisation rates with the statins compared to the placebo (RR 0.62, 95% CI 0.54 to 0.72, 7 trials, n= 42403 patients). The pooled analyses reported significantly reduced total cholesterol (Mean difference [MD] -1.05, 95% CI -1.35 to -0.76, 14 trials, n= 34122 patients), LDL Cholesterol (MD -1.00, 95% CI -1.16 to -0.85, 16 trials, n= 41380 patients) with the statin compared to the placebo.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were reported based on study characteristics. No restrictions were reported based on sources of information.** **Domain 2: Identification and Selection of Studies** **The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE OVID, and EMBASE OVID were searched for relevant studies. The reference lists of identified articles were reviewed to identify other relevant articles. The search strategy was reported and appeared appropriate. Searches were not restricted to date, publication format or language. Two review authors were independently involved in study selection.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process and any disagreements were resolved by discussion and consensus and finally by a discussion with a third review author. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of the included studies was assessed using the Cochrane Handbook for Systematic Reviews of Interventions. Two reviewers were independently assessed the quality of the included studies and any disagreements were resolved by discussion and consensus and finally by a discussion with a third author.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity for total cholesterol, LDL cholesterol, and number of study participants who stopped treatment due to adverse events. No evidence of significant publication bias was found using the funnel plot. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary** **This review shown no important concerns in any of the ROBIS domains.**

Bottom line:
Evidence indicates that statins may reduce all-cause mortality, major vascular events and revascularisations with no excess of adverse events among people without evidence of cardiovascular disease. The results must be interpreted cautiously due to the presence of heterogeneity. Further cost-effectiveness analyses are now needed to guide widening their use to these low-risk groups.

KSRA64940 2018 Texakalidis P, et al. Carotid Artery Endarterectomy versus Carotid Artery Stenting for Restenosis After Carotid Artery Endarterectomy: A Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 13 **Number of participants** 4163 **Last search date** July 20, 2017 **Review type** Intervention **Objective** To determine whether carotid artery stenting or redo carotid endarterectomy is the optimal treatment for postendarterectomy carotid restenosis. **Population** Adults with carotid artery restenosis after primary endarterectomy. **Interventions** Carotid endarterectomy (CEA). **Comparator** Carotid artery stenting (CAS). **Outcome** Primary outcome: Incidence of stroke within 30 days of the procedure. Secondary outcomes: Transient ischemic attack (TIA), cranial nerve (CN) injuries, myocardial infarction (MI), death within 30 days and long-term target carotid artery recurrent restenosis (tertiary restenosis) and target lesion revascularization (TLR). **Study design** Randomised controlled trials (RCTs) or prospective and retrospective real-world studies.	The pooled analysis reported that the risk for any type of cranial nerve injury was higher in the redo carotid endarterectomy (CEA) group compared to carotid artery stenting (CAS) group (odds ratio [OR] 13.61, 95% confidence interval [CI] 5.43 to 34.16, 11 studies). However, no significant differences were found between the CEA and CAS groups regarding outcomes periprocedural and/or short-term (within 30 days) stroke, transient ischemic attack (OR 0.62, 95% CI 0.24 to 1.60, 10 studies), myocardial infarction (OR 1.32, 95% CI 0.71 to 2.44, 7 studies), temporary cranial nerve injury and death (OR 1.82, 95% CI 0.94 to 3.53, 11 studies). CAS was associated with a significantly lower risk for long-term recurrent carotid artery restenosis when defined as stenosis >60% (OR 2.16, 95% CI 1.13 to 4.12, 6 studies) or >70% (OR 2.31, 95% CI 1.13 to 4.72, 4 studies), during a median follow-up of 28 months. However, no difference was found in long term target lesion revascularisation rates between redo CEA and CAS (OR 1.08, 95% CI 0.34 to 3.50, 8 studies).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. Only published English language studies were considered for inclusion in the review.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching PubMed, Scopus and the Cochrane Central databases. In addition, reference lists of included studies were manually searched for additional findings. Search terms were provided and appeared limited; a full search strategy was not reported.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and disagreements were resolved by discussion with the third reviewer. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Risk of bias assessment was performed by two investigators with the ROBINS-I tool for included non-randomised studies.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all the relevant studies. The method of analysis was explained and appeared appropriate. No significant (high) heterogeneity was found between the studies in the pooled analysis. Sensitivity analysis was performed to check the robustness of the study results. The quality of the individual studies was considered in the synthesis.** **Overall summary** **Only published English language studies were considered for inclusion in the review. A limited range of database was searched for the study selection process. Search terms appeared limited and a full search strategy was not reported.**

Bottom line: The current evidence suggests that both carotid artery stenting and carotid endarterectomy have similar risks of periprocedural stroke, transient ischemic attack, myocardial infarction, and death, however, the former may have fewer cranial nerve palsies. Carotid artery stenting did not provide any benefit in other periprocedural complications. A limited range of databases searched and inclusion of only English language studies means some of the relevant studies may have been missed. A complete search strategy was not reported.

KSRA83276 2018 Texakalidis P, et al. A meta-analysis of randomized trials comparing bovine pericardium and other patch materials for carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 11 **Number of participants** 233,411 **Last search date** June 2016 **Review type** Aetiological **Objective** To evaluate the relationship between the volume of carotid procedures and outcomes, including mortality and stroke. **Population** Patients undergoing extracranial carotid procedures in Europe. Outcome Mortality, stroke, length of hospital stay and complications. **Study design** Observational studies (retrospective). Exposure Volume of carotid procedures.	Two large studies reported an inverse relationship between hospital volume and mortality and combined mortality and stroke, following carotid endarterectomy (CEA). However, three smaller studies found no statistically significant evidence of a relationship. One study reported no evidence of a relationship between the hospital volume of elective or emergency CEAs undertaken and complication rates (renal, respiratory, infection, shock, local complications, thrombotic or embolic events, cardiac and disseminated intravascular coagulation or transfusion reactions). One study found evidence of a statistically significant association between increased hospital volume of CEA and reduced length of hospital stay. No clear convincing evidence of an association was found following carotid artery stenting (CAS) regarding mortality and combined mortality and stroke. One study reported no significant evidence of a relationship between hospital CAS volume and stroke, or between hospital CAS volume and acute myocardial infarction. Additionally, no clinically relevant volume-related trends were identified regarding the length of hospital stay and CAS.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics. No information was provided about the restrictions related to sources of information.** **Domain 2: Identification and Selection of Studies** **Literature searches were conducted in MEDLINE, EMBASE, the Cochrane Library, Science Citation Index and CINAHL. In addition, subsequent handsearches of key journals, conference proceedings, citation and reference list searches (of included studies and relevant systematic reviews) were conducted. The search strategy was reported in full and appeared to be adequate. There were no restrictions reported based on the date, publication format or language. Two authors independently screened titles, abstracts and full texts to assess the study eligibility.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and risk of bias assessment. Sufficient study characteristics have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using appropriate criteria.** **Domain 4: Synthesis and Findings** **The synthesis included all relevant studies and was appropriate. Due to the high risk of bias and the methodological and clinical heterogeneity among the included studies, meta-analysis was considered inappropriate. A narrative synthesis was performed to summarise the findings of the review. Quality of the individual studies was considered in the synthesis.** **Overall summary** **Only published English language studies were considered for inclusion in the review. Search terms were provided and appeared very limited, and a full search strategy was not reported.**

Bottom line: The current review suggests the existence of a relationship between the hospital volume of elective carotid endarterectomy and mortality in European populations and thereby supports the centralisation of carotid endarterectomy. Further larger reviews incorporating studies from the rest of the world is needed.

KSRA72932 2018 Texakalidis P, et al. Outcome of Carotid Artery Endarterectomy in Statin Users versus Statin-Naive Patients: A Systematic Review and Meta-Analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 6 **Number of participants** 7053 **Last search date** 26 August 2017 **Review type** Prognostic/Predictive ObjectiveTo determine whether the use of statins is beneficial in patients undergoing carotid artery endarterectomy. **Population** Patients undergoing carotid artery endarterectomy (CEA). **Interventions** Statin use before CEA. **Comparator** No statin use before CEA. **Outcome** Outcomes of carotid artery endarterectomy. Primary outcome: Incidence of stroke within 30 days after the procedure (stroke was consistently defined as any new neurological deficit lasting >24 hours) Secondary outcomes: 30- day myocardial infarction and death rates. **Study design** Randomised controlled trials or observational studies. Only real world studies were included. Case reports, secondary review papers, letter to the editors, or commentaries were excluded. **Reference standard** NA **PP factor** Use of statins	The pooled analysis reported no significant differences between statin-user and statin-naive patients in terms of risk of stroke (odds ratio [OR] 0.40, 95% confidence interval [CI] 0.15 to 1.09, 6 studies, n=7033) and myocardial infarction (OR 0.77, 95% CI 0.26 to 2.24, 5 studies, n=6725) within 30 days after the procedure in patients undergoing carotid artery endarterectomy (CEA). However, patients who received statins before CEA were at a significantly lower risk for 30-day death compared to statin-naive patients (OR 0.26, 95% CI 0.10 to 0.61, 5 studies, n=6725).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were applied to eligibility criteria based on study characteristics. Only English language studies were included.** **Domain 2: Identification and Selection of Studies** **PubMed, Scopus and Cochrane were searched for relevant studies. The reference lists of retrieved articles were manually searched for additional relevant studies. Search terms provided appeared very limited, and a full search strategy was not reported.** **Domain 3: Data Collection and Study Appraisal** **Two review authors were independently involved in the data extraction process. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Two review authors were involved in the assessment of the methodological quality of included studies using the Risk of Bias Assessment for Observational Studies (Robins-I) tool for non-randomised studies, any discrepancies in the quality assessment were resolved by consensus.** **Domain 4: Synthesis and Findings** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity for stroke and myocardial infarction. Appropriate attempts were not made to explore the possible sources of heterogeneity. The quality of individual studies was considered in the synthesis.** **Overall summary** **The authors acknowledged the presence of significant heterogeneity between the studies. Only English language studies were included. PubMed, Scopus and Cochrane were searched for relevant studies. Search terms were limited and a full search strategy was not reported.**

Bottom line: Current evidence suggests that statin users undergoing carotid artery endarterectomy (CEA) seems to be significantly at lower risk for periprocedural death compared to statin-naive patients. However, no significant differences observed between statin-user and statin-naive patients undergoing CEA for 30-day stroke rate and myocardial infarction rates. The review had significant methodological weaknesses, so the findings should be interpreted with caution.

KSRA72933 2018 Texakalidis P, et al. Effect of Open- vs Closed-Cell Stent Design on Periprocedural Outcomes and Restenosis After Carotid Artery Stenting: A Systematic Review and Comprehensive Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 33 **Number of participants** 20291 **Last search date** October 31, 2017 **Review type** Intervention **Objective** To examine the effect of open versus closed stent design on carotid artery stenting related peri-procedural outcomes and restenosis in follow-up. **Population** Patients undergoing carotid artery stenting (CAS). **Interventions** Open-cell stent. **Comparator** Closed-cell stent. Studies that compared hybrid or mixed-design stents were excluded. **Outcome** Peri-procedural outcomes and restenosis in follow-up. Primary outcome: Incidence of stroke within 30 days of the procedure. Secondary outcomes: Transient ischemic attack (TIA), myocardial infarc- tion (MI), hemodynamic depression and death within 30 days. **Study design** Randomised controlled trials (RCTs) and prospective or retrospective observational studies.	Studies showed that stroke occurred in 417 of 18,062 patients (2.3%) while transient ischemic attack (TIA) occurred in 178 of 9194 (1.9%) patients. No differences in stroke (odds ratio [OR] 1.13, 95% confidence interval [CI] 0.91 to 1.39; 19 studies, N=18062) or TIA rates (OR 1.16, 95% CI 0.65 to 2.05; 16 studies, N=9194) were observed between the open- and closed-cell stent groups. New ischemic lesions were detected at diffusion-weighted magnetic resonance imaging (DW-MRI) in 138 of 385 (35.8%) patients and were similar between the study groups (OR 1.55, 95% CI 0.97 to 2.47; 6 studies, N=381). The frequencies of MI (23/3390, 0.6%; OR 0.80, 95% CI 0.34 to 1.86; 8 studies, N=3390) and hemodynamic depression (205/936, 22.6%; OR 1.22, 95% CI 0.44 to 3.34; 6 studies, N=936) also did not differ between the open- and closed-cell stent groups. Overall, 112 of 18,039 (0.6%) patients died within 30 days after carotid artery stenting (CAS) and no differences were detected in death rates between the study groups (OR 0.84, 95% CI 0.57 to 1.23; 21 studies, N=18039). A significantly lower risk for any restenosis was observed in the open-cell stent group (OR 0.42, 95% CI 0.19 to 0.92; 7 studies, N=1237). Restenosis ≥70% diagnosed in 27 of 905 (2.9%) patients was also significantly less in the open-cell stent group (OR 0.23, 95% CI 0.10 to 0.52; 5 studies, N=905).	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. Studies with high risk of bias/low quality were excluded. Only English language studies were considered for inclusion in the review.** **Domain 2: Identification and Selection of Studies:** **Studies were identified by searching PubMed, Scopus and the Cochrane Central databases. The references of the included studies were also manually reviewed in order to identify further eligible articles. Search terms were provided but a full search strategy was not reported. There was no information on whether the searches were restricted by publication format or language.** **Domain 3: Data Collection and Study Appraisal:** **Two reviewers were independently involved in the data extraction process and disagreements were resolved by discussion with the third reviewer. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Risk of bias was assessed by two independent investigators using the Cochrane tool for the RCTs and the Robins-I tool for nonrandomized studies. Discrepancies in quality assessment were resolved via consensus.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to have included all relevant studies. The method of analysis was explained. Low to high heterogeneity was present between studies. Subgroup and meta-regression analyses were performed to address the between-study heterogeneity. Funnel plots and Egger's regression tests were used to assess publication bias. Sensitivity analysis was performed to check the robustness of the study results. The quality of the individual studies was considered in the synthesis.** **Overall summary. High risk of bias in the review** **Only English language studies were considered for inclusion in the review. A limited range of database was searched for study selection process. Search terms were provided but a full search strategy was not reported. There was no information on whether the searches were restricted by publication format or language.**

Bottom line: Current evidence suggests that after carotid artery stenting, open-cell stent designs are associated with a statistically significantly lower risk for restenosis without an increase in periprocedural complications. A limited range of databases searched and restriction to English language means some of the relevant studies may have been missed.

KSRA56918 2018 Texakalidis P, et al. Proximal embolic protection versus distal filter protection versus combined protection in carotid artery stenting: A systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 29 **Number of participants** 16307 **Last search date** April 1st, 2017 **Review type** Intervention **Objective** To compare the effectiveness of proximal embolic protection versus distal filter protection versus combined protection in carotid artery stenting. **Population** Patients with carotid artery stenosis. **Interventions** Carotid artery stenting: proximal balloon occlusion vs distal filter vs combination of the two methods. **Comparator** Carotid artery stenting: proximal balloon occlusion vs distal filter vs combination of the two methods. **Outcome** Incidence of new ischemic lesions/patient during a carotid artery stenting procedure, ipsilateral and contralateral ischemic lesions, stroke, death, and the combined endpoint of death/CVA. **Study design** Randomised controlled trials or prospective and retrospective observational studies.	The pooled analysis reported a significant reduction in ischemic lesions with the use of Proximal embolic protection devices (P-EPD) among observational studies (OS) (risk ratio [RR] 0.66, 95% confidence interval [CI] 0.45 to 0.97, 5 studies) compared to distal filter (DF). However, the difference in ischemic lesions between the two groups was not significant among randomised controlled trials (RCTs) (RR 0.75, 95% CI 0.53 to 1.06, 9 trials). Similarly, there were no differences between the groups in terms of stroke rates (OS: RR 0.77; 95% CI 0.34 to 1.78, 8 studies; RCTs: RR 0.49; 95% CI 0.34 to 1.78, 6 studies) and mortality risk (OS: RR 0.75; 95% CI 0.28 to 1.99, 9 studies, RCTs: RR 1.01; 95% CI 0.20 to 5.07, 5 studies). Patients who were treated with a combination strategy (P-EPD and DF) had a lower risk of ischemic lesions (RR 0.50; 95% CI 0.33 to 0.76) compared to DF only.	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated and appropriate inclusion criteria were defined. Only studies published in English were included in the review. Studies with a high risk of bias were excluded.** **Domain 2: Identification and Selection of Studies:** **Relevant trials were identified from the PubMed, Scopus and Cochrane Central. References of included studies were screened in order to identify additional relevant studies. The search strategy was reported and had a limited number of keywords. The searches were not restricted to publication format or language. Two review authors independently identified the studies for inclusion. Disagreements were resolved by a third investigator.** **Domain 3: Data Collection and Study Appraisal:** **Two review authors independently extracted the data. Any disagreements were resolved by discussion with a third reviewer. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was performed by two review authors independently using the Cochrane tool for randomized studies and with the Robins tool for non-randomized studies. Discrepancies in the quality assessment were resolved via consensus.** **Domain 4: Synthesis and Findings:** **The synthesis appeared to have included all relevant studies. The method of analysis was explained and appeared appropriate. Significant heterogeneity was found between the studies. Robustness of the findings was not demonstrated. Bias in primary studies was addressed while interpreting findings.** **Overall summary. High risk of bias in the review** **Only studies published in English were included in the review. Studies with a high risk of bias were excluded. The search strategy had a limited number of keywords. Significant heterogeneity was found between the studies. Robustness of the findings was not demonstrated.**

Bottom line: Current evidence suggests a significant reduction in ischemic lesions with the use of proximal embolic protection devices compared to distal filter among observational studies. However, there was no difference for the other outcomes between the two treatment groups. Only studies published in English were included in the review, and the search strategy had limitations. Results must be interpreted with caution due to significant heterogeneity between the studies.

KSRA60338 2018 Texakalidis, P. et al. Revascularization of radiation-induced carotid artery stenosis with carotid endarterectomy vs. carotid artery stenting: A systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 5 **Number of participants** 143 **Last search date** 20 July 2017 **Review type** Intervention **Objective** To compare the carotid endarterectomy versus carotid artery stenting for revascularisation of radiation-induced carotid artery stenosis. **Population** Patients with radiation-induced carotid artery stenosis **Interventions** Carotid endarterectomy (CEA) **Comparator** Carotid artery stenting (CAS) **Outcome** Primary outcome: incidence of stroke within 30 days of the procedure Secondary outcomes: transient ischemic attack (TIA), cranial nerve (CN) injuries, myocardial infarction (MI) and death within 30 days, and long-term target carotid artery restenosis and target lesion revascularisation (TLR) **Study design** Randomised controlled trials (RCT) or real-world studies. Studies with a higher risk of bias were excluded, as were studies where there was only one patient in either study arm.	A pooled analysis of three studies reported that patients in the carotid endarterectomy (CEA) group had a significantly higher risk of cranial nerve (CN) injuries in comparison with carotid artery stenting (CAS) (odds ratio (OR) 7.09, 95% confidence interval (CI) 1.17 to 42.88). However, CEA was safer with respect to the incidence of death after 30 days (OR 0.29, 95% CI: 0.09 to 0.97, 3 studies). There were no statistically significant differences between the CEA and CAS groups with respect to stroke within 30 days (OR 0.69, 95% CI: 0.13 to 3.48, 4 studies); myocardial infarction within 30 days (OR 2.35, 95% [CI] 0.29 to 18.59, 3 studies); death within 30 days (OR 1.95, 95% CI 0.29 to 12.97, 4 studies); or restenosis after 30 days (OR 0.57, 95% CI: 0.19 to 1.67, 4 studies).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and inclusion criteria defined. Studies which had a higher risk of bias were excluded. No restrictions were reported based on the sources of information. However, two studies were reported as excluded due to not being in English, so it would appear that a language limitation was applied.** **Domain 2: Identification and Selection of Studies** **PubMed, Scopus and Cochrane Central databases were searched for relevant studies. Additionally, the references of the included studies were also manually reviewed in order to identify further eligible articles. The search terms were provided but a full search strategy was not reported. There was no information regarding the restrictions imposed based on date, publication format, or language. The number of reviewers involved in the study selection was not reported.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers, blind to each other, independently extracted the relevant data from the eligible studies. All disagreements were resolved following discussion and the final decision was reached by consensus with the addition of a third reviewer. Sufficient study characteristics appear to have been extracted to allow for the interpretation of the results. Relevant study results appear to have been extracted. The risk of bias assessment was performed by two investigators with the Robins-I tool for non-randomised studies.** **Domain 4: Synthesis and Findings** **The synthesis included all of the relevant studies. The analyses, which had been predefined in the methodology section, were performed appropriately. No significant heterogeneity was found between the studies. Statistical tests for the detection of publication bias could not be performed because the number of included studies was too low. The quality of the individual studies was considered in the synthesis.** **Overall summary** **Studies which had a higher risk of bias were excluded. The search terms were provided, but a full search strategy was not reported so it was not possible to judge whether the search strategy was an effective one and relevant studies may have been missed. There was no information regarding the restrictions imposed based on date, publication format, or language, but two studies were excluded as 'non-English language' during the study selection process, which suggests that a language restriction may have been applied. The number of reviewers involved in the study selection process was not reported so reviewer error and bias could not be ruled out.**

Bottom line: The limited evidence, from non-randomised studies, suggests that patients undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS) for the treatment of radiation-induced carotid artery stenosis appear to have similar risks of periprocedural stroke, myocardial infarction and death. However, patients treated with CEA appear to have a higher risk for periprocedural cranial nerve injuries and a lower risk for long-term mortality. Some aspects of the review methodology were unclear and of concern, but the authors' recommendations for a cautious interpretation and the need for further evidence from randomised controlled trials, appear appropriate.

KSRA101143 2019 Texakalidis, P. et al. Carotid revascularization in older adults: a systematic review and meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 9 **Number of participants** 5955 **Last search date** May 2018 **Review type** Intervention **Objective** To compare carotid artery endarterectomy with carotid artery stenting for the elderly patient population (>80 years of age). **Population** Octogenarians or older patients. **Interventions** Carotid artery endarterectomy. **Comparator** Carotid artery stenting. Outcome Primary outcome: Incidence of stroke within 30 days after the procedure. **Secondary outcome:** Transient ischemic attack, myocardial infarction, death, and cranial nerve injury within 30 days. **Study design** Randomised controlled trials or prospective and retrospective observational studies. Only "real world studies" were identified and included.	The pooled analysis reported no significant difference between carotid artery endarterectomy (CEA) and carotid artery stenting (CAS) in terms of stroke (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.30 to 1.08; 7 studies, n = 5182 patients), cumulative risk of transient ischemic attack (OR 0.28, 95% CI 0.03 to 2.52; 3 studies, n = 264 patients), myocardial infarction (OR 1.67, 95% CI 0.37 to 7.46; 5 studies, n = 712 patients), risk of periprocedural mortality (OR 1.41, 95% CI 0.43 to 4.58; 7 studies, n = 954 patients) and cranial nerve injury (OR 4.74, 95% CI 0.5 to 44.98; 2 studies, n = 102 patients). Subgroup analysis of stroke reported that elderly patients who had CEA had a statistically significant lower risk of 30-day stroke (OR 0.38, 95% CI 0.29 to 0.50; 5 studies) compared with transfemoral CAS with distal or proximal protection.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were imposed based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **PubMed and Cochrane Central databases were searched for relevant studies. The references of the included studies were also manually searched to identify further eligible articles. Search terms were provided but full search strategy was not reported, therefore it cannot be assessed how efficient it was. There was no information as to whether searches were restricted by date, publication format or language. Whether the study selection process performed by two independent reviewers was unclear.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and any disagreements between them were resolved through discussion and the final decision was reached by consensus by consulting the third reviewer. Sufficient clinical study characteristics appear to have been extracted to allow interpretation of results, but there was insufficient information about the types of studies included. Relevant study results appear to have been extracted. The methodological quality of the non-randomised studies was assessed using the ROBINS-I tool. Two investigators were involved in the risk of bias assessment and any discrepancies between them were resolved via consensus.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all eligible studies. There was no evidence of significant heterogeneity for all outcomes. Meta-regression analysis was conducted to adjust for the ratio of symptomatic carotid stenosis in the study groups as a study-level covariate. Robustness of the findings was not assessed. The quality of individual studies was considered in the synthesis.** **Overall summary** **A limited range of database was searched for the study selection process. Search terms were provided but a full search strategy was not reported, therefore it cannot be assessed how efficient it was. There was insufficient information about the types of studies included. Robustness of the findings was not assessed. The authors' conclusions emphasized a sub-group analysis with significant results.**

Bottom line: No differences were identified in terms of 30-day stroke. The difference between CEA and CAS is not significant for the rates of periprocedural transient ischemic attack, myocardial infarction, death, and cranial nerve injury. There were some limitations with the review methods such as limited range of database search, the lack of full search strategy, unclear information regarding the number of authors involved in the study selection process and no assessment of robustness.

KSRA15775 2016 Thirumala PD, et al. Diagnostic accuracy of EEG changes during carotid endarterectomy in predicting perioperative strokes

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 30 **Number of participants** 8,765 **Last search date** August 2014 **Review type** Diagnostic **Objective** To investigate the diagnostic accuracy of the electroencephalogram in predicting perioperative neurological deficits after carotid endarterectomy. **Population** Patients (≥18 years of age) with carotid stenosis undergoing carotid endarterectomy. **Interventions** Index test: electroencephalogram monitoring. **Comparator** NA. **Outcome** Perioperative stroke rate, sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, negative likelihood ratio. **Study design** Randomised controlled trials, prospective or retrospective cohort studies. **Reference standard** Neurological status up to 24 hours postoperatively.	Thirty studies reported that the total incidence of the neurological deficit was 1.75% (153 of 8,765 patients) with 81 patients (52.94%) demonstrating ischaemic electroencephalogram [EEG] changes. EEG changes indicative of ischaemia were reported in 1,634 (18.64%) patients. The incidence of neurological deficits in patients with EEG changes and in patients without EEG changes were 4.96% (81 of 1,634 patients) and 1.01% (72 of 7,125 patients) respectively. 92.70% (635 of 685 patients) had reversible EEG changes while 7.30% (50 of 685 patients) had irreversible EEG changes. Among patients with perioperative stroke, 53.19% (25 of 47 patients) had reversible EEG changes and 46.81% (22 of 47 patients) had irreversible EEG changes. The pooled analysis of 30 studies reported that the intraoperative EEG changes were highly specific (84%, 95% confidence interval [CI] 81% to 86%), but not that sensitive (52%, 95% CI 43% to 61%). Summary estimates from 30 studies reported a diagnostic odds ratio (DOR) of 5.85 (95% CI 3.71 to 9.22) and an area under the curve of 0.725. Subgroup analysis with 18 studies using eight or more EEG channels for monitoring reported similar values for sensitivity (50%, 95% CI 38% to 61%), specificity (82%, 95% CI 78% to 84%), area under the curve (0.732) and a lower value of DOR (4.43, 95% CI 2.56 to 7.65). In a patient with perioperative stroke, the positive likelihood ratio of an EEG change was estimated at 3.25 while the negative likelihood ratio at 0.57. A Fagan's nomogram reported that the probability of having a perioperative stroke after experiencing an EEG change was 5.47% while the probability of not having a stroke after having no ischaemic EEG changes was 98.99%.	**Domain 1: Study Eligibility Criteria** **High** **The research objective was clearly stated and the eligibility criteria were explicitly defined. Studies with ≥50 patients were included, which was deemed inappropriate. Only studies published in the English language were included.** **Domain 2: Identification and Selection of Studies** **High** **PubMed and Web of Science were searched for relevant studies. No additional attempts were made to locate further studies. The search strategy was reported in full and appeared to be appropriate. Searches were restricted to the English language. Two reviewers were independently involved in the study selection and any disagreements were resolved by a third reviewer.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were involved in the data extraction. Sufficient study characteristics appear to have been extracted for interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using QUADAS-2. No information was provided regarding the number of reviewers involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **High** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared appropriate. There was significant evidence of heterogeneity for the outcome of specificity. Meta-regression analysis revealed that contralateral carotid stenosis and shunting might be the sources of heterogeneity. Significant asymmetry was found using the funnel plots. Quality of the individual studies was considered in the synthesis.** **Overall summary** **Studies with <50 patients were excluded, which was inappropriate. Studies and searches were restricted to the English language. Literature searches were performed only in PubMed and Web of Science. No additional attempts were made to locate further studies. No information was provided regarding the number of reviewers involved in the risk of bias assessment. The authors have acknowledged the presence of publication bias in the limitations section.**

Bottom line: The available evidence suggests that intraoperative electroencephalogram changes are highly specific in predicting perioperative strokes with six times higher odds of observing an electroencephalogram change in patients with perioperative stroke. The inclusion of studies involving ≥50 patients, a restriction to the English language, limited database searches and a lack of additional attempts to locate further studies means that some relevant studies may have been missed. The authors did not state whether the quality assessment was undertaken in duplicate, so reviewer error and bias could not be ruled out.

KSRA4518 2015 Tu J, et al. Repeated carotid endarterectomy versus carotid artery stenting for patients with carotid restenosis after carotid endarterectomy: Systematic review and meta-analysisKSRA42331

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 50 **Number of participants** 4,399 **Last search date** 30 September 2013 **Review type** Intervention **Objective** To compare the outcomes of repeated carotid endarterectomy and carotid artery stenting for carotid restenosis after carotid endarterectomy. **Population** Patients with carotid restenosis (restenosis was defined as a 50% diameter [75% area] reduction based on duplex ultrasonography. Severe restenosis was defined as >70% diameter reduction based on duplex ultrasonography. Tertiary stenosis was defined as restenosis after redo carotid endarterectomy (CEA) or carotid artery stenting for patients with primary CEA) after CEA. **Interventions** Repeated carotid endarterectomy. Studies that focused on the effects of redo CEA or carotid angioplasty stenting (CAS) between primary CRS and secondary CAS were excluded. **Comparator** Carotid artery stenting. Outcome Primary outcomes: any stroke or death occurring during the procedure or within 30 days after the procedure. Secondary outcomes: transient ischaemic attack (TIA), myocardial infarction, cranial nerve injuries occurring during the procedure or within 30 days after the procedure and TIA, stroke, and disease-related death occurring after 30 days. **Study design** Randomised controlled trials, prospective or retrospective non-randomised comparative studies and case reports. Commentaries and reviews were excluded.	The pooled analysis of comparative studies (nine studies) reported no significant difference between the CEA group and CAS groups in the stroke rate (odds ratio [OR] 1.32, 95% confidence interval [CI] 0.62 to 2.78, eight studies, n = 1,059 patients), TIA rate (OR 0.87, 95% CI 0.59 to 1.29, six studies, n = 951 patients) or myocardial infarction (MI) rate (OR 1.71, 95% CI 0.43 to 6.69, four studies, n = 800 patients) within 30 days. Similarly, no significant difference was found between the CEA and CAS groups in the stroke rate in both symptomatic (OR 1.1, 95% CI 0.20 to 5.70, one study) and asymptomatic patients (OR 0.7, 95% CI 0.20 to 3.00, one study). In the non-comparative studies, the CAS resulted in a significantly higher rate of late complications such as restenosis (person-years) after 30 days (4.5% versus 1.8%), restenosis within one year (8.3% versus 1.7%), two years (9.8% versus 2.6%), five years (13.5% versus 4.4%) after 30 days and tertiary interventions (19 versus 11 per 1,000 person-years) when compared with the redo CES group. Significantly higher mortality (seven versus one per 1,000 person-years), incidence of stroke (nine versus four per 1,000 person-years) after 30 days was found in the redo CES group than in the CAS group, whereas no significant difference was found in TIA after 30 days (0.8% versus 0.9%) and freedom from stroke at 12 months (94.7% versus 94.5%).	**Domain 1: Study Eligibility Criteri** **The research objective was clearly stated and appropriate inclusion criteria were defined. Only English language studies with >10 patients and 30 day perioperative data were included.** **Domain 2: Identification and Selection of Studies** **A literature search was conducted in MEDLINE, EMBASE, PubMed and the Cochrane Library databases. Conference abstracts and reference lists of the retrieved studies were also searched for additional studies. Some search terms were provided, but a full search strategy was not reported. The search was restricted to English language studies. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Data extraction was performed by two authors independently and discrepancies were resolved by discussion. Sufficient study characteristics appear to have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality of the included studies was assessed using the Methodological Index for Non-randomised Studies, which for comparative studies is not inappropriate. No information was provided regarding the number of authors involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The method of analysis was explained and appeared appropriate. There was no significant evidence of heterogeneity among the studies. Publication bias was not assessed and robustness of the findings was not addressed. The quality of individual comparative studies was considered in the synthesis using inappropriate criteria. Results in the text and in the figures did in some occasions not match up e.g. pooled odds ratio 95% CIs for total number of strokes were different in three places, i.e. text, figure one and table II, and clearly wrong in table two with the point estimate not being within the 95% CI.** **Overall summary** **Only English language studies were considered for inclusion in the review. The complete search strategy was not reported. No information was provided regarding the number of authors involved in the study selection process and risk of bias assessment. Robustness of the findings was not addressed. The quality of individual comparative studies was considered in the synthesis using inappropriate criteria. Results in the text and in the figures did in some occasions not match up.**

Bottom line: The evidence suggests that both repeated carotid endarterectomy and carotid artery stenting for carotid restenosis after carotid endarterectomy are equally effective and safe in terms of mortality, stroke and transient ischaemic attack rates within 30 days after surgery. However, patients treated with carotid artery stenting may develop restenosis at long-term follow-up periods, while redo carotid endarterectomy is associated with a higher rate of mortality and stroke after 30 days. There were some limitations with the review methods such as a restriction to English language studies, lack of a search strategy, no assessment of robustness of the findings, assessment of quality using inappropriate criteria, no information on the number of authors involved in the study selection and risk of bias assessment.

KSRA45255 2017 Udesh R, et al. Transcranial Doppler Monitoring in Carotid Endarterectomy: A Systematic Review and Meta-analysis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 25 **Number of participants** 4705 **Last search date** September, 2015 **Review type** Diagnostic and predictive study Objective (i)To evaluate the diagnostic accuracy of intraoperative transcranial Doppler monitoring (decreased middle cerebral artery velocity [MCAV] or microembolic signals [MES]) in detecting perioperative strokes after carotid endarterectomy (ii) to assess whether a simultaneous decrease in MCAV combined with positive MES predicts the risk of perioperative stroke. **Population** Patients (aged 18 years and older) who underwent carotid endarterectomy. **Interventions** Index test: intraoperative transcranial Doppler monitoring. **Comparator** NA **Outcome** Perioperative strokes after CEA within 30 days. The number of true positive, false positive, true negative, and false-negative results; patients with intraoperative transcranial Doppler changes (either MCAV or MES) with a new perioperative stroke and patients with intraoperative transcranial Doppler changes with no new perioperative deficits were considered to have true positive and false positive results, respectively. Patients with no transcranial Doppler changes and with no transcranial Doppler changes who developed perioperative stroke were considered to have true negative and false negative results perioperative stroke and patients. **Study design** Randomised clinical trials and prospective or retrospective cohort studies. **Reference standard** Postoperative neurologic assessments up to 30 days. **Exposure** NA **PP factor** Data from patients with simultaneous MCAV and MES monitoring.	Transcranial Doppler monitoring (either middle cerebral artery velocity [MCAV] or cerebral microembolic signals [MES]) had specificity of 72.7% (95% confidence interval [CI] 61.2% to 81.8%) and sensitivity of 56.1% (95% CI 46.8% to 65.0%) for predicting perioperative strokes. Moreover, the odds of observing an intraoperative transcranial Doppler change were 4 times greater for patients with perioperative stroke than in patients without perioperative stroke (odds ratio [OR] 4.035, 95% CI 2.175 to 7.486). The receiver operating characteristic (ROC) curve for transcranial Doppler changes had an area under the curve of 0.625. Subgroup analysis of MCAV (15 studies, n = 3454 patients) reported that intraoperative MCAV changes during carotid endarterectomy (CEA) had a specificity of 84.1% (95% CI 74.4% to 90.6) and sensitivity of 49.7% (95% CI 40.6% to 58.8) for predicting perioperative strokes. Subgroup analysis of MES (13 studies, n = 1809 patients) reported that the intraoperative MES had a specificity of 56.6% (95% CI 40.1% to 71.7%) and sensitivity of 61.1% (95% CI 47.6% to 73.2%) for predicting perioperative strokes after CEA. Two studies (n = 603 patients) that combined intraoperative monitoring using transcranial Doppler and somatosensory evoked potentials (SSEPs) during CEA revealed specificity of 90.6% (95% CI 68.2% to 97.8%) for SSEP and 88.2% (95% CI 85.1% to 90.8%) for transcranial Doppler monitoring (either MCAV change or MES). The sensitivity obtained was 78.5% (95% CI 43.5% to 94.5%) for SSEP and 52.2% (95% CI 32.1% to 71.7%) for transcranial Doppler monitoring, respectively. Two studies (n = 212 patients) that combined intraoperative monitoring with transcranial Doppler sonography and electroencephalography (EEG) revealed specificity of 73.8% (95% CI 66% to 80.3%) for EEG and 66.8% (95% CI 14.2% to 96.1%) for transcranial Doppler monitoring, respectively, for predicting perioperative strokes. The sensitivity obtained was 38.6% (95% CI 17% to 65.9%) for EEG and 42.3% (95% CI 22.7% to 64.6%) for transcranial Doppler monitoring. respectively.	**Domain 1: Study Eligibility Criteria** **The review adhere to pre-defined objectives and eligibility criteria. The eligibility criteria were clear and appropriate. Restrictions based on study characteristics (sample size of 50 or greater) were made. Only studies published in English language were included.** **Domain 2: Identification and Selection of Studies** **PubMed, Embase, and Web of Science were searched for relevant studies. No additional attempts were made to locate further studies. Only keywords were provided, full details of the search strategy were not reported. Studies published from January 1970 through September 2015 were considered. Two authors were independently involved in the study selection process. Any disagreements were resolved by a third reviewer.** **Domain 3: Data Collection and Study Appraisal** **Data extraction was performed by two authors independently and disagreements were resolved by a third author. Sufficient study characteristics appear to have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. The methodological quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies version 2 checklist. No information was provided regarding the number of authors involved in the risk of bias assessment.** **Domain 4: Synthesis and Findings** **The synthesis appeared to include all relevant studies. The methodological analysis section of the review was sufficiently elucidated. There was evidence of significant heterogeneity among the studies. Appropriate attempts were not made to explore the possible sources of heterogeneity. No evidence of significant publication bias was found using the funnel plot. The quality of individual studies was considered in the synthesis.** **Overall summary** **Authors had acknowledged the observed heterogeneity. Only studies published in English were included. No additional attempts were made to locate further studies. A complete search strategy was not provided. No information was provided regarding the number of authors involved in the risk of bias assessment.**

Bottom line: The evidence informs that patients with perioperative strokes are 4 times more likely to have had transcranial Doppler changes (either middle cerebral artery velocity [MCAV] or cerebral microembolic signals [MES]) and 5 times more likely to have MCAV changes during carotid endarterectomy compared to patients without strokes. Lack of clinical studies hinder to investigate the evidence regarding simultaneous MCAV and MES monitoring by transcranial Doppler sonography and combined intraoperative monitoring of transcranial Doppler sonography with somatosensory evoked potentials and electroencephalography during CEA to predict perioperative stroke. The review had significant methodological weaknesses in all the domains, so the findings should be interpreted with caution.

KSRA101553 2013 Vaniyapong T, et al. Local versus general anaesthesia for carotid endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 14 **Number of participants** 4596 operations **Last search date** 30 September 2013 **Review type** Intervention **Objective** To compare the effectiveness of local and general anaesthesia for carotid endarterectomy. **Population** Any type of patient undergoing unilateral or bilateral carotid endarterectomy. **Interventions** General anaesthetic of any type. **Comparator** A local anaesthetic of any type, including both epidural and skin or deep infiltration. **Outcome** Primary outcomes: The proportion of patients who had a stroke of any kind (i.e. fatal or non-fatal, contralateral or ipsilateral or brainstem, haemorrhage or infarction) within 30 days of surgery, and during long-term follow-up. Secondary outcomes: Stroke ipsilateral to the operated artery within 30 days of operation and during long-term follow-up, deaths from all causes within 30 days of surgery, the proportion of patients who had a stroke or died within 30 days of surgery, myocardial infarction (fatal or non-fatal) within 30 days of surgery, complications related to surgery, the numbers of participants with raised or lower blood pressure (hypertension or hypotension) during or after surgery, the percentage of participants in whom a shunt was used during surgery, the total duration of hospital and intensive care unit stay, the overall satisfaction and preference of participants with each type of procedure, the overall satisfaction and preference of surgeons and the feasibility of carrying out carotid endarterectomy under local anaesthetic. **Study design** Randomised and quasi-randomised controlled trials.	The pooled analysis reported no statistically significant differences between general anaesthetic and local anaesthetic groups regarding outcomes any stroke within 30 days of operation (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.67 to 1.28, 12 studies, 4453 participants), death within 30 days of operation (OR 0.61, 95% CI 0.35 to 1.06, 10 studies, 4181 participants) and stroke or death within 30 days of operation (OR 0.85, 95% CI 0.62 to 1.16, 10 studies, 4181 participants). Similarly, no statistically significant differences were found between the groups with respect to outcomes myocardial infarction within 30 days of operation (OR 1.53, 95% CI 0.67 to 3.47, 11 studies, 4357 participants), local haemorrhage (OR 0.95, 95% CI 0.75 to 1.19, 5 studies, 3976 participants) and cranial nerve injuries (OR 1.17, 95% CI 0.95 to 1.44, 4 studies, 3865 participants). However, the use of local anaesthetic was associated with significantly fewer shunts than a general anaesthetic (OR 0.24, 95% CI 0.08 to 0.73, 8 studies, 4133 participants).	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. No restrictions were reported based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching the Cochrane Stroke Group Trials Register (September 2013), MEDLINE (1966 to September 2013), EMBASE (1980 to September 2013) and Index to Scientific and Technical Proceedings (ISTP) (1980 to September 2013). In addition, the authors handsearched relevant journals and searched the reference lists of articles identified for relevant articles. The search strategy was reported in full and appeared adequate. No restrictions were reported based on date, publication format, or language. Three reviewers were independently involved in study selection and disagreements were resolved by discussion.** **Domain 3: Data Collection and Study Appraisal** **Three reviewers were independently involved in the data extraction process and risk of bias assessment. Discrepancies were resolved by discussion. Sufficient individual study characteristics have been extracted to allow interpretation of results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was performed by the Cochrane Risk of Bias Tool.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all the relevant studies. The method of analysis was explained and appeared appropriate. Low to high heterogeneity was present between studies. Subgroup analyses were performed to address the between-study heterogeneity. The authors planned to create and examine a funnel plot to explore the possibility of small-study biases if more than 10 trials were available. Sensitivity analysis was performed to check the robustness of the study results. The quality of the individual studies was considered in the synthesis.** **Overall summary** **All domains were considered at low concern.**

Bottom line: The current evidence suggests no significant differences between local and general anaesthesia for carotid endarterectomy. Hence, patients and surgeons can choose either anaesthetic technique, depending on the clinical situation and their own preferences. Further, well-designed high-quality randomised controlled trials are needed to support these findings.

KSRA16952 2015 Vincent S, et al. Meta-analysis of randomized controlled trials comparing the long-term outcomes of carotid artery stenting versus endarterectomy

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 8 **Number of participants** 7,091 **Last search date** 22 October 2014 **Review type** Intervention **Objective** To determine the long-term outcomes of carotid artery stenting compared to endarterectomy in patients with carotid stenosis. **Population** Patients with carotid stenosis. Younger or older patients (using the age categories reported by the individual trials), men or women, and symptomatic or asymptomatic patients. **Interventions** Carotid artery stenting (CAS). **Comparator** Carotid endarterectomy (CEA). **Outcome´** Any periprocedural and long-term stroke, myocardial infarction (MI), haematoma, cranial nerve palsy and death. **Study design** Randomised controlled trials. Observational studies (e.g. cohort, cross-sectional, or case-control), systematic reviews and meta-analyses, case reports and case series, as well as letters to the editor, editorials, reviews and commentaries were excluded.	The pooled analysis reported that stenting was associated with a significantly higher risk of any periprocedural stroke (risk ratio [RR] 1.49, 95% confidence interval [CI] 1.11 to 2.01, seven trials, n=6,962) and any long-term stroke (RR 1.36, 95% CI 1.16 to 1.61, seven trials, n=6,946). Similarly, stenting was associated with an increased periprocedural composite endpoint (RR 1.50, 95% CI 1.12 to 2.02, six trials, n=6,628) and long-term ipsilateral stroke (RR 1.45, 95% CI 1.20 to 1.75, six trials, n=6,195). However, no significant difference was observed between stenting and endarterectomy regarding procedural disabling or major stroke. Stenting was associated with a significantly lower risk of myocardial infarction (RR 0.47, 95% CI 0.29 to 0.78, seven trials, n=6,962), severe haematoma (RR 0.35, 95% CI 0.21 to 0.57, six trials, n=4,519) and cranial nerve palsy (RR 0.08, 95% CI 0.04 to 0.14, seven trials, n=5,853), but may be associated with an increased risk of bradycardia, hypotension and restenosis. The long-term incidence of disabling or major stroke was also higher with stenting.	**Domain 1: Study Eligibility Criteria** **The research objective was clearly stated and appropriate inclusion criteria were defined. Only English or French language studies with ≥50 patients were considered for inclusion in the review. Abstracts from conference proceedings were excluded because their results are often not final and they contain insufficient information to thoroughly assess the study quality.** **Domain 2: Identification and Selection of Studies** **Studies were identified by searching PubMed, EMBASE, MEDLINE and the Cochrane Library Register of Controlled Trials. Additionally, the bibliographies of previous systematic reviews and relevant trials and updates of already included trials that were not identified in the electronic search were manually searched. The search strategy was reported in full and appeared adequate. The search was restricted to English or French language studies. No information was provided on the number of reviewers involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal** **Two reviewers were independently involved in the data extraction process and risk of bias assessment. Discrepancies were resolved by discussion with a third reviewer. Sufficient study characteristics have been extracted to allow interpretation of the results. Relevant study results appear to have been extracted. Methodological quality assessment of included studies was performed by the Cochrane risk of bias tool.** **Domain 4: Synthesis and Findings** **The synthesis appeared to have included all relevant studies. Analyses predefined in the methodology section were performed appropriately. Low to high heterogeneity was present between studies. Subgroup and meta-regression analyses were performed to address the between-study heterogeneity, wherever possible. Sensitivity analysis was performed to check the robustness of study results. Quality of the individual studies was considered in the synthesis.** **Overall summary** **The authors acknowledged the presence of significant heterogeneity between the studies in outcome definitions in the limitations. Only English or French language studies with ≥50 patients were considered for inclusion in the review. No information was provided on the number of reviewers involved in the study selection process.**

Bottom line: The current evidence suggests that endarterectomy remains the treatment of choice for the management of carotid stenosis due to increased risk of stroke persisting throughout follow-up with stenting. However, stenting has more favourable periprocedural outcomes with respect to myocardial infarction, haematoma, and cranial nerve palsy and endarterectomy has more favourable periprocedural stroke outcomes. The results should be interpreted cautiously due to high heterogeneity between the studies. The inclusion of only English or French language studies with ≥50 patients means that some relevant studies may have been missed.

KSRA78784 2018 Wodarg F, et al. Influence of stent design and use of protection devices on outcome of carotid artery stenting: a pooled analysis of individual patient data

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 3 **Number of participants** 1557 **Last search date** NA **Review type** Intervention **Objective** To investigate the influence of stent design and the use of protection devices on the outcome of carotid artery stenting. **Population** Patients with moderate or severe carotid stenosis (≥50% according to the NASCET method) associated with a recent non-disabling ocular or cerebral ischemic event **Interventions** Stenting **Comparator** Endarterectomy **Outcome** Any procedural stroke or death (occurring from initiation of stenting until 30 days thereafter) **Study design** Randomised controlled trials (RCTs)	Procedural stroke or death occurred in 61 of 595 patients in the group treated with open-cell stents (10.3%) as compared with 58 of 962 patients treated with closed-cell stents (6.0%, risk ratio (RR) 1.76; 95% confidence interval (CI) 1.23 to 2.52). Further, 950 patients (61.0%) were treated with a protection device. The primary outcome event was found in 76 patients (8.0%) treated with protected stenting and in 43 patients (7.1%) treated with unprotected stenting (RR 1.10; 95% CI 0.71 to 1.70). A significant increase in the procedural stroke or death rate with increasing age (RR 1.53, 95% CI 1.25 to 1.87, P<0.001, per 10-year increase) was found among patients with increasing severity of the qualifying event (retinal ischemia<transient ischemic attack<stroke); in patients with a history of stroke prior to the qualifying event (RR 1.83, 95% CI 1.13 to 2.97); and with increasing level of functional disability at randomisation measured by the modified Rankin Score). Patients who smoked at randomisation or in the past were at lower risk of the primary outcome event (RR 0.63, 95% CI 0.44 to 0.92). Moreover, in the post hoc analysis the RR of procedural stroke or death in patients randomised to stenting versus patients randomised to endarterectomy continuously increased with decreasing use of closed-cell stents at the trial centers (>80% closed-cell stents: RR 1.31, 95%CI 0.84 to 2.03; 20–80% closed-cell stents: RR 1.93, 95% CI 1.25 to 3.00; <20% closed-cell stents: RR 3.24, 95% CI 1.32 to 7.69).	**Domain 1: Study Eligibility Criteria: NA, meta-analysis only** **The research describes the results of an individual patient data (IPD) meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 2: Identification and Selection of Studies: NA, meta-analysis only** **This research describes the results of an IPD meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 3: Data Collection and Study Appraisal: NA, meta-analysis only** **The research describes the results of an IPD meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 4: Synthesis and Findings:** **The research presents the results of an IPD meta-analysis of three RCTs. Individual patient data was pooled and analysed by binomial regression models with fixed-effects for the source trial. The log-link was used to obtain an overall unadjusted risk ratio (RR) and 95% CIs of procedural stroke or death. P values were calculated with the likelihood ratio test. Potential heterogeneity of effect measures in the contributing trials was examined by testing for interactions with the source trial in the regression model. Associations between technical variables and the primary outcome were first assessed on a univariable level providing unadjusted RR.** **Overall summary.** **Low risk of bias in the review**

Bottom line: The available evidence suggests that in symptomatic carotid stenosis, the use of stents with a closed-cell design may be independently associated with a lower risk of procedural stroke or death compared with open-cell stents. However, further large trials are required to confirm the current results.

KSRA65499 2018 Yuan G, et al. Carotid Artery Stenting Versus Carotid Endarterectomy for Treatment of Asymptomatic Carotid Artery Stenosis

Details of Review	Main results	Full Risk of Bias Assessment
Number of studies 5 **Number of participants** 4,414 **Last search date** 21 March 2016 **Review type** Intervention **Objective** To review the efficacy and safety of carotid artery stenting and carotid endarterectomy in patients with asymptomatic carotid artery stenosis. **Population** Patients with asymptomatic but still significant carotid artery stenosis. Patients with symptomatic carotid stenosis were excluded. **Interventions** Carotid artery stenting. **Comparator** Carotid endarterectomy. **Outcome** Risks of stroke, myocardial infarction and death. **Study design** Randomised controlled trials (RCTs). Non-RCTs, reviews, cost-effectiveness studies, single-arm studies, case series, letters, comments, editorials, proceedings or personal communications were excluded.	The pooled analysis of randomised controlled trials (RCTs) reported that carotid artery stenting (CAS) was significantly associated with a decreased risk of myocardial infarction compared to carotid endarterectomy (CEA) in patients with asymptomatic but still significant carotid artery stenosis (risk ratio [RR] 0.49, 95% confidence interval [CI] 0.26 to 0.91, 4 RCTs). However, no significant differences were observed between the two groups in terms of risk of stroke (RR 1.69, 95% CI 0.97 to 2.92, 3 RCTs) and death rates (RR 0.60, 95% CI 0.17 to 2.18, 3 RCTs).	**Domain 1: Study Eligibility Criteria:** **The research objective was clearly stated. Eligibility criteria were well described and appeared appropriate to address the present review question. No restrictions were applied to eligibility criteria based on study characteristics and sources of information.** **Domain 2: Identification and Selection of Studies:** **MEDLINE, PubMed, Cochrane, Embase and Google Scholar were searched for relevant studies. The reference lists of retrieved articles were manually searched for additional relevant studies. Search terms were provided, but a full search strategy was not reported. No information was provided regarding the number of authors involved in the study selection process.** **Domain 3: Data Collection and Study Appraisal:** **The research describes the results of an IPD meta-analysis but does not state that the meta-analysis was conducted as part of a systematic review.** **Domain 4: Synthesis and Findings:** **The synthesis included all of the relevant studies. The method of analysis was explained and appeared appropriate. There was no evidence of significant heterogeneity for all outcomes. Sensitivity analysis was performed to test the robustness of findings. The quality of individual studies was considered in the synthesis.** **Overall summary** **Search terms were provided and appeared limited. A full search strategy was not reported. No information was provided regarding the number of authors involved in the study selection process.**
Bottom line: Current evidence suggests that the use of carotid artery stenting (CAS) seems to be significantly associated with a lower risk of myocardial infarction and a slightly higher risk of stroke compared to carotid endarterectomy (CEA) in patients with asymptomatic but still significant carotid artery stenosis. However, both procedures appear to be equivalent in terms of the risk of death. The review had a number of shortcomings, so interpretation needs to be done with caution.		

NATIONALE UND INTERNATIONALE LEITLINIEN (LEITLINIENTABELLE 2014-2019)

Tabelle 1: 2014, Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association (1) (Update der Leitlinie aus 2011)

Grades of recommendation:

CLASS I: *benefit >>> risk*, procedure/treatment **SHOULD** be performed/administered

CLASS IIa: *benefit >> risk, additional studies with focused objectives needed*. **IT IS REASONABLE** to perform procedure/administer treatment

CLASS IIb: *benefit ≥ risk, additional studies with broad objectives needed; additional registry data would be helpful.* Procedure/Treatment **MAY BE CONSIDERED**

CLASS III: *no benefit.* Procedure/test not helpful, treatment has no proven benefit

or **CLASS III:** *harm.* Procedure/test with excess cost without benefit or harmful, treatment harmful to patients

Level of evidence:

Level A: Multiple populations evaluated, multiple RCTs or metanalyses

Level B: limited populations evaluated, single RCT or non-randomized studies

Level C: very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care

1. Recommendations for carotid disease	**Empfehlungsgrad**	**Evidenzlevel**
a) For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%	I	A
b) For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based maging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%	I	B
c) When the degree of stenosis is <50%, CEA and CAS are not recommended	III	A
d) When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 eeks of the index event rather than delay surgery if there are no contraindications to early revascularization	IIa	B
e) CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6%	IIa	B
f) It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (e.g., older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complication (e.g., stroke, MI, or death) and long-term risk for ipsilateral stroke	IIa	B
g) Among patients with symptomatic severe stenosis(>70%) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable (revised recommendation)	IIa	B
h) CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies	I	B
i) Routine, long term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended	III	B

j) For patients with a recent (within 6 months) TIA or ischemic stroke ipsilateral to a stenosis or occlusion of the middle cerebral or carotid artery, EC/IC bypass surgery is not recommended	III	A
k) For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational	IIb	C
l) Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke, as outlined elsewhere in this guideline	I	A
2. Recommendations for intracranial atherosclerosis	**Empfehlungsgrad**	**Evidenzlevel**
a) For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable	IIb	B
b) For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone	IIb	C
c) For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of systolic BP below 140 mm Hg and high-intensity statin therapy are recommended	I	B
d) For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke on medical management and the inherent periprocedural risk of endovascular treatment	III	B
e) For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA	III	B
f) For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational	IIb	C
g) For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of systolic BP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational	IIb	C
h) For patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational	IIb	C

Tabelle 2: 2014, Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Associaton/American Stroke Association (2) (Update der Leitlinie aus 2011)

Grades of recommendation: **CLASS I:** *benefit >>> risk.* Procedure/ Treatment **SHOULD** be performed/ administered **CLASS IIa:** *benefit >> risk, additional studies with focused objectives needed.* **IT IS REASONABLE** to perform procedure/ administer treatment **CLASS IIb:** *benefit ≥ risk, additional studies with broad objectives needed; additional registry data would be helpful*. Procedure/treatment **MAY BE CONSIDERED** **CLASS III:** *risk ≥ benefit.* Procedure/ Treatment should **NOT** be performed/ administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL** **Level of evidence:** **Level A:** Multiple populations evaluated, multiple RCTs or metanalyses **Level B:** limited populations evaluated, single RCT or non-randomized studies **Level C**: very limited populations evaluated, only consensus opinions of experts, case studies, or standard of care		
Empfehlungen	**Empfehlungsgrad**	**Evidenzlevel**
1. Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted	I	C
2. In patients who are to undergo CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated	I	C
3. It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established	IIa	A
4. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50%	IIa	C
5. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established	IIb	B
6. In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established	IIb	B
7. Screening low-risk populations for asymptomatic carotid artery stenosis is not recommended	III	C

Tabelle 3: 2014, Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/ American Stroke Association (3)

Grades of recommendation: **CLASS I:** *benefit >>> risk.* Procedure/ Treatment **SHOULD** be performed/ administered **CLASS IIa:** *benefit >> risk, additional studies with focused objectives needed.* **IT IS REASONABLE** to perform procedure/ administer treatment **CLASS IIb:** *benefit ≥ risk, additional studies with broad objectives needed; additional registry data would be helpful*. Procedure/treatment **MAY BE CONSIDERED** **CLASS III:** *risk ≥ benefit.* Procedure/ Treatment should **NOT** be performed/ administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL** **Level of evidence:** **Level A:** Multiple populations evaluated, multiple RCTs or metanalyses **Level B:** limited populations evaluated, single RCT or non-randomized studies **Level C**: very limited populations evaluated, only consensus opinions of experts, case studies, or standard of care		
Empfehlungen	**Empfehlungsgrad**	**Evidenzlevel**
(1) Women with asymptomatic carotid stenosis should be screened for other treatable risk factors for stroke, and appropriate lifestyle changes and medical therapies should be instituted	I	C
(2) In women who are to undergo CEA, aspirin is recommended unless contraindicated, because aspirin was used in every major trial that demonstrated efficacy of CEA	I	C
(3) Prophylactic CEA performed with <3% morbidity/mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound)	IIa	A
(4) For women with recent TIA or IS within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%	I	A
(5) For women with recent TIA or IS and ipsilateral moderate (50%–69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%	I	B
(6) When CEA is indicated for women with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery, if there are no contraindications to early revascularization	IIa	B
(7) Aspirin therapy (75–325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated	IIa	B
(8) If a high-risk (ie, 10-year predicted CVD risk ≥10%) woman has an indication for aspirin but is intolerant of aspirin therapy, clopidogrel should be substituted	I	B
(9) Aspirin therapy can be useful in women ≥65 years of age (81 mg/d or 100 mg every other day) if BP is controlled and the benefit for IS and MI prevention is likely to outweigh the risk of gastrointestinal bleeding and hemorrhagic stroke	IIa	B
• and may be reasonable for women <65 years of age for IS prevention	IIb	B

Tabelle 4: 2014, Canadian Best Practise Recommendations for STROKE CARE (4) (update der Leitlinie aus 2008)

Concensus based recommendations including the level of evidence	
1. Recommendations for management of symptomatic carotid stenosis	**Evidenzlevel**
a) Patients with TIA or nondisabling stroke and ipsilateral 50% to 99% internal carotid artery stenosis should have an evaluation by an individual with stroke expertise and selected patients should be offered CEA as soon as possible	B
b) Carotid stenosis should be measured by CTA alone or two concordant noninvasive imaging modalities such as MRA and carotid ultrasound or digital subtraction angiography (DSA)	C
c) Individuals with mild stroke or TIA should have CEA performed within 48 h of symptom onset (NASCET Trial, NNT = 3) (5), and within 14 days for patients who are not clinically stable within the first 48 h	B
d) CEA should be performed by a surgeon with a known perioperative morbidity and mortality of less than 6%	A
e) CAS may be considered for patients who are not operative candidates for technical, anatomic or medical reasons	A
f) Interventionalists should have expertise in carotid procedures and an expected risk of peri-procedural morbidity and mortality rate of less than 5%.	
g) CEA is more appropriate than CAS for patients over age 70 who are otherwise fit for surgery because stenting carries a higher peri-procedural risk of stroke and death	A
2. Recommendations for management of asymptomatic and remotely (> 6mo.) symptomatic carotid stenosis	**Evidenzlevel**
a) CEA may be considered for selected patients with 60% to 99% carotid stenosis who are asymptomatic or were remotely symptomatic (i.e. greater than six-months)	A
b) Stroke patients with asymptomatic carotid stenosis should receive aggressive medical management of risk factors as defined throughout the Prevention of Stroke Module (e.g. blood pressure, cholesterol, antiplatelet therapy)	B
c) Patients with asymptomatic carotid disease should be evaluated by a physician with expertise in stroke management	C
d) Patients should be evaluated to determine eligibility for CEA, such as a life expectancy of more than five-years, and an acceptable risk of surgical complications	A
e) In carefully selected patients, CEA should be performed by a surgeon with a less than 3% risk of perioperative morbidity and mortality	A
f) CAS may be considered in patients who are not operative candidates for technical, anatomic or medical reasons provided there is a less than 3% risk of peri-procedural morbidity and mortality	A
3. Recommendations for management of intracranial stenosis	**Evidenzlevel**
a) Intracranial stenting is not recommended for the treatment of recently symptomatic intracranial 70% to 99% stenosis	B
b) In the SAMMPRIS trial the medical management arm included dual antiplatelet therapy with ASA 325 mg and Clopidogrel 75 mg started within 30 days of stroke or TIA and treated for up to 90 days (6).	B
c) This should be considered for each patient on an individual basis. In addition, there should be aggressive management of all vascular risk factors including blood pressure, lipids, diabetes mellitus, and other at-risk lifestyle patterns	A
d) In patients who have been managed with maximal medical therapy in the presence of intracranial stenosis and experience a recurrent stroke, there is lack of clear evidence to guide further management decisions; intracranial stenting may be reasonable in carefully selected patients	C

Tabelle 5: 2014, ICSI Health Care Guideline: Diagnosis and Management of Type 2 Diabetes Mellitus (T2DM) in Adults (7)

Panel based recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology: **Strength of recommendation:** **Strong (for or against an intervention):** *Patients:* Most people in this situation would want the recommended course of action and only a small proportion would not. *Clinicians:* Most patients should receive the recommended course of action. *Policy makers:* The recommendation can be adapted as a policy in most situations. **Conditional/Weak:** *Patients:* The majority of people in this situation would want the recommended course of action, but many would not. *Clinicians:* Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making. *Policy makers:* There is a need for substantial debate and involvement of stakeholders. **Quality of evidence:** Depends on methodological quality of evidence, likelihood of bias, by outcome and across outcome. **High** (RCTs)/**Moderate**/**Low** (observational studies)/**Very low**		
Cardiovascular Risk Management Algorithm Annotations	**Strength of recommendation**	**Quality of Evidence**
1. Cardiovascular Risk Factors: Antihypertensive Therapy		
a) A clinician should initiate antihypertensive treatment for patients with T2DM with a blood pressure ≥ 140/90 mmHG and treat to a goal of < 140/90.	Strong	High
2. **Cardiovascular Risk Factors: Statin Therapy (High Risk)**		
a) A clinician should recommend high-intensity statin therapy for patients diagnosed with T2DM, between the ages of 40-75 with established Atherosclerotic Cardiovascular Disease (ASCVD), and	Strong	High
b) and may recommend high-intensity statin therapy for others at a 10-year ASCVD risk ≥ 7.5%.	Weak	High
3. **Cardiovascular Risk Factors: Statin Therapy (Moderate Risk)**		
c) A clinician should recommend moderate- or high-intensity statin therapy for all patients diagnosed with T2DM between the ages of 40-75 with a LDL ≥ 70 mg/dL.	Strong	High
4. **Cardiovascular Risk Factors: Aspirin Therapy**		
d) A clinician should recommend aspirin therapy for patients diagnosed with T2DM with established ASCVD and consider aspirin therapy for others where the benefits outweighs the risk in primary prevention.	Strong	High

Tabelle 6: 2014, ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) (8, 9)

Grades of recommendation: **CLASS I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. ("is recommended/indicated") **CLASS II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. **CLASS IIa**: Weight of evidence/ opinion is in favour of usefulness/efficacy ("should be considered") **CLASS IIb**: Usefulness/efficacy is less well established by evidence/opinion ("may be considered") **CLASS III**: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful ("is not recommended") **Level of evidence:** **Level A:** Data derived from multiple RCTs or metanalyses **Level B:** Data derived from a single RCT or large non-randomized studies **Level C**: Consensus of opinions of the experts and/or small studies, retrospective studies, registries		
Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention without considering the patient's comorbidities (adapted from Glance et al) **low-risk:** <1% Carotid asymptomatic (CEA oder CAS) **intermediate-risk:** 1-5%, carotid symptomatic (CEA oder CAS) **high –risk:** >5% (nicht CEA oder CAS)		
Clinical risk factors (according to the revised cardiac risk index, Lee 1999): • Ischaemic heart disease (angina pectoris and/or previous myocardial infarction, • Heart failure • Stroke or transient ischaemic attack • Renal dysfunction (serum creatinine >170 µmol/L or 2 mg/dL or a creatinine clearance of <60 mL/min/1.73 m2) • Diabetes mellitus requiring insulin therapy		
Unstable cardiac conditions • Unstable angina pectoris • Acute heart failure • Significant cardiac arrhythmias • Symptomatic valvular heart disease • Recent myocardial infarction (<30 days) and residual myocardial ischaemia		
1. Preoperative evaluation	**Empfehlungsgrad**	**Evidenzlevel**
a) Selected patients with cardiac disease undergoing low- and intermediate-risk non-cardiac surgery may be referred by the anaesthesiologist for cardiological evaluation and medical optimisation.	IIb	C
b) A multidisciplinary expert team should be considered for preoperative evaluation of patients with known or high risk of cardiac disease	IIb	C

undergoing high-risk non-cardiac surgery.		
2. Biomarkers	**Empfehlungsgrad**	**Evidenzlevel**
a) Clinical risk indices are recommended to be used for perioperative risk stratification.	I	B
b) The NSQIP model or the Lee risk index are recommended for cardiac perioperative risk stratification	I	B
c) Assessment of cardiac troponins in high-risk patients, both before and 48–72 hours after major surgery, may be considered.	IIb	B
d) NT-proBNP and BNP measurements may be considered for obtaining independent prognostic information for perioperative and late cardiac events in high-risk patients.	IIb	B
e) Universal preoperative routine biomarker sampling for risk stratification and to prevent cardiac events is not recommended.	III	C
3. Non-invasive testing	**Empfehlungsgrad**	**Evidenzlevel**
a) Preoperative ECG is recommended for patients who have risk factor(s)d and are scheduled for intermediate- or high-risk surgery.	I	C
b) Preoperative ECG may be considered for patients who have risk factor(s) and are scheduled for low-risk surgery.	IIb	C
c) Preoperative ECG may be considered for patients who have no risk factors, are above 65 years of age, and are scheduled for intermediate-risk surgery.	IIb	C
d) Routine Preoperative ECG is not recommended for patients who have no risk factors and are scheduled for low-risk surgery.	III	B
e) Rest echocardiography may be considered in patients undergoing high-risk surgery.	IIb	C
f) Routine echocardiography is not recommended in patients undergoing intermediate- or low-risk surgery.	III	C
g) Imaging stress testing is recommended before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (<4 METs).	I	C
h) Imaging stress testing may be considered before high- or intermediate-risk surgery in patients with one or two clinical risk factors and poor functional capacity (<4 METs)	IIb	C
i) Imaging stress testing is not recommended before low-risk surgery, regardless of the patient's clinical risk.	III	C
4. Invasive coronary angiography	**Empfehlungsgrad**	**Evidenzlevel**
a) Indications for preoperative coronary angiography and revascularization are similar to those for the non-surgical setting.	I	C
b) Urgent angiography is recommended in patients with acute ST-segment elevation myocardial infarction requiring nonurgent, non-cardiac surgery.	I	A
c) Urgent or early invasive strategy is recommended in patients with NSTE-ACS requiring non-urgent, noncardiac surgery according to risk assessment.	I	B
d) Preoperative angiography is recommended in patients with proven myocardial ischaemia and unstabilized chest pain (Canadian Cardiovascular Society Class III–IV) with adequate medical therapy requiring non-urgent, non-cardiac surgery.	I	C
e) Preoperative angiography may be considered in stable cardiac patients undergoing non-urgent carotid endarterectomy surgery.	IIb	B
f) Preoperative angiography is not recommended in cardiac stable patients undergoing low-risk surgery	III	C
5. Recommendations on betablockers	**Empfehlungsgrad**	**Evidenzlevel**
a) Perioperative continuation of beta-blockers is recommended in patients currently receiving this medication.	I	B
b) Preoperative initiation of betablockers may be considered in patients who have known IHD or myocardial ischaemia.	IIb	B

c) When oral beta-blockade is initiated in patients who undergo non-cardiac surgery, the use of atenolol or bisoprolol as a first choice may be considered.	IIb	B
d) Initiation of perioperative highdose beta-blockers without titration is not recommended.	III	B
e) Preoperative initiation of betablockers is not recommended in patients scheduled for low-risk surgery.	III	B
6. Recommendations on statins	**Empfehlungsgrad**	**Evidenzlevel**
a) Perioperative continuation of statins is recommended, favouring statins with a long half-life or extended-release formulation	I	C
b) Preoperative initiation of statin therapy should be considered in patients undergoing vascular surgery, ideally at least 2 weeks before surgery.	IIa	B
7. Recommendations on use of Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB)	**Empfehlungsgrad**	**Evidenzlevel**
a) Continuation of ACEIs or ARBs, under close monitoring, should be considered during non-cardiac surgery in stable patients with heart failure and LV systolic dysfunction.	IIa	C
b) Initiation of ACEIs or ARBs should be considered at least 1 week before surgery in cardiac-stable patients with heart failure and LV systolic dysfunction.	IIa	C
c) Transient discontinuation of ACEIs or ARBs before non-cardiac surgery in hypertensive patients should be considered.	IIa	C
8. Recommendations on antiplatelet therapy	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended that aspirin be continued for 4 weeks after BMS implantation and for 3–12 months after DES implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high.	I	C
b) Continuation of aspirin, in patients previously thus treated, may be considered in the perioperative period, and should be based on an individual decision that depends on the perioperative bleeding risk, weighed against the risk of thrombotic complications.	IIb	B
c) Discontinuation of aspirin therapy, in patients previously treated with it, should be considered in those in whom haemostasis is anticipated to be difficult to control during surgery.	IIa	B
d) Continuation of P2Y12 inhibitor treatment should be considered for 4 weeks after BMS implantation and for 3–12 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high.	IIa	C
e) In patients treated with P2Y12 inhibitors, who need to undergo surgery, postponing surgery for at least 5 days after cessation of ticagrelor and clopidogrel – and for 7 days in the case of prasugrel—if clinically feasible, should be considered unless the patient is at high risk of an ischaemic event.	IIa	C
9. Recommendations on timing of non-cardiac surgery in cardiacstable/asymptomatic patients with previous revascularization	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended that, except for high-risk patients, asymptomatic patients who have undergone CABG in the past 6 years be sent for nonurgent, non-cardiac surgery without angiographic evaluation.	I	B
b) Consideration should be given to performing non-urgent, non-cardiac surgery in patients with recent BMS implantation after a minimum of 4 weeks and ideally 3 months following the intervention.	IIa	B
c) Consideration should be given to performing non-urgent, non-cardiac surgery in patients who have had recent DES implantation no sooner than 12 months following the intervention. This delay may be reduced to 6 months for the newgeneration DES.	IIa	B
d) In patients who have had recent balloon angioplasty, surgeons should consider postponing non-cardiac surgery until at least 2 weeks after the intervention.	IIa	B

10. Recommendations for prophylactic revascularization in stable/ asymptomatic patients	Empfehlungsgrad	Evidenzlevel
a) Performance of myocardial revascularization is recommended according to the applicable guidelines for management in stable coronary artery disease.	I	B
b) Late revascularization after successful non-cardiac surgery should be considered, in accordance with ESC Guidelines on stable coronary artery disease.	I	C
c) Prophylactic myocardial revascularization before high-risk surgery may be considered, depending on the extent of a stress-induced perfusion defect.	IIb	B
d) Routine prophylactic myocardial revascularization before low- and intermediate-risk surgery in patients with proven IHD is not recommended.	III	B
11. Recommendations on routine myocardial revascularization in patients with NSTE-ACS	**Empfehlungsgrad**	**Evidenzlevel**
a) If non-cardiac surgery can safely be postponed, it is recommended that patients should be diagnosed and treated in line with the guidelines on NSTE-ACS.	I	A
b) In the unlikely combination of a life-threatening clinical condition requiring urgent non-cardiac surgery and revascularization for NSTEACS, the expert team should discuss, case by case, the priority of surgery.	IIa	C
c) In patients who have undergone non-cardiac surgery, aggressive medical treatment and myocardial revascularization according to the guidelines on NSTE-ACS are recommended following surgery.	I	B
d) If PCI is indicated before semiurgent surgery, the use of new-generation DES, BMS or even balloon angioplasty is recommended.	I	B
11. Recommendations on heart failure	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended that patients with established or suspected heart failure, and who are scheduled for noncardiac intermediate or high-risk surgery, undergo evaluation of LV function with transthoracic echocardiography and/or assessment of natriuretic peptides, unless they have recently been assessed for these.	I	A
b) It is recommended that patients with established heart failure, who are scheduled for intermediate or highrisk non-cardiac surgery, be therapeutically optimized as necessary, using beta-blockers, ACEIs or ARBs, and mineralocorticoid antagonists and diuretics, according to ESC Guidelines for heart failure treatment.	I	C
c) In patients with newly diagnosed heart failure, it is recommended that intermediate- or high-risk surgery be deferred, preferably for at least 3 months after initiation of heart failure therapy, to allow time for therapy uptitration and possible improvement of LV function.	I	C
d) It is recommended that beta blockade be continued in heart failure patients throughout the perioperative period, whereas ACEIs/ARBs may be omitted on the morning of surgery, taking into consideration the patient’s blood pressure. If ACEIs/ARBs are given, it is important to carefully monitor the patient's haemodynamic status and give appropriate volume replacement when necessary.	IIb	C
e) Unless there is adequate time for dose-titration, initiation of high-dose beta-blockade before non-cardiac surgery in patients with heart failure is not recommended.	III	B
12. Recommendations on arterial hypertension	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended that patients with a new diagnosis of hypertension preoperatively be screened for end-organ damage and cardiovascular risk factors.	I	C
b) Large perioperative fluctuations in blood pressure in hypertensive patients should be avoided.	IIa	B
c) Clinicians may consider not deferring non-cardiac surgery in patients with grade 1 or 2 hypertension (systolic blood pressure <180 mm	IIb	B

