



**S2e Leitlinie zur  
Akuttherapie des ischämischen Schlaganfalls**  
**AWMF-Registernummer 030-046**  
**Version 5.1**  
**inkl. Amendment Okt. 2022**

**LEITLINIENREPORT**

publiziert bei:

 **AWMF online**  
Das Portal der wissenschaftlichen Medizin

**DGN**

Deutsche Gesellschaft  
für Neurologie



**ÖSTERREICHISCHE  
GESELLSCHAFT FÜR  
NEURORADIOLOGIE**  
diagnostisch und interventionell



LEITLINIENREPORT zur S2e-LEITLINIE

# „AKUTTHERAPIE DES ISCHÄMISCHEN SCHLAGANFALLS“

AWMF Register Nummer 030-046

Version 5.1 (inkl. Amendment Oktober 2022)

Stand 09. November 2022

## AUTOREN DES LEITLINIENREPORTS:

P.A. Ringleb, M. Köhrmann, Ch. Hametner, B. Frank

## LEITLINIENBÜRO

Dr. Christian Hametner, Prof. Dr. Peter A. Ringleb  
Neurologische Universitätsklinik Heidelberg  
Im Neuenheimer Feld 400  
D-69120 Heidelberg  
Leitlinien@dgn.org

## Inhalt

1.	Geltungsbereich und Zweck der Leitlinie .....	4
1.1.	Begründung für die Auswahl des Leitlinienthemas.....	4
1.2.	Zielorientierung der Leitlinie .....	4
1.3.	Patientenzielgruppe .....	4
1.4.	Versorgungsbereich.....	4
1.5.	Adressaten der Leitlinie.....	4
1.6.	Schlüsselwörter / Keywords .....	4
2.	Zusammensetzung der Leitliniengruppe, Beteiligung von Interessensgruppen .....	5
3.	Methodologische Exaktheit.....	6
3.1.	Recherche, Auswahl und Bewertung wissenschaftlicher Belege (Evidenzbasierung) .....	6
3.1.1.	Formulierung der Schlüsselfragen.....	6
3.1.2.	Auswahl der Evidenz.....	14
3.1.3.	Verwendung existierender Leitlinien .....	15
3.1.4.	Systematische Literaturrecherche.....	18
3.1.5.	Bewertung der Evidenz .....	18
3.2.	Formulierung der Empfehlungen und strukturierte Konsensfindung.....	19
3.2.1.	Berücksichtigung von Nutzen, Nebenwirkungen, relevanten Outcomes .....	19
3.2.2.	Formulierung der Empfehlungen und Vergabe von Evidenzgraden und/ oder Empfehlungsgraden .....	20
3.2.3.	Formale Konsensfindung: Verfahren und Durchführung.....	21
4.	Externe Begutachtung und Verabschiedung.....	23
4.1.	Pilottestung .....	23
4.2.	Externe Begutachtung .....	23
4.3.	Verabschiedung durch die Vorstände der herausgebenden Fachgesellschaften/Organisationen.....	24
5.	Redaktionelle Unabhängigkeit .....	24
5.1.	Finanzierung der Leitlinie .....	24
5.2.	Darlegung von und Umgang mit potenziellen Interessenkonflikten .....	24
6.	Verbreitung und Implementierung .....	25
7.	Gültigkeit und Aktualisierungsverfahren .....	27
8.	Anhang .....	28
8.1.	Interessenanzeige der Autoren .....	28
8.2.	Leitlinien-Synopse .....	31
8.2.1.	Evidenzlevel und Empfehlungsstärken der externen Leitlinien .....	31
8.2.2.	Synopse der externen Leitlinien zu Kapitel 1 .....	34
8.2.3.	Synopse der externen Leitlinien zu Kapitel 2 .....	112
8.2.4.	Synopse der externen Leitlinien zu Kapitel 3 .....	153
8.3.	Suchalgorithmen und Ergebnis der systematischen Suche nach Übersichtsarbeiten oder Einzelstudien .....	160
8.4.	Literatur.....	247

## Tabellenverzeichnis

<b>Tabelle 1:</b> Auflistung der beteiligten Fachgesellschaften (alphabetisch sortiert) und der Nominierten für diese Leitlinie .....	5
<b>Tabelle 2:</b> Schwerpunktkapitel der Leitlinie und Kapitelverantwortliche.....	6
<b>Tabelle 3:</b> Konsensuierte Schlüsselfragen nach dem PICO-Prinzip .....	7
<b>Tabelle 4:</b> Anhand des DELBI-Werkzeugs als qualitativ hochwertig eingeordnete Leitlinien .....	15
<b>Tabelle 5:</b> Zuordnung der Schlüsselfragen zu externen Leitlinien .....	16
<b>Tabelle 6:</b> Beschreibung der modifizierten Rankin-Skala [25, 26] .....	19
<b>Tabelle 7:</b> Beschreibung der Heidelberg-Bleeding-Classification (modifiziert nach [27]) .....	19
<b>Tabelle 8:</b> Evidenzlevel nach der Oxford-Klassifizierung in der Version von 2011 (nach [28]).....	20
<b>Tabelle 9:</b> Codierung und textliche Beschreibung der Empfehlungsstärke .....	20
<b>Tabelle 10:</b> Übersicht der Konsensusstärke der Empfehlungen der einzelnen Schlüsselfragen .....	22
<b>Tabelle 11:</b> Auflistung der externen Reviewer.....	24

## Abbildungsverzeichnis

<b>Abbildung 1:</b> Elemente des PICO-Systems zur Erstellung suchfähiger Fragestellungen .....	7
<b>Abbildung 2:</b> Bewertungsbögen für systematische Übersichtsarbeiten, Diagnostik- und Therapiestudien .....	18
<b>Abbildung 3:</b> Zuordnung von Evidenzstärke zu einem Empfehlungsgrad, modifiziert nach den Kriterien des Oxford Centre of Evidence based Medicine (2011), empfohlen und herausgegeben von der AWMF .....	21

## 1. GELTUNGSBEREICH UND ZWECK DER LEITLINIE

### 1.1. BEGRÜNDUNG FÜR DIE AUSWAHL DES LEITLINIENTHEMAS

Der Schlaganfall zählt zu den häufigsten Erkrankungen in Deutschland mit ca. 270.000 Neuerkrankungen pro Jahr. Er ist weltweit eine der führenden Ursachen von Morbidität und Mortalität. Seit über 25 Jahren bestehen mit der systemischen Thrombolyse und der Stroke Unit-Therapie potenziell kurative Behandlungsmöglichkeiten. Seit wenigen Jahren hat die Schlaganfallakuttherapie mit der Etablierung endovaskulärer Therapieverfahren weitere große Fortschritte gemacht. Alle akuttherapeutischen Maßnahmen wirken besser, je früher und zielgerichteter sie angewendet werden.

### 1.2. ZIELORIENTIERUNG DER LEITLINIE

Evidenzbasierte Empfehlungen zur Diagnostik und Therapie von Patienten mit akutem ischämischen Hirninfarkt und TIA durch an der Behandlung akuter Schlaganfallpatienten beteiligter Fachdisziplinen.

### 1.3. PATIENTENZIELGRUPPE

Diese Leitlinie bezieht sich auf erwachsene Patienten mit akutem Hirninfarkt oder TIA in den ersten 48 Stunden nach Symptombeginn.

### 1.4. VERSORGUNGSBEREICH

Die Behandlung von Patienten mit akutem Schlaganfall umfasst überwiegend eine Betreuung im stationären Bereich. Die in dieser Leitlinie thematisierten Maßnahmen zur Akuttherapie werden größtenteils durch Neurologen, Neuroradiologen, Notfallmediziner, Intensivmediziner, Internisten und Kardiologen stationär initiiert.

### 1.5. ADRESSATEN DER LEITLINIE

Der Schwerpunkt dieser Leitlinie liegt eindeutig im medizinischen Akutbereich. Sie erhebt keinen Anspruch auf Vollständigkeit in der Behandlung von Schlaganfallpatienten.

Folgende Aspekte der Schlaganfallbehandlung werden nicht behandelt:

- Primär- und Sekundärprävention
- Rehabilitationstherapie
- Behandlung von Kindern

Die Empfehlungen richten sich an alle Ärzte und Angehörige von Berufsgruppen, die mit der Akutbehandlung von Schlaganfallpatienten befasst sind (Neurologen, Neuroradiologen, Radiologen, Internisten, Notfall- und Intensivmediziner), dienen der Information von Anästhesisten und von Patienten, die einen ischämischen Schlaganfall erlitten haben, sowie deren Angehörige.

### 1.6. SCHLÜSSELWÖRTER / KEYWORDS

ICD-Codes: I63.\* Akuter Hirninfarkt, G45.\* TIA

Schlüsselwörter (Deutsch): Schlaganfall, Hirninfarkt, transiente ischämische Attacke, Stroke Unit, Thrombolyse, Thrombektomie, endovaskuläre Schlaganfalltherapie

Keywords (Englisch): Stroke, ischemic stroke, transient ischemic attack, stroke unit, thrombolysis, mechanical thrombectomy, endovascular stroke treatment

## 2. ZUSAMMENSETZUNG DER LEITLINIENGRUPPE, BETEILIGUNG VON INTERESSENSGRUPPEN

Die Erstellung der Leitlinie wurde 2015 von der Leitlinienkommission der Deutschen Gesellschaft für Neurologie initiiert. Beauftragt wurden zunächst Herr Prof. Dr. Roland Veltkamp (damals London, UK) und Prof. Dr. Peter A. Ringleb (Heidelberg). Gemeinsam wurden zu beteiligende Fachgesellschaften identifiziert. Bei der Auswahl der Fachgesellschaften wurde gemäß den Kriterien zur Entwicklung einer Leitlinie auf S2e-Niveau geachtet, dass ein direkter Bezug zur Akuttherapie bestand.

**Tabelle 1:** Auflistung der beteiligten Fachgesellschaften (alphabetisch sortiert) und der Nominierten für diese Leitlinie

<b>DeGIR</b>	Deutsche Gesellschaft für Interventionelle Radiologie und minimal invasive Therapie	A. Berlis
<b>DEGUM</b>	Deutsche Gesellschaft für Ultraschall in der Medizin	M. Köhrmann <sup>1*</sup>
<b>DGIM</b>	Deutsche Gesellschaft für Innere Medizin	R. Wachter <sup>1</sup>
<b>DGK</b>	Deutsche Gesellschaft für Kardiologie	U. Laufs
<b>DGN</b>	Deutsche Gesellschaft für Neurologie	R. Veltkamp <sup>1</sup> , M. Köhrmann <sup>1*</sup> C. Weiller Sekretär B. Frank
<b>DGNC</b>	Deutsche Gesellschaft für Neurochirurgie	G.A. Schubert
<b>DGNI</b>	Deutsche Gesellschaft für Neurointensiv- und Notfallmedizin	P. Schellinger
<b>DGNR</b>	Deutsche Gesellschaft für Neuroradiologie	H. Urbach
<b>DRG</b>	Deutsche Röntgengesellschaft	O. Jansen <sup>1</sup>
<b>DSG</b>	Deutsche Schlaganfall-Gesellschaft	P.A. Ringleb <sup>1*</sup> , T. Neumann-Haefelin (2022) Sekretär Ch. Hametner
<b>ÖGNR</b>	Österreichische Gesellschaft für Neuroradiologie	M. Sonnberger
<b>ÖSG</b>	Österreichische Schlaganfall-Gesellschaft	M. Sykora
<b>SDSH</b>	Stiftung Deutsche Schlaganfall-Hilfe	M. Wagner
<b>SGNR</b>	Schweizerische Gesellschaft für Neuroradiologie	P. Mordasini
<b>SNG</b>	Schweizerische Neurologische Gesellschaft	U. Fischer

1: Mitglied der Steuergruppe; \*: Sprecher der Leitliniengruppe

Herr Prof. Dr. Roland Veltkamp wurde im Jahr 2017 durch Herrn Prof. Dr. Martin Köhrmann als Vertreter der DGN und als Sprecher der Leitliniengruppe ersetzt. Zudem wurde Herr Prof. Dr. Cornelius Weiller im Jahr 2018 von der DGN als weiteres interessenskonfliktfreies Mitglied der Leitliniengruppe bestellt.

Herr Prof. Dr. Tobias Neuman-Haefelin wurde in die Bearbeitung des Amendments Oktober 2022 involviert.

Wegen der parallelen Entwicklung einer S3-Leitlinie unter Federführung der Deutschen Gesellschaft für Allgemeinmedizin (AWMF Register-Nummer 053-011), an der mehrere Autoren dieser Leitlinie direkt beteiligt waren, wurde auf die Beteiligung von therapeutischen Berufsgruppen verzichtet. Durch die Beteiligung der Stiftung Deutsche Schlaganfallhilfe wurden Patienteninteressen berücksichtigt. Die Vorstände der Fachgesellschaften nominierten die in Tabelle 1 genannten Mitglieder der Leitliniengruppe. Die Leitliniengruppe wurde durch zwei Sekretäre der Sprecher ergänzt.

Die Mitglieder der Leitliniengruppe bearbeiteten die Schlüsselfragen, dabei konnten Mitarbeiter zur Unterstützung gewonnen werden. Auch diese mussten ihre möglichen Interessenskonflikte offenlegen (siehe Abschnitt 8.1).

### 3. METHODOLOGISCHE EXAKTHEIT

#### 3.1. RECHERCHE, AUSWAHL UND BEWERTUNG WISSENSCHAFTLICHER BELEGE (EVIDENZBASIERUNG)

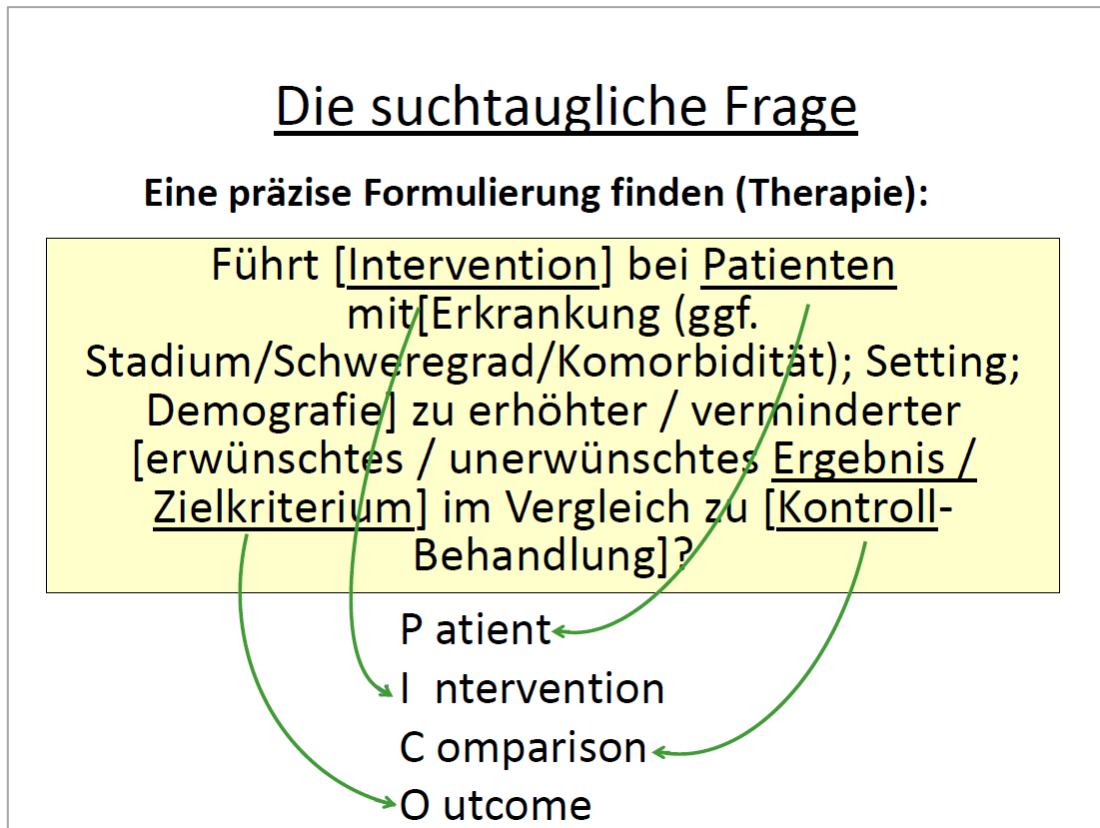
##### 3.1.1. Formulierung der Schlüsselfragen

Im Rahmen eines konsensuierenden Treffens wurden drei Schwerpunktkapitel der Leitlinie definiert und Kapitelverantwortlichen zugeordnet (siehe Tabelle 2).

**Tabelle 2:** Schwerpunktkapitel der Leitlinie und Kapitelverantwortliche

NR.	THEMA	VERANTWORTLICH
<b>Kapitel 1</b>	Allgemeines Management	P. Ringleb M. Wagner
<b>Kapitel 2</b>	Rekanalisationstherapie	M. Köhrmann P. Ringleb
<b>Kapitel 3</b>	Intensivtherapie	Ch. Hametner M. Sykora G. Schubert

Diese erstellten mit weiteren Mitgliedern der Leitliniengruppe Vorschläge für Schlüsselfragen nach dem PICO-Prinzip:



**Abbildung 1:** Elemente des PICO-Systems zur Erstellung suchfähiger Fragestellungen

Diese Schlüsselfragen wurden während eines zweiten Treffens und in einem eMail-Umlaufverfahren konsentiert. Zur besseren Lesbarkeit und den Regeln der deutschen Grammatik folgend wurden die Fragen immer mit einem Verb begonnen. Die endgültigen 53 Schlüsselfragen sind in der folgenden Tabelle wiedergegeben:

**Tabelle 3:** Konsensierte Schlüsselfragen nach dem PICO-Prinzip

SF	FORMULIERUNG
<b>1.1.1</b>	Führt bei P erwachsenen Patienten mit möglichem akutem Hirninfarkt oder TIA I die Anwendung von Screening Tools zur Schlaganfallerkennung C im Vergleich zur Nicht-Anwendung O a) zu einer rascheren Zuweisung ins Krankenhaus? oder b) zu einem verbesserten funktionellen Outcome?
<b>1.1.2</b>	Verbessert bei P erwachsenen Patienten mit akutem Hirninfarkt oder TIA I die Gabe von Sauerstoff C im Vergleich zu keiner Gabe O das funktionelle Outcome?
<b>1.1.3</b>	Verbessert bei P erwachsenen Patienten mit akutem Hirninfarkt oder TIA I die Kontrolle und ggfs. Korrektur erniedrigter oder erhöhter Glukosewerte C im Vergleich zu keiner Intervention O das funktionelle Outcome?