Hg; diastolic blood pressure <110 mm Hg).		
13. Recommendations on Valvular Heart Diseases (VHD)	**Empfehlungsgrad**	**Evidenzlevel**
a) Clinical and echocardiographic evaluation is recommended in all patients with known or suspected VHD, who are scheduled for elective intermediate or high-risk non-cardiac surgery.	I	C
b) Aortic valve replacement is recommended in symptomatic patients with severe aortic stenosis, who are scheduled for elective non-cardiac surgery, provided that they are not at high risk of an adverse outcome from valvular surgery.	I	B
c) Aortic valve replacement should be considered in asymptomatic patients with severe aortic stenosis, who are scheduled for elective high-risk non-cardiac surgery, provided that they are not at high risk of an adverse outcome from valvular surgery.	IIa	C
d) Elective low or intermediate-risk noncardiac surgery should be considered in asymptomatic patients with severe aortic stenosis if there has been no previous intervention on the aortic valve.	IIa	C
e) In symptomatic patients with severe aortic stenosis who are scheduled for elective non-cardiac surgery, TAVI or balloon aortic valvulo-plasty should be considered by the expert team if they are at high risk of an adverse outcome from valvular surgery.	IIa	C
f) Elective non-cardiac surgery should be considered in patients with severe valvular regurgitation, who do not have severe heart failure or LV dysfunction.	IIa	C
g) Percutaneous mitral commissurotomy should be considered in patients with severe mitral stenosis, who have symptoms of pulmonary hypertension and are scheduled for elective intermediate- or high-risk non-cardiac surgery.	IIa	C
14. Recommendations for ventricular arrhythmias	**Empfehlungsgrad**	**Evidenzlevel**
a) Continuation of oral antiarrhythmic drugs before surgery is recommended.	I	C
b) Anti-arrhythmic drugs are recommended for patients with sustained ventricular tachycardia (VT), depending on the patient's character-istics.	I	C
c) Anti-arrhythmic drugs are not recommended for patients with vebtricula premature beats (VPBs)	III	C
15. Recommendations on supraventricular arrhythmias	**Empfehlungsgrad**	**Evidenzlevel**
a) Continuation of oral antiarrhythmic drugs before surgery is recommended.	I	C
b) Electrical cardioversion when haemodynamic instability occurs is recommended.	I	C
c) Vagal manoeuvres and antiarrhythmic therapy for termination of supraventricula tachycardia (SVT) in haemodynamically stable patients is recommended.	I	C
16. Recommendations on bradyarrhythmias and pacemakers	**Empfehlungsgrad**	**Evidenzlevel**
a) The indications for temporary pacemakers during the perioperative period are generally the same as those for permanent pacemakers.	IIb	C
b) It is recommended that the hospital nominate a person who is responsible for programming of the implanted arrhythmia devices before and after surgery.	IIb	C
c) Patients with ICDs, whose devices have been preoperatively deactivated, should be on continuous cardiac monitor throughout the pe-riod of deactivation. External defibrillation equipment should be readily available.	IIb	C
d) Patients who have asymptomatic bifascicular or trifascicular block are not recommended for routine management with a perioperative temporary pacing wire.	IIb	C
17. Recommendations on renal function	**Empfehlungsgrad**	**Evidenzlevel**

a) Patients should be assessed for risk of contrast-induced acute kidney injury (CI-AKI)	IIa	C
b) Prevention of contrast-induced nephropathy in patients with moderate or moderate-to-severe CKD		
c) Hydration with normal saline is recommended before administration of contrast medium.	I	A
d) Use of low-osmolar contrast medium (LOCM) or iso-osmolar contrast medium (IOMC) is recommended.	I	A
e) It is recommended that the volume of contrast media be minimized.	I	A
f) Hydration with sodium bicarbonate should be considered before administration of contrast medium.	IIa	A
g) Short-term high-dose statin therapy should be considered.	IIa	B
h) Patients with severe CKD		
i) In patients with stage 4 or 5 CKD, prophylactic haemofiltration may be considered before complex intervention or high-risk surgery.	IIb	B
j) In patients with stage </=3 CKD, prophylactic haemodialysis is not recommended.	III	B
18. Recommendations on patients with suspected or established carotid artery disease	**Empfehlungsgrad**	**Evidenzlevel**
a) Preoperative carotid artery and cerebral imaging are recommended in patients with a history of TIA or stroke in the preceding 6 months.	I	C
b) Preoperative, routine carotid artery imaging may be considered in patients undergoing vascular surgery.	IIb	C
c) Whenever possible, continuation of anti-platelet and statin therapies should be considered throughout the perioperative phase in patients with carotid artery disease.	IIa	C
d) For patients with carotid artery disease undergoing non-cardiac surgery, the same indications for carotid revascularization should apply as for the general population.	Iia	C
e) Preoperative routine carotid artery imaging is not recommended in patients undergoing non-vascular surgery.	III	C
19. Recommendations on pulmonary artery hypertension (PAH) and pulmonary diseases	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended that patients with severe PAH, who are undergoing elective surgery, be managed in a centre with appropriate expertise.	I	C
b) It is recommended that interventions for high-risk patients with PAH be planned by the multidisciplinary pulmonary hypertension team.	I	C
c) It is recommended that patients with PAH have an optimized treatment regimen before any non-emergency surgical intervention.	I	C
d) It is recommended that patients receiving PAH-specific treatment continue this in the pre-, peri-, and postoperative periods without interruption.	I	C
e) It is recommended that monitoring of patients with PAH continue for at least 24 hours in the postoperative period.	I	C
f) In the case of progression of right heart failure in the postoperative period of patients with PAH, it is recommended that the diuretic dose be optimized and, if necessary, intravenous vasoactive drugs be initiated under the guidance of a physician experienced in the management of PAH.	I	C
g) In patients with COPD, smoking cessation (>2 months before surgery) is recommended before undertaking surgery.	I	C
h) In the case of severe right heart failure that is not responsive to supportive therapy, the temporary administration of pulmonary vasodilators (inhaled and/or intravenous) is recommended, under the guidance of a physician experienced in PAH.	I	C
i) In patients at high risk of obesity hypoventilation syndrome (OHS) additional specialist investigation before major elective surgery should be considered.	IIa	C

20. Recommendation on patients with congenital heart disease	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended that patients with complex congenital heart disease be referred for additional specialist investigation before undergoing elective non-cardiac surgery, if feasible.	I	C
21. Recommendations on electrocardiogram (ECG) monitoring	**Empfehlungsgrad**	**Evidenzlevel**
a) Perioperative ECG monitoring is recommended for all patients undergoing surgery.	I	C
b) Selected lead combinations should be considered for better detection of ischaemia in the operating room.	IIa	B
c) When feasible, twelve-lead ECG monitoring should be considered for high-risk patients undergoing surgery.	IIa	B
22. Recommendations on intraoperative and/or perioperative transoesophageal echocardiography (TOE) for detection of myocardial ischaemia	**Empfehlungsgrad**	**Evidenzlevel**
a) The use of TOE should be considered in patients who develop ST-segment changes on intraoperative or perioperative ECG monitoring.	IIa	C
b) The use of TOE may be considered in patients at high risk of developing myocardial ischaemia, who undergo high-risk non-cardiac surgery.	IIb	C
23. Recommendations on intraoperative and/or perioperative TOE in patients with or at risk of haemodynamic instability	**Empfehlungsgrad**	**Evidenzlevel**
a) TOE is recommended when acute sustained severe haemodynamic disturbances develop during surgery or in the perioperative period.	I	C
b) TOE monitoring may be considered in patients at increased risk of significant haemodynamic disturbances during and after highrisk non-cardiac surgery.	IIb	C
c) TOE monitoring may be considered in patients who present severe valvular lesions during high-risk non-cardiac surgery procedures accompanied by significant haemodynamic stresses.	IIb	C
24. Recommendations on blood glucose control	**Empfehlungsgrad**	**Evidenzlevel**
a) Postoperative prevention of hyperglycaemia [targeting levels at least <10.0 mmol/L (180 mg/dL)] by intravenous insulin therapy is recommended in adults after highrisk surgery that requires admission to the intensive care unit.	I	B
b) In patients at high surgical risk, clinicians should consider screening for elevated HbA1c before major surgery and improving preoperative glucose control.	IIa	C
c) Intraoperative prevention of hyperglycaemia with insulin may be considered.	IIb	C
d) Postoperative targets <6.1 mmol/L (110 mg/dL) are not recommended.	III	A

NSTE-ACS, non–ST-elevation acute coronary syndromes

Tabelle 7: 2015, Deutsche Gesellschaft für Neurologie, Akuttherapie des ischämischen Schlaganfalls (Ergänzung) – Rekanalisierende Therapie (10)

Konsensus basierte Empfehlungen der Deutschen Gesellschaft für Neurologie, Deutschen Schlaganfallgesellschaft und der Deutschen Gesellschaft für Neuroradiologie im Rahmen eines nicht-anonymisierten DELPHI-Verfahrens; Leitlinie auf S2k-Niveau
Empfehlungen zur mechanischen Rekanalisation
1. Eine mechanische Thrombektomie ist zur Behandlung von akuten Schlaganfallpatienten mit klinisch relevantem neurologischen Defizit und großem arteriellem Gefäßverschluss im vorderen Kreislauf bis zu 6 Stunden (Zeitpunkt der Leistenpunktion) nach Auftreten der Symptome empfohlen. Bei fehlenden Kontraindikationen sollen die Patienten im 4,5-Stunden-Zeitfenster auch systemisch mit rtPA behandelt werden (neue Empfehlung).
2. Die mechanische Thrombektomie kann bei selektierten Patienten auch später als 6 Stunden nach Symptombeginn noch wirksam sein. Erweiterte Bildgebungsparameter (z.B. Mismatch Bildgebung, Kollateraldarstellung) sollten herangezogen werden, um Patienten mit Risikogewebe zu identifizieren **(neue Empfehlung)**.
3. Die mechanische Thrombektomie sollte nicht die Einleitung der intravenösen Thrombolyse verzögern und die intravenöse Thrombolyse darf die mechanische Thrombektomie nicht verzögern, insbesondere wird nicht empfohlen, einen möglichen rtPA-Effekt vor der Thrombektomie abzuwarten **(neue Empfehlung)**.
4. Potenzielle Thrombektomie-Kandidaten sollten unverzüglich eine nicht-invasive Gefäßdiagnostik (CTA, MRA) erhalten, um die Indikation rasch stellen zu können **(neue Empfehlung)**.
5. Die mechanische Thrombektomie sollte möglichst rasch nach der Indikationsstellung erfolgen, die Zeit zwischen Eintreffen in der Klinik und Leistenpunktion (door-to-groin time) sollte maximal 90 Minuten und die Zeit zwischen Leistenpunktion und Thrombektomiebeginn maximal 30 Minuten betragen **(neue Empfehlung)**
6. Die mechanische Thrombektomie sollte eine Reperfusion TICI 2b/3 erreichen, für die Gesamtzahl der Patienten ist eine Quote von mind. 75% TICI 2b/3 zu fordern **(neue Empfehlung)**.
7. Bei Diagnose von akuten proximalen intrakraniellen Gefäßverschlüssen in einem Krankenhaus ohne Möglichkeit zur mechanischen Thrombektomie soll ein „Bridging-Konzept" verwendet werden. Nach Beginn der intravenösen Thrombolyse mit rtPA soll unverzüglich die Verlegung in ein Zentrum mit endovaskulärer Therapiemöglichkeit erfolgen **(veränderte Empfehlung)**. Eine ergänzende Bildgebung nach klinischer Verschlechterung bzw. lang dauernden Verlegungen liegt im Ermessen des Neuroradiologen **(neue Empfehlung)**.
8. Für die mechanische Thrombektomie sollten Stent-Retriever verwendet werden **(neue Empfehlung)**. Andere Thrombektomiesysteme können nach dem Ermessen des Neuroradiologen verwendet werden, wenn eine schnelle, vollständige und sichere Rekanalisation des Gefäßes erreicht werden kann **(neue Empfehlung)**.
9. Wenn eine intravenöse Thrombolyse kontraindiziert ist, ist die mechanische Thrombektomie als Erstlinien-Therapie bei Patienten mit Verschluss einer proximalen Hirnbasisarterie empfohlen **(neue Empfehlung)**.
10. Patienten mit akutem Basilarisverschluss sollten mit einer mechanischen Thrombektomie behandelt werden, und wenn keine Kontraindikationen vorliegen, gemeinsam mit einer intravenösen Thrombolyse **(veränderte Empfehlung)**. Eine eindeutige Obergrenze des Zeitfensters kann nicht angegeben werden, vermutlich ist es länger als bei Verschlüssen der vorderen Zirkulation. Alternativ ist der Einschluss in randomisierte Studien möglich.
11. Die Wahl der Sedierung hängt von der individuellen Situation ab; unabhängig von der gewählten Methode sollten alle Anstrengungen unternommen werden, um Zeitverzögerungen bei der Thrombektomie zu vermeiden **(neue Empfehlung)**.
12. Patienten mit radiologischen Zeichen eines großen Infarktes (z.B. ASPECTS <5) sind nicht grundsätzlich von einer mechanischen Thrombektomie auszuschließen, wenn sonstige Gründe für die Durchführung sprechen (wie z.B. Nachweis zusätzlicher noch relevanter rettbarer Hirngewebe in der Perfusionsbildgebung) **(neue Empfehlung)**.
13. Hohes Alter alleine ist kein Grund, auf eine mechanische Thrombektomie zu verzichten **(neue Empfehlung)**.
14. Die mechanische Thrombektomie ist ein kompliziertes interventionelles Verfahren, das Zentren mit entsprechender Erfahrung vorbehalten ist. Durchgeführt werden sollte sie nur von darin ausgebildeten Interventionalisten (z.B. DGNR Zertifizierung Modul E) **(neue Empfehlung)**.
15. Zentren, die eine Thrombektomie durchführen, sollten zur Qualitätssicherung prospektiv Leistungszahlen (z.B. Door-to-imaging-Zeit, Door-to–groin-Zeit, Rekanalisationsrate etc.) erfassen **(neue Empfehlung)**.

Tabelle 8: 2015, Deutsche Gesellschaft für Neurologie und Deutsche Schlaganfallgesellschaft, S3-Leitlinie zur Sekundärprophylaxe ischämischer Schlaganfall und transitorische ischämische Attacke, Teil 1 (11)

Grades of recommendation: **A:** **"**Soll"-Empfehlung: Zumindest eine randomisierte kontrollierte Studie von insgesamt guter Qualität und Konsistenz, die sich direkt auf die jeweilige Empfehlung bezieht und nicht extrapoliert wurde (Evidenzebenen Ia und Ib) **B:** „Sollte"-Empfehlung: Gut durchgeführte klinische Studien, aber keine randomisierten klinischen Studien, mit direktem Bezug zur Empfehlung (Evidenzebenen II oder III) oder Extrapolation von Evidenzebene I, falls der Bezug zur spezifischen Fragestellung fehlt **0:** „Kann"-Empfehlung: Berichte von Expertenkreisen oder Expertenmeinung und/oder klinische Erfahrung anerkannter Autoritäten (Evidenzkategorie IV) oder Extrapolation von Evidenzebene IIa, Iib oder III. Diese Einstufung zeigt an, dass direkt anwendbare klinische Studien von guter Qualität nicht vorhanden oder nicht verfügbar waren **GCP:** „Good Clinical Practice": Empfohlen als gute klinische Praxis („Good Clinical Practice") im Konsens und aufgrund der klinischen Erfahrung der Mitglieder der Leitliniengruppe, bei dem keine experimentelle wissenschaftliche Erforschung möglich oder angestrebt ist **Evidenzlevel (Studien zu diagnostischen Interventionen):** **Ia**: Evidenz aus einem systematischen Review guter Diagnosestudien vom Typ Ib **Ib:** Evidenz aus mindestens einer Studie an einer Stichprobe der Zielpopulation, bei der bei allen Patienten der Referenztest unabhängig, blind und objektiv eingesetzt wurde **II**: Evidenz aus einem systematischen Review von Diagnosestudien vom Typ II oder mindestens eine, bei der an einer selektierten Stichprobe der Zielpopulation der Referenztest unabhängig, blind und unabhängig eingesetzt wurde **III:** Evidenz aus einem systematischen Review von Diagnosestudien vom Typ III oder mindestens eine, bei der der Referenztest nicht bei allen Personen eingesetzt wurde **IV:** Evidenz aus Berichten von Expertenkomitees oder Expertenmeinung und/oder klinische Erfahrung anerkannter Autoritäten **Evidenzlevel (Studien zu therapeutischen Interventionen:** **Ia:** Evidenz aus einer Metaanalyse von mindestens drei randomisierten kontrollierten Studien (randomized controlled trials, RCTs) **Ib:** Evidenz aus mindestens einer randomisierten kontrollierten Studie oder einer Metaanalyse von weniger als drei RCTs **IIa:** Evidenz aus zumindest einer methodisch guten, kontrollierten Studie ohne Randomisierung **IIb**: Evidenz aus zumindest einer methodisch guten, quasi-experimentellen deskriptiven Studie. **III:** Evidenz aus methodisch guten, nichtexperimentellen Beobachtungsstudien, wie z. B. Vergleichsstudien, Korrelationsstudien und Fallstudien **IV:** Evidenz aus Berichten von Expertenkomitees oder Expertenmeinung und/oder klinische Erfahrung anerkannter Autoritäten		
	Empfehlungsgrad	**Evidenzebene**
1. Thrombozytenfunktionshemmer		
a) Patienten mit ischämischem Schlaganfall oder TIA sollen mit einem Thrombozytenfunktionshemmer im Rahmen der Sekundärprävention behandelt werden, sofern keine Indikation zur Antikoagulation vorliegt.	**A**	**Ia**
b) Patienten mit ischämischem Schlaganfall oder TIA sollen mit ASS (allein oder in Kombination mit verzögert freisetzendem Dipyridamol) oder	**A**	**Ib**

	Clopidogrel behandelt werden. Keine der beiden Substanzen ist der jeweils anderen sicher überlegen.		
c)	ASS soll in einer Dosis von 100 mg verabreicht werden.	**A**	**Ia**
d)	Patienten nach ischämischem Schlaganfall oder TIA sollen ASS zur Sekundärprävention erhalten. Alternativ sollte die Kombination aus ASS und retardiertem Dipyridamol oder Clopidogrel zur Sekundärprävention verabreicht werden.	**A** (für ASS 100mg), **B** für Kombination aus ASS (25mg) und Dipyridamol (200mg), **C** für Clopidogrel (75mg)	**modif. LL (AUS 2010)**
e) f)	Die Kombination von ASS mit Clopidogrel soll bei Patienten nach ischämischem Schlaganfall oder TIA nicht zur langfristigen Sekundärprävention eingesetzt werden. Dies betrifft nicht Patienten nach ischämischem Schlaganfall, die eine zusätzliche Indikation wie akutes Koronarsyndrom oder koronare Stentimplantation haben.	**A**	**Ia**
g)	Die Sekundärprophylaxe mit ASS soll innerhalb der ersten 48 Stunden nach dem klinischen Verdacht eines ischämischen Schlaganfalls oder TIA und nach dem Ausschluss eines hämorrhagischen Schlaganfalls begonnen werden.	**A**	**Ia**
h) i)	Bei Patienten mit akutem ischämischen Schlaganfall, die aufgrund einer Schluckstörung nicht in der Lage sind, ASS oral aufzunehmen, kann alternativ eine Verabreichung über eine nasogastrale Sonde oder parenteral als intravenöse Infusion oder Injektion appliziert werden.	**0**	**IV**
j)	Es liegen keine ausreichenden Daten vor, die die Durchführung eines TFH-Funktionstests rechtfertigen.	-	-
k)	Eine Empfehlung zur Therapieeskalation bei wiederholtem Schlaganfall oder TIA kann mangels Daten nicht gegeben werden. Die Ätiologie des Schlaganfalls sollte erneut evaluiert werden.	**GCP**	
l)	Bei Patienten nach ischämischem Schlaganfall oder TIA mit vorangegangenem abgeheilten gastrointestinalen Ulkusleiden kann die Gabe von Thrombozytenfunktionshemmern durch eine Gabe eines Protonenpumpen-Inhibitors (PPI) begleitet werden.	**0**	**IV**
m)	Die Therapie mit Thrombozytenfunktionshemmern soll dauerhaft erfolgen, es sei denn, dass Kontraindikationen auftreten oder im Verlauf sich eine Indikation zur Antikoagulation ergibt.	**A**	**modif. LL (AUS 2010)**
n)	Aufgrund der hohen Komorbidität von Schlaganfällen und anderen kardiovaskulären Erkrankungen soll ein Absetzen von zur Sekundärprophylaxe verordneten Thrombozytenfunktionshemmern allenfalls in gut begründeten Ausnahmefällen erfolgen.	**GCP**	
2.	**Hyperlipidämie**	**Empfehlungsgrad**	**Evidenzebene**
a)	Patienten mit ischämischem Schlaganfall oder TIA sollen mit einem Statin behandelt werden.	**A**	**Ia**
b)	Patienten mit Hirnblutungen sollten nur unter Abwägen von Risiko und Nutzen mit einem Statin behandelt werden, wenn eine andere eigenständige Indikation vorliegt.	**B**	**Ib**
c)	Basierend auf den Ergebnissen kardiovaskulärer Studien sollte auch bei der Behandlung von Schlaganfallpatienten mit einem Statin ein LDL-Cholesterinwert < 100 mg/dl (<2,6 mmol/L) angestrebt werden.	**GCP**	
d)	Bei Patienten mit akutem ischämischen Schlaganfall oder TIA, die bereits mit einem Statin behandelt werden, soll die Statingabe fortgeführt werden.	**A**	**Ib**

e)	Nikotinsäurederivate, Fibrate oder Ezetimibe sollen bei Patienten nach ischämischem Schlaganfall oder TIA zur Sekundärprophylaxe nicht routinemäßig eingesetzt werden.	**GCP**	
3.	**Orale Antikoagulation bei Vorhofflimmern**	**Empfehlungsgrad**	**Evidenzebene**
a)	Patienten mit ischämischem Schlaganfall oder TIA mit permanentem, persistierendem oder paroxysmalem Vorhofflimmern sollen eine orale Antikoagulation erhalten.	**A**	**Ib**
b)	Thrombozytenfunktionshemmer sollten in der Sekundärprävention nach ischämischem Schlaganfall oder TIA mit Vorhofflimmern nicht mehr verwendet werden, sofern keine kardiologische Indikation für die Gabe von Thrombozytenfunktionshemmern vorliegt.	**GCP**	
c)	Höheres Lebensalter per se ist bei Patienten nach ischämischem Schlaganfall oder TIA mit Vorhofflimmern keine Kontraindikation für eine orale	**B**	**Ib**
d)	Antikoagulation. Auch Patienten in höherem Lebensalter sollten antikoaguliert werden.		
e)	Patienten mit ischämischem Schlaganfall oder TIA und nicht valvulärem Vorhofflimmern sollen eine orale Antikoagulation erhalten.	**A**	**Ib**
f)	Die neuen Antikoagulantien (d.h. Dabigatran, Rivaroxaban und Apixaban) stellen eine Alternative zu den Vitamin-K-Antagonisten dar und sollten aufgrund des günstigeren Nutzen-Risiko-Profils zur Anwendung kommen	**B**	**Ib**
g)	Zu Beginn der Behandlung mit den neuen oralen Antikoagulantien (Dabigatran, Apixaban oder Rivaroxaban) und im Verlauf der Behandlung mindestens einmal jährlich muss die Nierenfunktion mittels Creatinin-Clearance (CrCl) überprüft werden. Eine CrCl < 30 ml/min stellt eine Kontraindikation für eine Behandlung mit Dabigatran dar.	**GCP**	
h)	Eine Behandlung mit Apixaban oder Rivaroxaban ist bei einer CrCl < 15 ml/min kontraindiziert.		
i)	Bei Patienten mit einem Alter über 75 Jahre und bei Patienten mit eingeschränkter Nierenfunktion muss die Dosierung nach Herstellerangabe angepasst werden. Ferner sollte bei diesen Patienten oder in klinischen Situationen, in denen eine mögliche Abnahme oder Verschlechterung der Nierenfunktion zu vermuten ist (z. B. Hypovolämie, Dehydratation und bestimmte Komedikation), die Nierenfunktion öfter überprüft werden.	**GCP**	
j)	Patienten nach ischämischem Schlaganfall oder TIA mit Vorhofflimmern, die für Vitamin-K-Antagonisten ungeeignet sind und bisher dauerhaft mit einem Thrombozytenfunktionshemmer behandelt wurden und bei denen keine Kontraindikation für die Gabe von Apixaban vorliegt, sollten mit Apixaban behandelt werden.	**B**	**Ib**
k)	Alternativ zu Apixaban können in dieser Konstellation auch Dabigatran oder Rivaroxaban eingesetzt werden.	**GCP**	
l)	Thrombozytenfunktionshemmer sollten in der Sekundärprävention nach ischämischem Schlaganfall oder TIA mit Vorhofflimmern nicht mehr verwendet werden, sofern keine kardiologische Indikation für die Gabe von Thrombozytenfunktionshemmern vorliegt (siehe Empfehlung 3.2).	**GCP**	
m)	Die Behandlung von Patienten nach ischämischem Schlaganfall oder TIA mit Vorhofflimmern mittels Antiarrhythmika ist einer Behandlung mit Placebo hinsichtlich des Auftretens des kombinierten Endpunktes oder eines Schlaganfalls nicht überlegen. Es sollte keine Behandlung mit Antiarrhythmika erfolgen, soweit sie nicht aus anderem Grund (kardiologische Indikation, z.B. aufgrund eines tachykarden Vorhofflimmerns) notwendig ist.	**GCP**	
4.	**Therapie der arteriellen Hypertonie**	**Empfehlungsgrad**	**Evidenzebene**
a)	Patienten nach ischämischem Schlaganfall oder TIA mit arterieller Hypertonie sollen langfristig antihypertensiv behandelt werden.	**A**	**Ia**
b)	Grundsätzlich soll der Blutdruck unter 140/90 mmHg gesenkt werden.	**GCP**	
c)	Da der Blutdruck nicht auf einen exakten Wert titriert werden kann, wird ein Zielkorridor empfohlen: Der Therapiekorridor des Zielblutdrucks	**GCP**	

	sollte dabei zwischen 120/70 mmHg und 140/90 mmHg unter Berücksichtigung der Komorbiditäten und unerwünschten Wirkungen liegen.	
d)	Werte < 120/70 mmHg sollen nicht angestrebt werden.	**GCP**
e)	Grundsätzlich sollen bei der Festlegung der Zielblutdruckwerte die individuellen Gegebenheiten und Beschwerden des Patienten sowie die Begleiterkrankungen in die Entscheidung einbezogen werden. Eine Festlegung des Zielblutdrucks ist deshalb immer individuell vorzunehmen.	**GCP**
f) g)	Welche Zielwerte des systolischen und diastolischen Blutdrucks sollen bei Patienten nach ischämischem Schlaganfall oder TIA und Diabetes mellitus hinsichtlich des Auftretens des kombinierten Endpunkts (Myokardinfarkt, Schlaganfall, vaskulärer Tod) oder eines Schlaganfalls angestrebt werden?	**GCP**
h)	Bei Patienten mit Diabetes, die einen ischämischen Schlaganfall oder eine TIA erlitten haben, sollten als Zielkorridor für eine antihypertensive Therapie systolische Werte von 120 bis < 140 mmHg und diastolische Werte von 70 bis < 90 mmHg angestrebt werden.	**GCP**

Tabelle 9: 2016, ESC/EAS Guidelines for the Management of Dyslipiaemias (12)

Grades of recommendation: **CLASS I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective **CLASS II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure **CLASS IIa:** *weight of evidence/opinion is in favour of usefulness/efficacy* **CLASS IIb:** *Usefulness/efficacy is less well established by evidence/opinion* **CLASS III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful **Level of evidence:** **Level A:** Data derived from multiple randomised clinical trials or meta-analyses **Level B:** Data derived from a single randomised clinical trials or large non-randomised studies **Level C**: Consensus of opinion of the experts and/or small studies, retrospective studies, registries		
1. Recommendations for risk estimation	**Empfehlungsgrad**	**Evidenzlevel**
a) Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD or familial hypercholesterolaemia.	**I**	**C**
b) High and very high-risk individuals can be detected on the basis of documented CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors , familial hypercholesterolaemia or a high SCORE risk and are a high priority for intensive advice with regard to all risk factors.	**I**	**C**
2. Recommendations for lipid analyses in cardiovascular disease risk estimation	**Empfehlungsgrad**	**Evidenzlevel**
a) TC is to be used for the estimation of total CV risk by means of the SCORE system	**I**	**C**
b) LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	**I**	**C**
c) Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	**I**	**C**
3. Recommendations for lipid analyses for characterization of dyslipidaemias before treatment	**Empfehlungsgrad**	**Evidenzlevel**
a) LDL-C has to be used as the primary lipid analysis.	**I**	**C**
b) It is recommended to analyse HDL-C before treatment.	**I**	**C**
c) TG adds information about risk, and is indicated for diagnosis and choice of treatment.	**I**	**C**
d) Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	**I**	**C**
4. Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease	**Empfehlungsgrad**	**Evidenzlevel**
a) LDL-C is recommended as the primary target for treatment	**I**	**A**
b) HDL-C is not recommended as a target for treatment	**III**	**A**
c) The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment	**III**	**B**
5. Recommendations for treatment goals for low-density lipoprotein-cholesterol	**Empfehlungsgrad**	**Evidenzlevel**
a) In patients at VERY HIGH CV riskc, an LDL-C goal of <1.8 mmol/L (70 mg/dL), or a reduction of at least 50% if the baseline LDL-Cd is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	**I**	**B**

b) In patients at HIGH CV riskc, an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-Cd is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	**I**	**B**
6. Recommendations for the pharmacological treatment of hypercholesterolaemia	**Empfehlungsgrad**	**Evidenzlevel**
a) Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal. I	**I**	**A**
7. Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia	**Empfehlungsgrad**	**Evidenzlevel**
a) FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	**I**	**C**
b) Family cascade screening is recommended to be performed when an index case of FH is diagnosed	**I**	**C**
c) FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	**I**	**C**
d) In children, testing is recommended from age 5 years, or earlier if homozygous FH is suspected. I	**I**	**C**
8. Recommendations for the treatment of dyslipidaemia in older adults	**Empfehlungsgrad**	**Evidenzlevel**
a) Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients.	**I**	**A**
9. Recommendations for the treatment of dyslipidaemia in diabetes	**Empfehlungsgrad**	**Evidenzlevel**
a) In all patients with type I diabetes and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration	**I**	**C**
b) In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are >40 years of age with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (< 70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (< 100 mg/dL) and for apoB is <80 mg/dL.	**I**	**B**
c) In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB <100 mg/dL are the secondary goals.	**I**	**B**
10. Recommendation for lipid-lowering therapy in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention	**Empfehlungsgrad**	**Evidenzlevel**
a) It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	**I**	**A**
11. Recommendations for the treatment of dyslipidaemia in heart failure or valvular disease	**Empfehlungsgrad**	**Evidenzlevel**
a) Cholesterol lowering therapy with statins is not recommended (but is not harmful either) in patients with heart failure in the absence of other indications for their use.	**III**	**A**
b) Cholesterol-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD in the absence of other indications for their use.	**III**	**A**
12. Recommendations for the treatment of dyslipidaemia in autoimmune diseases	**Empfehlungsgrad**	**Evidenzlevel**
a) The universal use of lipid-lowering drugs is not recommended	**III**	**C**
13. Recommendations for lipid management in patients with moderate to severe chronic kidney disease	**Empfehlungsgrad**	**Evidenzlevel**
a) Patients with stage 3–5 CKD have to be considered at high or very high CV risk.	**I**	**A**

b) The use of statins or statin/ezetimibe combination is indicated in patients with non-dialysis-dependent CKD	**I**	**A**
c) In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	**III**	**A**
14. 1. Recommendations for lipid-lowering drugs in patients with peripheral arterial disease (PAD), including carotid artery disease	**Empfehlungsgrad**	**Evidenzlevel**
a) PAD is a very-high-risk condition and lipid-lowering therapy (mostly statins) is recommended in these patients.	I	A
Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke	**Empfehlungsgrad**	**Evidenzlevel**
a) Statin therapy to reach established treatment goals is recommended in patients at high or very high CV risk for primary prevention of stroke.	I	A
b) Lipid-lowering therapy is recommended in patients with other manifestations of cardiovascular disease for primary prevention of stroke.	I	A
c) Intensive statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA for secondary prevention of stroke	I	A

Tabelle 10: 2016, National Clinical Guideline for Stroke, London, Royal College of Physicians (13) (update der Leitlinie aus 2008/2012)

Consensus based recommendations for the management of symptomatic carotid stenosis
1. Patients with non-disabling stroke or TIA who after specialist assessment are considered candidates for carotid intervention should have carotid imaging performed urgently within 24 hours.
2. Following stroke or TIA, the degree of carotid artery stenosis should be reported using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.
3. People with non-disabling carotid artery territory stroke or TIA should be considered for carotid revascularisation, and if they agree with intervention: a) they should have carotid imaging (duplex ultrasound, MR or CT angiography) performed urgently to assess the degree of stenosis; b) if the initial test identifies a relevant severe stenosis (greater than or equal to 50%), a second or repeat non-invasive imaging investigation should be performed to confirm the degree of stenosis. This confirmatory test should be carried out urgently to avoid delaying any intervention.
4. People with non-disabling carotid artery territory stroke or TIA should be considered for carotid revascularisation if the symptomatic internal carotid artery has a stenosis of greater than or equal to 50%. The decision to offer carotid revascularisation should be: a) based on individualised risk estimates taking account of factors such as the time from the event, gender, age and the type of qualifying event; b) supported by risk tables or web-based risk calculators (e.g. the Oxford University Stroke Prevention Research Unit calculator, www.stroke.ox.ac.uk/model/form1.html).
5. People with non-disabling carotid artery territory stroke or TIA and a carotid stenosis of less than 50% should not be offered revascularisation of the carotid artery.
6. Carotid endarterectomy for people with symptomatic carotid stenosis should be: a) the treatment of choice, particularly for people who are 70 years of age and over or for whom the intervention is planned within seven days of stroke or TIA; b) performed in people who are neurologically stable and who are fit for surgery using either local or general anaesthetic according to the person's preference; c) performed as soon as possible and within 1 week of first presentation; d) deferred for 72 hours in people treated with intravenous thrombolysis; e) only undertaken by a specialist surgeon in a vascular centre where the outcomes of carotid surgery are routinely audited.
7. Carotid angioplasty and stenting should be considered for people with symptomatic carotid stenosis who are: a) unsuitable for open surgery (e.g. high carotid bifurcation, symptomatic re-stenosis following endarterectomy, radiotherapy-associated carotid stenosis); or: b) less than 70 years of age and who have a preference for carotid artery stenting. c) The procedure should only be undertaken by an experienced operator in a vascular centre where the outcomes of carotid stenting are routinely audited.
8. People who have undergone carotid revascularisation should be reviewed post-operatively by a stroke physician to optimise medical aspects of vascular secondary prevention
9. Patients with atrial fibrillation and symptomatic internal carotid artery stenosis should be managed for both conditions unless there are contraindications.

Tabelle 11: 2018 European Society for Vascular Surgery ESVS: Recommendations on the management of Carotid Artery Disease (14)

Grades of recommendation: **CLASS I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective **CLASS II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure **CLASS IIa:** *weight of evidence/opinion is in favour of usefulness/efficacy* **CLASS IIb:** *Usefulness/efficacy is less well established by evidence/opinion* **CLASS III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful **Level of evidence:** **Level A:** Data derived from multiple randomised clinical trials or meta-analyses **Level B:** Data derived from a single randomised clinical trials or large non-randomised studies **Level C**: Consensus of opinion of the experts and/or small studies, retrospective studies, registries		
1. Recommendations for imaging strategies in carotid artery diseases and role of the multidisciplinary team	**Empfehlungsgrad**	**Evidenzlevel**
a) Duplex ultrasound (as first-line), computed tomographic angiography and/or magnetic resonance angiography are recommended for evaluating the extent and severity of extracranial carotid stenoses	I	A
b) When carotid endarterectomy is being considered, it is recommended that Duplex ultrasound stenosis estimation be corroborated by computed tomographic angiography or magnetic resonance angiography, or by a repeat Duplex ultrasound performed by a second operator	I	A
c) When carotid stenting is being considered, it is recommended that any Duplex ultrasound study be followed by computed tomographic angiography or magnetic resonance angiography which will provide additional information on the aortic arch, as well as the extra- and intracranial circulation	I	A
d) Units who base management decisions on Duplex ultrasound stenosis measurement should state which measurement method is being used	I	C
e) Intra-arterial digital subtraction angiography should not be performed in patients being considered for revascularisation, unless there are significant discrepancies on non-invasive imaging	III	A
f) Multidisciplinary assessment is recommended to achieve consensus regarding the indication and optimal treatment of patients by carotid endarterectomy or carotid stenting	I	C
g) Independent assessment after carotid interventions is recommended to audit procedural risks	I	C
2. Recommendations for secondary prevention in asymptomatic patients	**Empfehlungsgrad**	**Evidenzlevel**
(1) Optimal medical therapy		
a) A healthy diet, smoking cessation, and physical activity are recommended for all patients with asymptomatic carotid disease	I	B
b) Low-dose aspirin (75-325 mg) is recommended in patients with asymptomatic carotid stenoses for prevention of late myocardial infarction and other cardiovascular events	I	A
c) Clopidogrel 75 mg daily should be considered in asymptomatic carotid stenosis patients if aspirin intolerant	IIa	C
d) Statin therapy is recommended for long-term prevention of stroke, myocardial infarction and other cardiovascular events in patients with asymptomatic carotid disease	I	A
e) Antihypertensive treatment is recommended for patients with hypertension and asymptomatic extracranial internal carotid artery stenoses to maintain long-term blood pressure <140/90 mmHg	I	A

f) In diabetic patients with asymptomatic carotid stenoses, strict glycaemic control is recommended	I	C
g) In diabetic patients with asymptomatic carotid stenoses, the target blood pressure should be <140/85 mmHg	I	B
(2) Screening for asymptomatic carotid stenoses		
a) Routine population screening for asymptomatic carotid stenosis is not recommended	III	C
b) Selective screening for asymptomatic carotid stenoses may be considered in patients with multiple vascular risk factors to optimise risk factor control and medical therapy to reduce late cardiovascular morbidity and mortality, rather than for identifying candidates for invasive carotid interventions	IIb	C
(3) Interventions in asymptomatic patients		
a) In "average surgical risk" patients with an asymptomatic 60-99% stenosis, carotid endarterectomy should be considered in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years	IIa	B
b) In "average surgical risk" patients with an asymptomatic 60-99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,a carotid stenting may be an alternative to carotid endarterectomy, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years	IIb	B
c) Carotid stenting may be considered in selected asymptomatic patients who have been deemed by the multidisciplinary team to be "high-risk for surgery" and who have an asymptomatic 60-99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,a provided documented procedural risks are <3% and the patient's life expectancy exceeds 5 years	IIb	B
d) Until a causal association between severe asymptomatic carotid stenoses and cognitive decline has been established, carotid interventions are not recommended for the prevention of cognitive impairment in patients with severe asymptomatic carotid stenoses	III	B
3. Recommendations for tertiary prevention in recently symptomatic patients	**Empfehlungsgrad**	**Evidenzlevel**
(1) Optimal medical therapy		
a. A healthy diet, smoking cessation and physical activity are recommended for all patients with symptomatic carotid disease	I	B
b. Antiplatelet therapy is recommended in symptomatic patients with 50e99% stenoses not undergoing carotid endarterectomy or carotid stenting. First choice therapy is clopidogrel 75 mg daily or aspirin 75 mg daily plus modified release dipyridamole 200 mg twice daily. If intolerant of dipyridamole or clopidogrel, aspirin monotherapy (75e325 mg) should be used. If aspirin and clopidogrel intolerant, use modified release dipyridamole 200 mg twice daily	I	A
c. It is recommended that all patients undergoing carotid endarterectomy should receive antiplatelet therapy throughout the perioperative period and also in the long term	I	B
b) Low-dose aspirin (75-325 mg daily) is recommended rather than higher doses (>625 mg daily) in patients undergoing carotid endarterectomy	I	B
c) Early institution of aspirin + clopidogrel (or aspirin plus modified release dipyridamole) after transient ischaemic attack or minor stroke may be considered to reduce early recurrent events in patients with a >50% carotid stenosis awaiting carotid endarterectomy	IIb	C
d) It is recommended that patients undergoing carotid stenting should receive dual antiplatelet therapy with aspirin (75-325 mg daily) and clopidogrel (75 mg daily). Clopidogrel should be started at least 3 days prior to stenting or as a single 300 mg loading dose in urgent cases. Aspirin and clopidogrel should be continued for at least 4 wks after stenting and then optimal long-term secondary preventive antiplatelet therapy should be continued indefinitely	I	B

e)	Long-term aspirin plus clopidogrel therapy is not recommended in patients undergoing carotid endarterectomy or carotid stenting unless indicated for cardiac reasons	III	C
f)	Concurrent gastro-protection treatment or proton pump inhibition with pantoprazole should be considered in patients prescribed clopidogrel who have one or more risk factors that increase the patient's risk of gastrointestinal bleeding (prior history of gastrointestinal bleeding, older age, Helicobacter pylori infection, and concomitant use of aspirin, or other non-steroidal anti-inflammatory agents, anticoagulants, selective serotonin re-uptake inhibitors or steroids)	IIa	B
g)	Statin therapy is recommended for the prevention of longterm stroke, myocardial infarction, and other cardiovascular events in patients with symptomatic carotid disease	I	A
h)	It is recommended that patients start statin therapy prior to endarterectomy or stenting and that statins should not be stopped during the perioperative period and should be continued long term	I	B
i)	Antihypertensive treatment is recommended for patients with hypertension and symptomatic extracranial internal carotid artery carotid stenoses to maintain long-term blood pressure <140/90 mmHg	I	A
j)	Caution should be exercised in significantly reducing blood pressure immediately prior to carotid endarterectomy or stenting in the early period after onset of symptoms, but uncontrolled hypertension (>180/90 mmHg) should be treated	IIa	C
k)	In diabetic patients with symptomatic carotid stenoses, strict glycaemic control is recommended	I	C
l)	In diabetic patients with symptomatic carotid stenoses, the target blood pressure should be <140/85 mmHg	I	B
(2)	**Randomised trials comparing endarterectomy with stenting**		
a)	Carotid endarterectomy is recommended in patients reporting carotid territory symptoms within the preceding 6 months and who have a 70-99% carotid stenosis, provided the documented procedural death/stroke rate is <6%	I	A
b)	Carotid endarterectomy should be considered in patients reporting carotid territory symptoms within the preceding 6 months and who have a 50-69% carotid stenosis, provided the documented procedural death/stroke rate is <6%	IIa	A
c)	It is recommended that most patients who have suffered carotid territory symptoms within the preceding 6 months and who are aged >70 years and who have 50-99% stenoses should be treated by carotid endarterectomy, rather than carotid stenting	I	A
d)	When revascularisation is indicated in patients who have suffered carotid territory symptoms within the preceding 6 months and who are aged <70 years, carotid stenting may be considered an alternative to endarterectomy, provided the documented procedural death/stroke rate is <6%	IIb	A
e)	Carotid endarterectomy or carotid stenting are not recommended in symptomatic patients with a chronic internal carotid near-occlusion, unless associated with recurrent ipsilateral symptoms (despite optimal medical therapy) and following multidisciplinary team review	III	C
(3)	**Timing of interventions after onset of symptoms**		
a)	When revascularisation is considered appropriate in symptomatic patients with 50-99% stenoses, it is recommended that this be performed as soon as possible, preferably within 14 days of symptom onset	I	A
b)	Patients who are to undergo revascularisation within the first 14 days after onset of symptoms should undergo carotid endarterectomy, rather than carotid stenting	I	A
c)	Revascularisation should be deferred in patients with 50-99% stenoses who suffer a disabling stroke (modified Rankin score ≥3), whose area of infarction exceeds one-third of the ipsilateral middle cerebral artery territory, or who have altered consciousness/drowsiness, to minimise the risks of postoperative parenchymal haemorrhage	I	C

d) Patients with 50-99% stenoses who present with stroke-inevolution or crescendo transient ischaemic attacks should be considered for urgent carotid endarterectomy, preferably <24 hours	IIa	C
(4) Timing of carotid interventions after intravenous thrombolysis		
a) Early carotid endarterectomy (within 14 days) should be considered after intravenous thrombolysis in symptomatic patients if they make a rapid neurological recovery (Rankin 0-2), the area of infarction is less than one-third of the ipsilateral middle cerebral artery territory, a previously occluded middle cerebral artery mainstem has recanalised, there is a 50e99% carotid stenosis and no evidence of parenchymal haemorrhage or significant brain oedema	IIa	C
b) It is recommended that intravenous heparin and antiplatelet therapy be withheld for 24 hours after completion of intravenous thrombolysis, but antiplatelet therapy should then be commenced before any carotid intervention is undertaken	I	C
c) It is recommended that patients undergoing early carotid interventions after thrombolysis should have post-interventional hypertension actively treated to reduce the risks of parenchymal haemorrhage	I	C
(5) Is there a subgroup with <50% stenosis who might benefit from surgery?		
a) Carotid endarterectomy or carotid stenting may be considered in recently symptomatic patients with <50% stenoses if they suffer recurrent symptoms despite best medical therapy and following multidisciplinary team review	IIb	C
(6) "High-risk for surgery" symptomatic patients		
a) In recently symptomatic patients with 50-99% stenoses and anatomical and/or medical comorbidities that are considered by the multidisciplinary team to make them "higher-risk for carotid endarterectomy," carotid stenting should be considered as an alternative to endarterectomy, provided the documented procedural death/stroke rate is <6%	IIa	B
4. Recommendations for carotid surgical techniques	**Empfehlungsgrad**	**Evidenzlevel**
(1) Carotid endarterectomy		
a) It is recommended that choice of anaesthesia for carotid endarterectomy (general versus locoregional) be left to the surgical team's discretion	I	A
b) The choice of carotid exposure (antegrade/retrojugular) should be left to the discretion of the operating surgeon	I	B
c) Routine carotid sinus nerve blockade is not recommended as there is no evidence it reduces the prevalence of perioperative hypotension, hypertension, and arrhythmias	III	A
d) Protamine reversal of heparin should be considered to prevent neck haematomas requiring re-exploration	IIa	B
e) It is recommended that the choice of shunting (routine, selective, never) be left to the discretion of the operating surgeon	I	C
f) Routine patching is recommended, rather than routine primary closure. There is no evidence that patch type influences outcome	I	A
g) Eversion endarterectomy is recommended over routine primary arteriotomy closure	I	A
h) The choice between eversion or patched endarterectomy should be left to the discretion of the operating surgeon	I	A
i) Surgical intervention for asymptomatic isolated coils/kinks of the internal carotid artery is not recommended	III	C
j) Symptomatic patients with isolated coils/kinks may be considered for surgical correction, but only following multidisciplinary team review and provided no other cause for transient ischaemic attack or stroke symptoms can be identified	IIb	B
k) Targeted monitoring and quality control strategies may be considered to reduce the risk of perioperative stroke	IIb	C
l) The surgeon should anticipate the presence of distal disease extension preoperatively and plan for this in advance	I	C

(2) Carotid bypass		
a) Extracranial to Intracranial bypass surgery is not recommended in patients with an extracranial internal carotid occlusion	III	A
5. Recommendations for carotid artery stenting	**Empfehlungsgrad**	**Evidenzlevel**
i. Adjuvant medical therapy		
a) It is recommended that atropine or glycopyrrolate be administered prior to balloon inflation during carotid stenting to prevent hypotension, bradycardia, or asystole	I	B
i. **Use of cerebral protection devices**		
a) The use of embolic protection devices should be considered in patients undergoing CAS	IIa	B
b) Proximal protection devices are not recommended in patients with advanced common carotid disease, or those with external carotid artery disease (where an occlusion balloon is to be positioned in the external carotid artery) or in patients with contralateral occlusion and insuffi-cient collateralisation	III	C
6. Recommendations for handling complications following carotid interventions	**Empfehlungsgrad**	**Evidenzlevel**
a. The first 30 days		
a) First-line treatment of post-carotid intervention hypotension should be the administration of intravenous crystalloids together with volume expanders. If this fails to improve blood pressure, titrated intravenous vasopressors (dobutamine, dopamine, noradrenaline, phenylephrine) should be considered to maintain systolic blood pressure >90 mmHg	IIa	C
b) It is recommended that intra-arterial blood pressure monitoring be continued for the first 3-6 hours after carotid endarterectomy and carotid stenting, followed by hourly noninvasive blood pressure monitoring for the first 24 hours	I	C
c) It is recommended that vascular units have written criteria for treating post-carotid intervention hypertension	I	C
d) Any patient who develops a postoperative neck haematoma in association with stridor or tracheal deviation must be reexplored immediately	I	C
b. Late complications		
a) Patch excision and autologous venous reconstruction is recommended for most patients with prosthetic patch infection	I	C
b) Insertion of a covered stent may be considered in selected “high-risk for surgery” patients with suspected prosthetic patch infection	IIb	C
c) Patch excision and prosthetic reconstruction is not recommended for patients with patch infection after carotid endarterectomy	III	C
d) Patients suffering a late ipsilateral stroke/TIA in the presence of an ipsilateral 50-99% restenosis should undergo redo carotid endarterectomy or carotid artery stenting	I	A
e) It is recommended that patients suffering a late ipsilateral stroke/transient ischaemic attack in the presence of an ipsilateral <50% restenosis should be treated medically	I	A
f) Reintervention may be considered in carotid endarterectomy patients with an asymptomatic 70-99% restenosis, following multidisciplinary team review	IIb	B
g) It is recommended that carotid stent patients who develop an asymptomatic restenosis >70% are treated medically	I	A
h) Serial surveillance and reintervention for asymptomatic restenoses >70% is recommended in patients who developed neurological symptoms during carotid clamping under local anaesthesia, or during balloon inflation (or proximal flow reversal) during carotid stenting	I	C

i) Serial surveillance and reintervention for asymptomatic restenoses >70% is recommended in carotid endarterectomy patients who developed significant electrophysiological changes during carotid clamping or whose mean middle cerebral artery velocities fell below 15 cm/s on transcranial Doppler monitoring during carotid clamping under general anaesthesia	I	C
j) When a decision has been made to undertake revascularisation in patients with a restenosis, it is recommended that the choice of redo endarterectomy or stenting should be based on multidisciplinary team review, local surgeon/interventionist preference, and patient choice	I	C
7. Recommendations for the management of concurrent coronary and carotid disease	**Empfehlungsgrad**	**Evidenzlevel**
a) Routine screening for carotid disease prior to open-heart surgery is not recommended	III	C
b) Ultrasound screening for carotid disease prior to coronary bypass should be considered in patients aged>70 years, those with a history of transient ischaemic attack or stroke, a carotid bruit or left mainstem disease so that the patient can be better informed of the increased risks associated with coronary artery bypass surgery in patients with concurrent carotid disease	IIa	C
c) Staged or synchronous carotid intervention should be considered in coronary artery bypass surgery patients with a history of stroke or transient ischaemic attack in the preceding 6 months and a 50-99% carotid stenosis	IIa	B
d) Staged or synchronous carotid endarterectomy should be considered, instead of stenting plus coronary bypass, in patients with a history of stroke or transient ischaemic attack in the preceding 6 months and a 50-99% carotid stenosis	IIa	B
e) A staged or synchronous carotid intervention is not recommended in coronary artery bypass patients with an asymptomatic unilateral 70-99% carotid stenosis for the prevention of stroke after coronary bypass	III	B
f) A staged or synchronous carotid intervention may be considered in coronary artery bypass patients with bilateral asymptomatic 70-99% carotid stenoses, or a 70-99% stenosis with contralateral occlusion	IIb	C
g) The choice between carotid endarterectomy and carotid stenting in asymptomatic patients in whom a carotid intervention is deemed necessary prior to coronary artery bypass should be based on the urgency of performing surgery, choice of antiplatelet strategy during coronary bypass, individual patient characteristics, symptom status, and local expertise	IIa	C
8. Recommendations for carotid disease and major non-cardiac surgery	**Empfehlungsgrad**	**Evidenzlevel**
a) Patients undergoing elective, non-cardiac surgery with a history of stroke or transient ischaemic attack within the preceding 6 months should undergo carotid artery imaging	I	B
b) Patients with a history of stroke or transient ischaemic attack in the preceding 6 months who are to undergo elective, noncardiac surgery with an ipsilateral 50-99% carotid stenosis should undergo carotid revascularisation before elective non-cardiac surgery	I	A
c) It is recommended that, where possible, elective non-cardiac surgery should be delayed for 6 months in patients with a history of recent stroke and no significant carotid disease. The decision to proceed with semi-urgent elective surgery will have to be individualised, based on the underlying pathology	I	B
d) Routine carotid imaging in asymptomatic patients undergoing non-cardiac surgery procedures is not recommended	III	B
e) Patients undergoing major non-cardiac, non-vascular surgical procedures should undergo a comprehensive cardiovascular risk assessment to aid the consent process regarding the risk of perioperative stroke	I	B
f) Wherever possible, statin and antiplatelet therapy should not be stopped prior to major non-vascular surgical procedures in patients with asymptomatic 50-99% carotid stenoses. Anticoagulant therapy withdrawal should be based on an assessment of thromboembolic and haemorrhagic risks	III	B

g) Prophylactic carotid endarterectomy and carotid stenting are not recommended in patients with asymptomatic carotid stenoses prior to major non-cardiac, non-vascular surgical procedures	III	B
9. Recommendations for occlusive disease of proximal common carotid and innominate arteries	**Empfehlungsgrad**	**Evidenzlevel**
a) Open or endovascular interventions to treat proximal common carotid artery or innominate artery stenoses/ occlusions are not recommended in asymptomatic patients	III	C
b) Most proximal common carotid artery and innominate stenoses should be considered for treatment via open retrograde angioplasty and stenting	IIa	C

Tabelle 12: 2018, ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the ESVS (15)

Grades of recommendation: **CLASS I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective **CLASS II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure **CLASS IIa:** *weight of evidence/opinion is in favour of usefulness/efficacy* **CLASS IIb:** *Usefulness/efficacy is less well established by evidence/opinion* **CLASS III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful **Level of evidence:** **Level A:** Data derived from multiple randomised clinical trials or meta-analyses **Level B:** Data derived from a single randomised clinical trials or large non-randomised studies **Level C**: Consensus of opinion of the experts and/or small studies, retrospective studies, registries		
1. Recommendations in patients with peripheral arterial diseases: best medical therapy	**Class**	**Level**
a) Smoking cessation is recommended in all patients with PADs.	I	B
b) Healthy diet and physical activity are recommended for all patients with PADs.	I	C
c) Statins are recommended in all patients with PADs.	I	A
d) In patients with PADs, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by >50% if baseline values are 1.8e3.5 mmol/L (70-135 mg/dL).	I	C
e) In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
f) Antiplatelet therapy is recommended in patients with symptomatic PADs.	I	C
g) In patients with PADs and hypertension, it is recommended to control blood pressure at <140/90 mmHg.	I	A
h) ACEIs or ARBs should be considered as first-line therapy[c] in patients with PADs and hypertension.	IIa	B

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-receptor blockers; LDL-C = low-density lipoprotein cholesterol; PADs = peripheral arterial diseases. c Calcium channel blockers should be proposed in black individuals. d Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in corresponding sections.

2. Recommendations on antithrombotic therapy in patients with Carotid artery disease	**Class [a]**	**Level [b]**
a) In patients with symptomatic carotid stenosis, long-term SAPT is recommended.	I	A
b) DAPT with aspirin and clopidogrel is recommended for at least 1 month after CAS.	I	B
c) In patients with asymptomatic >50% carotid artery stenosis, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low.	IIb	C

CAS = carotid artery stenosis; DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy.

3. Recommendations for imaging of extracranial carotid arteries	**Class**	**Level**
a) DUS (as first-line imaging), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.	I	B

b)	When CAS is being considered, it is recommended that any DUS study be followed by either MRA or CTA to evaluate the aortic arch as well as the extra- and intracranial circulation.	I	B
c)	When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated by either MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory).	I	B

4.	Recommendations on revascularization in patients with symptomatic carotid disease*	Class	Level
a)	CEA is recommended in symptomatic patients with 70-99% carotid stenoses, provided the documented procedural death/stroke rate is <6%.	I	A
b)	CEA should be considered in symptomatic patients with 50-69% carotid stenoses, provided the documented procedural death/stroke rate is <6%.	IIa	A
c)	In recently symptomatic patients with a 50-99% stenosis who present with adverse anatomical features or medical comorbidities that are considered to make them 'high risk for CEA', CAS should be considered, provided the documented procedural death/stroke rate is <6%.	IIa	B
d)	When revascularization is indicated in 'average surgical risk' patients with symptomatic carotid disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/stroke rate is <6%.	IIb	B
e)	When decided, it is recommended to perform revascularization of symptomatic 50-99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.	I	A
f)	Revascularization is not recommended in patients with a <50% carotid stenosis.	III	A
g)	The use of embolic protection devices should be considered in patients undergoing carotid artery stenting.	IIa	C

* Stroke or TIA occurring within 6 months.

5.	Recommendations for management of asymptomatic carotid artery disease	Class	Level
a)	In 'average surgical risk' patients with an asymptomatic 60-99% stenosis, CEA should be considered in the presence of clinical and/or more imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years.	IIa	B
b)	In asymptomatic patients who have been deemed 'high risk for CEA'[d] and who have an asymptomatic 60-99% stenosis in the presence of clinical and/or imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years.	IIa	B
c)	In 'average surgical risk' patients with an asymptomatic 60-99% stenosis in the presence of clinical and/or imaging characteristics[d] that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years.	IIb	B

BP = blood pressure; CAS = carotid artery stenting; CEA = carotid endarterectomy. c See Table 4 and Web Table 5. d Age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

6.	Recommendations on screening for carotid disease in patients undergoing coronary artery bypass grafting	Class	Level
a)	In patients undergoing CABG, DUS is recommended in patients with a recent (<6 months) history of TIA/stroke.	I	B
b)	In patients with no recent (<6 months) history of TIA/stroke, DUS may be considered in the following cases: age _70 years, multivessel coronary artery disease, concomitant LEAD or carotid bruit.	IIb	B
c)	Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA..	III	C

7. Recommendations on the management for carotid stenosis in patients undergoing coronary artery bypass grafting	Class	Level
a) It is recommended that the indication (and, if so, the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
b) In patients with a recent (<6 months) history of TIA/stroke who are scheduled for CABG:		
• Carotid revascularization should be considered in patients with 50-99% carotid stenosis	IIa	B
• Carotid revascularization with CEA should be considered as the first choice in patients with 50-99% carotid stenosis.	IIa	B
• Carotid revascularization is not recommended in patients with carotid stenosis <50%.	III	C
c) In neurologically asymptomatic patients scheduled for CABG:		
• Routine prophylactic carotid revascularization in patients with a 70e99% carotid stenosis is not recommended.	III	B
• Carotid revascularization may be considered in patients with bilateral 70-99% carotid stenoses or 70-99% carotid stenosis . contralateral occlusion.	IIb	B
• Carotid revascularization may be considered in patients with a 70-99% carotid stenosis in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke[c] in order to reduce stroke risk beyond the perioperative period.	IIb	C

CABG = coronary artery bypass grafting; DUS = duplex ultrasound; LEAD = lower extremity artery disease; TIA = transient ischaemic attack

Tabelle 13: 2017, An update on Italian Stroke Organization guidelines on CEA and CAS (16)

Grades of recommendation according to GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) (17): • ''Strong for'' for recommendations on interventions that ''should'' be used—the guideline development group is confident that the intervention will do more good than harm for the vast majority of people; • ''Strong against'' for recommendations on interventions that ''should not'' be used—the guideline development group is confident that the intervention will do more harm than good for the vast majority of people; • ''Weak'' for recommendations on interventions that ''should be considered''—the guideline development group is confident that the intervention will do either more good than harm (''weak for'') or more harm than good (''weak against'') for most patients, but the choice of intervention is more likely to vary depending on a person's values and preferences. The healthcare professional should therefore spend more time discussing the options with the patient; • ''Good-practice point'' (GPP) for recommendations that the guideline development group is confident will be based on clinical experience and best practice. • In addition, the ISO-SPREAD group deemed it opportune to introduce the new term ''P-medicine'' to indicate recommendations on Precision or Personalized Medicine (18).	
Recommendations on CEA and CAS	**Empfehlungsgrad**
1. By convention, carotid stenosis is defined as symptomatic if the last correlated cerebral or ocular ischemic episode has occurred within the previous six months. On the basis of recent revisions, it is recommended to reduce this period to no more than three months.	GPP
2. CEA should be performed on **symptomatic patients** with >/= 70% stenosis if the periprocedural (up to 1-month post-intervention) risk of death and all types of stroke is less than 6%.	strong for
3. CEA should not be performed on **symptomatic patients** with < 50% stenosis or with chronic occlusion or near-occlusion of the internal carotid artery	strong against
4. CEA should be performed on **symptomatic patients with 50–69% stenosis** if they present with at least one of the following: recent ischemia (encountered < 2 months from the initial symptom); a non-ocular cerebral symptom; an ulcerated or vulnerable plaque; male sex; absence of diabetes mellitus; and in any case if the periprocedural (up to 1-month postintervention) risk of death and any type of stroke is less than 6%.	weak for
5. Endarterectomy for carotid stenosis should be performed within the first 2 weeks from the initial ischemic event.	strong for
6. For **symptomatic carotid stenosis**, it should be considered to perform CEA within the first week from the initial ischemic event. It is to be presumed that CEA offers maximal benefit if performed within 48 h from the TIA or minor stroke. Further studies should be conducted to demonstrate this conclusively.	GPP
7. For **symptomatic carotid stenosis** referred to surgery, the patient's risk score for stroke upon medical therapy alone—and thus the benefit gained from surgery—should be considered: in patients with a highscore (>/=4, according to the NASCET and ECST revisions), the benefit from endarterectomy is maximal (NNT, 3); in those with a low score (< 4), benefit is minimal (NNT, 100). Score points are assigned as follows: +1, for non-ocular cerebral ischemic events; +1, for an irregular plaque surface; +1, for an event in the previous 2 months; +1, for each decile of stenosis from 70% (0 points) to 99% (+2 points); -0.5, for females; -0.5, for the presence of peripheral vascular disease; and -0.5, for the presence of systolic blood pressure > 180mmHg.	weak for; personalized-medicine
8. When performing endarterectomy for symptomatic carotid stenosis, the following predictive factors of high periprocedural risk should be considered: non-ocular cerebral ischemic event; ipsilateral ischemic lesion at CT or MR scan; occlusion of the contralateral carotid artery; and irregular or ulcerated carotid plaque	weak for; personalized-medicine
9. CEA should be considered for **asymptomatic patients with ≥70% carotid stenosis** if survival is expected to be ≥3 years and if the periprocedural (up to 1-month post-intervention) risk of complications (death or any type of stroke) is particularly low (i.e. < 3%), with the benefit from surgery increasing with diminishing risk.	weak for
10. Endarterectomy should be considered for the treatment of carotid stenosis in **asymptomatic patients** deemed ''at risk'' from medical therapy alone if at least one of the following is encountered: previous brain infarction; vulnerable, ulcerated, or rapidly growing plaque; pre-occlusive stenosis; and 70–80% stenosis in the presence of contralateral carotid occlusion or signs of ipsilateral microemboli at transcranial Doppler ultrasonography. In contrast, best medical therapy alone	weak for; personalized-medicine

	should be considered if survival is estimated to be shorter than that presumably obtained by endarterectomy, such as in ultra-octogenarians and in patients with insulin-dependent diabetes, serious cardiopathy or bronchopathy, or chronic renal insufficiency receiving dialysis	
11.	In order to assess the risks/benefits from surgical intervention for **asymptomatic carotid stenosis**, the predictive periprocedural score for major complications (stroke, myocardial infarction, death) should be considered. According to the most recent models, the expected benefit from endarterectomy is marked in patients with a low score (i.e. < 4, corresponding to a periprocedural risk of < 3%); marginal in patients with an intermediate score (i.e. 4–7, corresponding to a periprocedural risk of 3–6%); and negligible in patients with a high score (i.e. > 7, corresponding to a periprocedural risk of > 6%), in which case the best medical therapy alone should be administered. Score points are assigned as follows: 0, for age < 60 years; -1, for age 60–79 years; +2, for age >/=80 years; +3, for the presence of dyspnea; +3, for the presence of chronic obstructive bronchopathy; +3, for previous revascularization of the legs or amputation of an extremity; +4, for angina pectoris in the previous month; and +5, if the patient is totally dependent on others for their everyday.	weak for; personalized-medicine
12.	Up to now, evidence of clinical equipoise for CAS and CEA - or at least of no inferiority of the former procedure - is available only from centers of excellence. Thus, until more data are obtained, CEA should be performed as the surgical intervention of choice for carotid stenosis. CAS should be performed as an alternative only as part of a controlled clinical trial or in centers with interventionalists showing a documented case history on the periprocedural risk of stenting that is at least not inferior to that for endarterectomy.	strong for
13.	CAS - executed with appropriate procedural quality and cerebral protection - should be performed on patients presenting with a major cardiac and/or pulmonary comorbidity or with at least one of the following: paralysis of the contralateral laryngeal nerve; stenosis extending cranially or clavically; restenosis; and prior tracheotomy or neck surgery/radiotherapy. By convention, major cardiac comorbidity includes: congestive heart failure and/or left ventricular dysfunction; heart surgery in the previous 6 weeks; cardiac infarction in the previous 4 weeks; and unstable angina.	strong for
14.	In ultra-septuagenarians not presenting with a major comorbidity, it should be considered to prefer CEA over CAS for the surgical treatment of carotid stenosis, especially if disease is symptomatic and if intervention is early.	weak for
15.	Carotid stenting should not be considered when there is the suspicion of endoluminal thrombotic or thromboembolic carotid material or when the anatomy of the supraaortic trunks is particularly challenging.	weak against
16.	When the choice between performing CEA or CAS for carotid revascularization is not clear, the ISO-SPREAD group deems it opportune to: use an integrated interdisciplinary approach, with specialists in the cerebrovascular, cardiovascular, diagnostic imaging, traditional and endovascular surgery, and anesthesiology fields; consider the experience of the center and operator; adopt the locally agreed, coordinated, and shared standard operating procedure; consider the option of best medical therapy alone, especially in patients with asymptomatic carotid stenosis and/or at high risk from surgery; and to consider enrolling the patient in a controlled, comparative, prospective study.	GPP
17.	For CAS, the following predictive factors of high periprocedural risk for major complications (stroke, myocardial infarction, death) should be considered: ischemic or dilated cardiomyopathy; diabetes mellitus; symptomatic stenosis; calcified and/or ulcerated carotid plaque; stenosis with a length > 65% of the diameter of the common carotid artery; bovine or type III aortic arch; calcification of the aortic arch; preocclusive stenosis; and evidence of major lesions of the white matter upon brain CT/MR scan.	weak for; personalized-medicine

CI, confidence interval; GPP, good practice point; RCT, randomized controlled trial.

Tabelle 14: 2017, Australian clinical guidelines for stroke management (19), ersetzt das Dokument aus 2010

Grades of recommendation (nach GRADE, https://app.magicapp.org/app#/guideline/2437/section/29701): • Strong recommendations: where guideline authors are certain that the evidence supports a clear balance towards either desirable or undesirable effects • Weak recommendations: where the guideline panel is uncertain about the balance between desirable and undesirable effects	
Empfehlungen	**Empfehlungsgrad**
1. In pre-hospital settings, high risk indicators (e.g. crescendo TIA, current or suspected AF, current use of anticoagulants, carotid stenosis or high ABCD2 score) can be used to identify patients for urgent specialist assessment.	strong
2. In TIA patients, use of the ABCD2 risk score in isolation to determine the urgency of investigation may delay recognition of atrial fibrillation and symptomatic carotid stenosis in some patients and should be avoided.	weak AGAINST
3. All TIA patients with anterior circulation symptoms should undergo early carotid imaging with CT angiography (aortic arch to cerebral vertex), carotid Doppler ultrasound or MR angiography. Carotid imaging should preferably be done during the initial assessment but should not be delayed more than 2 days	strong
4. All other patients with carotid territory symptoms who would potentially be candidates for carotid re-vascularisation should have early vascular imaging to identify stenosis in the ipsilateral carotid artery. CT angiography (if not already performed as part of assessment for reperfusion therapies), Doppler ultrasound or contrast-enhanced MR angiography are all reasonable options depending on local experience and availability.	strong
5. For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced within six hours of stroke onset.	strong
6. Carotid endarterectomy is recommended for patients with recent (<3 months) non-disabling carotid artery territory ischaemic stroke or TIA with ipsilateral carotid stenosis measured at 70-99% (NASCET criteria) if it can be performed by a specialist team with audited practice and a low rate (<6%) of perioperative stroke and death.	strong
7. Carotid endarterectomy can be considered in selected patients with recent (<3 months) non-disabling ischaemic stroke or TIA patients with symptomatic carotid stenosis of 50–69% (NASCET criteria) if it can be performed by a specialist team with audited practice and a very low rate (<3%) of perioperative stroke and death	strong
8. Carotid endarterectomy should be performed as soon as possible (ideally within two weeks) after the ischaemic stroke or TIA.	strong
9. All patients with carotid stenosis should be treated with intensive vascular secondary prevention therapy.	strong
10. Carotid endarterectomy should be performed in preference to carotid stenting due to a lower perioperative stroke risk. However, in selected patients with unfavourable anatomy, symptomatic re-stenosis after endarterectomy or previous radiotherapy, stenting may be reasonable.	weak
11. In patients aged <70 years old, carotid stenting with an experienced proceduralist may be reasonable.	weak
12. In patients with asymptomatic carotid stenosis, carotid endarterectomy or stenting should not be performed.	weak AGAINST
13. In patients with symptomatic carotid occlusion, extracranial/ intracranial bypass is not recommended	strong AGAINST

Tabelle 15: 2018, Guidelines for the Early Management of Patients With Acute Ischemic Stroke (20), American Heart Association/American Stroke Association (ersetzt das Dokument aus 2013)

Grades of recommendation: **CLASS I (STRONG): Benefit >>> Risk** **CLASS IIa (MODERATE): Benefit >> Risk** **CLASS IIb (WEAK): Benefit ≥ Risk:** **Class III: No benefit (MODERATE): Benefit = risk** **Class III: No benefit (HARM): Risik > benefit** **Level of evidence:** **Level A: High-quality evidence from > 1 RCTS, metaanalyses from high-qulity RCT and one or more RCTs coorobarted by high-quality registries** **Level B-R:** moderarte-quality evidence from 1 or more RCTs, metaanlyses of moderate-quality RCTs **Level B-NR:** moderarte-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies or registry studies, metanalyses of such studies **Level C-LD:** Randomized or non-randomized observational or registry studies with limitations of design and execution, metaanalyses of such studies… **Level C-EO:** Consensus of expert opinion based on clinical experience		
1. In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, is reasonable to provide useful information on patient eligibility and endovascular procedural planning.	IIa	B-NR
2. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	I	A
3. Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Additional randomized trial data are needed.	IIb	B-R
4. The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established.	IIb	B-NR
5. The safety and usefulness of short-term anticoagulation for nonocclusive, extracranial intraluminal thrombus in the setting of AIS are not well established.	IIb	C-LD
6. The usefulness of emergent or urgent CEA when clinical indicators or brain imaging suggests a small infarct core with large territory at risk (eg, penumbra), compromised by inadequate flow from a critical carotid stenosis or occlusion, or in the case of acute neurological deficit after CEA, in which acute thrombosis of the surgical site is suspected, is not well established.	IIb	B-NR
7. In patients with unstable neurological status (eg, stroke-inevolution), the efficacy of emergency or urgent CEA is not well established.	IIb	B-NR
8. For patients with nondisabling (mRS score 0–2) AIS in the carotid territory who are candidates for CEA or stenting, noninvasive imaging of the cervical vessels should be performed routinely within 24 hours of admission.	I	B-NR
9. When revascularization is indicated for secondary prevention in patients with minor, nondisabling stroke (mRS score 0–2), it is reasonable to perform the procedure between 48 hours and 7 days of the index event rather than delay treatment if there are no contraindications to early revascularization.	IIa	B-NR

Tabelle 16: 2018, Society for Vascular Surgery (SVS) practice guidelines on follow-up after vascular surgery (21)

Grades of recommendation: **1 STRONG:** Benefit >> Risk, Risks >> benefits **2 Weak:** Benefit = risks, Quality of evidence precludes accurate assessment of risks and benefits. **Level of evidence:** **A (high):** Additional research is considered very unlikely to change confidence in the estimate of the effect. **B (Moderate):** Further research is likely to have an important impact on the estimate of the effect. **C (Low):** Further research is very likely to change the estimate of the effect.		
1. After CEA or CAS, we recommend surveillance with DUS at baseline and every 6 months for 2 years and annually thereafter until stable (ie, until no restenosis or ISR is observed in two consecutive annual scans). The first or baseline DUS should occur soon after the procedure, preferably within 3months, with the goal of establishing a post-treatment baseline. Considering the small risk of delayed restenosis or ISR, some interval of regular surveillance (eg, every 2 years) should be maintained for the life of the patient.	strong	B
2. For patients undergoing CAS with diabetes, aggressive patterns of ISR (type IV), prior treatment for ISR, prior cervical radiation, or heavy calcification, in addition to the baseline DUS we recommend surveillance with DUS every 6 months until a stable clinical pattern is established and annually thereafter.	strong	B
3. We recommend that DUS after CAS include at least the following assessments:	strong	C
• A. Doppler measurement of PSV and EDV in the native CCA; in the proximal, mid, and distal stent; and in the distal native ICA. As discussed before, modified threshold velocity criteria should be used to interpret the significance of these velocity measurements after CAS		
• B. B-mode imaging should be used to supplement and to enhance the accuracy of velocity criteria to estimate the severity of luminal narrowing.		

- >/= 20% In-Stent-Restenose (ISR): PSV >/=150 cm/s and ICA/CCA ratio >/=2.15
- >/=50% ISR: PSV >/=220 cm/s and ICA/CCA ratio >/=2.7
- >/=80% ISR: PSV >/=340 cm/s and ICA/CCA ratio >/=4.15

CCA, Common carotid artery; ICA, internal carotid artery; ICA/CCA ratio, PSV in the stented ICA/PSV in the native CCA; PSV, maximum peak systolic velocity. A PSV threshold of >/=300 cm/s was used to identify >/=70% stenosis in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Adapted from Lal BK, Hobson RW 2nd, Goldstein J, Chakhtoura EY, Duran WN. Carotid artery stenting: is there a need to revise ultrasound velocity criteria? J Vasc Surg 2004;39:58-66; and Lal BK, Hobson RW 2nd, Tofighi B, Kapadia I, Cuadra S, Jamil Z. Duplex ultrasound velocity criteria for the stented carotid artery. J Vasc Surg 2007;47:63-73.

Tabelle 17: 2018, ESC/ESH Guidelines for the management of arterial hypertension (22)

Grades of recommendation: **CLASS I:** Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective **CLASS II:** Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure **CLASS IIa:** *weight of evidence/opinion is in favour of usefulness/efficacy* **CLASS IIb:** *Usefulness/efficacy is less well established by evidence/opinion* **CLASS III:** Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful **Level of evidence:** **Level A:** Data derived from multiple randomised clinical trials or meta-analyses **Level B:** Data derived from a single randomised clinical trials or large non-randomised studies **Level C**: Consensus of opinion of the experts and/or small studies, retrospective studies, registries		
1. Classification of BP	**Class**	**Level**
a) It is recommended that BP be classified as optimal, normal, or high–normal, or grades 1–3 hypertension, according to office BP.	I	C
2. Screening for hypertension		
a) Screening programmes for hypertension are recommended. All adults (>_18 years) should have their office BP measured and recorded in their medical file, and be aware of their BP.	I	B
3. Diagnosis of hypertension		
a) It is recommended to base the diagnosis of hypertension on: • Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1–2 min apart, and additional measurements performed if the first two readings differ by >10 mmHg. The patient's BP is the average of the last two BP readings. OR • Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and economically feasible.	I I	C C
4. Office BP thresholds for the initiation of drug treatment for hypertension		
a) Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneously with the initiation of lifestyle changes.	I	A
b) In patients with grade 1 hypertension: • Lifestyle interventions are recommended to determine if this will normalize BP. • In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention. • In patients with grade 1 hypertension at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions.	 I I I	 B A A

a)	In fit older patients with hypertension (even if aged >80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is >_160 mmHg.	I	A
b)	BP-lowering drug treatment and lifestyle intervention are recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.	I	A
c)	In patients with high–normal BP (130–139/85–89 mmHg), lifestyle changes are recommended	I	A
d)	Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of >_80 years, is not recommended, provided that treatment is well tolerated.	III	A
5.	**Office BP treatment targets**		
a)	It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients, and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.	I	A
b)	In patients <65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.d	I	A
c)	In older patients (aged >_65 years) receiving BP-lowering drugs, it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.	I	A
6.	**Treatment of hypertension: lifestyle interventions**	**Class**	**Level**
a)	Salt restriction to <5 g per day is recommended.	I	A
b)	It is recommended to restrict alcohol consumption to <14 units per week for men and <8 units per week for women.	I	A
c)	Increased consumption of vegetables, fresh fruits, fish, nuts, unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended.	I	A
d)	Body weight control is indicated to avoid obesity (BMI >30 kg/m2, or waist circumference >102 cm in men and >88 cm in women) and aim for healthy BMI (about 20–25 kg/m2) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk.	I	A
	Regular aerobic exercise (e.g. >_30 min of moderate dynamic exercise on 5–7 days per week) is recommended.	I	A
f)	Smoking cessation and supportive care and referral to smoking cessation programmes are recommended.	I	B
g)	It is recommended to avoid binge drinking.	III	A
7.	**Treatment of hypertension: drug treatment**	**Class**	**Level**
a)	Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations (e.g. angina, post-myocardial infarction, heart failure, or heart rate control).	I	A
b)	It is recommended to initiate antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).	I	B
c)	It is recommended that if BP is not controllede with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and thiazide/thiazide-like diuretics, preferably as an SPC.	I	A
d)	It is recommended that if BP is not controllede with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.	I	B
e)	The combination of two RAS blockers is not recommended	I	A
8.	**Treatment of hypertension: device-based therapies**		

	a) Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available	I	B
9.	**Management of CVD risk in hypertensive patients**	**Class**	**Level**
	a) CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes.	I	B
	b) For patients at high or very high CV risk, statins are recommended.	I	B
	c) Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients. Aspirin is not recommended for primary prevention in hypertensive patients without CVD	III	A
	d) Routine genetic testing for hypertensive patients is not recommended	III	C

ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; CCB = calcium channel blocker; CV = cardiovascular; CVD = cardiovascular disease; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; RAS = renin–angiotensin system; RCT = randomized controlled trial; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation; SPC = single-pill combination.

cIn patients with grade 1 hypertension and low-moderate-risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range (i.e. the likelihood of achieving BP control with lifestyle intervention
alone) and the opportunities for significant lifestyle change in individual patients.

dLess evidence is available for this target in low-moderate-risk patients.

Adherence to medication should be checked.