SF	FORMULIERUNG
<b>1.1.4</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die Reduktion einer erhöhten Körpertemperatur</p> <p>C im Vergleich zu keiner Intervention</p> <p>O das funktionelle Outcome?</p>
<b>1.1.5</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die Reduktion erhöhter Blutdruckwerte</p> <p>C im Vergleich zu keiner Intervention</p> <p>O das funktionelle Outcome?</p>
<b>1.1.6</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die Erhöhung erniedrigter Blutdruckwerte</p> <p>C im Vergleich zum Verzicht hierauf</p> <p>O das funktionelle Outcome?</p>
<b>1.1.7</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine medikamentöse oder mechanische Thromboseprävention</p> <p>C im Vergleich zu keiner Thromboseprävention</p> <p>O das funktionelle Outcome?</p>
<b>1.1.8</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I ein systematisches Dysphagie-Screening</p> <p>C im Vergleich zum Nicht-Screening</p> <p>O das funktionelle Outcome?</p>
<b>1.1.9</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt und Dysphagie</p> <p>I die enterale Ernährung mittels Magensonde</p> <p>C im Vergleich zu Nahrungskarenz   parenteraler Ernährung</p> <p>O das funktionelle Outcome?</p>
<b>1.1.10</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die prophylaktische Gabe eines Antibiotikums</p> <p>C im Vergleich zum Verzicht hierauf</p> <p>O das funktionelle Outcome?</p>
<b>1.1.11</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die prophylaktische Gabe eines Antiepileptikums</p> <p>C im Vergleich zum Verzicht hierauf</p> <p>O das funktionelle Outcome?</p>
<b>1.1.12</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die Gabe eines Antiepileptikums nach einem ersten epileptischen Anfall</p> <p>C im Vergleich zum Verzicht hierauf</p> <p>O das funktionelle Outcome?</p>

SF	FORMULIERUNG
<b>1.1.13</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I ein systematisches Delir-Screening und ggfs. Delir-Behandlung</p> <p>C im Vergleich zur konventionellen Therapie</p> <p>O das funktionelle Outcome?</p>
<b>1.2.1</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I verbessert die Zuweisung auf eine Stroke Unit</p> <p>C im Vergleich zur Behandlung auf einer Normalstation</p> <p>O das funktionelle Outcome?</p>
<b>1.2.2</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit kürzlicher TIA</p> <p>I die Zuweisung auf eine Stroke Unit</p> <p>C im Vergleich zur ambulanten Behandlung</p> <p>O das funktionelle Outcome?</p>
<b>1.2.3</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I eine direkte Zuweisung in ein Comprehensive Stroke Center</p> <p>C im Vergleich zur Behandlung auf einer Stroke Unit</p> <p>O das funktionelle Outcome?</p>
<b>1.3.1</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine umgehende Bildgebung des Gehirns mit MRT</p> <p>C im Vergleich zu einer CT-Untersuchung</p> <p>O das funktionelle Outcome?</p>
<b>1.3.2</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine umgehende nicht-invasive Gefäßdiagnostik mit CTA/MRA</p> <p>C im Vergleich zur alleinigen Parenchymdiagnostik</p> <p>O das funktionelle Outcome?</p>
<b>1.3.3</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I das kontinuierliche apparative Monitoring der Herz-Kreislauf- und der Stoffwechsel-Funktion auf der Stroke Unit</p> <p>C im Vergleich zum Nicht-Monitoring</p> <p>O das funktionelle Outcome?</p>
<b>1.3.4</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die regelmäßige neurologische Untersuchung und Erfassung mittels etablierter klinischer Scores</p> <p>C im Vergleich zu einer selteneren Kontrolle</p> <p>O das funktionelle Outcome?</p>

SF	FORMULIERUNG
<b>1.3.5</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine frühzeitige transoesophageale Echokardiografie</p> <p>C im Vergleich zur transthorakalen Echokardiografie</p> <p>O das funktionelle Outcome?</p>
<b>1.3.6</b>	<p>Führt bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine mehrtägige Kontrolle des Herzrhythmus auf der Stroke Unit</p> <p>C im Vergleich zu einem konventionellen 24Std.-Langzeit-EKG</p> <p>O a) zu einer erhöhten Detektionsrate für VHF? oder b) zu einem verbesserten funktionellen Outcome?</p>
<b>1.3.7</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die duplexsonografische Untersuchung der extra- und intrakraniellen Arterien</p> <p>C im Vergleich zur CTA/MRA/DSA</p> <p>O die Genauigkeit der ätiologischen Einordnung?</p>
<b>1.3.8</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I die zusätzliche Untersuchung des Herzens mittels CT/MRT</p> <p>C ergänzend zur Echokardiografie</p> <p>O die Genauigkeit der ätiologischen Einordnung?</p>
<b>1.4.1</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I die Stimulation des Ganglion sphenopalatinum</p> <p>C im Vergleich zur konventionellen Therapie ohne Stimulation</p> <p>O das funktionelle Outcome?</p>
<b>1.5.1</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine frühzeitige antithrombotische Therapie mit ASS</p> <p>C im Vergleich zum Verzicht auf eine antithrombotische Therapie</p> <p>O das funktionelle Outcome?</p>
<b>1.5.2</b>	<p>Führt bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt oder TIA</p> <p>I eine frühzeitige duale antithrombotische Therapie</p> <p>C im Vergleich zu einer singulären antithrombotischen Therapie</p> <p>O a) zur Reduktion des Risikos früher Schlaganfallrezidive?; b) zu einer veränderten Risiko-Nutzen-Abwägung?; c) zur Verbesserung des funktionellen Outcomes?</p>
<b>1.6.1</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I eine frühzeitige Physiotherapie</p> <p>C im Vergleich zum Verzicht darauf</p> <p>O das funktionelle Outcome?</p>

SF	FORMULIERUNG
<b>1.6.2</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I eine frühzeitige Ergotherapie</p> <p>C im Vergleich zum Verzicht darauf</p> <p>O das funktionelle Outcome?</p>
<b>1.6.3</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I eine frühzeitige logopädische Behandlung</p> <p>C im Vergleich zum Verzicht darauf</p> <p>O das funktionelle Outcome?</p>
<b>2.1.1</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt und einem Zeitfenster von bis zu 4,5 Std. seit Symptombeginn</p> <p>I eine systemische Thrombolyse mit Alteplase</p> <p>C im Vergleich zur Nicht-Anwendung</p> <p>O zu einem besseren funktionellem Ergebnis?</p>
<b>2.1.2</b>	<p>Führt bei</p> <p>P Patienten über 80 Jahre mit Hirninfarkt, die für eine Thrombolyse in Frage kommen,</p> <p>I eine systemische Thrombolyse mit Alteplase</p> <p>C im Vergleich zur Thrombolyse bei Patienten bis zu 80 Jahren</p> <p>O zu einem vergleichbaren klinischen Nutzen der Therapie?</p>
<b>2.1.3</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt und einem Zeitfenster von 4,5-9 Std. seit Symptombeginn oder unklarem Zeitfenster (z.B. Symptome beim Erwachen)</p> <p>I eine Thrombolyse basierend auf erweiterter Bildgebung und einem CT/MRT-basiert dargestellten Mismatch von Infarktkern und Penumbra</p> <p>C im Vergleich zur Nicht-Anwendung</p> <p>O zu einem besseren funktionellem Ergebnis?</p>
<b>2.1.4</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt mit Symptomen beim Erwachen oder einem unbekanntem Zeitfenster und einer Vorstellung innerhalb von 4,5 Std. nach Erkennen der Symptome</p> <p>I eine Thrombolyse mit Alteplase basierend auf einem DWI-FLAIR-Mismatch</p> <p>C im Vergleich zur Nicht-Anwendung</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.1.5</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt und einem Symptombeginn bis zu 4,5 Std.</p> <p>I eine Thrombolyse mit Tenecteplase</p> <p>C im Vergleich zur Thrombolyse mit Alteplase</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.1.6</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt im 4,5 Std. Zeitfenster</p> <p>I eine Thrombolyse mit einer reduzierten Dosis von 0,6mg/kg Körpergewicht</p> <p>C im Vergleich zur Standarddosis von 0,9mg/kg Körpergewicht</p> <p>O nicht zu einem schlechteren funktionellen Ergebnis?</p>

SF	FORMULIERUNG
<b>2.1.7</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt im 4,5 Std. Zeitfenster, die mit Alteplase behandelt werden,</p> <p>I eine zusätzliche Behandlung mit Ultraschall (Sonothrombolyse)</p> <p>C im Vergleich zur alleinigen systemischen Thrombolyse</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.1.8</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt im 4,5 Std. Zeitfenster mit leichtem, aber behindernden Defizit oder sich rasch verbessernden Symptomen</p> <p>I eine systemische Thrombolyse</p> <p>C im Vergleich zur Nicht-Anwendung</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.1.9</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt und sehr schweren Symptomen</p> <p>I eine systemische Thrombolyse mit Alteplase</p> <p>C im Vergleich zur Nicht-Anwendung</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.1.10</b>	<p>Führt bei</p> <p>P Thrombolyse-Patienten, die initial einen entgleisten Blutdruck haben (&gt;185mmHg syst. und/oder &gt;110 mmHg diast.)</p> <p>I eine Senkung des Blutdrucks unter die genannten Grenzen</p> <p>C im Vergleich zur Nicht-Senkung</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.2.1</b>	<p>Führt bei</p> <p>P Hirninfarkt-Patienten mit einem proximalen Gefäßverschluss in der vorderen Zirkulation im 6 Std. Zeitfenster nach Symptombeginn</p> <p>I eine interventionelle Thrombektomie zusätzlich zur bestmöglichen medizinischen Management</p> <p>C im Vergleich zum alleinigen bestmöglichen medizinischen Management</p> <p>O zu einem verbesserten funktionellen Ergebnis?</p>
<b>2.2.2</b>	<p>Führt bei</p> <p>P Hirninfarkt-Patienten mit einem proximalen Gefäßverschluss in der vorderen Zirkulation, die sich in einem unklaren aber maximal 24 Stunden bzw. gesichertem max. 24 Std. Zeitfenster befinden und zum Zeitpunkt der Behandlung in einer erweiterten Bildgebung</p> <p>1) bei schwerer Symptomatik einen kleinen Infarktkern aufweisen und/oder</p> <p>2) ein CT/MRT-basiert dargestelltes Mismatch von Infarktkern und Penumbra aufweisen</p> <p>I eine interventionelle Thrombektomie zusätzlich zur bestmöglichen medizinischen Management</p> <p>C im Vergleich zum alleinigen bestmöglichen medizinischen Management</p> <p>O zu einem verbesserten funktionellem Ergebnis?</p>

SF	FORMULIERUNG
<b>2.2.3</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt und einem proximalem Gefäßverschluss, bei denen sowohl eine systemische Thrombolysse als auch eine interventionelle Thrombektomie möglich und empfohlen ist,</p> <p>I eine kombinierte Therapie mit systemischer Thrombolysse und interventioneller Thrombektomie</p> <p>C im Vergleich zu einer alleinigen interventionellen Thrombektomie</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.2.4</b>	<p>Führt bei</p> <p>P Patienten &gt;80 Jahren mit Hirninfarkt und einem proximalen Gefäßverschluss in der vorderen Zirkulation und den in Fragen 2.2.1 und 2.2.2 beschriebenen Situationen</p> <p>I eine interventionelle Thrombektomie zusätzlich zur bestmöglichen medizinischen Therapie</p> <p>C im Vergleich zu einer bestmöglichen medizinischen Therapie allein</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.2.5</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt und proximalem Gefäßverschluss</p> <p>I eine vollständige Reperfusion (TICI 3)</p> <p>C im Vergleich zu einer unvollständigen Reperfusion</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.2.6</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt, die mit einer interventionellen Thrombektomie behandelt werden</p> <p>I eine Behandlung in „conscious sedation“</p> <p>C im Vergleich zu einer Behandlung in Vollnarkose</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.2.7</b>	<p>Führt bei</p> <p>P Patienten mit Hirninfarkt, die mit einer interventionellen Thrombektomie behandelt werden,</p> <p>I eine Senkung des Blutdrucks unter einen bestimmten Schwellenwert</p> <p>C im Vergleich zur Nichtanwendung eines Schwellenwertes</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>2.2.8</b>	<p>Führt bei</p> <p>P Patienten mit akutem Hirninfarkt und Verschluss von großen Gefäßen der hinteren Zirkulation (A. basilaris, Aa. vertebrales)</p> <p>I eine interventionelle Thrombektomie zusätzlich zu einer bestmöglichen medizinischen Therapie</p> <p>C im Vergleich zu einer alleinigen bestmöglichen medizinischen Therapie</p> <p>O zu einem besseren funktionellen Ergebnis?</p>
<b>3.1.1</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten (<math>\leq 60</math> Jahre) mit großem, raumforderndem Hirninfarkt im Stromgebiet der A. cerebri media rechts oder links (supratentoriell)</p> <p>I eine Hemikraniektomie innerhalb von 48 Stunden nach Beginn der Schlaganfallsymptome</p> <p>C zusätzlich zum konservativen intensivmedizinischen Management</p> <p>O a) die Überlebensrate, b) das neurologische Funktionsniveau bei Überleben</p>

SF	FORMULIERUNG
<b>3.1.2</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten (&gt;60 Jahre) mit großem, raumforderndem Hirninfarkt im Stromgebiet der A. cerebri media rechts oder links (supratentoriell)</p> <p>I eine Hemikraniektomie innerhalb von 48 Stunden nach Beginn der Schlaganfallsymptome</p> <p>C zusätzlich zum konservativen intensivmedizinischen Management</p> <p>O a) die Überlebensrate, b) das neurologische Funktionsniveau bei Überleben?</p>
<b>3.1.3</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit großem, raumforderndem Kleinhirninfarkt und klinischer Verschlechterung</p> <p>I eine neurochirurgische Intervention</p> <p>C zusätzlich zum maximal konservativen Management</p> <p>O a) die Überlebensrate, b) das neurologische Funktionsniveau bei Überleben?</p>
<b>3.2</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt</p> <p>I eine therapeutische Hypothermie</p> <p>C zusätzlich zur Standardtherapie</p> <p>O a) die Überlebensrate, b) das neurologische Funktionsniveau bei Überleben?</p>
<b>3.3</b>	<p>Verbessert bei</p> <p>P erwachsenen Patienten mit akutem Hirninfarkt und einer durch Hirnödemen bedingten klinischen Verschlechterung</p> <p>I die intravenöse Gabe von osmotisch wirksamen Arzneimitteln</p> <p>C zusätzlich zur Standardtherapie</p> <p>O a) die Überlebensrate, b) das neurologische Funktionsniveau bei Überleben?</p>

Im Verlauf der Bearbeitung der Schlüsselfragen fiel – leider sehr spät – auf, dass bei der Planung dieser Leitlinie und Erstellung der Schlüsselfragen mögliche oder wahrscheinliche Geschlechtsspezifika vernachlässigt worden waren. Daher wurde noch ein viertes Kapitel „Geschlechtsspezifische Unterschiede in der Schlaganfall Akutbehandlung“ eingefügt, ohne jedoch weitere Schlüsselfragen zu formulieren.

Im Mai 2022 beauftragte der Vorstand der DSG die Leitliniengruppe mit der Überarbeitung der Schlüsselfrage 2.1.5 zur systemischen Thrombolyse mit alternativen Thrombolytika und der Schlüsselfrage 2.2.3 zur Kombination von systemischer Thrombolyse und endovaskulärer Schlaganfalltherapie, nachdem neue Studien hierzu publiziert worden waren und ein Produktionsengpass von Alteplase angekündigt worden war. Der Text der Schlüsselfragen wurde dabei nicht verändert, so dass die vorstehende Tabelle nicht angepasst werden musste. Die Bearbeitung erfolgte als Amendment „Oktober 2022“ und führte zur Version 5.1 der Leitlinie. Im Rahmen des Amendments angefügte Empfehlungen sind mit „Neu22“ gekennzeichnet, veränderte Empfehlungen mit „Mod22“.

### 3.1.2. Auswahl der Evidenz

Die Auswahl der zur Beantwortung der einzelnen Schlüsselfragen zu verwendenden Evidenz erfolgte gemäß Empfehlung der AWMF auf Basis der jeweils besten verfügbaren Evidenz in folgender, absteigenden Reihenfolge:

1. Leitlinien hoher methodischer Qualität

2. Systematische Reviews
3. Meta-Analysen
4. Einzelne randomisierte klinische Studie
5. Sonstige Studien (Kohortenstudien, Fall-Kontroll Studien)

Dieses Vorgehen wurde auch für das Amendment „Oktober 2022“ beibehalten.

### 3.1.3. Verwendung existierender Leitlinien

Für die einzelnen Schlüsselfragen wurde die vorhandene Evidenz gesammelt. Hierfür wurden in einem ersten Schritt mittels einer systematischen Suche vorhandene Leitlinien identifiziert. Gesucht wurde 2015 bei Medline, Google, im „Guidelines international network“ (g-i-net) und auf den Seiten der AWMF nach dem Stichwort „stroke“ in englischer oder „Schlaganfall“ in deutscher Sprache. Diese Suche ergab 86 Treffer, von denen anhand des Titels die Mehrzahl der Treffer als nicht relevant beurteilt wurde. Nach Ausschluss von vor 2005 publizierten Leitlinien wurden insges. 29 Leitlinien detektiert. Diese Suche wurde im Feb. 2019 mit dem Stichwort „Stroke“ in g-i-net wiederholt und ergab 92 Treffer, von denen 15 nach 2014 publiziert worden waren. Eine Leitlinie aus Qatar wurde nicht berücksichtigt. Daneben sind aber noch erschienen: Leitlinie der AHA [1], Consensus-Statement der KSU [2], NCCS/DGNI Hemisphäreninfarkte [3], AHA Update EST [4], ESO Leitlinie zum Temperaturmanagement [5], Australian Clinical Guideline 2017 [6]; Canadian update 2015 [7] und 2018 [8], Dual-antiplatelet therapy aus Großbritannien [9], und eine Leitlinie der Royal society of physicians (RCP) 2016 [10]. Im Verlauf der Bearbeitung dieser Leitlinie publizierte die AHA eine aktualisierte Leitlinie zu zahlreichen wichtigen Aspekten, weswegen sie Berücksichtigung fand (Powers 2019 [11]). Außerdem wurde auf der Homepage der ESO gesucht, wo vier weitere Leitlinien zu Einzelaspekten der Schlaganfallakutbehandlung detektiert wurden [12-15]. Und zwischenzeitlich wurde die S3-Leitlinie Schlaganfall unter Federführung der DEGAM veröffentlicht [16], PR und MK waren Mitautoren dieser Leitlinie. Während der Phase der externen Reviews publizierte die ESO Leitlinien zur systemischen Thrombolysetherapie des ischämischen Schlaganfalls [17] und zum TIA-Management [18]. Diese Leitlinien konnten wegen des Erscheinungsdatums nicht bei der systematischen Evidenzgewinnung berücksichtigt werden. Die jeweiligen Kapitelautoren überprüften jedoch, dass es keine relevanten Widersprüche zwischen den Empfehlungen dieser Leitlinie und den Empfehlungen der ESO gibt. Im Jahr 2022 publizierte die ESO gemeinsam mit ESMINT eine Leitlinie zur Kombination von systemischer Thrombolyse und endovaskulärer Schlaganfalltherapie (dem sog. bridging) [19].

Die so gefundenen Leitlinien wurden unter Verwendung des DELBI-Werkzeuges der AWMF (<https://www.leitlinien.de/leitlinien-grundlagen/leitlinienbewertung/delbi>) von mehreren Mitgliedern der Leitliniengruppe auf methodische Exaktheit überprüft. Nur die Leitlinien die bei den Kriterien 3.8 bis 3.14 mehr als 50% der maximalen Punktzahl hatten, wurden im weiteren als Quelle zur Beantwortung von Schlüsselfragen herangezogen. Nachdem auch die 2021/2022 publizierten ESO-Leitlinien zur systemischen Thrombolyse [17] und zum bridging [19] mit dem DELBI-Werkzeug evaluiert worden war, wurde diese bei hoher methodischer Qualität für die Erstellung des Amendments Oktober 2022 herangezogen.

**Tabelle 4:** Anhand des DELBI-Werkzeugs als qualitativ hochwertig eingeordnete Leitlinien

LEITLINIE	QUELLE	DURCHSCHNITT DER DELBI-BEWERTUNG
Royal College of Physicians (2016)	[10]	100,0%
Canadian Heart and Stroke Foundation (2018)	[8]	89,3%
UK (2018)	[9]	83,9%



American Heart Association (2018)	[1]	82,1%
American Heart Association (2019)	[11]	82,1%
Australian Stroke Foundation (2017)	[6]	75,0%
ESPEN Clinical Nutrition (2018)	[20]	66,1%
German Society for Clinical Nutrition (2013)	[21]	53,6%
NCCS und DGNI (2015)	[3]	78,6%
European Stroke Organisation - Thrombosis (2016)	[12]	85,7%
European Stroke Organisation - Seizure (2017)	[13]	82,1%
European Stroke Organisation - Glycemia (2018)	[14]	76,8%
European Stroke Organisation – IVT (2021)	[17]	89,3%
European Stroke Organisation – bridging (2022)	[19]	89,3%
European Stroke Organisation - Fever (2015)	[5]	85,7%
EAN/ESO Prehospital (2018)	[15]	60,7%
NICE Endovascular Stroke Treatment (2016)	[22]	67,9%
European Stroke Organisation -Endovascular Stroke Treatment (2018)	[23]	85,7%
NICE (2019)	[24]	82,1%
Deutsche Gesellschaft für Allgemeinmedizin (2020)	[16]	100,0%

Der Volltext dieser Leitlinien wurden von den Kapitelverantwortlichen daraufhin untersucht, zu welcher Schlüsselfrage darin Stellung bezogen ist.