Tabelle 18: 2019, European Stroke Organization (ESO) and European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke (23)

Quality of evidence (QoE): **high:** Further research is considered very unlikely to change confidence in the estimate of the effect. **Moderate:** Further research is likely to have an important impact on the estimate of the effect. **Low:** Further research is very likely to change the estimate of the effect. **Very low:** Any estimate of effect is uncertain **Strength of recommendation (SoR):** **Strong:** **Conditional (weak):**	**QoE**	**SoR**
10. In adults with anterior circulation LVO-related acute ischaemic stroke presenting within 6 hours after symptom onset, we recommend MT plus BMM, including IVT whenever indicated, over BMM alone to improve functional outcome	High	Strong pro
11. In adults with anterior circulation LVO-related acute ischaemic stroke presenting between 6 and 24 hours from time last known well and fulfilling the selection criteria of DEFUSE-3 or DAWN, we recommend MT plus BMM over BMM alone to improve functional outcome.	Moderate	Strong pro
12. In LVO-related ischaemic stroke patients eligible for both treatments, we recommend IVT plus MT over MT alone. Both treatments should be performed as early as possible after hospital arrival. MT should not prevent the initiation of IVT, and IVT should not delay MT.	Very low	Strong pro
13. In LVO-related ischaemic stroke patients not eligible for IVT, we recommend MT as standalone treatment	Low	Strong pro
14. In patients with suspected stroke, we cannot make a recommendation on the use of a prehospital scale for improving identification of patients eligible for MT. We suggest enrolling patients in a dedicated randomized controlled trial, whenever possible	Very low	-
15. We cannot make recommendations on whether for adults identified as potential candidates for MT in the prehospital field, the mothership or the drip-and-ship model should be applied to improve functional outcome	Very low	-
16. We recommend that patients aged 80 years or more with LVO-related acute ischaemic stroke within 6 hours of symptom onset should be treated with MT plus BMM, including IVT whenever indicated. Application of an upper age limit for MT is not justified.	Moderate	Strong pro
17. We suggest that patients aged 80 years or more with LVO-related acute ischaemic stroke between 6 and 24 hours from time last known well should be treated with MT plus BMM if they meet the eligibility criteria of the DEFUSE-3 or DAWN trials	Low	Weak pro
18. We do not recommend an upper NIHSS score limit for decision-making on MT. We recommend that patients with high stroke severity and LVO-related acute ischaemic stroke be treated with MT plus BMM, including IVT whenever indicated. These recommendations also apply for patients in the 6-24h time window, provided that they meet the inclusion criteria for the DAWN or DEFUSE-3 studies	High	Strong pro
19. We recommend that patients with low stroke severity (NIHSS 0-5) and LVOrelated acute ischaemic stroke within 24 hours from time last known well be included in randomized controlled trials comparing MT plus BMM versus BMM alone.	Very low	-
20. In the 0-6 hour time window, we recommend MT plus BMM (including IVT whenever indicated) over BMM alone in LVOrelated anterior circulation stroke patients without evidence of extensive infarct core (e.g. ASPECTS _6 on non-contrast CT scan or infarct core volume _70 ml).	High	Strong pro

21. In the 6-24 hour time window, we recommend MT plus BMM (including IVT whenever indicated) over BMM alone in LVOrelated anterior circulation stroke patients fulfilling the selection criteria of DEFUSE-3 or DAWN, including estimated volume of infarct core.	Moderate	Strong pro
22. We recommend that anterior circulation stroke patients with extensive infarct core (e.g. ASPECTS <6 on non-contrast CT scan or core volume >70 ml or >100 ml) be included in RCTs comparing mechanical thrombectomy plus best medical management versus best medical management alone.	Very low	-
23. In adult patients with anterior circulation LVO-related acute ischaemic stroke presenting from 0-6 hours from time last known well, advanced imaging is not necessary for patient selection.	Moderare	Strong pro
24. In adult patients with LVO-related acute ischaemic stroke, we recommend treatment in a comprehensive stroke center.	Very low	Strong pro
25. For adults with LVO-related acute ischaemic stroke, we recommend that interventionalists should attempt a TICI Grade 3 reperfusion, ifachievable with reasonable safety.	Low	Strong pro
26. There is currently no evidence that contact aspiration alone improves functional outcome compared with BMM in patients undergoing MT. 27. There is currently no evidence that contact aspiration alone increases the rate of reperfusion over thrombectomy using a stent retriever. 28. Therefore, we suggest the use of a stent retriever over contact aspiration alone for MT in patients with acute ischaemic stroke.	Very low	Weak pro
29. We cannot provide recommendations to use general anesthesia or conscious sedation in patients undergoing MT, due to a low quality of evidence and conflicting results between 3 small single-center randomized clinical trials and the best available observational evidence. Therefore, we recommend the enrollment of patients in multicenter randomized controlled trials addressing this question	Very low	-
30. We suggest to keep blood pressure below 180/105 mmHg during and 24 hours after MT. No specific blood pressure-lowering drug can be recommended.	Very low	Weak pro
31. During MT, systolic blood pressure drops should be avoided.	Very low	Strong against
32. No recommendation can be provided regarding which treatment modality should be favored in patients with LVO-related cute ischaemic stroke and associated extracranial carotid artery stenosis or occlusion. We recommend the inclusion of such patients in dedicated randomized controlled trials	Very low	.

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1 Evidenztabellen

1.1 Evidenztabelle 1: RCTs zur asymptomatischen Carotisstenose - CEA + BMT versus BMT allein

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
1. VA TRIAL 1993 [1, 2]				
Hobson RW. The role of carotid endarterectomy in asymptomatic carotid stenosis: status of the Veterans Administration study. JVS 9: 400-401 **Hobson RW et al for Veterans Affairs Cooperative Study Group.: Efficacy of Carotid Endarterectomy for Asymptomatic Carotid Stenosis (VA Study). NEJM 1993: 328:221-227**	RCT, 11 VA Hospitals (USA), 1983-1991 444 Männer mit asymptomatischer Stenose >/=50% (NASCET Kriterien, Angiografie) mittleres Follow-up 48 Monate, intention-to-treat-Analyse	CEA + 325-1300 mg ASS/Tag (n=211) versus 325-1300 mg ASS/Tag (n=233)	CEA vs. konservativ insgesamt: • Letalität + alle Schlaganfälle: 41,2% vs. 44,2% (RR 0,02, 95%CI 0,69-1,22) • Letalität: 21,4% vs. 21,9% • Alle neurolog. Events: 12,8% vs. 24,5% (AR 11,6%, p<0.002, RR 51% • Alle ipsilat. Neurolog. Events: 8,0% vs. 20,6% (AR 12,6%, p<0,001, RR 38% • alle Strokes: 8,1% vs. 12,1% • alle Ipsilat strokes: 4,7% vs. 9,4% (p<0,06) • Ipsilat AF/TIA: 3,2% vs. 11,2% • CEA 30 Tage: Schlaganfall/Tod 4,7% (Letalität 1,9% (4x MI), HN-Läsion 3,8%, Schlaganfall (non-fatal) 2,4%, TIA 0,9%, MI (non-fatal) 1,9%)	CEA reduced the overall incidence of ipsilateral neurologic events in a selected group of male patients with asymptomatic carotid stenosis. no significant influence of CEA on the combined incidence of stroke and death Kommentare: • keine Frauen untersucht • ungewöhnlicher EP inkl. alle strokes und TIAs/AF • ipsilaterale Events nach CEA seltener • alle angiografie-verursachten strokes wurden der CEA zugerechnet (3/714, 0,4%) • n=1935 Patienten wurden gescreent, n=444 ran-domisiert
2. ACAS 1995 [3]				
Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the	RCT, 39 Hospitals (USA, Canada), 1987-1993	CEA + 325mg ASS (n=825)	Primärer Endpunkt:	Patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
Asymptomatic Carotid Atherosclerosis Study (ACAS): JAMA 1995;273:1421-8	40-79 Jahre, 66% Männer asymptomat. Stenose 60-99% (NASCET Krit., Angio. immer vor CEA) follow-up im Median 2,7 Jahre, hochgerechnet auf 5 Jahre, ITT	versus 325 mg ASS (n=834)	ipsilat. Stroke (5 Jahre) +any periop. Stroke/death: 5,1% vs. 11% (AR 5,9%, RR 0.53, 95%CI 0,22-0,72, p=0.004) Sekundärer Endpunkt: major ipsilat. Stroke +any major periop. Stroke/death: 3,4% vs. 6% (AR 2,6%, RR 0.43, 95%CI -0,17-0,72, p=0.12)	reduced 5-year risk of ipsilateral stroke if CEA performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors.
3. ACST 2004/2010 [4, 5]				
Halliday AW for the Steering Committee and for the Collaborators. The Asymptomatic Carotid Surgery Trial (ACST) rationale and design. EJVES 1994;8:703-10. **MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363(9420): 1491-502.** **Perioperative stroke or death in various subcategories. http://image.thelancet.com/extras/04art3083webtable.pdf.**	Internationale multizentrische RCT (126 Zentren, 30 Länder, 1993-2003 n=3120, 66% männlich, Durchschnittsalter 68 Jahre (40-91) 60-99%ige asymptomatische Stenose (Angiografie oder Ultraschall) Follow-up durchschnittlich 3,4 Jahre ITT Kein Screening-Log	CEA + BMT (n=1560) Versus BMT allein(ASS, später auch Statine etc, n=1560)	Primärer Endpunkt: Any periop. Stroke/death + the incidence of non-perioperative strokes: 6,4% vs. 11,8%, (ARR 5,4%, 95%CI 2,96-7,75, p<0.0001) Sekundäre Endpunkte: • Fatal or disabling stroke or perioperative death 3,5% vs. 6,1% (ARR 2,6%, 95%CI 0,77-4,32, p=0.004) • Any type of non-perioperative stroke 3,8% vs. 10,9% (ARR 7,1%, 95% CI 4,95-9,39, p<0,0001) • Fatal or disabling non-perioperative stroke 1,9% vs. 5,8% (ARR 3,9%, 95% CI 2,20-5,48, p<0,0001) • Non-perioperative carotid territory ischaemic stroke 2,7% vs. 95% (ARR 6,8%, 95% CI 4,75-8,82, p<0,0001) • Fatal or disabling non-perioperative carotid territory ischaemic stroke 1,6% vs. 5,3% (ARR 3,7%, 95% CI 2,12-5,22, p<0,0001) • Alle strokes (5-yeards-follow-up): 3,8% vs. 11% • Alle periop. Schlaganfälle/Tod (<30 Tagen): 3,1% (2,8% im CEA Arm und 4,5% bei 201 im Verlauf durchgeführten CEAs im kons. Arm) 5-Jahres Risiko eines nicht-prozeduralen carotis-bedingten Schlaganfall (Subgruppen, CEA vs. konservativ): • Männer: 2,4% vs. 10,6% (ARR 8,2%, p<0,0001) • Frauen: 3,4% vs. 7,5% (ARR 4,1, p=0.02) • Lebensalter <65 Jahre: 1,8% vs. 9,6% (ARR 7,8%, p<0,0001) • Lebensalter 65-74 Jahre: 2,2% vs. 9,7% (ARR 7,5%, p<0,0001) • Lebensalter >75 Jahre: (ARR 3,3%, n.s.)	In asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of whom were on aspirin, antihypertensive, and, in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard). Half this 5-year benefit involved disabling or fatal strokes. But, outside trials, inappropriate selection of patients or poor surgery could obviate such benefits. Kommentare: 10-Jahresdaten sollen in Kürze publiziert werden

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
			• Stenosegrad 60-<80% (Ultraschall) 2,1% vs. 9,5% (ARR 7,4%, p<0,0001) • Stenosegrad 80-99% (Ultraschall) 3,2% vs. 9,6% (ARR 6,4%, p<0,00001)	
Halliday A et al. 10-year stroke prevention after successful caroti-dendarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial Lancet 2010; 376: 1074-84			• Any stroke or perioperative death was 6,9% versus 10,9% at 5 yrs (gain 4,1%; 95%CI 2,0-6,2, p<0.0001) and 13,4% and 17,9% at 10 yrs (gain 4,6% (95%CI 1,2-7,9, p=0.009) • Excluding perioperative events and non-stroke mortality, stroke risks (immediate vs deferred CEA) were 4·1% vs. 10·0% at 5 years (gain 5·9%, 95% CI 4·0–7·8, p<0.0001) and 10·8% vs. 16·9% at 10 years (gain 6·1%, 2·7–9·4, p=0.0004) • ratio of stroke incidence rates 0·54, 95% CI 0·43–0·68, p<0·0001. • 62 versus 104 had a disabling or fatal stroke, and 37 versus 84 others had a non-disabling stroke. • Medication was similar in both groups; throughout the study, most were on antithrombotic and antihypertensive therapy. • Net benefits were significant both for those on lipid-lowering therapy and for those not, and both for men and for women up to 75 years of age at entry (although not for older patients). • Any stroke or perioperative death in patients on lipid-lowering therapy was 4,9% versus 7,0% at 5 years (gain 2,1% (95%CI 0,0-4,3, p=0.005) and 9,6% versus 14,5% at 10 years (gain 5,0%, 95%CI 1,1-8,8, p=0.01) • Any stroke or perioperative death in patients NOT on lipid-lowering therapy was 10,8% versus 18,7% at 5 years (gain 7,9% (95%CI 3,4-12,4, p=0.0005) and 21,2% versus 24,9% at 10 years (gain 3,6%, 95%CI -2,9-10,2, p=0.28, n.s.) • Any stroke or perioperative death in MALE patients <75 years was 5,8% versus 12,3% at 5 years (gain 6,5% (95%CI 3,6-9,4, p<0.0001) and 12,7% versus 18,1% at 10 years (gain 5,5%, 95%CI 0,9-10,0, p=0.02) • Any stroke or perioperative death in FEMALE patients <75 years was 5,9% versus 8,4% at 5 years (gain 2,5% (95%CI 1,2-6,1, p00.19, n.s.) and 10,2% versus 16,0% at 10 years (gain 5,8%, 95%CI 0,1-11,4, p=0.05)	Successful CEA for asymptomatic patients younger than 75 years of age reduces 10-year stroke risks. Half this reduction is in disabling or fatal strokes. Net benefit in future patients will depend on their risks from unoperated carotid lesions (which will be reduced by medication), on future surgical risks (which might differ from those in trials), and on whether life expectancy exceeds 10 years.

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
4. KOLOS 2015 [6]				
Kolos I et al. Modern medical treatment with or without carotid endarterectomy for severe asymptomatic carotid atherosclerosis. Journal of Vascular Surgery. 2015;62(4):914-22.	RCT, n=55, 70-79%ige Carotisstenose, 3 russische Zentren primary end point: nonfatal ipsilateral stroke or death from any cause during a follow-up period of 5.0 years. Secondary end points: any nonfatal stroke, carotid revascularization, or death from any cause during follow-up.	CEA n=31 n= 24 modern medical treatment (MMT)	• The trial was stopped after a median follow-up of 3.3 years (maximum, 5.0 years). • two primary events in the CEA group and nine events in the MMT group. The 3.3-year cumulative primary event rates were 6.5% in the CEA group and 37.5% in the MMT group (hazard ratio for the MMT group, 5.06; 95%CI 1.53-16.79; P= .008). • The 3.3-year cumulative secondary end point was 12.9% in the CEA group and 50.0% in the MMT group (hazard ratio for the MMT group, 4.23; 95%CI 1.55-11.53; p=.0048).	CEA as an initial management strategy could reduce the risk of death and major cerebrovascular events when added to MMT.
5. Nicht-berücksichtigte Studien				
Association Universitaire de Recherche en Chirurgie (AURC): 1983-1989, keine Ergebnisse publiziert, Methodik unklar (Lagneau P. Asymptomatic carotid stenosis: analysis of randomised studies [Sténoses carotidiennes asymptomatiques: analyse des études randomisées]. Journal des Maladies Vasculaires 1993;18:209-12)				
Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA): 50-90% ige Stenosen wurden randomisiert, >90%ige Stenosen operiert, bei bds. Stenosen war auch in der medik. Gruppe eine CEA möglich. Kein direkter Vergleich mit den anderen Studien möglich (The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. Stroke 1991;22:1229-35)				
Mayo Asymptomatic Carotid Endarterectomy Study (MACE): CEA ohne Aspirin vs. Aspirin. Studie wurde vorzeitig abgebrochen, aufgrund einer hohen Myokardinfarktrate im CEA-Arm. Kein Vergleich mit den anderen Studien möglich, in denen CEA+BMT vs. BMT allein verglichen wurde (Mayo Asymptomatic Carotid Endarterectomy Study Group. Effectiveness of carotid endarterectomy for asymptomatic carotid stenosis: design of a clinical trial. Mayo Clinic Proceedings 1989;64:897-904. Mayo Asymptomatic Carotid Endarterectomy Study Group. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Clinic Proceedings 1992;67:513-8.				
Walter Reed Army Medical Centre Study (WRAMC): CEA ohne Aspirin vs. Aspirin. Kein Vergleich mit den anderen Studien möglich, in denen CEA+BMT vs. BMT allein verglichen wurde: Clagett GP, Youkey JR, Brigham RA, Orecchia PM, Salander JM, Collins GJJr, et al. Asymptomatic cervical bruit and abnormal ocular pneumoplethysmography: a prospective study comparing two approaches to management. Surgery 1984;96:823-30				

ITT: Intention-to-treat-Analyse, ARR: Absolute Risikoreduktion, RRR: Relative Risikoreduktion, BMT: best medical treatment, ASS: Azetylsalizylsäure, AF: Amaurosis fugax, TIA: Transitorisch-ischämische Attacke, S: Schlaganfall, stroke, D: Death

1.2 Evidenztabelle 2: RCTs zur asymptomatischen Carotisstenose - CEA + BMT versus CAS + BMT

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
1. KENTUCKY 2004 [7, 8]				
Brooks WH et al. Carotid angioplasty and stenting vs carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. (Kentucky 2004**). Neurosurgery 2004; 54:318-24**	RCT, single-center, n=85 Mean age 67yrs. Asymptomat.>/=80%ige (Angiografie, NASCET Krit.) Stenosen Follow-up 4 yrs.	CEA + BMT (n=42) Versus CAS + BMT (n=43) No protection devices	• Stenosis decreased to an average of 5% after CAS. The patency of the reconstructed artery remained satisfactory (ultrasound). • No major complications (cerebral ischemia or death). • Procedural complications with CAS (n=5) were hypotension and/or bradycardia; those with CEA (n=3) were CNP or complications related to general anesthesia (n=4). • Both procedures well tolerated (pain and discomfort). • LOS similar in both groups (mean, 1.1 versus 1.2 d). The occurrence of complications prolonged LOS by 3 days (mean, 4.0 versus 4.5 d). Return to full activity was achieved within 1 wk by >85% of pat; all returned to usual lifestyle by 2 wks • hospital charges were slightly higher for CAS but costs were similar	CAS and CEA may be equally effective and safe in treating individuals with asymptomatic carotid stenosis.
Brooks WH et al.: Carotid angioplasty with stenting versus endarterectomy: 10-year randomized trial in a community hospital. JACC Cardiovasc Interv 2014; 7: 163-8.	10-Jahres Daren für intial asymptomatische und symptomatische Carotisstenosen		• Long-term follow-up was achieved in 173 patients (91%). • Eighty-seven (50.2%) died within this period, most commonly of nonvascular causes. • No difference in the risk of stroke ipsilateral to the treated artery was noted among treatment groups (p > 0.05). • Restenosis determined by sequential ultrasound was assessed only in the CAS group (3.3%) and remained asymptomatic. • The combined risk of fatal or nonfatal heart attack over the 10-year period was highest in individuals with symptomatic versus asymptomatic stenosis (27.5% vs. 11.0%; HR: 2.32, 95%CI: 1.298 - 4.146, p=0.005) and was higher in all patients treated with CEA (HR: 2.27, 95%CI: 1.35 - 3.816, p=0.002).	Long-term protection against ipsilateral stroke provided by CAS and CEA did not differ in this trial. The 10-year risk of fatal/nonfatal myocardial infarction was highest in all patients harboring symptomatic carotid stenosis at enrollment. The risk of fatal/nonfatal heart attack was significantly more prevalent in those symptomatic or asymptomatic patients randomized to CEA.
2. SAPPHIRE [9, 10], s. Evidenztabelle 5				
6. CREST 2010 [11], s Evidenztabelle 5				
7. KOUGIAS 2015 [12]				
Kougias P et al.: Comparison of domain-specific cognitive function after carotid endarterectomy and stenting. J Vasc Surg 2015; 62: 355-61.	RCT >80%ige asymptomatische Carotisstenose	CAS n=29 CEA n=31	• Baseline cognitive performance was similar between CAS and CEA. • Relative to baseline, verbal and visual memory and attention functions substantially improved in the CAS and CEA groups at 6 months (multiple cognitive tests achieved statistical significance).	Carotid revascularization improves memory and attention within the first 6 postoperative months. Compared with CEA, CAS produces improvements in cognitive processing speed, executive functioning, and motor function.

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
	RCT mit Endpunkten zur Kognition!		• Compared with CEA, cognitive processing speed (Stroop Color test: 9.0 vs 7.3, p=.04; and Stroop Word test: 9.0 vs 7.4, p=.05) was superior in the CAS group at 6 weeks. E • xecutive functioning (phonemic verbal fluency: 10.6 vs 8.4, p=043) and motor function (Grooved Pegboard of nondominant extremity: 45.7 vs 38.9, p=.022) were also superior in the CAS group at 6 months. • Tests of attention, memory, and visual-spatial skills were similar between CAS and CEA patients at 6 weeks and 6 months.	
8. ACT-1 2016 [13]				
Rosenfield K, Matsumura JS, Chaturvedi S, et al.: Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med 2016; 374: 1011-20.	RCT <80 Jahre, ohne erhöhtes OP-Risiko 70-99%ige asymptomatische Carotisstense (keine Symptome < 180 Tage), ohne >60%ige kontralaterale Stenose Follow-up 5 Jahre Primary end point: composite of death, stroke (ipsi- or contralateral, major or minor, or MI during the 30 days after the procedure or ipsilateral stroke during 1 year after the procedure. Secondary end points at 30 days after the procedure: composite of cranial-nerve and peripheral-nerve injury, vascular injury, non-cerebral bleeding, wound complications related to the neck incision or femoral puncture site, and other complications (e.g., related to the anesthesia).	CEA n=364 CAS n=1089	• Stenting was noninferior to endarterectomy with regard to the primary composite end point (event rate, 3.8% and 3.4%, respectively; p=0.01 for noninferiority). • The rate of stroke or death within 30 days was 2.9% in the stenting group and 1.7% in the endarterectomy group (p=0.33). • The rates of all strokes within 30 days was 2.8% after stenting and 1.4% after endarterectomy (p=0.23) • The rates of MI within 30 days was 0.5% after stenting and 0.9% after endarterectomy (p=0.41) • From 30 days to 5 years after the procedure the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group (P = 0.51) • The overall survival rates were 87.1% and 89.4%, respectively (p=0.21). • The cumulative 5-year rate of stroke-free survival was 93.1% in the stenting group and 94.7% in the endarterectomy group (p=0.44). • The event rate of the composite measure of complications through 30 days after the procedure was 2.8% in the stenting group and 4.7% in the endarterectomy group (p=0.13) • the rate of cranial-nerve injury was 0.1% in the stenting group and 1.1% in the endarterectomy group (p=0.02). • The rates of acute device success and procedural success in the stenting group were 98.4% and 95.6%, respectively. • The rate of freedom from clinically driven target-lesion revascularization at 6 months was 99.8% in the stenting group and 99.7% in the endarterectomy group (p=0.72); at 1 year, the rates	In this trial involving asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications, stenting was noninferior to endarterectomy with regard to the rate of the primary composite end point at 1 year. In analyses that included up to 5 years of follow-up, there were no significant differences between the study groups in the rates of non–procedure-related stroke, all stroke, and survival. The trial was funded by ABBOTT, immer Protektionssystem verwendet

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
			were 99.4% and 97.4%, respectively (p=0.005).	
9. MANNHEIM 2017 [14]				
Mannheim D, Falah B, Karmeli R. Endarterectomy or Stenting in Severe Asymptomatic Carotid Stenosis. Isr Med Assoc J. 2017;19(5):289-92.	RCT The primary objectives of the study were: 1) periprocedural complications – stroke (CVA), TIA MI, and death; 2) long-term results: mortality, prevention of ipsilateral stroke or TIA, and freedom from restenosis. Follow-up 26 Montae	CEA CAS 136 Patienten	• There was no difference in short and long term results between the two groups. • Thirty day morbidity included: 1 CVA in each group with no MI (1,5% each). • Long-term results included 4 deaths in each group; none from CVA. • One TIA was noted after CAS • 3 cases of restenosis were found in CEA and one in CAS.	CAS is a maturing procedure and has improved significantly over the past several years. Future developments of stents and protection devices will achieve better perioperative results. This along with our excellent long term results will promote the use of stenting for suitable patients. nur ABSTRACT verfügbar!
8. SPACE-2 2019 [15, 16]				
Eckstein HH, Reiff T, Ringleb P, Jansen O, Mansmann U, Hacke W, et al. SPACE-2: A Missed Opportunity to Compare Carotid Endarterectomy, Carotid Stenting, and Best Medical Treatment in Patients with Asymptomatic Carotid Stenoses. European Journal of Vascular and Endovascular Surgery. 2016;51(6):761-5. **Reiff T, Eckstein HH, Mansmann U, Jansen O, Fraedrich G, Mudra H, et al. Angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy compared to best medical treatment: One-year interim results of SPACE-2. Int J Stroke. 2019:1747493019833017.**	RCT, 3-armig, 36 Zentren Intention-to-treat und Per-protocol 70-99%ige Stenosen (ECST) bzw. >50%ige Stenosen (NACSET) Beginn in 2009, Änderung des Protokolls in 2013 (2 Studien CEA+BMT vs BMT allein und CAS+BMT vs BMT allein, Abbruch der Rekrutierung in 2014 Safety endpoint (only for interventional groups): rate of any stroke within 30 days from intervention and death from any cause within 30 days. Primary efficacy endpoint: cumulative rate of any stroke or death from any cause	CEA, n=203 CAS, n=197 BMT allein, n=113	• 30-day rates of any stroke or death: 2.5% in CEA and 2.5% in CAS. At the day of intervention, four strokes occurred after CEA (2.0%,all ipsilateral) and three strokes after CAS (1.5%, all ipsilateral). Further strokes occurred in the CEA group on day 2 (contralateral) and in the CAS group on days 11 and 22 (both ipsilateral) after intervention. No stroke occurred in the BMT group within the first 30 days; no patient died or had a MI. Stroke risk did not differ significantly between CEA, CAS and BMT (p=0.240). In the CEA and CAS groups, there were no pre-interventional endpoint events after randomization and before intervention. • The one-year rate of the major secondary endpoint did not significantly differ between groups (CEA 2.5%, CAS 3.0%, BMT 0.9%; p=0.530) as well as rates of any stroke (CEA 3.9%, CAS 4.1%, BMT 0.9%; p=0.256) and all-cause mortality (CEA 2.5%, CAS 1.0%, BMT 3.5%; p=0.304). • About half of all strokes occurred in the peri-interventional period. • Higher albeit statistically non-significant rates of restenosis occurred in the stenting group (CEA 2.0% vs. CAS 5.6%; p=0.068) without evidence of increased stroke rates.	The low sample size of this prematurely stopped trial of 513 patients implies that its power is not sufficient to show that CEA or CAS is superior to a modern medical therapy (BMT) in the primary prevention of ischemic stroke in patients with an asymptomatic carotid stenosis up to one year after treatment. Also, no evidence for differences in safety between CAS and CEA during the first year after treatment could be derived. Follow-up will be performed up to five years. Data may be used for pooled analysis with ongoing trials.

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
	within 30 days plus any ipsilateral ischemic stroke within five years Major secondary end-point: cumulative rates of any stroke or death from any cause within 30 days plus ipsi-lateral ischemic stroke within one year of follow-up			

ITT: Intention-to-treat-Analyse, ARR: Absolute Risikoreduktion, RRR: Relative Risikoreduktion, BMT: best medical treatment, ASS: Azetylsalizylsäure, AF: Amaurosis fugax, TIA: Transitorisch-ischämische Attacke, S: Schlaganfall, stroke, D: Death

1.3 Evidenztabelle 3: RCTs zur symptomatischen Carotisstenose - CEA + BMT versus CAS + BMT (versus BMT allein)

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
1. VA Trial 309[17]				
Carotid Endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Mayberg MR et al. **JAMA 1991; 266: 3289-3294**	16 VA-Hospitals, n=189 (5000 Patienten wurden gescreent), nur Männer 1988-1991 Symptomat. Carotisstenose (angiografischer Stenosegrad >50%), Symptome innerhalb 4 Monate (AF, TIA, leichter Schlaganfall) Stroke: jedes Defizit >24h	50:50 CEA + BMT (n=91) Versus BMT (n=98) Empfohlene Dosis ASS:325mg	At a mean follow-up of 11.9 months, there was a significant reduction in stroke or crescendo transient ischemic attacks in patients who received CEA (7.7%) compared with non-surgical patient (19.4%), or an ARR of 11.7% (P=.011). The benefit of surgery was more profound in patients with internal carotid artery stenosis greater than 70% (ARR, 17.7%; P=0.004). The benefit of surgery was apparent within 2 months after randomization, and only one stroke was noted in the surgical group beyond the 30-day perioperative period.	For a selected cohort of men with symptoms of cerebral or retinal ischemia in the distribution of a high-grade internal carotid artery stenosis, CEA can effectively reduce the risk of subsequent ipsilateral cerebral ischemia. The risk of cerebral ischemia in this subgroup of patients is considerably higher than previously estimated.
2. European Carotid Surgery Trialists' Collaborative Group (ECST) [18-20]				
MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe 70-99%) or with mild (0-29%) carotid stenosis **Lancet 1991; 337: 1235-1243** **Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST)** **Lancet 1998; 351: 1379–87** **Reanalysis of the Final Results of the European Carotid Surgery Trial. Rothwell PM et al.** **Stroke. 2003;34:514-523**	RCT, multizentrisch, 100 Zenten, 14 Länder, 1981-1994, n=3018 Patienten Symptomat. Carotisstenose innerhalb 6 Monate (AF, TIA, leichter Schlaganfall) 72% Männer, mean age 62,5 Jahr Mean follow-up 73 Monate Unsicherheitsprinzip Angiografischer Stenosegrad: 0-29%: 44%/30-49%: 16%/ 50-69%: 22%/70-99%: 14% / Near occlusion: 4% Klinische Endpunkte: Stroke: jedes zerebrales/retinales Ereignis >24h major stroke: jeder Schlaganfall > 7 Tage Disabling stroke: Rankin 3-5 nach 6 Monaten	60:40 CEA + BMT (n=1807) Versus BMT (n=1211) ASS ohne spezifische Dosisempfehlung	• Risiko der CEA: 7,5% any stroke or death <30 Tage • The risk of major stroke or death complicating surgery (7·0%) did not vary substantially with severity of stenosis. • overall outcome (major stroke or death) occurred in 37·0% after CEA and (36·5%) BMT patients. • the risk of major ischaemic stroke ipsilateral to the unoperated symptomatic carotid artery increased with severity of stenosis, particularly above about 70–80% of the original luminal diameter, but only for 2–3 years after randomisation. • Surgery reduced the 5-year risk of any stroke or surgical death by 5.7% (95% CI, 0 to 11.6) in patients with 50% to 69% stenosis (n=646, P=0.05) and by 21.2% (95% CI, 12.9 to 29.4) in patients with 70% to 99% stenosis without "near occlusion" (n=429, P<0.0001). These benefits were maintained at the 10-year follow-up. • surgery was of no benefit in patients (n=125) with near occlusion. The effect of surgery in this group was highly significantly different from that in patients with 70% to 99% stenosis without near occlusion (P=0.002).	CEA is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the symptomatic stenosis is greater than about 80%. Age and sex should also be taken into account in decisions on whether to operate (1998) Results of the ECST and NASCET were consistent when analyzed in the same way. In ECST, surgery was highly beneficial for 70% to 99% stenosis and moderately beneficial for 50% to 69% stenosis. However, contrary to clinical recommendations and current practice, surgery was of little benefit in patients with carotid near occlusion (2003).

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
			• Surgery was harmful in patients with 30% stenosis (n=1321,P=0.007) and of no benefit in patients with 30% to 49% stenosis (n=478, P=0.6).	
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) [21, 22]				
Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. **NEJM 1991; 325:1235-1243** **The final results of the NASCET trial.** **NEJM 1998; 339: 1415–25.**	106 Zentren Symptomat. Carotisstenose (angiografischer Stenosegrad >30%), Symptome innerhalb 4 Monate (AF, TIA, leichter Schlaganfall, geändert 1991 auf <6 Monate) 1991 Abbruch der Randomisierung von Patienten mit >70%igen Stenosen (n=659) Bis 1991 maximal 80 Jahre, danach keine Altersgrenze ITT-Analyse	50:50 70-99%ige Stenose CEA + BMT (n=328) Versus BMT (n=331) <70%ige Stenose CEA + BMT (n=1108) Versus BMT (n=1118) Empfohlene Dosis ASS:1300mg	NEJM 1991 • Life-table estimates of the cumulative risk of any ipsilateral stroke at 2 yrs were 26% in the 331 medical patients and 9% in the 328 surgical patients (ARR 17 +/- 3.5% (P< 0.001). For a major or fatal ipsilateral stroke, the corresponding estimates were 13.1% and 2.5% (ARR 10.6 +/- 2.6% (P<0.001). CEA was still found to be beneficial when all strokes and deaths were included in the analysis (P <0.001) NEJM 1998 • Among patients with stenosis of 50-69%, the five-year rate of any ipsilateral stroke was 15.7% among patients treated surgically (n=430) and 22.2% among those treated medically (n=428, p=0.045) • to prevent one ipsilateral stroke during the five-year period, 15 patients would have to be treated with CEA. • Among patients with less than 50% stenosis, the failure rate was not significantly lower in the CEA group (n=678, 14.9%) than in the medically treated group (n=690, 18.7%, p=0.16). • Among the patients with severe stenosis who underwent CEA the 30-day rate of death or disabling ipsilateral stroke persisting at 90 days was 2.1%; this rate increased to only 6.7% at 8 yrs • Benefit was greatest among men, patients with recent stroke as the qualifying event, and patients with hemispheric symptoms.	NEJM 1991 CEA is highly beneficial to patients with recent hemispheric and retinal transient ischemic attacks or nondisabling strokes and ipsilateral high-grade stenosis (70 to 99 percent) of the internal carotid artery NEJM 1998 CEA in patients with symptomatic moderate carotid stenosis of 50 to 69% yielded only a moderate reduction in the risk of stroke. Decisions about treatment for patients in this category must take into account recognized risk factors, and exceptional surgical skill is obligatory if CEA is to be performed. Patients with stenosis of <50% did not benefit from surgery. Patients with severe stenosis >70% had a durable benefit from CEA at eight years of follow-up.
4. Pooled data from VA Trial 309, ECST and NASCET 2003/2004 [23, 24]				
Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis.	Analyse aller Daten aus ECST (n=3018), NASCET (n=2885) und VA 309 (n=189), zusammen n=6092 (35000 Patientenjahre)	CEA + BMT (n=3248) Versus BMT (n=2758)	Schlaganfall/Tod <30 Tagen nach CEA: • Near occlusion (n=148): 5,4% • 70-99%ige Stenose (n=581): 6,2% • 50-69%ige Stenose (n=812): 8,4%	Re-analysis of the trials with the same measurements and definitions yielded highly consistent results. Surgery is of some benefit for patients with 50–69% symptomatic stenosis, and highly beneficial for those with 70% symptomatic stenosis or greater but without near-occlusion. Benefit in patients with carotid near-occlusion is marginal in the short-term and uncertain in the long-term.

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
Rothwell et al. Lancet 2003; 361: 107–16	Alle Angiografien reanalysiert (NASCET Kriterien) Near occlusion: severe stenosis with evidence of reduced flow in the distal ICA (delayed arrival of contrast into the distal ICA, or evidence of collateral flow of contrast towards the symptomatic cerebral hemisphere from other arterial territories, or both) and evidence of narrowing of the poststenotic ICA (lumen diameter similar to, or less than, the ipsilateral external carotid artery and less than the contralateral ICA) Stroke: jeder Schlaganfall >24h Disabling stroke: Rankin 3-5 nach 6 Monaten Stratifizierung der Stenosegrade (<30%, 30-49%, 50-69%, >/=70%, near-occlusion) ITT-Analyse	3334 wurden zur CEA randomisiert, davon 3248 tatsächlich operiert	• <50%ige Stenose (n=1707): 6,7% • Alle Stenosegrade (n=3248): 7,1% Tod <30 Tagen nach CEA: • Near occlusion (n=148): 0,7% • 70-99%ige Stenose (n=581):0,9% • 50-69%ige Stenose (n=812): 1,4% • <50%ige Stenose (n=1707): 1,0% • Alle Stenosegrade (n=3248): 1,1% 5-Jahres-ARR für den EP „jeder Schlaganfall und jeder perioperative Tod: CEA + BMT vs. BMT: • Near occlusion (n=262): -0,1%, p=0.6 • 70-99%ige Stenose (n=954): 15,3%, p<0,0001 • 50-69%ige Stenose (n=1502): 7,8%, p=0.002 • 30-49%ige Stenose (n=1429): 2,6%, p=0.7 • <30%ige Stenose (n=1746): -2,6%, p=0.03 5-Jahres-ARR für den EP „Ipsilateraler ischämischer Schlaganfall und jeder perioperative stroke or death: • Near occlusion (n=262): 1,7%, p=0.9 • 70-99%ige Stenose (n=954): 16%, p<0,0001 • 50-69%ige Stenose (n=1502): 4,6%, p=0.04 • 30-49%ige Stenose (n=1429): 3,2%, p=0.6 • <30%ige Stenose (n=1746): -2,2%, p=0.05 5-Jahres-ARR für den EP „disabling ipsilat. ischämischer Schlaganfall und jeder perioperative stroke or death: • Near occlusion (n=262): -2,3%, p=0.6 • 70-99%ige Stenose (n=954): 7%, p=0,001 • 50-69%ige Stenose (n=1502): 2,3%, p=0.19 • 30-49%ige Stenose (n=1429): 0,5%, p=0.6 • <30%ige Stenose (n=1746): -1,7%, p=0.08	Kommentar: Der Benefit der CEA (ipsilat. Schlaganfall und periop. Strokes/Death) wird bei 70-99%igen Stenosen schon im 1.Jahr erzielt, die ARR von ca. 16% ist bereits nach 3 Jahren erreicht und besteht auch noch nach 8 Jahren Bei 50-69%igen Stenosen nimmt die ARR über die Jahre zu (nach 3 Jahren ca. 2%, nach 5 Jahren ca. 5% und nach 8 Jahren 5-9%) Nur n=262 Patienten in der „near-occlusion“ – Subgruppe, nach 2 Jahren ARR zugunsten der CEA von ca. 5%, im weiteren Verlauf kein Vorteil der CEA. Alle Daten wurden nach ITT analysiert, keine per-Protokoll-Analyse m konservativen Arm wurden n=458 Patienten später (1-2 Jahre) operiert (ECST 10%, NASCET 23%), insbesondere nach Publikation der ersten positiven Ergebnisse für >70%ige Stenosen 1991
Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Rothwell PM et al. **Lancet 2004; 363: 915–24**	Subgruppenanalyse aus ECST und NASCET, n=5893 Definierte Subgruppen: Geschlecht, Lebensalter, Intervall Indikatorereignis-CEA, initiale Symptome (AF, TIA, Schlaganfall), Diabetes mellitus, irregulärer/ ulzerierter	CEA + BMT (n=3236) Versus BMT (n=2657)	5-Jahres ARR (EP: periprozeduraler Schlaganfall/Tod + ipsilateraler ischämischer Schlaganfall für 50-69%ige und 70-99%ige Stenosen (CEA n=1474, BMT n= 1244) • Männer 8%/15% - Frauen -2,7%/9,9% • <65 Jahre 1,3%/9,8% - 65-74 Jahre5,4%/13,5% - >/=75 Jahre 10,7%/37,2% • Intervall < 2 Wochen 14,8%/23% - Intervall 2-4 Wochen 3,3%/15,9% - Intervall 4-12 Wochen 4%/7,9% - Intervall > 12 Wochen -2,9%/7,4%	Benefit from CEA depends not only on the degree of carotid stenosis, but also on several other clinical characteristics such as delay to surgery after the presenting event. Ideally, the procedure should be done within 2 weeks of the patient’s last symptoms. Kommentar:

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
	Plaque, kontralaterlaler Verschluss Post hoc Subgruppen: Dauer der initialen TIA (< vs. >/= 1 Stunde, vorherige TIA oder Schlaganfall, Myokardinfarkt, Angina pectoris, behandelter Hypertonus, behandelte Hyperlipidämie, Nikotin		• Primäres Symptom AF 1,5%/5,5% - TIA 3,8%/15,4% - Schlaganfall 7,5%/17,7% • Diabetes ja 6,2%/16,7% - Diabetes nein 4,3%/12,9% • Glatter Plaque 3,3%/7,8% - Unregelmäßig 5,7%/17,1% • Kontralateraler Verschluss ja -16%/23,6% - nein 5,7%/12,7% Posthoc-Subgruppen: • TIA <h -0,4%/14,4% - TIA >/= 1 h 15,6%/19,9% • Vorherige TIA/Schlaganfall 1,9%/21% - nein 6,1%9,5% • Myokardinfarkt ja 8,3%/16,2% - nein 3,6%/13% • Angina pectoris 6,9%/14,8% - nein4%/13,1% • Behandelte Hypertonie 6,5%/16,6% - nein3,4%/10,1% • Behandelter Hyperlipidämie 4,9%/6,6% - nein 4,5%/15,1% Nikotinabusus 1,4%/12,9% - nein 7,5%/14,1%	Bei Frauen, die erst > 2 Wochen operiert wurden ist kein signifikanter Benefit mehr nachweisbar, bei Männern ist dieser Benefit auch > 12 Wochen nachweisbar
5. Overview of the Principal Results and Secondary Analyses from ECST and NASCET 2003 [107]				
Overview of the Principal Results and Secondary Analyses from the European and North American Randomised Trials of Endarterectomy for Symptomatic Carotid Stenosis **Naylor RA et al. EJVES 2003; 26: 115-129**	Review aller primären und sekundären Ergebnisse aus ECST (12 Publikationen) und NASCET (32 Publikationen)	CEA + BMT Versus BMT	• Late ipsilateral stroke (ARR 5yrs) incl. periop s/d: ECST 70-99%: ARR 8,5% (NNT 12), RRR 45%, ECST <70% kein Benefit • NASCET 30-49%: ARR 3,8%, RRR 20%, NNT 26 • NASCET 50-69%: ARR 6,5%, RRR 29%, NNT 15 • NASCET 70-99%: ARR 19,4%, RRR 69%, NNT 5 • Risiko der CEA unabhängig von Stenosegrad und Alter. Erhöhtes OP-Risiko in ECST (multivariate Analyse): Frauen (10,4% vs. 5,8%, p=0.0001), PAVK (12,0% vs. 6,1%, p<0.0001), systol. Blutdruck (>120mmHg 3,4%, 121-159 6,5%, 160-180 7,7%, >180 13%, p=0,04), Indikatorereignis (AF 3,2%, TIA 9,1%, ipsilat. Schlaganfall 6,3%, p<0.006). Erhöhtes OP-Risiko in NASCET (multivariate Analyse): hemisphärische Symptome vs. retinal (6,3% vs. 2,7%), OP linke Seite vs. rechte Seite (6,7% vs. 3%), Kontralat.Verschluss (9,4% vs. 4,4%), ipsilateraler CT /MR-Infarkt (6,3% vs. 3,5%), irregulärer vs. glatter Plaque(5,5% vs. 3,7%) • Periop. Sonstige Komplikationen in NASCET: 10% nach CEA, 3,4% im BMT-Arm: kardiovaskulär 8,1% (davon 0,3% mit MI) vs. 1,2%, respirator. 0,8% vs. 0,5% (keine LE). In ECST 0,2% MI und 0,1% LE nach CEA	• The simple assumption that ALL patients with a symptomatic stenosis >70% will benefit from CEA is untenable. Approximately 75% will not have a stroke if treated medically. • Development of local protocols for patient selection (or exclusion) should involve surgeons and physicians and should take local operative risk into account. • There is anecdotal evidence that the investigation and referral of patients for CEA is taking too long. The ECST and NASCET have identified subgroups who should have expedited investigation and surgery (male sex, 90±99% stenosis, hemispheric symptoms, recurrent events for 46 months, contralateral occlusion, multiple risk factors). • Surgeons must quote their own results and be aware that a high operative risk reduces long-term benefit. Accordingly, in those centres with higher operative death/stroke rate, certain ``lower risk'' patients should probably be considered for best medical therapy alone. • The ECST and NASCET have shown that the ubiquitous string sign is not associated with a high risk of stroke, and emergency endarterectomy is unnecessary.

Quelle	Studiendesign	Interventionen	Endpunkt (EP)/Ergebnisse	Schlussfolgerungen/Kommentare
			• Wundkomplikationen und Nervenläsionen: in NASCET 9,3% Wundkomplikationen (Hämatom, Infektion etc.), 0,3% “severe”. HN Läsionen in 8,6%, keine schwere HN-Verletzung. In ECST 6,4% HN-Läsionen (in 0,5% permanent), 3,1% Hämatom mit Re-OP, 0,3% Infekt. • Lebensalter (NASCET): 2-Jahres ARR bei >70%ige Stenose >75 /65-74/<65 Jahre 28,9%/15,1%/9,7%. Bei 50-69%ige Stenose 17,3%/5,3%/-1,2% • „string sign“ (near occlusion, NASCET): 1-Jahres stroke risk: 90-94%ige Stenose 35,1%, 95-99% (no string) 18,3%, 95-99% (string sign) 11%.5-Jahres Risiko in ECST 90-99%ige Stenose 32%, near occlusion 8% • Zeitpunkt CEA (NASCET): OP-Risiko <30/>30 Tg. 4,8/ 5,2% • Multimorbidität (NASCET): 2-Jahres stroke risk 17% vs. 39% (BMT) und 9% (CEA +BMT) • Recurrent symptoms (NASCET): 2-Jahres stroke risk 18,6% (BMT und 7.8% CEA) bei einmaliger Symptomatik und 41,2% (vs. 10,8% nach CEA) bei recurrent symptoms • Kontralateraler Carotisverschluss (NASCET): ARR 47,3% nach 2 Jahren(trotz OP Risiko von 14,3%) • Kortikaler (nicht-lakunärer) vs. lakunärer Schlaganfall (NASCET): ARR nach 3 Jahren 15,2% vs.8-9% • Tandemläsionen (ja/nein, NASCET): 3-Jahres ARR bei 70-84%Iger Stenose 22,7%/13,4%, bei 85-99%iger Stenose 37,1%/15,3% • Intracranielle Kollateralen (ja/nein, NASCET): 2-Jahres ARR. 70-84%ige Stenose 18,3%/4,2%, 85-99%uge Stenose 31,4%/13,7%. OP-Risiko erhöht bei fehlenden Kollateralen • Irregulärer vs. glatter Plaque: in ECST 2-Jahres stroke risk (BMT) 26-31% vs. 15-20% bei 80-99%igen Stenosen. In NASCET 2-Jahres ARR bei 75%iger Stenose 19,4% vs. 10,6%, bei 85%iger Stenose 32,4% vs. 10,7%, bei 95%iger Stenose 54% vs. 10,6%	

1.4 Evidenztabelle 4: RCTs zur symptomatischen Carotisstenose - CEA + BMT versus CAS + BMT

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
1. Leicester 1998 [25]				
Naylor AR et al. (Leicester**) Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. JVS 1998;28:326-34**	RCT, single-center, n=23, n=17 treated before suspension of the trial Sympt sten >/=70% No protection device	CEA + BMT (n=10) Versus CAS + BMT (n=7)	**Outcomes at 30 days CEA vs. CAS** • Death, diasabling or non-disabling strokes at 30 days 0% vs. 5/7 pat (p=0.0034), • 3 strokes were disabling at 30 days.	Data Monitoring Committee invoked the stopping rule and the trial was suspended. The investigators and the Ethics Committee subsequently concluded that the trial could not be restarted--even in an amended format, primarily because of problems with informed consent.
2. CAVATAS 2001 [26-28]				
Endovascular versus surgical treatment in patiens with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): **a randomised trial. Lancet 2001; 357: 1729–37**	RCT, multi-center, n=22 centers (Europe, Canada, Australia) 1992-1997 69% male, mean age 67yrs Angiography in >80%, mean grade of sten 86% Sympt sten (96%) ITT analysis	CEA (n=253) versus Endovascular (n=252) 26% of endovasc with stents	Primärer Endpunkt: • disabling stroke/death CEA vs. CAS: 6.4% vs.5.9% (n.s.) Sekundärer Endpunkte CEA vs. CAS: • any stroke > 7 days/death 10,0% vs. 9,9% (n.s.) • Cranial neuropathy 8.7% vs. 0%, p<0.0001 • MI: 1.2% vs. 0% (n.s.) • Major groin or neck hematoma 6.7% vs. 1.2%, p<0.0015). • recurrent 70–99% ipsilat. Car. sten./occl. 5% vs. 18%, p<0.001). • Severe stenosis/occlusion within one year after CAS in 22% vs.17% in endovascular treatment without Stenting (n.s.) • Disabling stroke or death after 3 years 14.2% vs. 14.3% (adjusted HR 1.04, 95%CI 0.63–1.70, p=0.9).	2001: Endovascular treatment had similar major risks and effectiveness at prevention of stroke during 3 years compared with carotid surgery, but with wide CIs. Endovascular treatment had the advantage of avoiding minor complications. Kommentar: sehr hohe Komplikationsraten, keine Centereffekte mitgeteilt, 3 (Endo) bzw. 1 Patient (CEA) verstarb vor der Behandlung, jeweils ein Patient erlitt einen Schlaganfall vor Behandlung (Diese Ereignisse wurden nicht im 30-Tages-Ergebnis gezählt, aber in der Überlebensanalyse), keine PP Analyse
Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): **long-term follow-up of a randomised trial. Ederle et al. Lancet Neurol 2009; 8:898-907**	s.o. Median length of follow up in both groups was 5 years (IQR 2–6)	s.o.	Endovascular vs. CEA after 8 years (HR, 95%CI) • Disabling stroke/death 50.2% vs. 45.2%, HR 1.02 (0.79-1.32) • Any stroke or periop. death 29.7% vs. 23.5%, HR 1.35 (0.94-1.93) • non-periop. stroke/TIA 36.9% vs. 30.2%, HR 1.37 (0.95-1.97) • ipsilat. non-periop. stroke 11.3% vs 8.6% (HR 1.22, 0.59–2.54) • ipsilat. non-periop. stroke/TIA 19.3% vs 17.2% (1.29, 0.78–2.14) • any non-perioperative stroke 21.1% vs 15.4% (1.66, 0.99 –2.80)	More patients had stroke during follow-up in the endovascular group than in the surgical group, but the rate of ipsilateral non-perioperative stroke was low in both groups and none of the differences in the stroke outcome measures was significant. However, the study was underpowered and the confidence intervals were wide. More long-term data are needed from the ongoing stenting versus endarterectomy trials.
Bonati et al. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised	s.a.	s.a.	• Severe carotid restenosis (≥70%) or occlusion more often in the endovascular arm than in the CEA arm (adjusted HR 3.17, 95% CI 1.89–5.32; p<0·0001). The estimated 5-year incidence of restenosis was 30.7% in the endovascular arm and 10.5% after CEA • endovascular arm with a stent (n=50) had a significantly lower risk of restenosis of >/=70% compared with those treated with balloon angioplasty alone (n=145; HR 0.43, 0.19–0.97; p=0.04). • Current smoking/history of smoking was a predictor of a >/=70% restenosis (2.32, 1.19–4.54; p=0.01)	Restenosis is about three times more common after endovascular treatment than after endarterectomy and is associated with recurrent ipsilateral cerebrovascular symptoms; however, the risk of recurrent ipsilateral stroke is low. Further data are required from on-going trials of stenting versus endarterectomy to ascertain whether long-term ultrasound follow-up is necessary after carotid revascularisation.

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
trial. Lancet Neurol 2009; 8: 908-917			• the early finding of moderate stenosis (50–69%) up to 60 days after treatment was associated with the risk of progression to restenosis of 70% or more (3.76, 1.88–7.52; p=0·0002). • The composite endpoint of ipsilateral non-periop stroke or TIA occurred more often in patients in whom restenosis of >/=70% was diagnosed in the first year after treatment compared with patients without >/=70% restenosis (5-year incidence 23% vs 11%; HR 2.18, 1.04–4.54; p=0.04), but the increase in ipsilateral stroke alone was not significant (10% vs 5%; 1.67, 0.54–5.11).	
3. WALLSTENT-Studie 2001[29]				
Alberts MJ et al. Results of a multicenter prospective randomized trial of carotid artery stenting vs. Carotid endarterectomy. Stroke. 2001;32:325 (Abstract).	RCT, multi-center, 219 pat with a 60-99% sympt sten (NASCET crit.) Mean age 66 yrs, 66% male Sponsored by Boston Sc.	CEA + BMT (n=112) Versus CAS + BMT (n=107)	Outcome CAS versus CEA • 30 day peri-procedure complication rate (any stroke or death) 12.1% vs. 4.5% (p = 0.049). • 2 day peri-procedure complication rate: 7.5% vs. 1.8% (p=0.055) • any major stroke: 3.7% vs. 0.9% for CEA (p = 0.204) ipsilateral stroke, procedure-related death, or vascular death within 1 yr 12,1% vs. 3,6% (p=0.022)	This study did not find that CAS was equivalent to CEA in patients with symptomatic carotid artery stenosis. Based on these data and a futility analysis, the study was terminated before the planned maximum of 700 patients were enrolled. comment: Study was stopped due to high complication rates after CAS No full-paper available
4. KENTUCKY 2001 [8, 30]				
Brooks WH et al. Carotid Angioplasty and Stenting vs. Carotid Endarterectomy: Randomized Trial in a Community Hospital. (Kentucky 2001**)** **J Am Coll Cardiol 2001; 38:1589–95**	RCT, single-center, n=104 Mean age 67yrs. Symptomat.>/=70%ige (Angiografie, NASCET Krit.) Stenosen Symptoms <3 months Follow-up 2 yrs.	CEA + BMT (n=51) Versus CAS + BMT (n=53) Wallstent (provided by Boston Sc.)	• Stenosis decreased to an average of 5% after CAS. • patency remained satisfactory regardless of the technique as determined by sequential ultrasound. • One death occurred in the CEA group (1/51); one transient ischemic attack occurred in the CAS group (1/53); no individual sustained a stroke. • The perception of procedurally related pain/discomfort was similar. • Hospital stay was similar, although the CAS group tended to be discharged earlier (mean 1.8 days vs. 2.7 days). • Complications associated with CAS prolonged hospitalization when compared with those sustaining a CEA-related complication (mean 5.6 days vs. 3.8 days). • Return to full activity was achieved within one week by 80% of the CAS group and 67% of the patients receiving CEA. • Hospital charges were slightly higher for CAS.	CAS is equivalent to CEA in reducing carotid stenosis without increased risk for major complications of death/stroke. Because of shortened hospitalization and convalescence, CAS challenges CEA as the preferred treatment of symptomatic carotid stenosis if a reduction in costs can be achieved.
Brooks WH et al.: Carotid angioplasty with stenting versus endarterectomy: 10-year randomized trial in a community hospital.	10-Jahres Daren für intial asymptomatische und symptomatische Carotisstenosen		• Long-term follow-up was achieved in 173 patients (91%). • Eighty-seven (50.2%) died within this period, most commonly of nonvascular causes. • No difference in the risk of stroke ipsilateral to the treated artery	Long-term protection against ipsilateral stroke provided by CAS and CEA did not differ in this trial. The 10-year risk of fatal/nonfatal myocardial infarction was highest in all patients harboring symptomatic carotid stenosis at enrollment. The

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
JACC Cardiovasc Interv 2014; 7: 163-8.			was noted among treatment groups (p > 0.05). • Restenosis determined by sequential ultrasound was assessed only in the CAS group (3.3%) and remained asymptomatic. • The combined risk of fatal or nonfatal heart attack over the 10-year period was highest in individuals with symptomatic versus asymptomatic stenosis (27.5% vs. 11.0%; HR: 2.32, 95%CI: 1.298 - 4.146, p=0.005) and was higher in all patients treated with CEA (HR: 2.27, 95%CI: 1.35 - 3.816, p=0.002).	risk of fatal/nonfatal heart attack was significantly more prevalent in those symptomatic or asymptomatic patients randomized to CEA.
SPACE 1 [31-34]				
Ringleb PA et al. 30 day results from the SPACE **trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: A randomized non-inferiority trial.** **Lancet. 2006;368:1239–1247** Second interim analysis	RCT, 2001-2006 35 centers, GER, CH, AUS, N=1200, 72% male sympt. >/50% Sten (NASCET crit, DSA, US, MRA symptoms <180 d: AF, TIA, S <3 mod. RS Non-inferiority design ITT and PP analysis	CEA + BMT (n=584) Versus CAS + BMT (n=599)	Primary EP CAS vs. CEA • proc ipsilat stroke/death: 6.84% vs. 6.34% (ITT), AD. 0,51% (90%CI -1.89-2.91, OR 1.09 (95%CI 0.69-1.72), p=0.09 • proc ipsilat stroke/death: 6.95% vs. 5.64% (PP), AD 1,32% (90%CI -1.10-3.76) secondary EP and subgroups s. below	SPACE failed to prove non-inferiority of CAS compared with CEA for the periprocedural complication rate. The results of this trial do not justify the widespread use in the short-term of CAS for treatment of carotid-artery stenoses. Results at 6–24 months are awaited.
Stingele R et al. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE **study.** **Lancet Neurol 2008; 7:216-22.**	N=1214 Patienten (1196 ausgewertet) Subgruppenanalyse für den Einfluss von 6 Variablen auf den primärer EP (periproz. ipsilateraler S/T)	CEA + BMT (n=589) Versus CAS + BMT (n=607)	Risk of ipsilateral stroke or death CAS vs. CEA: • Lebensalter </= 62 Jahre 2,2% vs. 8,1%, 62-68 Jahre 2,8% vs. 4,3%, 68-75 Jahre 10,8% vs. 3,9%, >75 Jahre 11% vs. 5,6% • Männer 6,3% vs. 5,5%; Frauen 8,3% vs. 5,6% • Qualifizierendes Ereignis AF: 3,3% vs. 3,4%, TIA 8,3% vs. 5,2%, S 6,6% vs. 7,5%, andere 6,7% vs.=%, multipel 9,8% vs. 1,8% • Kontralaterale Stenose/Verschluss 2,6% vs. 12,8% • Rechte Seite 7,7% vs. 4,9%, linke Seite 6% vs. 6,1% • Stenosegrad <60% 8,8% vs. 2,1%, 60-69% 3,3% vs. 4%, 70-70% 12,3% vs. 7%, 80-89% 7,2% vs. 6,6%, >/=90% 5,6% vs. 7,7% • The risk of ipsilateral stroke or death increased significantly with age in the CAS group (p=0.001) but not in the CEA group (p=0.534). Classification and regression tree analysis showed that the age that gave the greatest separation between high-risk and low-risk populations who had CAS was 68 years: the rate of primary outcome events was 2·7% in patients who were 68 years old or younger and 10·8% in older patients. • When age was used as a continuous variable, the estimated relative risk increase (OR) was 7,2% (95% CI 2,8–11,7%) per year of age in the CAS group (p=0.001) • Other variables did not differ between the CEA and CAS groups.	Of the predefined covariates, only age was significantly associated with the risk of stroke and death. The lower risk after CAS versus CEA in patients up to 68 years of age was not detectable in older patients. This finding should be interpreted with caution because of the drawbacks of post-hoc analyses. Kommentar: keine PP Analyse keine Angaben zum EP “Jeder prozedurale S/T“

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
Fiehler J et al. Differences in complication rates among the centres in the SPACE **study. Neuroradiology (2008) 50:1049–1053**	centers were categorized in class I (>/=25 pat enrolled), class II (10-24 apt enrolled (class III (</=10 pat enrolled) random effects logistic regression analysis	s.a.	• CAS: increase in ipsilat stroke/death (pOE) with decreasing no of pat enrolled (−0.0190±0.0085, p=0.025,deviance 35.7 with 32 df) • CEA: no such effect (−0.010±0.008,p=0.24,dev 39.8 with 32df • significant interaction between treatment, no. of pat per centre and SOE (any stroke/death, p=0.023). The OR for sOE in the enrolment classes (CAS vs. CEA) were 0.98 (95% CI 0.50–1.94, p=0.95) for class I, 1.13 (95% CI 0.47–2.77, p=0.77) for class II and 11.56 (95% CI 1.40–253.45, p=0.01) for class III centres.	Despite rigorous standardisation and quality requirements for operator qualification, there seemed to be a decrease in complication rate with increasing patient enrolment numbers in the CAS arm while this signal could not be detected in the CEA arm of SPACE.
Eckstein HH, Ringleb PA et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE**) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. Lancet Neurol 2008; 7: 893–902.** **Final analysis**	See above 89% of all pat with a 2-year-follow-up Definition der Rezidivstenose: ITT and PP analysis	ITT-Analyse: CEA + BMT (n=589) Versus CAS + BMT (=607) PP-Analyse: CEA + BMT (n=563) Versus CAS + BMT (=573)	<u>30-Tages-Outcome measures CAS vs. CEA (ITT und PP), (95%CI)</u> • proc. Ipsilat.stroke/death ITT: 6.9% vs. 6.5% (RR 1.07 (0.70-1.63), AD 0.47% (-2.41-3.35, p=0.09); PP 6.8% vs. 5.5% (RR 1.24, 0.78-1.95), AD 1.3% (-1,53%-4,17%). • Any proc. stroke/death ITT: 7.4% vs. 6.6% (RR 1.12, 0.74-1.69), PP 7.3% vs. 5.7% (RR 1.29, 0.83-2.01) • Any disabling proc. stroke/death ITT: 5.1% vs. 3.9% (RR 1.31, 0.78-2.21), PP 4.9% vs.3.2% (RR 1.53, 0.82-2.93) <u>2-yrs -outcomes CAS vs. CEA (ITT und PP) (HR, 95%CI)</u> • any proc s/d + ipsilat ischaemic strokes up to 2 yrs ITT 9.5% vs 8.8%; HR 1.10 (0.75 – 1.61); PP 9.4% vs 7.8%; HR 1.23 (0.82-1.83) • any disabl proc s/d + ipsilat disable ischemic strokes up to 2 yrs ITT 5.7% vs 4.7%; HR 1.24 (0.7-2.05); PP 5.5% vs 4.0%; HR 1,41 (0.82-2.41) • ipsilat stroke between day 31 and two yrs ITT 2.2% vs. 1.9%, RR1.17 (0.51-2.70); PP 2.3% vs. 2%, RR 1.18(0.51-2.73) • recurrent stenosis of 70% or more: ITT 10.7% vs 4.6% (p=0.0009); PP 11.1% vs 4.6% (p=0.0007), • two incidences of rec sten after CAS led to neurolog symptoms. <u>Subgroups after two yrs CAS vs. CEA (ITT and PP)</u>, (HR 95%CI): • age <68 yrs ITT: 5% vs. 9%, HR 0.54 (0.28-1.03); PP 4.8% vs. 8%, HR 0,57 (0,29-1,14) • age>/= 68 Jahre ITT: 13.7% vs. 8.6%, HR 1.80 (0.96-3.40); PP 13.8% vs. 7.6%, HR 2.00, (0.90-4.44) • Multiple Indikator-Events ITT 19.2% vs. 1.8%, HR 10.7 (1.24-91.5) PP 21% vs. 1.9%, HR 11.8 (1.37-102) • Contralat sten 70-99%/occl: CAS lower compl rates (n.s.) • No significant differences for male vs. female, right or left side, grade of sten, single indicator event (AF, TIA, stroke)	• After 2 years' follow-up, the rate of recurrent ipsilateral ischaemic strokes is similar for both treatment groups. • The incidence of recurrent carotid stenosis at 2 yrs, as defined by ultrasound, is significantly higher after CAS. • However, it cannot be excluded that the degree of in-stent stenosis is slightly overestimated by conventional ultrasound criteria.
EVA 3 S [35-37]				

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
Carotid Angioplasty and Stenting With and Without Cerebral Protection: Clinical Alert from the Endarterectomy vs Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S**) Trial. Stroke 2004;35:e18-e2**	RCT, multi-center, France	CAS + BMT mit/ohne Protektion (n=80)	any stroke/death with/without cerebral protection 10,3%/26,7% (age-adjusted OR 2,5 (95%CI 0,6-10,8)	Although this result was not based on a randomized comparison of unprotected versus protected CAS, it suggests that the use of cerebral protection devices during CAS reduces periprocedural strokes.
Mas JL et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis (EVA-3S**).** **NEJM 2006;355:1660–1671.**	RCT, multi-center, n=527 pat (520 assessed in ITT analysis) 2000-2005 Mean age 70yrs, 75% male Non-inferiority design No upper age limit 60-99%ige sympt sten (NASCET crit, DAS or US+MRA) symptoms <120 days	CEA + BMT (n=259) Versus CAS + BMT (n=261) 91% CAS with cerebral protection (obligatory since 2003)	Outcomes CEA vs. CAS • 30-day incidence of any stroke or death 3.9% vs.9,6% (p=0.01). Relative risk of any stroke or death after CAS as compared with CEA was 2.5 (95% CI, 1.2-5.1). • The 30-day incidence of any disabling stroke or death was 1.5% vs. 3,4% (p=0.26); Relative risk was 2.2 (95% CI, 0.7-7.2). • any stroke or death at 6 months: 6.1% vs. 11.7% (p=0.02) • any proc stroke or death + ipsilat strokes at 6 months: 4.2% vs. 10.2% (p = 0.008) • Myocardial infarction 0,4% vs. 0,8% (n.s.) • major local complications (hematoma, false aneurysm, lower limb arterial occlusion) 1,2% vs. 3,1% (n.s.) • systemic complications (mainly pulmonary) 1,9% vs.3,1% (n.s.) Cranial-nerve injury 7,7% vs. 1,1% (p<0,001).	In this study of patients with symptomatic carotid stenosis of 60% or more, the rate of death and stroke at 1 and 6 months were lower with endarterectomy than with stenting. Kommentar: Study was stopped due to high complications rates after CAS
Mas JL et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S**) trial: results up to 4 years from a randomised, multicentre trial.** **Lancet Neurol 2008; 7: 885–92.**	s.o.	s.o.	Outcomes of CAS vs. CEA after 4 years: • proc stroke or death and non-proc ipsilat stroke rates 11.1% vs 6.2%, [HR] 1·97, 95% CI 1.06–3.67; p=0.03). • The HR for proc disabling stroke or death and non-procedural fatal or disabling ipsilateral stroke was 2.00 (0.75–5.33; p=0.17) • After the periprocedural period, the risk of ipsilat stroke was low and similar in both groups. For any stroke or proc death, the HR was 1.77 (1.03–3.02; p=0.04). For any stroke or death, the HR was 1.39 (0.96–2.00; p=0.08). Subgroups: • Higher risk associated with CAS in men, in patients aged 70 years or older, in those with prior stroke, and in those who had stroke as a qualifying event compared with those who had cerebral TIA and ocular events.	The results of this study suggest that CAS is as effective as CEA for middle-term prevention of ipsilateral stroke, but the safety of CAS needs to be improved before it can be used as an alternative to CEA in patients with symptomatic carotid stenosis.
Mas JL, Arquizan C, Calvet D, Viguier A, Albucher JF, Piquet P, et al. Long-term follow-up study of endarterectomy versus	Follow-up (mean) 7.1 yrs	s.o.	• During a median follow-up of 7.1 years (interquartile range, 5.1–8.8 years; maximum 12.4 years), the primary end point occurred in 30 patients in the CAS group compared with 18 patients in the CEA group.	The long-term benefit–risk balance of carotid stenting versus endarterectomy for symptomatic carotid stenosis favored endarterectomy, a difference driven by a lower risk of procedural stroke after endarterectomy. Both techniques were associated with low and similar long-

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
angioplasty in patients with symptomatic severe carotid stenosis trial. Stroke. 2014;45(9):2750-6.			• Cumulative probabilities of this outcome were 11.0% (95%CI 7.9–15.2) versus 6.3% (4.0–9.8) in the CEA group at the 5-year follow-up (hazard ratio, 1.85; 1.00–3.40; p=0.04) and 11.5% (8.2–15.9) versus 7.6% (4.9–11.8; hazard ratio, 1.70; 0.95–3.06; p=0.07) at the 10-year follow-up. • No difference was observed between treatment groups in the rates of ipsilateral stroke beyond the procedural period, severe carotid restenosis (≥ 70%) or occlusion, death, myocardial infarction, and revascularization procedures.	term risks of recurrent ipsilateral stroke beyond the procedural period.
7. TESCAS 2006 (China) [38]				
Ling F, Jiao LQ. Preliminary report of trial of endarterectomy versus stenting for the treatment of carotid atherosclerotic stenosis in china (TESCAS-C**). Chinese J Cerebrovasc Dis. 2006;3:4–8.**	RCT, multi-center asympt. and sympt. sten Randomization unclear BMT unclear Protection unclear	CEA (n=84) Versus CAS (n=82)	Death, stroke or MI at 30 days after treatment plus ipsilateral stroke between 31 days and 6 months after treatment: 9,7% after CAS and 11,9% after CEA	Engl. Abstract, Publikation in Chinesisch (s. Cochrane Review) Keine weitergehenden Informationen erhältlich
8. BACASS 2008 [39]				
Hoffmann A et al. Carotid artery stenting versus carotid endarterectomy. A prospective, randomised trial with long term follow up (BACASS). Schweizer Archiv für Neurologie und Psychiatrie 2008;159:84-89.	RCT, single-center, 1998-2002, n=20 pat Symp sten >/=70% 82 pat were screened 80% male, mean age 68yrs	CEA + BMT (n=10) Versus CAS + BMT (n=10) With protection device	<u>Primary outcome CEA vs CAS</u> • periprocedural stroke, death or MI: 10% (one non-disabling stroke vs. 0% (0/10) <u>Secondary outcome CEA vs. CAS</u> • During follow-up (48.1 +/- 21.3 months with CAS and 43.5 +/- 19.5 months with CEA) neither strokes nor myocardial infarctions occurred in both groups. • LOS was 3.5+/-1.8 days for CAS vs 7.3 +/-3.3 days for CEA • No difference in peri-interventional TIA, haematoma, cranial nerve paralysis, patency and stroke prevention	CAS and CEA seem to be comparably safe in our setting. More importantly, data useful for a systematic meta-analysis are provided, which include long-term results.
9. STEINBAUER 2008 [40]				
Steinbauer MG, Pfister K, Greindl M, Schlachetzki F, Borisch I, Schuirer G, et al. Alert for increased long-term follow-up after carotid artery stenting: results of a prospective, randomized, single-center trial of carotid artery stenting vs carotid endarterectomy. J Vasc Surg. 2008;48(1):93-8.	RCT Recruitment: Between August 1999-April 2002 87 patients, mean age 68 yrs symptomatic high-grade carotid stenosis (>70%)	CEA, n=44 CAS, n=43	• Riskof stroke or death at one year: CAS (1/43) and CEA (0/44) • During the observation period, 23 patients (25.2%) died (10 CAS, 13 CEA), and three were lost to follow up. • The incidence of strokes was higher after CAS, with four strokes in 42 CAS patients vs none in 42 CEA patients. One transient ischemic attack occurred in each group. • A significantly higher rate of restenosis >70% (6 of 32 vs 0 of 29) occurred after CAS compared with CEA. Five of 32 CAS patients	The long-term results of this prospective, randomized, single-center study revealed a high incidence of relevant restenosis and neurologic symptoms after CAS. CEA seems to be superior to CAS concerning the development of restenosis and significant prevention of stroke. However, the long-term results of the ongoing multicenter trials have to be awaited for a final conclusion.

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
	After a median observation time of 66 months (CAS) and 64 months (CEA), 42 patients in each group were re-evaluated retrospectively by clinical examination and documentation of neurologic events. Duplex ultrasound imaging was performed in 61 patients (32 CAS, 29 CEA), and patients with restenosis >70% were re-evaluated by angiography.		(15.6%) presented with high-grade (>70%) restenosis as an indication for secondary intervention or surgical stent removal, and three presented with neurologic symptoms. No CEA patients required reintervention (P < .05 vs CAS). • A medium-grade (<70%) restenosis was detected in eight of 32 CAS patients (25%) and in one of 29 CEA patients (3.4%). In five of 32 CAS (15.6%) and three of 29 CEA patients (10.3%), a high-grade stenosis of the contralateral carotid artery was observed and treated during the observation period.	
10. ICSS (CAVATAS 2) 2004/2010/2015 [41-43]				
Featherstone R et al. on behalf of the ICSS **Investigators International Carotid Stenting Study: Protocol for a Randomised Clinical Trial Comparing Carotid Stenting with Endarterectomy in Symptomatic Carotid Artery Stenosis. Cerebrovasc Dis 2004;18:69–74** **International Carotid Stenting Study Investigators, Ederle J et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet. 2010;375(9719):985-97.**	RCT, multicenter (n=1713 pat in 50 centres, 3 pat excluded from analysis, 15 countries, mainly UK, Netherlands, Sweden, Australia) Recruitment 2002 - 2008 Sympt sten >/=50% (NASCET crit) Age >40 yrs >(no upper limit), mean age 70yrs, male 71% ITT and PP analysis Primary EP: long-term survival free of disabling stroke	ITT analysis CEA + BMT (n=857) CAS + BMT (n=853) PP analysis CEA + BMT (n=821) CAS + BMT (n=828)	• Between randomisation and 120 days, there were 34 (Kaplan-Meier estimate 4.0%) events of disabling • stroke or death in the stenting group compared with 27 (3.2%) events in the endarterectomy group (HR 1.28, 95% CI 0.77–2.11). • The incidence of stroke, death, or procedural MI was 8.5% in the stenting group compared with 5.2% in the endarterectomy group (72 vs 44 events; HR 1.69, 1.16–2.45, p=0.006). • Risks of any stroke (65 vs 35 events; HR 1.92, 1.27–2.89) and all-cause death (19 vs seven events; HR 2.76, 1.16–6.56) were higher in the stenting group than in the endarterectomy group. • Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all non-fatal, in the endarterectomy group. • There was one event of cranial nerve palsy in the stenting group compared with 45 in the endarterectomy group. • There were also fewer haematomas of any severity in the stenting group than in the endarterectomy group (31 vs 50 events; p=0.0197). MRI substudy (5 centres): new ischemia 46.3% vs. 14.1% (OR 5.24, 2.61-10.53), p<0.001	Completion of long-term follow-up is needed to establish the effi cacy of carotid artery stenting compared with endarterectomy. In the meantime, carotid endarterectomy should remain the treatment of choice for patients suitable for surgery.
Bonati LH, Dobson J, Featherstone RL, Ederle J,	s.o.		• The number of fatal or disabling strokes (52 vs 49) and cumulative 5-year risk did not differ significantly between the stenting	Long-term functional outcome and risk of fatal or disabling

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
van der Worp HB, de Borst GJ, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet. 2015;385(9967):529-38.			and endarterectomy groups (6·4% vs 6·5%; HR 1·06, 95% CI 0·72–1·57, p=0·77). • Any stroke was more frequent in the stenting group than in the endarterectomy group (119 vs 72 events; ITT population, 5-year cumulative risk 15·2% vs 9·4%, HR 1·71, 95% CI 1·28–2·30, p<0·001; • per-protocol population, 5-year cumulative risk 8·9% vs 5·8%, 1·53, 1·02–2·31, p=0·04), but were mainly non-disabling strokes. • The distribution of modifi ed Rankin scale scores at 1 year, 5 years, or final follow-up did not differ significantly between treatment groups.	stroke are similar for stenting and endarterectomy for symptomatic carotid stenosis. Overall we found that CAS and CEA are durable procedures that are equally effective in preventing severe strokes that lead to disability or death. CAS has the disadvantage of causing more minor non-disabling strokes in the procedural period and possibly in the long term. This feature, however, must be weighed against the increased risk of procedural MI, cranial nerve palsy, and access-site haematoma associated with CEA. The modified Rankin scale scores suggested similar short-term and long-term functional outcomes with the two treatments. The choice between CAS and CEA should take into account the different procedure-related risks in line with other characteristics of individual patients.
11. CREST 2010, s Evidenztabelle 5				

1.5 Evidenztabelle 5: RCTs zur asymptomatischen und symptomatischen Carotisstenose - CEA + BMT versus CAS + BMT

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
1. TESCAS 2006 (China) [38]				
Ling F, Jiao LQ. Preliminary report of trial of endarterectomy versus stenting for the treatment of carotid atherosclerotic stenosis in china (TESCAS-C**). Chinese J Cerebrovasc Dis. 2006;3:4–8.**	RCT, multi-center asympt. and sympt. sten Randomization unclear BMT unclear Protection unclear	CEA (n=84) Versus CAS (n=82)	Death, stroke or MI at 30 days after treatment plus ipsilateral stroke between 31 days and 6 months after treatment: 9,7% after CAS and 11,9% after CEA	Engl. Abstract, Publikation in Chinesisch (s. Cochrane Review) Keine weitergehenden Informationen erhältlich
2. SAPPHIRE 2004/2008 [9, 10]				
Yadav JS et al. for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators* (SAPHHIRE**)** **Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients. NEJM 2004; 351: 493-501**	RCT, multizentrisch, 29 centres, n=334, mean age 73yrs (46-91), male 67% 2000-2002 Non-inferiority design, ITT Asympt. (>/=80%) und sympt. Stenosen (>/=50%), NASCET criteria Criteria for high risk (at least one factor): Clinically significant cardiac disease (congestive heart failure, stress test, or need for open-heart surgery), Severe pulmonary disease; Contralateral carotid occlusion; Contralateral laryngeal-nerve palsy; Previous radical neck surgery or radiation; Recurrent stenosis after CEA; Age >80 yr Use of protection system in 95,6%	CEA +BMT (n=167) Versus CAS +BMT (n=167) N=413 patients outside the trial in a CAS registry (n=407), or a CEA registry (n=7)	Primary EP: • death, stroke, or myocardial infarction within 30 days after the intervention or death or ipsilateral stroke between 31 days and 1 year: CAS 12,2% vs. CEA 20,1% (AD 7.9%, 95%CI 16.4-0.7, p=0.004 for noninferiority, and P=0.053 for superiority). Secondary EP CAS vs. CEA: • 30-day death rate 1.2% vs. 2.5% (n.s.) • 30-day stroke rate 3.6% vs. 3.1% (n.s.) • 30-day rate of MI: 2.4% vs. 6.1%, >80% non-q-wave, (n.s) • 30-day rate of s/d/MI 4.8% vs. 9.8% (p=0.09) • 30-day s/d rate+ipsilat strokes at one yr: 5.5% vs. 8.4% (n.s.) • Death rate at one yr 7.4% vs. 13.5% (p=0.08) • primary EP in sympt pat: 16.8% vs. 16.5% (p=0.95) • primary 30-day EP in sympt pat: 2.1% vs. 9.3% (p=0.18) • primary EP in asympt pat: 9.9% vs. 21.5% (p=0.02) • primary 30-day EP in asymp pat: 5.4% vs. 10.2% (p=0.20) • carotid revascularization at one yr: 0,6% vs. 4.3%; P=0.04). • Estimated rate of cranial-nerve palsy at one yr: 0% vs. 4.9% (p=0.004) Estimated rate of target-vessel revascularization at one yr 0,6% vs. 4.3% (p=0.04)	Among patients with severe carotid-artery stenosis and coexisting conditions, CAS with the use of an emboli-protection device is not inferior to CEA. Comments: • Primary author was suspected to have an conflict of interest, some co-authors were employees from Cordis • Mix of asymptomatic (about 70%) and symptomatic patients (about 30%) • Also recurrent stenoses were added (22% of patients) • primary endpoint quite unusual including non-q-wave-infarcts • The trial was terminated early because of a slowdown in recruitment. • The trial was sponsored by Cordis

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
Gurm HS et al. for the SAPPHIRE **investigators. Long-Term Results of Carotid Stenting versus Endarterectomy in High-Risk Patients. NEJM 2008; 338: 1572-9**	s.o. follow-up three yrs	s.o. data of 260 patients were available after 3 yrs (CAS group 85.6%, CEA group 70.1%)	3 yrs outcomes CAS vs. CEA: • Procedural d/s/MI (30 days) or death or ipsilateral stroke within 3 yrs: 24.6% vs. 26.9%; AD −2.3%; 95%CI, −11.8 to 7.0), p=0.71. • Death rate 18.6% vs. 21% (n.s.) • Stroke rate 9% vs. 9% (n.s.) • There were 15 strokes in each of the two groups, of which 11 in the CAS group and 9 in the CEA group were ipsilateral.	In our trial of patients with severe carotid artery stenosis and increased surgical risk, no significant difference could be shown in long-term outcomes between patients who underwent CAS with an emboli-protection device and those who underwent CEA. Comments see above
3. CREST 2010 [11, 44-49]				
Hobson RW et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST **lead-in phase. JVS 2004;40:1106-11** **Hobson RW II. Update on the Carotid Revascularization Endarterectomy vs. Stent Trial (**CREST**) protocol. J Am Coll Surg 2002;194(1Suppl):S9-14.**	RCT, prosp., multicenter „to assess the differential efficacy of CEA and CAS in preventing stroke, MI, and death in the 30-day periprocedural period, and ipsilateral stroke over the FU period" Sympt. (>50%) und asympt. (>70%) Stenosen Ab 18 Jahre, keine obere Altersgrenze	CEA + BMT Versus CAS + BMT	Lead-in-Phase CAS: Schlaganfall/Tod (30 Tage) nach CAS: <80 vs. >/=80.LJ: 3,2% vs. 12,1% (p<0.0001)	Interim results from the lead-in phase of CREST show that the periprocedural risk of stroke and death after CAS increases with age in the course of a credentialing registry. This effect is not mediated by potential confounding factors. Randomized trial data are needed to compare the CAS versus CEA periprocedural risk of stroke and death by age. Pending results from randomized studies, care should be taken when CAS is performed in older patient populations.
Sheffet AJ, Roubin G, Howard G, et al . Design of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST). Int J Stroke 2010;5:40-6. **Howard VJ, Lutsep HL, Mackey A et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol 2011.**	"when CREST was designed in the late 1990s, prespecified plans for sex-specific subgroup analyses were included, as were recruitment strategies targeted for women. A recruitment goal of 40% women was set to provide reasonable power to detect potential treatment diff erences between sexes—ie, to assess whether the overall difference in risk between carotid artery	See above	Primary endpoint (procedural stroke or death or MI plus postprocedural ipsilateral stroke: • Men: 6.8% after CEA and 6.2% after CAS, p= 0.94 • Women: 6.7% after CEA and 8.9% after CAS, p=0.24 procedural stroke or death or MI: • Men: 4.9% after CEA and 4.3% after CAS, p= 0.64 • Women: 3.8% after CEA and 6.8% after CAS, p=0.047 Myocardial infarction • Men: 2.6% after CEA and 0.9% after CAS, p=0.015 • Women: 1.7% after CEA and 1.5% after CAS, p=0.87 Any procedural stroke • Men: 2.4% after CEA and 3.3% after CAS, p=0.26 • Women: 2.2% after CEA and 5.5% after CAS, p=0.013	"Periprocedural risk of events seems to be higher in women who have carotid artery stenting than those who have carotid endarterectomy whereas there is little difference in men. Additional data are needed to confirm whether this differential risk should be taken into account in decisions for treatment of carotid disease in women

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
	stenting and carotid endarterectomy is shared equally by men and women. We present the results of this a-priori plan"		Any procedural stroke plus any postprocedural ipsilateral stroke • Men: 4.5% after CEA and 5.2% after CAS, p=0.22 • Women: 5.0% after CEA and 7.8% after CAS, p=0.11 Any procedural stroke or death • Men: 2.4% after CEA and 3.7% after CAS, p=0.13 • Women: 2.2% after CEA and 5.5% after CAS, p=0.013 Any procedural stroke or death or postprocedural ipsilateral stroke • Men: 4.5% after CEA and 5.6% after CAS, p=0.12 Women: 5.0% after CEA and 7.8% after CAS, p=0.11	
Brott TG, Hobson RW, Howard G et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363(1):11-23.	RCT, prospect, multicenter (108 centers in USA, 9 centers in Kanada), 477 Chirurgen, 224 Interventionalisten "The primary aim of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) was to compare the outcomes of carotid artery stenting with those of carotid endarterectomy among patients with symptomatic or asymptomatic extracranial carotid stenosis" Sympt. (>50%) und asympt. (>70%, seit 2005) stenoses 18 Jahre, keine obere Altersgrenze	CEA + BMT Versus CAS + BMT 2522 pat randomized (1271 CAS, 1251 CEA) Superiority design	Primary outcome CEA vs CAS: composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 4 years after randomization was 4.5% after CEA and 5.2% after CAS, p=0.38 Secondary outcome CEA vs. CAS (periprocedural period) • Periprocedural death 0.3% after CEA and 0.6% after CAS, p=0.18 • Any periprocedural stroke after CEA 2.3% and 4.1% after CAS, p=0.01 • Any periprocedural stroke or death 2.3% after CEA and 4.4% after CAS, p=0.005 • Any major ipsilateral periprocedural stroke 0.3% after CEA and 0.9% after CAS, p=0.09 • Any minor ipsilateral periprocedural stroke 1.4% after CEA and 2.9% after CAS, p=0.009 • Any periprocedural stroke 1.4% after CEA and 2.9% after CAS, p=0.009 • Myocardial infarction 2.3% after CEA and 1.1% after CAS, p=0.03 Secondary outcome CEA vs. CAS (periprocedural + postprocedural) • Any periprocedural stroke or death plus any ipsilateral stroke 4.7% after CEA and 6.4% after CAS , p=0.03 • Any procedural and postprocedural stroke after CEA 7.9% after CEA and 10.2% after CS , p=0.03 • Any major ipsilateral procedural and postprocedural stroke 0.5% after CEA and 1.4% after CAS, p=0.05 • Any minor ipsilateral procedural and postprocedural stroke 3.5% after CEA and 4.5% after CAS, p=0.10	"In conclusion, carotid revascularization performed by highly qualified surgeons and interventionists is effective and safe. Stroke was more likely after carotid-artery stenting. Myocardial infarction was more likely after carotid endarterectomy, but the effect on the quality of life was less than the effect of stroke. Younger patients had slightly fewer events after carotid-artery stenting than after carotid endarterectomy; older patients had fewer events after carotid endarterectomy. The low absolute risk of recurrent stroke suggests that both carotid-artery stenting and carotid endarterectomy are clinically durable and may also reflect advances in medical therapy"

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
			• Any periprocedural stroke or postprocedural ipsilateral stroke 4.7% after CEA and 6.2% after CAS , p=0.049 • Any periprocedural stroke or death or postprocedural ipsilateral stroke 4.7% after CEA and 6.4% after CAS , p=0.03	
CREST **asympt vs symptomatisch**	s.o.	s.o.	<u>Periprocedural results in asymptomatic patients (n=1.181):</u> • Any periprocedural stroke or death or MI 3.6% after CEA and 3.5% after CAS, p=0.96 • Any periprocedural stroke or postprocedural ipsilateral stroke 1.4% after CEA and 2.5% after CAS, p=0.15 • Any periprocedural stroke or death or postprocedural ipsilateral stroke 1.4% after CEA and 2.5% after CAS, p=0.15 • Periprocedural myocardial infarction 2.2% after CEA and 1.2% after CAS , p=0.20 <u>Peri- + postprocedural results in asymptomatic patients (n=1.181):</u> • Any periprocedural stroke or death or MI or postprocedural ipsilateral stroke 4.9% after CEA and 5.6% after CAS, p=0.56 • Any periprocedural stroke or death or postprocedural ipsilateral stroke 2.7% after CEA and 4.5% after CAS, p=0.07 • Any periprocedural stroke or postprocedural ipsilateral stroke 2.7% after CEA and 4.5% after CAS, p=0.07 <u>Periprocedural results in symptomatic patients (n=1.321):</u> • Any periprocedural stroke or death or MI 5.4% after CEA and 6.7% after CAS, p=0.30 • Any periprocedural stroke or postprocedural ipsilateral stroke 3.2% after CEA and 5.5% after CAS, p=0.04 • Any periprocedural stroke or death or postprocedural ipsilateral stroke 3.2% after CEA and 6.0% after CAS, p=0.02 • Periprocedural myocardial infarction 2.3% after CEA and 1.0% after CAS , p=0.08 <u>Peri- + postprocedural results in asymptomatic patients (n=1.321):</u> • Any periprocedural stroke or death or MI or postprocedural ipsilateral stroke 6.5% after CEA and 8.0% after CAS, p=0.14 • Any periprocedural stroke or death or postprocedural ipsilateral stroke 2.7% after CEA and 4.5% after CAS, p=0.07 Any periprocedural stroke or postprocedural ipsilateral stroke 6.4% after CEA and 7.6% after CAS, p=0.25	

Source	Design of the study	Interventions	Endpoints (EP)/ results	Conclusions/comments
Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. N Engl J Med. 2016;374(11):1021-31.	see above		• Among 2502 patients, there was no significant difference in the rate of the primary composite end point between the stenting group (11.8%; 95%CI 9.1-14.8) and the endarterectomy group (9.9%; 95%CI 7.9-12.2) over 10 years of follow-up (HR 1.10; 95% CI, 0.83-1.44). • With respect to the primary long-term end point, postprocedural ipsilateral stroke over the 10-year follow-up occurred in 6.9% (95%CI, 4.4-9.7) of the patients in the stenting group and in 5.6% (95%CI, 3.7-7.6) of those in the endarterectomy group; the rates did not differ significantly between the groups (hazard ratio, 0.99; 95%CI 0.64-1.52). • No significant between-group differences with respect to either end point were detected when symptomatic patients and asymptomatic patients were analyzed separately.	Over 10 years of follow-up, we did not find a significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of postprocedural ipsilateral stroke also did not differ between groups.
4. KULIHA 2015 [50]				
Kuliha M, Roubec M, Prochazka V, Jonszta T, Hrbac T, Havelka J, et al. Randomized clinical trial comparing neurological outcomes after carotid endarterectomy or stenting. Br J Surg. 2015;102(3):194-201.	RCT >70%ige Stenose, asymptomatisch oder symptomatisch age 40-80yrs	CEA, n=73 CA, n=77	• New infarctions on MRI were found more frequently after CAS (49 versus 25 per cent; p=0.002). • Lesion volume was also significantly greater after CAS (p=0.010). • Multiple logistic regression analyses identified intervention in the right ICA as the only independent predictor of brain infarction (odds ratio 2.10, 95%CI 1.03-4.25; p=0.040). • Stroke or transient ischaemic attack occurred in one patient after CEA and in two after CAS. • No significant differences were found in cognitive test results between the groups.	These data confirm a higher risk of silent infarction in the brain on MRI after CAS in comparison with CEA, but without measurable change in cognitive function.

1.6 Literatur

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Übersicht über die zu konsentierenden Empfehlungen:

Kapitel 7

7.6.1	B	konsentiert in 2. Runde

Kapitel 8

8.4.4.1	H	konsentiert in 3. Runde

Kapitel 9

9.9.1	G	konsentiert in 3. Runde

Kapitel 12

12.3.1	C	konsentiert in 2. Runde
12.3.1	D	konsentiert in 2. Runde
12.3.1	E	konsentiert in 1. Runde
~~12.3.1~~	~~F~~	~~vorab gestrichen~~
12.3.1	G	konsentiert in 2. Runde
12.4.1	A	konsentiert in 1. Runde
12.4.1	B	konsentiert in 1. Runde
12.4.1	C	konsentiert in 1. Runde
12.4.1	D	konsentiert in 3. Runde
12.4.1	E	konsentiert in 2. Runde
~~12.4.1~~	~~F~~	~~vorab gestrichen~~
12.4.1	G	konsentiert in 1. Runde

Empfehlung Nr.	Konsentiert in Delphi Runde	Konsentierte Formulierung	dafür	dagegen	Enthaltung	Konsens
7.6.1 B	2	Bei Vorliegen vaskulärer Risikofaktoren und / oder bestehenden arteriosklerotischen Erkrankungen in anderen Territorien kann eine DUS sinnvoll sein. Die Untersuchung sollte auf solche Patienten beschränkt werden, bei denen therapeutische Konsequenzen zu erwarten sind.	12	1	0	92%
8.4.4.1 H	3	Da ein kontralateraler Carotisverschluss das Behandlungsrisiko der CEA erhöhen kann, sollen Indikationsstellung und Verfahrenswahl (CEA oder CAS) anhand klinischer und morphologischer Variablen erfolgen. (Expertenkonsens EK)	14	1	0	93%
9.9.1 G	3	Eine präoperative Therapie mit Antikoagulantien (bei Vorhofflimmern, künstlicher Herzklappe, Z.n. Lungenembolie, etc.) soll unter Berücksichtigung des individuellen Blutungs- und Thromboembolie-Risikos überbrückt werden. (Expertenkonsens EK)	14	0	1	100%
12.3.1 C	2	Routinemäßige DUS-Kontrollen sollten nach CEA und CAS im Jahresabstand durchgeführt werden, sofern daraus eine therapeutische Konsequenz erwachsen könnte. (Expertenkonsens EK)	15	1	0	94%
12.3.1 D	2	Empfehlung komplett streichen.	15	1	0	94%
12.3.1 E	1	Ursprüngliche Empfehlung angenommen: Bei Patienten mit vermutetem erhöhten Risiko einer Rezidivstenose während des Follow-up (Frauen, Diabetes mellitus, Dyslipoproteinämie, Nikotinabusus) sollten DUS-Kontrollen nach CEA und nach CAS in halbjährlichen Abständen durchgeführt werden. Sobald ein gleichbleibender Befund in zwei aufeinanderfolgenden Untersuchungen vorliegt, können die Intervalle bei CEA und CAS auf 12 Monate verlängert werden. (Expertenkonsens EK)	15	0	0	100%
12.3.1 G	2	Empfehlung komplett streichen	14	2	1	88%
12.4.1 A	1	Ursprüngliches Statement angenommen: Eine Carotis-Rezidivstenose liegt vor ab einem Stenosegrad von ≥50% (red. Änderung "nach NASCET" einfügen) vor, mit und ohne klinischer Symptomatik im ipsilateralen Stromgebiet. Für die Diagnostik von Rezidivstenosen nach CAS gelten gesonderte Kriterien. (Expertenkonsens EK)	16	0	0	100%

12.4.1 B	1	Ursprüngliche Empfehlung angenommen: Beim sonographischen Verdacht auf das Vorliegen einer 70-99%igen Carotis-Rezidivstenose nach CEA oder CAS sollte zur Bestätigung eine weitere Bildgebung (bevorzugt CTA) erfolgen, sofern daraus eine therapeutische Konsequenz zu erwarten ist. (Expertenkonsens EK)	15	1	0	94%
12.4.1 C	1	Ursprüngliche Empfehlung angenommen: Beim Vorliegen einer symptomatischen 50-99%igen Carotis-Rezidivstenose soll eine erneute Revaskularisierung mittels CEA oder CAS erfolgen. (Expertenkonsens EK)	16	0	0	100%
12.4.1 D	3	Beim Vorliegen einer symptomatischen <50%igen Carotis-Rezidivstenose soll keine erneute Revaskularisierung mittels CEA oder CAS erfolgen, es sei denn, es kam trotz bestmöglicher medikamentöser Therapie, zu wiederholten Stenose-assoziierten Symptomen. (Expertenkonsens EK)	8	3	1	73%
12.4.1 E	2	Beim Vorliegen einer asymptomatischen 70-99%igen Carotis-Rezidivstenose kann eine erneute Revaskularisierung mittels CEA oder CAS erwogen werden. Dies gilt insbesondere dann, wenn • eine unzureichende intracranielle kollaterale Blutversorgung in der Bildgebung vorliegt • bei der initialen CEA klinisch eine Clamping-Ischämie beobachtet wurde • bei der initialen CEA beim Clamping die ipsilaterale Strömungsgeschwindigkeit der cerebri media <15cm/sec im TCD betrug. • bei der initialen CEA in Allgemeinanästhesie signifikante Veränderungen des neurophysiologischen Monitorings beobachtet wurden • beim initialen CAS bei der distalen oder proximalen Ballonokklusion neurologische Symptome auftraten • wenn die Rezidivstenose innerhalb von 12 Monaten aufgetreten ist. (Expertenkonsens EK)	13	3	0	81%
12.4.1 G	1	Ursprüngliche Empfehlung angenommen: Die Indikation zu CEA oder CAS einer Carotis-Rezidivstenose soll interdisziplinär (Neurologie, Gefäßchirurgie, Endovaskuläre Therapie, Neuroradiologie, Radiologie, (red. Änderung "Angiologie" einfügen)) gestellt werden. (Expertenkonsens EK)	15	0	1	100%

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

(for definitions of terms used see glossary at http://www.cebm.net/?o=1116)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

EITHER a single result with a wide Confidence Interval

OR a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

Erklärung von Interessen

Extracranielle Carotisstenose; Diagnostik, Therapie und Nachsorge

Registernummer 004 - 028

zu Händen

Prof. Dr. P. Ringleb (CoI Beauftragter der Steuergruppe)
Peter.Arthur.Ringleb@med.uni-heidelberg.de

Vorbemerkung

Alle Mitglieder der Leitliniengruppe sind gehalten, die nachstehende Erklärung von Interessen auszufüllen. Die Erklärung wird gegenüber dem CoI-Beauftragten der Steuergruppe abgegeben. Dies soll bereits zu Beginn des Leitlinienprojekts erfolgen bzw. zu dem Zeitpunkt, an dem die Mitglieder ihre Teilnahme am Leitlinienprojekt gegenüber dem Koordinator bestätigen. Bei länger andauernden Projekten ist eine Erneuerung der Erklärung einmal pro Jahr bis zum Abschluss der Leitlinienentwicklung, zumindest aber vor der Konsensfindung, erforderlich.

In der Erklärung sind alle Interessen aufzuführen, unabhängig davon, ob der/die Erklärende selbst darin einen thematischen Bezug zur Leitlinie oder einen Interessenskonflikt sieht oder nicht. Ob Interessenkonflikte bestehen und ob dadurch die erforderliche Neutralität für die Mitarbeit bei der Leitlinienentwicklung in Frage gestellt ist oder in welchen speziellen Bereichen /Fragestellungen der Leitlinie das professionelle Urteilsvermögen eines Experten durch sekundäre Interessen beeinflusst sein könnte, ist durch einen Dritten zu bewerten und in der Leitliniengruppe zu diskutieren. Die Erklärung betrifft Interessen innerhalb **des laufenden Jahres sowie der zurückliegenden 3 Jahre.**

Die Originale der Erklärungen verbleiben vertraulich beim CoI-Beauftragten der Steuergruppe. Die Inhalte der Erklärungen sind in der Langfassung der Leitlinie bzw. im Leitlinienreport in standardisierter Zusammenfassung offen darzulegen (siehe beigefügte Beispieltabelle/Zusammenfassung). Ergänzend sind das Verfahren der Sammlung und Bewertung der Erklärungen sowie die Ergebnisse der Diskussion zum Umgang mit Interessenkonflikten darzulegen.

Informationen zur Datenerhebung gemäß Artikel 13 DSGVO

Der CoI-Beauftragte der Steuergruppe erhebt Ihre Daten zum Zweck des o.g. Leitlinienvorhabens sowie zur Erfüllung des Regelwerkes der AWMF. Die Datenerhebung und Datenverarbeitung sind für die Durchführung des Leitlinienvorhabens erforderlich und beruhen auf Artikel 6 Abs. 1 b) DSGVO. Eine Weitergabe der Daten an Dritte findet nur zum Zweck der Erfüllung des Regelwerkes der AWMF statt. Die Daten werden gelöscht, sobald sie für den Zweck ihrer Verarbeitung nicht mehr erforderlich sind. Sie sind berechtigt, Auskunft der im Rahmen des Leitlinienvorhabens über Sie gespeicherten Daten zu beantragen sowie bei Unrichtigkeit der Daten die Berichtigung oder bei unzulässiger Datenspeicherung die Löschung der Daten zu fordern.

Erklärung

1. Allgemeine Angaben

Name, Vorname, Titel		
Arbeitgeber / Institution	Gegenwärtig	Früher(e) innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor
Position / Funktion in der Institution		
Adresse		
e-mail-Adresse		
Bei Rückfragen telefonisch zu erreichen unter		
Funktion in der Leitliniengruppe		
Datum		
Zeitraum, auf den sich die Erklärung bezieht		

2. Direkte, finanzielle Interessen

Hier werden finanzielle Beziehungen zu Unternehmen, Institutionen oder Interessenverbänden im Gesundheitswesen erfasst. Haben Sie oder die Einrichtung, für die Sie tätig sind, innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor Zuwendungen erhalten von Unternehmen der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), industriellen Interessenverbänden, kommerziell orientierten Auftragsinstituten, Versicherungen/Versicherungsträgern, oder von öffentlichen Geldgebern (z.B. Ministerien), Körperschaften/Einrichtungen der Selbstverwaltung, Stiftungen, oder anderen Geldgebern? Machen Sie bitte in folgender Tabelle zu allen zutreffenden Aspekten konkrete Angaben.

Art der Beziehung/Tätigkeit	Name des/der Kooperations-partner/s	Zeitraum der Beziehung/ Tätigkeit[1]	Thema, Bezug zur Leitlinie[2]	Art der Zuwendung[3]	Höhe der Zuwendung[4]	Empfänger [5]
Berater-/Gutachtertätigkeit						
Mitarbeit in einem Wissenschaft-lichen Beirat (advisory board)						
Vortrags-/oder Schulungstätigkeit						
Autoren-/oder Coautorenschaft						
Forschungsvorhaben/ Durchführung klinischer Studien						
Eigentümerinteressen (Patent, Urheberrecht, Aktienbesitz[6])						

[1] Innerhalb des Erfassungszeitraums, d.h.im gegenwärtigen und den zurückliegenden 3 Jahren, Angabe: von (Monat/Jahr) bis (Monat/Jahr)
[2] Angabe des Themas, bei Präparaten/Geräten auch Handelsname bzw. Wirkstoffname (Freitext), zusätzlich Angabe einer Selbsteinschätzung des Bezugs zur Leitlinie: „Nein“ oder „Ja“
[3] Honorar, Drittmittel, geldwerte Vorteile (z.B. Personal-oder Sachmittel; Reisekosten, Teilnahmegebühren, Bewirtung i.R. von Veranstaltungen), Verkaufslizenz
[4] Es können gerundete Beträge angeben werden (z.B. bei Beiträgen > 1000 € jeweils auf die nächste Tausenderstelle): Die Angaben beziehen sich auf die Gesamtsumme der Zuwendungen für eine angegebene Tätigkeit über den Erfassungszeitraum, Angabe: von (Monat/Jahr) bis (Monat/Jahr).
Diese Angaben werden vertraulich behandelt.
[5] Bitte angeben: a) wenn Sie persönlich Empfänger der Zuwendung sind oder b) wenn es die Institution ist, für die Sie tätig sind und Sie innerhalb Ihrer Institution direkt entscheidungsverantwortlich für die Verwendung der Zuwendung/Mittel sind. Sind Sie nicht direkt entscheidungsverantwortlich, sind keine Angaben nötig.
[6] Betrifft nur Eigentümerinteressen im Gesundheitswesen; auch sind Angaben zu Mischfonds nicht erforderlich.

3. Indirekte Interessen

Hier werden persönliche Beziehungen zu Interessenverbänden im Gesundheitswesen, „intellektuelle“, akademische, und wissenschaftliche Interessen oder Standpunkte sowie Schwerpunkte klinischer Tätigkeiten/Einkommensquellen erfasst (für den Zeitraum des laufenden Jahres oder der 3 Kalenderjahre davor). Hierunter fallen auch solche, die indirekt mit finanziellen persönlichen Interessen verbunden sein können.

- Sind oder waren Sie in Wissenschaftlichen Fachgesellschaften, Berufsverbänden, Institutionen der Selbstverwaltung, Patientenselbsthilfegruppen, Verbrauchervertretungen oder anderen Verbänden aktiv? Wenn ja, in welcher Funktion (z.B. Mandatsträger für diese/andere Leitlinien, Vorstand)?
- Können Sie Schwerpunkte Ihrer wissenschaftlichen und /oder klinischen Tätigkeiten benennen? Fühlen Sie sich bestimmten „Schulen“ zugehörig?
- Waren Sie an der inhaltlichen Gestaltung von Fortbildungen federführend beteiligt?
- Haben Sie persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft?

Machen Sie bitte in folgender Tabelle zu allen zutreffenden Aspekten konkrete Angaben.

Art der Beziehung/Tätigkeit	Namen / Schwerpunkte (bitte konkret benennen)	Zeitraum der Beziehung/ Tätigkeit[7]	Themenbezug zur Leitlinie[8]
Mitgliedschaft /Funktion in Interessenverbänden			
Schwerpunkte wissenschaftlicher Tätigkeiten, Publikationen			
Schwerpunkte klinischer Tätigkeiten			
Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten			
Persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft			

[7] Innerhalb des Erfassungszeitraums, d.h. im gegenwärtigen und den zurückliegenden 3 Jahren, Angabe: von (Monat/Jahr) bis (Monat/Jahr)
[8] Angabe einer Selbsteinschätzung „Nein“ oder „Ja“

4. Sonstige Interessen

Sehen Sie andere Aspekte oder Umstände, die von Dritten als einschränkend in Bezug auf Ihre Objektivität oder Unabhängigkeit wahrgenommen werden könnten?

Ich erkläre hiermit nach bestem Wissen und Gewissen, dass ich alle mir derzeit bekannten Umstände aufgeführt habe, die gegebenenfalls zu einem persönlichen Interessenkonflikt bei der themenbezogenen Mitwirkung bei der Erstellung der Leitlinie führen können. Ich erkläre weiterhin, dass ich die Diskussion der Erklärungen anderer Mitglieder in der Leitliniengruppe absolut vertraulich behandeln werde. Ich bin darüber informiert, dass die Angaben in standardisierter Zusammenfassung mit der Leitlinie/in einem begleitenden Leitlinienreport veröffentlicht werden, und dass das vorliegende Formular vor der Einsicht unberechtigter Dritter geschützt aufbewahrt wird. Hiermit bin ich einverstanden.

Datum **Unterschrift**

Ergänzende Hinweise

- Bitte füllen Sie das Formular vollständig aus.
- Falls Sie zu bestimmten Fragen keine Angaben machen können oder wollen, begründen Sie dies bitte.
- Bitte speichern Sie das ausgefüllte Formular und senden es an Prof. Dr. Peter Ringleb: Peter.Arthur.Ringleb@med.uni-heidelberg.de

Leitlinie Carotis-Stenose

Im Folgenden sind die Interessenerklärungen als tabellarische Zusammenfassung dargestellt (Stand 03.03.2020) sowie die Ergebnisse der Interessenkonflikt-bewertung und Maßnahmen, die nach Diskussion der Sachverhalte von der der LL-Gruppe beschlossen und im Rahmen der Konsensuskonferenz umgesetzt wurden[1]

	Berater-bzw. Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Einstufung bzgl. der Relevanz, Konsequenz
Berkefeld, Prof. Dr. J.	./.	./.	./.	./.	./.	./.	Mitglied der SG	Keine
Czerny, Dr. M.	./.	./.	./.	./.	./.	./.	./.	Keine
Diel, Prof. Dr. R.	./.	./.	./.	./.	./.	./.	./.	Keine
Dörfler, Prof. Dr. A.	./.	./.	./.	./.	./.	./.	Mitglied der SG	Keine
Eckstein, Prof. Dr. H.H.	./.	ROADSTER-Studie (Fa Silkroad)	./.	./.	Steering-Committe SPACE1 und 2 ACST2-Studie	./.	Koordinator der LL	Keine
Engelhard, Prof. Dr. K.	./.	./.	./.	./.	./.	./.	./.	Keine
Fraedrich, Prof. Dr. G.	./.	./.	./.	./.	Steering-Committe SPACE1 und 2, ACST	./.	./.	Keine
Fründ, A.	./.	./.	./.	./.	./.	./.	./.	Keine
Görtz, Dr. H.	./.	./.	./.	./.	./.	./.	./.	Keine
Gross-Fengels, Prof. Dr. W.	./.	./.	./.	./.	./.	./.	./.	Keine
Hörstgen, A.	./.	./.	./.	./.	./.	./.	./.	Keine
Huppert, Prof. Dr. P	./.	./.	./.	./.	./.	./.	./.	Keine
Köhrmann, Prof. Dr. M.	./.	./.	./.	./.	./.	./.	./.	Keine
Kopp, Prof. Dr. I	./.	./.	./.	./.	./.	./.	Mitglied der SG	Keine

	Berater-bzw. Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Einstufung bzgl. der Relevanz, Konsequenz
Knüttel, Dr. rer. nat. H.	./.	./.	./.	:7.	./.	./.	./.	Keine
Kühnl, Prof. Dr. A.	./.	./.	./.	./.	./.	./.	Mitglied der SG	Keine
Langhoff, Dr. R.	./.	Beratung von BSC, Contego und Medtronic bzgl CAS und Studiendesign	Schulungsvorträge für Contego Medical und Termuo über CAS	./.	CAS-Studien	./.	./.	Keine
Lawall, Dr. H.	./.	./.	./.	./.	./.	./.	Mitglied der SG	Keine
Litz, Dr. R.								
Lüdeking, C.	./.	./.	./.	./.	./.	./.	./.	Keine
Mudra, Prof. Dr. H.	./.	./.	./.	./.	./.	./.	./.	Keine
Nabavi, Prof. Dr. D.	./.	./.	./.	./.	./.	./.	./.	Keine
Ploenes, Dr. Ch.	./.	./.	Ultraschallkurs (Fa Philips)	./.	./.	./.	./.	Keine
Rantner, PD. Dr. B.	./.	./.	./.	./.	ACST2-Studie	./.	./.	Keine
Ringleb, Prof. Dr. P.	./.	./.	./.	./.	Steering Committee SPACE-2	./.	Mitglied der SG	Keine
Rittig, PD Dr. K.	./.	./.	./.	./.	./.	./.	./.	Keine
Sander, Prof. Dr. D.	./.	./.	./.	./.	./.	./.	Mitglied der SG	Keine
Schamberger, R.	./.	./.	./.	./.	./.	./.	./.	Keine
Schnell, Prof. Dr. O.	./.	./.	./.	./.	./.	./.	./.	Keine
Schwerdtfeger, Prof. Dr. K.	./.	./.	./.	./.	./.	./.	./.	Keine
Steinbauer, Prof. Dr. M.	./.	./.	./.	./.	./.	./.	./.	Keine
Stingele, Prof. Dr. R.	./.	./.	./.	./.	./.	./.	./.	Keine

	Berater-bzw. Gutachter-tätigkeit	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autoren-/oder Coautoren-schaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz)	Indirekte Interessen	Einstufung bzgl. der Relevanz, Konsequenz
Storck, Prof. Dr. M.	./.	Rivaroxaban low dose (Bayer)	./.	./.	ACST2-Studie	./.	./.	Keine Beteiligung an der Abstimmung zur Bewertung der COMPASS-Studie
Zeller, Prof. Dr. T.	./.	./.	./.	./.	./.	./.	./.	Keine

[1] **In die tabellarische Zusammenfassung wurden nur die Angaben übertragen, für die nach Diskussion und Bewertung der vollständig entsprechend Formblatt der AWMF offengelegten Sachverhalte in der Leitliniengruppe ein thematischer Bezug zur Leitlinie festgestellt wurde. Die vollständigen Erklärungen sind im Leitliniensekretariat hinterlegt.**

F. Wein hatte lediglich organisatorische und redaktionelle Aufgaben. K. L. Schulte und M. Hanke waren am Update nicht beteiligt, nur an der ersten Version der Leitlinie.

Seit > 5 Jahren nicht aktualisiert, Leitlinie zur Zeit überarbeitet

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose

Leitlinienreport: S3-Leitlinie Carotisstenose

AWMF-Registernummer 004-028

08. August 2012

H.-H. Eckstein [2] (Sprecher der Steuergruppe), A. Kühnl (Sekretär der Steuergruppe), J. Berkefeld [5], R. Diel, A. Dörfler [5], I. Kopp [1], R. Langhoff [8], H. Lawall [8], P. Ringleb [3], D. Sander [3], M. Storck [2] (Steuergruppe)

und

G. Antoniadis [14], C. Arning [10], H. Brückmann [5], C. Diehm [17], I. Flessenkämper [15], G. Fraedrich [20], A. Fründ [19], S. George [18], M. W. Görtler [10], H. Görtz [12], W. Gross-Fengels [6], M. Hennerici [3], U. Hoffmann [8], A. Hörstgen [18], P. Huppert [6], O. Jansen [5], R. Litz [16], H. Mudra [9], D. G. Nabavi [4], E. Neugebauer [15], H. Niedermeier [2], Ch. Ploenes [12], R. Stingele [4], B. Rantner [20], Ruge, J. Tacke [7], O. Schnell [11], K.L. Schulte [8], K. Schwerdtfeger [14], D. Vorwerk [6], K. P. Walluschek [13], G. Walterbusch [13] (Leitliniengruppe)

Beteiligte Fachgesellschaften/Organisationen (* Mitglieder der Steuergruppe)

1. Institut für Medizinisches Wissensmanagement der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF-IMWi, I. Kopp *)
2. Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG, H.-H. Eckstein *, M. Storck *, H. Niedermeier)
3. Deutsche Gesellschaft für Neurologie (DGN: P. Ringleb *, D. Sander *, M. Hennerici)
4. Deutsche Schlaganfallgesellschaft (inkl. Deutsche Schlaganfallhilfe, R. Stingele, D. G. Nabavi)
5. Deutsche Gesellschaft für Neuroradiologie (DGNR: A. Dörfler *, O. Jansen, H. Brückmann, J. Berkefeld *)
6. Deutsche Röntgen-Gesellschaft (DRG, W. Gross-Fengels, P. Huppert, D. Vorwerk)
7. Deutsche Gesellschaft für Interventionelle Radiologie (DEGIR, J. Tacke)
8. Deutsche Gesellschaft für Angiologie /Gesellschaft für Gefäßmedizin (DGA, H. Lawall *, R. Langhoff *, K.L. Schulte, U. Hoffmann)
9. Deutsche Gesellschaft für Kardiologie (DKG, H. Mudra)
10. Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM, Sektion Neurologie, C. Arning, M.W. Görtler)
11. Deutsche Diabetes Gesellschaft (DDG, O. Schnell)
12. Deutsche Gesellschaft für Geriatrie (DGG, Ch. Ploenes, H. Görtz)
13. Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie (DGTHG, K. P. Walluschek, G. Walterbusch)
14. Deutsche Gesellschaft für Neurochirurgie (DGN, G. Antoniadis, K. Schwerdtfeger)
15. Deutsche Gesellschaft für Chirurgie (DGCh, I. Flessenkämper, E. Neugebauer)
16. Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI, R. Litz)
17. Deutsche Gefäßliga e.V. (C. Diehm)
18. Deutscher Verband der Ergotherapeuten (S. George, A. Hörstgen)
19. Deutscher Verband für Physiotherapie – Zentralverband der Physiotherapeuten/Krankengymnasten (ZVK) e.V. (A. Fründ)
20. Österreichischer Verband für Gefäßmedizin (G. Fraedrich, B. Rantner)

1 INHALT

2 PRÄAMBEL

Epidemiologische Untersuchungen zeigen, dass bei 1-3% aller Erwachsenen arteriosklerotisch bedingte extracranielle Carotisstenosen mit einem Stenosegrad von ≥50% vorliegen. Ab dem 65. Lebensjahr steigt die Prävalenz auf >6% an. Dies bedeutet, dass in Deutschland ca. 1 Mio. Menschen mit einer ≥50%igen Carotisstenose leben. Das Risiko eines carotis-assoziierten, ischämischen Schlaganfall beträgt bei klinisch asymptomatischen >50%igen Stenosen 1-5%/Jahr, bei >50%igen symptomatischen Stenosen 10-30%/Jahr.

Ca. 80% aller Schlaganfälle werden durch eine zerebrale Ischämie verursacht, hiervon 15-20% durch Stenosen oder Verschlüsse der extracraniellen, hirnversorgenden Gefäße. Unter Berücksichtigung zerebralen Ischämien im hinteren Kreislauf und zerebralen Embolien aus dem Aortenbogen kann 226.581 ischämisch bedingten Schlaganfällen (Statistisches Bundesamt 2009) für Deutschland von einer Anzahl von ca. 30.000 carotis-assoziierten Schlaganfällen/Jahr ausgegangen werden.

Hieraus folgt, dass einer effektiven Primär- und Sekundärprävention carotis-bedingter Schlaganfälle große Bedeutung zukommt. Aufgrund des enormen Wissenszuwachs in den Themengebieten Schlaganfallprävention, Carotisstenose und Atherosklerose, die aus einer Vielzahl randomisierter Studien, internationaler Leitlinien und Empfehlungen hervorgehen, ist die Erstellung einer deutschen, interdisziplinären, evidenzbasierten Leitlinie zur Diagnostik und Therapie extracranieller Carotisstenosen geboten.

3 GELTUNGSBEREICH UND ZWECK

3.1 ZIELSETZUNG

Zielsetzung der Leitlinie ist die Sicherstellung einer evidenz-basierten, flächendeckenden, optimalen Versorgung von Patienten mit extracraniellen Carotisstenosen in Deutschland. Die Leitlinie richtet sich dabei an alle in der Diagnostik, Therapie und Nachsorge Beteiligten aus dem ärztlichen und nicht-ärztlichen Bereich. Sie soll entsprechend der Definition von Leitlinien zur Entscheidungsfindung für Arzt und Patient bei diagnostischen und therapeutischen Maßnahmen dienen. Die Leitlinienempfehlungen verstehen sich als Orientierungshilfe im Sinne von Handlungs- und Entscheidungskorridore, von denen in begründeten Fällen abgewichen werden kann. Sämtliche Leitlinien der wissenschaftlichen medizinischen Fachgesellschaften sind für Ärzte rechtlich nicht bindend und haben daher weder haftungsbegründende noch haftungsbefreiende Wirkung. Was im juristischen Sinne den ärztlichen Standard in der konkreten Behandlung eines Patienten darstellt, kann nur im Einzelfall entschieden werden. Auch die vorliegende Leitlinie entbindet die Ärztin/den Arzt nicht von ihrer/seiner Verpflichtung, individuell unter Würdigung der Gesamtsituation des Patienten die adäquate Vorgehensweise zu prüfen.

Die vorliegende Leitlinie hat zum Ziel, dem Leser die für die Behandlung der extracraniellen Carotisstenose wichtigsten Erkenntnisse und Informationen aus den verschiedenen Spezialgebieten zusammenzutragen, um so eine Handlungshilfe im praktischen und klinischen Alltag zu geben.

Der Entwicklung der vorliegenden Leitlinie ging eine S1-Leitlinie zur extracraniellen Carotisstenose der Deutschen Gesellschaft für Gefäßchirurgie (DGG) im Jahre 1998, eine S1-Leitlinie der Deutschen Gesellschaft für Neurologie (DGN) und Deutschen Schlaganfall-Gesellschaft (DSG) zur Primär- und

Sekundärprävention der zerebralen Ischämie (zuletzt aktualisiert 2008) sowie eine S1-Leitlinie zur Diagnostik zerebrovaskulärer Erkrankungen der DGN (zuletzt aktualisiert 2008) voraus. Nach den Vorgaben der AWMF für S3-Leitlinien wurden die bisherigen Leitlinienempfehlungen auf der Basis systematischer Literaturrecherchen und Literaturbewertungen neu konzipiert und in einem interdisziplinären mehrstufigen Konsensus Prozess unter Moderation von Fr. Prof. Dr. I. Kopp (AWMF, Marburg) verabschiedet. Grundlage dieses Prozesses war das Regelwerk der AWMF (http://www.awmf-leitlinien.de) sowie die im Deutschen Instrument zur methodischen Leitlinien-Bewertung von AWMF und ÄZQ formulierten Anforderungen (DELBI, http://www.delbi.de).

Die Leitlinie nimmt insbesondere zu folgenden Fragen und Themenkreisen Stellung

- Epidemiologie, Risikofaktoren und Co-Morbidität
- Symptome und Diagnostik
- Konservative, operative und endovaskuläre Therapieverfahren
- Nachsorge, Rezidivtherapie und Lebensqualität
- Gesundheitsökonomische Aspekte (Erstellung in 2012/2013 geplant)

3.2 Anwendungshinweise

Die Leitlinie besteht aus folgenden Dokumenten:

- **Langversion** mit Empfehlungstexten und der diesen zugrunde liegenden wissenschaftlichen Evidenz, Hintergrundinformationen, ausführlichem Bericht zur Methodik sowie Dokumentationshilfen für die Qualitätssicherung
- **Kurzversion** mit den wichtigsten Empfehlungen und Tabellen in Kurzform (Erstellung im Herbst 2012)
- **Leitlinienreport**
- **Patientenleitlinie (Erstellung im Herbst 2012)**

3.3 Geltungsbereich

Die Leitlinie bezieht sich auf erwachsene Patienten jeglichen Alters mit nachgewiesener Stenose der extracraniellen A. carotis communis oder A. carotis interna. Sie gilt auch für Patienten, bei denen ein deutlich erhöhtes Risiko einer extracraniellen Carotisstenose besteht (z.B. Arteriosklerosepatienten mit Koronarer Herzerkrankung oder peripherer arterieller Verschlusskrankheit). Sie deckt alle Bereiche der Epidemiologie, Diagnostik, Therapie und Nachsorge von Patienten mit Carotisstenose sowie gesundheitsökonomische Aspekte ab. Sie gilt nicht für Kinder. Die Behandlung nicht-atheromatöser Ursachen extracranieller Carotisstenosen (Vaskulitis, Dissektion, Riesenzellarteriitis, Fibromuskuläre Dysplasie [FMD], postradiogene Stenosen) wird in jeweiliger Abgrenzung zu arteriosklerotischen Stenosen diskutiert, steht aber nicht im Fokus dieser Leitlinie.

3.4 Adressaten der Leitlinie

Die Leitlinie richtet sich an alle, die mit der Betreuung und Behandlung von Patienten mit extracranieller Carotisstenose befasst sind. Zum Adressatenkreis der Leitlinie gehören alle Ärztinnen

und nicht-ärztliche MitarbeiterInnen aus dem ambulanten und stationären Versorgungsbereich, sowie aus dem Bereich der Rehabilitationsmedizin, die Patienten mit extracraniellen Carotisstenosen betreuen oder behandeln. Die Leitlinie soll auch eine aktuelle Informationsquelle für alle im Gesundheitswesen tätige Institutionen sein. Die Leitlinie richtet sich aber auch an interessierte Patienten und deren Angehörige mit dem Ziel, den Kenntnisstand über das Krankheitsbild sowie die verschiedenen diagnostischen und therapeutischen Optionen zu verbessern und den Betroffenen eine partizipative Entscheidungsfindung zu ermöglichen. Dies soll durch eine laienverständliche Version (Patientenversion) unterstützt werden.

4 Beteiligung von Interessengruppen

4.1 Organisation, Finanzierung und redaktionelle Unabhängigkeit

Im Auftrag des Vorstands der Deutschen Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG) wurde im Jahr 2003 die Entwicklung einer interdisziplinären S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose unter der Federführung von Prof. Dr. H.-H. Eckstein initiiert. Die konstituierende Sitzung der interdisziplinären Steuergruppe fand am 12.7.2004 in Heidelberg statt. Die Steuergruppe führte zahlreiche Telefon-Konferenzen durch. Ein 1. Konsensus-Treffen fand am 13.9.2005 in Frankfurt unter der Moderation von Fr. Prof. Dr. I. Kopp/AWMF statt. Für die fünf verschiedenen Themenbereiche (Epidemiologie, Diagnostik, Therapie, Nachsorge, Ökonomie) wurden im Rahmen der Konsensus-Konferenz und eines anschließenden DELPHI-Verfahrens insgesamt 68 Schlüsselfragen konsentiert. Diese Fragen wurden in den Arbeitsgruppen schrittweise bearbeitet und im August 2009 in einer 2. Konsensus-Konferenz (Leitung Prof. I. Kopp) diskutiert und konsentiert. Zur Vereinfachung des Prozesses wurden die initial 68 Schlüsselfragen in 30 Schlüsselfragen zusammengefasst.

Die anfallenden Kosten der Leitlinienerstellung übernahm die Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG). Es bestanden keine finanziellen Unterstützungen außerhalb der DGG. Insbesondere gibt es keine Unterstützung durch die Industrie oder durch Kostenträger. Reisekosten für Mandatsträger wurden von den beteiligten Fachgesellschaften übernommen. Alle Mitglieder der Leitliniengruppe haben potentielle Interessenkonflikte schriftlich offen gelegt. Den Autoren und Teilnehmern am Konsensusverfahren ist zu danken für ihre ausschließlich ehrenamtliche Arbeit.

<u>Mitglieder der Steuergruppe:</u>

Fr. Prof. Dr. I. Kopp, AWMF, Marburg

Prof. Dr. H.-H. Eckstein, Gefäßchirurgie, Klinikum rechts der Isar der TU München (Sprecher)

Prof. Dr. A. Dörfler, Neuroradiologie, Univ. Klinikum Erlangen

Prof. Dr. J. Berkefeld, Neuroradiologie, Univ. Klinikum Frankfurt (seit 2011)

Prof. Dr. D. Sander, Fachbereich Neurologie, Benedictus Krankenhaus Tutzing

Prof. Dr. P. Ringleb, Neurologische Klinik, Univ. Klinikum Heidelberg

Prof. Dr. M. Storck, Gefäßchirurgie, Städt. Klinikum Karlsruhe

Prof. Dr. K. L. Schulte, Angiologie, Evang. Krankenhaus Königin Elisabeth Herzberge, Berlin (bis 2006)

Dr. med. R. Langhoff, Angiologie, Evang. Krankenhaus Königin Elisabeth Herzberge, Berlin (seit 2007)

Dr. H. Lawall, Angiologie, Klinikum Karlsbad-Langensteinbach

Prof. Dr. R. Diel, Leiter des Gesundheitsamtes Hamburg-Harburg

Dr. M. Hanke, Gefäßchirurgie, Klinikum rechts der Isar der TU München (Sekretär bis 31.3.2008)

Dr. A. Kühnl, Gefäßchirurgie, Klinikum rechts der Isar der TU München (Sekretär seit 1.4.2008)

4.2 Leitliniengruppe: Beteiligte Fachgesellschaften und Organisationen

Ende 2004/Anfang 2005 wurden insgesamt 26 medizinische Fachgesellschaften/Organisationen und drei Selbsthilfegruppen schriftlich zur Mitarbeit eingeladen. Insgesamt haben 20 Fachgesellschaften/Organisationen eigene Vertreter benannt und 6 Organisationen (inkl. aller Selbsthilfegruppen) kein Interesse an einer Mitarbeit bekundet. Im August 2009 wurden erneut die Vorstände aller beteiligten Fachgesellschaften, Organisationen und Selbsthilfegruppen angeschrieben und um offizielle Bestätigung bzw. Neubesetzung der Mandatsträger gebeten. Bis zum 27.09.2009 haben insgesamt 20 Fachgesellschaften/Organisationen geantwortet, die alle ihr Interesse an einer weiteren Mitarbeit signalisierten (Tabelle 1).

	Fachgesellschaft/Verband	Vertreter	Leitlinie verabschiedet (Datum)
1.	Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften (AWMF) , www.awmf-online.de	Prof. Dr. I. Kopp, Marburg *	-
2.	Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG) www.gefaesschirurgie.de	Prof. Dr. H.-H. Eckstein, München * Prof. Dr. M. Storck, Karlsruhe * Dr. H. Niedermeier München als Sekretäre der Steuergruppe: Dr. M. Hanke, München (bis 2007) Dr. A. Kühnl , München, ab 2008 *	16.6.2012
3.	Deutsche Gesellschaft für Neurologie DGN www.dgn.org	Prof. Dr. P. Ringleb, Heidelberg * Prof. Dr. D. Sander, Tutzing* Prof. Dr. M. Hennerici, Mannheim	02.07.2012
4.	Deutsche Schlaganfallgesellschaft (inkl. Deutsche Schlaganfallhilfe, DSG)	Prof. Dr. K. Nabavi, Berlin Prof. Dr. R. Stingele, Kiel Prof. Dr. P. Ringleb, Heidelberg	25.06.2012
5.	Deutsche Gesellschaft für Neuroradiologie (DGNR) www.neuroradiologie.de	Prof. Dr. A. Dörfler, Erlangen * Prof. Dr. J. Berkefeld, Frankfurt * Prof. Dr. O. Jansen, Kiel	25.06.2012
6.	Deutsche Röntgen-Gesellschaft (DRG) www.drg.de	Prof. Dr. med. W. Gross-Fengels, Harburg Prof. Dr. D. Vorwerk, Ingolstadt Prof. Dr. P. Huppert, Darmstadt	25.06.2012
7.	Deutsche Gesellschaft für Interventionelle Radiologie (DEGIR), www.degir.de/	Prof. Dr. J. Tacke, Passau	11.06.2012
8.	Deutsche Gesellschaft für Angiologie /Gesellschaft für Gefäßmedizin (DGA) www.dga-online.org	Dr. H. Lawall, Langensteinbach * Prof. Dr. K.L. Schulte, Berlin (bis 2007) * Dr. R. Langhoff, Berlin (seit 2008) * Prof. Dr. U. Hoffmann, München	21.06.2012
9.	Deutsche Gesellschaft für Kardiologie (DGK) www.dgk.org	Prof. Dr. H. Mudra, München	02.07.2012
10.	Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM), Sektion Neurologie	Prof. Dr. C. Arning, Hamburg PD Dr. M.W. Görtler, Magdeburg	10.06.2012

11.	Deutsche Diabetes Gesellschaft DDG www.deutsche-diabetes-gesellschaft.de	Prof. Dr. O. Schnell, München-Neuherberg	26.06.2012
12.	Deutsche Gesellschaft für Geriatrie (DGG), www.dggeriatrie.de	Dr. Ch. Ploenes, Düsseldorf Dr. H. Görtz, Lingen	29.6.2012
13.	Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie (DGTHG)	Prof. Dr. G. Walterbusch, Dortmund Dr. K. P. Walluschek, Flensburg	04.07.2012
14.	Deutsche Gesellschaft für Neurochirurgie (DGNC)	Prof. Dr. Antoniadis, Ulm Prof. Dr. K. Schwerdtfeger, Homburg/Saar	03.07.2012
15.	Deutsche Gesellschaft für Chirurgie (DGCh), www.dgch.de	Prof. Dr. E. Neugebauer, Köln Dr. I. Flessenkämper, Berlin	7.6.2012
16.	Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI) www.dgai.de	Dr. R. Litz, Dresden	05.07.2012
17.	Deutsche Gefäßliga e.V., www.deutsche-gefaessliga.	Prof. Dr. C. Diehm, Langensteinbach	30.6.2012
18.	Deutscher Verband der Ergotherapeuten	Sabine George, Karlsbad Andreas Hörstgen, Karlsbad	21.6.2012
19.	Deutscher Verband für Physiotherapie – Zentralverband der Physiotherapeuten/ Krankengymnasten (ZVK) e.V.	Andreas Fründ, Petershagen	18.06.2012
20.	Dachverband der Österreichischen Gefäßmedizinischen Gesellschaften	Prof. Dr. G. Fraedrich, Innsbruck Dr. B. Rantner, Innsbruck	11.6.2012

Tabelle 1: Liste aller beteiligten Fachgesellschaften/Verbände und deren Vertreter an der Erstellung der S3 Leitlinie "Carotisstenose“

Fachgesellschaften/Organisationen, die keine Vertreter benannt haben
Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)
Deutsche Gesellschaft für Prävention und Rehabilitation von Herz-Kreislauferkrankungen (DGPR)
Deutscher Pflegerat
Dachverband Deutsche Selbsthilfegruppen (Gießen)
Bayerischer Verband Schlaganfall-Betroffener München
Deutsche Schlaganfallhilfe (Bertelsmann, Liz Mohn), über DSG vertreten

Folgende weitere Fachgesellschaften und Organisationen wurden über das Vorhaben informiert:

- Deutsche Gesellschaft für Innere Medizin (vertreten durch die Deutsche Gesellschaft für Angiologie)
- Bundesgeschäftsstelle Qualitätssicherung BQS, Düsseldorf
- Ärztliches Zentrum für Qualität in der Medizin ÄZQ
- Wissenschaftliches Institut der AOK WIDO
- Deutscher Physiotherapeutenverband

Als weitere Mitarbeiter an der Leitlinie wurden folgende Personen benannt:

Für den Bereich Gesundheitsökonomie/Public Health

- PD Dr. R. Diel, Leiter des Gesundheitsamts Hamburg-Harburg

5 METHODOLOGISCHE EXAKTHEIT DER LEITLINIENENTWICKLUNG

5.1 FESTLEGUNG DER SCHLÜSSELFRAGEN FÜR DIE LITERATURRECHERCHE

Das erste Konsensus-Treffen von insgesamt 28 Vertretern der teilnehmenden Fachgesellschaften und Organisationen fand unter der Moderation von Fr. Prof. Dr. I. Kopp (AWMF) am 13.9.2005 in Frankfurt statt. Hier wurde zunächst mit 22/28 Stimmen der Titel der S3 Leitlinie konsentiert. Für die von der Steuergruppe festgelegten Arbeitsgruppen wurden Schlüsselfragen (SF) diskutiert und konsentiert. Für die Gruppen 3-5 (Therapie, Nachsorge, Ökonomie) erfolgte die Abstimmung über die Schlüsselfragen schriftlich anhand eines Fragebogens (Delphi-Verfahren). Die insgesamt 68 Schlüsselfragen und die Ergebnisse der Abstimmung sind in den Tabellen 1-5 hinterlegt. Einzelne Schüsselfragen wurden auf Wunsch der Steuergruppe hinzugefügt. Im September 2009 wurden die initial 68 SF zu 30 SF zusammengefasst.

5.2 RECHERCHE UND AUSWAHL DER WISSENSCHAFTLICHEN BELEGE (EVIDENZBASIERUNG)

Nach den AWMF-Vorgaben für eine S3-Leitlinie wurden auf der ersten Konsensus-Konferenz klinische Schlüsselfragen konsentiert und im Anschluss gezielte Literaturrecherchen und Literaturbewertungen nach folgendem Algorithmus durchgeführt:

Zunächst erfolgte unter Mitarbeit von Dr. rer. nat. H. Knüttel von der Universität Regensburg eine systematische Literaturrecherche beim DIMDI. Die Recherche umfasste dabei einen Zeitraum vom 01.01.1990 bis zum 6.12.2011. Es wurde folgende Datenbanken mit einbezogen:

1. Medline/Alert
2. Embase/Alert
3. SciSearch
4. NHS Economic (NHSEED)
5. Elsevier Biobase
6. Verlagsdatenbanken: Thieme, Springer, Kluwer, Karger, LWW, DAEB, GMS

Die systematische Suche nach Primärliteratur, deren Algorithmus in Tabelle 13 aufgeführt ist erbrachte für die jeweiligen Gruppen folgende Treffermengen:

Gruppe	Treffer
A: Ausgangsmenge	>20.000
B: Epidemiologie	433
C: Diagnostik	924
D: Therapie	2316

E1: Nachsorge	32
E2: Rehabilitation	42
F: Kosten	154
G: Sonstige	653

- Zunächst erfolgte eine systematische Recherche nach nationalen und internationalen Leitlinien in der Datenbank des Guidelines International Network (http://www.g-i-n.net/, bis 30.Juni 2009) unter den Suchbegriffen „carotid“ und „stroke“. Im Verlauf wurden weitere internationale Leitlinien bis zum 30.6.2011 berücksichtigt. Die Leitlinien wurden in Leitlinien/Empfehlungen zur CEA und zu CAS (Tabelle 8) und Leitlinien zur Primärprävention, Diagnostik, Therapie und Nachsorge der zerebralen Ischämie (Tab. 9) unterteilt. Die aktuellsten Leitlinien der Jahre 2006 bis 2011 wurden separat zusammengestellt (Tab. 10).
- Die Auswahl möglicher Referenzleitlinien erfolgte auf der Grundlage der im Instrument DELBI zusammengefassten methodischen Qualitätskriterien. Besonderer Wert wurde dabei auf eine systematische Entwicklung und nachvollziehbare Evidenzbasierung der abgegebenen Empfehlungen gelegt. Hierzu wurden alle Leitlinien der Jahre 2006-2009 zur operativen, endovaskulären oder konservativen Therapie der extracraniellen Carotisstenose und/oder zur Therapie oder Prävention der zerebralen Ischämie systematisch entsprechend der DELBI-Domäne 3 durch 5 Gutachter bewertet. Hierbei musste ein Summenscore von mindestens 50% der maximal möglichen Punkte erzielt werden (Tabelle 11). Unter Berücksichtigung dieser Bewertung wurden alle Leitlinien in einem ersten Schritt hinsichtlich der Beantwortung der klinischen Fragestellungen der Leitliniengruppen analysiert (Schlüsselfragen). Die bis zum 30.6.2011 zusätzlich berücksichtigten Leitlinien wurden in der Steuergruppe gesichtet und für die Erstellung der S3-Leilinie wegen der Berücksichtigung neuer Daten als essentiell erachtet.
- Im zweiten Schritt wurden alle verfügbaren Cochrane Reviews zum Thema CEA, CAS, konservative Therapie bei Carotisstenosen und bei der zerebralen Ischämie erfasst (Tabelle 12).
- Basierend auf den Treffern der Gruppen B-G erfolgte eine systematische Recherche nach systematischen Reviews oder Metaanalysen unter Verwendung der Suchbegriffe „system?“ und „review?“ oder „meta?“

  Es ergaben sich folgende Treffermengen. Die PDFs der Studien wurden allen Mitarbeitern an der Leitlinie elektronisch zur Bewertung zugesandt.

Gruppe	**Treffer an systematischen Reviews oder Metaanalysen**
B: Epidemiologie	33
C: Diagnostik	52
D: Therapie	122
E1/2: Nachsorge/Rehabilitation	8
F: Kosten	2

G: Sonstige	91

- Alle ermittelten Systematischen Reviews (inkl. der Cochrane Reviews) wurden ebenfalls einem Bewertungsalgorithmus unterzogen (Tabelle 15) und danach hinsichtlich der Beantwortung der noch nicht oder unzureichend beantworteten Schlüsselfragen analysiert.
- Für die nun noch unzureichend oder gar nicht beantworteten Schlüsselfragen wurden Therapie- und Diagnosestudien aus der Primärliteratur ebenfalls einem standardisierten Bewertungsalgorithmus unterzogen (Tabelle 14 und 16) und dann zur Beantwortung der Schlüsselfragen herangezogen. Einschlusskriterien für die Bewertung von Primärliteratur waren demnach Themenrelevanz und Nicht-Beantwortbarkeit der Schlüsselfrage aufgrund der eingeschlossenen Leitlinien und Systematischen Reviews.
- Die Zuordnung der Evidenzklasse erfolgte für einzelne Diagnose- und Therapiestudien sowie für die Beantwortung der Schlüsselfragen entsprechend der Klassifizierung der Evidenzgrade des Oxford Center of Evidence-based medicine (Tabelle 17-18, 2001).
- alle Schlüsselfragen wurden in Evidenztabellen hinterlegt.

5.3 Formulierung der Empfehlungen und Konsensfindung

Der Text der Leitlinie wurde auf der Basis der Synopse internationaler Leitlinienempfehlungen und der Ergebnisse der eigenen Literaturrecherche und –bewertung erstellt. Bei der Darstellung der Inhalte wurde zwischen Kernaussagen/Schlüsselempfehlungen (in Tabellen), deren Herleitung (Fließtext, Quellenangaben) und der Darstellung der Primärliteratur (Evidenztabellen) unterschieden. Bei den Empfehlungen wird zwischen drei Empfehlungsgraden unterschieden, deren unterschiedliche Qualität bzw. Härte durch die Formulierung ("soll", "sollte", "kann") und Pfeilsymbole ausgedrückt wird. Empfehlungen *gegen* eine Intervention werden entsprechend sprachlich ausgedrückt („soll nicht“, „sollte nicht“) bei Verwendung der gleichen Symbole. In der Regel bestimmt die Qualität der Evidenz (Evidenzstärke) den Empfehlungsgrad. Dies bedeutet, dass eine Empfehlung auf Basis einer mittleren Evidenzstärke in der Regel mit einem mittleren Empfehlungsgrad verknüpft ist:

Studienqualität	**Evidenzstärke**	**Empfehlung**	**Beschreibung**	**Symbol**
Systematische Übersichtsarbeit (Meta-Analyse) oder RCT (Therapie) oder Kohortenstudien (Risikofaktoren, Diagnostik) von hoher Qualität	hoch	„soll“ “soll nicht“	Starke Empfehlung	↑↑ ↓↓
RCT oder Kohortenstudien von eingeschränkter Qualität	Mäßig	„Sollte“ „sollte nicht“	Empfehlung	↑ ↓
RCT oder Kohortenstudien von schlechter Qualität, alle anderen Studiendesigns, Expertenmeinung	schwach	„kann“	Empfehlung offen	↔
Unzureichende Studienlage	keine	„good clinical practise“, klinischer Konsens		GCP

Tabelle 2: Graduierung der Evidenz- und Empfehlungsstärke

Die aufgeführten Empfehlungen richten sich nach der jeweils verfügbaren Evidenz. Empfehlungen mit fehlender oder lückenhafter Evidenz wurden als Ergebnis der interdisziplinären Diskussionen als Konsensusempfehlungen aufgeführt (GCP = good clinical practise, klinischer Konsens). Die Empfehlungsgrade orientieren sich an den Vorgaben des Oxford Center of evidence-based medicine und des Europarates 2001.

Bei der Festlegung dieser Empfehlungsgrade im formalen Konsensusverfahren wurden neben der Güte der zugrundeliegenden Evidenz auch die Direktheit/externe Validität und Homogenität der Gesamtevidenz, die Nutzen-Risiko-Abwägung, die klinische Relevanz der Effektivitätsmaße der Studien, die Umsetzbarkeit in der Versorgungsrealität und ethische Verpflichtungen mitbetrachtet. Auf Grund der genannten Aspekte wurde in Einzelfällen eine Auf- oder Abwertung des Empfehlungsgrades gegenüber der Evidenzstärke vorgenommen. Die jeweiligen Begründungen für solche Abweichungen sind dem Hintergrundtext zu den Empfehlungen zu entnehmen.

Eine erste Fassung der vorliegenden Leitlinie wurde im Rahmen eines ersten formalen Konsensusverfahrens (Nominaler Gruppenprozess nach Black N et al. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy 1999; 4: 236-48.61) im September 2005 diskutiert. Aufgrund laufender randomisierter Studien zum Vergleich der CEA mit der endovaskulären Therapie (CAS) und der Notwendigkeit der umfassenden Sichtung internationaler Leitlinien, Reviews und Originalia wurden die Arbeitsgruppen zunächst beauftragt, schrittweise die Schlüsselfragen zu beantworten. Zwischenzeitlich erfolgte die Aktualisierung der Literatur bis zum 30.6.2009 bzw. zum 30.6.2011. Ergebnisse (Vorträge, Web-Präsentationen) aus laufenden bzw. noch nicht publizierten randomisierten Studien wurden nach Abstimmung in der Steuergruppe ebenfalls berücksichtigt. Nach Fertigstellung des Fließtextes und der einzelnen Evidenztabellen erfolgte die Diskussion des Evidenzberichts, sowie der Kernaussagen und Empfehlungen in weiteren Arbeitstreffen der Leitliniengruppe am 4.8., 5.10., 16.11. und 16.12.2009 in Frankfurt a.M.. Weitere formale Konsensusverfahren erfolgten am 21./22.03.2010 und am 02.09.2010 in München. Im Jahr 2011 wurden dann die offenen Empfehlungen in einem DELPHI-Verfahren in insgesamt 6 Runden konsentiert.

Der Ablauf der Konsensusverfahren erfolgte in mehreren Schritten:

- Stille Durchsicht des zuvor mitgeteilten Leitlinienmanuskripts (Gesamtentwurf)
- Schriftliche oder mündliche Aussagen der einzelnen Fachvertreter zu den Kernaussagen, Schlüsselempfehlungen und der vorgeschlagenen Graduierung;
- Registrierung der Stellungnahmen und Alternativvorschläge aller Teilnehmer zu allen Aussagen und Empfehlungen im Einzelumlaufverfahren durch die Moderatorin, dabei Rednerbeiträge nur zur Klarstellung; Projektion per Beamer
- Vorabstimmung aller Empfehlungen und Empfehlungsgrade und der genannten Alternativen;
- Diskussion der Punkte, für die im ersten Durchgang kein Konsens erzielt werden konnte
- Endgültige Abstimmung.

Alle Empfehlungen wurden im „Konsens“ verabschiedet (Zustimmung von >75% der teilnehmenden Fachgesellschaften/-verbände) die Mehrzahl aller Empfehlungen sogar mit "starkem Konsens" (Zustimmung von >95% der der teilnehmenden Fachgesellschaften/-verbände). Somit repräsentiert

die vorliegende Textfassung der S3-Leitlinie Carotisstenose die Ansicht aller beteiligten Fachgesellschaften. Die Abstimmungs- und Ergebnisprotokolle der Sitzungen können über das Leitliniensekretariat angefordert und eingesehen werden.

5.4 KONSENTIERUNG VON QUALITÄTSZIELEN UND QUALITÄTSINDIKATOREN (QI)

Qualitätsindikatoren (QI) liefern Informationen zur Akzeptanz und Umsetzung der Leitlinie in Klinik und Praxis und zur Auswirkung der Leitlinienanwendung auf die Versorgungsqualität. Ihre Erfassung dient der Identifikation von Verbesserungspotentialen sowohl für die Patientenversorgung als auch für die Fortschreibung der Leitlinie.

In Deutschland wurde über viele Jahre eine verpflichtende Dokumentation/Qualitätssicherung über die Bundesgeschäftsstelle Qualitätssicherung (BQS, Düsseldorf) organisiert und publiziert. Seit 2009 hat das AQUA Institut diese Aufgabe übernommen, im Jahr 2012 soll zudem ein Qualitätssicherungsprojekt zu CAS etabliert werden. Die Erfassung von Qualitätsindikatoren bei der konservativen, operativen und endovaskulären Therapie ist sinnvoll und möglich und sollte in die 2.Auflage dieser S3-Leitlinie implementiert werden.

6 VERABSCHIEDUNG DER LEITLINIE

Die endgültige Abstimmung des Gesamtmanuskripts durch die Leitliniengruppe erfolgte im Umlaufverfahren. Die Beschlussfassung über die Berücksichtigung begründeter Änderungswünsche erfolgte im Rahmen einer Telefonkonferenz der Steuergruppe. In einem zweiten Schritt wurde die von der Steuergruppe verabschiedete Version der gesamten Leitliniengruppe zur Diskussion zur Verfügung gestellt. Die Berücksichtigung begründeter Änderungswünsche erfolgte im Umlaufverfahren.

Abschließend wurde die Leitlinie formal den Vorständen der mitherausgebenden Fachgesellschaften/Organisationen zur Verabschiedung und Autorisierung im Dezember 2011 vorgelegt. Mit Schreiben vom 23.1.2012 teilten die Präsidenten der Deutschen Röntgengesellschaft und der Deutschen Gesellschaften für Neuroradiologie, Interventionelle Radiologie, Angiologie und Kardiologie mit, dass diese fünf Fachgesellschaften dem Entwurf der Leitlinie vom Dezember 2011 nicht zustimmen können. Mit Schreiben vom 20.3.2012 wurden der AWMF, der Steuergruppe und der Leitlinienkommission Änderungsvorschläge (Empfehlungen, Hintergrundtext) übermittelt. Auf Basis dieser Vorschläge hat die Steuergruppe in zwei Telefonkonferenzen am 26.3.2012 und 4.4.2012 die bisherigen Empfehlungen überarbeitet und einstimmig konsentiert. Die geänderten Empfehlungen wurden den Präsidenten der o.g. Fachgesellschaften mit der Bitte um prinzipielle Zustimmung übermittelt. Am 4. Mai 2012 wurden die revidierten Empfehlungen erneut den Vertretern der beteiligten Fachgesellschaften (Leitlinienkommission) zur Zustimmung vorgelegt. Nach erfolgter Konsentierung erfolgte dann im zweiten Schritt die Überarbeitung des Hintergrundtextes, der in revidierter Form am 30.Mai 2012 von der Steuergruppe einstimmig konsentiert wurde. Der gesamte Leitlinientext (Empfehlungen, Hintergrundtext, Methodenreport) wurde abschließend am 6.6.2012 allen Fachgesellschaften zur erneuten Abstimmung vorgelegt. Bis zum 11.Juli 2012 haben alle 19 beteiligten Fachgesellschaften/Verbände ihre Zustimmung zur am 6.6.2012 vorgelegten Version erklärt (Tabelle 1). Einige wenige redaktionelle Änderungen wurden auf Wunsch der DGAI zuvor in Absprache mit Fr. Prof. Kopp und der Steuergruppe in den Hintergrundtext eingearbeitet.

Die finale Langversion dieser Leitlinie wurde danach der AWMF zur Publikation auf der AWMF-Homepage zur Verfügung gestellt.

7 VERBREITUNG, IMPLEMENTIERUNG UND EVALUIERUNG

Die S3-Leitlinie „**Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose“** wird als Langversion einschließlich Leitlinienreport, Kurzversion und Patientenversion kostenfrei über die Internetseite der AWMF zur Verfügung gestellt. Darüber hinaus wird sie in folgenden Formaten publiziert:

- Langversion als Supplement einer Zeitschrift mit Peer-review-Verfahren (GEFAESSCHIRURGIE)
- Kurzversion im Deutschen Ärzteblatt
- Deutschsprachige und englische Kurzversion fachspezifisch in den entsprechenden nationalen und internationalen Organen der Fachgesellschaften
- Kurzversion in englischer Sprache im Internet (Guidelines International Network, www.g-i-n.net)
- Geplant ist die Publikation einer kurzgefassten Patientenversion.
- Geplant ist außerdem eine englische Übersetzung der Langversion

Die geplanten Publikationen sind Bestandteil der Implementierungsstrategie. Es wird explizit angeregt, die Leitlinie unter Bezugnahme auf die genannten Publikationen in die Praxis zu überführen. Hierzu sind z.B. zu empfehlen:

- Einbindung der Leitlinienempfehlungen in einrichtungsinterne Behandlungspfade
- Berücksichtigung der Leitlinie in lokalen Patienteninformationen/Broschüren

Die Verbreitung und Implementierung wird von der Leitliniensteuergruppe aktiv unterstützt durch:

- Pressemeldung an den Informationsdienst Wissenschaft (idw-online.de)
- Vorstellung der Leitlinie im Rahmen der Fachkongresse der beteiligten Gesellschaften/ Organisationen
- Unterstützung der Erstellung von Materialien für die kontinuierliche Fort- und Weiterbildung (CME-Beiträge entsprechend der Anforderungen der Landesärztekammern)

Mit diesen Empfehlungen wird eine Verknüpfung der Leitlinie mit zertifizierten Fortbildungsmaßnahmen und Qualitätsmanagementsystemen angestrebt. Die begleitende Evaluierung der Leitlinienimplementierung ist ein wichtiges Anliegen. Insbesondere für die Implementierung der Qualitätsziele und die Evaluation der Versorgungswirklichkeit wird eine enge Abstimmung mit der Bundesgeschäftsstelle Qualitätssicherung (BQS) und den Qualitätssicherungsorganen der Landesärztekammern und der Ärztekammern angestrebt.

8 GÜLTIGKEITSDAUER UND AKTUALISIERUNGSVERFAHREN

Die Leitlinie wird laufend aktualisiert. Spätestens 3 Jahre nach der online-Publikation dieser Leitlinie bei der AWMF wird eine Aktualisierung erscheinen. Verantwortlich für das Aktualisierungsverfahren sind die Koordinatoren. Neu erscheinende wissenschaftliche Erkenntnisse werden von der Leitliniengruppe beobachtet und sich hieraus ergebende zwischenzeitliche Neuerungen/Korrekturen als Addendum publiziert (Internetversion, Fachzeitschriften). Gültig ist nur die jeweils neueste Version gemäß dem AWMF-Register. Kommentierungen und Hinweise für den Aktualisierungsprozess aus der Praxis sind ausdrücklich erwünscht und können an das Leitliniensekretariat gerichtet werden.

09.07.2015: Gültigkeit der Leitlinie auf Antrag der Steuergruppe nach Überprüfung verlängert bis 07.08.2017

9 DARLEGUNG UND UMGANG MIT INTERESSENKONFLIKTEN

Die Mitglieder der Leitliniengruppe legten eine schriftliche Erklärung zu eventuell bestehenden Interessenskonflikten, vor allem gegenüber der Industrie, vor. Erhoben wurden die Konflikterklärungen mit dem zum Zeitpunkt der Erstellung der Leitlinie gültigen Formblatt der AWMF. Die Tabellen 19 und 20 zeigen eine tabellarische Zusammenfassung dieser Konflikterklärungen. Die Inhalte der Interessenkonflikterklärungen können bei begründetem Antrag im Sekretariat des Leitlinienkoordinators eingesehen werden.

Im Rahmen der Konsensustreffen wurden alle Teilnehmer über die Empfehlungen der AWMF zum Umgang mit Interessenkonflikten informiert. Die Teilnehmer wurden gebeten, sich von der Abstimmung für eine bestimmte Fragestellung zu enthalten, sofern für diese ein relevanter Interessenkonflikt vermutet wurde. Im Übrigen wurde die die multidisziplinäre Zusammensetzung der Leitliniengruppe auf Ausgewogenheit der Interessen geachtet sowie durch die Evidenzbasierung und das formalisierte Konsensusverfahren potentiellen Verzerrungen entgegengewirkt.