**Tabelle 5:** Zuordnung der Schlüsselfragen zu externen Leitlinien

Schlüsselfrage (No   Stichwort)	AHA (2018/2019)	Australia (2017)	Canada (2018)	DEGAM (2020)	ESO Fever (2015)	ESO Glycemia (2018)	ESO MT (2018)	ESO Prehospital (2018)	ESO Seizure (2017)	ESO Thrombosis (2016)	ESPEN Nutrition (2018)	German Nutrition (2013)	NCCS DGNI (2015)	NICE (2019)	NICE EST (2016)	dAPT UK (2018)	RCP (2016)	ESO IVT (2021)	ESO-bridging (2022)
1.1.1 Screening-Tools	X	X	X	X	-	-	-	X	-	-	-	-	-	X	-	-	-	X	
1.1.2 Sauerstoff	X	X	X	X	-	-	-	X	-	-	-	-	-	X	-	-	-	X	
1.1.3 Glukose	X	X	X	X	-	X	-	X	-	-	-	-	-	X	-	-	-	X	
1.1.4 Fieber	X	X	X		X	-	-	X	-	-	-	-	-	-	-	-	-	-	
1.1.5 Hypertonie	X	X	X	X	-	-	-	X	-	-	-	-	-	X	-	-	-	X	
1.1.6 Hypotonie	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1.1.7 Thromboseprävention	X	X	X		-	-	-	-	-	X	-	-	-	-	-	-	-	X	
1.1.8 Dysphagiescreening	X	-	X	X	-	-	-	-	-	-	X	X	-	X	-	-	-	X	
1.1.9 Magensonde	-	X	X	X	-	-	-	-	-	-	-	X	-	X	-	-	-	-	
1.1.10 Antibiose	-	-	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1.1.11 AE-Prophylaxe	X	-	X		-	-	-	-	X	-	-	-	-	-	-	-	-	-	
1.1.12 AE-Therapie	X	-	X		-	-	-	-	X	-	-	-	-	-	-	-	-	-	
1.1.13 Delir	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	
1.2.1 Stroke Unit, IS	X	X	X		-	-	-	-	-	-	-	-	-	-	-	-	-	X	
1.2.2 Stroke Unit, TIA	X	X	X	X	-	-	-	-	-	-	-	-	-	X	-	-	-	X	
1.2.3 CSC	X	-	X		-	-	X	X	-	-	-	-	-	-	-	-	-	-	
1.3.1 Parenchymbildgebung	X	X	X		-	-	-	-	-	-	-	-	-	-	-	-	-	X	
1.3.2 Gefäßdiagnostik	X	X	X		-	-	X	-	-	-	-	-	-	-	-	-	-	X	

1.3.3	Monitoring, apparativ	-	X	X		-	-	-	-	-	-	-	-	-	-	-	X		
1.3.4	Monitoring, klinisch	-	-	X		-	-	-	-	-	-	-	-	-	-	-	X		
1.3.5	TEE	X	X	X		-	-	-	-	-	-	-	-	-	-	-	-		
1.3.6	Herzrhythmus	X	X	-		-	-	-	-	-	-	-	-	-	-	-	X		
1.3.7	Duplex	-	X	X		-	-	-	-	-	-	-	-	-	-	-	-		
1.3.8	Cardio-CT/MR	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-		
1.4.1	GSP	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-		
1.5.1	ASS	X	X	X		-	-	-	-	-	-	-	-	X	-	-	X		
1.5.2	Duale AT	X	X	-		-	-	-	-	-	-	-	-	-	-	X	-		
1.6.1	Physiotherapie	X	X	X		-	-	-	-	-	-	-	-	-	-	-	X		
1.6.2	Ergotherapie	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-		
1.6.3	Logopädie	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-		
2.1.1	Lyse rtPA <4,5h	X	X	X	-	-	-	-	-	-	-	-	-	X	-	-	X	X	
2.1.2	Lyse rtPA > 80J	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	
2.1.3	Lyse rtPA 4,5-9	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	
2.1.4	Lyse rtPA wake up	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	
2.1.5	Lyse Tenecteplase	X	-	X	-	-	-	X	-	-	-	-	-	-	-	-	-	X	
2.1.6	Lyse rtPA 0,6mg	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	
2.1.7	Sonolyse	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	
2.1.8	Lyse rtPA minor stroke	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
2.1.9	Lyse rtPA major stroke	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
2.1.10	Lyse rtPA Hypertonus	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
2.2.1	EST <6Std	X	X	X	-	-	-	X	-	-	-	-	-	-	-	X	-	X	
2.2.2	EST bis 24Std	X	X	X	-	-	-	X	-	-	-	-	-	-	-	X	-	X	
2.2.3	Bridging	X	X	X	-	-	-	X	-	-	-	-	-	-	-	-	-	X	X
2.2.4	EST >80J	X	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	
2.2.5	EST TIC1	X	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	
2.2.6	EST Sedierung	X	-	X	-	-	-	X	-	-	-	-	-	-	-	-	-	-	
2.2.7	EST Blutdruck	X	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	
2.2.8	EST Basilaris	X	X	X	-	-	-	X	-	-	-	-	-	-	-	X	-	-	
3.1.1	DCS, supratent. ≤60y	X	-	X	-	-	-	-	-	-	-	-	-	X	-	-	-	X	
3.1.2	DCS, supratent. >60y	X	-	X	-	-	-	-	-	-	-	-	-	X	-	-	-	X	
3.1.3	DCS, infratentoriell	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
3.2.	Hypothermie	X	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	
3.3	Osmotherapie	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	
3.4	Andere Maßnahmen	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	

Die Empfehlungen und Stellungnahmen zu den einzelnen Schlüsselfragen wurden unter Berücksichtigung der zugrundeliegenden Evidenz in Form einer Leitlinien-Synopse zusammengefasst (Anhang 8.2). Dabei wurden die in der Quell-Leitlinie verwendeten Referenzen an das Literaturverzeichnis dieser Leitlinie (Anhang 8.5) angepasst. Bei widersprüchlichen Empfehlungen wurden Leitlinien mit ähnlichem Hintergrund (Europa > Amerika > Australien > Asien) priorisiert.

Für Kapitel 1 wurden fünf Schlüsselfragen (1.1.13 Delir, 1.3.8 Cardio-CT/MRT, 1.4.1 Ganglion sphenopalatinum, 1.6.2 Ergotherapie, und 1.6.3 Logopädie) in keiner der Leitlinien bearbeitet. Zur Schlüsselfrage 1.6.1. (Physiotherapie) beziehen sich die meisten Empfehlungen der bisherigen Leitlinien auf frühe Mobilisation. Für zwei Schlüsselfragen (1.1.10 Antibiose, 1.3.4 Scores) gibt es nur jeweils eine Leitlinie, für die Schlüsselfragen zum apparativen und klinischen Monitoring (1.3.3. und 1.3.4) gab es in den externen Leitlinien als nicht hinreichend zu bewertende Stellungnahmen. Für Kapitel 2 fanden sich für die Schlüsselfragen 2.1.3 (Mismatch-basierte Thrombolyse), 2.1.4 (Wake Up Stroke), und 2.1.10 (Blutdruckmanagement) in den externen Leitlinien keine ausreichenden Informationen zur Beantwortung; für Kapitel 3 traf dies auf die Schlüsselfrage 3.2 (Hypothermie) zu.

### 3.1.4. Systematische Literaturrecherche

Falls eine Schlüsselfrage nicht ausreichend anhand der externen Leitlinien beantwortet werden konnte, erfolgte eine systematische Literatursuche nach weiterer Evidenz unter Verwendung der Datenbanken von MedLine (<https://pubmed.ncbi.nlm.nih.gov/>), WebOfScience ([www.webofknowledge.com](http://www.webofknowledge.com)), Cochrane ([www.cochranelibrary.com](http://www.cochranelibrary.com)) und der AWMF ([www.awmf.org](http://www.awmf.org)).

In Anbetracht der Anzahl der zu bearbeitenden Schlüsselfragen erfolgte keine zentrale Literatursuche, sondern jeder Kapitelverantwortlicher führte diese – nach vorheriger methodischer Absprache – selbst durch. Zunächst erfolgte gemäß der in Kapitel 3.1.2 beschriebenen Hierarchie eine Suche nach systematischen Übersichtsarbeiten / Meta-Analysen und falls auch diese nicht vorhanden waren, wurde nach randomisierten Studien (RCTs) gesucht.

Die Suchalgorithmen zu den einzelnen Schlüsselfragen sind in Anhang 8.3 wiedergegeben.

Da nach der Publikation der ESO-Leitlinie zu systemischen Thrombolysetherapie weitere Studien zur Schlaganfalltherapie mit Tenecteplase publiziert worden waren, erfolgte für das Amendement „Oktober 2022“ eine aktualisierte systematische Literatursuche (Details siehe in Kapitel 8.3) und mit entsprechender Begründung eine metaanalytische Beurteilung einer selektierten Patientenpopulation (siehe Langfassung der Leitlinie für Details).

### 3.1.5. Bewertung der Evidenz

Die auf diese Weise gefundenen Arbeiten wurden mit einem strukturiertem Bewertungsbogen (siehe Abbildung 2) bewertet.

Erhebungsbogen für Systematische Übersichtsarbeiten (Reviews)		Erhebungsbogen für Diagnostische Studien		Erhebungsbogen für Therapiestudien	
Studie		Studie		Studie	
Bearbeiter		Bearbeiter		Bearbeiter	
Ausschluss	nein <input type="checkbox"/> ja <input type="checkbox"/>	Ausschluss	nein <input type="checkbox"/> ja <input type="checkbox"/>	Ausschluss	nein <input type="checkbox"/> ja <input type="checkbox"/>
Begründung		Begründung		Begründung	
<b>I. Beschreibung des Reviews</b>		<b>I. Beschreibung der Studie</b>		<b>I. Beschreibung der Studie</b>	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)?		1. Welche diagnostische Intervention wurde untersucht (Prüfzeit)?		1. Welche Intervention wurde untersucht?	
2. Welche Interventionen sind betrachtet/untersucht worden?		2. Wie viele Studienteilnehmer wurden eingeschlossen?		2. Welche Zielkriterien (Endpunkte) wurden bestimmt?	
3. Welche Zielkriterien (Endpunkte) wurden bestimmt?		3. Wie war die Studienpopulation definiert?		3. Wie viele Studienteilnehmer (gesamt und pro Studienarm, bzw. Gruppe)?	
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basivariablen - z.B. Alter, Schweregrad der Erkrankung, Geschlechtsverteilung, Risiken - z.B. relevante Begleiterkrankung)?		a) Einschlusskriterien: b) Ausschlusskriterien:		4. Wie war die Studienpopulation definiert?	
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?		4. Was waren die Charakteristika der Studienpopulation (Basivariablen - z.B. Alter, Schweregrad der Erkrankung, Geschlechtsverteilung, Risiken - z.B. relevante Begleiterkrankung)?		a) Einschlusskriterien: b) Ausschlusskriterien:	
<b>II. Interne Validität</b>		5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?		5. Was waren die wichtigsten Charakteristika der Studienpopulation (Basivariablen - z.B. Alter, Schweregrad der Erkrankung, Geschlechtsverteilung, Risiken - z.B. relevante Begleiterkrankung)?	
1. Ist die Fragestellung angemessen und klar eingegrenzt?		6. Mit welchem Referenztest wurde der Prüftest verglichen?		6. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?	
2. Ist die Literatursuche angemessen beschrieben?		7. Wie waren die Teilnahmequoten (N-Angabe oder Angabe der Anzahl der drop-out-Fälle)?		7. Wie waren die Teilnahmequoten (N-Angabe oder Angabe der Anzahl der drop-out-Fälle)?	
3. Wurde die Qualität der eingeschlossenen Studien ermittelt?		a) In so großem diagnostischen Test: b) Im Referenztest:		8. Wurde ein prospektives Design verwendet?	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		1. Wurde ein prospektives Studiendesign verwendet?		9. Wurden die Ein- und Ausschlusskriterien eindeutig definiert?	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Interventionen?		2. Wurden die Ein- und Ausschlusskriterien eindeutig definiert?		10. Waren die Teilnehmer der Studie einseitig definiert und adäquat erhoben?	
6. Was es sinnvoll, die für dieses Review ausgewählten Studien miteinander zu kombinieren?		3. Wurde die Randomisierung geheim gehalten (allocation concealment)?		11. Wurden die Gruppen, mit Ausnahme der Prüf-Intervention, gleich behandelt?	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		4. War die Studienpopulation repräsentativ?		12. Wurden Nebenwirkungen dokumentiert?	
Gesamtbewertung		5. Wurde der zu prüfende diagnostische Test mit einem ein äquivalenten, validen Referenztest („gold-Standard“) verglichen?		13. Wurden alle Probanden in der Gruppe ausgewertet, die der ursprünglich zugeordnet waren (intention-to-treat-Prinzip)?	
<b>III. Ergebnisse</b>		6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?		14. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	
<b>IV. Ableitbare Empfehlung</b>		7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?		Gesamtbewertung	
Bemerkungen:		8. Wurden Prüftest und Referenztest zeitlich aufeinander folgend durchgeführt?		<b>III. Ergebnisse</b>	
		9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?		<b>IV. Ableitbare Empfehlung</b>	
		10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		Bemerkungen:	
		11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht: b) wenn nein, lassen sich diese errechnen (z. B. Felder, Tafel vollständig abbildbar)?			
		12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?			
		Gesamtbewertung			
		<b>III. Ergebnisse</b>			
		<b>IV. Ableitbare Empfehlung</b>			
		Bemerkungen:			

**Abbildung 2:** Bewertungsbögen für systematische Übersichtsarbeiten, Diagnostik- und Therapiestudien

Publikationen, die thematisch zur Schlüsselfrage passen und bei der Bewertung mit ‚+‘ oder ‚++‘ bewertet wurden, konnten zur Beantwortung der Schlüsselfrage verwendet werden. Falls eine Publikation nicht weiterverwendet werden konnte, wurde in dem Bewertungsbogen der Ausschlussgrund angegeben. Auch die Bewertungsbögen der einzelnen Arbeiten sind in Anhang 8.3 wiedergegeben.

## 3.2. FORMULIERUNG DER EMPFEHLUNGEN UND STRUKTURIERTE KONSENSFINDUNG

### 3.2.1. Berücksichtigung von Nutzen, Nebenwirkungen, relevanten Outcomes

In Anbetracht der Vielzahl zu bewertender Verfahren ist die Betrachtung eines einheitlichen Endpunktes nicht möglich. Für die meisten Schlüsselfragen wurde als primärer Endpunkt das **funktionelle klinische Outcome** (Ergebnis) untersucht. Dieses wird in der Schlaganfallmedizin meist anhand der modifizierten Rankin-Skala (mRS) bestimmt [25, 26]. Am gebräuchlichsten ist in RCTs die Bestimmung der mRS nach drei Monaten, seltener werden andere Zeitpunkte bewertet.

**Tabelle 6:** Beschreibung der modifizierten Rankin-Skala [25, 26]

CODE	BESCHREIBUNG
0	Keine Symptome
1	Keine relevante Beeinträchtigung. Kann trotz gewisser Symptome Alltagsaktivitäten verrichten.
2	Leichte Beeinträchtigung. Kann sich ohne Hilfe versorgen, ist aber im Alltag eingeschränkt.
3	Mittelschwere Beeinträchtigung. Benötigt Hilfe im Alltag, kann aber ohne Hilfe gehen.
4	Höhergradige Beeinträchtigung. Benötigt Hilfe bei der Körperpflege, kann nicht ohne Hilfe gehen.
5	Schwere Behinderung. Bettlägerig, inkontinent, benötigt ständige pflegerische Hilfe.
6	Tod infolge des Apoplex

Bei einzelnen Schlüsselfragen wurde auch die **Letalität** (entweder während des Krankenhausaufenthaltes oder ebenfalls nach drei Monaten) untersucht. Bei den Schlüsselfragen zu den Rekanalisationstherapien spielte zur Einschätzung des Komplikationsrisikos das Auftreten von sekundären **Einblutungen** eine Rolle, hierzu wird die Heidelberg-Bleeding-Classification verwendet [27].

**Tabelle 7:** Beschreibung der Heidelberg-Bleeding-Classification (modifiziert nach [27])

CODE	TYP	BESCHREIBUNG
1		Hämorrhagische Transformation von infarziertem Hirngewebe
1a	HI1	Einzelne kleine Petechien, kein Raumforderungseffekt
1b	HI2	Konfluierende Petechien, kein Raumforderungseffekt
1c	H1	Hämatom im Infarkt (<30% der Infarktgröße), kein relevanter Raumforderungseffekt
2		Intrazerebrale Blutung inner- oder außerhalb des infizierten Hirngewebes
	PH2	Hämatom im Infarkt (mind. 30% des infarzierten Gewebes), mit offensichtlichem Raumforderungseffekt
3		Intrazerebrale Blutung außerhalb des infizierten Hirngewebes oder intrakranielle-extrazerebrale Blutung
3a		Parenchymlutung außerhalb des Hirninfarktes
3b		Intraventrikuläre Blutung
3c		Subarachnoidalblutung
3d		Subduralhämatom

Bei Schlüsselfragen zur frühen Sekundärprävention wurde auch die Häufigkeit von **Schlaganfall-rezidiven** beurteilt.

### 3.2.2. Formulierung der Empfehlungen und Vergabe von Evidenzgraden und/ oder Empfehlungsgraden

Nach Selektion der relevanten Literatur (siehe Anhang 8.3) wurde in Anlehnung an eine 2011 publizierte Evidenzgraduierung nach Oxford je nach Art der zugrundeliegenden Literatur ein Evidenzlevel vergeben [28].

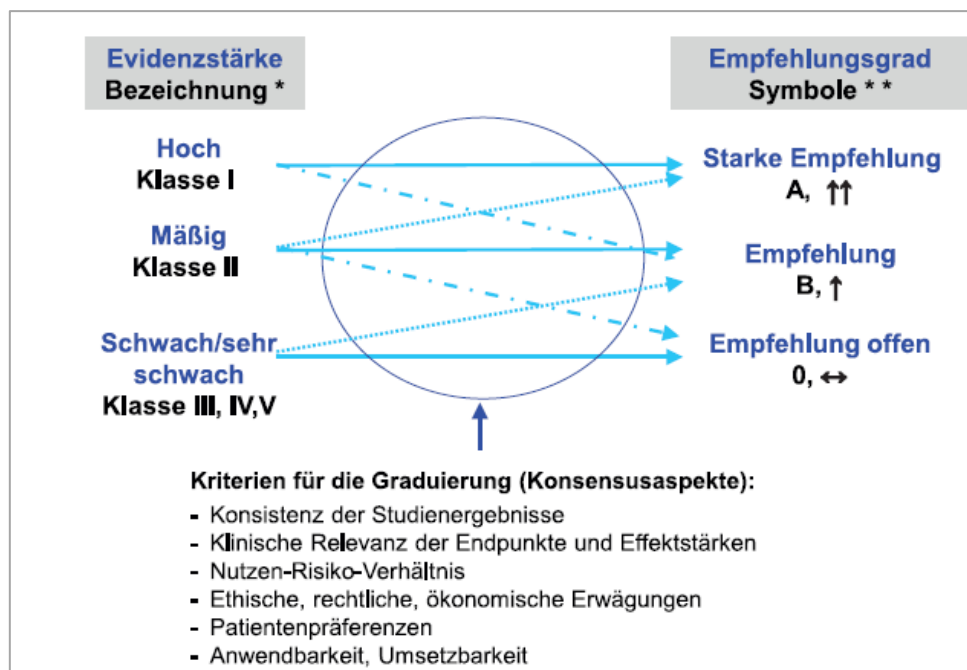
**Tabelle 8:** Evidenzlevel nach der Oxford-Klassifizierung in der Version von 2011 (nach [28])

CODE	EVIDENZLEVEL
1	Metaanalysen oder systematische Reviews (SRs) randomisierter kontrollierter Studien (RCTs) bzw. einzelne RCTs
2	SRs von Kohortenstudien bzw. einzelne Kohortenstudien
3	SRs von Fall-Kontrollstudien bzw. einzelne Fall-Kontrollstudien
4	Fallserien
5	Expertenkonsens, vormals Good clinical practice

Die Autoren erstellten auf Basis dieser Evidenz dann die Textabschnitte und formulierte Empfehlungen. Zur Vereinfachung und besseren Übersicht werden aus den Evidenzstufen die „Stärke der Empfehlung“ (stark bis schwach) abgeleitet. In der Regel führt ein bestimmter Evidenzlevel zu einer bestimmten Empfehlungsstärke. Abweichungen sind jedoch möglich (siehe Abbildung 3), werden dann aber im Einzelfall begründet.

**Tabelle 9:** Codierung und textliche Beschreibung der Empfehlungsstärke

CODE	EMPFEHLUNGSSTÄRKE	SYNTAX
↑↑	starke Empfehlung	soll   soll nicht
↑	Empfehlung	sollte   sollte nicht
↔	Empfehlung offen	kann   kann verzichtet werden
EK	Expertenkonsens	



**Abbildung 3:** Zuordnung von Evidenzstärke zu einem Empfehlungsgrad, modifiziert nach den Kriterien des Oxford Centre of Evidence based Medicine (2011), empfohlen und herausgegeben von der AWMF

### 3.2.3. Formale Konsensfindung: Verfahren und Durchführung

Die Empfehlungen wurden zunächst im Umlaufverfahren abgestimmt. Zur Erhaltung der Unabhängigkeit der Mitglieder der Leitliniengruppe wurde zunächst in einem modifizierten DELPHI-Verfahren Zustimmung, Ablehnung oder Enthaltung zu jeder Empfehlung und jedem Statement erhoben. Nach Überarbeitung der Empfehlungen ohne vollständigen Konsens erfolgte eine zweite anonymisierte DELPHI-Runde (unter Verwendung von Google-Forms). Nach Einarbeitung der Hinweise aus beiden DELPHI-Runden wurde eine - wegen der COVID-19 Pandemie - virtuelle Konsensuskonferenz abgehalten. Weitere Modifikationen der Empfehlungen sowie der Fließtext wurden im eMail-Umlauf verabschiedet.

Zur Feststellung der Konsensstärke wurde bei allen DELPHI-Runden sowie bei Abstimmungen während der Konsensuskonferenzen die absolute Anzahl der Ja-Stimmen, der Nein-Stimmen und der Enthaltungen dokumentiert. Der Grad der Zustimmung wurde als prozentualer Anteil der Ja-Stimmen an allen Ja- und Nein-Stimmen berechnet (d.h. Enthaltungen ging nicht in die Bestimmung der Konsensstärke ein). Die Konsensstärke wurde gemäß folgender Tabelle klassifiziert:

KONSENSSTÄRKE	ZUSTIMMUNG <sup>1</sup>
<b>Starker Konsens</b>	>95%
<b>Konsens</b>	>75-95%
<b>Mehrheitliche Zustimmung</b>	>50-75%
<b>Kein Konsens</b>	≤50%

1: Zustimmung = Anzahl Ja-Stimmen / (Anzahl Ja-Stimmen + Anzahl Nein-Stimmen)

Empfehlungen und Statements wurden so lange überarbeitet, bis sie mit ‚Konsens‘ oder ‚starkem Konsens‘ verabschiedet werden konnten. Von 116 Empfehlungen und 28 Statements wurden 128 (89%) mit 100%iger Übereinstimmung verabschiedet, bei 10 Empfehlungen und Statements lag die Zustimmungsquote bei 93%, und bei den übrigen zwischen 80 und 87%. Die folgende Tabelle gibt einen

Überblick, welche evidenzbasierten Empfehlungen der Schlüsselfragen mit welcher Konsensstärke verabschiedet wurden.

**Tabelle 10:** Übersicht der Konsensusstärke der Empfehlungen der einzelnen Schlüsselfragen

SCHLÜSSELFRAGE	EMPFEHLUNG	KONSENSSTÄRKE
SF 1.1.1	B	Starker Konsens
SF 1.1.2	A, B	
SF 1.1.3	A, C, D, E	
SF 1.1.4	A, B, C, D	
SF 1.1.5	A, B, C, E, F, G	
SF 1.1.6	D	
SF 1.1.7	A, B, C	
SF 1.1.8	A, B, C, D, E, F, J	
SF 1.1.9	G, H, I	
SF 1.1.10	A	
SF 1.1.11	A	
SF 1.1.12	B	
SF 1.1.13	A, B, C, D, E	
SF 1.2.1	A	
SF 1.2.3	A, B, C	
SF 1.3.1	A, B	
SF 1.3.2	A, B, C, D	
SF 1.3.3	A, B, C	
SF 1.3.4	A	
SF 1.3.5	A	
SF 1.3.6	B, C, D	
SF 1.3.7	E	
SF 1.3.8	F	
SF 1.4.1	A	
SF 1.5.1	A, B, C, D	
SF 1.5.2	E	
SF 1.5.3	G, H, I	
SF 1.6.1	C	
SF 1.6.2	A	
SF 2.1.1	A, B, D	
SF 2.1.2	C	
SF 2.1.3	A	
SF 2.1.4	B	
SF 2.1.5	A (Mod 22), B-C (Neu22)	
SF 2.1.7	A	
SF 2.1.8	A, B	
SF 2.1.10	A, B	
SF 2.2.1	A, B, C, E	
SF 2.2.2	D	
SF 2.2.3	A (Mod22), B-D (Neu22),	
SF 2.2.4	A, B	
SF 2.2.5	A	

SCHLÜSSELFRAGE	EMPFEHLUNG	KONSENSSTÄRKE
SF 2.2.6	B	
SF 2.2.7	C, D, E	
SF 2.2.8	A	
SF 3.1.1	A, B, C	
SF 3.1.2	D	
SF 3.1.3	F, G	
SF 3.2	H, I	
Kap 4	A	
SF 1.1.1	A	Konsens
SF1.1.3	B	
SF 1.2.2	B	
SF 1.3.7	F	
SF 1.5.2	F	
SF 1.6.1	A, B	
SF 2.1.6	A	
SF 3.3	J	

Für Empfehlung der Arbeitsgruppe ohne Evidenzbelegung (sog. Statements) wird die Konsensusstärke, ermittelt nach dem gleichen Algorithmus, direkt im Text angegeben.

Von der Möglichkeit der Formulierung eines Sondervotum bei fehlende Zustimmung zu einer Empfehlung wurde kein Gebrauch gemacht.

Dieses Konsensus-Verfahren wurde auch für das Amendment „Oktober 2022“ beibehalten. Die veränderten Empfehlungen der SF 2.1.5 und 2.2.3 wurden – im Unterschied zur Ursprungsfassung in Version 5.0 - jeweils mit starkem Konsens in der Leitliniengruppe abgestimmt.

## 4. EXTERNE BEGUTACHTUNG UND VERABSCHIEDUNG

### 4.1. PILOTTESTUNG

Zur Steigerung der Akzeptanz einer Leitlinie wird empfohlen vor einer umfassenden Implementierung der Leitlinie eine Pilotstudie innerhalb der Anwendergruppe oder mindestens eines repräsentativen Teils der Anwendergruppe durchzuführen (DELBI-Domäne 7). Aufgrund der Komplexität der Leitlinie, der großen Anzahl besprochener Interventionen und der erheblichen personellen und finanziellen Ausmaßes einer derartigen Implementierungsstudie wurde von einer solchen Testung vor Verabschiedung der Leitlinie abgesehen.

### 4.2. EXTERNE BEGUTACHTUNG

Die Leitlinie wurden zur externen Begutachtung von mehreren externen Experten bewertet. Kriterien für die Auswahl der Reviewer waren: fachliche Expertise, Unabhängigkeit von der Leitliniengruppe, aktuell nicht im Vorstand einer beteiligten Fachgesellschaft, Frauen und Männer, Deutsche und Nicht-Deutsche, Neurologen und Neuroradiologen. Die Leitliniengruppe fragte bei fünf Kollegen an, die alleamt ihre Bereitschaft zur Erstellung einer Beurteilung erklärten. Die Namen und Institutionen der externen Reviewer sind in der folgenden Tabelle gelistet.



**Tabelle 11:** Auflistung der externen Reviewer

Name	Position
Frau Prof. Dr. Valeria Caso	Leiterin der Schlaganfallabteilung der Universität von Perugia
Herr Prof. Dr. Frank Erbguth	Chefarzt der Neurologischen Klinik des Klinikums Nürnberg
Herr Prof. Dr. Rüdiger von Kummer	Emeritus Neuroradiologie Universität Dresden
Herr Prof. Dr. Thomas Liebig	Direktor der Neuroradiologie LMU München
Herr Prof. Dr. Patrick Michel	Associate Professor Neurologie Université de Lausanne

Ergänzungs- und Veränderungsvorschläge aus den externen Bewertungen wurden in der Leitliniengruppe diskutiert und im Falle eines starken Konsenses berücksichtigt. Als Folge des externen Review-Prozesses wurde eine neue Empfehlung formuliert (SF 1.1.5, Nr. B) und die Empfehlungen zu den Schlüsselfragen 1.1.3 (Nr. C), 1.1.4 (Nr. C), 1.3.3 (Nr. B), 1.3.6 (Nr. B), 1.6.1. (Nr. A), 2.2.8 (Nr. A), 3.1.2 (Nr. D) inhaltlich gering modifiziert.

Das Amendment „Oktober 2022“ wurde keiner externen Begutachtung unterzogen.

#### **4.3. VERABSCHIEDUNG DURCH DIE VORSTÄNDE DER HERAUSGEBENDEN FACHGESELLSCHAFTEN/ORGANISATIONEN**

Schließlich wurden diese Empfehlungen und der Text von der Kommission Leitlinien der Deutschen Gesellschaft für Neurologie (DGN), dem Vorstand der DGN, sowie von den Vorständen der Deutschen Schlaganfall-Gesellschaft (DSG) und der anderen Fachgesellschaften beurteilt. Auch hierbei gab es inhaltliche Anregungen, die erneut im Umlaufverfahren bearbeitet wurden. Die finale Version (Stand 17.05.2021) wurde von den Vertretern aller Fachgesellschaften freigegeben. Es handelt sich um somit um gemeinsame Empfehlungen der beteiligten Fachgesellschaften.

Die Vorstände der DSG und DGN stimmten dem Inhalt des Amendments „Oktober 2022“ zu. Die Vorstände weiterer Fachgesellschaften wurde nur dann involviert, falls der Delegierte dies für notwendig hielt. In Anbetracht der geringen Änderungen durch das Amendment wurde dies aber in keinem Fall für notwendig erachtet.

### **5. REDAKTIONELLE UNABHÄNGIGKEIT**

#### **5.1. FINANZIERUNG DER LEITLINIE**

Es erfolgte keine finanzielle Unterstützung von pharmazeutischen Unternehmen oder anderen Unternehmen des Gesundheitswesens.

Alle Autoren arbeiteten unentgeltlich. Fahrkosten, die im Rahmen der Leitlinienentwicklung entstanden, wurden von den einzelnen Fachgesellschaften getragen.

#### **5.2. DARLEGUNG VON UND UMGANG MIT POTENZIELLEN INTERESSENKONFLIKTEN**

Alle Mitwirkenden an der Leitlinie haben ihre Interessenerklärungen (AWMF-Formular zur Erklärung von Interessen im Rahmen von Leitlinienvorhaben; zuletzt in der Version 23.05.2018) zu Beginn der Tätigkeit in der Leitliniengruppe und vor der Konsensuskonferenz aktualisiert und vollständig ausgefüllt eingereicht. Im Formblatt wurden die Ausfüllenden gebeten, bei den dargelegten Interessen mit anzugeben, ob ein thematischer Bezug zur Leitlinie/zum Leitlinienthema besteht. Bei

unvollständigen Angaben wurden Nachbesserungen eingefordert. Abgefragt wurde auch die Höhe der Bezüge, die jedoch nicht veröffentlicht werden. Alle Interessenerklärungen wurden von den Sekretären Ch. Hametner, F. Benedikt, die als nicht stimmberechtigte „Interessenkonfliktbeauftragte“ fungierten, und per Diskussion in der Leitliniengruppe geprüft. Eine Selbsteinschätzung fand nicht statt.

Für das Amendment „Oktober 2022“ wurden die Erklärungen der Autoren des Amendments und der Kapitelautoren, die an der Abstimmung des Amendments beteiligt wurden, zu potentiellen Interessenskonflikten aktualisiert und bei relevanten Änderungen erneut bewertet.

Gemäß dem Algorithmus der AWMF (aktuelle Version 2.4 vom 17.01.2018)<sup>1</sup> erfolgte die Einschätzung potenzielle Interessenskonflikte in „gering“, „moderat“ oder „hoch“ anhand Art und Höhe der Zuwendung, dem Empfänger (Institution oder persönlich), sowie Art, Intensität und Dauer einer Beziehung zu Unternehmen der Gesundheitswirtschaft. Für die Höhe der Zuwendung galt, dass persönlich erhaltene jährliche Beträge bis 1000€ als gering, 1001-5000€ als moderat und ab 5000€ als hoch klassifiziert wurden. Hauptamtliche Mitarbeiter von Unternehmen der Gesundheitswirtschaft waren von der Entwicklung der Leitlinie ausgeschlossen.

Folgende Kriterien/Angaben wurden im Hinblick auf einen vorliegenden thematischen Bezug, die absolute Höhe der Bezüge sowie die Art und die Intensität der Beziehung geprüft:

- Gutachter-/Beratertätigkeit: bezahlte Gutachter-/Beratertätigkeit
- Mitarbeit in einem wissenschaftlichen Beirat/Advisory Board
- Vorträge
- Autoren- oder Ko-Autorenschaft
- Forschungsvorhaben/Durchführung klinischer Studien/Eigentümerinteressen (Patente, Aktienbesitz)
- Indirekte Interessen (Mitgliedschaft/Funktion in Interessenverbänden, Schwerpunkte wissenschaftlicher und klinischer Tätigkeiten)

Die DGN hatte 2019 unabhängig von diesem Verfahren die potenziellen Interessenskonflikte ihrer Delegierten (und auch die der DSG) geprüft<sup>2</sup>. Aufgrund von Zuwendungen der Fa. Boehringer Ingelheim an die Institution von P. Ringleb zur Durchführung der ECASS4-Studie zu Actilyse® wurden dessen Interessenskonflikte als hoch eingeschätzt, so dass M. Köhrmann als Ko-Koordinator benannt wurde. Da die Finanzierung der ECASS4-Studie, deren finanzielle Unterstützung der Universitätsklinik Heidelberg bei der Bewertung der Interessenskonflikte 2019 seitens der DGN zur Empfehlung geführt hatte, dass Prof. Ringleb nicht an den Abstimmungen bzgl. Präparaten der Firma Boehringer Ingelheim teilnehmen sollte, seit über 5 Jahren abgeschlossen ist, war Prof. Ringleb wieder voll in Entwurf und Abstimmung der Empfehlungsaktualisierung beteiligt.

Gemäß dem Reglement der AWMF fungierten Leitliniengruppenmitglieder mit mind. geringen potenziellen Interessenskonflikten nicht als Kapitelverantwortlicher und waren nicht in führender Position an der Evidenzgewinnung beteiligt. Autoren mit moderaten Konflikten wurden instruiert an Abstimmungen zu Empfehlungen, bei denen konfliktbehaftete Präparate oder Medizinprodukte

---

<sup>1</sup> [www.awmf.org/leitlinien/awmf-regelwerk/II-entwicklung/awmf-regelwerk-01-planung-und-organisation/po-interessenkonflikte.html](http://www.awmf.org/leitlinien/awmf-regelwerk/II-entwicklung/awmf-regelwerk-01-planung-und-organisation/po-interessenkonflikte.html)

<sup>2</sup> Eine Vorgabe der Deutschen Gesellschaft für Neurologie (DGN) sieht seit Mai 2014 vor, dass für eine ausgewogene Zusammensetzung der Leitliniengruppe mindestens 50% der an der Leitlinie Beteiligten keine oder nur geringe für die Leitlinie relevanten Interessenskonflikte haben dürfen. Die DGN hat sich zur Einführung der 50%-Regel entschieden, weil damit bei Abstimmungen kein Überhang von Partikularinteressen entstehen kann

vorkamen, nicht teilzunehmen. Die Sekretäre der Leitliniengruppe achteten darauf, dass bei der Konsensuskonferenz diese Regel eingehalten wurde.

Die dargelegten Interessen der Beteiligten (zuletzt aktualisiert Sept. 2022) sind in der tabellarischen Zusammenfassung im Anhang 8.1 aufgeführt. Wegen der Implementierung eines Ko-Koordinators, der ausgewogenen Verteilung der Kapitelverantwortlichen und anhand der Bewertung dieser Tabelle kam die Leitliniengruppe zur Auffassung, dass wegen der Ausgewogenheit der Leitliniengruppe, des Pluralismus der Interessen und der ergriffenen Maßnahmen zur Reduktion des Bias-Risikos die Leitliniengruppe im gesamten Prozess der Leitlinienerstellung arbeitsfähig war.

## 6. VERBREITUNG UND IMPLEMENTIERUNG

Medizinische Leitlinien sind urheberrechtlich als Gemeinschaftswerk anzusehen. Entsprechend der Zielsetzung und den Maßgaben der Leitlinienentwicklung der Fachgesellschaften und der AWMF sollen sie über die AWMF und die Präsidien der Fachgesellschaften in Fachkreisen und bei den Patienten Verbreitung finden. Die S2e-Leitlinie „Akuttherapie des ischämischen Schlaganfalls“ wird als Langversion und einer zusammenfassenden Kurzversion einschließlich dieses Methodenreports kostenfrei über die Internetseite der AWMF, und einiger Fachgesellschaften (zumindest DGN und DSG) zur Verfügung gestellt werden. Darüber hinaus ist die Publikation, z.B. im Deutschen Ärzteblatt, vorgesehen.

Erstmalig für eine Leitlinie der DSG wurde mit Unterstützung der Stiftung Deutsche Schlaganfallhilfe und des Patientenrates der neurologischen Universitätsklinik Heidelberg eine Patientenversion dieser Leitlinie erstellt und im Sept. 2021 veröffentlicht. Diese wurde im Rahmen des Amendments „Oktober 2022“ an einer Stelle modifiziert, worüber die Leitlinien-Gruppe in Kenntnis gesetzt wurde.

Zur Unterstützung des Ziels der weiteren Verbreitung wurden in einer vertraglichen Vereinbarung zwischen den Leitlinienkoordinatoren und dem Vorstand der DGN sowie der AWMF die Nutzungsrechte unentgeltlich übertragen. Die Autoren als Urheber verstehen dies als ihren ehrenamtlichen Beitrag zur Verwirklichung der satzungsmäßigen Ziele der AWMF und der beteiligten Fachgesellschaften.

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 die Einbindung der Leitlinienempfehlungen in einrichtungsinterne Behandlungspfade (Stroke Unit SOPs) sowie die Berücksichtigung der Leitlinie in lokalen Patienteninformationen/Broschüren empfohlen.

Die Verbreitung und Implementierung wird von der Leitliniensteuergruppe aktiv unterstützt durch Vorstellung der Leitlinie im Rahmen von Fachkongressen der beteiligten Gesellschaften und Organisationen und Unterstützung der Erstellung von Materialien für die kontinuierliche Fort- und Weiterbildung (CME-Beiträge entsprechend der Anforderungen der Landesärztekammern).

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.

Mit diesen Empfehlungen wird eine Verknüpfung der Leitlinie mit zertifizierten Fortbildungsmaßnahmen und Qualitätsmanagementsystemen angestrebt. Die begleitende Evaluierung der Leitlinien-

Implementierung ist ein wichtiges Anliegen. Für den akuten Schlaganfall existieren eine Reihe von multizentrischen Qualitätssicherungsmaßnahmen, die von der Arbeitsgemeinschaft deutschsprachiger Schlaganfallregister (ADSR, [www.schlaganfallregister.org](http://www.schlaganfallregister.org)) koordiniert werden. Es wird eine enge Abstimmung mit diesen Registern angestrebt.