10 ANHANG: WEITERE TABELLEN

Tabelle 3-7: Schlüsselfragen (1.Kons.-Konferenz 09/2005, Modifikation 09/2009)

10.1 TABELLE 3: SCHLÜSSELFRAGEN GRUPPE 1 - -EPIDEMIOLOGIE, RISIKOFAKTOREN UND CO-MORBIDITÄT

Modifizierte Schlüsselfragen (SF)		SF alt	Bearbeiter
1.	Wie hoch ist die Prävalenz extracranieller Carotisstenosen in Deutschland?	1.1	Sander
2.	Wie hoch sind Prävalenz und Inzidenz der carotis-assoziierten zerebralen Ischämie in Deutschland?	1.2	Sander
3.	Welche klinischen und morphologischen Faktoren beeinflussen das Auftreten einer carotis-bedingten zerebralen Ischämie bei bislang asymptomatischer Carotisstenose?	1.6	Sander
4.	Welche klinischen und morphologischen Faktoren beeinflussen das Auftreten und die Prognose einer carotis-bedingten zerebralen Ischämie bei symptomatischer Stenose bzw. stattgehabter carotis-bedingter zerebraler Ischämie (Frage 1.4, 1.5, 1.7)?	1.4, 1.5, 1.7	Sander
5.	Wie häufig kommt es zu einem Verschluss der extracraniellen A.carotis interna und wie hoch ist das Schlaganfallrisiko eines akuten/chronischen Carotisverschluss?	1.8, 1.9	Sander

1.Konsensus-Konferenz 09/2005

Prävalenz und Inzidenz der Carotisstenose und carotis-assoziierter Schlaganfälle		Abstimmung
1.1	Wie viele Carotisstenosen gibt es in Deutschland derzeit?	28/28
1.2	Wie hoch ist die Prävalenz und Inzidenz von carotis-assoziierten Schlaganfällen derzeit und im Trend der letzten Jahre?	28/28
1.3	Wie ist die Prognose der carotis-assoziierten zerebralen Ischämie/Schlaganfälle?	28/28
1.4	Welchen Einfluss haben Lebensalter und Geschlecht?	28/28
1.5	Welchen Einfluss hat die ethnische Herkunft?	26/28
Anmerkungen: Prävalenz und Inzidenz der Carotisstenosen, Bezugs- und Zielpopulation angeben (pro 100.000 Einwohner), Vergleich zu anderen Volkskrankheiten ziehen		
Risikofaktoren und Komorbiditäten		
1.6	Gibt es klinische Faktoren/Begleiterkrankungen, die bei asymptomatischen Carotisstenose das Schlaganfall-Ereignisrisiko im natürlichen Verlauf erhöhen oder reduzieren?	28/28
1.7	Gibt es klinische Faktoren/Begleiterkrankungen, die bei symptomatischen Stenosen das Schlaganfallrisiko im natürlichen Verlauf erhöhen oder reduzieren?	28/28
Anmerkungen: Wunsch des Expertenkreises aus dem Clearingverfahren: Darstellung der RF (z.B. Diabetes mellitus) möglichst geordnet, z.B. nicht modifizierbar, nachgewiesen modifizierbar, potentiell modifizierbar		
Natürlicher Verlauf und Prognose		
1.8	Wie hoch ist das Verschlussrisiko von Carotisstenosen?	28/28
1.9	Wie hoch ist das Schlaganfallrisiko bei chronischem Carotisverschluss? (Anm.: Schlaganfallätiologie differenzierbar? Rolle bilateraler Prozesse?)	28/28
Anmerkungen: Hinweis Prognose: Achten auf Altersgruppen, Geschlecht ethnische Herkunft, auch wenn bei heutiger Datenlage vermutlich keine Handlungsänderung, Jährliches Schlaganfallrisiko		

10.2 TABELLE 4: SCHLÜSSELFRAGEN GRUPPE 2 – SYMPTOME UND DIAGNOSTIK

Modifizierte Schlüsselfragen (SF)	SF alt	Bearbeiter
Definition der asymptomatischen und symptomatischen Carotisstenose	2.1-2.5	Ringleb
Welche Skalen sind zur Beurteilung des Schweregrades einer zerebralen Ischämie notwendig, geeignet und zu empfehlen? (NIHSS, Rankin)	2.6	Ringleb
Welche apparativen Untersuchungsverfahren sind valide zur Diagnose und zur Verlaufsbeobachtung einer extracraniellen Carotisstenose?	2.6-2.8, 2.10- 2.15, 2.18,2.19	Ringleb
Sind Screening Untersuchungen (von Risikogruppen) sinnvoll?	2.9, 2.16	Ringleb
Welche prätherapeutische Diagnostik ist notwendig vor geplanter OP oder Intervention?	2.17	Ringleb

1.Konsensus-Konferenz 09/2005

Definition asymptomatische / symptomatische Stenose		Abstimmung
2.1.	Definition der asymptomatischen Carotisstenose; welche Symptome sind carotis-assoziiert und welche nicht?	28/28
2.2.	Definition der symptomatischen Carotisstenose, welche Symptome sind carotis-assoziiert und welche nicht?	28/28
2.3.	Nach welchen Kriterien sollte eine Differenzierung und zwischen asymptomatischen und symptomatischen Stenosen erfolgen und wer übernimmt die klinische Differenzierung?	28/28
2.4.	Ist es notwendig, bei symptomatischen Stenosen die Pathogenese der Ischämie zu klären (embolisch vs. hämodynamisch), z.B. im Blick auf die postoperative Überwachung (Reperfusionstrauma)?	19/28
2.5	Welche Bedeutung hat der Zeitraum bzw. das zeitliche Intervall zum klinischen Ereignis, um die Stenose als asymptomatisch oder symptomatisch einzuordnen?	28/28

Anmerkungen:

- Symptomatik muss definiert werden, welche Symptome sind carotis-assoziiert und welche nicht
- Welche Rolle spielt der Zeitraum des Eintretens eines klinischen Ereignisses, um die Stenose als asymptomatisch oder symptomatisch einzuordnen?

Stadieneinteilung Carotisstenose / Stadien der zerebralen Ischämie		
2.6	Welche Skalen sind zur Beurteilung des Schweregrades einer zerebralen Ischämie notwendig, geeignet und zu empfehlen? (NIHSS, Rankin)	28/28

Anmerkungen:

- Angesprochen und bewertet sollten sein: Stadieneinteilung nach Vollmar, Skalen wie NIHSS, Rankin, Dokumentation der Ischämieursache nach standardisierten Klassifikationssystemen gemäß pathologischer (Infarkt, Thrombose, Blutung) und ätiologischer Subtypen (TOAST),
- Klinische Symptomatik vs Nachweis struktureller Hirnläsionen
- Angaben zur Validität und Reliabilität der Skalen

Diagnostik		
2.7	Welchen Stellenwert hat die Auskultation der A. Carotis?	21/28
2.8	Welchen Stellenwert haben die apparativen Verfahren: Neurosonologie/Duplex-Sonographie, CCT, CTA, MRT, MRA, DWI, PWI, Angiographie (DSA), iv DSA? Wann ist welches Verfahren indiziert? Anm.: Sensitivität, Spezifität, Risiko	28/28

Anmerkungen:

Apparative Diagnostik: Angaben zu Sensitivität, Spezifität, Risiken; spezifischen Indikationen zur Durchführung der einzelnen Verfahren

Lebensqualitätsdiagnostik: Angaben zu Spezifität, Reliabilität der Fragebögen, Änderungssensitivität

2.9	Sind Screening Untersuchungen (von Risikogruppen) sinnvoll?	28/28

2.10	Wann ist der Ausschluss einer Tandemkonstellation erforderlich?	27/28
2.11	Asymptomatische Stenose: wie ist der diagnostische Stellenwert von Tests zur Erfassung der Vasomotorenreserve und zur Mikroembolusdetektion?	27/28
2.12	Mit welchen Verfahren, bzw. mit welcher Kombination einzelner Verfahren kann die Diagnose gesichert werden?	28/28
2.13	Wie ist eine Stenose quantifizierbar in Hinblick auf Ausmaß und Progredienz?	26/26
2.14	Wie ist vorzugehen, wenn eine Kombination von Verfahren verschiedene Ergebnisse erbracht hat?	28/28
2.15	Welches Verfahren stellt die „letzte Instanz“ dar (diagnostischer Gold-Standard)?	28/28

Anmerkungen:

Ergänzende Zielkriterien zur Bewertung der diagnostischen Verfahren: Eignung zur Beurteilung von Stenosegrad, Plaquemorphologie, Kollateralkreisläufen, Tandemstenosen

Reicht Ultraschall als alleiniges Verfahren aus? Ist eine Angiographie sinnvoll, wenn man unmittelbar vor Durchführung eines endovaskulären Manövers steht?

Wunsch des Expertenkreises Clearingverfahren: Wie können die Befunde verschiedener Messmethoden zur Beurteilung des Stenosegrads miteinander verglichen werden?

Diagnostische Verfahren zur Verlaufsbeobachtung asymptomatischer Stenosen

2.16	Mit welchen Verfahren und in welchen Intervallen sollten asymptomatische Stenosen im Verlauf beobachtet werden?	26/26

Anmerkungen: Verlaufsdokumentation: Definition von Progredienz; was ist „rasch progredient“?

Diagnostische Verfahren vor Revaskularisation

2.17	Welche prätherapeutische Diagnostik ist ausreichend (auch Umgebungsdiagnostik, EKG etc….), welche notwendig für den Chirurgen und den Interventionalisten?	26/26

Anmerkungen: Hinweis Zielkriterien der Diagnostik aus Sicht des Interventionalisten sind folgende Informationen vor Revaskularisierung wichtig:

- Anatomie des Aortenbogens
- Gesamte Darstellung des Carotiskreislaufs
- Schwere und Morphologie der Stenose
- Projektion, in der die Stenose am ausgeprägtesten ist
- Informationen über den Hirnkreislauf (Anatomische Besonderheiten, zusätzliche Stenosen, Kollateralsituation)
- Ausgangsbefund Hirn, um einen Vergleich nach durchgeführter Revaskularisierung in Händen zu haben (z.B. wichtig bei Auftreten von Komplikationen)

Qualitätsindikatoren der Diagnosekette

2.18	Wie kann die Durchführungsqualität der Doppler-/Duplexsonographie mit dem Ziel der Feststellung des Stenosegrades sichergestellt werden?	25/25
2.19	Wie kann die Durchführungs-qualität der radiologischen Diagnostik sichergestellt werden?	25/25

Anmerkungen: Was sollte bei der Diagnostik dokumentiert werden?

Erläuterung: Prozessqualität, aber auch Strukturqualität, z.B. Zertifizierung der Ultraschall-Anwender,

Bei allen Verfahren sollte auch eine möglichst „qualitativ“ hohe Vorgabe der technischen Parameter erfolgen (z.B. welche Matrix bei MRA-Bildgebung etc.) um die einzelnen Methoden auch auszureizen und natürlich auch die entsprechenden Leistungserbringer auf diese hohe Qualität in den Leitlinien festzulegen.

10.3 TABELLE 5: SCHLÜSSELFRAGEN GRUPPE 3 – THERAPIEVERFAHREN

	Modifizierte Schlüsselfragen	SF alt	Bearbeiter
Kriterien für die Entscheidungsfindung			
1.	Wer soll die Indikation auf der Basis welcher klinischen und apparativen Befunde zu den einzelnen Therapieverfahren stellen?	3.1, 3.2	Ringleb Eckstein Storck Dörfler, Berkefeld
2.	Wann und zu welchem Zeitpunkt besteht die Indikation zur OP oder zur Intervention einer asymptomatischen oder symptomatischen Stenose (einschl. Notfallindikation), inkl. Subgruppen, die eher von einer operativen, endovaskulären oder konservativen Therapie profitieren?	3.3, 3.4	Ringleb, Eckstein Storck Dörfler, Berkefeld
3.	Wie sehen Patienten die Alternative CEA oder CAS?	3.5	Eckstein
Bewertung der alternativen Therapieverfahren			
4.	Gibt es bei Patienten mit einer hochgradigen extracraniellen Carotisstenose die EEA im Vergleich zur TEA mit Patch im Vergleich zur TEA ohne Patch unterschiedlich hohe Erfolgs-/Komplikations-/ /Rezidivraten?	3.6	Eckstein
5.	Gibt es bei Patienten mit einer hochgradigen extracraniellen Carotisstenose die PTA im Vergleich zur PTA mit Stent unterschiedlich hohe Erfolgs-/Komplikations-/ /Rezidivraten?	3.7	Dörfler, Berkefeld
6.	Bei welchen Patienten mit einer hochgradigen extracraniellen Carotisstenose sollte intraoperativ obligat oder selektiv ein Shunt eingelegt werden?	3.10	Storck
7.	Verbessert ein intraoperatives Monitoring bei OP in Allgemeinanästhesie bei Patienten mit einer hochgradigen extracraniellen Carotisstenose das Outcome? Wenn ja, wie ist der Stellenwert der einzelnen Monitoringverfahren?	3.11	Storck
8.	Wie sieht das optimale Management von operationsspezifischen prozeduralen Komplikationen aus?	3.12	Eckstein
9.	Welches Anästhesieverfahren ist bei der operativen Therapie zu bevorzugen?	3.13	Eckstein
10.	Wie soll beim Vorliegen einer behandlungsbedürftigen Carotisstenose und einer behandlungsbedürftigen KHK vorgegangen werden? Operativ oder endovaskulär?, simultan oder zweizeitig? (Frage 3.14 modifiziert, da bisher CAS und PTCA nicht als Frage formuliert worden sind!)	3.14	Storck
11.	Evidenzbasiertes perioperatives Management	3.15, 3.16	Storck
12.	Welche Materialien (Katheter, Stents, Protektionssysteme) sind beim Carotis-Stenting zu bevorzugen?	3.17, 3.18	Dörfler, Berkefeld
13.	Was ist zu beachten für ein optimales periinterventionelles Management?	3.19, 3.21-3.23	Dörfler, Berkefeld
14.	Wie sieht das optimale periinterventioneller Komplikationen aus?	3.20	Dörfler, Berkefeld
15.	Wie sind die klinischen und morphologischen Langzeitergebnisse nach endovaskulärer Therapie, inkl. Subgruppen?	3.25, 3.26	Dörfler, Berkefeld
16.	Welche Patienten sollten mit welcher Medikation konservativ behandelt werden?	3.27, 3.28	Ringleb
Versorgungskoordination und strukturelle Qualitätsindikatoren			
17.	Ist eine ambulante operative oder endovaskuläre Therapie der Carotisstenose möglich und sinnvoll?	3.29	Storck, Berkefeld
18.	Welche Anforderungen an Weiterbildung und Strukturqualität ist an Einrichtungen zu stellen, in denen Angiographien oder operative/endovaskuläre Revaskularisationen der A. carotis durchgeführt werden?	3.30, 3.32	Storck, Berkefeld
19.	Gibt es einen Zusammenhang zwischen Qualifikation, Volume (individuell, Klinik) und Outcome für die operative oder endovaskuläre Therapie?	3.31, 3.32	Eckstein, Berkefeld

1.Konsensus-Konferenz 09/2005 (Delphi-Verfahren)

Kriterien für die Entscheidungsfindung bez. der alternativen Revaskularisationsverfahren		Abstimmung
3.1	Durch wen soll/darf die Indikation zu den einzelnen Therapieverfahren gestellt werden (interdisziplinär, Neurologie,...)?	10/17
3.2	Welche apparativ-diagnostischen Befunde sind für die Indikationsstellung relevant?	
	- Muss die Plaquemorphologie Auswirkung auf die Behandlungsmodalität (OP vs. PTA), und im Falle der PTA (ohne/mit Protektion) haben?	13/17
	- Inwieweit kann die Anatomie des Aortenbogens und der A. carotis ausschlaggebend für die Entscheidung für oder wider die endovaskuläre Therapie sein, und reicht hier immer die Information aus der ce-MRA?	15/17
	- Was ist im Falle einer erheblich kalzifizierten, "starren" Stenose für die Therapiemodalität zu bedenken, ergo diagnostisch zur Identifikation vorzuschalten?	13/17
3.3	Wann und zu welchem Zeitpunkt besteht die Indikation zur OP oder Intervention einer symptomatischen Stenose (einschl. Notfallindikation)? , inkl. Subgruppen, die eher von einer OP oder eher von einer endovaskulären Therapie profitieren?	16/17
3.4	Wann besteht bei Patienten mit asymptomatischer extracranieller Carotisstenose die Indikation zur OP oder Intervention? inkl. Subgruppen, die eher von einer OP oder eher von einer endovaskulären Therapie profitieren	15/17
3.5	Wie sehen Patienten die Alternative CEA oder CAS?	10/17

Anmerkungen: Es sollte ein Algorithmus resultieren, der folgende Aspekte berücksichtigt

- Rolle der Diagnostik (Einfluss von Stenose-/bzw. Gefäßmorphologie auf die Indikationsstellung):
- Muss die Plaquemorphologie Auswirkung auf die Behandlungsmodalität (OP vs. PTA), und im Falle der PTA (ohne/mit Protektion) haben?
- Inwieweit kann die Anatomie des Aortenbogens und der A. carotis ausschlaggebend für die Entscheidung für oder wider die endovaskuläre Therapie sein, und reicht hier immer die Information aus der ce-MRA?
- Was ist im Falle einer erheblich kalzifizierten, "starren" Stenose für die Therapiemodalität zu bedenken, ergo diagnostisch zur Identifikation vorzuschalten?

Rolle der Symptomatik:

- Wann besteht bei Patienten mit asymptomatischer oder symptomatischer Stenose die Indikation zur OP oder Intervention (einschl. Notfallindikation)?
- Optimaler Zeitpunkt für eine Revaskularisation
- Vergleichende Outcome-Bewertung der alternativen Optionen zur Revaskularisation (siehe folgende Tab.)

Bewertung der alternativen Revaskularisationsverfahren		
3.6	Gibt es bei Patienten mit einer hochgradigen extracraniellen Carotisstenose die EEA im Vergleich zur TEA mit Patch im Vergleich zur TEA ohne Patch unterschiedlich hohe Erfolgs-/Komplikations-/ /Rezidivraten?	14/17
3.7	Gibt es bei Patienten mit einer hochgradigen extracraniellen Carotisstenose die PTA im Vergleich zur PTA mit Stent unterschiedlich hohe Erfolgs-/Komplikations-/ /Rezidivraten?	

Anmerkungen: Zielgrößen der vergleichenden Beurteilung (Outcome-Bewertung) der operativen und interventionellen Verfahren: Nutzen, Risiko (Mortalität, Apoplex, lokale und systemische Komplikationen), Reststenosen, Dauer der stationären Behandlung, Lebensqualität; Langzeitergebnisse (z.B. Spätrezidive)

Häufigkeit schwerer (MACE) kardiovaskulärer Ereignisse nach Carotisrevaskularisation, insbesondere im ersten Jahr danach?

Welche Einschränkungen können als Nebenwirkungen einer CEA auftreten (z.B. Nervenläsionen, Beeinträchtigungen der Stimme), und wie können diese Einschränkungen Alltagsleistungen und/oder Lebensqualität beeinträchtigen?

Carotis-Chirurgie: Beurteilung des OP-Risikos		
3.8	Wie ist das periprozedurale Risiko bei Patienten mit asymptomatischen, symptomatischen oder bilateralen Stenosen und wie wird es erfasst?	16/17

3.9	Gibt es klinische und morphologische Kriterien bei Patienten mit extracranieller Carotisstenose, die mit einem erhöhten periprozeduralen Risiko verknüpft sind?	15/17

Carotischirurgie: OP-Verfahren, intraoperatives Monitoring, Umgang mit Komplikationen

3.10	Bei welchen Patienten mit einer hochgradigen extracraniellen Carotisstenose sollte intraoperativ obligat oder selektiv ein Shunt eingelegt werden?	13/17
3.11	Verbessert ein intraoperatives Monitoring bei OP in Allgemeinanästhesie bei Patienten mit einer hochgradigen extracraniellen Carotisstenose das Outcome? Wenn ja, wie ist der Stellenwert der einzelnen Monitoringverfahren?	12/17
3.12	Wie sieht das optimale Management von operationsspezifischen prozeduralen Komplikationen aus?	12/17

Anmerkungen: Monitoring: wenn ja, welches?, wann-nur bei Allgemeinanästhesie?

Komplikationsmanagement:

- auf charakteristische Komplikationen beschränken.
- Sollen/müssen unerwünschte Eingriffsfolgen (Dissektionen, andere Gefäßwandverletzungen, Residualstenosen, Aneurysmen) behandelt werden? Wenn ja, wann und wie (medikamentös, operativ, interventionell)

Carotischirurgie: Anästhesieverfahren, Eingriffsplanung

3.13	Ist bei Patienten mit einer hochgradigen extracraniellen Carotisstenose, die operiert wird, das Outcome besser bei Verwendung der Lokalanästhesie im Vergleich zur Allgemeinanästhesie (Apoplexrate, Nervenschäden, Rekonvaleszenz, verfahrenstypische Komplikationen, etc.)?	14/17
3.14	Simultane oder sequentielle Herz- und Carotischirurgie/ Intervention?	15/17

Anmerkungen: Zielgrößen zur vergleichenden Bewertung von Lokal- und Allgemeinanästhesie: Apoplexrate, Nervenschäden, Rekonvaleszenz, verfahrenstypische Komplikationen, etc.

Carotischirurgie: Perioperatives Management

3.15	Sollen bei Patienten mit einer hochgradigen extracraniellen Carotisstenose intraoperativ Antikoagulantien (z.B. Heparin) gegeben werden?	12717
3.16	Ist eine Nachbehandlung auf einer Intensiv- oder Intermediate-Care-Station notwendig? Wenn ja, wie lange?	14/17

Anmerkungen: Intraoperative Antikoagulantien: ist die Gabe mit einem besseren Outcome assoziiert? Postoperative Überwachung: Vergleich zur unmittelbaren Betreuung auf der Normalstation, Zielgrößen: Komplikationen. Wenn ja, notwendiger Zeitraum der Überwachung?

Endovaskuläre Therapie: Technische Standards (Materialien)

3.17	Gibt es bei der interventionellen Behandlung Untersuchungen, die die Empfehlung des Einsatzes bestimmter Materialien zulassen?	12/17
3.18	Welchen Stellenwert haben Neuroprotektionssysteme bei der interventionellen Therapie?	13/17

Anmerkungen: Einsatz eines Protektionssystems bei stentgestützten Angioplastien: da es keine randomisierten Studien zu diesem Thema gibt, Frage streichen, man muss auf große Register zurückgreifen können - Vergleich PTA mit/ohne Stent und Vergleich PTA mit/ohne Protektionssystem

Endovaskuläre Therapie: Monitoring und Umgang mit Komplikationen

3.19	Ist ein Anästhesist/entsprechend qualifizierter Arzt für die Überwachung während der Intervention erforderlich?	13/17
3.20	Wie sieht das optimale Management von periprozeduralen Komplikationen aus?	

Anmerkungen: Komplikationsmanagement

- auf charakteristische konzentrieren; welche Rahmenbedingungen sind notwendig (neurologische Überwachung, ambulant oder stationär, Möglichkeit zur intrakraniellen Rekanalisation, Dekompressive Kraniotomie
- Sollen/müssen unerwünschte Eingriffsfolgen (Dissektionen, andere Gefäßwandverletzungen, Residualstenosen, Aneurysmen) behandelt werden? Wenn ja, wann und wie (medikamentös, operativ,

	interventionell)	
Endovaskuläre Therapie: periinterventionelles Management		
3.21	Was ist die optimale periprozedurale Medikation Medikament, Dosis, Dauer?	14/17
3.23	Soll Heparin, welches bei der Intervention gegeben wird, postinterventionell antagonisiert werden?	12/17
3.24	Ist eine Nachbehandlung auf einer Intensiv- oder Intermediate-Care-Station notwendig? Wenn ja, wie lange?	14/17
Anmerkungen: Periprozedurale Medikation: Medikamente zusätzlich zu Clopidogrel und ASS, wann sollte die Medikation begonnen werden?		
Endovaskuläre Therapie: Langzeitergebnisse		
3.21	Gibt es bez. der Langzeitergebnisse, Patienten(sub)gruppen, die besonders viel oder besonders wenig von der endovaskulären Behandlung profitieren?	11/17
3.22	Sind nach Stentangioplastie Spätrezidive zu erwarten? Wenn ja: welchen klinische Bedeutung haben diese Rezidivstenosen?	14/17
Konservative Therapie		
3.25	Welche medikamentöse (z.B. antithrombotische etc.) Therapie ist zu empfehlen?	15/17
3.26	Gibt es Patienten-Subgruppen, die von einer rein konservativen Therapie profitieren?	Steuergruppe
Anmerkungen: Zielgrößen der vergleichenden Beurteilung (Outcome-Bewertung) von Revaskularisation vs. konservative Therapie: Nutzen, Risiko (Mortalität, Apoplex, lokale und systemische Komplikationen), Dauer der stationären Behandlung, Lebensqualität; Langzeitergebnisse		
Versorgungskoordination und Qualitätsindikatoren der Therapieverfahren		
3.27	Ist bei Patienten mit einer hochgradigen extracraniellen Carotisstenose die operative oder interventionelle Behandlung ambulant möglich? Wenn nein, wie lange dauert die stationäre Therapie?	14/17
3.28	Welche Anforderungen an die Weiterbildung und an die Strukturqualität ist an Einrichtungen zu stellen, in denen Angiographien oder operative/endovaskuläre Revaskularisationen der A. Carotis durchgeführt werden?	16/17
3.29	Gibt es einen Zusammenhang zwischen Qualifikation, Volume (individuell, Klinik) und Outcome? - Bei der OP - Bei der Intervention	11/17
3.30	Welche klinischen Messgrößen sind zur Beurteilung der Prozess-/Ergebnisqualität geeignet?	Steuergruppe
Anmerkungen: Strukturqualität: Qualifikation des Durchführenden bei Angiographie und Revaskularisation, Rahmenbedingungen, Untersucher- und Zentrums-Volume getrennt analysieren		

10.4 Tabelle 6: Schlüsselfragen Gruppe 4 – Nachsorge, Rezidivtherapie und Lebensqualität

Modifizierte Schlüsselfragen		SF alt	Bearbeiter
1.	Welche Patienten nach einer Carotis-Revaskularisation profitieren von einer Reha/AHB?	4.1	Lawall
2.	Welche medikamentösen und nicht-medikamentösen Maßnahmen sollten wie lange zur Rezidivprophylaxe eingesetzt werden und in welchen Intervallen ist eine Nachuntersuchung angezeigt?	4.2, 4.3	Lawall
3.	Wie wird ein Therapieversagen bzw. ein Rezidiv klinisch und morphologisch definiert und wie muss dann diagnostisch und therapeutisch vorgegangen werden?	4.4, 4.5	Lawall
4.	Gibt es eine Einschränkung der Lebensqualität nach operativer oder endovaskulärer Therapie einer Carotisstenose und wie wird diese erfasst?	4.6, 4.7	Lawall
5.	Wie oft treten im ersten Jahr nach operativer oder endovaskulärer Therapie von Carotisstenosen schwere kardiovaskuläre Ereignisse auf?	4.9	Lawall

1. Konsensus-Konferenz 09/05 (Delphi-Verfahren)

Nachsorge		Abstimmung
4.1	Welche Patienten nach einer Carotis-Revaskularisation profitieren von einer Reha/AHB?	Steuergruppe
4.2	Welche Maßnahmen sollten wie lange zur posttherapeutischen Prophylaxe eingesetzt werden?	14/17
4.3	Welche Kontrolluntersuchungen sind nach einer Revaskularisation der A. Carotis sinnvoll?	15/17

Anmerkungen:

Posttherapeutische Prophylaxe: Wie lange sollte nach Intervention bei Patienten mit extracranieller Carotisstenose eine kombinierte Thrombozytenaggregationshemmung erfolgen? Unterschiede nach OP/endovaskulärer Therapie?

Diagnostisches Prozedere nach Revaskularisation: Methode? Häufigkeit? Intervalle? Wer? (Fachdisziplin; nur klinisch neurologisch oder mit Bildgebung?)

Rezidivtherapie		
4.4	Was gilt als Therapieversager: Restenose (und Grad), erneuter Schlaganfall, TIA?	15/17
4.5	Wie ist bei Patienten mit rezidivierender Symptomatik oder Nachweis einer Rezidivstenose vorzugehen?	14/17

Anmerkungen:

Procedere bei Therapieversagen nach Revaskularisation?

Procedere bei Rezidiv: vor allem für postoperative Situation betrachten; konservativ, OP, Intervention?

Lebensqualität		
4.6	Wie ist die Lebensqualität bei Patienten mit extracranieller Carotisstenose mit und ohne Carotis-OP/Intervention?	11/17
4.7	Welche Instrumente sind zur Erfassung der Lebensqualität geeignet bei Patienten mit extracranieller Carotisstenose vor und nach konservativer, interventioneller oder operativer Therapie?	Steuergruppe
4.8	Welche Einschränkungen können als Nebenwirkungen einer CEA oder CAS auftreten (z.B. Nervenläsionen, Beeinträchtigungen der Stimme), und wie können diese Einschränkungen Alltagsleistungen und/oder Lebensqualität beeinträchtigen?	11/17
4.9	Häufigkeit schwerer (MACE) kardiovaskulärer Ereignisse nach Carotisrevaskularisation, insbesondere im ersten Jahr danach?	Steuergruppe

10.5 Tabelle 7: Schlüsselfragen Gruppe 5 – Gesundheitsökonomie (Delphi-Verfahren)

Nachsorge		Abstimmung
5.1	Welche Kosten sollen standardmäßig erfasst werden, um verschiedene medizinische Eingriffe aus ökonomischer Sicht zu vergleichen?	13/17
	- Welche ökonomische Perspektive soll eingenommen werden - nur GKV oder auch Rentenversicherungsträger, gesamtgesellschaftlich incl. Produktivitätsverlust?	10/17
	- Kosteneffektivität Screening-Untersuchungen?	13/17
	- Was kostet der Schlaganfall?	10/17
	- Kosteneffektivität der konservativen, chirurgischen und endovaskulären Therapie von extracraniellen Carotisstenosen?	13/17
	- Welche Kosten sollen standardmäßig erfasst werden, um verschiedene medizinische Eingriffe aus ökonomischer Sicht zu vergleichen?	12/17
	- Gibt es Vergleiche bezüglich der Kosten einer endovaskulären und einer operativen Behandlung? Werden beide DRG-mäßig abgedeckt?	12/17

Anmerkung: Ergänzende Recherche:

- prospektive/retrospektive Kohortenstudien zur Kosteneffektivität einzelner Aspekte der Sekundärprävention carotis-assoziierter Schlaganfälle in Deutschland mit gemäß der Leitlinie definierten Einschlusskriterien (Schweregrad Stenose/Ischämie, Altersgruppen), Beobachtungsdauer (postoperativ und für das Zielkriterium Schlaganfall) und Endpunkten (Schlaganfallhäufigkeit, Letalität)
- Auf DRG-Abdeckung einzelner Verfahren sollte eingegangen werden.
- Es soll versucht werden, auch Daten zur Frage der Kosteneffektivität von Screening-Untersuchungen zu ermitteln.

10.6 TABELLE 8: LEITLINIEN ZUR CAROTIS-TEA UND ZUM CAROTIS STENT

Titel	Herkunft	Jahr
Moore W et al. Guidelines for Carotid Endarterectomy. A Multidisciplinary Consensus Statement From the Ad Hoc Committee, American Heart Association, *Stroke* 1995; 26:188-201.	USA	1995
Prevention of stroke/clinical practice guideline - the role of anticoagulants, antiplatelet agents and Carotid Endarterectomy. National Health and Medical Research Council, Australia 1997	Australien	1997
Management of patients with stroke II: Management of Carotid Stenosis and Carotid Endarterectomy. Scottish Intercollegiate Guidelines Network (SIGN) No.14, 1997,www.sign.ac.uk Ersetzt durch SIGN No.108, 2008	Schottland	1997
Leitlinie zu Stenosen der Arteria carotis (Leitlinie zur Schlaganfallprophylaxe bei Stenosen und Verschlüssen der A. carotis communis, interna und externa). AWMF-Leitlinien-Register Nr. 004/002 Entwicklungsstufe. Leitlinien zu Diagnostik und Therapie in der Gefäßchirurgie. Hrsg. vom Vorstand der Dt. Ges. f. Gefäßchirurgie; *Deutscher Ärzteverlag*, Köln 1998	Deutschland	1998
Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1998; 97:501-509	USA	1998
Stroke prevention. Carotid intervention. In: Canadian best practice recommendations for stroke care: 2006. Ottawa (ON): Canadian Stroke Network, Heart & Stroke Foundation of Canada; 2006. p. 39-42	Kanada	2006
Management of atherosclerotic carotid artery disease: Clinical practice guidelines of the Society for Vascular Surgery. Hobson RB et al. *J Vasc Surg* 2008; 48:480-6	USA	2008
Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, Biasi G, Norgren L on behalf of the ESVS Guidelines Collaborators. ESVS Guidelines. Invasive Treatment for Carotid Stenosis: Indications, Techniques. *Eur J Vasc Endovasc Surg* 2009, 37, S1eS19	Europa	2009
ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease. Executive Summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practise Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Vascular Medicine, and Society for Vascular Surgery	USA	2011
Tendera M, Aboyans V, Bartelink ML et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries * The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011	Europa	2011
Ricotta JJ, AbuRahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. J Vasc Surg 2011;54(3):e1-31.	USA	2011

10.7 TABELLE 9: LEITLINIEN ZUR PRIMÄRPRÄVENTION, SOWIE DIAGNOSTIK, THERAPIE UND NACHSORGE DER ZEREBRALEN ISCHÄMIE

Titel	Herkunft	Jahr
Deutsche Leitlinien		
Primäre und Sekundäre Prävention der zerebralen Ischämie: Leitlinie der Deutschen Gesellschaft für Neurologie, Entwicklungsstufe S2	Deutschland	2002
Leitlinien Clearingbericht „Schlaganfall“. Leitlinien-Clearingverfahren von Bundesärztekammer und Kassenärztlicher Bundesvereinigung in Kooperation mit Deutscher Krankenhausgesellschaft, Spitzenverbänden der Krankenversicherungen und Gesetzlicher Rentenversicherung. Ärztliches Zentrum für Qualität in der Medizin, Leitlinien-Clearingstelle (Hg.), 2005, Deutsche Nationalbibliografie; http://dnb.ddb.de	Deutschland	2005
Primär- und Sekundärprävention der zerebralen Ischämie. Gemeinsame Leitlinie der DGN und der Deutschen Schlaganfallgesellschaft (DSG)	Deutschland	2005
Schlaganfall. S3 Leitlinie der Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin, AWMF-Leitlinien-Register Nr. 053/014, 2006	Deutschland	2006
Primär- und Sekundärprävention der zerebralen Ischämie: Leitlinien der Deutschen Gesellschaft für Neurologie gemeinsam mit der Deutschen Schlaganfallgesellschaft (DSG): Leitlinien für Diagnostik und Therapie in der Neurologie; 4. überarbeitete Auflage 2008, S. 654 ff, ISBN 978-3-13-132414-6; Georg Thieme Verlag Stuttgart	Deutschland	2008
S3-Leitlinie zur Prophylaxe der venösen Thromboembolie (VTE), AWMF 2009, Registernummer 003/001, www.awmf-online.de	Deutschland	2009
Europäische Leitlinien		
Swedish National Guidelines for the Management of Stroke Version for Health and Medical Personnel, 2000	Schweden	2000
Management of patients with stroke. Rehabilitation, Prevention and management of complications, and discharge planning. Scottish Intercollegiate Guidelines Network (SIGN) No.64. www.sign.ac.uk	Schottland	2002
Stroke Prevention and Educational Awareness Diffusion. Italian guidelines for stroke prevention and management: syntheses and recommendations. Milan, Italy: Stroke Prevention and Educational Awareness Diffusion, 2003:38	Italien	2003
Leys D, Kwiecinski H, Bogousslavsky J, et al. Prevention. European Stroke Initiative. *Cerebrovasc Dis*. 2004;17 (suppl 2):15-29	Europa	2004
Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, Berry E, Young G, Rothwell P, Roditi G, Gough M, Brennan A, Bamford J, Best J. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. *Health Technology Assessment* 2006; Vol. 10: No. 30	United Kingdom	2006
Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A nationale clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN) No. 108, December 2008. www.sign.ac.uk	Schottland	2008
Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008/2009. The European Stroke Organization (ESO) Executive Committee and the ESO Writing Committee. http://www.eso-stroke.org/recommendations.php?cid=9&sid=1	Europa	2009
Sonstige Internationale Leitlinien		
Stroke and transient ischaemic attacks: assessment, investigation, immediate management and secondary prevention. Singapore Ministry of Health; 2003 Mar. 44	Singapur	2003
Life after stroke. New Zealand guideline for management of stroke. Best practice evidence-based guideline November 2003. www.stroke.org.nz	Neuseeland	2003
Acute stroke management. Carotid artery imaging. In: Canadian best practice recommendations for stroke care: 2006. Ottawa (ON): Canadian Stroke Network, Heart & Stroke Foundation of Canada; 2006.	Kanada	2006

National Stroke Association Guidelines for the Management of Transient Ischemic Attacks. Johnston C., Ann Neurol 2006; 60:301-313	USA	2006
Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke et al., Sacco RL et al. *Stroke* 2006 Feb;37(2):577-617	USA	2006
Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Adams RJ, et al. *Stroke* 2008 May; 39 (5):1647-52.		2008
Primary Prevention of Ischemic Stroke. A Guideline From the American Heart Association/ American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group, Goldstein. *Stroke* 2006;37;1583-1633;	USA	2006
Secondary prevention. In: National Stroke Foundation. Clinical guidelines for acute stroke management. Melbourne (Australia): National Stroke Foundation; 2007 Oct. p. 43-51.	Australien	2007
Guidelines for the Early Management of Adults With Ischemic Stroke. A Guideline From the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Adams et al. *Circulation.* 2007;115:e478-e534	USA	2007
ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Fleisher LA et al. *Circulation* 2007;116;1971-1996;	USA	2007
Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update, Mosca L et al., *Circulation* 2007;115;1481-1501;	USA	2007
Antithrombotic Therapy for Peripheral Artery Occlusive Disease* American College of Chest Physicians Evidence- Based Clinical Practice Guidelines (8th Edition). Sobel M, Verhaeghe R, *Chest* 2008;133;815S-843S	USA	2008
Intercollegiate Stroke Working Party. National clinical guideline for stroke, 3rd edition. London: Royal College of Physicians	United Kingdom	2008
Canadian Best Practice Recommendations for Stroke Care: Lindsay P et al.CMAJ 2008; 179 (12)	Kanada	2008
Definition and Evaluation of Transient Ischemic Attack. A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Easton D et al., *Stroke*. 2009;40:2276-2293	USA	2009
Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009: 17;150(6):396-404	USA	2009
Australia: Clinical guidelines for stroke management	Australien	2010
Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association	USA	2011
Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association	USA	2011

10.8 Tabelle 10: Systematisch bewertete Leitlinien der Jahre 2006 – 2009 (DELBI Domäne 3)

Titel	Herkunft	Jahr
Stroke prevention. Carotid intervention. In: Canadian best practice recommendations for stroke care: 2006. Ottawa: Canadian Stroke Network, Heart & Stroke Foundation of Canada; 2006. 39-42	Kanada	2006
Schlaganfall. S3 Leitlinie der Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin, AWMF-Leitlinien-Register Nr. 053/014, 2006	Deutschland	2006
Primary Prevention of Ischemic Stroke. A Guideline From the American Heart Association/ American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group, Goldstein. Stroke 2006;37;1583-1633;	USA	2006
National Stroke Association Guidelines for the Management of Transient Ischemic Attacks. Johnston C., Ann Neurol 2006; 60:301-313	USA	2006
Secondary prevention. In: National Stroke Foundation. Clinical guidelines for acute stroke management. Melbourne (Australia): National Stroke Foundation; 2007 Oct. p. 43-51.	Australien	2007
Guidelines for the Early Management of Adults With Ischemic Stroke. A Guideline From the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Adams et al. *Circulation.* 2007;115:e478-e534	USA	2007
Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke et al., Sacco RL et al. Stroke 2006 Feb;37(2):577-617	USA	2006 und 2008
Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Adams RJ, et al. Stroke 2008 May; 39 (5):1647-52.		
Intercollegiate Stroke Working Party. National clinical guideline for stroke, 3rd edition.London: Royal College of Physicians	United Kingdom	2008
Canadian Best Practice Recommendations for Stroke Care, Lindsay P et al.CMAJ 2008; 179 (12)	Kanada	2008
Primär- und Sekundärprävention der zerebralen Ischämie: Leitlinien der Deutschen Gesellschaft für Neurologie gemeinsam mit der Deutschen Schlaganfallgesellschaft (DSG): Leitlinien für Diagnostik und Therapie in der Neurologie; 4. überarbeitete Auflage 2008, S. 654 ff, ISBN 978-3-13-132414-6; Georg Thieme Verlag Stuttgart	Deutschland	2008
Diagnostik zerebrovaskulärer Erkrankungen: Leitlinien der Deutschen Gesellschaft für Neurologie, Leitlinien für Diagnostik und Therapie in der Neurologie; 4. überarbeitete Auflage 2008, S. 654 ff, ISBN 978-3-13-132414-6; Georg Thieme Verlag Stuttgart	Deutschland	2008
Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A nationale clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN) No. 108, December 2008. www.sign.ac.uk	Schottland	2008
Management of atherosclerotic carotid artery disease: Clinical practice guidelines of the Society for Vascular Surgery. Hobson RB et al. J Vasc Surg 2008; 48:480-6	USA	2008
Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008/2009. The European Stroke Organization (ESO) Executive Committee and the ESO Writing Committee. http://www.eso-stroke.org/recommendations.php?cid=9&sid=1	Europa	2008
Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, Biasi G, Norgren L on behalf of the ESVS Guidelines Collaborators. ESVS Guidelines. Invasive Treatment for Carotid Stenosis: Indications, Techniques. Eur J Vasc Endovasc Surg 2009, 37, S1eS19	Europa	2009

10.9 Tabelle 11: Systematisch bewertete Leitlinien der Jahre 2006–2009 (DELBI Domäne 3: Methodologische Exaktheit der Leitlinien-Entwicklung, 1=trifft überhaupt nicht zu, 2=trifft nicht zu, 3=trifft zu, 4=trifft uneingeschränkt zu (DELBI 2008))

	Bewertung HH Eckstein (08/09)	Royal College,UK	LL DEGAM, Deutschl.	AHA/ASA, USA	NSA, USA	AHA/ASA, USA	Kanada	Australien	AHA/ASA, USA	SVS, USA	DGN / DSG, Deutschland	DGN, Deutschland	SIGN 50/108 Schottland	ESO, Europa	ESVS, Europa
		2008	2006	2006	2006	2008	2006/08	2007	2007	2008	2008	2008	2008	2008	2009
		Nationale guidelines for stroke	Schlaganfall	Primary prevention of ischemic stroke	Guidelines for TIA	Secondary prevention of stroke	Best practise recommendations for stroke	Secondary prevention	Management of Adults With Ischemic Stroke	Carotid stenosis-practise guidelines	Primär- und Sekundär-prävention zerebrale Ischämie	Diagnostik zerebro-vaskulärer Erkrankungen	Management of patients with TIA or stroke	Management of Ischaemic Stroke and TIA	Invasive Treatment for Carotid Stenosis
8	Bei der Suche nach der Evidenz wurden systematische Methoden angewandt	4	2	2	4	2	3	4	2	1	1	1	4	1	1
9	Die Kriterien für die Auswahl der Evidenz sind klar beschrieben.	4	1	2	4	2	3	4	2	1	2	2	4	1	1
10	Die zur Formulierung der Empfehlungen verwendeten Methoden sind klar beschrieben	4	2	3	4	3	4	4	3	2	2	2	4	4	4
11	Bei der Formulierung der Empfehlungen wurden gesundheitlicher Nutzen, Nebenwirkungen und Risiken berücksichtigt.	3	2	4	3	4	3	4	4	2	3	3	4	4	4
12	Die Verbindung zwischen Empfehlungen und der zugrunde liegenden Evidenz ist explizit dargestellt.	4	2	4	4	4	4	4	4	2	3	3	4	4	4
13	Die Leitlinie ist vor ihrer Veröffentlichung durch externe Experten begutachtet worden	4	4	4	4	1	4	4	1	1	1	1	4	4	1
14	Ein Verfahren zur Aktualisierung der Leitlinie ist angegeben	4	4	1	1	4	4	1	4	1	4	4	4	4	1
	Gesamtscore (max. 28)	27	17	20	24	20	25	25	20	10	16	16	28	22	16

Bewertung M Storck (09/09)		Royal College,UK	LL DEGAM, Deutschl.	AHA/ASA, USA	NSA, USA	AHA/ASA, USA	Kanada	Australien	AHA/ASA, USA	SVS, USA	DGN / DSG, Deutschland	DGN, Deutschland	SIGN 50/108 Schottland	ESO, Europa	ESVS, Europa
		2008	2006	2006	2006	2008	2006/08	2007	2007	2008	2008	2008	2008	2008	2009
		Nationale guidelines for stroke	Schlaganfall	Primary prevention of ischemic stroke	Guidelines for TIA	Secondary prevention of stroke	Best practise recommendations for stroke	Secondary prevention	Management of Adults With Ischemic Stroke	Carotid stenosis-practise guidelines	Primär- und Sekundär-prävention zerebrale Ischämie	Diagnostik zerebro-vaskulärer Erkrankungen	Management of patients with TIA or stroke	Management of Ischaemic Stroke and TIA	Invasive Treatment for Carotid Stenosis
8	Bei der Suche nach der Evidenz wurden systematische Methoden angewandt	4	3	2	4	2	2	4	2	1	1	1	4	1	1
9	Die Kriterien für die Auswahl der Evidenz sind klar beschrieben.	3	1	2	4	3	3	4	2	1	1	2	3	1	1
10	Die zur Formulierung der Empfehlungen verwendeten Methoden sind klar beschrieben	4	3	2	4	2	3	4	2	2	2	2	4	3	2
11	Bei der Formulierung der Empfehlungen wurden gesundheitlicher Nutzen, Nebenwirkungen und Risiken berücksichtigt.	4	1	3	2	3	3	4	3	3	2	2	4	4	3
12	Die Verbindung zwischen Empfehlungen und der zugrunde liegenden Evidenz ist explizit dargestellt.	4	2	4	4	3	4	4	4	3	3	3	4	4	4
13	Die Leitlinie ist vor ihrer Veröffentlichung durch externe Experten begutachtet worden	4	3	4	4	1	4	4	2	2	1	1	4	2	2
14	Ein Verfahren zur Aktualisierung der Leitlinie ist angegeben	4	4	1	2	4	4	3	1	1	1	1	4	3	1
	Gesamtscore (max. 28)	27	17	18	24	18	23	27	16	13	11	12	27	18	14

1=trifft überhaupt nicht zu, 2=trifft nicht zu, 3=trifft zu, 4=trifft uneingeschränkt zu (DELBI 2008)

Bewertung D. Sander (09/09)		Royal College,UK	LL DEGAM, Deutschl.	AHA/ASA, USA	NSA, USA	AHA/ASA, USA	Kanada	Australien	AHA/ASA, USA	SVS, USA	DGN / DSG, Deutschland	DGN, Deutschland	SIGN 50/108 Schottland	ESO, Europa	ESVS, Europa
		2008	2006	2006	2006	2008	2006/08	2007	2007	2008	2008	2008	2008	2008	2009
		Nationale guidelines for stroke	Schlaganfall	Primary prevention of ischemic stroke	Guidelines for TIA	Secondary prevention of stroke	Best practise recommendations for stroke	Secondary prevention	Management of Adults With Ischemic Stroke	Carotid stenosis-practise guidelines	Primär- und Sekundär-prävention zerebrale Ischämie	Diagnostik zerebro-vaskulärer Erkrankungen	Management of patients with TIA or stroke	Management of Ischaemic Stroke and TIA	Invasive Treatment for Carotid Stenosis
8	Bei der Suche nach der Evidenz wurden systematische Methoden angewandt	4	4	3	4	3	3	4	3	4	2	2	4	3	3
9	Die Kriterien für die Auswahl der Evidenz sind klar beschrieben.	4	4	2	3	2	4	4	2	3	3	3	4	4	3
10	Die zur Formulierung der Empfehlungen verwendeten Methoden sind klar beschrieben	4	3	2	3	2	3	4	2	3	2	2	4	4	2
11	Bei der Formulierung der Empfehlungen wurden gesundheitlicher Nutzen, Nebenwirkungen und Risiken berücksichtigt.	2	1	1	2	1	3	3	1	2	2	2	2	2	1
12	Die Verbindung zwischen Empfehlungen und der zugrunde liegenden Evidenz ist explizit dargestellt.	3	3	3	3	3	3	4	3	4	4	4	3	3	3
13	Die Leitlinie ist vor ihrer Veröffentlichung durch externe Experten begutachtet worden	4	4	4	2	4	4	4	4	1	1	1	4	1	4
14	Ein Verfahren zur Aktualisierung der Leitlinie ist angegeben	3	3	1	1	1	1	1	1	1	1	1	3	1	1
	Gesamtscore (max. 28)	24	22	16	18	16	24	24	16	18	15	15	24	18	17

1=trifft überhaupt nicht zu, 2=trifft nicht zu, 3=trifft zu, 4=trifft uneingeschränkt zu (DELBI 2008)

10.10 Tabelle 12: Cochrane Reviews: CEA, CAS, Medikamentöse Therapie

Titel des Reviews	Jahr
Ederle J, Featherstone RL, Brown M. Randomized Controlled Trials Comparing Endarterectomy and Endovascular Treatment for Carotid Artery Stenosis: A Cochrane Systematic Review. Stroke 2009;40;1373-1380	2009
Rerkasem K, Bond R, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy (Cochrane Review). *Cochrane Database of Systematic Reviews* 2008, Issue 4.	2008
Engelter S, et al. Antiplatelet therapy for preventing stroke and other vascular events after carotid endarterectomy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester,	2004
Algra A et al. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004
Cao PG, De Rango P, Zannetti S, Giordano G, Ricci S, Celani MG. Eversion versus conventional carotid endarterectomy for preventing stroke (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004
Bond R, Rerkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004
Bond R, Rerkasem K, Naylor R, Rothwell PM. Patches of different types for carotid patch angioplasty (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004
Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester	2004
Bond R, Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting) (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004
McCollum CN, O'Neill PA, Welsh SJ. Urgent carotid surgery for acute ischaemic stroke. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD004701. DOI: 10.1002/14651858.CD004701.	2004
Chambers BR, You RX, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004
Cina CS, Clase CM, Haynes RB. Carotid endarterectomy for symptomatic carotid stenosis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.	2004

10.11 Tabelle 13: Literatursuchen entsprechend dem Stand vom 30.Juni 2009

Gruppe	Suchbegriffe und Einschränkungen (×)	Treffer
A: Ausgangsmenge	Carotis?#####	>20.000
	(stenosis, stenotic, obstruct?, arteriosclero?, dissect?, stent?, angioplast?, thrombarterect?, thrombendarterec?)	
	× in Titel und Hauptaspekt vorkommend	
	× Nur in Menschen	
	× Nur in Deutsch oder Englisch	
	× Ausschluss von Meeting Abstracts	
B: Epidemiologie	Risk#, prognosis	348
	Treatment outcome, prediction, forecasting, survival	
	Epidemiology, Etiology, Mortality, prevention + control	
	Genetics	
	× in Titel und Hauptaspekt vorkommend	
	Crossmatch (in Gruppen A-E2)	
	Multicenter	
	Guidelines	
	Randomized clinical trial	
	Controlled trial	
	Review	
	Metaanalysis	
	× Ausschluss von case reports	
C: Diagnostik	asymptoma?, symptoma?, stenosis	768
	ischemi?, stroke	
	sonograph?, neurosono?, angiograph?	
	imaging, radiograph?, tomography?	
	diagnosis, pathology, radiology	
	radionuclide imaging	
	ultrasonography	
	× in Titel und Hauptaspekt vorkommend	
D: Therapie	surgical, surgery, operative	1847
	operation	
	intraoperative, perioperative	
	treatment, therapy, therapeutics	
	conservative, diet therapy, drug therapy	
	radiotherapy	
	endarterectomy	
	× in Titel und Hauptaspekt vorkommend	
E1: Nachsorge	aftercare, after treatment, post treatment	18
	post operative care	
	Surveillance, follow? # #, treatment, ambulant, investigat?	
	ambulatory care	
	hospitalisation, hospital care, length of stay	
	long term care	
	× in Titel und Hauptaspekt vorkommend	
E2: Rehabilitation	stroke, ischemi#, cardiovascular	35
	Crossmatch:	
	rehabilitation	

	physical medicine language, speech, voice dysphag?	
	Crossmatch: caroti#	
F: Kosten	economics, health economics cost, costs financ? kein crossmatch	140
G: Sonstige	Crossmatch wie B-E2	444

10.12 Tabelle 14: Erhebungsbogen für Therapiestudien

Fragestellung der Leitlinie:

Studientyp und Identifikation:

Referenznummer:

Bearbeiter:

Ausschluss: nein ☐ ja ☐

Begründung:

I. Beschreibung der Studie				
1. Welche Intervention wurde untersucht?				
2. Welche Zielkriterien (Endpunkte) wurden bestimmt?				
3. Wie viele Studienteilnehmer (insgesamt und pro Studienarm, bzw. Gruppe)?				
4. Wie war die Studienpopulation definiert? a) Einschlusskriterien: b) Ausschlusskriterien:				
5. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)?				
6. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?				
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der Drop-out-Fälle)? a) Bei Einschluss b) Bei Auswertung				
II. Interne Validität	Ja		Nein	
1. Wurden die Probanden den Gruppen randomisiert zugeordnet?				
2. Waren die Probanden und Untersucher bezüglich der Zuordnung verblindet?				
3. Wurde die Randomisierung geheim gehalten (allocation concealment)?				
4. Wurde ein prospektives Design verwendet?				
5. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?				
6. Waren Interventions- und Kontrollgruppe zu Studienbeginn vergleichbar?				
7. Wurden die Zielkriterien der Studie eindeutig definiert und adäquat erhoben?				
8. Wurden die Gruppen, mit Ausnahme der Prüf-Intervention, gleich behandelt?				
9. Wurden Nebenwirkungen dokumentiert?				
10. Wurden alle Probanden in der Gruppe ausgewertet, der sie ursprünglich zugeordnet waren (intention-to-treat-Regel)				
11. Rechtfertigen die Ergebnisse die Schlussfolgerungen?				
Gesamtbeurteilung	**++**	**+**	**-**	**--**
III. Ergebnisse				
IV. Ableitbare Empfehlung				

10.13 Tabelle 15: Erhebungsbogen für Systematische Übersichtsarbeiten (Reviews)

Fragestellung der Leitlinie:

Studientyp und Identifikation::

Referenznummer:

Bearbeiter:

Ausschluss: **nein** ☐ **ja** ☐

Begründung:

I. Beschreibung des Reviews				
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)?				
2. Welche Interventionen sind betrachtet/untersucht worden?				
3. Welche Zielkriterien (Endpunkte) wurden bestimmt?				
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)?				
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?				
II. Interne Validität	Ja		Nein	
1. Ist die Fragestellung angemessen und klar eingegrenzt?				
2. Ist die Literatursuche angemessen beschrieben?				
3. Wurde die Qualität der gefundenen Studien ermittelt?				
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?				
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?				
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?				
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?				
Gesamtbeurteilung	**++**	**+**	**+**	**--**
III. Ergebnisse				
IV. Ableitbare Empfehlung				

10.14 Tabelle 16: Erhebungsbogen für Diagnostische Studien

Fragestellung der Leitlinie:

Studientyp und Identifikation:

Referenznummer:

Bearbeiter:

Ausschluss: nein ☐ ja ☐

Begründung:

I. Beschreibung der Studie				
1. Welche diagnostische Intervention wurde untersucht (Prüftest)?				
2. Wie viele Studienteilnehmer wurden eingeschlossen?				
3. Wie war die Studienpopulation definiert? a) Einschlusskriterien: b) Ausschlusskriterien:				
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)?				
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?				
6. Mit welchem Referenztest wurde der Prüftest verglichen?				
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der Drop-out-Fälle)? a) Im zu prüfenden diagnostischen Test b) Im Referenztest				
II. Interne Validität	Ja		Nein	
1. Wurde ein prospektives Studiendesign verwendet?				
2. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?				
3...Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?				
4. War die Studienpopulation repräsentativ?				
5. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validen Referenztest („Gold-Standard“) verglichen?				
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?				
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?				
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?				
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?				
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?				
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?				
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?				
Gesamtbeurteilung	**++**	**+**	**-**	**--**
III. Ergebnisse				
IV. Ableitbare Empfehlung				

10.15 Tabelle 17: Methodische Qualität der wiss. Belege: Klassifizierung der Evidenzgrade für Therapie-, Präventions-Ätiologie-studien (nach Oxford Centre of Evidence Based Medicine (2001))

Grad	Studien zu Therapie/ Prävention / Ätiologie
1a	Systematische Übersicht über randomisierte kontrollierte Studien (RCT)
1b	Eine RCT (mit engem Konfidenzintervall)
1c	Alle-oder-Keiner-Prinzip
2a	Systematische Übersicht gut geplanter Kohortenstudien
2b	Eine gut geplante Kohortenstudie oder ein RCT minderer Qualität
2c	Outcome-Studien, Ökologische Studien
3a	Systematische Übersicht über Fall-Kontrollstudien
3b	Eine Fall-Kontroll-Studie
4	Fallserien oder Kohorten- / Fall-Kontroll-studien minderer Qualität
5	Expertenmeinung ohne explizite Bewertung der Evidenz oder basierend auf physiologischen Modellen / Laborforschung

10.16 Tabelle 18: Methodische Qualität der wiss. Belege: Klassifizierung der Evidenzgrade für Diagnostikstudien (nach Oxford Centre of Evidence Based Medicine (2001))

Grad	Studien zu Diagnose
1a	Systematische Übersicht über Level 1 diagnostische Studien oder diagnostische Entscheidungsregel, begründet auf 1b Studien, validiert in verschiedenen klinischen Zentren
1b	Validierungs- Kohortenstudie mit gutem Referenzstandard oder diagnostische Entscheidungsregel, validiert in einem Zentrum
1c	Alle-oder-Keiner-Prinzip (absolute SpPins und SnNouts)
2a	Systematische Übersicht über Level 2 diagnostische Studien
2b	Explorative Kohortenstudie mit gutem Referenzstandard
3a	Systematische Übersicht über Level 3 diagnostische Studien
3b	Nicht-konsekutive Studie; oder ohne Konsistenz der angewendeten Referenzstandards
4	Fall-Kontrolle Studie, schlechte oder nicht unabhängige Referenzstandards
5	Expertenmeinung ohne explizite Bewertung der Evidenz oder basierend auf physiologischen Modellen / Laborforschung

10.17 Tabelle 19: Zusammenfassung der Erklärungen zu „Conflicts of Interest“ aller Mitglieder der Steuergruppe

		Leitlinienkoordinator: Prof. Dr. H.-H. Eckstein Leitlinie: Deutsche Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose										
		J. Berkefeld	R. Diel	A. Dörfler	H.H. Eckstein	I. Kopp	A. Kühnl	R. Langhoff	H. Lawall	P. Ringleb	D. Sander	M. Storck
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheits-wirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Ja	Nein	Ja	Nein	Nein	Nein	Ja	Nein	Nein	Nein	Nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Ja	Nein	Ja	Ja	Nein	Nein	Ja	Nein	Ja	Ja	Nein
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Ja	Nein	Ja	Ja	Nein	Nein	Nein	Nein	Nein	Nein	Nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unter-nehmen der Gesundheitswirtschaft	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	Ja	Nein	Ja	Ja	Ja	Ja	Ja	Ja	Ja	Ja	Ja
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	Nein	Nein	Nein	Nein	Ja	Nein	Nein	Nein	Ja	Nein	Nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*11

*1: Universitätsklinikum Frankfurt a.M.,*2: Freie und Hansestadt Hamburg, *3: Universitätsklinikum Erlangen, *4: Klinikum rechts der Isar der Technischen Universität München, *5: AWMF-IMWi, *6: Klinikum rechts der Isar der Technischen Universität München, *7: Ev. Krankenhaus Königin Elisabeth gGmbH, *8: Asklepios Westklinikum Hamburg, 2001-2011 SRH Klinikum Karlsbad-Langensteinbach, *9: Universitätsklinikum Heidelberg, *10: Benedictus Krankenhaus Tutzing und Feldafing,*11: Städtisches Klinikum Karlsruhe gGmbH

10.18 Tabelle 20: Zusammenfassung der Erklärungen zu „Conflicts of Interest“ aller Mitglieder der Leitliniengruppe

		Leitlinienkoordinator: Prof. Dr. H.-H. Eckstein Leitlinie: Deutsche Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose									
		G. Antoniadis	C. Arning	H. Brückmann	C. Diehm	I. Flessenkämper	G. Fraedrich	A. Fründ	S. George	M.W. Görtler	H. Görtz
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheits-wirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Nein	Nein	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Nein	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Ja	Ja
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unter-nehmen der Gesundheitswirtschaft	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	Ja	Ja	Nein	Ja	Ja	Ja	Ja	Ja	Ja	Ja
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10

*1: Neurochirurgische Klinik der Universität Ulm am BKH Günzburg, *2: Asklepios Klinik Wandsbek, *3: LMU München, Klinikum der Universität München, *4: SRH Klinikum Karlsbad-Langensteinbach, *5: Helios Klinikum Emil von Behring, DRK-Schwesternschaft Berlin, *6: Medizinische Universität Innsbruck, *7: Herz-und Diabeteszentrum NRW, *8: Deutscher Verband der Ergotherapeuten e.V. (DVE), *9: Land Sachsen-Anhalt, Universitätsklinikum Magdeburg, *10: St. Bonifatius Hospital Lingen

	Leitlinienkoordinator: Prof. Dr. H.-H. Eckstein **Leitlinie: Deutsche Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose**										
		W. Gross-Fengels	M. Hennerici	U. Hoffmann	A. Hörstgen	P. Huppert	O. Jansen	H. Mudra	D. G. Nabavi	E. Neugebauer	H. Niedermeier
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheits-wirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Ja	Nein	Ja	Nein	Ja	Ja	Nein	Ja	Ja	Nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Ja	Nein	Ja	Nein	Ja	Ja	Ja	Ja	Ja	Nein
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Ja	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Ja	Nein
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8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	*11	*12	*13	*14	*15	*16	*17	*18	*19	*20

*11: Asklepios Kliniken Hamburg-Harburg, *12: Universität Heidelberg Land BW, *13: Klinikum der Universität München, *14: Enzkreis-Kliniken Mühlacker *15: Klinikum Darmstadt GmbH, *16: UKSH Kiel *17: Städt. Klinikum München GmbH, *18: Vivantes GmbH, *19: Universität Witten/Herdecke *20: Städt. Klinikum München GmbH, Klinikum Neuperlach

Leitlinienkoordinator: Prof. Dr. H.-H. Eckstein

Leitlinie: Deutsche Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose

		Ch. Ploenes	B. Rantner	O. Schnell	K.L. Schulte	K. Schwerdtfeger	R. Stingele	J. Tacke	D. Vorwerk	K. P. Walluschek	G. Walterbusch
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheits-wirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Nein	Nein	Ja	Ja	Nein	Nein	Ja	Nein	Nein	Nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftrags-instituts oder einer Versicherung	Nein	Nein	Ja	Ja	Nein	Nein	Nein	Ja	Ja	Nein
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8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	*21	*22	*23	*24	*25	*26	*27	*28	*29	*30

*21: Dominikus-Krankenhaus Düsseldorf, Cherubine-Willimann-Stiftung, *22: Medizinische Universität Innsbruck, *23: Forschergruppe Diabetes e.V. am Helmholtz Zentrum München, *24: Ev. Krankenhaus Königin Elisabeth Herzberge gGmbH, *25: Universitätsklinikum des Saarlandes, *26: Universitätsklinikum Schleswig Holstein, Kiel (Land SH), *27: Klinikum Passau, *28: Klinikum Ingolstadt, *29: DIAKO Flensburg, UKSH Campus Kiel *30: Kath. St. Johannes Gesellschaft Dortmund

| EVIDENZBERICHT

Therapie der extrakraniellen Karotisstenose mittels Endarteriektomie oder Angioplastie mit Stenting – Analyse der vorliegenden Evidenz

Version 0.1 – August 2010

Impressum

Auftraggeber

S3-Leitliniengruppe „Therapie der extrakraniellen Karotisstenose“ unter Federführung der Deutschen Gesellschaft für Gefäßchirurgie und Gefäßmedizin (Präsident: Prof. Dr. med. Hans-Henning Eckstein)

Titel

Therapie der Karotisstenose mittels Endarteriektomie oder Angioplastie mit Stenting – Analyse der vorliegenden Evidenz

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Zusammenfassung

1. Hintergrund und Auftrag

Im Rahmen der Erstellung einer S3-Leitlinie zur Diagnostik und Therapie der Karotisstenose erhielt das ÄZQ den Auftrag, einen Evidenzbericht zur Therapie der Karotisstenose mittels Endarteriektomie (CEA) versus Angioplastie mit Stenting (CAS) zu erstellen. Die randomisierten kontrollierten Studien zu dieser Fragestellung lagen der Leitliniengruppe vor. Eine systematische Literaturrecherche wurde daher nicht durchgeführt. Auftrag war vielmehr, die vorliegende Evidenz anhand bestimmter Kriterien im Hinblick auf die Validität der abzuleitenden Aussagen bzw. mögliche Verzerrungsrisiken (Bias) zu analysieren. Die Kriterien wurden vorab durch Experten der Leitliniengruppe festgelegt.

2. Fragestellung

Bearbeitet wurden methodische und inhaltliche Fragstellungen:

1. Wie waren das Studiendesign und die Power der Studien? Welche Gründe führten ggf. zum Studienabbruch?
2. Inwieweit sind Angaben zur Patientenselektion und zum Patientenfluss (nach CONSORT) vorhanden?
3. Sind die Ein- und Ausschlusskriterien der Studien vergleichbar? Sind Risikopatienten gleich verteilt?
4. Sind die Endpunkte und die Evaluationszeitpunkte in den Studien vergleichbar? Waren Subgruppenanalysen geplant? Ist die Altersabhängigkeit valide ableitbar? Wurden Angaben zur Restenosierung und den verwendeten Diagnosekriterien gemacht?
5. War ein vollständiges externes Datenmonitoring während der Studie gegeben?
6. Wie war der jeweilige Erfahrungsstand der Behandler?
7. Inwieweit waren die durchgeführten Therapien standardisiert?
8. War die periinterventionelle antithrombotische Therapie vergleichbar?

3. Vorgehensweise

Die Studien wurden im Hinblick auf die Fragestellungen analysiert. Die Ergebnisse wurden nach den Fragestellungen deskriptiv dargestellt. Geprüft wurden mögliche Assoziationen zwischen den Kriterien und der Rate an Endpunktereignissen. Es wurden keine statistischen Berechnungen im Sinne von uni- oder multivariaten Analysen, Sensitivitätsanalysen oder Metaanalysen durchgeführt.

4. Ergebnisse

Von den analysierten 12 Studien wies keine Studie eine ausreichende Fallzahl und Power auf, um die Gleichwertigkeit der Behandlungen sicher zu belegen. Die Studien mit Fallzahlberechnung waren als Äquivalenzstudien bzw. Nichtunterlegenheitsstudien angelegt. Die Gründe für einen Abbruch der Studien waren weit höhere als erwartete Komplikationsraten für die Karotis Angioplastie mit Stenting (CAS) und/oder eine weit höhere als geplante erforderliche Fallzahl und langsame Rekrutierung. Während die Angaben zum Patientenfluss (nach CONSORT) in fast allen Studien gegeben waren, wiesen nur wenige Studien Angaben zur Patientenselektion auf. Lediglich 2 der Studien wiesen ein vollständiges externes Datenmonitoring auf. Die Studien zeigten heterogene Einschlusskriterien und unterschiedliche kombinierte Endpunkte. Subgruppenanalysen waren nur in wenigen Fällen mehr als explorativ. Eine Altersabhängigkeit für die CAS-Ergebnisse ist aus den Studien ableitbar, nicht jedoch eine bestimmte Altersgrenze. Die Vorerfahrung der Behandler, die Standardisierung der Techniken sowie die gegebene antithrombotische Therapie waren unterschiedlich. Eindeutige Assoziationen zu den erzielten Ergebnissen waren nicht abzuleiten. Bei unterschiedlichen Kriterien und Erhebungszeitpunkten wiesen 3 (größere) Studien signifikant höhere Raten an schweren Restenosen bei CAS und 3 (kleinere) Studien keinen Unterschied auf. Eine statistisch signifkante Korrelation des Grades an Restenosierung mit entsprechenden klinischen Symptomen im Zeitraum wurde nicht nachgewiesen.

Im Hinblick auf die Heterogenität der Studien ist ein Nichteinschluss in eine Metaanalyse gerechtfertigt zum Beispiel im Hinblick auf eingesetzte Techniken, Risikofaktoren für die Behandlungen oder unterschiedliche Ereigniswahrscheinlichkeiten für symptomatische bzw. asymptomatische Patienten.

In die aktuelle Metaanalyse von Meier et al, 2010 gingen Ergebnisse aus elf Studien ein. Meier et al. schlossen aus inhaltlichen Erwägungen keine Studie aus. Sie analysierten die Ergebnisse von CAS und Karotis Endarteriektomie (CEA) im Hinblick auf das jeweilige relative Risiko für Endpunktereignisse, nicht im Hinblick auf absolute Werte. Die Metaanalyse zeigt für den primär untersuchten kombinierten Endpunkt „Risiko für periinterventionellen Tod oder Schlaganfall“ ein statistisch signifikant besseres Ergebnis für CEA als für CAS (Odds Ratio 0,67 95 % KI 0,47-0,95). Dieses Ergebnis wurde vor allem durch ein niedrigeres Risiko für Schlaganfall bei CEA im Vergleich zu CAS erzielt (Odds Ratio 0,65, 95%KI 0,43-1,00 p=0,049). Der Unterschied wird wesentlich durch das Auftreten von nicht stark funktionsbeeinträchtigendem Schlaganfall erzielt. Weiterhin zeigte sich ein statistisch signifikant höheres Risiko für Herzinfarkte für CEA als für CAS (Odds Ratio 2,69; 95 % KI 1,06-6,79 p=0,036) sowie ein statistisch signifikant höheres Risiko für Hirn- oder Halsnervenläsionen. Die Konfidenzintervalle der Ergebnisse sind jeweils sehr breit. Dies macht die Heterogenität der Ergebnisse der Einzelstudien deutlich und die hierfür insgesamt zu kleine Fallzahl, um sichere Ergebnisse zu erzielen.

Die im Mai 2010 nach der Publikation der Metaanalyse von Meier et al. veröffentliche Studie CREST zeigt für ein Kollektiv von symptomatischen und asymptomatischen Patienten keinen statistisch signifikanten Unterschied der CAS

im Vergleich mit der Karotisendarteriektomie (CEA) für einen primären kombinierten Endpunkt für periinterventionelle Ereignisse. Dieser Endpunkt beinhaltet neben Schlaganfall und Tod auch das Auftreten eines Herzinfarkts sowie den gleichseitigen Schlaganfall bis nach 4 Jahren (bei im Median 2,5 Jahren Nachbeobachtungszeit). Das 95%-Konfidenzintervall der erreichten Hazard Ratio von 1,11 liegt zwischen 0,81-1,51 und zeigt damit ebenfalls eine große Unsicherheit des Ergebnisses. Wird der periinterventionelle Endpunkt von Meier et al. betrachtet: „Risiko für periinterventionellen Tod oder Schlaganfall“ zeigt sich für symptomatische Patienten wie in der Metaanalyse ein statistisch signifikant niedrigeres Risiko für CEA im Vergleich zu CAS (angegeben ist die höhere Hazard Ratio für CAS: 1,89; 95% KI 1,11-3,21), für asymptomatische Patienten ist das Risiko ebenfalls niedriger, aber nicht statistisch signifikant unterschiedlich (Hazard Ratio für CAS 1,88 95% KI 0,74-4,42). Bei Betrachtung beider Gruppen ist das Ergebnis wiederum statistisch signifikant unterschiedlich zugunsten von CEA (höhere Hazard Ratio CAS: 1,90 95%KI 1,21-2,98). Die Einzelergebnisse von CREST zeigen periinterventionell ebenso weniger Schlaganfälle für CEA im Vergleich zu CAS, statistisch signifikant für die Gruppe symptomatischer Patienten (angegeben ist das erhöhte Risiko von CAS : HR 1,74 95%KI 1,02-2,98), nicht statistisch signifikant für asymptomatische Patienten bei ebenfalls gleichem Ergebnis (CAS HR 1,88 95% KI 0,79-4,42) und statistisch signifikant für die Gesamtgruppe (CAS HR 1,79 95%KI 1,14-2,82). Die aufgetretenen Schlaganfälle wurden zu über 75% als „Minor Strokes“ klassifiziert.

Bezüglich des Herzinfarktrisikos weist CREST ebenso wie Meier et al. einen statistisch signifikanten Vorteil für CAS aus (HR 0,5 95%KI 0,26-0,94). Die Schwere des Herzinfarkts wird nicht ausgewiesen.

Intermediäre Ergebnisse für CEA und CAS über 1-5 Jahren zeigen weder in der Metaanalyse noch in der CREST-Studie einen statistisch signifikanten Unterschied in der Rate von ipsilateralem Schlaganfall oder Tod bei nicht in allen Studien gewährleistetem vollständigen Follow up. Darüber hinausgehende Langzeitergebnisse liegen für die CAS im Gegensatz zur CEA noch nicht vor.

5. Fazit

Bisher liegt kein sicherer Vergleich von CAS mit CEA unter randomisierten kontrollierten Bedingungen vor. Das Ergebnis der CREST-Studie stimmt bei Betrachtung der entsprechenden Ereignisse mit dem Ergebnis der Metaanalyse von Meier et al, 2010 überein. Der Unterschied liegt in der Definition des primären Endpunktes. Dieser muss hinsichtlich seiner klinischen Wertigkeit diskutiert werden. Im Hinblick auf Einflussfaktoren für ein besseres oder schlechteres Ergebnis der CAS-Intervention können aus den Studiendaten keine sicheren Aussagen hinsichtlich der geprüften Kriterien getroffen werden. Dies bedeutet nicht, dass diese für die erzielten Ergebnisse nicht relevant sind. Sowohl für CEA als auch für CAS sind Bedingungen größtmöglicher periinterventioneller Sicherheit zu gewährleisten.

Inhaltsverzeichnis

Abkürzungsverzeichnis

ASS	Acetylsalicylsäure
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BACASS	Basel Carotid Artery Stenting Study
CAS	Carotid Angioplasty with Stenting (Karotis Angioplastie mit Stenting)
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CCA	common carotid artery (A. Karotis communis)
CEA	Carotid Endarterectomy (Karotis – Endarteriektomie)
CE-MRA	contrast-enhanced MRA (kontrastverstärkte Magnetresonanzangiographie)
CONSORT	Consolidated Standards of Reporting Trials
CREST	Carotid Revascularization Endarterectomy vs. Stenting Trial
CT	Computertomographie
DMC	Data Monitoring Committee
DSA	Digitale Substraktions-Angiographie
DUS	Duplex Ultraschall
ECG	Electrocardiography
EKG	Elektrokardiogramm
EQ-5D	EuroQol-5D (Europäischer Fragebogen zu Gesundheit/Lebensqualität)
EVA-3S	Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis
HR	hazard ratio
ICA	internal carotid artery (A.Karotis interna)
ICAVL	Accreditation of Vascular Laboratories
ICSS	International Carotid Stenting Study
ITT	Intention-to-treat
k.A.	Keine Angabe
K-ASYMP	Abkürzung für „ Kentucky asymptomatic“, die Studie von Brooks et al, 2004 [24]
KH	Krankenhaus
KI	Konfidenzintervalle
K-SYMP	Abkürzung für „Kentucky symptomatic“, die Studie von Brooks et al, 2001 [25]
LQ	Lebensqualität

MB	MB- (Muscle (Muskel), Brain (Gehirn))-Fraktion der Kreatinkinase
MRT	Magnetresonanztomographie
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institute of Health Stroke Scale
PTT	Partial Thromboplastin Time (partielle Thromboplastinzeit)
RC	Research Coordinator
RCT	Randomized Controlled Trial (randomisierte kontrollierte Studie)
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy
TIA	transient ischemic attack
US	Ultraschall

Tabellenverzeichnis

1. Hintergrund

1.1 Auftrag

Im Rahmen der Erstellung der S3-Leitlinie zur Diagnostik und Therapie der extrakraniellen Karotisstenose erhielt das ÄZQ von der Leitliniengruppe den Auftrag, einen Evidenzbericht zur Therapie der Karotisstenose mittels Endarteriektomie versus Stenting zu erstellen. Federführend bei der Auftragserteilung war die Deutsche Gesellschaft für Gefäßchirurgie. Alle randomisierten kontrollierten Studien zu dieser Fragestellung lagen der Leitliniengruppe vor. Eine systematische Literaturrecherche wurde deshalb nicht durchgeführt. Auftrag war vielmehr, die vorliegende Evidenz anhand bestimmter Kriterien im Hinblick auf die Validität der abzuleitenden Aussagen bzw. mögliche Verzerrungsrisiken (Bias) zu analysieren. Die Kriterien wurden vorab durch Experten (Gefäßchirurgen, Neurologen und Neuroradiologen) festgelegt.

1.2 Therapie der Karotisstenose

Die Rationale zur Therapie der symptomatischen, schweren Karotisstenose mittels chirurgischer Endarteriektomie basiert wesentlich auf zwei großen randomisierten Studien aus Europa und den USA, in denen gezeigt wurde, dass die Rate an Schlaganfällen bzw. die Mortalität im Vergleich zur konservativ-medikamentösen Therapie statistisch signifikant gesenkt werden kann [1; 2]. Diese Studien wurden 1998 publiziert. Im gleichen Jahr wurden Ergebnisse der ersten randomisierten Studie zum Vergleich der Endarteriektomie mit Angioplastie mit Stenting veröffentlicht. Bis Mai 2010 wurden Daten zu weiteren elf randomisierten kontrollierten Studien aus dem europäisch-amerikanischen Raum publiziert. Es wurde die Frage nach der Gleichwertigkeit der Angioplastie mit Stenting im Vergleich zur Endarteriektomie gestellt.

2. Fragestellung

Bearbeitet wurden methodische und inhaltliche Fragstellungen:

1. Wie waren das Studiendesign und die Power der Studien? Welche Gründe führten ggf. zum Studienabbruch?
2. Inwieweit sind Angaben zur Patientenselektion und zum Patientenfluss vorhanden?
3. Sind die Ein- und Ausschlusskriterien vergleichbar? Sind Risikopatienten gleich verteilt?
4. Sind die Endpunkte und die Evaluationszeitpunkte in den Studien vergleichbar? Waren Subgruppenanalysen geplant? Ist die Altersabhängigkeit valide ableitbar? Wurden Angaben zur Restenosierung und den verwendeten Diagnosekriterien gemacht?
5. War ein vollständiges Monitoring während der Studie gegeben?
6. Wie war der jeweilige Erfahrungsstand der Behandler?
7. Inwieweit waren die durchgeführten Therapien standardisiert?
8. War die periinterventionelle antithrombotische Therapie vergleichbar?

3. Vorgehensweise

3.1 Einschluss von Studien

Für die vorliegende Analyse wurde keine systematische Evidenzrecherche durchgeführt. Vielmehr orientierte sich die Auswahl der Studien systematischen Übersichtsarbeit und Metaanalyse von 2010 (systematische Literaturrecherche bis 7/2009): *Meier et al., 2010: Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled trials [3]* (siehe Kapitel 4.1 Aufbereitete Evidenz).

Es wurden alle RCTs berücksichtigt, die in dieser systematisch recherchierten Arbeit eingeschlossen waren. Eine frühere systematische Übersichtsarbeit von Ederle et al., 2009 [4] berücksichtigt zusätzlich eine Arbeit von Ling F und Jiao LQ, 2006 (n=166, preliminary analysis) [5]. Diese Arbeit wurde hier nicht eingeschlossen, da sie in chinesischer Sprache verfasst ist.

Zusätzlich zu den genannten RCTs wurde die CREST-Studie [6; 7] aufgenommen, die nach Abschluss der Recherchen für die Metaanalyse von Meier et al., 2010 [3] (25.7.2009) im Mai 2010 publiziert wurde.

Alle eingeschlossenen Studien sind randomisierte kontrollierte Studien zur Frage der Behandlung der Karotisstenose mittels Endarteriektomie oder endovaskulärer Therapie (Angioplastie mit Stenting).

3.2 Methodik

Die Publikationen zu den eingeschlossenen Studien wurden von den Experten zur Verfügung gestellt. Die Studien wurden formal-methodisch analysiert und bewertet. Darüber hinaus wurden die Studien bezüglich des Designs, der Durchführung und erreichten Power, der technischen Voraussetzungen, des Monitorings, des Einschlusses und der Vergleichbarkeit der Studienkollektive sowie der verwendeten Endpunkte und der erreichten statistischen Power im Hinblick auf ihre Validität und Vergleichbarkeit geprüft. Um die erforderlichen Angaben zu erhalten, wurden zusätzlich in den Studien genannte, frühere Publikationen berücksichtigt, die von den Experten zum Teil nicht zur Verfügung gestellt worden waren. Statistische Methoden wie Sensitivitätsanalysen oder metaanalytische Verfahren wurden zur Analyse der Effekte nicht angewandt. Geprüft wurden mögliche Assoziationen der untersuchten Faktoren im Hinblick auf die Häufigkeit von Endpunktereignissen.

4. Ergebnisse

4.1 Aufbereitete Evidenz

Im Folgenden werden die Ergebnisse der Metaanalyse dargestellt, die Grundlage für die Studienauswahl war.

Meier et al., 2010 [3], schlossen in ihre Metaanalyse elf Studien mit insgesamt 4.796 Patienten ein. Die im Juni 2010 publizierten Daten der CREST-Studie (2.502 Patienten) konnten von Meier et al. noch nicht berücksichtigt werden. Der Recherchezeitraum endete im Juli 2009.

Zehn der Studien (n=4.709) berichten über periprozedurale Endpunkte, neun über intermediäre Endpunkte nach 1-4 Jahren.

Das periprozedurale Risiko für Tod oder Schlaganfall (jegl. Schlaganfall) war in der Metaanalyse statistisch signifikant geringer für Karotis Endarteriektomie (CEA) als für Karotis Angioplastie mit Stenting (CAS) – Odds Ratio 0,67 95 % KI 0,47-0,95 p=0,025. Dies lag vor allem am Risiko des nicht stark funktionsbeeinträchtigenden Schlaganfalls. Das Risiko für Tod oder für den kombinierten Endpunkt aus Mortalität und persistierend stark funktionsbeeinträchtigendem Schlaganfall war periinterventionell nicht statistisch signifikant unterschiedlich.

Die Wahrscheinlichkeit, einen periinterventionellen Herzinfarkt zu erleiden, war statistisch signifikant niedriger bei CAS als bei CEA (Odds Ratio 2,69; 95 % KI 1,06-6,79 p=0,036), die Rate periinterventioneller Hirnnervenschädigungen war ebenfalls statistisch signifikant niedriger (Odds Ratio 10,02 95 % KI 4-26,1 p<0,001).

Die intermediär erhobenen Endpunkte Schlaganfall oder Tod nach 1-4 Jahren differierten nicht statistisch signifikant. Das bedeutet, nach 1-4 Jahren war das Risiko für Schlaganfall oder Tod ähnlich bei CAS wie bei CEA (HR 0,9 95 % KI 0,74-1,1 p=0,314).

Für die eingeschlossenen Studien zeigte sich bei konsekutivem Einschluss in die Metaanalyse eine Verbesserung der Ergebnisse für CAS über die Zeit.

4.2 Eingeschlossene Einzelstudien

Tabelle 1: In die Analyse eingeschlossene Studien und berücksichtigte Publikationen

Name der Studie, Autor, Jahr		Anzahl Teilnehmer
CREST	Brott et al., 2010 + Supplementary Appendix [6] Hopkins et al., 2010 [7]	n=2.502
ICSS	Ederle et al., 2010 [8] ICSS Protocol 2003 [9]/ICSS Protocol 2007 [10]	n=1.713
SPACE	Eckstein et al., 2008 [11] Stingele et al., 2008 [12] Fiehler et al., 2008 [13] Ringleb et al., 2006 [14] Ringleb et al., 2004 [15]	n=1.214
CAVATAS	Bonati/Ederle et al., 2009 [16] Cavatas Investigators, 2001 [17]	n=504
EVA-3S	Mas et al., 2008 [18] Mas et al., 2006 [19]	n=527
BACASS	Hoffmann et al., 2008 [20]	n=20
SAPPHIRE	Gurm et al., 2008 [21] Yadav et al., 2004 [22]	n=334
REGENSBURG	Steinbauer et al., 2008 [23] Link et al., 2000 [35]	n=87
KENTUCKY Asymptomatisch	= K-ASYMP Brooks et al., 2004 [24]	n=85
KENTUCKY Symptomatisch	= K-SYMP Brooks et al., 2001 [25]	n=104
WALLSTENT[1]	Alberts, 2001 (Abstract) [26]	n=219
LEICESTER	Naylor et al., 1998 [27]	n=23

[1] Die WALLSTENT-Studie wurde in die vorliegende Analyse mit einbezogen, da sie Teil der Metanalyse von Meier et al., 2010 ist. Ergebnisse von Abstracts sind grundsätzlich als nicht sicher zu werten. Die Richtigkeit der Darstellung ist bei negativem Ergebnis der Studie allerdings weniger in Frage zu stellen.

Tabelle 2: Überblick der wichtigsten Studienergebnisse

(n)DS = (nicht-)persistierend funktionsbeeinträchtigender Schlaganfall, **FS** = fataler Schlaganfall **HI**= Herzinfarkt ; **IS** = ipsilateraler Schlaganfall; KM = Kaplan-Meier; **P**= Durchgängigkeit; **PT**= behandlungsbedingter Tod, **Re**= Restenosierung mind. 70%; **S**= jeglicher Schlaganfall; **T**= Tod, **US**= Ultraschall, **VT** = vaskulär bedingter Tod

Studie	Follow up	primärer Endpunkt	Ergebnis CEA	Ergebnis CAS	Stat. Signifikanz	Nur periinterventionelle Ergebnisse (bis 30 Tage nach Beh., falls nicht anders angegeben)	Ergebnisse über periinterventionellen Zeitraum hinaus oder zusätzlich zum primären Endpunkt
CREST	med. 2.5J	30-Tage S+ HI+ T + geschätzt KM 4J IS	6,8%	7,2%	HR 1,11 n.s. 95%KI 0,81-1,51	S : CEA: 2,3% /CAS 4,1% (HR p= 0,01) ; HI : CEA: 2,3%, CAS: 1,1% (HR P= 0,03); T : CEA: 0,3%; CAS:0,7% n.s.	Alle S+T geschätzt KM 4J: CEA: 4,7%, CAS 6,4% HR 1,5 p=0,03 nur IS ab 30 Tage: CEA: 2,4%; CAS 2% n.s.
ICSS	? 120 T	3J-DS+FS	steht aus	steht aus	-	120Tage S+HI+T: CEA: 5,2%; CAS: 8,5% (HR p=0,006)	k.A.
SPACE	2J	30-Tage-IS+T	6,34%	6,84%	p=0,09 f. Non-inferiorität	Diff. 30T-IS+T 0,51% (90%KI -1,89-**2,91)** deshalb Ziel Noninfer. 2,5% nicht erreicht	30-Tage-IS+T+2J IS:CEA: 8,8%; CAS: 9,5% HR 1,1 (95%KI 0,75-1,61) n.s.
CAVATAS	med. 5J/ 4J für US	30-Tage-DS+T	5,9%	6,4%	n.s.	Alle-S (Sympt>7T) +T: CEA:9,9%, CAS:10%	5J- Re (geschätzt KM) CEA: 10,9%, CAS: 30,7% (HR 3,17 95%KI 1,89-5,32) p<0,0001 IS bei Re vs Nicht Re 10% vs 5% n.s.
EVA-3S	4J	30-Tage-S+T	3,9%	9,6%	KI überlappen	siehe primärer Endpunkt	6Mo S+T: CEA: 6,1%, CAS:11,7% p=0,02 30Tage S+T+4JIS : CEA : 6,2% CAS : 11,1% p=0,03
BACASS	48/43M	30-Tage-S+HI+T	10% (1/10)	0%(0/10)	n.berechnet	siehe primärer Endpunkt , CEA: 1xnDS	CEA nach 48 Mo: wie 30Tage, CAS nach 43Mo: 0%
SAPPHIRE	3J	30-Tage S, HI, T+ 1J IS+T	20,1%	12,2%	p=0,004 f. Noninferiorit.	S+HI+T : n.s.	30-Tage S, HI, T+ 3J IS+T: CEA: 26,9%; CAS: 24,6% Diff. -2,3% (95%KI -11,8-7,0) n.s.
REGENSB.	ca.5J	n.a. S+T+Hi +Re 1J?	2,2%	6,9%	n.a.	n.a.	5J IS CEA: 0%CAS:9,5%; Re: CEA: 0%, CAS 18,7%
K-ASYMP	4J	P, S, T?	0%	0%	n. berechnet	keine Ereignisse	P gleich CEA/CAS, keine weiteren Ereignisse
K-SYMP	2J	P , S, T?	1,9%	0%	n.a.	1T CEA= fataler HI postop.; P gleich CEA/CAS	2J: keine weiteren Ereignisse CEA/CAS
WALLSTENT	ca. 1J	1J IS+PT+VT	3,6%	12,1%	p=0,022	S+T: CEA: 4,5%; CAS: 12,1% p= 0,049	Alle DS+T bis zu 1J: CEA:0,9%; CAS 3,7% n.s.
LEICESTER	?30T	30-Tage S+T	0% (0/10)	71% (5/7)	p=0,034	5/7 Pat. mit CAS mit S, 3 mit DS	k.A.

Tabelle 3: Überblick – wichtigste analysierte Fragestellungen

Anmerkung: ●=ja; Exp = keine Zahl angegeben, aber Hinweis auf Expertise der Behandler; - = keine Angabe; ? Poolbarkeit aus inhaltlichen Gründen zu diskutieren,T=Ticlopidin.

Studie	DESIGN			Poolbarkeit gegeben	Studienabbruch/vorzeitige Beendigung	adäquate Power	Angabe rand. vs. nichtrand. Pat. im Zeitraum	asymptomatische Patienten	Aat.-morph. Ausschluss	Änd. Kriterien f. Zentren	Komplettes Monitoring	Komb. periintervent. Endpunkt mit Herzinfarkt	Periintervent. Endpunkt mit jegl. Schlaganfall	Auswertung periinterventionell	Nachverfolgung 1 J	Nachverfolgung 2 J	Nachverfolgung >2-5 J	Geplante Subgruppenanalysen	Ungeplante Subgruppenanalysen	Auswertung nach Alter	Evaluation unabh. Neurologe	Vorerfahrung CAS Min.	Proktoring CAS	Vorerfahr. CEA Min/J/ges.	Stand. CAS-Technik	Embolieprotektion	Stand, CEA-Technik	Angabe Shunt/Patch	Angabe Heparin CAS	Angabe Heparin CEA	ASS + ClopidogrelCAS	ASS CEA
	Äquivalenzst.	Noninferioritätsst.	Feasibility/keine Powerberechnung																													
CREST	●			●?			-	●	●		●	●	●				●	●	●	●	●	30?	●	12/J	●	●		●	●	-	●	●
ICSS	●			●			-		●			●	●	●				●	●			10	●	10/50		●		●	●	●	●	●
SPACE		●		●	●		-		●	●				●		●		●	●	●	●	25/10	●	25		●		●	-	-	●	-
CAVATAS			●	?			-	●	●					●			●		●	●		Exp		Exp				●	●	-	-	●
EVA-3S		●		●	●		-						●	●			●		●	●		5	●	25/J		●		●	●	●	●	●
BACASS			●	●	●		●					●	●	●								15		50/J	●	●		●	-	-	●	●
SAPPHIRE		●		?	●		●	●	●		●	●	●		●		●		●			20		15	●			-	●	●	●	●
REGENSB.			●	●	●		●		●			●	●	●			●				●	Exp		-	●		●	-	-	-	●	●
K-ASYMP			●	?			-	●					●				●				●	Exp		Exp	●		●	-	●	-	●	●
K-SYMP			●	●			-						●			●					●	Exp		Exp	●		●	-	●	-	●	●
WALLSTENT	●			●	●		-								●							-		-	-	-	-	-	-	-	T	-
LEICESTER		●		●	●		●						●	●							●	8		Exp	●		●	●	●	●	-	●

4.3 Evidenzanalyse der Einzelstudien

4.3.1 Methodische Konzeption und Durchführung der Studien

4.3.1.1 Studiendesign und Studienabbruch/Auswirkungen auf die Power

Im Folgenden werden die Studien nach Studiendesign gruppiert, der Studienaufbau beschrieben, sowie Gründe genannt, die ggf. zu einem Studienabbruch führten. Die Auswirkungen auf die Power der Studien werden benannt. Auch für die nicht vorzeitig beendeten Studien wird die statistische Power besprochen. Um das Gesamtverständnis für die Studien zu erleichtern, werden ggf. wichtige Ergebnisse aufgeführt.

Bei sechs der 12 Studien erfolgte eine prospektive Power- und Fallzahlkalkulation. Diese Studien sind als Äquivalenz – oder Noninferioritätsstudien konzipiert.

Bei **Aquivalenz-** und **Noninferioritätsstudien** wird eine Prozentspanne definiert, innerhalb derer das Ergebnis für den primären Endpunkt für die Testintervention im Vergleich zur Standardintervention abweichen darf. Bei Noninferioritätsstudien ist dies die Spanne, die nach unten abgewichen werden kann, ohne dass die zu testende Intervention als schlechter angesehen wird („Irrelevanzbereich“). Die Rationale einer Noninferioritätsstudie ist zu erläutern. Dies betrifft vor allem die Vorteile der Test-Intervention, aufgrund derer ein schlechteres Ergebnis des vereinbarten Endpunkts im Vergleich zur Standardtherapie toleriert würde. Solche Vorteile können zum Beispiel eine signifikante Reduktion von Nebenwirkungen oder von Kosten sein. Die Studien sollten so konzipiert und durchgeführt sein, dass die Interventionen durch die erreichten Studienergebnisse sicher vergleichbar sind. Der Patient soll – auf seine individuellen Merkmale bezogen – das Verfahren identifizieren können, das für ihn den größten Nutzen bei geringstem Schaden hat. Als Rationale für den Vergleich CAS-CEA wird in den Studien genannt:

- Alternative zu CEA bei nicht operablen Patienten oder Patienten mit hohem Operationsrisiko

- geringere Invasivität

- geringeres anästhesiologisches Risiko (Vermeidung von Vollnarkose)

- Vermeidung einer lokalen Inzision und damit Vermeidung des Risikos von Hirn- und Halsnervenläsionen

- Vermeidung weiterer chirurgischer Komplikationen (Infektionen/Hämatome)

- Minderung des hämodynamischen Ischämierisikos

Im Rahmen dieses Berichts werden diese Annahmen nicht überprüft, wenn sie nicht Teil der vereinbarten Fragestellungen waren.

Äquivalenzstudien

Drei der sieben Studien mit Power- und Fallzahlkalkulation sind als Äquivalenzstudien einzustufen (CREST, ICSS, WALLSTENT). Davon wurde eine, WALLSTENT, vorzeitig beendet.

CREST (2010) ist eine Studie mit 2502 Patienten, davon 47,2 % asymptomatische Patienten mit einer Karotisstenose von mindestens 60% (nach NASCET, mind. 70% im Ultraschall) und 52,8% symptomatische Patienten mit einer Karotisstenose von mindestens 50%.

Für CREST wird in der Publikation beschrieben, dass auf Superiorität getestet wurde. Als Alternative zur Nullhypothese (beide Behandlungen sind nicht unterschiedlich) ist jedoch angegeben, dass beide Behandlungen verschieden sind. Es wird insofern nicht die Annahme der Superiorität von CAS ausgewiesen, sondern die der Nicht-Äquivalenz. Die Studie weist – wie aus dem aktualisierten Protokoll im Appendix E der Publikation hervorgeht- zwei unterschiedliche Powerberechnungen aus. Diese richten sich an das amerikanische National Institute of Health und an die FDA (Food and Drug Administration). In diesen Fallzahlberechnungen werden die eingeschlossenen asymptomatischen und symptomatischen Patienten jeweils mit einer angenommenen 50:50 Verteilung berücksichtigt. Die Fallzahlberechnung bezieht sich jeweils auf die Gesamtgruppe.

1. Für das Nationale Institute of Health gilt folgende Berechnung:

Für die NIH-Berechnung gilt die Annahme, dass die Behandlungen nicht unterschiedlich sind. Die Studie ist dann dafür gepowert, mit einer 90%igen Wahrscheinlichkeit für den kombinierten Endpunkt (Schlaganfall, Tod oder Herzinfarkt innerhalb von 30 Tagen und ipsilateraler Schlaganfall nach 30 Tagen im mehrjährigen Verlauf) Unterschiede in der CAS-Behandlung versus CEA zu finden, wenn diese außerhalb eines Hazard Ratio-Bereichs von 0,54-1,49 liegen. Das heißt, innerhalb dieser Spanne gilt die CAS als gleichwertig, sowohl bei einer relativen Verringerung der Endpunktereignisse gegenüber CEA um 46% (HR 0,54) als auch bei einer relativen Verschlechterung der Ergebnisse gebenüber CEA um 49% (HR 1,49) im Zeitraum.

Die Hazard Ratios ergeben sich aus der Annahme der Autoren, dass ein Unterschied von 1,2% pro Jahr zwischen den Behandlungen nicht klinisch signifikant ist. Die angenommene Ereignisrate ist für symptomatische Patienten berechnet. Dies folgt der Rationale, dass sich bei Einschluss von asymptomatischen Patienten die Abweichungen der Ereignisse bei geringeren Ereignisraten eher verkleinern. Die Ereignisrate für symptomatische Patienten wird mit 5,8% periinterventionell angenommen. Dies die Rate, die in der NASCET-Studie durch die Endarteriektomie erreicht wurde [33]. 1% wird für den zusätzlich einbezogenen Herzinfarkt dazugerechnet. Als jährliche Ereignisrate für ipsilateralen Schlaganfall wird, ebenfalls abgeleitet von den Daten aus NASCET, 1,68% angenommen. Die Fallzahlberechnung von CREST basiert auf der Ereignisrate nach 5 Jahren. Diese wird mit 13,35% angenommen. Der tolerierte Unterschied nach 5 Jahren beträgt 5,9%. Durch den Einschluss von 2500 Personen sollte eine Power erreicht werden, die einen Unterschied von mehr als +/-5,9% zu 90% sicher

als statistisch signifikant unterschiedlich nachweist, d.h. einen Wert niedriger als 7,45% oder größer als 19,25%. Aufgrund der sehr breiten tolerierten Spanne der Hazard-Ratios wird bei Betrachtung der symptomatischen Patienten unter Annahme der genannten Ereignisraten allein eine Power von 70% für diesen Nachweis erreicht.

2. Für die FDA gilt folgende Berechnung

Die Powerberechnung für die FDA folgt der methodischen Konzeption einer klassischen Noninferioritätsstudie – mit der Nullhypothese, dass die Behandlungen verschieden sind und der Alternativhypothese, dass die CAS der CEA gleichwertig ist. Als Noninferioritätsgrenze (Irrelevanzbereich) legten die Autoren eine Abweichung von 2,6% für den primären kombinierten Endpunkt nach einem Jahr fest. Die Patientenzahl von n=2500 ermöglicht laut Studienprotokoll den Nachweis der Gleichwertigkeit mit einer Power von 82% bei einem 90% Konfidenzintervall. Die Verteilung symptomatisch – asymptomatisch wird mit 50:50 angenommen. Die Berechnung gilt unter der Annahme einer für symptomatische und asymptomatische Patienten gemittelten Ereignisrate von 5,54% (asymptomatisch 4,35%, symptomatisch 6,8%) periinterventionell und 6,76% nach einem Jahr (asymptomatisch +1,07%, symptomatisch +1,68% pro J).In der Publikation der Studie werden die Ergebnisse für diesen Endpunkt nach einem Jahr nicht thematisiert.

Der Zeiitraum zur Erfassung von Endpunktereignissen nach der periinterventionellen Zeit von ursprünglich einem Jahr wurde ausgeweitet. Die erreichte Ereignisrate für den primären kombinierten Endpunkt beträgt nach einer medianen Nachbeobachtungszeit von 2,5 Jahren anhand von Kaplan-Meier-Kurven für 4 Jahre geschätzt 7,2 % für CAS und 6,8 % für CEA und ist damit niedriger als angenommen. Die Differenz von + 0,4% nach 4 Jahren entspricht einer Hazard Ratio von 1,11. Das 95%-Konfidenzintervall zeigt mit 0,81 bis 1,51, in welchen Grenzen der „wahre Wert“ der Hazard Ratio liegen kann. Im ungünstigen Fall (HR 1,51) beträgt die anhand der Kaplan-Meier-Kurven geschätzte Differenz nach 4 Jahren + 3,468% = 10,268. Dieser Unterschied würde nicht als statistisch signifikant ausgewiesen werden. Damit erreicht die CREST-Studie nicht ganz die berechnete Power für die NIH-Analyse (HR max. 1,49). Die Ergeniss für die FDA-Analyse sind nicht dargestellt. Aufgrund der niedirgeren Ereignisraten kann nicht von einem sicheren Nachweis der Noninferiorität von Cas ausgegangen werden. Die Ergebnisse gelten für die heterogene Gruppe symptomatischer und asymptomatischer Patienten. Pro Patientengruppe weisen die Ergebnisse jeweils ein sehr breites Konfidenzintervall auf, so dass die Ergebnisse pro Gruppe nicht sicher sind.

Als Studienziel für die **ICSS** (2010) ist der Vergleich von Risiken, Nutzen und Kosteneffektivität der Behandlung mit CAS vs. CEA angegeben. Es wurde „kein großer Unterschied“ der Endpunktereignisraten angenommen. Aus der Publikation von 2010 [8], nicht jedoch aus dem Protokoll [26; 27], geht hervor, dass die Rate der primären Endpunktereignisse entsprechend der vorausgehenden CAVATAS-Studie jeweils mit ca. 10 % angenommen wurde. Durch die kalkulierte Fallzahl von 1.500

Patienten aus erfahrenen Zentren sollte ein 3 %iges Konfidenzintervall des Unterschieds für den primären Endpunkt nach 30 Tagen (Schlaganfall, Herzinfarkt oder Tod) und ein 3,3 %iges Konfidenzintervall des Unterschied für den Langzeitendpunkt (Überleben ohne persistierend funktionsbeeinträchtigenden Schlaganfall nach drei Jahren) erreicht werden. Die Studie hat laut den Autoren eine 80 %ige Power, einen Unterschied von 4,7 % für den 30-Tages-Endpunkt nachzuweisen und von 5,1 % für den Langzeitendpunkt. Eine Rationale für diese Ereignisspannen wird nicht angegeben. Die Rekrutierung wurde planmäßig durchgeführt. Die Auswertung 120 Tage nach Randomisierung ergab einen Risikounterschied von 3,3 % (Endpunktrate 4,0 % für CEA und 7,4 % für CAS; p = 0,003) mit einem 95 %-Konfidenzintervall von 1,1-5,6. Damit wurde das Ziel eines 3%-Konfidenzintervalls trotz Rekrutierung von insgesamt 1.713 Personen nicht erreicht und die Studie ist als nicht ausreichend gepowert zu werten.

Im **WALLSTENT**-Abstract (2001) ist angegeben, dass der Einschluss von n=700 Patienten geplant war, um die Gleichwertigkeit von CAS gegenüber CEA zu testen. Details zur Fallzahlberechnung sind dem Abstract nicht zu entnehmen. Eine Vollpublikation erfolgte nicht. Die Studie wurde nach Einschluss von 219 Patienten nach einem medianen Follow-up von ca. einem Jahr abgebrochen, da die Rate an gleichseitigem Schlaganfall und periinterventionell bedingtem bzw. vaskulär bedingtem Tod bei CAS statistisch signifikant weit höher lag als bei CEA (12,1 % vs. 3,6 % p=0,022). Die Ergebnisse sind als nicht ausreichend gepowert zu werten.

Noninferioritätsstudien

Vier Studien wurden als Noninferioritätsstudien geplant (SPACE, EVA-3S, SAPPHIRE, LEICESTER). Alle diese Studien wurden - aus unterschiedlichen Gründen - vorzeitig beendet.

SPACE (2004) wurde mit einer Noninferioritätsgrenze von 2,5% für die Rate der periinterventioneller Ereignisse gleichseitiger Schlaganfall und Tod geplant. Es wurde eine Rate an Endpunktereignissen von ca. 5% pro Studienarm angenommen. Um die Noninferiorität mit einer Power von 80% bei einer (einseitigen) Irrtumswahrscheinlichkeit von 5% nachzuweisen, wurden pro Studienarm 950 Patienten berechnet. Nach dem Einschluss von 1.200 Patienten erfolgte eine Zwischenanalyse. Die Ereignisrate war mit jeweils über 6 % höher als bei der ursprünglichen Berechnung (5 %) angenommen. Die Neukalkulation der benötigten Fallzahl ergab eine notwendige Rekrutierung von 2.500 Patienten, um statistisch valide Ergebnisse zu erhalten. Die Rekrutierung für die Studie wurde nach dieser Zwischenauswertung geschlossen, u. a. mit der Begründung, dass die Mittel für die Rekrutierung der höheren Patientenzahl nicht gegeben waren. Im Ergebnis erbrachte SPACE einen absoluten Unterschied von n=4 an gleichseitigem ischämischem Schlaganfall oder Tod bis 30 Tage nach Behandlung. Der Unterschied zwischen den Ereignisraten (CAS 6,84%, CEA 6,34%) lag bei 0,51 % und war nicht statistisch signifikant (90 % KI -1,89-2,91%, p=0,09). Die Studie erbrachte jedoch den statistischen Nachweis der Nichtunterlegenheit nicht, da die obere Grenze des Konfidenzintervalls bei 2,91 % über der gegebenen Noninferioritätsgrenze der Studie von 2,5 % lag. Die Ergebnisse sind nicht ausreichend gepowert.

Die französische **EVA-3S**-Studie (2004) wurde mit einer Noninferioritätsgrenze von 2% für den 30-Tages-Endpunkt Schlaganfall oder Tod geplant. Die Autoren berechneten eine Fallzahl von n=872, um mit einer statistischen Power von 80% bei einseitigem Alpha von 5% den Nachweis der Noninferiorität zu erbringen. Es wurde eine Ereignisrate von 5,6% für den 30-Tages-Endpunkt (Schlaganfall oder Tod) für CEA und von 4% für CAS angenommen. Der Studienabbruch erfolgte nach einer Rekrutierungszeit von fast 5 Jahren (2001-2005) nach Einschluss von 527 Patienten. Eine Zwischenanalyse war jeweils nach dem Auftreten von 30 Ereignissen vorgesehen. Das Auftreten eines Schlaganfalls oder das Eintreten von Tod im CAS-Arm war in der Auswertung 30 Tage nach Behandlung stark erhöht mit 9,6 % (95 % KI 6,4-14) gegenüber CEA mit 3,9 % (95 % KI 2,0-7,2; relatives Risiko 2,5 (95 % KI 1,2-5,1)). Das 95% Konfidenzintervall des Risikounterschieds von 5,7% schloss die angegebene Irrelevanzgrenze von 2% nicht ein (2,1-9,3%). Die Rate an periinterventionellen Komplikationen nach 30 Tagen war für die CEA mit 3,9% niedriger als die 5,6 %, mit denen auf Grundlage der RCTs zu Endarteriektomie versus medikamentöse Therapie kalkuliert worden war. Die Neuberechnung der Power für diese Noninferioritätsstudie erbrachte eine erforderliche Patientenzahl von n=4.000 für einen möglichen Nachweis auf Noninferiorität für den 30-Tage-Endpunkt. Dies anzustreben erschien nicht durchführbar aufgrund der erzielten Ergebnisse, die eine Superiorität der CEA gezeigt hatten. Der Unterschied nach sechs Monaten für Schlaganfall und Tod fiel ebenso statistisch signifikant zugunsten der CEA aus (CEA 6,1 %, CAS 11,7 % p=0,02). Die Studienergebnisse sind statistisch als nicht ausreichend gepowert einzuschätzen.

Die Autoren von **SAPPHIRE** (2004) geben eine Fallzahlkalkulation für bis zu 2.400 Patienten für den Nachweis der Noninferiorität von CAS mit einer Noninferioritätsgrenze von 3% an. Die Methode zu exakten Berechnung der Fallzahl wird als „triangular sequential method“ beschrieben. Diese Methode erlaubt laut den Autoren eine flexible Studiengröße, die anhand von Zwischenanalysen berechnet wird. Die Autoren rekrutierten Hochrisikopatienten (siehe Abschnitt „Einschlusskriterien“). Sie begründen den Studienabbruch nach ca. zwei Jahren Rekrutierungszeit mit der schwierigeren Rekrutierung nach Eröffnen mehrerer Stent-Register. Bis zur Auswertung traten 20 Endpunktereignisse im CAS-Arm (12,2 %)und 32 (20,1 %) im CEA-Arm auf (p=0,05). Die absolute Differenz betrug -7,9 % zugunsten von CEA mit einem 95 % KI von -16,4 bis 0,7 % (p=0,004). Aufgrund der oberen Grenze des Konfidenzintervalls von 0,7% wurde das Ziel der Noninferiorität < 3 % erreicht und zu diesem Zeitpunkt der Studie sogar eine Überlegenheit der CAS (p=0,034) nachgewiesen. Die Studie war mit 334 Teilnehmern nicht adäquat gepowert.

Die Autoren der **LEICESTER**-Studie (1998) geben eine kalkulierte Fallzahl von n=300 für den Nachweis der Noninferiorität der CAS an. Details der Powerkalkulation sind nicht genannt. Mit einer „group sequential method“ wurden 15 Interimsanalysen berechnet (nach Einschluss von jew. 20 Pat), bei denen der Unterschied zwischen CAS und CEA kleiner als 0,086 sein sollte, um einen statistisch signifikanten Unterschied von p<0,05 am Ende der Studie zu vermeiden. In die LEICESTER-Studie wurden nur 23 Patienten eingeschlossen, davon waren 17 zum Zeitpunkt der Auswertung behandelt. Die erste Interimsanalyse zeigte bei 10 mit CEA behandelten Patienten keine Komplikationen, während bei fünf von sieben Patienten (71 %) mit CAS ein Schlaganfall auftrat, davon in drei Fällen mit

persistierender Funktionsbeeinträchtigung nach 30 Tagen. Die Studie wurde daraufhin vorzeitig beendet. Die Studie ist von der Anzahl eingeschlossener Personen als Feasibility-Studie einzuschätzen.

Machbarkeitsstudien

Fünf der 12 Studien wurden ohne eine ausgewiesene Power- bzw. Fallzahlberechnung durchgeführt. Diese können als Machbarkeitsstudien bzw. hypothesengenerierende Studien klassifiziert werden. Davon wurden 2 Studien (BACASS, REGENSBURG) vorzeitig beendet.

Als Machbarkeitsstudie explizit ausgewiesen ist die multizentrische Studie **CAVATAS** (2001) aus Großbritannien (n=504), die Autoren geben an, keine Powerberechnung durchgeführt zu haben, die Studie wurde nicht vorzeitig beendet. Im Anschluss an diese Studie wurde die ICSS-Studie mit geplanter Fallzahl aufgelegt, da die CAVATAS-Studie für beide Interventionen identische Raten an Todesfällen plus jeglichem Schlaganfall 30 Tage nach Behandlung zeigte (jeweils 10 %) und eine Noninferiorität damit als möglich angenommen werden konnte.

Die anderen vier Studien in dieser Kategorie (BACASS, REGENSBURG, K-SYMP, K-ASYMP) sind kleine unizentrische Studien zur Gleichwertigkeit von CAS gegenüber CEA mit fehlender statistischer Power (n=20 bis n=104).

Die Autoren von **BACASS** (2008) beendeten die Rekrutierung nach n=20 Patienten wegen des Beginns der ICSS-Studie. Die Autoren der **REGENSBURG**-Studie (2008) geben an, dass die Rekrutierung nach Einschluss von n=87 Patienten beendet wurde, da die multizentrische SPACE-Studie begann. Ursprünglich war die Rekrutierung von 200 Patienten vorgesehen [28]. Auswirkungen auf die Power sind hier nicht relevant.

Für die beiden Studien **K-SYMP** (2001) und **K-ASYMP** (2004) ist keine vorzeitige Beendigung beschrieben.

Zusammenfassung:

Von sieben Äquivalenz-/Noninferioritätsstudien wurden fünf vorzeitig beendet. (SPACE, EVA-3S, SAPPHIRE, WALLSTENT, LEICESTER). Zwischenanalysen ergaben in drei Fällen (EVA-3S, WALLSTENT, LEICESTER) weit höhere periprozedurale Komplikationsraten der CAS als erwartet und die Studien wurden aus ethischen Gründen abgebrochen.

Weitere Gründe für die vorzeitige Studienbeendigung waren von den Kalkulations-Annahmen abweichende Raten an CEA – höher bei SPACE und niedriger bei EVA-3-S. Die Rekalkulation der erforderlichen Studiengrößen ergab eine höhere Fallzahl. SAPPHIRE wurde wegen zu langsamer Rekrutierung geschlossen.

Von den 5 Studien ohne angegebene Fallzahlberechnung wurden 2 aufgrund des Beginns von internationalen multizentrischen Studien beendet (BACASS, REGENSBURG). Auswirkungen auf die Power dieser kleinen Studien sind nicht relevant. In der Gesamtschau weist keine der Studien eine ausreichende Power im Hinblick auf die festgelegte Berechnung auf. Eine Poolbarkeit bei unterschiedlichem

Studiendesign ist grundsätzlich möglich. Im Hinblick auf eine Poolbarkeit zu prüfen sind jedoch wesentlich unterschiedliche Einschlusskriterien für die Studien.

4.3.1.2 Patientenselektion/Zuteilung zu Intervention/Follow-up/Analyse

In diesem Abschnitt wird beschrieben, inwieweit die CONSORT-Kriterien [29] für Einschluss („enrollment"), Zuteilung zu Intervention („allocation of intervention"), Follow-up und Analyse der Patienten in den Studien erfüllt sind.

Patienteneinschluss im Zeitraum („Enrollment")

Lediglich vier Studien (SAPPHIRE, REGENSBURG, BACASS, LEICESTER) enthalten Angaben zum Anteil randomisierter Patienten im Verhältnis zu allen in Frage kommenden. Für SAPPHIRE wird die Zahl in Frage kommender Patienten im Zeitraum von ca. zwei Jahren mit n=747 beziffert. Davon wurden 413 nicht randomisiert, da beurteilt wurde, dass nicht beide Therapieoptionen gleichwertig möglich seien. Sieben erhielten eine CEA, 406 eine CAS. Ergebnisse für diese Patienten werden nicht genannt.

Bei BACASS lehnten 45 der in Frage kommenden 82 Patienten im Zeitraum von 11/98 bis 2/02 die Randomisierung ab, für 35 der Patienten sind ohne Spezifizierung „weitere Gründe" für den Nichteinschluss genannt.

In der LEICESTER-Studie wurden in dem kurzen Zeitraum der Randomisierung (6-9/1996) 23 Patienten randomisiert und bei 4 wurde aufgrund zu schwerwiegender klinischer Symptomatik oder Ablehnen des Einverständnisses eine komplikationslose CEA außerhalb der Studie durchgeführt.

In REGENSBURG wird für den Rekrutierungszeitraum 8/99 bis 2/02 die Behandlung von insgesamt 137 Patienten angegeben. Davon erfüllten 26 die Einschlusskriterien, drei davon lehnten eine Randomisierung ab.

In den anderen acht Studien fehlen Angaben darüber, wie viele Patienten hinsichtlich ihrer Eignung für die Studie bewertet wurden, aber nicht randomisiert wurden.

Zuteilung zu Intervention („allocation of intervention")

Für vier Studien liegen keine expliziten Angaben darüber vor, ob alle randomisierten Patienten die zugeteilte Intervention erhielten (WALLSTENT, K-SYMP, K-AYMP, REGENSBURG).

Für die restlichen acht Studien ist dies jeweils angegeben. Bei BACASS erhielten alle Patienten den zugeteilten Eingriff. In den drei Studien ICSS, SPACE, und CAVATAS lagen die angegebenen Raten zugeteilter Interventionen jeweils bei mindestens 95,6 %. Bei EVA-3S erhielten 98 % der Patienten die zugeteilte CEA-Behandlung, aber nur 93 % die zugeteilte CAS-Behandlung. Bei CREST erhielten 90 % der CAS Patienten den zugeteilten Eingriff, 5,7 % erhielten CEA statt CAS und 4,3 % keine Intervention. Im CEA-Arm wurde bei 95 % die CEA durchgeführt, 1 % erhielten CAS und 4 % keine Intervention.

Bei SAPPHIRE lag die Rate an durchgeführten CEA im CEA-Arm bei 90,4 %, während 95,2 % die vorgesehene CAS erhielten. Bei LEICESTER erhielten alle CEA-Patienten den zugeteilten Eingriff und 70 % der CAS-Patienten. Für die Studien mit tatsächlich durchgeführter zugeteilter Intervention unter 95 % ist es sinnvoll, die Ergebnisse auch „per protocol" zu analysieren. Ein ähnliches Ergebnis erhöht die Sicherheit der „intention to treat-" Analyse. Für die vorliegenden Studien ist das – mit jeweils gleichlautendem Ergebnis – für die SAPHHIRE-Studie und die ICSS-Studie und für die 2-Jahresauswertung der SPACE-Studie der Fall. Eine „per protocol" Analyse von EVA-3-S und CREST - in beiden Studien ist v.a. der Anteil an nicht erhaltener zugeteilter Intervention im CAS-Arm relativ hoch - mit einer entsprechenden Bestätigung der Ergebnisse fehlt.

Follow-up

In der CREST-Studie werden Raten an „Lost of Follow-up" von 5,4 % für CAS und 8,87 % für CEA angegeben. Dieser Verlust ist mit < 10 % formal zu tolerieren (als unzureichend gelten RCTs mit weniger als 80% Follow up). SPACE geben einen Verlust von 12,4% der Patientendaten bei der 2 Jahresauswertung an. CAVATAS weisen für die Auswertung von 5 Jahren im Median bzw. die sonographische Beurteilung ca. 4 Jahren im Median eine Datenvollständigkeit von 81,9% aus.

Die 3-Jahresauswertung von SAPPHIRE [21] wurde nur mit 77,8 % der Patientendaten vorgenommen. Diese Auswertung ist mit mehr als 20 % fehlenden Daten als unsicher zu werten, ebenso wie die Langzeitauswertung von REGENSBURG mit ca. 70% der Daten.

In den übrigen Studien werden mehr als 90 % der Daten randomisierter Patienten analysiert.

Sekundärer Ausschluss von Patienten nach Randomisierung

In den Studien sind die anatomischen Einschlusskriterien jeweils gekoppelt an das Vorliegen einer Angiographie bei Randomisierung. Ein sekundärer Studienausschluss aufgrund des Ergebnisses einer nach der Randomisierung durchgeführten Angiographie wird in der ICSS-Studie beschrieben. Laut dem Flussdiagramm wurden diese Patienten jedoch in die Intention-to-Treat-Analyse eingeschlossen.

Zusammenfassung:

Insgesamt besteht aufgrund der großen Anteile nichtrandomisierter Patienten im Zeitraum und aufgrund der fehlenden Angaben eine Unsicherheit hinsichtlich der Repräsentativität der Studienkollektive im Verhältnis zu allen Patienten.

Für SAPPHIRE und REGENSBURG sind auch die intermediären Daten aufgrund von Follow up Verlusten von > 20% nur als eingeschränkt sicher zu werten.

4.3.2 Ein- und Ausschlusskriterien/Umgang mit/Verteilung von Risikopatienten

Die Studien wurden hinsichtlich ihrer Einschlusskriterien und hinsichtlich der Risikofaktoren und deren Verteilung bei den eingeschlossenen Patienten („baseline characteristics") analysiert.

4.3.2.1 Änderung von Einschlusskriterien im Studienverlauf

Bei zwei Studien wurden die Einschlusskriterien im Studienverlauf geändert.

CREST rekrutierten von 2000-2005 ausschließlich symptomatische Patienten und ab 2005 bis zum Ende der Rekrutierungszeit 7/2008 auch nichtsymptomatische Patienten. Aufgrund einer Interimsanalyse von 749 Pat (ca. 70% asymptomatisch), die ein stark erhöhtes Risiko für Endpunktereignisse bei 80-Jährigen zeigte [32], wurden diese ab 2005 von der Randomisierung ausgeschlossen.

EVA-3S rekrutierten von 2000-2003 symptomatische Patienten mit einer Karotisstenose ab 70 % (es werden jeweils die % nach Kriterien nach NASCET angegeben) und von 2003-2005 auch Patienten mit einer Stenose ab 60 %. Studienergebnisse hatten einen Nutzennachweis der Endarteriektomie auch in dieser Gruppe gezeigt.

4.3.2.2 Einschluss symptomatischer und asymptomatischer Patienten

Die Studien zur Etablierung der CEA wurden für symptomatische und nicht symptomatische Patienten getrennt vorgenommen. Die Ereigniswahrscheinlichkeiten in den beiden Gruppen sind deutlich unterschiedlich.

Die Studien zum Vergleich von CEA und CAS gelten im Wesentlichen für symptomatische Patienten. Ein gleichzeitiger Einschluss von symptomatischen und asymptomatischen Patienten wurde bei CREST, SAPHHIRE und CAVATAS vorgenommen.

Der Einschluss von asymptomatischen Patienten erfolgte bei CREST nach fast 5 Jahren Rekrutierungszeit. Im aktualisierten Protokoll werden die aufgrund der CEA-Studien unterschiedlichen angenommenen Endpunktereignisraten für symptomatische und asymptomatische Patienten ausgewiesen und dann als eine Gesamtrate kombiniert. Die angenommenen periinterventionellen Ereignisraten aus den CEA-Studien differieren mit 5,8% und 3,35% erheblich. Ziel war eine Verteilung der beiden Gruppen zu jeweils 50%. Tatsächlich wurden 52,8% symptomatische Patienten eingeschlossen. Die Powerberechnung erfolgte jedoch für die Gesamtgruppe. Die periinterventionellen Ereignisraten der Gruppen bestätigten sich als unterschiedlich. Dies betrifft sowohl die Anzahl der periinterventionellen Endpunktereignisse zwischen den Gruppen als auch ein unterschiedliches Verhältnis von Ereignisraten zwischen CAS und CEA (asymptomatische Patienten: CAS 3,5%, CEA 3,6%; symptomatische Patienten CAS 6,7%: CEA 5,4%). Die unterschiedliche Ereignisrate zwischen den Gruppen bleibt für den 4-Jahresendpunkt bestehen, die Ereignisraten zwischen den Behandlungsn nähern sich an (asymptomatische Patienten: CAS 5,6%, CEA 4,9%; symptomatische Patienten CAS 8,6%, CEA 8,4%)

Für die SAPPHIRE-Studie stand das Protokoll nicht zur Verfügung. Die Studie nahm 28,8% Patienten mit symptomatischer Stenose auf. Die Ergebnisse gelten demzufolge vorwiegend für Patienten mit asymptomatischer Karotisstenose. Auch in dieser Studie zeigte sich eine Heterogenität der Ergebnisse zwischen den Gruppen (asymptomatische Patienten: CAS 30 Tage 5,4%, CEA 30 Tage 10,2%; CAS 1 Jahr

9,9%, CEA 1 Jahr 21,5%; symptomatische Patienten: CAS 30 Tage 2,1% CEA 30 Tage 9,3%, CAS 1Jahr 16,8% CEA 1Jahr 16,5%).

Der Anteil symptomatischer Patienten in CAVATAS beträgt 3%. Weitere 7% hatten Symptome mehr als 6 Monate vor Randomisierung. Dieser Anteil ist mit 10% für das Gesamtergebnis nicht relevant.

Bei Brooks et al., 2004 (K-ASYMP) wurden ausschließlich nicht symptomatische Patienten eingeschlossen mit einer Stenose > 80 % (n=84). In der kleinen Studie traten in beiden Armen keine Endpunktereignisse auf.

In der Metaanalyse fanden Meier et al., 2010 [3] keinen Unterschied in den relativen Ereignisraten bei Ausschluss der beiden Studien mit überwiegend asymptomatischen Patienten (K-ASYMP, SAPPHIRE). Die CREST-Studie wurde dort nicht berücksichtigt.

Charakteristika symptomatischer Karotisstenosen

Der Grad der Stenose (nach NASCET) als Voraussetzung für den Einschluss von symptomatischen Patienten ist bei vier der elf Studien (CREST, ICSS, SPACE, SAPHHIRE) mit > 50 % angegeben. Die Mehrzahl der eingeschlossenen Patienten wiesen Stenosen ab 70 % auf (CREST: 85,6 %, ICSS: 90 %, SPACE: 63 %, SAPPHIRE: n. a.). Bei zwei Studien (EVA-3S, WALLSTENT) wurden Patienten ab einer Stenose von 60 % eingeschlossen (davon Stenose ab mind. 70 % bei EVA-3S 93 %, bei WALLSTENT n. a).und bei vier Studien ab mind. 70 % (BACASS, REGENSBURG, K-SYMP, LEICESTER). CAVATAS nennen ohne Mindestangabe einen mittl. Stenosegrad von 86,4 % +/-9,1 %.

Die hinsichtlich des Auftretens der Symptome berücksichtigten Zeiträume vor Randomisierung sind unterschiedlich. Eine Rationale für den gewählten Zeitraum ist jeweils nicht angegeben. Die Zeiträume betragen drei Monate (BACASS, K – SYMP), 4 Monate (EVA-3S), sechs Monate (CREST, SPACE) sowie 12 Monate (ICSS, REGENSBURG). Patienten mit Symptomen, die mehr als 6 Monate zurücklagen, wurden bei CREST als asymptomatische Patienten gewertet. In drei Studien fanden sich keine Angaben (SAPPHIRE, WALLSTENT, LEICESTER). Die angegebenen klinischen Symptome sind übereinstimmend die transitorisch ischämische Attacke, Amaurosis fugax, Retinainfarkt sowie nicht stark funktionsbeeinträchtigender Schlaganfall. Zu beachten ist, dass bei SPACE und ICSS auch Patienten mit einem Rankin Score von mehr als 2 eingeschlossen wurden.

Eine Assoziation zwischen Grad der Stenose, Auftreten und Verteilung der angegebene Symptome und der Häufigkeit von Endpunktereignissen ist nicht zu erkennen.

Charakteristika asymptomatischer Karotisstenosen

Für die nichtsymptomatischen Patienten wurde bei CREST der Nachweis einer Stenose von mehr als 60 % in der Angiographie oder mehr als 70 % in der Duplexsonographie gefordert. Bei einer sonographisch diagnostizierten Stenose von 50-69 % musste in einem MRT oder CT, das durch einen designierten CREST-

Befunder beurteilt wurde, eine mind. 80 %ige Stenose festgestellt werden. War das nicht eindeutig möglich, wurde eine Angiographie durchgeführt.

Unter die asymptomatischen Patienten wurden auch solche gerechnet, die Symptome in der kontralateralen Hemisphären oder vertebrobasiläre Symptome aufwiesen oder Symptome jeglicher Hemisphäre vor > 180 Tagen vor der Randomisierung. Insgesamt wurden bei CREST 47,2 % nichtsymptomatische Patienten eingeschlossen.

Bei SAPPHIRE wurden Patienten ohne Symptome mit einer Stenose von mehr als 80 % eingeschlossen. Die Diagnose wurde mittels Duplexsonographie nach standardisierten Kriterien gesichert. Bei K-Asymp wurden Patienten mit mind. 80% Stenose nach NASCET eingeschlossen.

4.3.2.4 Anatomisch-morphologische vaskuläre Ein – und Ausschlusskriterien

In vier Studien wird explizit darauf hingewiesen, dass die Gefäßanatomie des betreffenden Gefäßabschnittes (in der Angiographie) kein Selektionskriterium war (EVA-3S, K-SYMP, K-ASYMP, LEICESTER). Im Abstract von WALLSTENT sind dazu keine Angaben vorhanden.

In den Studien mit Angaben zu anatomisch-morphologischen vaskulären Kriterien beziehen sich diese auf CAS und CEA. Es wird jeweils darauf hingewiesen, dass durch das beurteilende interdisziplinäre Team CEA als auch CAS gleichermaßen als technisch durchführbar eingeschätzt werden musste, bzw. der Behandler (so wird es bei ICSS beschrieben) „unsicher“ sein sollte, welche der Behandlungen die beste für den Patienten ist. Damit bleiben die Gründe für den Ausschluss der individuellen Patienten zu einem großen Teil offen.

Spezifische (d.h. über die Definition der Stenose hinausgehende) anatomische Einschlussgründe werden für CREST ausgewiesen, es wird ein Gefäßdurchmesser von mindestens 4mm und höchstens 9mm im Referenzgefäßabschnitt (distal der Läsion) gefordert.

Im Folgenden wird auf die Ausschlusskriterien fokussiert.

Ausschlusskriterien, die sich eher auf CAS beziehen

Ein Ausschluss von Patienten aufgrund der anatomisch-morphologischen Kriterien starke Gefäßwindung, bzw. Gefäßelongation unterhalb der Stenose, „tortuosity“, Pseudookklusion oder flottierender Thrombus, die ein sicheres Einführen eines Führungskatheters oder Stents nicht erlauben, ist bei sechs Studien explizit angegeben (CREST, ICSS, SPACE, SAPPHIRE, CAVATAS, REGENSBURG).

Für CREST werden vorausgegangene Stenteingriffe ipsilateral und Okklusion als weitere Ausschlussgründe genannt, ebenso das Vorhandensein einer extensiven oder diffusen Atherosklerose des Aortenbogens und der proximalen Karotis kommunis, (aufgrund der Risiken bei Einführen eines Führungskatheters). Ein Ausschlussgrund ist weiterhin ein intraluminaler Füllungsdefekt, der in der Angiographie nachgewiesen wurde, bzw. ohne Angiographie der Nachweis einer Verkalkung, wenn die Veränderung nicht mit dem ulzerierten Zielgefäß vereinbar ist. Für ICSS sind die Kriterien weniger spezifisch angegeben. Neben den eingangs genannt wird als Ausschlussgrund eine Stenose der proximalen Karotis kommunis

genannt. SAPPHIRE nennen sehr allgemein „Gefäßerkrankungen, die Katheter-basierte Techniken nicht erlauben“. REGENSBURG weisen als Ausschlussgrund „technisch nicht möglicher perkutaner Zugang“ mit Beispielen aus.

Ausschlusskriterien, die sich eher auf CEA beziehen

Als Kontraindikationen für CEA werden bei CREST spezifiziert: ipsilaterale intrakranielle oder extrakranielle Stenose größer als die Stenose im Zielbereich, cerebrales Aneurysma >5mm, arteriovenöse cerebrale Malformationen, oder - und mit diesem allgemeinen Hinweis endet die Liste - andere abnormale Befunde, die eine Kontraindikation gegen CEA darstellen.

Höhergradige Tandemstenosen werden auch bei SAPCE, BACASS, EVA-3S und REGENSBURG als Ausschlussgrund genannt. Für ICSS wird beim Hinweis auf Ausschluss von Patienten „not suitable“ für CEA als beispielhafter Ausschlussgrund eine hochsitzende Stenose genannt. Eine unerreichbare Stenose wird auch bei CAVATAS angeführt. SAPPHIRE geben Aneurysmen > 9mm an.

SPACE nennen als generelle Ausschlussgründe - nicht atherosklerotisch bedingte Stenosen (z.B. nach Dissektion, Bestrahlung oder vorausgegangener Operation/Stent-Applikation). BACASS und EVA-3S geben ebenfalls nicht atherosklerotische Gefäßerkrankung an.

Zusammenfassend kann festgestellt werden, dass in den Studien neben sehr spezifischen Kriterien jeweils auch „weiche“ Angaben gemacht werden. Die spezifischsten Angaben liegen für CREST vor.

4.3.2.5 Weitere Ein- und Ausschlusskriterien

Hinsichtlich weiterer Ein- und Ausschlusskriterien der Studien muss zunächst beachtet werden, dass SAPPHIRE explizit ein Hochrisikokollektiv einschließt. Alle Patienten mussten mindestens eines der definierten „Hochrisiko“-Kriterien (klinisch signifikante kardiale Erkrankung wie kongenitale Herzinsuffizienz, abnormaler Stresstest oder offene Herzchirurgie in der Vorgeschichte, schwere pulmonale Erkrankung, kontralateraler Carotisverschluss, kontralaterale laryngeale Nervenlähmung, vorausgegangene Halsoperation oder -bestrahlung, Restenose nach CEA, Alter über 80 Jahren) erfüllen. In den anderen Studien sind diese Kriterien überwiegend als Ausschlusskriterien genannt. Damit sind die Studienergebnisse nicht mit den Ergebnissen der anderen Studien vergleichbar.

Speziell bezüglich kardialer Risiken wurden bei CREST- und CAVATAS Patienten mit einem Herzinfarkt innerhalb der letzten 30 Tage vor Randomisierung bzw. „recently“ ausgeschlossen. Für CREST sind darüber hinaus als weitere kardiale Ausschlusskriterien benannt: jegliche bekannte kardiale Erkrankung mit erhöhtem Embolierisiko, chronisches oder paroxysmales Vorhofflimmern (in den letzten 6 Monaten) sowie eingeschränkt oder nicht operabel aufgrund kardialer Vorerkrankung, z.B. bei instabiler Angina pectoris. Bei ICSS wurden Patienten mit geplanter Bypass-Operation ausgeschlossen. K-SYMP/K-ASYMP nennen kardiale Arrhythmien als Ausschlussgrund, EVA-3S instabile Angina Pectoris,

REGENSBURG vorausgegangener Herzinfarkt in den letzten 6 Monaten ohne Revaskularisierung.

Bei den anderen Studien (SPACE, BACASS, WALLSTENT, LEICESTER) wurden keine expliziten kardialen Ausschlussgründe identifiziert. SAPCE nennen allgemein jegliche Kondition, die für einen Patienten ein Risiko bedeuten könnte, wenn CEA oder CAS initiiert wird, als Ausschlussgrund.

Insgesamt kann eine zunehmende Spezifizierung von Ein- und Ausschlussgründen über die Zeit festgestellt werden. Das CREST-Protokoll führt diese über sieben Seiten auf. Bei der Interpretation der Studienergebnisse ist deshalb immer zu beachten, für welche Population die Ergebnisse gelten.

4.3.2.6 Verteilung von kardiovaskulären Risikofaktoren zwischen CEA- und CAS-Patienten und zwischen den Studien

Eine generelle Ungleichverteilung von Risikofaktoren zwischen den Studienarmen konnte anhand der in den Publikationen dargelegten, ausreichend beschriebenen Charakteristika der eingeschlossenen Patienten für die prospektiv Fallzahl-geplanten Studien nicht festgestellt werden.

Folgende Auffälligkeiten wurden festgestellt: bei CREST wiesen von den Patienten im CEA-Arm ca. 3% mehr Dyslipidämien auf als im CAS-Arm (p=0,048). Bei EVA-3S finden sich im CEA-Arm mehr Patienten mit Schlaganfall in der Vorgeschichte (p=0,02) und mehr Patienten > 75 J, im CAS-Arm dagegen mehr Patienten mit TIA in der Vorgeschichte (6 %, kein p-Wert angegeben) und ohne Angabe einer Größenordnung, mehr Pat. mit kontralateraler Karotisokklusion.

Bei SAPPHIRE weisen die Patienten in der CAS-Gruppe sowohl mehr koronare Herzkrankheit (+10 %) auf als auch 12,6 % mehr an vorausgegangenen Bypass-Operationen sowie 11,4 % mehr an vorausgegangenen angioplastischen Eingriffen.

Ein Vergleich der Studien zeigte unterschiedliche Raten an bestehender koronarer Herzkrankheit bzw. vorausgegangenen Herzinfarkten oder Bypassoperationen (s.u.).

Koronare Herzkranheit/vorausgegangener Herzinfarkt – Vergleich der Studien

Studie	**% Pat. mit KHK oder vorausgegangenem Herzinfarkt**	**% Pat. mit kard. Bypass**
CREST	CAS:42,5% CEA: 45%	CAS: 19,9% CEA: 21,5%
ICSS	CAS: 41% CEA: 41%	CAS: 13% CEA: 14%
SPACE	CAS: 21% CEA: 24%	n.a.
CAVATAS	CAS: 39%	n.a.

	CEA: 37%	
EVA-3S	(Angegeben nur Pat. mit vorausgeg, Herzinfarkt: CAS: 10.7% CEA: 13,1%	CAS: 13,4% CEA: 13,4%
BACASS	CAS: 20% CEA: 40%	n.a.
SAPPHIRE	CAS: 85,8% CEA: 75,5%	n.a.
REGENSB.	CAS: 42% CEA: 45%	n.a.
K-ASYMP	CAS: 81% CEA: 48%	n.a.
K-SYMP	CAS: 74% CEA: 60%	n.a.
WALLSTENT	n.a.	n.a.
LEICESTER	n.a.	n.a.

Von den großen Studien mit Fallzahlberechnung sind für SPACE und EVA-3S die geringsten Raten an koronarer Vorerkrankung / Herzinfarkt angegeben.

Eine Assoziation zu Endpunktereignissen kann aufgrund der Daten nicht gesichert erfolgen.

4.3.3 Endpunkte und Evaluation

4.3.3.1 Vergleichbarkeit der primären Endpunkte

Kombinierte Endpunkte

Alle zwölf Studien haben kombinierte primäre Endpunkte. Diese sind zum Teil unterschiedlich definiert und deshalb nicht ohne Weiteres vergleichbar.

Das Ziel der Intervention CEA oder CAS ist das Verhindern eines gleichseitigen, u.U. fatalen Schlaganfalls. Ipsilateraler Schlaganfall ist deshalb immer Bestandteil des Endpunkts.

In die Endpunkte gehen jedoch auch die möglichen Komplikationen durch die Intervention mit ein. Hierbei werden unterschiedliche Ereignisse berücksichtigt.

Ein kombinierter Endpunkt, der das Auftreten von jeglichem (beidseitigen) Schlaganfall und Myokardinfarkt und Eintreten des Todes periinterventionell mit beinhaltet, wird in vier Studien (CREST, ICSS, SAPPHIRE, BACASS) angegeben.

Der primäre Endpunkt von CREST ist jeglicher Schlaganfall, Herzinfarkt oder Tod von der Randomisierung bis max. 36 Tage nach dem Eingriff sowie zusätzlich der ipsilaterale Schlaganfall bis zu vier Jahren nach Randomisierung.

SAPPHIRE geben als primären Endpunkt jeglichen Schlaganfall, Herzinfarkt oder Tod ab Behandlung bis 30 Tage danach an sowie zusätzlich alle gleichseitigen Schlaganfälle ab Tag 31 bis zu einem Jahr.

BACASS nennen nur den periprozeduralen Schlaganfall, Tod oder Herzinfarkt als primären Endpunkt.

Bei ICSS ist der ursprüngliche primäre Endpunkt das Langzeitüberleben ohne stark funktionsbeeinträchtigenden Schlaganfall (Rankin-Score > 3) nach drei Jahren. Diese Auswertung konnte noch nicht durchgeführt werden. Im Studien-Register wurde 2007 auch Herzinfarkt als primärer Endpunkt ergänzt. In der Publikation von 2010 [8] wurde die Rate an jeglichem Schlaganfall, Tod oder Herzinfarkt 120 Tage nach Randomisierung ausgewertet.

REGENSBURG geben keinen primären Endpunkt im Methodenteil an, werten aber jeden Schlaganfall, Tod oder weitere behandlungsassoziierte adverse Ereignis und jede Restenose im Zeitraum ab Randomisierung. Sie führen auch Herzinfarkt auf.

Auch Studien CAVATAS und LEICESTER werten sowohl ipsi- als auch kontralateralen Schlaganfall für ihre Endpunkte. Bei CAVATAS ist der primäre Endpunkt die Rate an stark funktionsbeeinträchtigendem Schlaganfall (Rankin-Score > 3) oder Tod bis 30 Tage nach Behandlung. LEICESTER und EVA-3S werten jeden Schlaganfall oder Tod bis 30 Tage nach Behandlung,

In die Endpunktdefinition von SPACE und WALLSTENT geht nur der ipsilaterale Schlaganfall ein. Die Autoren von SPACE geben als primären Endpunkt alle gleichseitigen ischämischen Schlaganfälle oder Tod von der Randomisierung bis zu 30 Tage nach Behandlung an. WALLSTENT definierten als primären Endpunkt gleichseitigen Schlaganfall, interventionsbedingter Tod oder vaskulärer Tod innerhalb eines Jahres.

Die beiden unizentrischen Studien K-SYMP und K-ASYMP nennen als Endpunkte die Durchgängigkeit der Carotis nach 24 bzw. 48 Monaten und die Rate an Komplikationen (u. a. Schlaganfall + Tod).

Definition Schlaganfall

Als Schlaganfall sind in den Studien übereinstimmend entsprechende neurologische klinische Symptome über mind. 24 Stunden definiert. Nur die Autoren von CAVATAS geben an, dass erst über mindestens sieben Tage anhaltende Symptome als Schlaganfall gewertet wurden. Dies wird damit begründet, dass die Patienten mit CEA postoperativ nicht routinemäßig von einem Neurologen untersucht wurden (erst nach einem Monat), so dass die Autoren ein Underreporting bei kürzeren Episoden verhindern wollten.

Die Schlaganfälle werden in den Studien hinsichtlich des Grades der durch sie ausgelösten Funktionsbeeinträchtigung unterteilt in „disabling“ – stark funktionsbeeinträchtigend (ab Rankin Score 3) – und „non disabling“ – nicht stark funktionsbeeinträchtigend (Rankin Score 1 und 2).

Diese Einteilung wird anhand der modifizierten Rankin Skala vorgenommen:

Modifizierte Rankin Skala:

0 = Keine Symptome

1 = Keine wesentliche Funktionseinschränkung trotz Symptomen; kann alle gewohnten Aufgaben und Aktivitäten verrichten

2 = Geringgradige Funktionseinschränkung; unfähig alle früheren Aktivitäten zu verrichten, ist aber in der Lage, die eigenen Angelegenheiten ohne Hilfe zu erledigen

3 = Mäßiggradige Funktionseinschränkung; bedarf einiger Unterstützung, ist aber in der Lage, ohne Hilfe zu gehen

4 = Mittelschwere Funktionseinschränkung; unfähig, ohne Hilfe zu gehen und unfähig, ohne Hilfe für die eigenen körperlichen Bedürfnisse zu sorgen

5 = Schwere Funktionseinschränkung; bettlägerig, inkontinent, bedarf ständiger Pflege und Aufmerksamkeit

Zu beachten ist, dass ein „non disabling stroke“ mit einem Rankin Score 2 die Funktionseinschränkung beinhaltet, dass nicht alle früheren Aktivitäten verrichtet werden können.

Die Beurteilung des Ausmasses eines Schlaganfalls nach den Interventionen wird in 2 Studien (CREST, SAPPHIRE) mit der Stroke Skala des National Institutes of Health (NIHSS) vorgenommen. Als Major Stroke gilt ein Schlaganfall mit einer Bewertung nach NIHSS von mindestens 9 (von 42 möglichen Punkten gesamt) nach 3 Monaten. Der in den Publikationen aufgeführte Minor Stroke ist im CREST Protokoll nicht definiert und kann als NIHSS <9 angenommen werden. In den im Protokoll enthaltenen Aufklärungsinformationen für Patienten wird angegeben, dass die Symptome des Minor Stroke nur bis zu 30 Tage anhalten. Bei SAPPHIRE sind Major und Minor Stroke anhand des NIHSS nicht explizit definiert.

Es wird in den Publikationen nicht klar, ob Minor Stroke und non disabling stroke gleichgesetzt werden können.

Definition Herzinfarkt

Die Herzinfarkt-Definition ist bei SAPPHIRE laborchemisch als zweifache Erhöhung des Troponins mit positiver CK-MB-Fraktion (Kreatinkinase aus Herz- oder Skelettmuskel) ausgewiesen, während bei CREST und ICSS zusätzlich

Beschwerden über ca. 30 Minuten oder entsprechende EKG-Veränderungen vorliegen mussten. BACASS geben keine Definition für den Herzinfarkt an.

Die CREST-Autoren weisen zusätzlich im Studienprotokoll aus, dass auch alle Herzinfarkte nur aufgrund von Labor- oder EKG-Veränderungen registriert wurden.

Eine Unterteilung der Herzinfarkte in Bezug auf das Ausmass des betroffenen Herzmuskelareals bzw. die klinische Bedeutung wird nur bei SAPPHIRE in der Angabe von Q-Wave (n=2) und Non-Q-Wave-Infarkt (n=15) vorgenommen.

Fatale Herzinfarkte werden bei CREST (CEA =1), ICSS (CAS = 3), Regensburg (CEA =1) und K-SYMP (CEA = 1) angegeben.

Wertung der primären Endpunkte

Die klinische Einschätzung, inwieweit die jeweils gewählten klinischen Endpunkte adäquat sind, muss innerhalb der Leitlinien-Gruppe diskutiert werden. Eine diesbezügliche Anfrage an einzelne Experten unter Einschluss von Gefäßchirurgen, eines Neuroradiologen und eines Kardiologen zeigte Differenzen in der Einschätzung der Wichtigkeit der Endpunkte, insbesondere der Bedeutung von nicht stark funktionsbeeinträchtigendem Schlaganfall (Rankin Score <3), Herzinfarkt und Tod nach mehr als einem Jahr.

Vergleich der erzielten periinterventionellen Endpunktereignisse

Ein Vergleich wird für die aktuellen großen Studien CREST, ICSS, SPACE und EVA-3S vorgenommen. Für CREST wurde die Gruppe symptomatischer Patienten herangezogen.

Vergleich periinterventioneller Ergebnisse

Studie	30-Tages-Endpunkt Tod oder Schlaganfall		30-Tages-Endpunkt Herzinfarkt		30-Tages-Endpunkt Tod oder Schlaganfall oder Herzinfarkt	
	CAS	CEA	CAS	CEA	CAS	CEA
CREST (sympt.)	6%	3,2%	1%	2,3%	6,7%	5,4%
ICSS	7,4%	3,5%[2]	0,3%	0,6%	7,7%	4,1%
SPACE	6,84%[3]	6,34%	n.a.	n.a.	n.a.	n.a.
EVA-3S	9,6%	3,9%	0,4%	0,8%	n.a.	n.a.

Im Vergleich wird deutlich, dass CREST die niedrigsten Ereignisraten für periinterventionellen Tod oder Schlaganfall aufweist. Der relative Unterschied zwischen CAS und CEA beträgt 46,7%. Der relative Unterschied zwischen CAS und

[2] Per protocol
[3] Nur ipsilateraler Schlaganfall

CEA Unterschied nach Einbeziehung des Herzinfarkts beträgt 20%. SPACE weist die höchsten Ereignisraten für den kombinierten periinterventionellen Endpunkt für CEA aus mit dem geringsten relativen Unterschied zu CAS bei Berücksichtigung nur ipsilateraler Schlaganfälle. Bezüglich der Rate an Herzinfarkten weist CREST deutlich höhere Ereignisraten auf als ICSS und EVA-3S. In der SPACE-Publikation wird das Auftreten von Herzinfarkt nicht thematisiert.

Hinsichtlich der Schwere der Schlaganfälle machen die nicht stark funktionsbeeinträchtigenden Schlaganfälle / Minor strokes bei CREST 76,5% aller Schlaganfälle aus, bei ICSS 55,3%, bei SPACE 49,4% und bei EVA -3S 73%.

4.3.3.2 Sekundäre Endpunkte

Kombinierter Endpunkt mit stark funktionsbeeinträchtigendem Schlaganfall oder Tod / Einzelne Endpunkte

Ein Vergleich der sekundären Endpunkte für die Studien bzw. für die einzelnen Endpunkte der Studien wurde nicht vorgenommen.

Beeinträchtigung der Funktion von Hirn- oder Halsnerven

Eine Beeinträchtigung der Funktion von Hirn- oder Halsnerven tritt ausschließlich bei CEA auf. Der Unterschied ist im Vergleich zu CAS in der Regel statistisch signigikant. Eine Beurteilung dieses Endpunkts, der in den Studien z.T. unterschiedlich definiert wurde (nicht generell vorübergehende von dauerhafter Beeinträchtigung unterschieden) wurde für die einzelnen Studien nicht vorgenommen.

Angaben zu Restenosierung/ Diagnosekriterien

Nicht alle Studie enthalten Aussagen zur Restenosierung nach den jeweiligen Eingriffen. Keine Angaben dazu finden sich bei kurzer Beobachtungszeit bei ICSS, EVA-3S und LEICESTER. Das WALLSTENT-Abstract enthält ebenfalls keine Aussagen zu Restenosierung. Bei CREST wird die Restenosierungsrate als sekundärer Endpunkt angegeben, es waren jedoch in den Publikationen keine Angaben dazu zu finden.

SPACE geben nach 2 jähriger Nachbeobachtung eine statistisch signifikant höhere Rate an schweren Stenosen (70-99%) für CAS im Vergleich zu CEA an (10,7%, n=54 versus 4,6% n=23; p=0,009). Als Diagnosekriterien für die Duplexsonographie werden die ECST- oder NASCET-Kriterien genannt. Dabei wird berücksichtigt, dass eine Stenose von 50% nach NASCET einer Stenose von 70% im Ultraschall entspricht.

CAVATAS nennen zunächst Kriterien nach Sidhu et Allan, 1997 [31] und weisen nach ca. 1 Jahr für CAS 18% schwere Stenosen aus versus 5% bei CEA (p<0,001). Zu beachten ist, dass >70% der Patienten in der Gruppe mit endovaskulärer Behandlung keinen Stent erhielten. Für die Auswertung nach median 4 Jahren werden die NASCET-Kriterien herangezogen. Die geschätzte 5-Jahresrate an schweren Restenosen oder Okklusion liegt bei 30,7% für CAS und bei 10,9% für CEA (HR 3,17 95%KI 1,89-5,32 p<0,001). Patienten mit schweren Restenosen nach einem Jahr erlitten nach 5 Jahren in 10% einen ipsilateralen Schlaganfall, im

Gegensatz zu 5% in der Gruppe ohne schwere Restenose nach einem Jahr. Der Unterschied ist statistisch nicht signifikant. Zu beachten ist, dass sich die Auswertung nur auf knapp 82% der ursprünglich eingeschlossenen Patienten bezieht und für die Studie keine Powerberechnung vorlag. Patienten mit Stent hatten eine geringere Raten an Restenosen.

Die Autoren von BACASS beziehen sich auf die CAVATAS-Kriterien. Nach 2 Jahren werden keine schweren Restenosen angegeben.

Die Autoren von REGENSBURG geben nach einer Nachbeobachtung von mehr als 5 Jahren (von 70% der Patienten) eine Rate schwerer Restenosierung von 18,75% bei CAS an und keine bei CEA. Die Bestimmung des Stenosegrads erfolgte unter Berücksichtigung des Peaks der systolischen Geschwindigkeit, dem ICA/CCA-Index, der enddiastolischen Geschwindigkeit und Turbulenzen.

Die Autoren von K-SYMP und K-ASYMP werteten die systolische Ratio von ICA/CCA aus und geben bei symptomatischen Patienten nach 2 Jahren eine Ratio von ca. 1,7 für CEA und CAS an. Für asymptomatische Patienten werden nach 4 Jahren fast identische Raten angegeben (für CAS ca. 1, 8, für CEA ca. 1,9).

Für SAPPHIRE wird in der 3-Jahresauswertung nicht der Grad der Restenosierung ausgewiesen sondern Revaskularisierungsraten von 3% nach CAS und 7,1% nach CEA. Die Ultraschallkriterien für Stenosen werden nach Huston et al, 2000 [30] angegeben.

Damit zeigen bei unterschiedlichen Kriterien und Erhebungszeitpunkten 3 (größere) Studien signifikant höhere Raten an schweren Restenosen bei CAS und 3 (kleinere) Studien keinen Unterschied, sowie eine Studie eine geringeren Revaskularisierungsrate für CAS. Eine statistisch signifkante Korrelation des Grades an Restenosierung mit entsprechenden klinischen Symptomen im Zeitraum wurde nicht nachgewiesen.

Untersuchung der Lebensqualität

Lediglich in zwei Studien werden Angaben zur Lebensqualitätsuntersuchungen als sekundäre Endpunkte gemacht (CREST, CAVATAS). Für CAVATAS liegen Auswertungen aus einer Subgruppe von zwei Zentren anhand der Fragebögen SF-36 und EUROQuol vor, die keine Unterschiede in der (periinterventionellen) Lebensqualität von Patienten mit CEA oder CAS angeben, Die Autoren von CREST fokussierten auf die Bedeutung der Endpunkte Schlaganfall und Herzinfarkt für die betroffenen Patienten bis zu einem Jahr. Verwendet wurde der SF-36. Eine Erhebung der körperlichen und mentalen Gesundheit fand vor der Intervention und eine Woche sowie ein und zwölf Monate danach statt. Ein statistisch signifikanter Unterschied in der subjektiven Einschätzung der körperlichen Gesundheit fand sich nach einem Jahr für Patienten, die einen Schlaganfall erlitten hatten – auch einen Schlaganfall mit nicht persistierender Funktionsbeeinträchtigung – nicht aber für Patienten mit einem Herzinfarkt. Eine kleine, statistisch signifikante Verschlechterung der mentalen Gesundheit nach einem Jahr zeigte sich nur für Schlaganfall mit nicht persistierender Funktionsbeeinträchtigung.

Da in den anderen Studien keine Erhebungen zur Lebensqualität erfolgten, kann hinsichtlich dieses Endpunktes keine sichere Aussage abgeleitet werden.

4.3.3.3 Subgruppenanalysen

Keine Subgruppenanalysen liegen für die 6 folgenden Studien vor: BACASS, REGENSBURG, K-SYMP, K-ASYMP, WALLSTENT, LEICESTER.