## 7. GÜLTIGKEIT UND AKTUALISIERUNGSVERFAHREN

Datum der letzten inhaltlichen Überarbeitung: 09.11.2022

Datum der letzten formalen Änderungen: 09.11.2022

Gültig bis: Mai 2024

Die Notwendigkeit zu vorzeitigen Ergänzungen wird von den Vorständen der DGN und DSG, sowie den Leitlinienkoordinatoren (Prof. Dr. Peter A. Ringleb und Prof. Dr. Martin Köhrmann) fortwährend überprüft. Im Mai 2022 beauftragte der Vorstand der DSG die Leitliniengruppe mit der Überarbeitung der Schlüsselfrage 2.1.5 zur systemischen Thrombolyse mit alternativen Thrombolytika und der Schlüsselfrage 2.2.3 zur Kombination von systemischer Thrombolyse und endovaskulärer Schlaganfalltherapie, nachdem neue Studien hierzu publiziert worden waren und ein Produktionsengpass von Alteplase angekündigt worden war. Dieses Amendment Oktober 2022 führt zur Version 5.1 der Leitlinie

Ein Jahr vor Ablauf der oben genannten Frist, werden die Vorstände der DGN und DSG die Aktualisierung in Auftrag geben. Darüber hinaus sind alle Leser dieser Leitlinie nachdrücklich aufgefordert, Vorschläge zu Ergänzungen (z.B. neue zu bearbeitende Themenkomplexe) an die Autoren (Kontakt siehe Leitlinienbüro) oder per E-Mail an [Leitlinien@dgn.org](mailto:Leitlinien@dgn.org) zu senden.

## 8. ANHANG

### 8.1. INTERESSENANZEIGE DER AUTOREN

#### Tabelle zur Erklärung von Interessen und Umgang mit Interessenkonflikten zur Leitlinie "Akuttherapie des ischämischen Schlaganfalls"

Im Folgenden sind die Interessenerklärungen der Leitliniengruppen-Mitglieder (Stand 12.01.2021 bzw. für das Amendments Okt 2022 Stand 07.09.2022) und der externen reviewer (Stand 18.03.2021) als tabellarische Zusammenfassung dargestellt, sowie die Ergebnisse der Interessenkonfliktbewertung und Maßnahmen, die nach Diskussion der Sachverhalte von der LL-Gruppe beschlossen und im Rahmen des Konsensusverfahrens umgesetzt wurden.

Mitglied der LL-Gruppe (Stand 12.01.2021 bzw. 07.09.2022)	Berater- bzw. Gutachter- tätigkeit	Mitarbeit in einem wissen- schaftlichen Beirat (advisory board)	Bezahlte Vor- trags-/oder Schulungs-tätig- keit	Bezahlte Auto- ren-/oder Coau- toren-schaft	Forschungs- vorhaben/ Durchführung klinischer Studien	Eigentümer- interessen (Patent, Urheber- recht, Aktien- besitz)	Indirekte Interessen	Von COI betroffene Themen / SF der Leitlinie <sup>1</sup> (Einstufung bzgl. der Relevanz) Konsequenz
Berlis, Prof. Dr. A. (updated 07.11.2022)	Ja (bis 2020)	Ja (bis 2020)	Ja	Nein	Ja	Nein	Nein	2.2.5-2.2.7 Endovaskuläre Schlaganfalltherapie, technische Aspekte ( <b>moderat</b> ), Enthaltung aus Diskussion (V5.0)
Fischer, Prof. Dr. U.	Ja	Nein	Ja	Nein	Ja	Nein	Nein	2.2.5-2.2.7 Endovaskuläre Schlaganfalltherapie, technische Aspekte (gering),
Hametner, Dr. C.	Nein	Nein	Nein	Nein	Ja	Nein	Nein	Keine
Harloff, Prof. Dr. A.	Nein	Nein	Ja	Nein	Nein	Nein	Nein	1.5.1, 1.5.2. Frühe antithrombotische Sekundärprävention (gering)
Jansen, Prof. Dr. O. (updated 07.11.2022)	Ja	Nein	Nein	Nein	Ja	Nein	Nein	2.2.5-2.2.7 Endovaskuläre Schlaganfalltherapie, technische Aspekte (gering)
Köhrmann, Prof. Dr. M. (updated 07.09.2022)	Nein	Ja	Ja	Nein	Ja	Nein	Nein	1.1.1 Anwendung von Screening Tools (gering) 1.5.1, 1.5.2. Frühe antithrombotische Sekundärprävention (gering), 2.1.1, 2.1.2 Systemische Thrombolyse (gering) 2.2.3 Bridging Therapie (gering)
Langguth, Dr. P.	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Laufs, Prof. Dr. U.	Ja	Ja	Ja	Nein	Nein	Nein	Nein	1.5.1, 1.5.2. Frühe antithrombotische Sekundärprävention (gering)
Mordasini, PD Dr. P. (updated 07.11.2022)	Nein	Nein	Ja	Nein	Ja	Nein	Nein	2.2.3 Bridging Therapie (gering)
Neumann-Haefelin, Prof. Dr. T. (Neu 07.09.2022)	Nein	Nein	Nein	Nein	Nein	Nein	Nein	keine

## Akuttherapie des ischämischen Schlaganfalls - AWMF Reg.-Nr. 030-046, Version 5.1

Ringleb, Prof. Dr. P.A. (updated 07.09.2022)	Nein	Ja	Ja	Nein	Ja	Nein	Nein	1.5.1, 1.5.2. Frühe antithrombotische Sekundärprävention (gering) 2.1.1-2.1.4. Systemische Thrombolyse (gering)
Schellinger, Prof. Dr. P.D. (updated 07.09.2022)	Ja	Ja	Ja	Nein	Nein	Nein	Ja	1.5.2 Duale antithrombotische Therapie ( <b>moderat</b> ) Enthaltung aus Diskussion 2.1.1.-2.1.4. Systemische Thrombolyse (gering) 2.2.3 Bridging Therapie (gering)
Schubert, Prof. Dr. G. (updated 07.11.2022)	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Sonnberger, Dr. M. (update 07.11.2022)	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Sykora, Prof. Dr. M.	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Urbach, Prof. Dr. H. (updated 07.11.2022)	Nein	Nein	Ja	Nein	Ja	Ja	Nein	1.3.1 Initiale Schnittbildgebung (gering) 1.3.2 Initiale Gefäßdiagnostik (gering) 2.1.1, 2.1.2. Frühe antithrombotische Sekundärprävention (gering) 2.2.5, 2.2.6 Endovaskuläre Schlaganfalltherapie, technische Aspekte (gering)
Wachter, Prof. Dr. R.	Nein	Ja	Ja	Nein	Ja	Nein	Nein	1.3.3, 1.3.6 Apparatives Monitoring (gering) 2.1.1, 2.1.2. Frühe antithrombotische Sekundärprävention (gering)
Wagner, M.	Ja	Nein	Ja	Nein	Nein	Nein	Nein	2.1.1, 2.1.2. Frühe antithrombotische Sekundärprävention (gering) 2.1.1-2.1.4. Systemische Thrombolyse (gering) 2.2.3 Bridging Therapie (gering)
Weiller, Prof. Dr. C.	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine

**1: In die tabellarische Zusammenfassung wurden hier 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.**

## Akuttherapie des ischämischen Schlaganfalls - AWMF Reg.-Nr. 030-046, Version 5.1

Reviewer (Stand 18.03.2021)	Berater-bzw. Gutachter- tätigkeit	Mitarbeit in einem Wissenschaftlich en 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
Caso, Prof. Dr. V	JA	JA (paid to institution)	JA (paid to institution)	JA	JA	JA	JA
Erbguth, Prof. Dr. F.	Nein	JA	JA	Nein	JA	Nein	Nein
Liebig, Prof. Dr. Th.	JA	Nein	JA	Nein	JA	JA	Nein
v. Kummer, Prof. Dr. R.	Nein	Nein	Nein	Nein	Nein	Nein	Nein
Michel, Prof. Dr. P.	JA (paid to institution)	Nein	Nein	Nein	JA	Nein	JA

## 8.2. LEITLINIEN-SYNOPSE

Ausgehend von der Kreuztabelle (siehe Tabelle 5 auf Seite 16) sind hier die Stellungnahmen der einzelnen Leitlinien in Bezug auf die jeweilige Schlüsselfrage zusammengefasst (zumeist in Englisch). Diese Auflistung wird auch als Evidenztabelle verwendet. Da die Leitlinien viele unterschiedliche Systeme zur Evidenz-Bewertungs- und -Graduierung verwenden, werden diese zum Vergleich mit der in dieser Leitlinie verwendeten System (siehe auch 3.1.5) in Kapitel 8.2.1 wiedergegeben.

### 8.2.1. Evidenzlevel und Empfehlungsstärken der externen Leitlinien

Oxford Centre of Evidence Based Medicine (OCEBM, in dieser Leitlinie verwendet)

#### Codierung des Evidenzlevels:

- 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

#### Codierung der Empfehlungsstärke

- ↑↑ starke Empfehlung („soll“)
- ↑ Empfehlung („sollte“)
- ↔ Empfehlung offen („kann“)
- EK Expertenkonsens

AHA 2018 [1]; AHA 2019 [11]:

#### Level (Quality) of evidence [LoE]:

- A high quality evidence from more than one RCT, meta-analyses of high quality RCTs, one or more RCTs corroborate by high-quality registry study
- B-R moderate-quality evidence from one or more RCTs, meta-analyses of moderate-quality RCTs
- B-NR moderate quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies
- C-LD randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subjects
- C-EO Consensus of expert opinion based on clinical experience

#### Grades of recommendation:

- I Strong; Benefit >>> Risk



- IIa Moderate; Benefit >> Risk
- IIb Weak; Benefit >/= Risk
- III No benefit (moderate); Benefit = Risk
- IV Harm (strong) Risk > Benefit

Canada 2018 [8]:

**Level of evidence [LoE]:**

- A Evidence from a meta-analysis of randomized controlled trials or consistent findings from two or more randomized controlled trials. Desirable effects clearly outweigh undesirable effects or vice versa
- B Evidence from a single randomized controlled trial or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies. Meta-analysis of non-randomized and/or observational studies. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa
- C Writing group consensus on topics supported by limited research evidence. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa, as determined by writing group consensus
- CC<sup>1</sup> Writing group consensus on topics supported by limited research evidence. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa, as determined by writing group consensus

1: Clinical consideration

ESPEN [29], NICE 2019 [24]:

**Level of evidence [LoE]:**

- 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
- 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
- 1– Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
- 2++ High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
- 2– Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.\*
- 3 Non-analytic studies (for example case reports, case series).
- 4 Expert opinion, formal consensus.

**Grades of recommendation [GOR]:**

- A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or  
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

- B A body of evidence including studies rated as 2++, directly applicable to the target population;  
or  
A body of evidence including studies rated as 2+, directly applicable to the target population,  
and demonstrating overall consistency of results; or  
Extrapolated evidence from studies rated as 1++ or 1+
- C Evidence level 3 or 4; or  
extrapolated evidence from studies rated as 2++ or 2+
- GPP Good practice points/expert consensus: Recommended best practice based on the clinical  
experience of the guideline development group

ESO [30]; Australia 2017 [6]:

**Grades of quality of evidence:**

High	We are very confident that the true effect lies close to that of the estimate of the effect	⊕ ⊕ ⊕ ⊕
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	⊕ ⊕ ⊕
Low	We have limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the true effect	⊕ ⊕
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect	⊕

**Strength of recommendation**

Strong for	The desirable effects of an intervention outweigh its undesirable effects	↑↑
Weak for	The desirable effects probably outweigh the undesirable effects but appreciable uncertainty exists	↑?
Weak against	The undesirable effects probably outweigh the desirable effects but appreciable uncertainty exists	↓?
Strong against	The undesirable effects of an intervention outweigh its desirable effects	↓↓

DGEM [21]:

**Level of evidence [LoE]:**

- Ia Evidence obtained from meta-analysis of randomized controlled trials (RCTs)
- Ib Evidence obtained from at least one randomized controlled trial (RCT)
- IIa Evidence obtained from at least one well designed controlled study without randomisation
- IIb Evidence obtained from at least one well designed “quasi-experimental” study
- III Evidence obtained from well-designed nonexperimental descriptive studies such as comparative studies, correlation studies and case studies
- IV Evidence obtained from expert committee reports and/or opinions or clinical experience of respected experts on the field

**Grades of recommendation [GOR]:**

- A good evidence: Requires at least one randomized controlled trial as part of a body of literature of overall quality and consistency addressing the specific recommendation.
- B fair evidence: Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of the clinical recommendation.
- C poor evidence: Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected experts. Indicates the absence of directly applicable clinical studies of good quality.
- CCP clinical consensus point: Decision of the consensus conference, due to strong clinical evidence without evidence from clinical trials

**DEGAM 2020 [16]**

**Codierung des Evidenzlevels:**

- 1 Metaanalysen oder systematische Reviews (SRs) randomisierter kontrollierter Studien (RCTs) bzw. einzelne RCTs
- 2 SRs von Kohortenstudien bzw. einzelne Kohortenstudien
- 3 SRs von Fall-Kontrollstudien bzw. einzelne Fall-Kontrollstudien
- 4 Fallserien
- GCP Good Clinical Practice bzw. Expertenkonsens

**Codierung der Empfehlungsstärke:**

- A hohe Empfehlungsstärke
- B mittlere Empfehlungsstärke
- 0 Niedrige Empfehlungsstärke

**8.2.2. Synopse der externen Leitlinien zu Kapitel 1**

SF 1.1.1: Führt bei erwachsenen Patienten mit möglichem akutem Hirninfarkt oder TIA die Anwendung von Screening Tools zur Schlaganfallerkennung im Vergleich zur Nicht-Anwendung a) zu einer rascheren Zuweisung ins Krankenhaus? oder b) zu einem verbesserten funktionellen Outcome?

Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	The use of a stroke assessment system by first aid providers, including EMS dispatch personnel, is recommended
Stärke	I   B-NR
Begründung	In 1 study, the positive predictive value for a hospital discharge diagnosis of stroke/transient ischemic attack (TIA) among 900 cases for which EMS dispatch suspected stroke was 51% (95% CI, 47–54), and the positive predictive value for ambulance personnel impression of stroke was 58% (95% CI, 52–64) [31]. In another study of 21 760 dispatches for stroke, the positive predictive value of the dispatch stroke/TIA symptoms identification was 34.3% (95% CI, 33.7–35.0), and the sensitivity was 64.0% (95% CI, 63.0–64.9) [32]. In both cases, use of a prehospital tool for stroke screening improved stroke identification, but better stroke identification tools are needed in the prehospital setting.

Empfehlung	EMS leaders, in coordination with local, regional, and state agencies and in consultation with medical authorities and local experts, should develop triage paradigms and protocols to ensure that patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized instrument for stroke screening, such as the FAST (face, arm, speech test) scale, Los Angeles Prehospital Stroke Screen, or Cincinnati Prehospital Stroke Scale.
Stärke	I   B-NR
Begründung	2013er Leitlinie

LL	<b>Canada 2018 [8]</b>
Empfehlung	Public and healthcare provider education should focus on recognizing the signs and symptoms of stroke and actions to take when experiencing or witnessing the signs of stroke
Stärke	C
Empfehlung	Public awareness campaigns and education should include use of the FAST (Face, Arms Speech, Time) acronym to facilitate memory and recognition of these signs
Stärke	B
Begründung	<p>Bray et al. surveyed 12,439 individuals <math>\geq 40</math> years of age from the general population in Australia and reported that from 2004 to 2010 there was a significant increase in the number of respondents who were aware of the national multimedia stroke awareness campaigns (31% vs 50%), which included FAST [33].</p> <p>Rasura et al. conducted a review of 22 studies, of which 14 targeted the general public using mass media campaigns [34]. The duration of these campaigns varied from 3 months to 4 years. Three popular stroke signs and symptoms were included in all of the studies using mass media campaigns: FAST, SUDDEN and Give-Me-Five. Effectiveness of the interventions was assessed in most studies through questionnaires administered pre-and post-intervention. The authors concluded that large public health campaigns using mass media are expensive and short lived and may not be effective, although the increased costs could be mitigated through more prompt treatment with t-PA.</p> <p>Mass media campaigns have also been shown to be associated with increases in the use of Thrombolytic agents following acute stroke. Advani et al. reported that the average number of patients treated with t-PA increased significantly from 7.3 to 11.3 patients per month (an increase of 54.7%, <math>p=0.02</math>) in the 6-month period following the introduction of a mass media intervention that featured the FAST mnemonic, compared to the preceding 12 month-period [35]. The average number of patients treated in the ER increased significantly from 37.3 to 72.8 patients per month (an increase of 95.7%, <math>p&lt;0.001</math>) during the same period. Although the mean number of patients treated with t-PA dropped to 9.5 per month after the first 6 months of the campaign, it was still significantly higher than the preceding 12 months</p>
Empfehlung	All regions should implement a dispatch process through the EMS communications centre to recognize the probable stroke signs (such as FAST – Face, Arms, Speech), potential stroke diagnosis, and need for priority response to the scene and transport to a hospital capable of providing acute services for the rapid diagnosis and time sensitive treatment of stroke (such as neuroimaging, and acute thrombolysis)
Stärke	C
Empfehlung	EMS personnel should use validated acute stroke out-of-hospital diagnostic screening tools as part of on-scene assessment

	<p>a) Patients should be screened for <b>signs of stroke</b> using a validated stroke assessment tool that includes the components of FAST (Face, Arm, Speech, and Time)</p> <p>b) Patients who demonstrate any FAST signs should then undergo a second screen using a tool validated to assess <b>stroke severity</b>, which may be considered in decisions for transportation destination</p>
Stärke	B
Begründung	<p>Patients arriving to hospital using EMS (emergency medical services) following a stroke experience fewer delays in receiving appropriate diagnostic tests (e.g. brain imaging) and are more likely to receive t-PA, if eligible. Patients are also more likely to receive timely transportation and care when pre-notification systems, including the use of trained EMS dispatchers, are adopted. Watkins et al. reported that the percentage of patients whose final diagnosis was stroke increased significantly (63% to 80%, <math>p &lt; 0.01</math>) after EMS dispatchers completed training, aimed at improving their ability to detect suspected stroke patients [36].</p> <p>In the last several years, as endovascular techniques are becoming more widely available, several on scene screening tools to identify patients with large vessel occlusions (LVO), designed for use by EMS technicians, have emerged. Examples of these scales include Field Assessment Stroke Triage for Emergency Destination (FAST-ED) [37], Vision, Aphasia, and Neglect (VAN) [38], the Prehospital Acute Stroke Severity Scale (PASS) [39], Cincinnati Prehospital Stroke Severity Scale (CPSSS) [40], and The Los Angeles Motor Scale (LAMS) [41]). Most of these scales are based on 3-6 selected items from the National Institutes of Health Stroke Scale. The sensitivities and specificities associated with these scales range from 61% to 100% and 40% to 92%, respectively. Smith et al. included the results from 36 studies evaluating the accuracy of LVO prediction scales in patients with suspected stroke or presumed acute ischemic stroke in pre-hospital or emergency department settings. The authors concluded that no scale had both high sensitivity and specificity to determine the presence vs. absence of LVO, and that in clinical practice that the probability of LVO given a negative test could still be <math>\geq 10\%</math>. [42]</p>
LL	<b>NICE 2019, Kapitel 5.1 [24]</b>
Empfehlung	In people with sudden onset of neurological symptoms a validated tool, such as FAST (Face Arm Speech Test), should be used outside hospital to screen for a diagnosis of stroke or TIA
Stärke	1+
Begründung	Ab Seite 26 umfangreiche Beschreibung verschiedener Skalen inkl. Tabelle 5.1
LL	<b>Australia 2017 [6]</b>
Empfehlung	The use of clinical screening tools to identify stroke by ED staff is recommended where an expert stroke team is unable to immediately assess a patient.
Stärke	Weak
Begründung	Stroke screening tools can assist in the identification of stroke in the initial ED assessment. FAST and ROSIER have been validated and have a strong correlation for large vessel occlusion [43, 44].
LL	<b>DEGAM 2020, Kap 4.1 ([16])</b>
Empfehlung	Die initiale Untersuchung des Notfallpatienten soll standardisiert nach dem ABCDE-Schema erfolgen. Ergibt sich aus ABC ein sofortiger Handlungsbedarf, soll entsprechend gehandelt werden.