Eine geplante Subgruppenanalyse wurde bei CREST in Bezug auf das Geschlecht durchgeführt. Die Altersauswertung war laut den Autoren ebenfalls geplant, aber nicht im Protokoll angegeben. Als nicht gepant, da durch Änderung der Einschlusskriterien erst ab 2004 aufgenommen, kann die Auswertung in symptomatische und asymptomatische Patienten gelten. Diese zeigt im Vergleich der Verfahren keinen statistisch signifikanten Unterschied für den primären Endpunkt.

SPACE geben vordefinierte Subgruppenanalysen an, die Publikation von 2006 [14] weist Alter und Geschlecht aus. In der Publikation 2008 [11] zeigen sich für die angegebenen Subgruppenanalysen Geschlecht, Grad der behandelten (cut off 70%) oder kontralateralen Stenose (cut-off 70% und Okklusion), Seite der behandelten Stenose und Klinik der zur Randomisierung führenden Symptome keine statistisch signifikanten Unterschiede. Während 2006 ein prädefinierter cut-off von 75 Jahren für das Alter anegegben ist, wird 2010 ein statistisch signifikanter Unterschied für das Risiko von Endpunktereignissen zwischen CEA und CAS bei Patienten ab 68 Jahren ausgewiesen. Die Rate bei CEA bleibt etwa gleich (bei 8,6% bzw, 9%), während sich die Rate bei CAS mehr als verdoppelt (5% vs 13,7%). Die nicht geplante Subgruppenanalyse hinsichtlich des Nutzens eines Protektionsystems (bei 27% angewendet) zeigt keine Unterschiede bei Anwendung bzw. Nicht-Anwendung. Die Anwendung wurde nicht randomisiert zugeteilt (Publikation Jansen O. et al, 2009).

ICSS geben mehrere geplante Subgruppenanalysen an, die sie als explorativ charakterisieren. In der entsprechenden Übersicht sind aufgeführt: Alter (cut off 70 Jahre), Geschlecht, Vorhandensein von Diabetes oder behandeltem Bluthochdruck, Schweregrad der ispsilateralen (cut off bei 70%) oder kontralateralen (cut off bei 50% und 70%) Stenose, Klinik des letzten symptomatischen Ereignisses, Vorhandensein multipler Symptome, Anzahl rekrutierter Patienten pro Zentrum (cut off n=50) und Zeit von der Randomisierung bis zur Behandlung. Für keine dieser Subgruppenanalysen wurde ein sicher statistisch signifikanter Unterschied ($p<0,05$) zwischen den Gruppen nachgewiesen. Vorhandene Unterschiede können demzufolge nur Hinweise geben.

EVA-3S weisen in der Publikation 2008 verschiedene nicht geplante Subgruppenanalysen aus (Geschlecht, Alter (cut-off 70 Jahre), Vorhandensein von Hypertonie, Diabetes, positiver Raucherstatus, vorausgegangener Schlaganfall, Klinik des zur Randomisierung führenden Ereignisses, Vorhandensein einer kontralateralen Stenose, Zeit zwischen Randomisierung und Behandlung (cut off 14 Tage)) Einen statistisch signifikanten Unterschied ergibt sich lediglich beim Geschlecht hinsichtlich eines höheren Risikos für Männer, bei CAS Endpunktereignisse zu erleiden. Die Konfidenzintervalle überlappen jedoch.

Für CAVATAS wurde in einer nicht geplanten Subgruppenanalyse die Rate an Schlaganfall bei dem Drittel der Patienten mit Stent ausgewertet.

Für SAPPHIRE liegt wie für CREST eine Analyse der Gruppe der symptomatischen und nichtsymptomatischen Patienten vor, die keine Unterschiede in den Behandlungsergebnisse zeigt.

Für Subgruppenanalysen kann insgesamt festgestellt werden, dass Ergebnisse aus nicht randomisiert zugeteilten Merkmalen oder Behandlungen als nicht sicher zu werten sind, sie enthalten erhebliches Verzerrungspotential. Nicht geplante Subgruppenanalysen können nur hypothesengenierend sein.

Stratifizierung der Ergebnisse nach Alter der Patienten

Eine Auswertung der Ergebnisse in Bezug auf das Alter der Patienten wurde post hoc in vier Studien vorgenommen (CREST, ICSS, SPACE, EVA-3S). Die Autoren von CREST geben allerdings an, die Auswertung geplant, nur nicht im Protokoll angegeben zu haben. Für CREST zeigte sich eine Altersabhängigkeit mit einem cut-off hinsichtlich besserer Ergebnisse für CAS unter 70 Jahren und für CEA über 70 Jahren. Das 95% Konfidenzintervall liegt zwischen 50 und ca. 80 Jahren. Die SPACE-Autoren zeigen nach der 30-Tages-Auswertung ein höheres Risiko für Endpunktereignisse bei CAS ab 75 Jahren. Für die 2-Jahresauswertung wurde für CAS ein statistisch signifikant höheres Risiko für Endpunktereignisse für einen cut-off ab 68 Jahren ermittelt. Für CEA wird keine Altersabhängigkeit angegeben. Für ICSS wurde ebenfalls nach < 70/>70 Jahren stratifiziert. Es zeigen sich höhere Ereignisraten sowohl für CAS als auch für CAS bei Patienten ab 70 Jahren (Relatives Risiko CAS +52%, relatives Risiko +CEA: 44%). Für die Studien sind die Konfidenzintervalle dieser Auswertungen jeweils so weit, dass sie keine valide Angaben hinsichtlich einer Altersgrenze erlauben. Für EVA-3S liegt mit einer explorativen Subgruppenauswertung mit höherem Risiko für CAS ab 70 Jahren ebenfalls keine verlässliche Auswertung vor.

Eine feste Altersgrenze für höheres Risiko bei CAS kann aus den Daten nicht valide ermittelt werden. Allerdings weisen die Auswertungen alle in dieselbe Richtung eines höheren Risikos für CAS bei älteren Patienten. Für CEA liegen keine konsistenten Ergebnisse vor.

4.3.3.4 Nachuntersuchung – Unabhängigkeit und Zeitpunkte der Erhebung

Unabhängigkeit der Endpunkt-Erhebung

Für sechs der Studien ist eine klinische Beurteilung durch einen unabhängigen Neurologen explizit ausgewiesen (CREST, SPACE, REGENSBURG, K-SYMP, K-ASYMP, LEICESTER). Für CREST ist allerdings angegeben, dass die Beurteilung bei Nichtverfügbarkeit auch durch einen unabhängigen „physician“ erfolgen konnte. Eine Beurteilung durch einen Neurologen ohne explizite Angabe darüber, ob dieser unabhängig war, wird auch für die sechs anderen Studien (ICSS, EVA-3S, SAPPHIRE, BACASS und WALLSTENT) angegeben. FÜR ICSS und CAVATAS wird im Text ausgeführt, dass es sich entweder um einen Neurologen oder um einen „stroke physician“ handelte. In der Langzeitauswertung von CAVATAS wird dagegen beschrieben, dass die Beurteilung grundsätzlich durch einen unabhängigen Neurologen erfolgte.

Eine Assoziation zu den Ergebnissen ist nicht abzuleiten.

Zeitpunkte der Endpunkt-Erhebung

Eine klinische Beurteilung der Patienten 1-2 Tage nach dem Eingriff ist in acht Studien angegeben (CREST (bis zu 56 Stunden), SPACE, EVA-3S, SAPPHIRE, BACASS, K-ASYMP, WALLSTENT, LEICESTER).

Eine Endpunkterhebung 30 Tage nach dem Eingriff wurde in neun Studien durchgeführt. Die Autoren der ICSS-Studie führten die Endpunkterhebung 30 Tage und 120 Tage nach Randomisierung durch. Bei K-SYMP und K-ASYMP gibt es dazu keine Angaben.

Mittelfristige mindestens jährliche Endpunkterhebungen liegen für CREST (geschätzte 4-Jahresergebnisse aus einer medianen Beobachtung von 2,5 Jahre), CAVATAS (5 bzw. 4 Jahre) EVA-3S und K-ASYMP (4 Jahre), SAPPHIRE (3 Jahre), SPACE und K-SYMP (jeweils 2 Jahre), REGENSBURG (1+5,5J) und WALLSTENT (1 Jahr) vor.

Beachtet werden muss hinsichtlich der Ergebnisse die Unvollständigkeit des Follow up und die fehlende statistische Power. Längerfristige Erhebungen (>5-6J) zu Nutzen und Schaden fehlen (siehe Tabelle 2).

Endpunkterhebung für Herzinfarkt

Die Endpunkterhebung für Herzinfarkte wurde bei CREST und SAPPHIRE zusätzlich zur klinischen Untersuchung durch prä- und postinterventionelle Laborbestimmungen durchgeführt. CREST geben darüber hinaus prä- und postinterventionelle EKG-Vergleiche an. Spezifische Angaben zur Endpunkterhebung Herzinfarkt finden sich in den anderen Studien mit Powerberechnung nicht.

4.3.4 Erfahrungsstand der Behandler

4.3.4.1 Vorerfahrung CAS

Eine Mindestzahl an Voreingriffen ist in vier Studien (CREST, ICSS, SPACE, EVA-3S) angegeben.

In der CREST-Studie wurde laut Protokoll eine Vorerfahrung von mind. 30 CAS-Interventionen gefordert. Falls diese nicht erreicht wurde, sollten nach einem obligaten Training vor Zulassung zur Randomisierung 20 CAS mit akzeptablen Komplikationsraten im Vergleich zur Literatur durchgeführt werden. Dies wurde als „Led in Phase“ bezeichnet. Die Auswertung von Hopkins et al, 2010 [7] nennt folgende Zahlen: 195 Applikanten wurden für die „Led in Phase“ zugelassen. 86 hatten mindestens 30 CAS und führten im Median weitere 8,5 während der Led in Phase aus. Die nicht so Erfahrenen (Vorerfahrung im Median 29, 15-30) führten im Median weitere 6,67 CAS aus. Von den 195 Applikanten nahmen 158 an der randomisierten Studie teil. Sie hatten als Training im Median neun (1-35) CAS durchgeführt. Die Daten werden dargestellt, um zu verdeutlichen, dass zwischen Protokoll und Durchführung eine gewisse Abweichung lag.

Für die EVA-3S wurden 12 CAS oder bei 35 angioplastischen Eingriffen gesamt mit mind. fünf CAS verlangt. Der Anteil an Behandler mit zwölf bzw. mit fünf CAS ist

nicht ausgewiesen. Falls diese Mindestmengen nicht erreicht wurden, erfolgte ein Proktoring (Supervision durch einen Erfahrenen bei CAS, siehe Kapitel 4.3.1.2).

Die ICSS forderte 50 angioplastische Eingriife und davon mindestens zehn vorausgegangene CAS. Wurde diese Zahl nicht erreicht erfolgte ein Proctoring von laut der Studie 20 Fällen, nach denen entschieden wurde, ob das Zentrum ohne Proctor arbeiten konnte. In der Studie werden 88% der Zentren in Bezug auf CAS als erfahrene Zentren klassifiziert. In einer explorativen Auswertung zeigen die Autoren von ICSS niedrigere Raten an Endpunktereignissen an Zentren, die mindestens 50 Patienten rekrutierten (7% vs 11%). Als erfahren ausgewiesene Zentren erzielten jedoch gegenüber solchen mit weniger Erfahrung höhere Komplikationsraten (8,7% vs 6,9%). Die Unterschiede zwischen den Gruppen sind nicht statistisch signifikant.

In der SPACE-Studie sind 25 CAS mit akzeptabler Morbiditäts- und Mortalitätsrate (Zahlen nicht genannt) genannt. In einem Amendment wurde die Zahl auf zehn gesenkt [13]. Voraussetzung war dann ein Proktoring (siehe Kapitel 4.3.1.2). Eine Auswertung der teilnehmenden Zentren in Bezug auf die Anzahl eingebrachter Patienten zeigte bessere Ergebnisse für die CAS bei höherer Rekrutierungsrate (am besten bei > 25 Patienten, am schlechtesten bei < 10 Patienten). Die Publikation weist die Gesamtzahl der in der Zeit behandelten Patienten, bzw. die Erfahrung des Zentrums nicht aus.

Von den oben genannten Studien wurde EVA-3S vorzeitig aufgrund hoher Komplikationsraten bei CAS abgebrochen. Allerdings gibt der Studienverantwortliche in einem Leserbrief an, dass die höhere Rate an Komplikationen nicht mit der mangelnden Erfahrung der Behandler korrelierte [34][4].

Bei drei der Studien, die keine Mindestmengen angeben, wird die tatsächlich vorhandene Vorerfahrung genannt.

Für die Behandler der SAPPHIRE-Studie betrug diese im Median 64 CAS-Eingriffe (20-700), zudem ist hier eine vorausgegangene Komplikationsrate unter 6 % (periprozeduraler Tod/Schlaganfall) gefordert. Die Autoren von BACASS geben 15 CAS pro Jahr an. LEICESTER weisen für den behandelnden Radiologen viel angioplastische Vorerfahrung und insgesamt acht CAS aus. Die Studie wurde nach Behandlung von 17 Patienten (sieben CAS) wegen hoher Komplikationsrate abgebrochen.

Fünf der Studien nennen keine Zahlen zur bestehenden Vorerfahrung. Vier davon weisen ausdrücklich auf die bestehende Expertise der Behandler hin (CAVATAS, K-ASYMP, K-SYMP, REGENSBURG). Bei CAVATAS wird darauf hingewiesen, dass Erfahrung in der Angioplastie, nicht notwendigerweise in der Karotisangioplastie vorliegen musste. Keine Angaben zu diesem Punkt werden in dem Abstract von Alberts, 2001 (WALLSTENT) gemacht. Diese Studie wurde wegen hoher Komplikationsraten der CAS abgebrochen.

[4] Zitat: Among the patients in the stenting group, 15.8% were treated by interventional physicians who had performed more than 50 carotid-stenting procedures, 45.4% by physicians who had performed 50 or fewer procedures, and 38.8% by physicians still in procedural training. The 30-day risk of stroke or death for these three groups was 12.2%, 11.0%, and 7.1%, respectively (P = 0.49)

Ein sicherer Zusammenhang von Vorerfahrung und Behandlungsergebnis ist aus den vorliegenden Studien und zusätzlichen Angaben nicht abzuleiten. Für die sieben Studien, zu denen Zahlenangaben vorliegen, kann nur vermutet werden, dass eine höhere Zahl durchgeführter Eingriffe bei geführtem Nachweis einer niedrigen Komplikationsrate dazu beiträgt, die Rate unerwünschter Ereignisse gering zu halten. Eine Mindestzahl ist aus den Daten nicht abzuleiten.

Vorerfahrung mit den verwendeten Materialien bei CAS

Eine Vorerfahrung mit den verwendeten Materialien wird nur in zwei Studien thematisiert (CREST, EVA-3S). Um an der CREST-Studie teilnehmen zu können, musste ein Trainingskurs absolviert werden, in dem mit dem zu verwendenden Material geübt wurde. Falls die Anzahl an CAS-Eingriffen für Erfahrene (n=30) nicht erreicht worden war, wurden 10-20 Patienten vor Zulassung zur Randomisierung mit dem entsprechenden Material behandelt (so genannte Led-in-Phase) . In der EVA-3S-Studie mussten die Behandler dagegen lediglich zwei Eingriffe mit dem Material durchgeführt haben, das sie verwenden wollten.

4.3.4.2 Proktoring (Supervision durch einen Erfahrenen) bei CAS

Ein mögliches Proktoring beim Stent wird in vier Studien angegeben (CREST, ICSS, SPACE, EVA-3S). Im CREST Studienprotokoll wird ausgeführt, dass bei mangelnder Vorerfahrung nach entsprechendem Training zwei Fälle mit Proktor behandelt werden konnten.

In der ICSS-Studie wurde ein Proktoring bei Nichterfüllen der geforderten Mindestmenge durchgeführt. Die Entscheidung, ob die CAS-Technik zufriedenstellend war, wurde nach 20 überwachten Fällen getroffen. 22% der Fälle wurden mit Proctoring durchgeführt. Die komplikationsreichen CAS-Ergebnisse von zwei supervidierten Zentren führten zum Ausschluss der dortigen Behandler und der Zentren (die elf Fälle wurden mit ausgewertet). Ein Zentrum nahm mit einem anderen Behandler in der Folge wieder an der Randomisierung teil.

Auch bei EVA-3S wurde bei Nichterreichen der Mindestmengen ein Proktoring durchgeführt. Die Studie selbst enthält keine Angabe über den Anteil der Fälle mit Proktoring. In einem Brief des Autors 2007 werden jedoch 38,8% genannt [34]. Die Komplikationsraten waren laut diesem Brief niedriger als bei Erfahrenen.

Die SPACE-Studie berichtet über Proktoring bei einer Vorerfahrung von nur zehn CAS. Die CAVATAS-Autoren berichten ohne Zahlenangaben, dass weniger erfahrene Radiologen erfahrenere Kollegen zur Seite gestellt bekamen.

In den übrigen acht Studien wird Proktoring nicht thematisiert. Sichere Aussagen zu einem generell die Ergebniss verschlechternden Effekt eines Proktorings sind anhand der vorliegenden Angaben nicht möglich. Zu beachten ist der erforderliche Ausschluss von Zentren bei der ICSS-Studie.

4.3.4.3 Vorerfahrung CEA

Eine geforderte Mindestzahl ist in vier Studien (CREST, ICSS, SPACE, EVA-3S) angegeben. CREST nennt zwölf Eingriffe/Jahr mit Komplikationsraten < 3 % (sympt.) und < 5 % (asympt.). CREST gibt bessere Ergebniss für CEA als für CAS

bei einm Alter unter 70 Jahren an, bei einem Konfidenzintervall zwischen 50 und 80 Jahren.

ICSS gibt 10/Jahr an und gesamt mind. 50. In der post hoc Auswertung für CEA zeigten einerseits sowohl Zentren mit mehr Erfahrung in der Tendenz bessere Ergebnisse als supervidierte Zentren (5,0% vs 6,6%), andererseits erzielten Zentren bessere Ergebnisse, die weniger Fälle eingebracht hatten (4,6% < 50 Fälle, 5,5% =/> 50 Fälle).

Für SPACE waren 25 Eingriffe gesamt und für EVA-3S 25 im Jahr vor Studienbeginn erforderlich. In der bereits oben genannten Auswertung von SPACE war für CEA kein Zusammenhang bezüglich der Anzahl eingebrachter Patienten pro Zentrum zu den erzielten Ergebnissen nachzuweisen.

Die Tatsächliche Erfahrung der Behandler ist in zwei Studien genannt und beträgt im Median 30 (15-100) pro Jahr bei SAPPHIRE und ca. 50 Eingriffe/Jahr bei BACASS.

Ein expliziter Hinweis auf bestehende Expertise der Behandler ohne Nennung von Zahlen erfolgt in vier Studien (CAVATAS, K-ASYMP, K-SYMP, LEICESTER). Keine Angaben finden sich bei Steinbauer et al., 2008 (REGENSBURG) und im Abstract von Alberts, 2001 (WALLSTENT).

– Supervision bei CEA –

ICSS geben an, dass 11% der CEA-Behandlungen supervidiert wurden. In der CAVATAS-Studie wird von einer Supervision der CEA bei Nichterfüllen der Mindestmengen berichtet. Bei Naylor et al., 1998 (LEICESTER) wird angegeben, dass die CEA entweder von einem Facharzt („consultant“) oder von einem Assistenzarzt unter Anleitung („supervised trainee“) durchgeführt wurde.

Eine eindeutige Assoziation der Endpunktereignisse zur Vorerfahrung der Behander oder zur CEA-Operation mit Supervision lässt sich aus den Angaben nicht erkennen.

4.3.4.4 Anpassung der Kriterien für die Selektion von Zentren im Verlauf der Studie

Angaben darüber, dass im Verlauf der Studie die Selektionskriterien für Zentren geändert wurden, wurden in den verfügbaren Publikationen für die SPACE-Studie gefunden [13; 15]. Dort wurde zu Beginn gefordert, mind. zwei Patienten pro Jahr pro Zentrum zu rekrutieren, dies wurde dann auf ggf. ein Patient pro Jahr reduziert. Ebenso wurde in einem Amendment die geforderte Mindestzahl von CAS-Eingriffe von 25 auf zehn heruntergesetzt. Bei einer Vorerfahrung von zehn CAS wurde ein Proktoring durchgeführt. In der ICSS-Studie führten die komplikationsreichen CAS-Ergebnisse von zwei Zentren zu dem Ausschluss der dortigen Behandler und der Zentren (die elf Fälle wurden mit ausgewertet). Ein Zentrum nahm mit einem anderen Behandler in der Folge wieder an der Randomisierung teil.

Die Änderungen können nur deskripktiv dargestellt werden.

4.3.5 Monitoring in der Vorbereitungsphase und im Verlauf der Studie

In den vorhandenen Publikationen wurde analysiert, ob in den Studien ein externes Datenmonitoring aller rekrutierten Patienten vor der Intervention durchgeführt wurde und ob die Angaben zu den Outcome-Ereignissen vollständig überprüft wurden. Angaben zu einem Monitoring sind sieben Studien zu entnehmen (CREST, SAPHHIRE, ICSS, SPACE, CAVATAS, EVA-3S, LEICESTER). Ein „safety committee“ ist darüber hinaus explizit in fünf Studien benannt (CREST, ICSS, SPACE, EVA-3S, SAPPHIRE, LEICESTER). Inwieweit diese Kommittees aktiv waren, ist den einzelnen Publikationen nicht zu entnehmen.

Ein vollständiges externes Monitoring der Daten ist für zwei Studien angegeben (CREST, SAPPHIRE).

Bei der Überprüfung der Daten der CREST-Studie wurden in einem Zentrum gefälschte Daten identifiziert (neun CAS und elf CEA). Die Daten dieses Zentrums wurden nicht ausgewertet.

Ein nicht vollständiges oder fraglich vollständiges externes Monitoring ist bei fünf Studien angegeben (ICSS, SPACE, CAVATAS, EVA-3S, LEICESTER). Für die ICSS-Studie wird berichtet, dass die in den Zentren erhobenen Endpunktereignisse regelmäßig ein Monitoring durch eine zentrale Stelle erfuhren. Über das Monitoring vor den Eingriffen wird nicht berichtet. Ebenso bleibt unklar, ob dem Office die gesamten Unterlagen vorlagen. Aufgrund des Monitorings wurden zwei Zentren mit einer hohen Komplikationsrate bei CAS (n=11, davon fünf mit funktionsbeeinträchtigendem Schlaganfall oder Tod) und CEA (n=9, davon einer mit tödlichem Schlaganfall) gesperrt. Die Fälle wurden bei der Auswertung mitgewertet.

In der SPACE-Studie wird angegeben, dass 10 % der kompletten Daten per Zufallsstichprobe überwacht wurden. Weiterhin wird ausgeführt, dass für alle Baseline-Daten zur Randomisierung und zu den Endpunktereignissen ein Monitoring stattfand und ein Mechanismus existierte, der nach Angaben der Autoren eine Verstärkung des Monitorings bei Problemen mit der Datenqualität nach sich zog. Aufgrund welcher Ereignisse dieser Mechanismus aktiviert wurde, wird nicht angegeben. Den Angaben ist ebenfalls nicht zu entnehmen, welchen Grad der Vollständigkeit das Monitoring insgesamt hatte.

In der EVA-3S-Studie ist angegeben, dass regelmäßig Sicherheitsüberprüfungen durchgeführt wurden. Der Umfang der Datenprüfungen ist den Angaben nicht zu entnehmen.

In der CAVATAS-Studie wird eine zentrale Überprüfung aller Diagnosen angegeben, insbesondere der Grad der angegebenen Karotisstenose. Bezüglich der Endpunktereignisse wird angegeben, dass relevante Unterlagen an die Zentrale weitergeleitet wurden. Die Vollständigkeit der Datenübermittlung ist den Angaben nicht zu entnehmen.

Naylor et al., 1998 (LEICESTER) berichten von einem unabhängigen Monitoringkommittee, das zur Auflage hatte, nach jeweils 20 eingeschlossenen Fällen eine Zwischenanalyse durchzuführen. Auch hier ist die vollständige Datenbasis nicht spezifiziert.

Keine Angaben zu einem externen Monitoring liegen für vier unizentrische Studien (REGENSBURG, BACASS, K-SYMP, K-ASYMP) und das WALLSTENT-Abstract vor.

Zusammenfassend kann festgestellt werden, dass nur 2 Studien ein komplettes externes Datenmonitoring angeben. Ein sicherer Effekt eines nicht vollständigen Datenmonitorings hinsichtlich der Angabe von Studienergebnissen kann aus den vorliegenden Publikationen nicht abgeleitet werden.

4.3.6 Standardisierung der Therapien

4.3.6.1 Standardisierung der CAS-Technik/Embolieprotektion

Ein standardisiertes Vorgehen beim Stenting lässt sich für sieben Studien ableiten (CREST, SAPPHIRE, BACASS, REGENSBURG, K-SYMP, K-ASYMP, LEICESTER). Für CREST kann einschränkend angemerkt werden, dass ein „Balloon Angioplasty pre-Procedure“ nur in 71,9 % der Fälle und eine „Balloon angioplasty“ nur in 67,7 % angegeben wird.

Für vier Studien ist die Standardisierung weniger stringent, d. a. es jeweils mehrere Vorgehensweisen möglich. Bei EVA-3S wurde im Verlauf eine Embolie-Protektion verpflichtend, diese war am Anfang freiwillig und es wurden unterschiedliche Stents und Protektionssysteme benutzt. In der SPACE und der ICSS-Studie wird angegeben, dass die Interventionstechnik nach den Maßgaben der Behandler erfolgte. In der CAVATAS-Studie wurde ein Stenting erst im Verlauf nach Indikation durch den Behandler eingeführt. Mehr als 70 % der Patienten erhielten lediglich eine Ballondilatation. Die Studienergebnisse sind insofern für die heutige Technik des Stenting nicht repräsentativ. Keine Angabe findet sich für WALLSTENT.

Ein festgelegter Stenttyp wurde in sieben Studien benutzt (CREST, SAPPHIRE, REGENSBURG, BACASS, K-ASYMP, WALLSTENT, LEICESTER), für die fünf Letztgenannten vom gleichen Hersteller. Brooks et al., 2001 setzten zwei unterschiedliche Marken ein. Mehrere unterschiedliche Stenttypen (alle mit CE-Zertifikation) wurden in vier Studien benutzt (ICSS, SPACE, CAVATAS, EVA-3S).

Zu den verwendeten Stents siehe Tabelle in Kapitel 6 auf Seite 86 (Zulassung von Karotisstenttypen innerhalb der Studien).

Eine Assoziation der Standardisierung zu den Outcome-Ergebnissen lässt sich nicht eindeutig erkennen.

Embolie-Protektion

Embolie-Protektionssysteme wurden in sechs der zwölf Studien benutzt (CREST (97,9 %), ICSS (72 %), SPACE (27 % – Angabe aus [3]), EVA-3S (78,4 % vor, 97,7 % nach Verpflichtung, insgesamt 91,1%), BACASS (100 %)). In fünf unizentrischen oder frühen Studien (REGENSBURG, CAVATAS, K-SYMP, K-ASYMP, LEICESTER) wurden keine Protektionssysteme benutzt. Keine Angaben dazu erfolgen im Abstract von Alberts et al., 2001 (WALLSTENT). Zu den verwendeten Protektionssystemen siehe Tabelle in Kapitel 6, Seite 88 (Zulassung

bzw. Einsatz von Protektionssystemen innerhalb der Studien). Die Autoren von SPACE werteten die Ergebnisse von Patienten mit Protektionssytemen versus Patienten ohne Protektionssysteme hinsichtlich der Endpunktereignisse aus. Diese Analyse muss als ungeplante Subgruppenanalyse angesehen werden, da die Protektionssysteme nach Gutdünken eingesetzt werden konnten und keine randomisierte Zuteilung erfolgte.

Eine Assoziation des Einsatzes von Protektionssystemen zu den Outcome-Ergebnissen lässt sich nicht erkennen.

4.3.6.2 Standardisierung der CEA-Technik

Für sieben der Studien ist angegeben, dass die Operationstechnik der CEA den jeweiligen Chirurgen überlassen wurde, insbesondere die Anlage eines temporären Shunts oder das Anbringen eines Patchs (CREST, ICSS, SPACE, CAVATAS, EVA-3S, BACASS, SAPPHIRE). Steinbauer et al., 2008 (REGENSBURG) geben grundsätzlich das Durchführen einer Eversionsendarteriektomie[5] an. Brooks et al., 2001 und 2004 (K-ASYMP, K-SYMP) geben an, dass „standard operative techniques“ angewendet wurden. Naylor et al., 1998 (LEICESTER) beschreiben die verwendete standardisierte OP-Technik detailliert. Keine Angaben dazu erfolgen im Abstract von Alberts et al., 2001 (WALLSTENT).

Anlage eines Shunts

Die Anlage temporärer Shunts wird in sieben Studien beschrieben (CREST (56,7 %), ICSS (Anteil n. a.), SPACE (Anteil n. a.), CAVATAS (64 %), EVA-3S (19,5 %), BACASS (Anteil n. a.), LEICESTER („routinely“)).

In fünf Studien finden sich keine Angabe zu Shunts (SAPPHIRE, REGENSBURG, K-ASYMP, K-SYMP, WALLSTENT).

Anbringen eines Patchs

Das Anbringen von Patchs ist in fünf Studien ausgewiesen (CREST (62,4 %), CAVATAS (63 %), EVA-3S (50,2 %), BACASS („routinely in local anesthesia“), LEICESTER („routinely“)).

Eine Assoziation der beschriebenen OP-Standardisierung oder OP-Techniken zu den Ergebnissen ist nicht erkennbar.

4.3.6.3 Änderung der technischen Vorschriften während der Studie

Eine Änderung der technischen Vorschriften in den Studien wurde in den zur Verfügung stehenden Publikationen für zwei Studien identifiziert:

Bei EVA-3S wurde im Verlauf das Verwenden eines Embolie-Protektionssystems Vorschrift (s. o.). Bei CAVATAS wurden erst während des Studienverlaufs Stents eingesetzt.

[5] Eversionsendarteriektomie = nach Durchtrennng der A. Carotis interna an der Bifurkation wird der stenosierende Gefäßabschnitt nach Umstülpen ausgeschält, ebenso im Bereich der Bifurkation.

4.3.7 Periinterventionelle antithrombotische Therapie

4.3.7.1 Heparinisierung

Für acht Studien wurden Angaben zur periinterventionellen Heparinisierung bei CAS identifiziert. Angaben zur Heparinisierung bei CEA finden sich in vier Studien (CREST (CAS 86,4 %, OP keine %-Angabe), ICSS („mandatory"), CAVATAS (nur angegeben zu CAS, nicht CEA), EVA-3S (vor OP 69,1 %, während OP 99,2 %, während CAS 97,6 %), SAPPHIRE (keine %-Angabe, PTT 250-300s), K-SYMP und K-ASYMP (beide zu CAS ohne %-Angabe, k. A. zu CEA), LEICESTER (5000 IE Heparin CAS + CEA).

Keine Angaben zur periinterventionellen Heparinisierung finden sich in vier Studien (SPACE, BACASS, REGENSBURG, WALLSTENT).

Aus den Angaben kann keine Assoziation zur Häufigkeit von Endpunktereignissen mit der Heparinisierung abgeleitet werden.

4.3.7.1 Therapie mit Thrombozytenaggregationshemmern

Gabe von Aspirin

In allen Studien wurde bei CAS periinterventionell Aspirin gegeben. Zur Aspiringabe bei CEA finden sich Angaben in zehn Studien. Die SPACE-Studie und das WALLSTENT-Abstract enthalten keine Angaben zum Vorgehen bei CEA.

Bei CREST wurde die höchste Dosis Aspirin gegeben: 48h vor CAS 2 x 325 mg/Tag sowie 4 Stunden vorher zusätzlich 650 mg. 48 Stunden vor CEA wurde 1x325 mg gegeben. Postinterventionell wurde die ASS-Therapie bei CAS (1-2 x 325 mg/Tag) mind. 30 Tage beibehalten bzw. auch danach eine Fortsetzung empfohlen. Auch bei CEA wurde die weitere Einnahme von ASS (325 mg/Tag über ein Jahr oder niedrigere Dosis, dann duale Therapie) empfohlen.

In zwei Studien [SPACE, EVA-3S] wurde ASS (100 mg/Tag SPACE/100-300 mg/Tag EVA-3S) drei Tage vor dem Eingriff begonnen und bis zu einem Monat danach fortgesetzt.

In der ICSS-Studie (Dosis nicht angegeben) und bei Steinbauer et al., 2001 (REGENSBURG) (100 mg/Tag) wird die Gabe von Aspirin ab Eingriff und bis 30 Tage danach angegeben. CAVATAS (ASS 150 mg mind. 24 Stunden vor Eingriff) und SAPPHIRE (ASS 81 mg oder 215 mg 72 Stunden vor OP) spezifizieren den Beginn der Aspirintherapie, aber nicht die Dauer. Drei Studien (K-SYMP, K-ASYMP, WALLSTENT) geben die Dosierung mit 325 mg/Tag an, WALLSTENT nennt eine Dauer von vier Wochen. LEICESTER geben an, das ASS vor den Eingriffen nicht gestoppt wurden. BACASS geben ASS ohne Dosis und Dauer an.

Kombinationstherapie mit Clopidogrel/Ticlopidin

Die Kombinationstherapie Aspirin plus Clopidogrel bei CAS wurde in neun der zwölf Studien angewandt (CREST, ICSS, SPACE, EVA-3S, SAPPHIRE, BACASS, REGENSBURG, K-SYMP, K-ASYMP). In der CREST-Studie wurde Clopidogrel präinterventionell in der höchsten Dosis (2 x 75 mg/Tag) ab 48 Stunden vor CAS

gegeben. 4h vor dem Eingriff wurde zusätzlich eine Loadingdose von 450 mg Clopidogrel oder Ticlopidin gegeben. Eine Loadingdose ist sonst in keiner Studie angegeben. Nach der Intervention wurde Clopidogrel 75 mg oder Ticlopidin 2 x 250 mg/Tag gegeben. Die Rate an präinterventioneller Therapie mit Thrombozytenaggregationshemmern 48 Stunden vor CAS wird mit 97,7 % angegeben, danach mit 99 %, für die duale Therapie 87,9 %.

Eine Clopidogreldosis von 75 mg/Tag bei CAS wurde in sechs Studien gegeben (SPACE, EVA-3S, SAPPHIRE, REGENSBURG, K-SYMP, K-ASYMP). Der präinterventionelle Beginn ist bei SPACE und EVA-3S mit drei Tagen angegeben, bei SAPPHIRE mit 24h. Die Dauer der Gabe wurde mit einem Monat (SPACE, EVA-3S, REGENSBURG) oder 2-4 Wochen (SAPPHIRE) spezifiziert. Brooks et al., 2001 und 2004 (K-SYMP, K-ASYMP) gaben keine Zeitdauer an. In der ICSS-Studie wird eine Einnahme von Clopidogrel über einen Monat angegeben, aber weder Dosis noch Loadingdosis ausgewiesen.

WALLSTENT verwendeten Ticlopidin 2 x 250 mg/Tag.

CAVATAS und LEICESTER setzten noch keine duale thrombozytenaggregations-hemmende Therapie ein, sondern nur Aspirin.

Für CEA wird bei CREST im Follow-up 75 mg Clopidogrel oder 2 x 250 mg/Tag Ticlopidin bzw. eine duale Therapie mit ASS angegeben.

Angegebene Rate der erfolgten Medikation mit Thrombozytenaggregations-hemmern periinterventionell und im Follow-up

Bei CREST wird 48 Stunden vor CAS die Rate der erfolgten Medikation mit 97,7 % angegeben, nach Intervention mit 99,8 %, eine duale Therapie mit 87,9 %. Für CEA wird die präinterventionelle Rate mit 92,1 %, die postinterventionelle mit 91,1 % angegeben. Die ICSS-Publikation enthält keine Angaben zur Rate der erfolgten Medikation.

SPACE gibt lediglich für das Follow-up nach 24 Monaten an, dass 69 % der Patienten mit CAS ASS einnehmen, 16 % Clopidogrel und 9 % eine duale Therapie. Für CEA werden 79 %, 11 % und 4 % angegeben. Periinterventionelle Angaben fehlen.

Bei EVA 3S wird angegeben, dass die präinterventionelle Thrombozytenaggregationshemmung bei CEA zu 87,6 % durchgeführt wurde und die postinterventionelle zu 93,7 %. Für CAS werden Raten von 82,9% duale Therapie präinterventionell angegeben (17,1% nicht duale Therapie) und präinterventionell 85,4% duale Therapie (14,6% nicht duale Therapie). Die 30-Tages Endpunktrate war 9% für Patienten mit dualer Therapie (19/211) und 11,1% für Patienten mit Monotherapie (4/36). Dieser Unterschied ist nicht statistisch signifikant. Nach einem Jahr wird eine Rate von 97 % aggregationshemmender Therapie CAS und CEA genannt und nach vier Jahren 99 % und 95 %.

Für die anderen Studien wurden keine Angaben identifiziert.

Eine sichere Quantifizierung eines möglichen Einflusses der periinterventionellen antithrombotischen Therapie bzw. der Therapie im Follow-up kann nicht erfolgen.

5. Diskussion

5.1 Diskussion der methodischen Fragestellungen

Studiendesign/Studienabbruch

Zur Frage der Wertigkeit der CAS gegenüber der CEA wurden zwölf randomisierte kontrollierte Studien analysiert. Fünf davon (REGENSBURG, CAVATAS, BACASS, K-Symp, K-ASYMP) weisen keine Fallzahlberechnung auf. Die Ergebnisse dieser Studien können aufgrund des Studiendesigns, das nicht auf einen statistisch validen Nachweis einer Noninferiorität oder Äquivalenz bzw. eines Unterschieds ausgelegt ist, von vorn herein nur in gepoolten Auswertungen zu validen Aussagen beitragen. Von den Studien mit prospektiver Fallzahlberechnung (CREST, ICSS, SPACE, EVA-3S, SAPPHIRE,WALLSTENT, LEICESTER) weist keine der Studien eine ausreichende Power aus, um einen sicheren Vergleich zwischen CAS und CEA zu führen. Für CREST wurde im Ergebnis kein satistisch signifikanter Unterschied zwischen CEA und CAS an einem Kollektiv symptomatischer und asymptomatischer Patienten ermittelt. Die angegebene Hazard Ratio von 1,11 bei einem absoluten Unterschied von 0,4% weist jedoch ein so breites Konfidenzintervaall von 0,81-1,51 auf, dass vom sicheren Nachweis einer Gleichwertigkeit der Verfahren CAS und CEA nicht ausgegangen werden kann. Die beiden eingeschlossenen Gruppen weisen unterschiedliche Ereignisraten auf und sollten getrennt betrachtet werden. Eine ausreichende Power für die beiden Gruppen ist jeweils nicht gegeben.

Die Studien sind – wenn angegeben – als Noninferioritätsstudien oder Äquivalenzstudien konzipiert. Von den zwölf Studien wurden sieben (SPACE, EVA-3S, BACASS, SAPPHIRE, REGENSBURG, WALLSTENT, LEICESTER) vorzeitig abgebrochen. Der Gründe dafür waren neben einer weit höheren als erwarteten Komplikationsrate in den CAS-Armen (LEICESTER, WALLSTENT, EVA-3S) auch andere als die erwarteten Ereignisraten in den CEA-Armen. Diese war niedriger bei EVA-3S und höher bei SPACE. Aufgrund der unterschiedlichen Ereignisraten zeigte sich jeweils eine erhöhte erforderliche Fallzahl. Im Ergebnis weist die relativ kleine SAPPHIRE-Studie (n=334) eine Besonderheit auf. An einem speziellen Kollektiv von Hochrisikopatienten wurde nicht nur die Noninferiorität von CAS zum Auswertezeitpunkt gezeigt, sondern eine statistisch signifikante Superiorität für einen kombinieren Endpunkt Schlaganfall, Herzinfarkt oder Tod periinterventionell und gleichseitiger Schlaganfall nach einem Jahr. Methodische Schwächen der Studie liegen im Einschluss symptomatischer und asymptomatischer Patienten und in der fehlenden transparenten Fallzahlberechnung. So kann nicht ausgeschlossen werden, dass der beobachtete Effekt zu einem späteren Zeitpunkt mit mehr eingeschlossenen Patienten nicht mehr statistisch signifikant ausgefallen wäre. Die Studie weist darüber hinaus sehr hohe Ereignisraten auf.

Erforderliche Angaben zur Patientenselektion und zum Patientenfluss in den Studien

Insgesamt weisen nur vier der Studien (SAPPHIRE, REGENSBURG, BACASS, LEICESTER) Angaben zum Anteil randomisierter Patienten im Verhältnis zu allen in Frage kommenden Patienten im Zeitraum auf. Dabei zeigt sich jeweils ein erheblicher Anteil nicht eingeschlossener Patienten. Es besteht insofern eine Unsicherheit hinsichtlich der Repräsentativität der Studienkollektive im Verhältnis zu allen Patienten mit Karotisstenose. Der Einfluss von Cross over Daten bei Intention to Treat Analysen kann ein valides Ergebnis bei Noninferioritätsstudien oder Äquivalenzstudien schwächen. Eine Bestätigung des Ergebnisses der Intention to Treat Analyse kann anhand vorliegender „per protocol" Auswertungen erfolgen, wenn diese gleichlautend sind. Eine Übereinstimmung der Ergebnisse ergab sich bei ICSS und bei SPACE in der 2 Jahresauswertung. Bei SAPPHIRE zeigte sich ebenfalls ein ähnlicher, wenn auch etwas abgeschwächter Effekt. Für CREST und Eva-3S fehlen per protocol Auswertungen, obwohl in beiden Studien ein nicht unerheblicher Anteil an cross over oder keiner erfolgten Intervention insbesondere für CAS besteht. Hinsichtlich der übrigen Angaben zum Patientenfluss sind fehlende Follow up Daten zu beachten.

Ein- und Ausschlusskriterien/Risikopatienten

Die Ein- und Ausschlusskriterien in den Studien differieren sowohl im Hinblick auf den Grad der Stenose, als auch auf die Zeiträume des Auftretens der Symptome.

Bezüglich des Einschlusses asymptomatischer Patienten CREST (ca. 50%) und bei SAPPHIRE (ca. 70 %) werden dort jeweils unterschiedliche relative und absolute Ereignisraten erzielt. Symptomatische und asymptomatische Patienten sollten deshalb getrennt betrachtet werden. Meier et al., 2010 [3] kamen in ihrer Metaanalyse ohne die beiden Studien [SAPPHIRE, K-ASYMP] mit vorwiegend oder ausschließlich asymptomatischen Patienten zu den gleichen relativen Ergebnissen wie bei deren Einschluss. Die CREST-Studie wurde dort nicht berücksichtigt.

Nur bei sechs Studien sind anatomisch-morphologische Kriterien für den betreffenden Gefäßabschnitt explizit angegeben. Dabei werden jeweils auch allgemein gehaltene Aussagen zur „technischen Durchführbarkeit" genannt, so dass die Gründe für den individuellen Patientenausschluss auch den jeweiligen Behandlern überlassen blieben. Keine anatomischen Einschlusskriterien für den betreffenden Gefäßabschnitt wurden bei den Studien mit schlechtem Ergebnis für die CAS EVA-3S und LEICESTER angewendet, aber auch bei den beiden unizentrischen Studien aus Kentucky K-SYMP und K-ASYMP, bei denen eine Gleichwertigkeit der CAS in Bezug auf die CEA gefunden wurde.

In Bezug auf kardiale Risiken sind die Kriterien unterschiedlich spezifiziert. Während CREST sehr detaillierte Kriterien aufführen, nennen andere Studien nur ein oder zwei Kriterien. Die für Verteilung von Risikofaktoren für die Studien mit Powerberechnung festgestellten wenigen Unterschiede zum Beispiel in der Rate der Dyslipidämien (3 %) bei CREST oder in der Rate an Patienten mit koronarer Herzerkrankung (ca. 10 %) bei SAPPHIRE lassen keine Rückschlüsse auf Endpunktereignisse zu. Für SPACE und EVA-3S sind weniger koronare Vorerkankungen angegeben als für CREST und ICSS. Insgesamt spezifiziert CREST die Ein- und Ausschlusskriterien am detailliertesten. In der Beurteilung der Ergebnisse der Studien ist immer mitzubedenken, für welche Studienpopulation sie gelten.

Endpunkte und Evaluation

Alle primären Endpunkte sind kombinierte Endpunkte, die zum Teil unterschiedlich definiert sind. Im Rahmen von Metaanalysen können diese Endpunkte validiert werden. Zwischen den Studien sind die Ergebnisse nicht direkt vergleichbar. Vier der Studien schließen in ihrem Endpunkt Herzinfarkt mit ein (CREST, ICSS, BACASS, SAPPHIRE).

Die Ergebnisse von CREST mit kombiniertem primären Endpunkt bestehend aus: jeglicher Schlaganfall, Herzinfarkt oder Tod periinterventionell plus gleichseitiger Schlaganfälle bis zu vier Jahren, sind beispielsweise nicht mit den Ergebnissen von SPACE vergleichbar, da bei dieser Studie nur seitengleiche Schlaganfälle gewertet wurden und der Endpunkt Herzinfarkt nicht eingeschlossen war. Die Erhebung des Endpunkts Herzinfarkt wird bei CREST detailliert erläutert inklusive prä- und postinterventionelle Laborkontrollen und EKG-Vergleiche. Die ICSS und EVA-3S-Studie, die ebenfalls Herzinfarkte als Endpunkt nennen (primär oder sekundär) geben nicht an, wie systematisch dieser Endpunkt erhoben wurde. Die Sinnhaftigkeit und Bedeutung der kombinierten Endpunkte und die Intensität deren Erhebung muss von klinischen Experten diskutiert werden. Bei einer Befragung einzelner Experten zur Wichtung der Endpunkte zeigte sich ein Dissens in der Einschätzung des Endpunkts Herzinfarkt aber auch hinsichtlich der Bedeutung von Tod nach 2-4 Jahren. Das Erfassen makrovaskulärer schwerer Komplikationen bei einer Intervention zur Prävention einer makrovaskulären Komplikation erscheint grundsätzlich nachvollziehbar.

Hinsichtlich der Vergleichbarkeit der Rate an Endpunktereignissen ist neben den unterschiedlich stark spezifizierten Einschlusskriterien für die Patienten auch die unterschiedliche Zählweise der Endpunkte zu beachten. So wurden bei CREST alle aufgetretenen Ereignisse erfasst und beispielsweise tödlicher Schlaganfall sowohl als Tod als auch als Schlaganfall gewertet. In der SPACE-Studie wurde dagegen nur jeweils das erste aufgetretene Ereignis gewertet.

Bezüglich der Evaluation der Ergebnisse liegt der periinterventionelle Endpunkt 30 Tage nach Behandlung für neun der zwölf Studien zur Auswertung vor. Eine unabhängige Evaluation ist in etwa der Hälfte der Studien angegeben.

Die in nur 2 Studien unternommenen Auswertungen zur Lebensqualität sind nicht als belastbar zu bezeichnen.

In Bezug auf eine Altersabhängigkeit der Behandlungsergebnisse weisen die post hoc Analysen der großen Studien jeweils ein höheres Risiko für CAS bei höherem Alter aus. Eine Altersgrenze ist aufgrund der sehr breiten Konfidenzintervalle nicht abzuleiten. Für CEA liegen keine konsistenten Ergebnisse vor. Für die Altersabhängigkeit der CAS kann vermutet werden, dass sie ein Surrogatparameter für bei älteren Menschen vermehrt vorliegende Gefäßaberrationen oder schwere disseminierte Atherosklerose ist.

Monitoring

Lediglich für zwei Studien (CREST, SAPPHIRE) wird ein komplettes Monitoring der Daten angegeben. Auffälligkeiten mit Konsequenzen bei der Überwachung der Daten werden für CREST (Ausschluss offensichtlich gefälschter Daten) und für ICSS (Ausschluss von zwei Zentren mit schlechten Ergebnissen für CAS, Daten wurden jedoch mit ausgewertet) berichtet. Bei der Bewertung des nicht komplett erfolgten Monitorings ist zu bedenken, dass negative Einflüsse für das jeweilige Ergebnis (v. a. komplikationsreich arbeitende Behandler) in beiden Gruppen übersehen werden können.

5.2 Diskussion der inhaltlichen Fragestellungen

In der vorliegenden Arbeit wurden die Studien nach unterschiedlichen inhaltlichen Aspekten untersucht. Hinsichtlich des Erfahrungsstands der Behandler bei CAS zeigten sich große Unterschiede in der Zahl der bereits durchgeführten Operationen. Hierzu zeigt sich in den Studien allerdings kein eindeutiger Zusammenhang mit der Rate an Endpunktereignissen. Die Studien zeigten auch Unterschiede in den anatomisch-morphologischen Einschlusskriterien, ebenso wie bei der Zulassung eines Proktorings, der Standardisierung der Therapien sowohl hinsichtlich der CEA- als auch hinsichtlich der CAS-Technik (Stent und Protektionssysteme). Eine eindeutige Assoziation zur Rate an Endpunktereignissen lässt sich jeweils nicht feststellen. Für die CAVATAS-Studie, bei der nur in ca. 30 % der Fälle Stents eingesetzt wurden, gelten die Ergebnisse überwiegend für eine Technik der Ballondilatation ohne Stenting. Die Anwendung unterschiedlicher Regime betrifft auch die periinterventionelle Heparinisierung und Therapie mit Thrombozytenaggregationshemmern, für die sich Hinweise auf einen Zusammenhang bei EVA-3S (höhere Komplikationsrate bei fehlender dualer Therapie), aber kein sicherer Beleg zeigen (nicht statistisch signifikant, zu kleine Fallzahl). Die Unterschiede in der Anwendung der Techniken tragen zur Unsicherheit bei der Interpretation der Ergebnisse bei. Eine Standardisierung der Therapien ist eine Voraussetzung für die bessere Vergleichbarkeit von Therapien. Die Standards sollten von dort übernommen werden, wo jeweils die besten Ergebnisse erzielt wurden.

5.3 Fazit

Bisher liegt kein sicherer Vergleich von CAS mit CEA unter randomisierten kontrollierten Bedingungen vor. Das Ergebnis der CREST-Studie stimmt bei Betrachtung der entsprechenden Ereignisse mit dem Ergebnis der Metaanalyse von Meier et al, 2010 überein. Der Unterschied liegt in der Definition des primären Endpunktes. Dieser muss hinsichtlich seiner klinischen Wertigkeit diskutiert werden. Im Hinblick auf Einflussfaktoren für ein besseres oder schlechteres Ergebnis der CAS-Intervention können aus den Studiendaten keine sicheren Aussagen hinsichtlich der geprüften Kriterien getroffen werden. Dies bedeutet nicht, dass diese für die erzielten Ergebnisse nicht relevant sind. Sowohl für CEA als auch für CAS sind Bedingungen größtmöglicher periinterventioneller Sicherheit zu gewährleisten.

6. Tabellen

Die folgenden Tabellen weichen von klassischen Evidenztabellen ab. In den einzelnen Tabellen werden von den Experten relevante Kriterien für die einzelnen Studien dargestellt. Zusammenfassende Evidenztabellen finden sich unter 6.8.

6.1 Methodische Konzeption und Durchführung der Studien

6.1.1 Studiendesign

Studie	Studiendesign	Angaben zu statistischer Berechnung	Studienabbruch//Auswirkungen auf die Power/gründe für Abbruch
CREST [6; 7]	Äquivalenzstudie, Gleichwertigkeit des Stent im Vergleich zur OP	Powerberechnung: Analyses were aimed at testing for superiority. The null hypothesis was that the two study treatments are equivalent; the alternative hypothesis was that the treatments differ. 2.500 erforderlich für 90% Power um eine HR für primären Endpunkt von 0,45 oder 1,49 für Stenting im Vergleich zu OP absolute Diff. a. 1,2%	Nein – Power erreicht Rekrutierung von 2.522 Pat. 12/00-7/08 in 117 Zentren USA und Kanada, 20 Pat. aus einem Zentrum wegen Datenfälschung ausgeschlossen
ICSS [8-10]	Am ehesten Äquivalenzstudie, keine Hypothese angegeben	Powerberechnung: n=1.500 erforderlich für Nachweis eines Unterschieds mit einem 95 % KI von 3% für primären Endpunkt Disabling Stroke or Death oder sekundärere Endpunkt, prozeduraler Schlaganfall, Tod oder Herzinfarkt innerhalb von 30 Tagen nach Intervention mit 95 % KI von 3,3% (wurde nur per Protokoll ausgewertet) ITT war 120 Tage nach Randomisierung bei Annahme keines großen Unterschiedes Ereignisrate ca. 10% (basieredn auf CAVATAS)	Nein – Power nicht erreicht [95%KI ist weiter als als angenommen]
SPACE [11-15]	Noninferioritätsstudie	Powerberechnung: Non –Inferioritätsgrenze von 2,5% für primären Endpunkt (gleichseitiger	Ja Studienabbruch nach Rekrutierung von **1.214**

Studie	Studiendesign	Angaben zu statistischer Berechnung	Studienabbruch//Auswirkungen auf die Power/gründe für Abbruch
		Schlaganfall – ischämisch oder hämorragisch oder Tod jeglicher Ursache 30 Tage nach Behandlung), Fallzahlkalkulation von 1900	Pat. 2001-2006 Update der Powerberechnung ergab eine benötigte Patientenzahl von 2.500, das schien nicht realistisch – auch wegen Finanzierung, Studie ist deshalb unterpowert
CAVATAS [16; 17]	explorative Studie (feasibility)	Keine Powerberechnung; “The study was planned as an exploratory trial. No formal sample size calculations were done”	Nein – keine Powerberechnung
EVA-3S [18; 19]	Noninferioritätsstudie	Powerberechnung: Non-Inferioritäts-Studie mit insgesamt **872** P mit 80% Power bei Messen der 30-Tages.Inzidenz of stroke or death, given an expected 30-day incidence of stroke or death of 5.6% after endarterectomy and 4% after stenting,20,21 a true absolute difference between groups in the 30-day risk of stroke or death of no more than 2% (noninferiority margin), and a onesided alpha of 0.05. Stopp im September 2005 wegen mangelnder Sicherheit von CAS. Bei der niedrigen Ereignisrate der CEA hätte man 4000 Pat. für Non.inferiorität gebraucht.	Ja –Power nicht erreicht Studienabbruch nach Rekrutierung von **527** Pat. 11/00-9/05 Angegebene Gründe = Sicherheit und Zwecklosigkeit Power der Studie ist nicht gegeben. Die erwartete Anzahl der Ereignisse bei CASwar viel höher als die tatsächliche, die bei CEA geringer man hätte nun 4000 Pat. gebraucht
SAPPHIRE [21; 22]	Noninferioritätsstudie	Powerberechnung triangular sequential-monitoring method, which allows flexibility in sample size (as many as 2400 patients could be enrolled) and in the timing of the interim analyses. An interim analysis according to this method was planned to determine whether enrollment in the trial should be terminated. The condition for termination was based on the upper boundary of the 95% CI for the difference in the monitoring end point between the two groups. If the upper boundary was calculated to be less than 3% (Definition of noninferiority) enrollment was to be terminated.	Ja – Power nicht erreicht, aber im Ergebnis gefordertes Konfidenzintervall kleiner Inferioritätsgrenze erreicht und sogar Nachweis von Superiorität Stopp im Juli 2002 wegen mangelnder Rekrutierung bei n=334 aus 29 Zentren Begründung war die Öffnung von Stentregistern
BACASS [20]	am ehesten Feasibility-Studie	Keine Powerberechnung “Our intention was to base the treatment decision on the best evidence and generate data on safety and effectiveness of CAS and CEA in our institution…” . Furthermore, we wanted to test the feasibility of this approach and provide data that can be used for a systematic meta-analysis.”	Nein – Studie ist nicht adäquat gepowert

Studie	Studiendesign	Angaben zu statistischer Berechnung	Studienabbruch//Auswirkungen auf die Power/gründe für Abbruch
REGENSBURG [23]	keine Hypothese	Keine Hypothese, keine Powerberechnung, am ehestens Nichtunterlegenheitsstudie, zunächst Einschluss von 200 Pat. geplant	Ja – Studie ist nicht adäquat gepowert Studienabbruch nach Rekrutierung von 87Pat. wegen Beginn der SPACE-Studie
K-ASYMP [24]		Keine Powerberechnung In Studie selbst nur: „This prospective randomized trial compares the efficacy and benefits of CAS and CEA in the treatment of asymptomatic carotid stenosis in a community hospital".	Nein – Studie ist nicht adäquat gepowert
K-SYMP [25]	s. o.	s. o.	s.o.
WALLSTENT [26]	multizentrische Äquivalenzstudie	Studie war für 700 Pat. geplant k. A. zur Powerberechnung	Ja - Studie ist nicht adäqut gepowert Abbruch wegen Sicherheit und „futility" Studienabbruch nach Rekrutierung von 219 Pat.
LEICESTER [27]	am ehesten Inferioritätsstudie	Keine Hypothese genannt, geht jedoch aus der Studie hervor. Keine %-Angabe von Inferiorität max. n=300 mit 15 geplanten Interimsanalysen A predetermined significance level of P < .0086 was to be used at each of the 15 interim analyses to achieve an overall significance level of P< .05 at the end of the trial. The DMC were informed that should any interim analyses yield a significance level of P < .0086, the stopping rule should apply."	Studienabbruch nach Rekrutierung von 23 Pat. 6/96-9/96 Studienabbruch wegen Sicherheit nach vordefinierter Stopping rule (Zwischenanalyse nach jew. 20 Pat. Ergebnis wurde ohne erforderliche Power erzielt

6.1.2 Subgruppenanalysen /Auswertung zu Altersabhängigkeit

Studie	Subgruppenanalysen/Geplant?/Welche	Altersabhängigkeit untersucht und valide ableitbar?
CREST [6; 7]	Post-hoc-Analysen (.Lebensqualität für Endpunkte Schlaganfall und Herzinfarkt, Berufsgruppe der CAS-Behandler – geplant. Geplant,aber nicht angegeben: Alter Geplant und angegeben: Geschlecht , Sympt. vs. asympt. Pat.	Secondary aims included estimating the modificationof the treatment effect by symptomatic status, sex, and age, which were assessed through inclusion of the interaction terms in the proportional-hazards models (as a single indicator variable for sex and symptomatic status and a linear term for age). The analyses of age were planned before data analysis began but were not described in the study protocol. An interaction between age and treatment efficacy was detected (P = 0.02) (Fig. 2B and 2C), with a crossover at an age of approximately 70 years; carotid-artery stenting tended to show greater efficacy at younger ages, and carotid endarterectomy at older ages." Cave: Konfidenzintervalle sehr weit
ICSS [8-10]	Several predefined exploratory subgroup analyses were undertaken to investigate whether the relative treatment effect for the 120-day ITT short-term composite outcome of stroke, death, or procedural myocardial infarction differed across various patient groups. Interaction tests were done with Cox proportional hazard models. Weitere Subgruppenanalyse: Vergleich der Restenose-Raten Aus dem Protokoll: "We estimate a prevalence of 10 to 20% in-stent restenosis (>50%) after one year based on the literature (in which estimates substantially differ, due to different definitions of restenosis and different Follow-up periods). To obtain estimates of sensitivity of approximately 90% with a confidence interval of maximum 10%, and a prevalence of restenosis after one year of 20%, we would require a minimum of 172 patients. The proposed number of 150 patients, however, is estimated based on the minimum number of patients we will be able to include in practice."	
SPACE [11-15]	Ja, auch geplant- "Several subgroup analyses were predefined in the protocol. Table 4 and figure 3 show the results for the primary endpoint for patients younger and older than 75 years and for women and men. The absolute-risk diff erence between groups was greater for women than it was	Publikation 2006: Stratifizierung mit cut-off 75J. : The absolute diff erence between the rates of primary-endpoint events in the two treatment groups for patients younger than 75 years was small, but even for this small diff erence, the upper limit of the 90% CI (3・07%) for the actual diff erence exceeds the non-inferiority

Studie	Subgruppenanalysen/Geplant?/Welche	Altersabhängigkeit untersucht und valide ableitbar?
	for men (table 4). In the carotid-artery stenting group, 151 (27%) patients were treated with an embolic protection device. Primary endpoint events occurred in 11 of 151 (7%) of the patients treated with and in 28 of 416 (7%) of those treated without such a device (OR 1・09, CI 0・53–2・25) [11] In Publikation 2008: Alter bei cut-off 68 stat- sign. Unterschiedlich, andere Parameter (Geschlecht, Grad der behandelten Stenose, Grad der kontralateralen Stenose (jew, cut off 70%) , Seite der behandelten Stenose, Art des auslösenden symptomatischen Ereignisses n.s.	margin of 2・5%." Publikation 2008: zu Altersabhängigkeit in Bezug auf Risiko Schlaganfall oder Tod: "Risk of ipsilateral stroke or death increased with age in the CAS group (p=0·001) but not in the CEA group (p=0·534). Classification and regression tree analysis showed that the age with greatest separation between high-risk and low-risk populations who had CAS was 68 years: the rate of primary outcome events was 2·7% (8/293) in patients who were 68 years old or younger and 10·8% (34/314) in older patients. Other variables did not differ between the CEA and CAS groups".
CAVATAS [16; 17]	Nein Post hoc subgroup analysis was done to examine the rate of stroke associated with stenting. 1/55 = 2% alle bis Tag 11 Ultrasound Follow-up (ca. 1 year) was done in 173 and 174 patients in the endovascular and surgery groups. CAS: 25 [14%] *vs CEA* seven [4%], respectively, p<0·001). US: severe stenosis or occlusion was noted at 1 year in 32 (18%) endovascular patients, compared with nine (5%) surgical patients (p<0·001)	k. A. keine Auswertung in der Studie beschrieben
EVA-3S [18; 19]	Nein The following exploratory subgroup analyses were done: men versus women; 70 years or older versus younger than 70 years; hypertension versus normotensive; diabetes versus no diabetes; smoking versus no smoking; prior stroke versus no prior stroke; qualifying event defined as stroke versus cerebral TIA versus ocular event; time from qualifying event to treatment of less than 2 weeks versus 2 weeks or more; ipsilateral carotid stenosis of 90% or more versus less than 90%; and contralateral carotid stenosis of 70% or more (or contralateral carotid occlusion) versus less than 70%. These subgroups were not prespecified [Mas et al., 2008]	in Subgruppenanalyse (2008) Risiko für Schlaganfall höher für >70, aber KI überschneiden sich.

Studie	Subgruppenanalysen/Geplant?/Welche	Altersabhängigkeit untersucht und valide ableitbar?
SAPPHIRE [21; 22]	Auswertung symptomatisch vs asymptomatischer Patienten in Bezug auf Endpunkte , kein fester Anteil symtpomatischer Pat. geplant	Keine Altersabhängigkeit untersucht.
BACASS [20]	nein	zu klein
REGENSBURG [23]	nein, Auswertungen nach über 5 J nur mit 70% der Pat.	zu klein
K-ASYMP [24]	nein	k. A.
K-SYMP [25]	nein	k. A.
WALLSTENT [26]	k.A.	k. A. Studie liegt nur als Abstract vor
LEICESTER [27]	nein	k. A. (nur 17 Pat. beh.)

Studie	Patientenselektion: Anwendung der dazu beschriebenen CONSORT-Kriterien **Vorhandene/fehlende Angaben**
CREST [6; 7]	Einschluss = „Enrollment“: Es fehlen Angaben darüber, wie viele Patienten im Zeitraum in Frage gekommen wären und wie viele davon aus welchen Gründen nicht randomisiert wurden. „Patients were assessed for eligibility before randomization, but the number of patients assessed is not available, because screening logs were not maintained.”

Studie	Patientenselektion: Anwendung der dazu beschriebenen CONSORT-Kriterien Vorhandene/fehlende Angaben
	Alle übrigen Angaben sind vorhanden (Figure 1, [6]). CAS: 90% erhielten Intervention/5,7% erhielten CEA; 4,3% keine Intervention/5,4% Lost of Follow-up CEA: 95% erhielten Intervention, 1% erhielt CAS, 4% erhielten keine Intervention/8,87% Lost of Follow-up
ICSS [8-10]	Einschluss ("Enrollment"): Es fehlen Angaben darüber, wie viele Patienten im Zeitraum in Frage gekommen wären und wie viele davon aus welchen Gründen nicht randomisiert wurden. "Data for the number of patients screened for eligibility were not recorded". Alle übrigen Angaben sind vorhanden (Figure 1, Brown et al., 2010 RefiD 18]. CAS: 96,8% erhielten zugeteilte Intervention, 1% erhielt CEA, 1,9% erhielt keine Intervention. CEA: 95,6% erhielten zugeteilte Intervention, 1,7% erhielt CAS, 2,4% erhielt keine Intervention.
SPACE [11-15]	Einschluss ("Enrollment"):Es fehlen Angaben darüber, wie viele Patienten im Zeitraum in Frage gekommen wären und wie viele davon aus welchen Gründen nicht randomisiert wurden. Alle übrigen Angaben sind vorhanden (Figure 1, [11]). CAS: 99% erhielten Intervention. CEA: 98% erhielten zugeteilte Intervention.
CAVATAS [16; 17]	Einschluss ("Enrollment"): Es fehlen Angaben darüber, wie viele Patienten im Zeitraum in Frage gekommen wären und wie viele davon aus welchen Gründen nicht randomisiert wurden. Alle übrigen Angaben sind vorhanden (Figure 1, [17]). CAS: 95,6% erhielten zugeteilte Intervention. CEA: 97% erhielten zugeteilte Intervention.
EVA-3S [18; 19]	Einschluss ("Enrollment"):Es fehlen Angaben darüber, wie viele Patienten im Zeitraum in Frage gekommen wären und wie viele davon aus welchen Gründen nicht randomisiert wurden. Alle übrigen Angaben sind vorhanden (Figure 1, [19]).

Studie	Patientenselektion: Anwendung der dazu beschriebenen CONSORT-Kriterien Vorhandene/fehlende Angaben
	CAS: 93% erhielten zugeteilte Intervention. CEA: 98% erhielten zugeteilte Intervention. Kein Lost of Follow-up angegeben.
SAPPHIRE [21; 22]	Kein Flow-Diagramm, aber alle erforderlichen Angaben S.1496 [22]. Von **747** in Frage kommende Patienten im Zeitraum wurden **334** randomisiert. Von den übrigen 413 wurden 406 nicht randomisiert, da sie als nicht geeignet für eine CEA gewertet wurden. Diese Patienten wurden einem Stent-Register zugeordnet. Ergebnisse dieser Patientengruppe sind nicht ausgewiesen. 7 Patienten wurden als nicht geeignet für eine CAS eingeordnet, diese wurden einem CEA-Register zugeordnet. Kein cross over angegeben. CAS: 95,2% (159/167) mit CAS beh.; CEA 90,4% (151/167) mit CEA behandelt.
BACASS [20]	Alle erforderlichen Angaben in Figure 1. Von 82 in Frage kommenden Patienten im Zeitraum lehnten 45 die Randomisierung ab. Für 35 weitere Patienten sind „weitere Ausschlussgründe“ angegeben, die nicht spezifiziert wurden. Angabe, dass keine cross over stattfand.
REGENSBURG [23]	keine Angabe, wie vielen Pat. die Randomisierung vorgeschlagen wurden, bzw. warum sie ablehnten , keine Angabe von cross over
K-ASYMP [24]	keine Angabe des Rekrutierungszeitraums und wer ausgeschlossen wurde ;keine Hypothese, Randomisierungsmethode n.a., Data collection n.a., Intervention nicht gut beschrieben, Verblindung nicht beschrieben, kein Flow Diagramm (keine Angabe zu cross over), keine Studiennummer, Protokoll nicht einsehbar angegeben.
K-SYMP [25]	Keine Angabe des Rekrutierungszeitraums und wer ausgeschlossen wurde und s. K-ASYMP.
WALLSTENT [26]	Studie liegt nur im Abstract vor, Kriterien können nicht alle beurteilt werden.
LEICESTER [27]	Alle eingeschlossenen und nicht eingeschlossenen im Zeitraum beschrieben. 23 randomisiert, 3 nachträglich ausgeschlossen (1 mit Okklusion, 2 lehnten zugeteilte Behandlung CEA/CAS ab). 4 CEA ohne Kompl. Im Zeitraum außerhalb der Studie.

6.2 Ein- und Ausschlusskriterien, Umgang mit/Verteilung von Risikopatienten

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
CREST [6; 7]	**Einschluss** Patients were considered to be symptomatic if they had had a transient ischemic attack, amaurosis fugax, or minor nondisabling stroke involving the study carotid artery within 180 days before randomization. Eligibility criteria were stenosis of 50% or more on angiography, 70% or more on ultrasonography, or 70% or more on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50 to 69%. Eligibility was extended in 2005 to include asymptomatic patients, for whom the criteria were stenosis of 60% or more on angiography, 70% or more on ultrasonography, or 80% or more on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50 to 69%. **Ausschluss** Patients were excluded if they had had a previous stroke that was sufficiently severe to confound the assessment of end points or if they had chronic atrial fibrillation, paroxysmal atrial fibrillation that had occurred within the preceding 6 months or that necessitated anticoagulation therapy, myocardial infarction within the previous 30 days, or unstable angina. Additional eligibility criteria were clinical and anatomical suitability, before randomization, for management by means of either of the study revascularization techniques. The full eligibility criteria have been published elsewhere **Aus dem Studienprotokoll:** Kardiale Ausschlusskriterien: Knowledge of cardiac sources of emboli (e.g. left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma). Chronic atrial fibrillation.	Ja, für Dyslipidämie 85,8% in OP Gruppe 82,9% in Stent Gruppe p=0,048	kein Score für Ausschluss weitere Ausschlussgründe: Lebenserwartung <5J Gefäßlumen zwischen 4-9mm Angiographie vor Randomisierung nicht zwingend. Falls Angiographie nach Randomisierung, kein Ausschluss mehr wegen anatomischer Besonderheiten nur Carotis interna-Stenosen (mit oder ohne Bifurkationsbeteiligung)

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	Any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation. Patient has had a MI within previous 30 days. Eingeschränkt oder nicht operabel wegen: Knowledge of two or more proximal or major diseased coronary arteries with >/=70% stenosis that have not, or cannot be revascularized. Ejection fraction <30% or New York Heart Association (NYHA) Functional Class III or higher. Unstable angina defined as rest angina with ECG changes. Currently on a list for major organ transplantation (i.e., heart, **Anatomische Ausschlusskriterien** 1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement. 2. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution. 3. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath. 4. An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) that is not associated with an ulcerated target lesion. 5.Abnormal angiographic findings that constitute a contraindication to CEA: ipsilateral intracranial or extracranial arterial stenosis greater in severity than the lesion to be treated, cerebral aneurysm > 5 mm, AVM (arteriovenous malformation) of the cerebral vasculature, or other abnormal angiographic findings that constitute contraindication to CEA. 6. Bilateral carotid stenosis if intervention is planned within the 30-day CRESTperiprocedural period. 7. Occlusion		

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
ICSS [8-10]	**1. Einschluss:** Pat. >40J vorausgegangenen Symptome einer Karotisstenose innerhalb der letzten 12 Monate und Stenose >50% gemessen auch noninvasiv mit Duplex Sonographie **2. Ausschluss:** vorausgegangene CAS/CEA Kontraindikation für CAS/CEA (entweder primär nicht eingeschlossen oder Ausschluss auch nach Randomisierung nach Angiographie siehe Komm.) Gepl. koronarer Bypass mit Grafting oder geplante größere andere OP vorausgegangener Schlaganfall ohne entspr. Restitution nicht explizit kardiales Risiko **Aus dem Studienprotokoll 2007:** **Inclusion criteria** - Symptomatic, extracranial, internal or bifurcation, atheromatous carotid artery stenosis that is suitable for both stenting and surgery and is deemed by the randomising clinician to require treatment. - The severity of the stenosis of the randomised artery should be at least 50% (as measured by NASCET method or non-invasive equivalent). - Symptoms must have occurred in the 12 months before randomisation. It is recommended that the time between symptoms and randomisation should be less than 6 months, but patients with symptoms occurring between 6 and 12 months may be included if the randomising physician considers treatment indicated. -The patient must be clinically stable following their most recent symptoms attributable to the stenotic vessel. - Patients must be willing to have either treatment, be able to provide informed consent, and be willing to participate in follow up. - Patients must be able to undergo their allocated treatment as soon as possible after randomisation. - Any age greater than 40 may be included. There is no upper age limit. - Patients should only be randomised if the investigator is	CAS: nach Randomisierung Ausschluss falls in Angiographie negative Kriterien CEA wird „ähnliches Verfahren“ beschrieben	Aus der ICSS-Auswertung: Patients unsuitable for stenting because of tortuous anatomy proximal or distal to the stenosis, visible thrombus, proximal common carotid artery stenosis, or internal carotid artery pseudo-occlusion were excluded, as were patients unsuitable for endarterectomy because of the distal site of the stenosis, a rigid neck, or risk factors for surgical complications. No record was kept of patients screened who were ineligible or treated outside the trial. It was recommended that patients randomised to stenting after non-invasive investigation, in which subsequent angiography before stenting showed one or more exclusion criteria, should have the procedure abandoned and be treated by surgery, if appropriate, or medical care alone. A similar approach was taken in patients randomised to surgery.

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	uncertain which of the two treatments is best for that patient at that time. Exclusion criteria - Patients refusing either treatment. - Patients unable or unwilling to give informed consent. - Patients unwilling or unable to participate in follow up for whatever reason. - Patients who have had a major stroke with no useful recovery of function within the territory of the treatable artery. - Patients with a stenosis that is known to be unsuitable for stenting prior to randomisation because of one or more of: Tortuous anatomy proximal or distal to the stenosis - Presence of visible thrombus - Proximal common carotid artery stenotic disease - Pseudoocclusion (‘string sign’). -Patients not suitable for surgery due to anatomical factors e.g. high stenosis, rigid neck. - Patients in whom it is planned to carry out coronary artery bypass grafting or other major surgery within 1month of carotid stenting or endarterectomy. - Carotid stenosis caused by non-atherosclerotic disease e.g. dissection, fibromuscular disease or neck radiotherapy. - Previous carotid endarterectomy or stenting in the randomised artery. - Patients in who common carotid artery surgery is planned. - Patients medically not fit for surgery. - Patients who have a life expectancy of less than two years due to a pre-existing condition, e.g. cancer.		
SPACE [11-15]	Symptomatic stenosis (amaurosis, transient ischaemic attack, or stroke) of carotid bifurcation or internal-carotid artery within past 180 days Modifi d Rankin scale score of 3 or less Older than 50 years	Nein	Ausschlusskriterien: Intracranial bleeding in past 90 days Uncontrolled arterial hypertension Known intracranial arteriovenous malformation or aneurysm

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	Negative pregnancy test for women with childbearing potential Possibility for Follow-up examinations Written informed consent provided Stenosis of carotid bifurcation or internal-carotid artery of at least 70% proven by duplex ultrasound or angiography corresponding to stenosis level of at least 70% according to criteria of European Carotid Surgery Trial13 or at least 50%.according to criteria of NASCET		Severe concomitant disease with poor prognosis (life expectance <2 years) Uncorrectable coagulation abnormality Contraindications for heparin, aspirin, or clopidogrel Contraindications for contrast media Planned simultaneous surgical procedures Any condition that could impose hazards to the patient if study therapy is iniated, left to discretion of investigator Occlusion of common-carotid or internal-carotid artery Stenosis due to external compression Stenosis due to dissection Recurrent stenosis after surgery or stenting Radiation-induced stenosis Stenosis due to fibromuscular dysplasia Floating thrombus Additional intracranial stenosis with higher grade
CAVATAS [16; 17]	For inclusion in the study patients had to have stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery that investigators believed needed treatment and was suitable for both carotid endarterectomy and endovascular treatment. Investigators included patients only if the best treatment was unclearie, patients were randomly assigned only if they and their	Nein	

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	carotid stenosis were equally suitable for both surgery and endovascular treatment. Hypertension 55% Ischemic heart disease 22% Previuos heart disease 18% Exclusion criteria incl uded patients thought to be unsuitable for surgery because of medical or surgical risk factors (eg, recent myocardial infarction, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis). We also excluded patients if they were unwilling to undergo either procedure, were unable to give informed consent, or if they had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery. Patients were not eligible for the study if angiography showed thrombus in the carotid artery, severe intracranial carotid artery stenosis beyond the skull base, or a stenosis unsuitable for endovascular reatmenteg, because of tortuous vascular anatomy. However, patients did not need to have catheter angiography if a reliable non-invasive investigation had confirmed carotid stenosis. We did not exclude patients if contraindications were noted after random assignment. There was no age limit.		
EVA -3S [18; 19]	**Einschluss:** Patients were eligible if they were 18 years of age or older, had had a hemispheric or retinal transient ischemic attack or a nondisabling stroke (or retinal infarct) within 120 days before enrollment, and had a stenosis of 60 to 99% in the symptomatic carotid artery, as determined by NASCET.The degree of stenosis warranting treatment, set at 70% or more at the start of the trial, was subsequently (in October 2003) set at 60% or more because endarterectomy was shown to benefit patients with symptomatic stenosis of 50 to 69%.3 The presence of an ipsilateral carotid stenosis of 60% or more had to be confirmed by means of catheter angiography or both duplex		CEA: mehr >75J (p=0,06) beide : 73% Hypertension, 56% Hypercholesterinämie, CEA: mehr vorausgegangener Schlaganfall p=0,02 sonst gleich verteilt. CAS: 6% mehr TIAs, aber kein p-Wert extra dafür angegeben

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	scanning and magnetic resonance angiography of the carotid artery. **Ausschluss:** Patients were excluded if one of the following was present: a modified Rankin score of 3 or more (disabling stroke) (on a scale of 0 to 5, with higher scores indicating more severe disability); nonatherosclerotic carotid disease; severe tandem lesions (stenosis of proximal common carotid artery or intracranial artery that was more severe than the cervical lesion); previous revascularization of the symptomatic stenosis; history of bleeding disorder; uncontrolled hypertension or diabetes; unstable angina; contraindication to heparin, ticlopidine, or clopidogrel; life expectancy of less than 2 years; or percutaneous or surgical intervention within 30 days before or after the study procedure. The appearance of the stenotic lesion on angiography was not a factor in the selection of patients.		
SAPPHIRE [21; 22]	**Einschluss:** Alter ≥18 J Unilateralel or bilaterale atherosclerotische or restenotische Läsion in nativer Carotisarterie Symptoms plus stenosis of more than 50 percent of the luminal diameter No symptoms plus stenosis of more than 80 percent of the luminal diameter Criteria for high risk (at least one factor required) Clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery) Severe pulmonary disease Contralateral carotid occlusion Contralateral laryngeal-nerve palsy		Patients were randomly assigned to a procedure only if all members of the team were in agreement that the patient was a suitable candidate for either endarterectomy or stenting. If the surgeon assessing the patient concluded that endarterectomy could not be safely performed but the interventional physician judged that stenting was feasible, the patient was not randomly assigned to a procedure but instead was entered into a stent registry. Likewise, if the surgeon deemed the patient suitable for surgery but the interventional physician did not think that stenting was feasible, the patient was entered into a surgical registry. Of the 413 patients who were not randomly assigned to treatment, 406 were entered into the stent registry and 7 were entered into the

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	Previous radical neck surgery or radiation therapy to the neck Recurrent stenosis after endarterectomy Age >80 yr **Ausschluss:** Ischemic stroke within previous 48 hr Presence of intraluminal thrombus Total occlusion of target vessel Vascular disease precluding use of catheter-based techniques Intracranial aneurysm >9 mm in diameter Need for more than two stents History of bleeding disorder Percutaneous or surgical intervention planned within next 30 days Life expectancy <1 yr Ostial lesion of common carotid artery or brachiocephalic artery Risiko im wesentlichen gleich verteilt. mehr als 10% Unterschied: Koronare Herzkrankheit: +10,3% CAS’ Vorausgeg. Perkutane Angioplasty: +11,4 CAS vorausgegang. Koronarer Bypass: +12,6%		surgical registry.
BACASS [20]	**Einschluss:** Patients with symptomatic highgrade internal carotid artery (ICA) stenosis. All treated stenoses measured at least 70% (range: 70–99%). The degree of the stenosis of the ICA was preprocedurally		

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	defined on Doppler/duplex ultrasound (US), according to the CAVATAS criteria (3) and on magnetic resonance angiography (CE-MRA). A diagnostic digital subtraction angiography study was only performed in discordant findings of US and MRA, which happened in one case. MR imaging of the brain was performed in all patients to document or exclude recent territorial infarction, bleeding or mass lesion. All patients were symptomatic within the last 3 months and had a neurological examination by a stroke neurologist. On a weekly held interdisciplinary conference about cerebrovascular interventions, we identified all consecutive patients, in whom CAS as well as CEA seemed technical feasible according to the surgeons and interventional neuroradiologists. Except for one patient with contralateral carotid occlusion (CAS group) all patients were stratified into low risk for CEA according to Gasparis et al. (7). Baseline Charakteristika ähnlich		
REGENSBURG [23]	**Einschluss:** patients with >70% symptomatic carotid artery stenosis as defined by NASCET criteria Alter >70 47% Hypertonie 78% KHK 44% Diabetes 39% Hyperchol. 52% Symptome: Schlaganfall 34,5% Amaurosis fugax: 24%		

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	TIA: 47% alles ca. gleich verteilt		
K-ASYMP [24]	**Einschluss:** asymptomatic individuals referred for revascularization and having digital subtraction angiography-documented internal carotid stenosis of more than 80%, as determined by the North American Symptomatic Carotid Endarterectomy Trial (45). Persons with any symptom of cerebrovascular ischemia were excluded.. The presence of contralateral total occlusion of the internal carotid artery, the angiographic appearance (smooth versus ulcerative) of the stenotic lesion, or the presence of an intracranial aneurysm was not a factor in treatment assignment. In addition to angiographic criteria, inclusion criteria included an anticipated life expectancy of 5 years, willingness to complete treatment within 1 month, and ability to sign an informed consent. **Ausschluss:** allergy or sensitivity to aspirin, heparin, or clopidogrel; a history of bleeding diathesis or coagulopathy; or cardiac arrhythmia. Bluthochdruck: CEA: 41 /CAS 35 kor. Herzkrank: CEA 20/CAS 35		
K-SYMP [25]	s.o.		
WALLSTENT [26]	nur Grad der Stenose angegeben		
LEICESTER [27]	**Einschluss:** Patients with carotid territory symptoms and evidence of an ipsilateral 70% to 99% ICA stenosis and who fulfilled our criteria for undergoing CEA, on the basis that there was currently no reliable method of excluding high-risk patients, plaques, or luminal thrombus.		

a) Baseline characteristics	Ein- und Ausschlusskriterien; ggf. Angaben morphologischer Daten/ kardiales Risiko „Risikopatienten“	Gibt es eine Präferenz zugunsten eines Studienarmes (CEA/CAS)?	Kommentar
	Ausschluss: Asymptomatic disease, symptomatic 0% to 69% stenosis, crescendo transient ischemic attack (TIA) or stroke in evolution, and vertebrobasilar or nonhemispheric symptoms and those patients who refused to give informed consent.		

6.3 Endpunkte und Evaluation

6.3.1 Erhebung der Endpunkte

a) Nach-untersuchung	Neurologe – unabhängig?	Arzt – unabhängig?	Kommentar
CREST [6; 7]	Ja, falls unabhängiger Neurologe nicht verfügbar, unabhängiger Arzt	falls unabhängiger Neurologe nicht verfügbar, unabhängiger Arzt	Aus dem Protokoll (Suppl. Appendix): All clinical sites will have a CREST team consisting of a neurologist, surgeon, interventionalist, experienced ultrasonographer and dedicated Research Coordinator (RC). If the study neurologist is unavailable, the neurological evaluation, including the NIHSS can be performed by an independent neuroscientist/ physician certified in the use of the NIHSS.
ICSS [8-10]	Nein, lokaler Neurologe oder Strike Physician	Nein, lokaler Neurologe oder Strike Physician	Arzt im Follow-up war nicht verblindet. Auswertung der Endpunkte erfolgte verblindet. Outcome Bericht erfolgte duch lokalen Neurologen oder Stroke Physician. Bei Major event Begutachtung durch verblindeten Bewerter. Bei Differenz ggf. zweiter Bewerter.
SPACE [11-15]	Ja		
CAVATAS [16; 17]	Ja, neurologist or clinician	neruologist or clinician	Im Abstract Neurologe genannt, in der Studie „neurologist or clinician“, nach OP neurologische Bewertung erst ab 1 Monat
EVA-3S [18; 19]	Ja	Ja	Teil des Teams. Machte auch Beurteilung vor Studienbeginn
SAPPHIRE [21; 22]	Ja		Beurteilung tägl. durch Neurologen, nicht ausgewiesen, ob unabhängig!
BACASS [20]	Ja		The patients were followed up by a neurologist with duplex US and clinical neurological examinations at day one and 1, 6 und 12 months after the procedure, subsequently once a year. Nicht explizit unabhängig
REGENSBURG [23]			Neurologic and clinical examinations were performed by an independent neurologist at 6 months and 1 year after treatment in all patients.
K-ASYMP [24]	independent		

a) Nach-untersuchung	Neurologe – unabhängig?		Arzt – unabhängig?		Kommentar
	neurological evaluations				
K-SYMP [25]	independent neurological evaluations				
WALLSTENT [26]					Neurologische Bewertung 24h post Intervention, nach 1, 6, und 12 Mo Vor Eingriff Beurteilung der Pat. durch interdiszipl. Team mit Neurologen
LEICESTER [27]	All patients were seen and examined by a neurologist; patients were re-examined by a consultant neurologist				

6.3.2 Definition der Endpunkte/Untersuchung von Lebensqualität

6.3.2.1 Endpunkte /Untersuchung Lebensqualität/ Untersuchung der Restenosierung

Studie	Endpunktdefinition	Einfluss der Endpunkte auf „Quality of Life“ untersucht? Score/ Ergebnis	Restenosen/Nachweismethode : - Doppler-Duplex Kriterien definiert? Kommentar
CREST [6; 7]	**Primärer Endpunkt:** komb. Endpunkt aus jegl. Schlaganfall, Herzinfarkt oder Tod während der periprozeduralen Periode (ab Rand. Bis 30/36 Tage nach Eingriff) oder gleichseitiger Schlaganfall bis 4 J nach Rand.	Ja post hoc? SF 36 Physical Health und Mental health nur Major Stroke und Minor Stroke hat stat. sign, Einfluss auf LQ, nicht Herzinfarkt	Rate an Restenosen als sekundärer Endpunkt in Studienprotokoll, nicht in Studienregister genannt, gemessen nach 6+12 Mo mit Ultraschall; nicht publiziert Stenosennachweis: Kriterien nicht berichtet, jedoch Angio bei Stenose < 70%; alle US durch zertifiziertes Labor

Studie	Endpunktdefinition	Einfluss der Endpunkte auf „Quality of Life“ untersucht? Score/ Ergebnis	Restenosen/Nachweismethode : - Doppler-Duplex Kriterien definiert? Kommentar
	Jedes Ereignis wird gezählt, “fatal stroke” als Schlaganfall und als Tod “Stroke = acute neurologic event with focal symptoms and signs, >/=24 h consistent with focal cerebral ischemia. “Major stroke” on the basis of clinical data or if the NIHSS score was 9 or higher 90 days after the procedure. Non-Disabling Stroke is defined as an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit. The deficit must have persisted for a minimum of 24 hours. In all cases, patients must be non-disabled, i.e., Modified Rankin Score of max. 2. Def. Herzinfarkt: wie ICSS		
ICSS [8-10]	**primärer Endpunkt:** Schlaganfall (Rankin-Score+3) oder Tod nach 3 Jahren (noch nicht publiziert) Zwischenanalyse 120 Tage nach Randomisierung : Schlaganfall, Herzinfarkt oder Tod Definition Herzinfarkt: „presence of two of the following three criteria: specific cardiac enzymes more than twice the upper limit of normal; history of chest discomfort for at least 30 min; or the development of specific	Nein	Rate an Restenosierung nach Stent im Protokoll als zu untersuchender Aspekt genannt. Geplant mit 150 Pat. bei angenommener Rate von 10-20%

Studie	Endpunktdefinition	Einfluss der Endpunkte auf „Quality of Life“ untersucht? Score/ Ergebnis	Restenosen/Nachweismethode : - Doppler-Duplex Kriterien definiert? Kommentar
	abnormalities (eg, Q waves) on a standard 12-lead electrocardiograph.		
SPACE [11-15]	**Primärer Endpunkt** : seitengleicher Schlaganfall (“ischaemic stroke or intracerebral bleeding or both, with symptoms lasting more than 24 h”) oder Tod nach Randomsiierung bis 30 T nach Behnadlung Nur jeweils das erste Ereignis wurde gezählt **Secondary 30-day endpoints** included (i) disabling ipsilateral stroke defi ned as a score on the modifi ed Rankin scale of at least 3, or death from any cause since randomisation, (ii) any stroke up to 30 days after treatment, and (iii) procedural failure including inability to treat the allocated technique, remaining stenosis of 50% or more measured with ultrasound at one of the Follow-up visits, or vessel occlusion assessed up to 30 days after treatment.	Nein	Doppler US nach 1Mo, dann 1x/J. Stenosis level of at least 70% according to the criteria of ECST or at least 50% according to the criteria of NASCET, after 6, 12 and 24 months, each B14 days, reckoned from the time of randomisation . At 1 year after treatment, severe (70–99%) ipsilateral carotid stenosis was more usual after endovascular treatment (25 [14%] *vs* seven [4%], p<0·001). However, no substantial difference in the rate of ipsi-lateral stroke was noted with survival analysis up to 3 years after randomisation (adjusted hazard ratio=1·04, 95% CI 0·63–1·70, p=0·9) nach 2 J Restenosierung mind. 70%: CAS: 10,7% (n=54) CEA: 4,6% (n=23) p=0,0009
CAVATAS [16; 17]	**primärer Endpunkt:** fktnsbeeinträchtig. Schlaganfall (Rankin+3 >30Tage) oder Tod 30 Tage nach Behandlung (Ereignisse vor Behandlung werden nicht gezählt, nur zu Überlebensdaten), außderdem: Schlaganfall mit Beschwerden mehr als 7 Tage oder Tod nach 30 Tagen, (Schlaganfall mit Symptomen <7 Tage nicht gezählt wegen V.a. Underreporting der	SF36 and EuroQol EQ-5D keine Unterschiede zwischen CAS und CEA	**Ultraschall Kriterien definiert (nach** Sidhu PS, Allan PL. Ultrasound assessment of internal carotid artery stenosis. *Clin Radiol* 1997; **52:** 654–58) **aber nur Subgruppenanalyse** Ultrasound Follow-up at around 1 year after treatment **was done in 173 and 174 patients** in the endovascular and surgery groups, respectively (figure 5). Severe stenosis (70–99%) was more common on ultrasound at 1 year in the endovascular group than in the surgical group (25 [14%] *vs*

Studie	Endpunktdefinition	Einfluss der Endpunkte auf „Quality of Life“ untersucht? Score/ Ergebnis	Restenosen/Nachweismethode : - Doppler-Duplex Kriterien definiert? Kommentar
	chirurgischen Patienten, die erst nach 1 Mo von einem Neurologen gesehen wurden Hirnnervenlähmung Hämatom mit chirurgischem Eingriff oder längerem KH Aufenthalt		seven [4%], respectively, p<0·001). There were also seven (4%) patients in the endovascular group with carotid occlusion at 1 year, compared with only two (1%) surgical patients, but the difference was not significant. Thus, severe stenosis or occlusion was noted at 1 year in 32 (18%) endovascular patients, compared with nine (5%) surgical patients (p<0·001).
EVA-3S [18; 19]	The primary end point was a composite of any stroke or death occurring within 30 days after treatment. Secondary outcomes were myocardial infarction, transient ischemic attack, cranial-nerve injury, major local complications, and systemic complications within 30 days after treatment; and composites of any stroke or death within 30 days after treatment plus ipsilateral stroke, any stroke, or any stroke or death within 31 days through the end of Follow-up.	Nein	k. A.
SAPPHIRE [21; 22]	**Primärer Endpunkt**: “cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. **The secondary end points** included target-vessel revascularization at one year, cranial-nerve palsy, and complications at the surgical site or the vascular access site. Stroke was defined as an ischemic neurologic deficit that persisted for more than 24 hours. Myocardial infarction was efined as a creatine kinase level higher than two times	Nein	k. A. zu Restenosierung , bei Gurm et al, 2008 Angaben zur Rate an Revaskularisierung der ipsilateralen Seite: CAS: 3% CEA: 7,1% Each center had a vascular laboratory that was fully accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories. The analyses of all measurements obtained with the use of carotid ultrasonography were performed by a core laboratory (Vascular Ultrasound Core Laboratory, Morristown, N.J.), according to published criteria.**12.** Huston J III, James EM, Brown RD Jr, et al. Redefined duplex ultrasonographic criteria for diagnosis of

Studie	Endpunktdefinition	Einfluss der Endpunkte auf „Quality of Life“ untersucht? Score/ Ergebnis	Restenosen/Nachweismethode : - Doppler-Duplex Kriterien definiert? Kommentar
	the upper limit of normal with a positive MB fraction.		carotid artery stenosis. Mayo Clin Proc 2000;75:1133-40
BACASS [20]	**Primärer Endpunkt :** periprocedural stroke, death or myocardial infarction. **Sekundärer Endpunkt:** peri-interventional transient ischaemic attack (TIA), haematoma, cranial nerve paralysis and length of stay. For the Follow-up secondary outcome measures were patency of the treated vessel and stroke prevention related to the treated side.	Nein	US nach CAVATAS-Kriterien und mit CRE -MRA. Follow-up durch Neurologe nach 1Tage und 1, 6 und 12 Mo Nach 1J : 1 CAS Pat Restenose 30–49% 2 CEA Pat Restenose of 30–45% / 50– 69%, Nach 2 J Keine Progression /keine neut. Ereignisse .
REGENSBURG [23]	stroke recurrence, restenosis, and death Keine Angabe primär/sekundär	Nein	The evaluation of restenosis was performed by DUS imaging and quantified as shown in Table I (Peak systolic velocity, ICA/CCA index, End-diastolic velocity, m/s, Turbulences) “A significantly higher rate of restenosis >70% (6 of 32 vs 0 of 29) occurred after CAS compared with CEA. Five of 32 CAS patients (15.6%) presented with high-grade (>70%) restenosis as an indication for secondary intervention or surgical stent removal, and three presented with neurologic symptoms. No CEA patients required reintervention (*P* < .05 vs CAS). A medium-grade (<70%) restenosis was detected in eight of 32 CAS patients (25%) and in one of 29 CEA patients (3.4%)”.
K-ASYMP [24]	Als Endpunkte im Ergebnisteil genannt: 1. Durchgängigkeit der ipsilateralen Carotisinterna nach 48 Mo. 2. Komplikationen (Berichtet wird von Schlaganfall/TIA/ Halsnervenschädigung/ Hypotension/Kompl. der Anästhesie/KH-	Schmerz-Score wurde erhoben	Carotid Ultrasound: internal carotid artery to common carotid artery ratio of peak systolic velocity Nach 48 Mo ICC/CCA Systolic Ratio ca. 1,8 CAS+1,9CEA

Studie	Endpunktdefinition	Einfluss der Endpunkte auf „Quality of Life“ untersucht? Score/ Ergebnis	Restenosen/Nachweismethode : - Doppler-Duplex Kriterien definiert? Kommentar
	Aufenthaltsdauer/Kosten		
K-SYMP [25]	Endpunkte im Methodenteil nicht gut beschrieben - 24-month patency of the reconstructed artery - MRI evidence of asymptomatic focal cerebral ischemia - Komplikationen (Tod/Schlaganfall/TIA/ Nervenschädigung/Hämatom, das Eingriff erfordert, Hypotension/Bradykardie)	Schmerz-Score	Carotid Ultrasound: internal carotid artery to common carotid artery ratio of peak systolic velocity Nach 24 Mo ICC/CCA Ratio ca. 1,7 CAS+CEA Schmerz-Score wurde erhoben
WALLSTENT [26]	primärer Endpunkt: gleichseitiger Schlaganfall, Tod durch Intervention oder Tod aufgrund vaskulärer Ursache innerhalb von einem Jahr	Nein	k. A.
LEICESTER [27]	The main outcome measures were death or disabling or nondisabling stroke within 30 days	Nein	k. A. zu Restenosierung

6.3.4 Zeitpunkte der Endpunkterhebung

c) Zeitpunkt der Endpunkterhebung	Kommentar

c) Zeitpunkt der Endpunkterhebung	Kommentar
CREST [6; 7]	Neurologic evaluation was performed at baseline and 18 to 54 hours after the study procedure, 1 month afterward, and every 6 months thereafter. The evaluation consisted of the use of the National Institutes of Health (NIH) Stroke Scale (NIHSS), the modified Rankin scale, and the Transient Ischemic Attack (TIA)–Stroke Questionnaire. Cardiac-enzyme levels were measured before the study procedure and 6 to 8 hours after the procedure. Electrocardiography (ECG) was performed before stenting or endarterectomy, as well as 6 to 48 hours and 1 month afterward. Carotid ultrasonography was performed before the study procedure; 1, 6, and 12 months afterward; and annually thereafter. (bis 4J)
ICSS [8-10]	vor Rand. 30 Tage nach Beh nicht direkt, sondern = 120 Tage nach Rand. 6 Mo nach Rand, jährlich (letzte nach 3J) Letzte Erhebung: nach 120 Tagen
SPACE [11-15]	vor Rand, 1 Tag vor, 1 Tag nach Beh., 7 Tage, 30 Tage nach Beh., 6, 12, 24 Mo.
CAVATAS [16; 17]	Patients were followed up at 1 month after treatment,and then at 6 months, 12 months, and yearly after random assignment
EVA-3S [18; 19]	48h, 30 Tage +alle 6 Monate nach Beh.,+ nachträglich 4J
SAPPHIRE [21; 22]	Follow-up visits were scheduled to take place 30 days and 6 and 12 months after the procedure and annually thereafter for 3 years.
BACASS [20]	The patients were followed up by a neurologist with duplex US and clinical neurological examinations at day one and 1, 6 und 12 months after the procedure, subsequently once a year.
REGENSBURG [23]	Neurologic and clinical examinations were performed by an independent neurologist 1, 6 months and 1 year after treatment in all patients. A duplex ultrasound (DUS) examination (Siemens Elegra, 2.5PL20, 7.5L40, Issaquah, Wash) was done after 3, 6, and 12 months, and cerebral magnetic resonance imaging (Magnetom Symphony, Siemens, Erlangen, Germany) and DSA (Angiostar Plus, Siemens) was done after 1 year according to the protocol. The retrospective long-term Follow-up with clinical, neurologic, and DUS examinations (Sonoline Antares, Siemens) were started in August 2006. The evaluation of restenosis was performed by DUS imaging and quantified DSA was performed. Follow-up examinations were done by a staff neurologist who was independent from the surgical/interventional trial staff.
K-ASYMP [24]	Carotid duplex scanning was performed within 24 hours and at specified intervals and expressed as the ratio of internal carotid artery to common carotid artery velocity. Rankin and Barthel scorings and independent neurological evaluations were performed concurrently with sequential duplex examinations. Zuletzt nach 48 Mo.
K-SYMP [25]	Carotid duplex scanning was performed within 24 h of either procedure and at 1, 3, 6, 12 and 24 months. Sequential neurologic examinations, Rankin and Barthel scorings were performed concurrent with Duplex scanning. Magnetic resonance imaging (MRI) was obtained at 6 and 12 months to detect the presence of asymptomatic ischemic events in the distribution of the

c) Zeitpunkt der Endpunkterhebung	Kommentar
	treated vessel
WALLSTENT [26]	Neurologische Beurteilung nach 24h und dann nach 1,6 und 12 Mo.
LEICESTER [27]	Patients were re-examined by a consultant neurologist 24 hours after intervention, and any new neurologic deficit was recorded. The neurologist reassessed all patients at 30 days where an Oxfordshire Handicap Stroke score was made.

6.4 Angaben zum Erfahrungsstand der Behandler

Mindesteinzahl von Voreingriffen/ erforderliche Qualifikation angegeben?	Operation			Stent			Kommentar:
	Ja	Nein	Wie viele Eingriffe	Ja	Nein	Wie viele Eingriffe	
CREST [6; 7]			mind. **12** /Jahr + <3% Komplikationen bei sympt. OP +<5% Kompl. bei asymptomatischer OP			1. Mit Vorerfahrung mind. **30 CAS**, Training mit Zertifikat akzeptable Raten an Kompl. 2. < 30 CAS: Training mit Zertifikat und 20 CAS unter Aufsicht des Komitees, ggf., 2 mit Proktoring!	Erst Randomisierung nach Zertifikat aufgrund validierten Auswahlprozesses (Datendokumentation) für OP und Stent
ICSS [8-10]			a) mind. **10 pro J** mind. 50 gesamt oder b) Supervision bis Proktor zufrieden war – Entscheidung			a) mind. **10 CAS** mind. 50 Stenting-Eingriffe gesamt oder b) < 10 CAS und Supervision bis Proktor zufrieden war –	

Mindesteinzahl von Voreingriffen/ erforderliche Qualifikation angegeben?	Operation			Stent			Kommentar:
	Ja	Nein	Wie viele Eingriffe	Ja	Nein	Wie viele Eingriffe	
			nach 20 Fällen			Entscheidung nach 20 Fällen	
SPACE [11-15]			mind. 25 OP			mind. 25 Stents einschließl. Bifurkation; ab 2002 auch mind. 10 +Proktoring möglich	Zulassung nach Auswahl durch Qualitätskommittee Zentren mußten Morbiditäts- und Mortalitätsraten für die Prozeduren angeben (keine Nennung von Zahlen) 10 Zentren wurden ausgeschlossen
CAVATAS [16; 17]			keine Mindestmengen			keine Mindestmengen	designates radiologist who hat received training in neuroradiology and the techniqes of angioplasty; “appropriate knowledge and expertise”: Centres with little skill in cerebro-vascular angioplasty received training and assistance from a radiologist from the more experienced centres
EVA-3S [18; 19]			mind. 25 CEA im Jahr vor Studienbeginn			mind. 12 CAS oder mind. 35 supraaortale Stents, davon mind. 5 in der Carotis, falls nicht, Stenting unter Aufsicht eines Protektors (der sich durch die Mindestzahl qualifiziert hatte), bis Interventionen nach Einschätzung des Protektors ok und Mindestanzahl gegeben war	
SAPPHIRE [21; 22]			keine explizite Mindestmenge med. jährl. OP-Volumen: 30 (15-100)			median Vorerfahrung mit 64 Interventionen (20-700)	Chirurgen mussten Kriterien der AHA genügen indkluve Komplikationsraten Stent: Vorerfahrung mit Komplikationsraten periproc. Tod oder Schlaganfall max. 6%
BACASS [20]			ca. 50 OPs pro Jahr			ca. 15 CAS pro Jahr	Teilnahme an CAVATAS

Mindesteinzahl von Voreingriffen/ erforderliche Qualifikation angegeben?	Operation			Stent			Kommentar:
	Ja	Nein	Wie viele Eingriffe	Ja	Nein	Wie viele Eingriffe	
REGENSBURG [23]			k. A.			"An experienced radiologist performed CAS"	
K-ASYMP [24]						keine Angaben zu Mindestmengen	… interventional team consisting of neurosurgeons, neurologists, and interventional cardiologists **who possessed experience in cerebrovascular disease as well as surgical and interventional skills before initiating a community hospital-based program** providing CAS as a treatment choice for carotid stenosis.
K-SYMP [25]						Keine Angaben zu Mindestmengen	"cerebral endovascular team" **possessing skills in endarterectomy and catheterbased techniques**, experienced interventional cardiologists and neurologists.
WALLSTENT [26]		k. A.			k. A.		Studie liegt nur als Abstract vor.
LEICESTER [27]		k. A.					**CEA:** was performed by a consultant (n = 5) or by a supervised trainee (n=5), keine Anagbe von Mindestmengen **CAS:** radiologist had personal experience of more than 4000 angio-plasties to the peripheral arteries. **8** uncomplicated but selected CAs had been performed

Wurde ein Proktoring beim Stent erlaubt? Anteil der mit Proktor behandelten Fälle?	Ja	Nein	Kommentar
CREST [6; 7]			Proktoring bei Interventionalisten mit und ohne Vorerfahrung an der Carotis nicht mehr als 2
ICSS [8-10]	ca. 20?		
SPACE [11-15]			
CAVATAS [16; 17]			keine Zahlenangaben, aber Angabe, dass weniger erfahrene Radiologen einen erfahrenen Radiologen aus anderem Zentrum zur Seite gestellt bekamen

Wurde ein Proktoring beim Stent erlaubt? Anteil der mit Proktor behandelten Fälle?	Ja	Nein	Kommentar
EVA- 3S [18; 19]	war gefordert bei Nichterfüllen der Mindest-mengen		Anteil der mit Proktor behandelten Fälle nicht genannt! Keine Anzahl der Zentren genannt, die Mindestmengen nicht erfüllten
SAPPHIRE [21; 22]		k. A.	k. A. zum Proktor, alle hatten Vorerfahrung (mind. n=20)
BACASS [20]		k. A.	
REGENSBURG [23]		Nein	
K-ASYMP [24]		k. A.	
K-SYMP [25]		k. A.	
WALLSTENT [26]		k. A.	
LEICESTER [27]		k. A.	50% der CEA Eingriffe wurden von Assistenzärzten unter Supervision durchgeführt

Anpassung der Kriterien für die Selektion von Zentren im Verlauf der Studie?	Ja	Nein	Kommentar
CREST [6; 7]			k. A. gefunden
ICSS [8-10]			ICSS PRotocoll 2003+2007 gleich
SPACE [11-15]			Amendment 2002: auch Vorerfahrung von nur 10 CAS erlaubt, dann Proktoring (Fiehler et al., 2008) Zunächst mind. 2 Pat. pro Zentrum pro Jahr, dann ggf. auch 1 Pat. pro Zentrum pro Jahr (Ringleb et al., 2004)
CAVATAS [16; 17]			keine Angaben gefunden
EVA-3S [18; 19]			Nur Anpassung der Kritererien für Patientenselektion: zurerst mehr als 70%, dann mehr als 60% Sympt. Stenose ab Oktober 2003; verpflichtende Emboli-Protektion ab 2003, vorher fakultativ
SAPPHIRE [21; 22]			
BACASS [20]			
REGENSBURG [23]			

Anpassung der Kriterien für die Selektion von Zentren im Verlauf der Studie?	Ja	Nein	Kommentar
K-ASYMP [24]			
K-SYMP [25]			
WALLSTENT [26]			
LEICESTER [27]			

6.5 Monitoring

a) Monitoring der CAS/CEA Fälle in der Vorbereitungs-phase und in der Studie?	Ja	Nein	Nicht vollständig (z. B. nur Outcome)	Stich-proben-artig	Kommentar (auch Safety Komitee ja/nein)
CREST [6; 7]					The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in CREST, within the framework of the definitions prespecified in this protocol. **Such criteria will be reviewed and approved by the Data and Safety Monitoring Board**. This committee will monitor the study CREST Investigational Plan results for evidence of adverse or beneficial treatment effects throughout the study period.
ICSS [8-10]	unklar, ob vollständig, mehr als stich-probenartig				Aus dem Protokoll 2007: "**The safety aspects of the trial will be overseen by a Data Monitoring Committee consisting** of an independent neurologist, medical statistician surgeon and interventionist. The progress of the study will be assessed at regular intervals determined by the Data Monitoring Committee. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to

a) Monitoring der CAS/CEA Fälle in der Vorbereitungs-phase und in der Studie?	Ja	Nein	Nicht vollständig (z. B. nur Outcome)	Stich-proben-artig	Kommentar (auch Safety Komitee ja/nein)
					treatment) will be supplied, in strict confidence, to the chairman of the Data Monitoring Committee, along with any other analyses that the Committee may request". Aus Brown et al., 2010: "The rate of reported events at individual centres was monitored at the central office. **The independent data monitoring committee met on a regular basis to review the accumulating data and to monitor trial safety.** Outcome events were reported in detail to the central office by the local neurologist or stroke physician. Major outcome events were submitted to an independent external adjudicator, who was masked to treatment allocation and who determined the cause, severity, and duration of the event. If this assessment differed from the initial assessment, a second externaladjudicator reviewed the event and any diff erences were resolved by consensus-Monitoring of adverse events led to concern about the stenting results of two investigators at supervised centres. These investigators were stopped from treating further patients within the trial and their centres were suspended from randomisation. All the patients allocated to stenting (n=11, fi ve with disabling stroke or death) or endarterectomy during the same time period (n=9, one with fatal stroke) at these centres were included in the analyses. One of the two centres subsequently restarted randomisation with a diff erent investigator performing stenting.
SPACE [11-15]	Nur für Base-line–Daten und Outcome-Ereignisse so-wie Einver-ständniserkläru ng als voll-ständig ange-geben			komplette Daten nur stichprob enartig (bei 10%)	Complete data monitoring was randomly allocated to 10% of the patients in each centre. Baseline data used for randomisation and good clinical practice details such as presence of informed consent and outcome events were rigorously monitored for all patients. A mechanism was in place to increase the number of monitored patients, in case of diffi culties with data quality. Additionally, **all primary outcome, fatal outcome events, and events of doubtful cause were adjudicated on by the external safety committee.** For this adjudication, the **outcomeevent forms were faxed to** one member of the coordinating centre (PR) and **one member of the safety committee (PM**).
CAVATAS [16; 17]	unklar ob vollständig, ,weit mehr als stichprobenarti g				Untersucher wiesen Pat. nach eigenem Protokoll zu, nicht invasive Diagnose war erlaubt (MR; CT; US). Alle Diagnose wurden vom zentralen Kommitte überprüft. Am Angiogramm wurde die STenose mit Mikrometer gemessen und nach 100/1-A/C beurteilt (216CAS/217CEA), bei MR oder CT ebenso (34 und 28), 7 nur US dort Schätzung. "Patients were followed up by the independent participating neurologist or clinician,.

a) Monitoring der CAS/CEA Fälle in der Vorbereitungs-phase und in der Studie?	Ja	Nein	Nicht vollständig (z. B. nur Outcome)	Stich-proben-artig	Kommentar (auch Safety Komitee ja/nein)
					Researchers reported outcome events and sent copies of relevant investigations, reports, or both to the central CAVATAS office. Details revealing treatment group were removed from reports of all stroke and death outcome events in the central office. Researchers at the central office, who were unaware of treatment group, then independently confirmed the classification of the event, by review of the other clinical details, CT scan, or necropsy report (if available). Two independent external adjudicators decided the classification if there was any doubt about the nature of the event or a difference of opinion between the central office and the reporting investigator." **Kein Safety Kommittee**
EVA-3S [18; 19]	unklar, ob vollständig, mehr als stich-probenartig				Our protocol required that an **independent** **safety committee** review safety issues each time 10 new validated primary outcome events occurred, with no predetermined rule for stopping the trial, and reassess the number of patients required to show an effect after 30 primary outcome events had occurred.
SAPPHIRE [21; 22]					All data were submitted to the data-coordinating center, which performed the analysis. The investigators had full access to the data. Cerebral angiography was performed before carotid stenting, and the results were submitted to the angiographic core laboratory, where they were analyzed with the use of a computerized system. The study design, all analyses, and the decision to publish were determined solely by the principal investigators and the study investigators. **An independent data and safety monitoring board, not affiliated with the study sponsor or the study investigators, reviewed the data periodically to identify safety concerns.**
BACASS [20]					k. A. zu externem Datenmonitoring
REGENSBURG [23]					k. A. zu unabhängigem Datenmonitoring
K-ASYMP [24]					k. A. zu unabhängigem Datenmonitoring
K-SYMP [25]					k. A. zu unabhängigem Datenmonitoring
WALLSTENT [26]					Studie liegt nur als Abstract vor

a) Monitoring der CAS/CEA Fälle in der Vorbereitungs-phase und in der Studie?	Ja	Nein	Nicht vollständig (z. B. nur Outcome)	Stich-proben-artig	Kommentar (auch Safety Komitee ja/nein)
					k.A: zu externem Monitoring
LEICESTER [27]	unklar, ob vollständig				The trial was monitored by an independent data monitoring committee (DMC). The Ethics Committee required the DMC to perform interim analyses after every 20 patients were treated

6.6 Standardisierung der Interventionen/Verwendete Techniken

Standardisierung der Therapien	Ja	Nein	Kommentar
CREST [6; 7]	für Stent beschrieben	für OP	Ballonprädilatation in 71,9%, Ballonangioplastie in 67,7%, Embolie-Protektion in 97,9%
ICSS [8-10]			Kein standardisiertes Protokoll “Stents and other devices used for carotid stenting were chosen at the discretion of the interventionist but had to have a CE mark. The protocol recommended that a cerebral protection device should be used whenever the local investigator thought that one could be used safely, but this was not mandatory. Surgeons were free to use standard or eversion endarterectomy. The use of local or general anaesthesia, shunts, and patches was left to the discretion of the surgeon.”
SPACE [11-15]			Stent mit oder ohne Protektionssystem möglich. (The use of protection devices, predilation, and balloon size were left to the discretion of the interventional physician.) For patients allocated carotid endarterectomy, surgeons used their usual operative technique. Shunting during surgery was optional.
CAVATAS [16; 17]			All patients assigned to endovascular treatment before 1994 underwent percutaneous transluminal angioplasty with balloon catheters. Stents suitable for use in the carotid artery were developed during the course of the study, and stenting was allowed from 1994 onwards when the radiologist believed this treatment necessary. Surgeons did carotid endarterectomy by the technique that they routinely used, and requirements for use of anaesthesia, shunts or patches, or heparin during the procedure were not specified.

Standardisierung der Therapien	Ja	Nein	Kommentar
EVA-3S [18; 19]		CAS: stand. Technik, verschied. Stents. Protektions-systeme erst im Verlauf eingeführt. CEA: Surgeons performed endarterectomy according to customary practice.	Carotid stenting had to be carried out through the femoral route with the use of stents and protection devices approved by the accreditation committee.
SAPPHIRE [21; 22]	Ja, Stent immer mit gleicher Technik	OP nach lokaler Technik	
BACASS [20]	Stent	OP	Shunts +Patch individuell sonst standardisiert.
REGENSBURG [23]			Ja, CAS immer mit gleichem Stent ohne Protection, CEA alle mit Eversionstechnik. Beide mit Regionalanästhesie
K-ASYMP [24]			CEA was performed by standard techniques under general anesthesia with electroencephalographic monitoring. CAS was performed as described previously (11).
K-SYMP [25]			CEA was performed by standard techniques under general anesthesia with electroencephalographic monitoring. CAS detailliert beschrieben.
WALLSTENT [26]		k. A.	Studie liegt nur als Abstract vor.
LEICESTER [27]			Techniken jeweils detailliert beschrieben, CAS mit Prädilatation und Stenting.

Interventionstechniken

a) Zulassung von Karotisstent-Typen innerhalb der Studien	Alle zugelassenen	OP: temporärer Shunt		Kommentar
		Ja	Nein	
CREST [6; 7]	Nur RX Abbulink Stent	Shunt 56,7% Patch 62,4%		
ICSS [8-10]	Stents and other devices used for carotid stenting were chosen at the discretion of the interventionist but had to have a CE mark.	Surgeons were free to use standard or eversion endarterectomy. The use of local or general anaesthesia, shunts, and patches was left to the discretion of the surgeon.		OP Shunt nach Ermessen des Chirurgen
SPACE [11-15]	Stents had to have a CE mark approved stents were; Carotid Wallstent (Boston Scientifi c, Natick MA, USA), Precise (Cordis, Miami FL, USA), and Acculink (Guidant, Santa Clara CA, USA);	Shunting during surgery was optional.		OP Shunt nach Ermessen des Chirurgen, keine Prozentangabe
CAVATAS [16; 17]	Investigators could use stents either as a secondary procedure after unsatisfactory balloon dilation or as a primary procedure in which the decision was to stent the lesion without attempting full balloon dilation first. Radiologists used their preferred type and manufacturer of guide wires, catheters, and stents. Of the patients stented 53% had Wallstents, 34% had Palmaz stents, and 13% had Strecker stents.	Surgeons did carotid end-arterectomy by the tech-nique that they routinely used, and requirements for use of anaesthesia, shunts or patches, or heparin during the procedure were not specified. perioperative patches were used in 155 (63% of the surgical operations) Peri-operative shunts were used in 157 (64%) of the surgical operations, respectively.		OP Shunt nach Ermessen des Chirurgen

a) Zulassung von Karotisstent-Typen innerhalb der Studien	Alle zugelassenen	OP: temporärer Shunt		Kommentar
		Ja	Nein	
EVA-3S [18; 19]	Zulassung durch Accr. Committee gefordert Wallstent Monaril 56,9% Acculink (Abbott) 28,5% Precise RX 10,6% Wallstent OTW 2% Zilver 2%	Shunt: 19,5%(n=50) Patch: 50,2% (n=129)		OP Technik nach Ermessen des Chirurgen
SAPPHIRE [21; 22]	The stent used was a self-expanding, nitinol stent (Smart or Precise, Cordis) with an emboli-protection device (Angioguard or Angioguard XP, Cordis).			keine Angaben zu Shunt/Patch bei OP: OP-Technik nach Ermessen des Chirurgen
BACASS [20]	Carotid Easy Wallstent			„Arterial shunting was selectively employed in patients with prolonged clamp time or when significant EEG changes could be noticed. Patch grafts were used routinely in the local anaesthesia patients' group“
REGENSBURG [23]	Carotid Wallstent			keine Angaben zu Shunt/Patch bei OP
K-ASYMP [24]	10-20-mm Wallstent (Boston Scientific/Medi-tech, Natick, MA) or 10-38-mm Dynalink (Guidant Corp., Indianapolis, IN) stent.			keine Angaben zu Shunt/Patch bei OP
K-SYMP [25]	10-20 mm Wallstent (Boston Scientific, Inc.)			keine Angaben zu Shunt/Patch bei OP
WALLSTENT [26]	Wallstent			keine Angaben zu Shunt/Patch bei OP
LEICESTER [27]	Wallstent	Routine patching (collagen-coated Dacron graft), and routine shunting (Pruitt-Inahara, Ideas for Medicine, Fla.)		

b) Zulassung bzw. Einsatz von Protektionssystemen innerhalb der Studien	Ja	Nein	Alle zugelassenen	Kommentar
CREST [6; 7]			RX Accunet Anteil an Protektion: **97,9%**	
ICSS [8-10]	The protocol recommended that a cerebral protection device should be used whenever the local investigator thought that one could be used safe ly, but this was not mandatory.		Protection devices were known to have been used in 593 **(72%)** of 828 patients. The following protection devices were each used in 10% or more of the patients in whom stenting was attempted: FilterWire EZ (Boston Scientific), Angioguard (Cordis), Spider FX (EV3), and Emboshield (Abbott).	A range of other protection devices were each used in less than 5% of patients. In 27 patients, it was not clear whether or not a protection device was used.
SPACE [11-15]	The use of protection devices, predilation, and balloon size were left to the discretion of the interventional physician.		approved embolic protection devices : PercuSurge GuardWire (Medtronic, Minneapolis MN, USA), FilterWire EX (Boston Scientifi c), AngioGuard (Cordis), NeuroShield (MedNova, Horsham, UK), and Carotid Trap (Microvena, White Bear Lake MN,US).	All CE certification and were approved for use in the study by the endovascular standards committee;
CAVATAS [16; 17]				keine Angabe zu Protektionssystemen identifiziert
EVA-3S [18; 19]			GuardWire Plus 29,5% Filterwire EZ 26,9% Spider RX 13,2% EmboShield 10,6% Angioguard 9,3 Spider 8,4%	Empfehlung ab 1/2003, danach 97,7% mit Protection device, vorher auch schon 78,4%!

b) Zulassung bzw. Einsatz von Protektionssystemen innerhalb der Studien	Ja	Nein	Alle zugelassenen	Kommentar
			Accunet 2,2%	
SAPPHIRE [21; 22]			emboli-protection device (Angioguard or Angioguard XP, Cordis).	Grundsätzlich dieses System!
BACASS [20]	A neuro-protection system was used in all cases		initially balloon occlusion system (FilterWire™, Boston Scientific®) followed by a filter system (Angioguard RX™, Cordis®), both systems mounted on 0.014-inch micro guide-wires.	
REGENSBURG [23]		An experienced radiologist performed CAS without a protection device		
K-ASYMP [24]		Distal protection devices were not used.		
K-SYMP [25]		Distal protection devices were not used in any case.		
WALLSTENT [26]		k. A.		
LEICESTER [27]				

c) Vorerfahrung mit verwendeten Materialien gefordert?	Ja	Nein	k. A.	Kommentar
CREST [6; 7]				

c) Vorerfahrung mit verwendeten Materialien gefordert?	Ja	Nein	k. A.	Kommentar
ICSS [8-10]				
SPACE [11-15]				
CAVATAS [16; 17]				
EVA-3S [18; 19]				Interventional physicians had to have performed at least two stenting procedures with any new device before its use in the trial.
SAPPHIRE [21; 22]				
BACASS [20]				
REGENSBURG [23]				
K-ASYMP [24]				
K-SYMP [25]				
WALLSTENT [26]				
LEICESTER [27]				

d) Änderung der technischen Vorschriften während der Vorbereitungsphase oder Studie?	Ja	Nein	Kommentar
CREST [6; 7]			
ICSS [8-10]			
SPACE [11-15]			
CAVATAS [16; 17]			All patients assigned to endovascular treatment before 1994 underwent percutaneous transluminal angioplasty with balloon catheters. Stents (…) were developed during the course of the study, and stenting was allowed from 1994 onwards when the radiologist believed this treatment necessary.
EVA-3S [18; 19]			ab 1/2003 Protektionssysteme gefordert (von 74% auf 96% Steigerung) ab 10/2003 auch Einschluss von Pat. mit 60%iger sympto-matischer Stenose
SAPPHIRE [21; 22]			

d) Änderung der technischen Vorschriften während der Vorbereitungsphase oder Studie?	Ja	Nein	Kommentar
BACASS [20]			
REGENSBURG [23]			
K-ASYMP [24]			
K-SYMP [25]			
WALLSTENT [26]			
LEICESTER [27]			

e) Angaben zum verwendeten Implantationsmaterial beim CAS	Ja	Nein	Welches Material?	Kommentar
CREST [6; 7]			Acculink/ Accunet Abbott	
ICSS [8-10]	Stents and other devices used for carotid stenting were chosen at the discretion of the interventionist but had to have a CE mark.		The following stents were each used in 10% or more of the 764 patients in whom stents were inserted: Carotid Wallstent (Boston Scientific), Precision (Cordis), and Protégé (EV3).	The following were each used in less than 10% of patients: Acculink (Guidant), Xact (Abbott), Smart (Cordis), Cristallo Ideale (Invatec), Exponent (Medtronic), Next Stent (Boston Scientific).
SPACE [11-15]	s.o. approved stents			
CAVATAS [16; 17]	s.o. approved stents			
EVA-3S [18; 19]	s.o. approved stents			
SAPPHIRE [21; 22]	s.o. Stent			
BACASS [20]	s.o. Stent			
REGENSBURG [23]	s.o. Stent			
K-ASYMP [24]	s.o.Stent			
K-SYMP [25]	s.o.Stent			
WALLSTENT [26]	s.o.Stent			

e) Angaben zum verwendeten Implantationsmaterial beim CAS	Ja	Nein	Welches Material?	Kommentar
LEICESTER [27]	s.o.Stent			

6.7 Periinterventionelle antithrombotische Therapie

f) Periinter-ventionelle anti-thrombotische Therapie	Heparin (während der OP/ präoperativ interventionell		ASS/Dosierung		Clopidogrel/Loading		Postinterventionelles/ Postoperatives Protokoll	
	Ja	Nein	Ja	Nein	Ja	Nein	Wie durchgeführt	keine Angaben
CREST [6; 7]	Stenting 86,4% OP k. A.		2x 325mg/Tag ab 48h vor Stenting 4h vor Stenting 650mg ASS 48h vor OP: 1x325mg /Tag		2x 75mg/Tag ab 48h vor Stenting 4h vor Stenting 450mg oder Ticlopidine 4h vor Stent 650mgASS +450mg Clopidogrel oder Ticlopidine		Stenting: 1-2xtgl 325mg Aspirin über 30 Tage und Clopidogrel 75mg oder Ticlopidine2x 250mg über 4 Wochen Für Stenting wurde Beibehalten der Therapie nach 4 Wo empfohlen OP: 325mg ASS über 1 Jahr oder 250mg Ticlopidine 2x/Tag Clopidogrel 75mg/Tag 81mg ASS oder ASS +Dipyridamole 2x/Tag Post Procedure Antiplatelet Therapy: 98,1%	
ICSS [8-10]	CAS: use of heparin and atropine or similar agent during the procedure was		CAS: A combination of aspirin and		CAS: A combination of aspirin and clopidogrel to cover stenting		aspirin and clopidogrel before stenting and for 1 month afterwards	

f) Periinter-ventionelle anti-thrombotische Therapie	Heparin (während der OP/ präoperativ interventionell		ASS/Dosierung		Clopidogrel/Loading		Postinterventionelles/ Postoperatives Protokoll	
	Ja	Nein	Ja	Nein	Ja	Nein	Wie durchgeführt	keine Angaben
	mandatory. CEA: k. A.		clopidogrel to cover stenting procedures was recommended. CEA: k. A.		procedures was recommended CEA: k.A:			
SPACE [11-15]		k. A.	100 mg aspirin at least 3 days before and 30 days after the intervention.		75 mg clopidogrel daily for at least 3 days before and 30 days after the intervention.		ASS im Follow-up n.24Mo CAS 69% CEA 79% Clopidogrel CAS 16% CEA 11% ASS+Clopidogrel oder Dipyridamol CAS 9% CEA 4% Phenprocumon nach 24 Mo 6% und 5% CEA/CAS Nichts CAS 1% CEA 2%	Keine Angabe zu Heparin
CAVATAS [16; 17]	Vorgeschrieben nur für CAS, nicht für CEA. Für CAS: Heparin während des Eingriffs und mind, 24h danach		CAS: ASS mind. 150mg/Tag oder Alternative mind 24h vor dem Eingriff CEA: k. A.				Thrombozytenaggregations-hemmung im Follow-up für beide Gruppen	Heparindosis nicht angegeben Ebenfalls nicht angegeben ist, wie viele CEA mit Heparin/ASS
EVA-3S [18; 19]	Heparin vor OP:		Aspirin (100 to		Clopidogrel			

f) Periinter-ventionelle anti-thrombotische Therapie	Heparin (während der OP/ präoperativ interventionell		ASS/Dosierung		Clopidogrel/Loading		Postinterventionelles/ Postoperatives Protokoll	
	Ja	Nein	Ja	Nein	Ja	Nein	Wie durchgeführt	keine Angaben
	69,1% während OP: 99,2% nach OP: 6,3% Heparin während Stent: 97,6%		300 mg) for 3 days before and 30 days after stenting OP: Antiplatelet vorher: 87,6% nachher: 88,7% Stent: vorher: 100% nachher: 100%		(75 mg) or ticlopidine (500 mg) for 3 days before and 30 days after stenting vorher : 82,9% nachher: 85,4%			
SAPPHIRE [21; 22]	Heparin während Eingriff PTT 250-300s		ASS ab 72h vor Eingriff (OP/STENT) mit 81 oder 215 mg und danach ohne Ende		Clopidogrel 75mg 24h vor Eingriff und 2-4 Wo danach bei OP kein Clopidogrel			
BACASS [20]	k. A.		ASS ohne Dosisangabe		Clopidogrel ohne Dosisangabe		Dual antiplatelet therapy with aspirin and clopidogrel, starting prior/ immediately after CAS, was used for one month. CEA: Antiplatelets were used as shown effective in a recent Cochrane Review	
REGENSBURG [23]	k. A.		ASS 100 mg vor Eingriff CAS oder		Clopidogrel 75mg vor Eingriff CAS oder CEA über 1 Mo Monat			

f) Periinter-ventionelle anti-thrombotische Therapie	Heparin (während der OP/ präoperativ interventionell		ASS/Dosierung		Clopidogrel/Loading		Postinterventionelles/ Postoperatives Protokoll	
	Ja	Nein	Ja	Nein	Ja	Nein	Wie durchgeführt	keine Angaben
			CEA über einen Monat dann ASS 300					
K-ASYMP [24]	CAS: heparinization with 100µg/kg, Activated clotting time was mainained at more than 250s CEA n.a.		ASS 325 mg vor Eingriff CAS oder CEA		Clopidogrel 75 mg vor Eingriff CAS oder CEA		kein postinterventionelles Management angegeben	
K-SYMP [25]	CAS: heparinization with 100µg/kg, Activated clotting time was mainained at more than 300s CEA: n.a.		ASS 325 mg vor Eingriff CAS oder CEA		Clopidogrel 75mg vor Eingriff CAS oder CEA		kein postinterventionelles Management angegeben	
WALLSTENT [26]	k. A.		ASS 325 mg 4 WO für CAS k. A. für CEA		Ticlopidinde 250mg für 4 Wo für CAS keine Angaben für CEA			
LEICESTER [27]	Heparin 5000IE vor CEA und CAS		ASS wurde nicht gestoppt vor CEA und CAS keine weitere Angabe					

6.8 Evidenztabellen

Anmerkung: Es wurde die Evidenzklassifikation nach SIGN benutzt. Danach wird ein RCT oder eine Metaanalyse von RCTs mit 1+ bei geringem Verzerrungsrisiko klassifiziert und mit 1- bei hohem Verzerrungsrisiko. Um die mangelnde statistische Power anzuzeigen, wurden nicht adäquat gepowerte Studie mit 1- versehen, auch wenn sie methodisch kein erhöhtes Verzerrungsrisiko aufwiesen.

6.8.1 Aufbereitete Evidenz

6.8.1.1 Systematischer Review

Autoren, Jahr/ Studien-typ	Untersuchte Studien/ Materialien	Welche Fragestellungen wurden untersucht	Befunde in Bezug auf Therapiewirkungen und Überleben	Methodische Besonderheiten/ Bemerkungen	Level of Evidence
Meier et al., 2010 [3] Meta-analyse	Systematische Recherche in Biosis, Embase, Medline, Cochrane, IPA, ISI Web of Sciende, Google Scholar 1.1.1990 bis 25.7.2009 + Handsuche Einschluss von RCT CEA vs Stenting (mit oder ohne Protektor) jegl. Sprache, Publikations-status, Follow-up Länge, Größe	Vergleich End-arteriektomie vs. Stenting mit dem kombinierten Endpunkt Schlaganfall und Tod (primärer Endpunkt)	**0. Studieneinschluss:** Eingeschlossen wurden LEICESTER, WALLSTENT, K-SYMP, K-ASYMP, BACASS, REGENSBURG, EVA-3S, SAPPHIRE, CAVATAS, SPACE, ICSS **1. Ergebnisse:** 10 trials reported on short term outcomes (n=4709) and nine on intermediate term outcomes (1-4 years). The periprocedural risk of mortality or stroke was lower for carotid endarterectomy (odds ratio 0.67, 95% confidence interval 0.47 to 0.95; P=0.025) than for carotid stenting, mainly because of a decreased risk of stroke (0.65, 0.43 to 1.00; P=0.049), whereas the risk of death (1.14, 0.56 to 2.31; P=0.727) and the composite end point mortality or disabling stroke (0.74, 0.53 to 1.05; P=0.088) did not differ significantly. The odds of periprocedural myocardial infarction (2.69, 1.06 to 6.79; P=0.036) or cranial nerve injury (10.2, 4.0 to 26.1; P<0.001) was higher in the carotid endarterectomy group than in the carotid stenting group. In the intermediate term, the two treatments did not differ significantly for stroke or death (hazard ratio 0.90, 95% confidence interval 0.74 to 1.1; P=0.314).	CREST noch nicht eingeschlossen	**1+**

Autoren, Jahr/ Studien-typ	Untersuchte Studien/ Materialien	Welche Fragestellungen wurden untersucht	Befunde in Bezug auf Therapiewirkungen und Überleben	Methodische Besonderheiten/ Bemerkungen	Level of Evidence

6.8.2 Primärliteratur

Tabelle 4: Primärliteratur

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
Brott T.G: et al., 2010 **RCT, multi-zentrisch** **USA + Canada** **CREST** **[6; 7]**	n= 2502 v. 2522 Pat. aus 108 Zentren USA+9 Zentren in Kanada rekrutiert 12/00 bis 7/08	**Carotis-Endarteriektomie (CEA)** **Nachverfolgung:** im Median 2,5J	**Carotis Angioplastie mit Stenting (CAS)** mit RX Accu-link stent, und wenn möglich, RX Accunet embolic-protection device (für alle Studien-eilnehmer Acculink+Accunet gestellt von Abbott Vascular Solutions)	**1. Primärer Endpunkt:** kombinierter Endpunkt aus jegl. Schlag-anfall, Herzin-farkt oder Tod periinterventionell (ab Randomisierung bi 30/36 Tage nach dem Eingriff und gleich-seitiger Schlaganfall bis 4 J) **1. Schlagan-fall** (Neurolgische Evaluation zu Beginn, 18-54 Stunden nach Eingriff, 1 Mo, alle 6 Mo.	**0. Studiengüte** **Non-Inferioritäts-Design** Randomisierungsverfahren: Web-basiert, Block-Design mit Größen 2,4,6,stratifiziert nach Zentrum und Symptomatik, erfolgt nach Arrangement des Eingriffs innerhalb 2 Wo Drop out: **1. Ergebnisse gesamt:** **a)** kombinierter Endpunkt n.s. unterschiedlich für geschätztes 4J Auftreten: CEA: 6,8% Stenting: 7,2% HR Stenting: 1,11 [95%KI 0,81; 1,51] p= 0,51 **b)** kombinierter Endpunkt bis zu 30/36 Tage nach Eingriff: CEA: 4,5% Stenting: 5,2% HR Stenting: 1,18 [95%KI 0,82-1,68]	Abbott hatte einen Sitz ohne Stimmrecht im Executive Committee und kommentierte die Entwurfsfassung der Studie Abbott war verant-worlich für das Monitoring in Kanada Studie war nur für kombinierten Endpunkt adäquat gepowert FDA-Zulassungsstudie	**1+**

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
				NIH Stroke Scale, mod. Rankin scale, TIA-Stroke Questionnaire tel. Interview nach 3 Mo, dann alle 6 Mo. **2. Herzinfarkt** Enzyme zu Beginn 6-8h nach Eingriff, EKG vor Eingriff, 6-48h nach Eingriff und nach 1Mo, dann jährl. **3. Allg. Gesundheit** zu Beginn, nach 2 Wo, 1 Mo +1J nach Eingriff mit SF 36	p=0,38 **c)** Endpunkt Tod allein CEA: 0,3% Stenting: 0,7% p=0,18 **d)** Schlaganfall allein CEA: 2,3% Stenting: 4,1% p=0,01 **e)** Herzinfarkt allein CEA: 2,3% Stenting: 1,1% p=0,03 **2. Subgruppenanalysen :** **a) symptomatische Patienten** komb. Endpunkt bis 30/36Tage nach Eingriff CEA: 5,4% Stenting: 6,7% HR 1,26 [95%KI 0,81-1,96] **b) asymptomatische Patienten** komb. Endpunkt bis 30/36Tage nach Eingriff CEA: 3,5% Stenting: 3,6% HR 1,02 [95%KI 0,55-1,86]		

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
					3. Sekundäranalysen (geplant) a) Hirnnervenlähmung bis max 30/36 Tage nach Eingriff CEA: 4,7% Stenting: 0,3% HR=0,07 [95%KI 0,02; 0,018] b) Schlaganfall und Tod nach 4 J CEA: 4,7% Stenting: 6,4% HR: 1,5 [95%KI 1,05;2,15] p=0,03 Diff. 1,6% bei symptomatischen und 1,8% bei asymptomatischen Patienten zugunsten CEA beides n.s. **4. post hoc Analysen** Langzeitmodelle zum Schätzen des Effekts von Schlaganfall und Herzinfarkt nach 1 J a) Physical Health Major Stroke: -15,8Pkte auf SF 36 stat. sign. Minor Stroke: - 4,5Pkte auf SF 36 stat. sign. Herzinfarkt: -3Pkte auf SF 36 n.s. b) mental health: nur Minor Stroke stat. sign.		

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
					mit -3,4Pkte		
Brown et al., 2010 **RCT, multi-zentrisch** **ICSS [8-10]**	n= 1.713 (855 Stenting/858 OP) rekrutiert 5/2001-10/2008 Pat. >40J vorausgegangenen Symptomen einer Karotisstenose innerhalb der letzten 12 Monate und Stenose >50% gemessen auch noninvasiv mit Duplex Sonographie Ausschluss: voraus-gegangene CAS/CEA Kontraindikation für CAS/CEA (entweder primär nicht einge-schlossen oder Ausschluss auch nach Randomisierung nach Angiographie) geplante größere andere OP	Endarteriektomie der Karotisstenose (CEA) **Nachverfolgung:** 120 Tage ab Randomisierung, insgesamt geplant: 3 Jahre	Stenting (CAS)	**1.** 3-Jahres-rate an funk-tionsbeein-trächtigendem Schlaganfall oder Tod ab Randomisieru ng (Zwischen-analyse nach 120 Tagen) **2.** Rate an Schlaganfall, Tod oder Herzinfarkt während des Eingriffs ab Randomisieru ng bis 120 Tage **3+4.** sekun-däre End-punkte:Hirnner venlähmung, Hämatome	**0. Studiengüte** Randomisierung zentral, computergestützt Nachverfolgung durch unabhängige Kliniker **1. funktionsbeeinträchtigender Schlaganfall oder Tod nach 120 Tagen** CEA: n= 27 (3,2%) CAS: n= 34 (4%) HR 1,28[95%KI 0,77-2,11] **2.** Rate an Schlaganfall, Tod oder Herz-infarkt während des Eingriffs nach 120 Tagen **CEA**: 44 (5,2%) 4 nicht fatale Herzinfarkte 35 Schlaganfälle 7 sonstige Todesfälle **CAS**: 72 (8,5%) 3 fatale Herzinfarkte 65 Schlaganfälle 19 sonstige Todesfälle HR 1,69 [95%KI 1,16-2,45] p=0,006 **3.** Hirnnervenlähmung:	geplantes Konfidenzintervall von 3% nicht erreicht	1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
					CEA: n=45 CAS: n=1 (wegen sekundär CEA innerhalb von 30 Tagen nach Behandlung) **4.** Hämatome jeglichen Schweregrads: CEA: 50 CAS: 31		
Eckstein et al., 2008 **Ringleb et al., 2004** **RCT multi-zentrisch** **SPACE [11-15]**	n=1.214 rekrutiert 3/01-2/06 Pat. mit schwerer symptomatischer Karotisstenose (mind. 70%) Patients were eligible for SPACE if they had amaurosis fugax, hemispherical TIA, or completed stroke in the previous 180 days and had stenosis of the ipsilateral carotid artery that was moderate to severe—ie, 50% or more according to criteria from the North American Symptomatic Carotid	CEA **Nachbeobachtung:** 2 Jahre	CAS	**1. primärer Endpunkt** 30 Tages Rate an ispilateralem Schlaganfall oder Tod	**0. Studiengüte:** Blockrandomisierung, Non-Inferioritätsstudie erforderl. stat. Power nicht erreicht Drop out/Lost of Follow-up nach 2J: 12,4% **1. Ergebnisse** a. 30-Tages-Rate an ipsilateralem Schlaganfall oder Tod CEA: 6,34% (37) CAS: 6,84% (41) Diff. 0,51% (90%KI -1,69-**2,91**), da Inferioritätsgrenze **2,5%** wurde der statistisch signifikante Nachweis der Noninferiorität nicht erreicht p=0,009	Studie finanziert über BMG und BMBF und 2 Firmen (175.000€)	1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
	Endarterectomy Trial (NASCET),or 70% or more according to criteria from the European Carotid Surgery Trial (ECST).5				Weitere Endpunkte: die ODDS Ratio für alle weiteren Endpunkte ist nicht stastisch signifikant unterschiedlich		
Cavatas investigators, 2001 **CAVATAS** **RCT** **multizentrisch** **[16; 17]**	n=504 rekr. 3/92-7/97 mittl. Alter 67 nur Pat. die für beide Beh. in Frage kamen sympt. CaSt ab 50% oder keine Symptome aber Beh. erforderl. mittl Grad der STenos 86,4% CAS 85,1% CEA Amaurosis fugax, TIA oder Retinainfarkt 64% 8% Minor strike 12% Major Stroke nicht fktnbeeinträcht. 5,5% MajorStroke fktn beeintr. 7% Symptome länger als 6 Mo vor Rand 3,5% keine Symptome	CEA nach Technik des lokalen Operateurs **Nachbeobachtung:** median 1,95/1,98 J pro Arm	CAS bis 1994 nur Ballondilatation insgesamt nur 24% STents	primär: **1.** fktnsbeeintr. Schlaganfall oder Tod innerhalb 30 Tage **2.** jegl. Schlaganfall mit mind. 7 Tgs Symptomatik oderTod innerhalb 30 Tage sekundär: **3.** siehe 1+2 aber nach 3J 4. Hirnnerven-lähmung 5. Hämatom (das chirurg. Eingriff oder Verlängerund des	**0.Studiengüte** keine Fallzahlberechnung „explorative Studie“, Rand. Mittels Computer Cross over Rate n=8=1,6% Mittl. Zeit bis zur Behandlung 20T (8-32)für CAS und 27T (14-41) für CEA (p<0,001) CAS bei 213/140 erfolgreich (89%) 14 Pat. dann CEA ohne Kompl., 4 I. Ergebnisse Analyse nach 30 Tagen Tod: CEA 2%: CAS: 3% Schlaganfall mit fktnsbeeintr. beide 4% Schlaganfall ohne fktnsbeeintr. beide 4% **1.** Tod oder Schlaganfall mit fktnbeeintr. beide 6% **2.** Tod oder jegl. Schlaganfall beide 10% alle n.s. **3.** 3J-Angaben: Schlaganfall fktnsbeeintr./Tod: CEA: 14,2%	unterpowert, Ergebnisse sind deshalb nicht als valide zu betrachten insgesamt nur 24% Stents also Behandlung nach aktueller Technik	1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
	Hypertonie 55,5% 22% peripher vascular disease			KHaufenthalte s bedeutet) **6.** Wieder-auftreten Stenose nach 1J	CAS: 14,3% n.s. **4.** CEA: 9% (22) CAS:0 p<0,001 **5.** CEA: 7% (17) , CAS: 1%(3) **6.**		
Mas et al., 2006 **Mas et al., 2008** **RCT ,** **multizentrisch (20 universitäre, 10 nicht universitäte Zentren in Frankreich)** **EVA-3S** **[18; 19]**	n= 527 vorzeitiger Studienabbruch Rekrutierung von 11/2000-9/2005	CEA	Stent	**primärer Endpunkt:** 1. 30 Tages-Überleben oder Schlag-anfall **sekundäre Endpunkte:** 2. 30-Tages-Überleben oder fktns. beintr. Schlag-anfall 3. Überleben oder Schlag-anfall nach 6 Mo. 4. Hirnnerven-lähmung 5. Kombina-tion aus 1 und gleichseitiger Schlaganfall bis zu 4 J	**0. Studiengüte** Randomization was carried out centrally by means of a computer-generated sequence, involving randomized blocks of two, four, or six patients that were stratified according to study center and degree of stenosis (stenosis of ≥90% or <90%). I. Ergebnisse **1. 30-Tages-Überleben oder Schlaganfall** CEA: 3,9% [95%KI 2; 7,2] CAS: 9,6% [95%KI 6,4-14] **2. 30-Tages-Überleben oder fktns.beintr. Schlaganfall** CEA: 1,5% [95%KI 0,5-4,2] CAS: 3,4% [95%KI 1,7-6,7] **3. Überleben oder Schlaganfall nach 6 Mo** CEA: 6,1% CAS: 11,7% p=0,02 **4. Hinrnervenlähmung**	gestoppt nach Randomisierung von 527 Pat. , da niedrigere Komplikationsrate als erwartet bei CEA und höhere Komplikationsrate als erwartet bei CAS, für den Nachweis der Unterlegenheit wären nun 4000 Patienten erforderlich gewesen, d.h. Studie ist nicht ausreichend gepowert.	1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
					CEA: 20 CAS: 3 (jeweils bei sek. Chirurgie) p<0,001 **5. Kombination aus 1 und gleichseitiger Schlaganfall bis zu 4 J** CEA: 6,2% CAS: 11,6% HR 1,97 [95%KI 1,06-3,67] p=0,03 bei Messung nur fktnsbeeinträchtigt. Schlaganfall : CEA: 2,4% CAS: 4,6% HR 2,00[95%KI 0,75-5,33]. Unterschiede v.a. periprocedural !!! Jegl. Schlaganfall oder Tod: HR 1,39 [0,96-2,00] p=0,08		
Yadav et al., 2004 **Gurm et al., 2008** **RCT multi-zentrisch** **SAPPHIRE [21; 22]**	n= 334 v. 747 rekrutiert 8/2000-7/2002 entweder mit symptomatischer CAS mind. 50% oder mit asymptomatischer CAS ab 80% und mind 1 zusätzlichem Risikofaktor	CEA **Nachverfolgung:** geplant 1 Jahr, dann 3 Jahre	CAS	**1. primärer Endpunkt:** Schlaganfall, Herzinfarkt oder Tod periinterventionell und gleichseitiger Schlaganfall oder Tod bis zu 1 Jahr	**0. Studiengüte** 1:1 Randomisierung mit Stratifizierung nach Zentrum und Symptomatik/Asymptomatik, automatisierte Verteilung der Nummer mittels Telefon **1. Ergebnisse:** **primärer Endpunkt 1J:** CEA: 20,1% (32)	gestoppt nach Randomisierung von 334 Pat. angebl. wegen mang. Rekrutierung frg. Positiver Effekt durch vorzeitige Beendigung? von 413 nicht randomisierten Patienten wurden 406 in das	1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
				2. Erweitert für Auswertung nach 3 Jahren	CAS: 12,2% (20) **Ergebnisse nach 3 Jahren:** CEA: 26,9% CAS: 24,6% Diff. 2,3% (95%KI -11,8 bis 7,0) stat. nicht signifikant	Stentregister gemeldet und 6 in da chirurgische Register Studie wurde gesponsert von Cordis(Johnson&Johnson), Hauptautor hielt dort zu Beginn Aktien, Cordis produziert Angioguard emboli protection	
Hoffmann et al., 2008 **RCT unizentrisch** **BACASS [20]**	n=20 v. 82 konsekutiven Patienten im Zeitraum rekrutiert 11/98-2/02 in Basel mind. 70% Stenose (70-99%) mit Doppler nach CAVATAS-Kriterien und CE-MRA diagnostiziert. Alle Pat. sympt. innerhalb der letzten 3 Monate und untersucht durch Neurologen.	CEA **Nachverfolgung :** 48 Mo/43Mo	CAS	**primärer Endpunkt** 1. peri-proceduraler Tod, Schlaganfall oder Herzinfarkt **sekundäre Endpunkte:** 2. periinter-ventionelle TIA Hämatom, Hirnnerven-	**0.Studiengüte** Randomisierung ok, Studie nicht gepowert. **1. Ergebnisse 30 Tage und 48/43 Mo:** CEA: 10% (1/10) Auftreten eines nicht persistierend beeinträchtigenden Schlaganfalls innerhalb von 30 Tagen danach keine weiteren Ereignisse CAS: 0% keine Ereignisse **sekundäre Endpunkte** nicht dargestellt		1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
	fast alls Patienten „Low Risk“			lähmung , Aufenthalts-dauer			
Steinbauer M. et al., 2008 **RCT uni-zentrisch** **REGENSBURG** **[23]**	n= 87 Rekrutierung 8/99-4/02 symptomatische CAS (>70%) nach NASCET	CEA **Nachverfolgung:** CEA: 64Mo (+/-12) CAS: 66Mo (+/-14)	CAS	**1. Schlag-anfall** **2. Restenose >70%** **3. Tod**	**0.Studiengüte** Randomisierung nicht beschrieben.Keine Powerberechnung 3 Lost of Follow-up **I.Ergebnisse n. 5,5J** **1. Schlaganfall** CEA: 0 CAS: 4 **2. Restenose >70%** CEA: 0/29 keine Reintervention CAS:6/32 davon 5 Indikation zu Reintervention, 3 mit neurolog. Symptomen p<0,05 **3. Tod** CEA: 13 CAS: 10		1-
Brooks et al., 2004 **K-ASYMP** **[24]**	n=84 Rekrutierungszeit n.a. Patienten mit asymptomatischer Karotisstenose nach	CEA **Nachverfolgung:** 48 Mo	CAS	**keine primären oder sekundären Endpunkte spezifiziert**	**0.Studiengüte:** Randomisierungsmethode nicht beschrieben, Verblindung nicht beschrieben, keine Powerberechnung **I. Ergebnisse**		1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
	NASCET >80%			gemessen: 1. Durch-gängigkeit der ispilateralen Carotis nach 48 Monaten 2. Komplika-tionen 3. Länge KH Aufenthalt 4. Kosten	**1.** Durchgängigkeit der ipsilateralen Carotis interna nach 48 Mo: Peak syst. Geschwindigkeit interne Carotis: Carotis communis Vor Eingriff ca. 6 CAS , 6,1 CEA Nach Eingriff ca. 1,1beide 48 Mo nach Eingriff ca. 1,4 CAS, ca. 1,5 CEA **2.** Komplikationen beide ohne Schlaganfall oder TIA CEA: 3 Halsnervenläsionen, Rekonstitution innerhalb von 3 Mo CAS 5x Bradykardie mit Medikamenten zu beheben CEA: 4x Kompl. Verursacht durch Anästhesie, jeweils zu beheben **3.** (gleich) und **4.** nicht dargestellt		
Brooks et al., 2001 **RCT unizentrisch (Kentucky)** **K-SYMP** **[25]**	n=104 Rekrutierungszeit n.a. Pat mit sympt. Stenose > 70% nach NASCET und Symptome bis zu 3 Mo vor Randomisierung	CEA **Nachverfolgung:**	CAS	**keine primären oder sekundären Endpunkte spezifiziert** gemessen: 1. Durch-gängigkeit der ispilateralen Carotis nach 24 Monaten 2. Komplika-tionen	**0.Studiengüte** Randomisierungsmethode nicht beschrieben, Verblindung nicht beschrieben, keine Powerberechnung **1. Ergebnisse:** **1.** Durchgängigkeit der ipsilateralen Carotis interna nach 24 Mo: Peak syst. Geschwindigkeit interne Carotis: Carotis communis CEA7CAS beide etwa gleich mit ca. 1,8/1,9 **2. Komplikationen** CEA: perioperativ 1 Tod aufgrund		1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
				3. Länge KH Aufenthalt 4. Kosten	Herzinfarkt, später keien Komplikationen CAS: keine		
Alberts, 2001 **WALL-STENT** **RCT multizentrisch (Abstract)**	n=219 von 700 geplant Rekrutierungszeit n.a.	CEA **Nachverfolgung:** bis 12 Mo (345 vs 351 Tage med.)	CAS	**primärer Endpunkt** 1. gleich-seitiger Schlaganfall, interventionsbedingter Tod oder vaskulärer Tod innerhalb eines Jahres **sekundäre Endpunkte:** 2. Major Stroke, any 3. 30-Tages-Kompl. (Tod oder Schlaganfall 4.2-Tages-Komplikation (Tod oder Schlaganfall)	**0.Studiengüte** kann nicht beurteil werden, Studie liegt nur als Abstract vor I.Ergebnisse **1. gleichseitiger Schlaganfall**, interventionsbedingter Tod oder vaskulärer Tod innerhalb eines Jahres CEA:3,6% CAS: 12,1% p=0,02 **2. jegl. "Major Stroke"** CEA: 0,9% CAS: 3,7% p=0,2 n.s. **3. 30 Tages-Komplikation (Tod oder Schlaganfall)** CEA:4,9% CAS: 12,1% p=0,049 **4. 2-Tages-Komplikation (Tod oder Schlaganfall)** CEA: 1,8% CAS: 7,5% p=0,055	Gestoppt nach Randomisierung von 219 Pat. Studie unterpowert, viele Angaben fehlen	1-
Naylor et al., 1998 **RCT uni-**	n=17 v. 23 konsekutiv randomisierten 6/96-9/96	CEA	CAS	1. Tod 2. fktnsbe-einträchtg.	**0.Studiengüte** Randomisierung /Allocationconcealment beschrieben	gestoppt nach Rand. V. 23 Pat., geplant 300	1-

Artikel (Autor, Jahr)/ Studientyp	Anzahl der Patienten/ Patienten-merkmale	Intervention/ Referenzstandard/ ggf. Nachverfolgung	Vergleichs-intervention	Outcomes	Ergebnisse	Bemerkungen	Evidenz-Niveau
zentrisch Universitätsklinik UK **LEICESTER [27]**	Pat mit symptomatischer Karotisstenose mind. 70% , Symptome bis zu 7 Monate for Randomisierung angegeben	**Nachverfolgung:** bis 30 Tage nach Behandlung		Schlaganfall 3. jegl. Schlaganfall alles nach 30 Tagen	I. Ergebnisse **1. Tod** - **2. fktn beeinträcht. Schlaganfall (nach 30Tagen)** CEA: 0/10 CAS: 3/7 **3. jegl. Schlaganfall** CEA: 0/10 CAS: 5/7 p<0,034		

6.9 Ausgeschlossene Studien

Tabelle 5: Ausgeschlossene Volltexte

Autor, Jahr	Inhalt/ggf. Ergebnisse	Grund für Ausschluss
Bonati L. et al., 2010 {Bonati, 2010 3 /id}	Subgruppenanalyse der ICSS Studie = MR-ICSS. Untersuchung eines Teils der randomisierten Patienten 1-7Tage vor, 1-7 Tage nach und 27-33 Tage nach Eingriff mit MRT insgesamt 233 (107 CEA, 124 CAS) stat. sign. mehr neue Ischämie-regionen bei CAS	Subgruppe ist nicht randomisiert, Surrogatendpunkt

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Versions-Nummer: **2.0**

Erstveröffentlichung: **08/2012**

Überarbeitung von: **02/2020**

Nächste Überprüfung geplant: **02/2025**