	Ein standardisierter neurologischer Untersuchungsalgorithmus (z. B. FAST) weist mit hoher Sicherheit neurologische Defizite nach und macht so eine gezielte Einweisung möglich.
Stärke	A, 1a
Begründung	RCP 2016 stellt konkret den FAST-Test als Testverfahren der Wahl zum schnellen Assessment neurologischer Defizite ins Zentrum und streicht heraus, dass er sowohl von Laien als auch von Erfahrenen einfach gehandhabt werden kann [10]. AHA/ASA 2018 empfiehlt die Verwendung von im örtlichen Rettungsverbund abgestimmten Triage-Algorithmen, um Schlaganfallpatienten rasch zu identifizieren und die Schwere ihrer Beeinträchtigung zu erkennen. Auch diese Leitlinie verweist u. a. explizit auf FAST als einen geeigneten Test [1].

LL	<b>ESO EST [23]</b>
Empfehlung	In patients with suspected stroke, we cannot make a recommendation on the use of a pre-hospital scale for improving identification of patients eligible for mechanical thrombectomy. We suggest enrolling patients in a dedicated randomised controlled trial, whenever possible
Stärke	QoE very low, SoR -
Begründung	However, two before-and-after studies allowed such a comparison. In the study by Zaidi et al., <sup>41</sup> emergency medical services personnel underwent training in the RACE score, a clinical scale designed for pre-hospital identification of patients with LVO. <sup>42</sup> All patients with a RACE score 5 (range 0–9) were taken to a facility with interventional capability. The authors used a historical control group to compare patients triaged before or after the implementation of the RACE scale. Patients assessed by the RACE score were more likely to have a discharge diagnosis of acute ischaemic stroke compared to those without RACE assessment (52.3% vs. 31%). There was an increase in the rate of MT (20.1% vs. 7.7%, p=0.03) and improvement in the treatment times (median arrival to-recanalisation times: 101 vs. 205 min, p=0.001). No statistically significant difference was found in the rate of functional independence (90-day mRS 2: 50% vs. 36.4%, p=0.3). A similar study conducted by Mohamad et al. <sup>43</sup> following the implementation of four-item screening showed the median system delay for MT fell from 234 min (IQR: 184–282) to 185 min (IQR: 141–226), corresponding to an adjusted relative delay of 0.79 (95% CI: 0.67–0.93). The reduction in the delay occurred in both the pre-hospital phase (adjusted relative delay 0.86, 95% CI: 0.71–1.04) and in the in-hospital phase (adjusted relative delay 0.76, 95% CI: 0.62–0.94) but did not reach statistical significance in the prehospital phase. There was significantly higher chance of functional independence at 90 days among the patients treated with MT in the post-interventional period than among the pre-interventional patients with a total of 62% (40/65) vs. 43% (15/35) achieving functional independence (OR=3.08, 95% CI: 1.08–8.78). The results of these studies suggest that the use of a pre-hospital scale may reduce the time to reperfusion. However, both studies had serious limitations, notably the use of a historical cohort as control group, the important risk of residual confounding and the lack of assessment of the impact of misclassification. As such, we believe that the associated level of evidence is too low to provide evidence-based recommendation on the use of such scales.

LL	<b>ESO Prehospital, PICO 2 [15]</b>
----	-------------------------------------

Empfehlung	It is recommended that all EMS technicians and paramedics are familiar with a simple pre-hospital stroke scale to identify potential stroke patients. No specific scale can be recommended.
Stärke	QoE low, SoR strong
Begründung	A recent systematic review was identified examining the accuracy of recognizing pre-hospital stroke patients using the QUADAS-2 tool. The following simple stroke scales were included: the Face Arm Speech Test (FAST), Cincinnati Pre-hospital Stroke Scale (CPSS), Los Angeles Pre-hospital Stroke Screen (LAPSS), Melbourne Ambulance Stroke Screen (MASS), Medic Pre-hospital Assessment for Code Stroke (Med PACS), Ontario Pre-hospital Stroke Screening Tool (OPSS) and Recognition of Stroke in the Emergency Room (ROSIER)[45]. All of the above studies were observational studies and excluded those in which physicians were involved in pre-hospital application of the stroke scale. Pre-hospital stroke scales varied in their accuracy and globally missed up to 30% of acute strokes in the field. All stroke scales had a high sensitivity, ranging from 74%–97%. Specificity of the comparable FAST (13%) and CPSS (24%–79%) was lower than scales including more items, such as LAPSS (85%–97%), MASS (74%– 86%) and OPSS (86%), with the exception of Med PACS (33%) and ROSIER (18%). Despite the low quality of evidence a strong recommendation is issued because the possible benefit of identifying potential stroke victims clearly outweighs any possible harm and the associated resource use is minimal.

LL	<b>RCP 2016 [10]</b>
Empfehlung	3.1.1.A: People seen by community-based clinicians (e.g. ambulance paramedics) with the sudden onset of focal neurological symptoms should be screened for hypoglycaemia with a capillary blood glucose, and for stroke or TIA <u>using a validated tool</u> .
Empfehlung	3.1.1 B: People who are negative when screened with a validated tool but in whom stroke is still suspected should be treated as if they have stroke until the diagnosis has been excluded by a specialist stroke clinician.
Stärke	./.
Begründung	Follows from the evidence concerning emergency stroke treatments (Sections 3.4-3.7)

**SF 1.1.2: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die Gabe von Sauerstoff im Vergleich zu keiner Gabe das funktionelle Outcome?**

LL	<b>AHA 2018, Kap 3.1 und 4.2 [1], AHA 2019 Kap 3.1 und 4.3[11]</b>
Empfehlung	Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway.
Stärke	I, C-EO
Empfehlung	Supplemental oxygen should be provided to maintain oxygen saturation >94%.
Stärke	I, C-LD
Empfehlung	Supplemental oxygen is not recommended in nonhypoxic patients with AIS.
Stärke	III: No Benefit; B-R
Begründung	Unchanged from 2013: Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of

	oxygen by nasal cannula at 2 L/min (baseline O <sub>2</sub> saturation >93%) or 3 L/min (baseline O <sub>2</sub> saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights [46].
<b>LL</b>	<b>Australia 2017, Kap 3.14 [6]</b>
Empfehlung	For acute stroke patients who are not hypoxic, the routine use of supplemental oxygen is not recommended
Stärke	Weak against
Begründung	Routine oxygen supplementation was shown to improve neurological outcome measured on NIHSS but not critical outcomes of death and disability [46, 47]. The overall quality is low due to high risk of bias and imprecision (data were from a single randomised controlled trial). A pilot RCT with 289 participants showed no benefits in death or disability, but improvement in neurological outcomes at one week ([46, 47]. The full trial of this pilot study (N=8003) has only been published in abstract version and concluded that routine oxygen therapy does not improve functional outcome at 90 days in any of the predefined subgroups including stroke type or severity. A previous quasi-RCT with 550 patients also did not find routine supplemental oxygen to be beneficial in nonhypoxic stroke patients [48]. Overall, the current evidence does not support the use of routine oxygen supplementation.
<b>LL</b>	<b>NICE 2019, Kap 9.1.5 [24]</b>
Empfehlung	People who have had a stroke should receive supplemental oxygen only if their oxygen saturation drops below 95%. The routine use of supplemental oxygen is not recommended in people with acute stroke who are not hypoxic
Stärke	1+
Begründung	Conventional practice is to give supplemental oxygen to patients with oxygen saturations of less than 95%. The study discussed showed no benefit of supplemental oxygen on mortality or morbidity. It was noted that baseline oxygen saturations had not been recorded in the study discussed, and that any study of oxygen saturation would need to control for other physiological variables such as glucose. No recommendation can be made on the benefit of supplemental oxygen after acute stroke, although a consensus recommendation that saturations of <95% should be treated was agreed.
<b>LL</b>	<b>Canada 2018, S. 60 [8]</b>
Empfehlung	Supplemental oxygen is not required for patients with normal oxygen saturation level
Stärke	C
Begründung	./.
<b>LL</b>	<b>ESO Prehospital, PICO 4 [15]</b>
Empfehlung	In patients with SaO <sub>2</sub> levels <95% the administration of O <sub>2</sub> titrated to maintain normoxia is suggested. Routine use of O <sub>2</sub> is not recommended.
Stärke	QoE low, SoR weak
Begründung	Studies investigating in-hospital routine O <sub>2</sub> therapy started <24 h after stroke onset (2 or 3 l/min for 24– 72 h), although showing slight improvement in neurological status 7 days after stroke onset, failed to show a benefit in terms of long-term survival and independence [47, 49, 50]. No RCT has compared O <sub>2</sub> administration versus no O <sub>2</sub> administration in persons suspected of acute stroke in the pre-hospital setting.



	Hypoxia should be avoided because it may amplify ischaemic brain damage and worsen outcome [51]. Although there are no supportive RCTs, the working group decided to follow the guidelines published by the British Thoracic Society advocating titrated O2 therapy [52].
--	---

LL	<b>DEGAM 2020, Kap 4.3 [16]</b>
Empfehlung	Die Gabe von Sauerstoff sollte erst ab einer Sättigung <95 % erfolgen.
Stärke	A
Begründung	Ein Nutzen der routinemäßigen Versorgung aller Notfallpatienten mit Sauerstoff ist nicht belegt; vielmehr häufen sich Hinweise, dass die zusätzliche Gabe von Sauerstoff bei normaler Sättigung im Blut nachteilig sein kann [53]. Allerdings ist der Zeitraum der prähospitalen Versorgung üblicherweise kurz, so dass Studiendaten, die keinen günstigen (bzw. einen eher negativen) Effekt der Dauerapplikation von Sauerstoff belegen, auf die prähospital Situation grundsätzlich nicht gut übertragbar sind [46]

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute stroke should only receive supplemental oxygen if their oxygen saturation is below 95% and there is no contraindication
Stärke	./.
Begründung	Roffe et al 2011 [50], Consensus

SF 1.1.3: [Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die Kontrolle und ggfs. Korrektur erniedrigter oder erhöhter Glukosewerte im Vergleich zu keiner Intervention das funktionelle Outcome?](#)

LL	<b>AHA 2018; Kap 3.4 und 4.5 [1]; AHA 2019 Kap 3.4 und 4.6 [11]</b>
Empfehlung	Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after AIS is associated with worse outcomes than normoglycemia and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in patients with AIS.
Stärke	Ila, C-LD
Begründung	Unchanged from 2013: So far, only 1 randomized efficacy trial of hyperglycemia treatment in acute stroke has been reported (the Glucose- Insulin-Stroke Trial–UK [GIST-UK]). Patients (n=933) with acute ischemic stroke within 24 hours of symptom onset, not previously treated with insulin, were randomized to unblinded intravenous treatment with insulin, potassium, and glucose versus saline. Protocol treatment continued for 24 hours. Although the results of this trial were neutral (no difference in clinical outcomes between the 2 treatment groups), the design was such that key questions remain unanswered. First, the GIST-UK trial was stopped early, because 2355 subjects were originally planned, and it was thus underpowered to detect a possible treatment effect. Second, the mean glucose level in the insulin-treated group was only 10 mg/d lower than in the saline control group, and the control group was only mildly hyperglycemic (≈122 mg/dL between hours 8–24). This was likely because of the inclusion of predominantly nondiabetic patients (84%). Larger decreases in glucose levels may be needed to detect a therapeutic effect. Third, the median time to initiation of protocol treatment was 13 hours. Although the optimal time to correct hyperglycemia during acute ischemic stroke has not been established, earlier treatment may have been therapeutic. Pilot clinical trials have demonstrated the feasibility and safety of rapid reductions in glucose levels with intravenous insulin

	during acute ischemic stroke. Thus, the definitive efficacy and safety of earlier and greater reductions in glucose levels during acute ischemic stroke remain to be studied [54].
Empfehlung	Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS.
Stärke	I, C-LD
Begründung	Unchanged from 2013: The combination of symptoms attributable to hypoglycemia and the threshold for such symptoms vary considerably between individuals. In healthy people, autonomic symptoms (such as sweating, trembling, or anxiety) usually begin to appear when the blood glucose level drops below 57 mg/dL, and manifestations of brain dysfunction (such as disorientation, dizziness, or slowing of speech) usually begin to appear when the glucose level drops below 47 mg/dL. However, in patients with poorly controlled diabetes mellitus, these thresholds are shifted to higher blood glucose levels [55]. Occasionally, brain dysfunction occurs before the autonomic symptoms. Hypoglycemia (blood glucose level <60 mg/dL) can be corrected rapidly in most patients with a slow intravenous push of 25 mL of 50% dextrose. Oral glucose-containing solutions are also reasonable treatment options but take longer to raise the blood glucose level and may not be feasible in patients with dysphagia.
Empfehlung	Only the assessment of blood glucose must precede the initiation of IV alteplase in all patients.
Stärke	I, B-R
Begründung	Recommendation reworded for clarity from 2013 AIS Guidelines. Recommendation was modified to clarify that it is only blood glucose that must be measured in all patients.

LL	<b>ESO Glycaemia 2018 [14]</b>
Empfehlung	In patients with acute IS, we suggest against the routine use of IV insulin to achieve a tight glycaemic control as a means to improve functional outcome, survival or infarct growth.
Stärke	QoE low, SoR weak
Begründung	The meta-analysis showed no statistically significant difference in rates of good functional outcome between patients treated with insulin per clinical trial protocol and controls (RR 1.09; 95%CI 0.87–1.37) with no sign of statistical heterogeneity. The meta-analysis showed no significant difference in survival rates between patients treated with IV insulin for intensive glycaemic reduction and controls managed by the standard protocol or without specific glucose-lowering treatment (RR 0.99; 95%CI 0.94–1.05). Patients in the intervention groups were at higher risk of any hypoglycaemic event (RR 4.75 95%CI 1.52– 14.85). There was substantial statistical heterogeneity ( $I^2$ 57%). Patients in the intervention groups also had a higher risk of symptomatic hypoglycaemic events (RR 3.09; 95%CI 0.98–9.71).

LL	<b>Australia 2017, Kap 3.5, Kap 3.16 [6]</b>
Empfehlung	All stroke patients should have their blood glucose level monitored for the first 72 hours following admission, and appropriate glycaemic therapy instituted to treat hyperglycaemia (glucose levels greater than 10 mmol/L), regardless of their diabetic status
Stärke	Strong

Begründung	<p>The Quality in Acute Stroke Care (QASC) trial reported by Middleton et al in 2011 [56] was a cluster randomised trial (N = 1696) of a treatment protocol FeSS for managing fever, glycaemia, and swallowing dysfunction. The trial demonstrated that when used as part of a bundled care package, monitoring of blood glucose levels and treatment of hyperglycaemia &gt;11 mmol/L in the first 72 hours improves outcomes at 90 days, although it is important to note the effects of individual components of the intervention cannot be separated. Therefore, the evidence for the benefits of hyperglycaemia management specifically is somewhat indirect.</p> <p>Drury et al provides evidence of current management practices in the pre-intervention cohort prospectively recruited for the QASC trial [57]. Retrospective medical record audits of all 19 participating stroke units (n=718) revealed: 138 (19%) had four hourly or more temperature readings and 204 patients (29%) had a fever, with 44 (22%) receiving paracetamol. A quarter of patients (n = 102/412, 25%) had six hourly or more glucose readings and 23% (95/412) had hyperglycemia, with 31% (29/95) of these treated with insulin. The majority of patients received a swallow assessment (n = 562, 78%) by a speech pathologist in the first instance rather than a swallow screen by a nonspeech pathologist (n = 156, 22%). Of those who passed a screen (n = 108 of 156, 69%), 68% (n = 73) were reassessed by a speech pathologist and 97% (n = 71) were reconfirmed to be able to swallow safely.</p>
Empfehlung	For stroke patients, an intensive approach to the maintenance of tight glycaemic control (between 4.0–7.5 mmol/L) is not recommended.
Stärke	Strong against
Begründung	Two systematic reviews [58, 59] were included. The Cochrane systematic review [58] included 11 trials (N=1583 participants) and the other review [59] included 9 trials (N=1491 participants). Both reviews were consistent and reported no benefits from intensive therapy with IV insulin but also an increased rate of complications (hypoglycemia). Early and intense therapy via IV insulin is not recommended.

LL	<b>NICE 2019, Kap 9.2 [24]</b>
Empfehlung	People with acute stroke should be treated to maintain a blood glucose concentration between 4 and 11 mmol/l.
Stärke	1++
Empfehlung	Optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, should be provided to all adults with diabetes who have threatened or actual myocardial infarction or stroke. Critical care and emergency departments should have a protocol for such management.
Stärke	1++
Begründung	<p>The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) was the only study identified that compared a glucose-lowering regimen with control. The study randomised patients within 24 hours of symptom onset and the intervention lasted for 24 hours. The GDG noted that hyperglycaemia after stroke tends to last longer than 24 hours, and that the intervention may have been too brief to have a lasting effect. There was no evidence to support the tight control of blood glucose in patients with mild to moderate elevated blood glucose levels (median 7–9 mmol/l).</p> <p>Patients with pre-existing diabetes should be treated according to current guidelines. The group consensus was that glucose levels above 11 mmol/l following stroke should be treated. The Type 2 diabetes guideline [60] recommends that patients with diabetes are treated to achieve or maintain their target HbA1c level. The consensus of the group was that where possible patients with acute stroke should be treated to</p>

	maintain blood glucose concentrations between 4–11 mmol/l. The group agreed to include the Type 1 diabetes recommendation on optimal insulin therapy.
--	---

LL	<b>Canada 2018, S. 58 [8]</b>
Empfehlung	All patients with suspected acute stroke should have their blood glucose concentration checked upon arrival to the Emergency Department
Stärke	B
Empfehlung	Hypoglycemia should be corrected immediately
Stärke	B
Empfehlung	Although no optimal glucose target has been identified, it is reasonable to treat hyperglycemia which has been associated with hemorrhagic transformation when treating with IV alteplase thrombolysis
Stärke	C
Begründung	Baseline hyperglycemia has been identified as independent predictor of poor stroke outcome and may be a marker of increased stroke severity. The presence of hyperglycemia may be of particular concern among patients without a history of premorbid diabetes. Using patient data from the ECASS II trial, Yong & Kaste [61] examined the association between stroke outcomes and four patterns of serum glucose over the initial 24-hour period post stroke. Among 161 patients with pre-morbid diabetes, the odds of poor outcome were not increased significantly for patients with persistent hyperglycemia, or among patients with hyperglycemia at 24 hours, compared with patients with persistent normoglycemia. However, among 587 non-diabetics, patients with persistent hyperglycemia experienced significantly worse outcomes compared to those with persistent normoglycemia. The odds of a good functional outcome at 30 days, minimal disability at 90 days or neurological improvement over 7 days were significantly reduced compared with patients with persistent normoglycemia, while the odds of 90-day mortality and parenchymal hemorrhage were increased significantly. Since initial hyperglycemia has been associated with poor stroke outcome, several trials have evaluated the potential benefit of tight blood glucose control early following stroke. The largest such study was the GIST-UK trial [54] in which 899 patients were randomized to receive variable-dose-insulin glucose potassium insulin (GKI) to maintain blood glucose concentration between 4-7mmol/L or saline (control) as a continuous intravenous infusion for 24 hours. For patients in the control group, if capillary glucose > 17 mmol/L, insulin therapy could be started, at the discretion of the treating physician. Treatment with GKI was not associated with a significant reduction in 90-day mortality (OR= 1.14; 95% CI 0.86 to 1.51; p=0.37) or the avoidance of severe disability (OR= 0.96; 95% CI 0.70 to 1.32). Rescue dextrose was given to 15.7% of GKI-treated patients for asymptomatic prolonged hypoglycemia. The trial was stopped prematurely due to slow enrolment. More recently, Rosso et al. [62] randomized 120 patients to receive intravenous administration of insulin (IIT) on a continuous basis or subcutaneous administration (every 4 hours) for 24 hours (SIT). The stop point for treatment was <5.5 mmol/L in the IIT group and 8 mmol/L in the SIT group. Although a significantly higher number of patients in the IIT group achieved and maintained a mean blood glucose level of <7mmol/L, the mean size of infarct growth was significantly higher among patients in the IIT group (27.9 vs. 10.8 cm <sup>3</sup> , p=0.04), there were significantly more asymptomatic hypoglycemia events among patients in the IIT group (8 vs. 0, p=0.02) and there was no significant difference in the number of patients who experienced a good outcome (45.6% vs. 45.6%) or death (15.6% vs. 10.0%) at 3 months. In a Cochrane review [58] used the results of 11 RCTs including 1583 adult

	patients with blood glucose level of > 6.1mmol/L obtained within 24 hours of stroke, Blood-glucose-lowering treatment was not associated with reductions in death or dependency (OR=0.99, 95% CI 0.79-1.2) or final neurological deficit, but treatment did increase the risk of was associated symptomatic and asymptomatic hypoglycemia events.
--	---

<b>LL</b>	<b>ESO Prehospital, PICO 6 [15]</b>
Empfehlung	Because of safety concerns pre-hospital administration of insulin in persons with suspected stroke and hyperglycaemia is not recommended
Stärke	QoE low, SoR weak
Begründung	Blood glucose should be measured in every patient with suspected stroke because symptoms of hypoglycaemia can mimic those of a stroke. Hypoglycaemia (<60 mg/dl or <3.3 mmol/l) needs to be treated with glucose 20%–40% in 25–50 ml infusion [63]. People with hyperglycaemia concomitant with large vessel acute ischaemic stroke have greater mortality, stroke severity and functional impairment compared with those with normoglycaemia. However, this has not been found in patients with a lacunar stroke [64, 65]. Only one small feasibility study dealing with lowering glucose in acute stroke patients in the pre-hospital setting was identified [66]. In this study, patients with stroke symptoms and plasma glucose >108 mg/dl or 6.0 mmol/l were randomized during the pre-hospital phase to receive either a single subcutaneous dose of short-acting insulin (n = 11) or a continuous intravenous insulin infusion (n = 12) at a rate adjusted by glucose levels measured every 10 min and targeted to plasma glucose 4.5–6.0 mmol/l. Plasma glucose levels were significantly decreased with no serious adverse events in the intravenously treated group in comparison to a non-randomized control group (n = 38). The subcutaneous insulin administration did not achieve significant lowering of plasma glucose. A systematic review showed that the in-hospital administration of intravenous insulin with the objective of maintaining serum glucose within a specific range in the first hours of acute ischaemic stroke does not provide benefit in terms of functional outcome, death or improvement in final neurological deficit, and significantly increased the number of hypoglycaemic episodes [58]. Specifically, the people whose glucose levels were maintained within a tighter range with intravenous insulin experienced a greater risk of symptomatic and asymptomatic hypoglycaemia than the people in the control group. The situation may therefore be even more risky in the pre-hospital phase.

<b>LL</b>	<b>DEGAM 2020, Kap 4.4 [16]</b>
Empfehlung	Die Blutzuckermessung soll erfolgen, um die Differentialdiagnose einer Hypoglykämie sicher auszuschließen. Bei niedrigen BZ-Werten (<60 mg/dl) soll Glucose i. v. gegeben werden.
Stärke	A
Begründung	Nahezu sämtliche analysierten Quell-Leitlinien zur Akutversorgung des Schlaganfalls betonen die Wichtigkeit der prähospitalen Blutzuckermessung, um die Hypoglykämie als relevante „Schlaganfall-Mimic“ zu identifizieren [1, 10].

<b>LL</b>	<b>RCP 2016 [10]</b>
Empfehlung	People seen by ambulance clinicians outside hospital with the sudden onset of focal neurological symptoms should be screened for <b>hypoglycaemia</b> with a capillary blood glucose, and for stroke or TIA using a validated tool. Those people with persisting

	neurological symptoms who screen positive using a validated tool should be transferred to a hyperacute stroke unit as soon as possible
Empfehlung	Patients with acute stroke should be treated to maintain a blood glucose concentration between 5 and 15 mmol/L with close monitoring to avoid hypoglycaemia.
Begründung	Harbison et al 2003 [67]; Working Party consensus In contrast to acute myocardial infarction, tight glycaemic control has not been shown to improve outcome in stroke (Gray et al, 2007) and studies have warned against aggressive lowering with insulin infusions due to the risk of hypoglycaemia. This has led the Working Party to recommend a broadening of the target range for blood glucose in acute stroke from 4-11 mmol/L to 5-15mmol/L.

SF 1.1.4: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die Reduktion einer erhöhten Körpertemperatur im Vergleich zu keiner Intervention das funktionelle Outcome?

LL		<b>ESO GL Fever 2015 [5]</b>
Empfehlung		In patients with acute ischemic stroke and hyperthermia, we cannot make any recommendation for treating hyperthermia as a means to improve functional outcome and/or survival.
Stärke		QoE low, SoR weak
Begründung		Recently, the QASC trial showed that rigorous implementation of common stroke treatment protocols including fever management, dysphagia, and hyperglycemia management improved patient outcomes [56]. Although it was not possible to identify directly which of the three components of this intervention exerted the beneficial effect which was actually the reason for excluding this cluster-randomized RCT from our meta-analysis [68], a multiple logistic regression analysis suggested that the main determinants were hyperglycemia and fever management . Administration of antipyretics to reduce temperature in a hyperthermic patient and clinical examination and investigation to identify the cause of fever are standard of care worldwide in routine clinical practice. In this context, treatment of hyperthermia in a hyperthermic stroke patient is a rational choice to reduce temperature and relieve the symptom of discomfort associated with hyperthermia; however, as analyzed above, existing data are very limited to show any effect (either beneficial or detrimental) in stroke patients on hard clinical outcomes like functional outcome or mortality. Further randomized trials are needed

LL		<b>AHA 2018; Kap 3.3 und 4.4 [1]; AHA 2019 Kap 3.3 und 4.5[11]</b>
Empfehlung		Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke
Stärke		I, C-EO
Begründung		Additional support for this recommendation unchanged from the 2013 AIS Guidelines is provided by a large retrospective cohort study conducted from 2005 to 2013 of patients admitted to intensive care units in Australia, New Zealand, and the United Kingdom. Peak temperature in the first 24 hours <37°C and >39°C was associated with an increased risk of in-hospital death compared with normothermia in 9366 patients with AIS [69].

LL	<b>Australia 2017, Kap 3.17 [6]</b>
Empfehlung	All acute stroke services should implement standardised protocols to manage fever, glucose and swallowing difficulties in stroke patients.
Stärke	Strong
Begründung	The Quality in Acute Stroke Care (QASC) study conducted by Middleton et al. [56] as a single-blind cluster randomised trial, assessing the benefits of evidence-based treatment protocols in acute stroke units. The Fever, Sugar, Swallowing (FeSS) intervention involved temperature monitoring, monitoring of blood glucose and dysphagia assessment and was aimed at promoting prompt nursing assessment and bedside treatment. The results showed a significant reduction in death or dependency at 90 days (modified Rankin Scale scores $\geq 2$ ), with an adjusted absolute risk reduction of 15.7%. The intervention group also showed higher rates of functional independence, both when independence was classified as a Barthel Index score $\geq 60$ or $\geq 95$ , although the difference was non-significant. Other outcomes suggested improved processes of care in the intervention stroke units, with significantly reduced temperatures and blood glucose, and higher proportions of swallowing screening. Patients with severe strokes may have been under-represented due to the exclusion of patients receiving palliation only, but in other respects the study was high quality and provides a high degree of certainty about the observed results.
Empfehlung	Stroke patients with fever $>37.5$ °C may be treated with paracetamol as an antipyretic therapy
Stärke	Weak
Begründung	A Cochrane review [70] included five pharmacological temperature reduction trials and three physical cooling trials (total of 423 participants). No benefits were found for either strategy in terms of reducing the risk of death or dependency (odds ratio (OR) 0.9, 95% confidence interval (CI) 0.6 to 1.4) or death (OR 0.9, 95% CI 0.5 to 1.5). One large subsequent trial [71] including 1400 patients found no benefits for routine high dose paracetamol but some groups (such as those with fever) may benefit based on subgroup analysis. An updated meta-analysis including this trial as well as the trials in the earlier review showed no significant increase in favourable outcomes.
LL	<b>Canada 2018, S. 59, S. 102 [8]</b>
Empfehlung	For temperature greater than 37.5 Celsius, increase frequency of monitoring, initiate temperature-reducing care measures, investigate possible infection such as pneumonia or urinary tract infection [Evidence Level C], and initiate antipyretic and antimicrobial therapy as required [Evidence Level B].
Stärke	Teil 1: C, Teil 2; B
Empfehlung	Temperature should be monitored as part of vital sign assessments; ideally every four hours for the first 48 hours, and then as per ward routine or based on clinical judgment
Stärke	C
Begründung	Elevated body temperature in the early post-stroke period has been associated with worse clinical outcomes. A meta-analysis conducted by Prasad & Krishnan [72], including the results from six studies demonstrated that fever within the first 24 hours of ischemic stroke onset was associated with twice the risk of short-term mortality (OR= 2.20, 95% CI 1.59–3.03). Fever may result from a secondary infection, such as pneumonia, or may have occurred as a cause of stroke (e.g. infective endocarditis). While interventions to reduce temperature may improve the viability

of brain tissue and/or prevent other medical complications post stroke, efforts to reduce fever, through a wide range of modalities, including pharmacological agents, (paracetamol) and physical interventions (cooling blankets and helmets and endovascular treatments) have not been convincingly shown to be effective in reducing/avoiding poorer outcomes.

Frank et al. [73] conducted a retrospective study of 6,015 ischemic stroke patients who were registered in Virtual International Stroke Trials Archive (VISTA). Patients who received paracetamol for the management of pain (n=1626) or fever (n=809) were compared to those who had not received the medication. In patients treated with paracetamol for fever or pain, there was no difference in the distribution of mRS scores at 90 days, the primary outcome, compared with patients who did not receive treatment, while the odds of pneumonia were significantly reduced (OR=0.73, 95% CI 0.56-0.94, p=0.017). However, among patients without pain or fever who were treated with paracetamol as a prophylactic measure, the odds of poor outcome were increased (mortality at 90 days: OR=1.59, 95% CI 1.13-2.23, p=0.008, mRS score 0-2: OR=0.55, 95% CI 0.41-0.74, p<0.001 and recurrent stroke within 7 days: OR=3.57, 95% CI 1.37-9.32, p=0.009). The largest trial examining the use of pharmacological agents for the reduction of fever was Paracetamol (Acetaminophen) In Stroke (PAIS) trial [71]. In this trial, 1,400 patients were randomized to receive 1 gram paracetamol, 6x daily for 3 days or placebo within 12 hours of symptom onset. While treatment with paracetamol did significantly lower body temperature by a mean of 0.26 °C, it was not associated with improvement beyond expectation (adjusted OR=1.20, 95% CI 0.96-1.50), the increased odds of a favourable outcome, or significant increases in QoL. Treatment with paracetamol was associated with a decrease in 14-day mortality (OR=0.60, 95% CI 0.36-0.90), but there was no difference at 3 months (OR=0.90, 95% CI 0.68-1.18). The PAIS 2 trial [74] was terminated after enrolling 26 of 1,500 planned patients. In this trial, high-dose (2 grams) or placebo was given for 3 days to patients with a temperature of  $\geq 36.5^{\circ}\text{C}$ . There was no significant difference between groups in the shift in mRS scores at 90 days associated with paracetamol (common adj OR=1.15, 95% CI 0.74-1.79). In a Cochrane review [70] included the results from 8 RCTs, 5 of which examined pharmacological agents (paracetamol, n=3, metamizole n=1, ibuprofen placebo n=1) versus placebo. Pharmacological treatment significantly reduced temperature at 24 hours following treatment (MD= -0.21, 95% CI -0.28, -0.15, p<0.0001), but was not associated with a reduction in the odds of death or dependency at 1-3 months (OR= 0.92, 95% CI 0.59- 1.42, p=0.69).

In terms of physical methods to reduce fever, the feasibility of endovascular and surface cooling strategies was examined in the COOLAID trial [75]. In this trial, 31 patients admitted to an ICU in two hospitals with acute ischemic stroke were randomized to receive therapeutic hypothermia (TH) using endovascular or surface methods, or standard supportive care (n=14). Patients in the TH group had body temperature lowered to 33 degrees C and were maintained for 24 hours, while patients in the standard care group received acetaminophen if body temp exceeded 37.5 degrees C. There were significantly more episodes of bradycardia associated with the TH group, and a non-significant increase in the incidence of pneumonia (6 vs. 1, p=0.09), although there were no significant differences between groups in other cardiac adverse events or pulmonary adverse events, or death. The authors concluded that the treatment was feasible, but associated with serious complications, particularly in anesthetized patients receiving endovascular cooling. A Health Technology Assessment [76] examined the use of any form of non-invasive head cooling following TBI, and cardiac arrest. The most effective techniques for



	which there were adequate data (nasal coolant and liquid cooling helmets) indicated that intracranial temperature could be reduced by 1 °C in 1 hour.
<b>LL</b>	<b>ESO Prehospital, PICO 7 [15]</b>
<b>Empfehlung</b>	In the absence of clinical studies no recommendations can be made on pre-hospital interventions for lowering elevated body temperature
<b>Stärke</b>	./.
<b>Begründung</b>	Data on 5305 patients from the Virtual International Stroke Trials Archive data set showed that delayed hyperthermia was more strongly associated with poor outcome than elevated body temperature seen in the hours after stroke [77]. A prospective study of 725 patients also found that initial elevated body temperature in hyperacute ischaemic stroke was not associated with worse outcome, but a rise in body temperature in severe strokes was related to poor outcome. It was concluded that elevated body temperature within 6 h of stroke onset had no prognostic influence on stroke outcome at 3 months [78]. Antipyretic drugs and cooling methods can lower body temperature in stroke patients. However, no clinical studies have investigated pre-hospital treatment of elevated body temperature in acute stroke patients

SF 1.1.5: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die Reduktion erhöhter Blutdruckwerte im Vergleich zu keiner Intervention das funktionelle Outcome?

<b>LL</b>	<b>AHA 2018, Kap 3.2 und 4.3 [1]; AHA 2019 Kap 3.2 und 4.3[11]</b>
<b>Empfehlung</b>	Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their systolic BP is <185 mm Hg and their diastolic BP is <110 mm Hg before IV fibrinolytic therapy is initiated.
<b>Stärke</b>	I, B-NR
<b>Begründung</b>	The RCTs of IV alteplase required the BP to be <185 mm Hg systolic and <110 mm Hg diastolic before treatment and <180/105 mm Hg for the first 24 hours after treatment. Options to treat arterial hypertension in patients with AIS who are candidates for acute reperfusion therapy are given in Table 5. Some observational studies suggest that the risk of hemorrhage after administration of alteplase is greater in patients with higher BPs and in patients with more BP variability. The exact BP at which the risk of hemorrhage after thrombolysis increases is unknown. It is thus reasonable to target the BPs used in the RCTs of IV thrombolysis.
<b>Empfehlung</b>	Until additional data become available, in patients for whom intra-arterial therapy is planned and who have not received IV thrombolytic therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure.
<b>Stärke</b>	Ila, B-R
<b>Begründung</b>	Of the 6 RCTs that each independently demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed <6 hours from stroke onset, 5 (REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, and MR CLEAN) had eligibility exclusions for BP >185/110 mm Hg. The sixth, ESCAPE had no BP eligibility exclusion. DAWN also used an exclusion for BP >185/110 mm Hg. RCT data for optimal BP management approaches in this setting are not available. Because the vast majority of patients enrolled in these RCTs had preprocedural BP managed below 185/110 mm Hg, it is reasonable to use this level as a guideline
<b>Empfehlung</b>	In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (eg, concomitant acute coronary event, acute heart failure, aortic dissection, postthrombolysis sICH, or preeclampsia/eclampsia). Lowering BP initially by 15% is probably safe.

Stärke	I, C-EO
Begründung	Patients with AIS can present with severe acute comorbidities that demand emergency BP reduction to prevent serious complications. However, it is important to keep in mind that excessive BP lowering can sometimes worsen cerebral ischemia [79]. Ideal management in these situations should be individualized, but in general, initial BP reduction by 15% is a reasonable goal.
Empfehlung	In patients with BP <220/120 mm Hg who did not receive IV alteplase or EVT and do not have a comorbid condition requiring acute antihypertensive treatment, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an AIS is not effective to prevent death or dependency
Stärke	III: No Benefit; A
Begründung	Multiple RCTs and meta-analyses of these trials have consistently shown that initiating or reinitiating antihypertensive therapy within the first 48 to 72 hours after an AIS is safe but this strategy is not associated with improved mortality or functional outcomes. However, none of these trials were designed to study BP reduction within the first 6 hours after stroke, and all excluded patients with extreme hypertension or coexistent indications for acute BP reduction.
Empfehlung	In patients with BP ≥220/120 mm Hg who did not receive IV alteplase or EVT and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.
Stärke	IIb, C-EO
Begründung	Patients with severe hypertension (most commonly >220/120 mm Hg) were excluded from clinical trials evaluating BP lowering after AIS [80-85]. BP reduction has been traditionally advised for these cases, but the benefit of such treatment in the absence of comorbid conditions that may be acutely exacerbated by severe hypertension has not been formally studied.
Empfehlung	Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mm Hg who are neurologically stable is safe and is reasonable to improve long-term BP control unless contraindicated.
Stärke	IIa, B-R
Begründung	Starting or restarting antihypertensive medications has been shown to be associated with improved control of the BP after discharge in 2 trials [81, 85]. Therefore, it is reasonable to start or restart antihypertensive medications in the hospital when the patient remains hypertensive and is neurologically stable. Studies evaluating this question included only patients with previous diagnosis of hypertension [81] or enrolled mostly patients with previous hypertension [85]. However, because hypertension is not uncommonly first diagnosed during the hospitalization for stroke, it is reasonable to apply this recommendation also to patients without preexistent hypertension
LL	<b>Australia 2017, Kap 3.11 [6]</b>
Empfehlung	Intensive blood pressure lowering in the acute phase of care to a target SBP of < 140 mmHg is not recommended for any patient with stroke.
Stärke	Weak against
Begründung	Two systematic reviews from Lee et al [86] and Bath et al [87] showed that there was no overall effect of treatment on death as an outcome in the studies analysed. No

	differences were observed when analysed by the subgroup of ischaemic stroke either.
Empfehlung	Pre-existing antihypertensive medication may be withheld until patients are neurologically stable and treatment can be given safely.
Stärke	Weak
Begründung	Bath et al conducted a systematic review of the effectiveness of altering blood pressure in acute stroke patients [87]. In a total of 2860 patients, they did not find a significant difference of death or dependency between patients who continued prestroke anti-hypertensive treatment and those who stopped. However, better functional outcomes measured by Barthel-Index were associated with discontinuation of antihypertensives.

LL	<b>Canada 2018, S. 57 [8]</b>
Empfehlung	The ideal level of blood pressure target to achieve and sustain in the hyperacute phase is unknown at this time. Pharmacological agents and routes of administration should be chosen to avoid precipitous falls in blood pressure
Stärke	C
Empfehlung	Ischemic stroke patients not eligible for thrombolytic therapy: Treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely treated
Stärke	C
Empfehlung	Extreme blood pressure elevation (e.g. systolic BP greater than 220 or diastolic BP greater than 120 mmHg) should be treated to reduce the blood pressure by approximately 15 percent, and not more than 25 percent, over the first 24 hours with further gradual reduction thereafter to targets for long-term secondary stroke prevention
Stärke	C
Begründung	There is no evidence to suggest that interventions to manage extreme perturbations in blood pressures with vasoactive agents help to improve stroke outcome. In the CATIS trial [85], 4071 patients with acute ischemic stroke were randomized to receive or not receive antihypertensive therapy during hospitalization. Although mean systolic blood pressure was significantly lower among patients in the intervention group, treatment was not associated with significant reduction in the risk of death or major disability at either 14-days (OR= 1.00, 95% CI 0.88 to 1.14) or 3-months (OR= 0.99, 95% CI 0.86 to 1.15) following study entry. Two Cochrane reviews have examined the potential benefits of artificially raising and lowering blood pressure with vasoactive drugs within the first week of stroke. One of the reviews was restricted to the inclusion of RCTs, and included the results from 12 trials [88], while the other included non RCTs as well [89]. In both reviews, the focus of most of the included studies was blood pressure reduction. Treatment was associated with significant early and late reductions in SBP and DBP, but was not associated with significant reduction in the risk of death or a poor outcome within one month, or the end of follow-up. However, the use of vasoactive drugs used to raise blood pressure significantly increased in the odds of death or disability at the end of the trial (OR= 5.41; 95% CI 1.87 to 15.64) [89]. Further evidence from a meta-regression study [90], which included the results from 37 trials, also suggests that large changes in blood pressure in the early post-stroke period are associated with an increased risk of death and the combined outcome of death/dependency. While the authors also suggested

	<p>that a decrease in blood pressure between 8mmHg and 14.6mmHg was associated with the lowest odds of poor outcome (death, dependency and intracerebral hemorrhage), the results were not statistically significant [90].</p> <p>For patients treated with thrombolysis, reductions in blood pressure may be indicated, when elevations are extreme (eg., SBP <math>\geq</math>220 mm Hg or DBP<math>\geq</math>120 mm Hg). Using the results of 11080 patients included in the SITS-ISTR study who were treated with thrombolysis, Ahmed et al (2009) reported that high systolic BP, 2 to 24 hours after thrombolysis was associated with worse outcome (<math>p &gt; 0.001</math>). Blood pressures greater than 170 mmHg were associated with higher odds of death, dependency and subsequent hemorrhage compared to blood pressures between 141 and 150 mmHg. The results from the blood pressure-lowering arm of the ENCHANTED trial, when released, will provide additional information to guide patient management.</p>
--	--

Anm: Verweist auf Enchanted-BP

LL	<b>NICE 2019, Kap 9.3 [24]</b>
Empfehlung	<p>Antihypertensive treatment in people with acute stroke is recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues:</p> <ul style="list-style-type: none"> <li>• hypertensive encephalopathy</li> <li>• hypertensive nephropathy</li> <li>• hypertensive cardiac failure/myocardial infarction</li> <li>• aortic dissection</li> <li>• pre-eclampsia/eclampsia</li> <li>• intracerebral haemorrhage with systolic blood pressure over 200 mmHg.</li> </ul>
Stärke	1++
Empfehlung	Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for thrombolysis
Stärke	./.
Begründung	<p>There was a lack of evidence in the studies assessed to suggest that manipulating blood pressure in acute stroke (within the first 72 hours) using beta-blockers or calcium channel antagonists compared to control/placebo had any beneficial effect on mortality, dependency or stroke recurrence. There is clinical concern that lowering blood pressure acutely may have a deleterious effect. There was discussion of the possible benefits of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers after acute stroke; it was agreed that no specific recommendations could be made until the publication of the current trials. The issue of severe hypertension was discussed. There are clearly circumstances such as hypertensive encephalopathy or co-existing cardiac or vascular emergency (e.g. aortic dissection) when active management of severe hypertension (consensus: systolic blood pressure <math>&gt;200</math> mmHg) may be indicated. The effects of this on acute stroke are unknown. The GDG acknowledged that current trial results will not be available until at least 2009.</p>

LL	<b>ESO Prehospital, PICO 5 [15]</b>
Empfehlung	Pre-hospital treatment of high blood pressure in people suspected of acute stroke is not recommended
Stärke	QoE low, SoR weak
Begründung	Both hypertension and marked hypotension are associated with poor outcome after stroke [91], and there is considerable clinical uncertainty as to the optimal management of blood pressure acutely after stroke. There are two small single centre feasibility RCTs in pre-hospital acute stroke patients who were hypertensive (systolic

	<p>blood pressure <math>\geq 140</math> mmHg or <math>&gt;160</math> mmHg) assessing the safety and outcome of antihypertensive therapy. The Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial and the Paramedic Initiated Lisinopril for Acute Stroke Treatment Trial showed that it was feasible to perform an ambulance based paramedic-delivered trial of blood pressure lowering in patients with acute stroke (<math>&lt;4</math> h of stroke onset) [92, 93]. Both trials selected the immediate blood pressure lowering effect as the primary outcome. Due to the small size of the studies (55 patients recruited in total) no conclusions on safety, efficacy and outcome could be drawn from this study. Even for systolic blood pressure <math>\geq 185</math> mmHg, which may prolong door to needle time, urgent pre-hospital antihypertensive treatment by paramedics holds a risk for sudden drops of the blood pressure; therefore treatment of high blood pressure in the pre-hospital phase should be avoided.</p> <p>Anm: Zwischenzeitliche Publikation von RIGHT-2 [94, 95]</p>
--	---

LL	<b>DEGAM 2020, Kap 4.5 ([16])</b>
Empfehlung	Blutdruckwerte $\geq 220$ mmHg können per vorsichtiger medikamentöser Titration um 15 % gesenkt werden.
Stärke	0
Begründung	Leitlinienmodifikation AHA 2018 [1]

LL	<b>RCP 2016 [10]</b>
Empfehlung	<p>Patients with acute ischaemic stroke should only receive blood pressure-lowering treatment if there is an indication for emergency treatment, such as:</p> <ul style="list-style-type: none"> <li>– systolic blood pressure above 185 mmHg or diastolic blood pressure above 110 mmHg</li> </ul> <p>when the patient is otherwise eligible for treatment with alteplase;</p> <ul style="list-style-type: none"> <li>– hypertensive encephalopathy;</li> <li>– hypertensive nephropathy;</li> <li>– hypertensive cardiac failure or myocardial infarction;</li> <li>– aortic dissection;</li> <li>– pre-eclampsia or eclampsia.</li> </ul>
Stärke	./.
Begründung	NICE, 2011a; Bath and Krishnan, 2014 [87]; Working Party consensus

SF 1.1.6: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die Erhöhung erniedrigter Blutdruckwerte im Vergleich zum Verzicht hierauf das funktionelle Outcome?

LL	<b>AHA 2018; Kap 3.2 [1]; AHA 2019; Kap 3.2 [11]</b>
Empfehlung	Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.
Stärke	I, C-EO
Begründung	<p>The blood pressure (BP) level that should be maintained in patients with AIS to ensure best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others have not [91, 96-102].</p> <p>No studies have addressed the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing colloids with crystalloids, the odds of death or dependence were similar. Clinically important benefits or harms could not be excluded [103]. There are no data to guide volume and duration of parenteral fluid delivery.</p>

Empfehlung	The usefulness of drug-induced hypertension in patients with AIS is not well established.
Stärke	IIb, C-LD
Begründung	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE revised

LL	<b>DEGAM 2020, Kap 4.5 ([16])</b>
Empfehlung	Bei einem Wert <120 mmHg systolisch und Hinweisen auf eine Exsikkose sollte kristalloide Infusionslösung verabreicht werden
Stärke	B
Begründung	Leitlinienmodifikation AHA 2018 [1]

SF 1.1.7: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine medikamentöse oder mechanische Thromboseprävention im Vergleich zu keiner Thromboseprävention das funktionelle Outcome?

LL	<b>ESO Thrombosis 2016 [12]</b>
Empfehlung	We recommend that graduated compression stockings should not be used in patients with ischaemic stroke.
Stärke	QoE moderate, SoR strong against
Begründung	The meta-analysis included one large (n=2518)[104] and one small trial (n=97),[105] and indicated that GCS had no significant effect on death (during treatment period and follow up), death or dependency at six months, DVT (symptomatic or asymptomatic) or pulmonary embolism during treatment. The CLOTS trial evaluated a single type of thigh-length GCS, whereas the small trial evaluated two types of thigh-length stocking. The quality of this evidence was judged to be moderate because of a lack of power to demonstrate an effect on the most important outcomes, e.g. survival, functional status, symptomatic PE.
Empfehlung	Intermittent pneumatic compression (IPC) (thigh-length, sequential) should be used for immobile patients with ischaemic stroke. It should not be used in patients with open wounds on the legs and should be used with caution in those with existing DVT, heart failure, severe peripheral vascular disease or confusion where attempts to mobilise when unsupervised could lead to falls and injury.
Stärke	QoE moderate, SoR strong for
Begründung	The meta-analysis included one large (n=2876)[106, 107] and two small trials[108]. This showed that IPC had no significant effect, despite a strong trend on deaths during treatment period (OR=0.82 95%CI 0.66 to 1.02) but improved survival to six months (hazard ratio=0.86) (95% CI 0.74 to 0.99). There was no statistically significant effect on functional status or pulmonary embolism or symptomatic DVT (OR=0.73 95%CI 0.53 to 1.01).
Empfehlung	Prophylactic anticoagulation with unfractionated heparin (UFH) (5000U 2, or 3 daily) or low molecular weight heparin (LMWH) or heparinoid should be considered in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of venous thromboembolism is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use.
Stärke	QoE moderate, SoR weak for
Begründung	The meta-analysis included one very large trial (n=14,578)[109] and four small trials of UFH, eight small trials of LMWHs or heparinoids and one of a heparinoid. Prophylactic anticoagulants were not associated with any significant effect on death during the treatment period or follow up, or functional status by final follow up

Empfehlung	Where a judgement has been made that prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort associated single daily dose vs. multiple daily injections but these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function
Stärke	QoE moderate, SoR weak for
Begründung	The meta-analysis included one large trial (n=1762)[110] and two smaller trials comparing LMWHs with UFH and four small trials comparing heparinoids with UFH. There were no significant effects on death during follow up, death or disability. We judged the quality of this evidence to be moderate due to imprecision with respect to these outcomes. There were non-significant trends towards reduction in pulmonary emboli and symptomatic intracranial haemorrhage but there was a statistically significant increase in major extracranial haemorrhage (OR=3.79) (95%CI 1.30 to 11.03) with LMWH. We judged the quality of this evidence to be moderate due to imprecision with respect to these outcomes. The use of LMWH was associated with a statistically significant reduction in DVTs (OR=0.55) (95%CI 0.44 to 0.70) which were mostly asymptomatic. We judged the quality of this evidence to be high.
LL	<b>AHA 2018, Kap 4.8 [1]; AHA 2019, Kap 4.9 [11]</b>
Empfehlung	In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).
Stärke	I; B-R
Begründung	CLOTS (Clots in Legs or stockings After Stroke) 3 was a multicenter trial enrolling 2867 patients in 94 centers in the United Kingdom and comparing the use of IPC with routine care to no IPC with routine care in immobile stroke patients for venous thromboembolism prophylaxis. Eligible patients were enrolled within 3 days of the acute stroke and could not mobilize to the toilet without the help of another person. Routine care was defined as the use of aspirin for nonhemorrhagic stroke, hydration, and possible compression stockings. A total of 31% of the patients received prophylactic or full-dose heparin or LMWH, but these patients were evenly distributed between both groups. After the exclusion of 323 patients who died before any primary outcome and 41 who had no screening, the primary outcome of DVT occurred in 122 of 1267 IPC participants (9.6%) compared with 174 of 1245 no-IPC participants (14.0%), giving an adjusted OR of 0.65 (95% CI, 0.51–0.84; P=0.001). Among patients treated with IPC, there was a statistically significant improvement in survival to 6 months (HR, 0.86; 95% CI, 0.73–0.99; P=0.042) but no improvement in disability. Skin breaks were more common in the IPC group (3.1% versus 1.4%; P =0.002). Contraindications to IPC include leg conditions such as dermatitis, gangrene, severe edema, venous stasis, severe peripheral vascular disease, postoperative vein ligation, or grafting, as well as existing swelling or other signs of an existing DVT [107]. A meta-analysis including this trial and 2 smaller trials confirmed these results [12].
Empfehlung	The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile patients with AIS is not well established.
Stärke	IIb; A
Begründung	The most recent and comprehensive meta-analysis of pharmacological interventions for venous thromboembolism prophylaxis in AIS included 1 very large trial (n=14 578) and 4 small trials of UFH, 8 small trials of LMWHs or heparinoids, and 1 trial of a

	heparinoid [12]. Prophylactic anticoagulants were not associated with any significant effect on mortality or functional status at final follow-up. There were statistically significant reductions in symptomatic pulmonary embolisms (OR, 0.69; 95% CI, 0.49–0.98) and in DVTs, most of which were asymptomatic (OR, 0.21; 95% CI, 0.15–0.29). There were statistically significant increases in symptomatic intracranial hemorrhage (OR, 1.68; 95% CI, 1.11–2.55) and symptomatic extracranial hemorrhages (OR, 1.65; 95% CI, 1.0–2.75). There may be a subgroup of patients in whom the benefits of reducing the risk of venous thromboembolism are high enough to offset the increased risks of intracranial and extracranial bleeding; however, no prediction tool to identify such a subgroup has been derived [12, 111, 112].
Empfehlung	When prophylactic anticoagulation is used, the benefit of prophylactic-dose LMWH over prophylactic-dose UFH is uncertain.
Stärke	IIb; B-R
Begründung	The most recent and comprehensive meta-analysis comparing LMWH or heparinoid with UFH for venous thromboembolism prophylaxis in AIS included 1 large trial (n=1762) and 2 smaller trials comparing LMWH with UFH and 4 small trials comparing heparinoids with UFH. There were no significant effects on death or disability for LMWH/heparinoids compared with UFH [12]. The use of LMWH/heparinoid was associated with a statistically significant reduction in DVTs (OR, 0.55; 95% CI, 0.44–0.70), which were mostly asymptomatic, at the expense of a greater risk of major extracranial hemorrhages (OR, 3.79; 95% CI, 1.30–11.03). LMWH can be administered once a day and thus is more convenient for nurses and comfortable for patients. Higher cost and increased bleeding risk in elderly patients with renal impairment are disadvantages of LMWH that should be kept in mind
Empfehlung	In ischemic stroke, elastic compression stockings should not be used.
Stärke	III: Harm; B-R
Begründung	2016 Rehab-GL
<b>LL</b>	<b>Australia 2017, Kap 6.5.15 [6]</b>
Empfehlung	For acute ischaemic stroke patients who are immobile, low molecular weight heparin in prophylactic doses may be used in the absence of contraindications.
Stärke	Weak
Begründung	In a randomised controlled trial [110], 1762 acute ischaemic stroke patients, within 48 h of the onset of stroke symptoms, received either enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 U subcutaneously every 12 h for 10 days (range 6–14). Study treatment was not blinded. The primary efficacy endpoint was the cumulative occurrence of confirmed venous thromboembolism, defined as the composite of symptomatic or asymptomatic deep vein thrombosis, or symptomatic or fatal pulmonary embolism during the study treatment phase (up to day 14). The primary safety endpoints were symptomatic intracranial haemorrhage, major extracranial haemorrhage, and all-cause mortality up to 48 h after treatment. Enoxaparin significantly reduced the frequency of venous thromboembolism in the efficacy population at day 14 compared with unfractionated heparin (relative risk [RR] reduction 43%; difference –7.9%, 95% CI –11.6 to –4.2).
Empfehlung	For acute stroke patients who are immobile, the use of intermittent pneumatic compression may be used, either as an alternative to low molecular weight heparin or in those with a contraindication to pharmacological DVT prophylaxis (including patients with intracerebral haemorrhage or within 24 hours of thrombolysis).
Stärke	Weak



Begründung	<p>A multicentre randomised trial [107] involving 2,876 participants assessed the effectiveness of intermittent pneumatic compression (IPC) on the prevention of deep vein thrombosis (DVT). The CLOTS3 trial is the largest randomised controlled trial of IPC to date. IPC was shown to significantly reduce proximal DVT (32 per 1000) and all DVTs (52 per 1000). There was a trend towards reduced pulmonary embolism at 30 days in the intervention group but the difference was not statistically significant (OR 0.83, 95% CI 0.60 - 1.36) and the investigators did not screen systematically for pulmonary embolism. The main risk of IPC is of skin breaks which were present to a small degree (3% in the treatment arm vs 1% in the control arm) but showed a statistically significant difference. This risk did not seem to lead to poorer outcomes overall. There also appears to be a reduction of death by 6 months (OR 0.85, 95%CI 0.70 - 1.01) which in sub-analyses seems to occur in the most disabled group of patients.</p> <p>Economic analyses of the CLOTS3 data [113] showed that the direct cost of preventing DVT using IPC was £1282 (95% CI £785 to £3077)</p> <p>A previous Cochrane review by Naccarato et al [114] had found a non-significant reduction in DVTs from IPC (OR 0.45, 95% CI 0.19 to 1.10). However, this was based on two small trials with only 177 participants. The CLOTS3 trial had much greater power to detect an effect.</p>
Empfehlung	Antithrombotic stockings are not recommended for the prevention of DVT or PE post stroke.
Stärke	Strong against
Begründung	A Cochrane review of physical methods for preventing deep vein thrombosis (DVT) after stroke included two randomised trials of graduated compression stockings (GCS), involving 2615 participants [114]. Meta-analysis showed that GCS did not significantly reduce the risk of DVT or death by the end of follow-up.
LL	<b>Canada 2018, S. 102 [8]</b>
Empfehlung	All stroke patients should be assessed for their risk of developing venous thromboembolism (deep vein thrombosis and pulmonary embolism). Patients at high risk include those who are unable to move one or both lower limbs; those who are unable to mobilize independently; a previous history of venous thromboembolism; dehydration; and comorbidities such as cancer
Empfehlung	Patients at high risk of venous thromboembolism should be started on thigh-high intermittent pneumatic compression devices (IPC) or pharmacological venous thromboembolism prophylaxis immediately if there is no contraindication (e.g. systemic or intracranial haemorrhage)
Stärke	A
Begründung	The use of external compression stockings/devices have been investigated in a series of three large, related RCTs, the Clots in Legs Or sTockings after Stroke (CLOTS) trials. In CLOTS 1 [104], 2,518 patients, admitted to hospital within 1 week of acute ischemic stroke or ICH and who were immobile were randomized to either routine care plus thigh-length graded compression stockings (GCS) or to routine care plus avoidance of GCS. Patients wore the garments day and night until they became mobile, were discharged, or there were concerns with skin breakdown. At 30 days there was no significant difference between groups in the incidence of proximal DVT (GCS 10.0% vs. avoid GCS 10.5%). GCS use was associated with a non-significant absolute reduction in risk of 0.5% (95% CI 1.9% to 2.9%). The incidence of any DVT or PE was non-significantly lower in the GCS group (17.0% vs. 18.4%, OR=0.91, 95% CI 0.74-

	<p>1.11), but the frequency of skin ulcers or breakdown were significant higher in the GCS group (5.1% vs. 1.3%, OR=4.18, 95% CI 2.40-7.27). The inclusion criteria for the CLOTS 2 trial [106] were similar to those of CLOTS 1. In this trial, 3,114 patients were randomized to wear thigh-length stockings or below-knee stockings while they were in the hospital, in addition to routine care, which could have included early mobilization, hydration, and/or the use of anticoagulants/antiplatelets. At 30 days, there was a significant reduction in the incidence of proximal DVT associated with thigh-length GCS (6.3% vs. 8.8%, adj OR=0.69, 95% CI 0.53-0.91, p=0.008). The incidence of asymptomatic DVT were also lower in the thigh length GCS group (3.2% vs. 4.8%, adj OR=0.64, 95% CI 0.44-0.93, p=0.02). The use of thigh-length GCS was associated with an increased risk of skin breakdown (9.0% vs. 6.9%, OR=1.33, 95% CI 1.031-1.73, p=0.03). Finally, in CLOTS 3 [107] 2,876 patients were randomized to wear thigh length intermittent pneumatic compression (IPC) device or to no IPC at all times except for washing and therapy, for a minimum of 30 days. The mean duration of IPC use was 12.5 days and 100% adherence to treatment was achieved in only 31% in the IPC group. The incidence of proximal DVT within 30 days was significantly lower for patients in the IPC group (8.5% vs. 12.1%, OR=0.65, 95% CI 0.51-0.84, p=0.001, ARR=3.6%, 95% CI 1.4%-5.8%). There were no significant differences between groups for the outcomes of: death at 30 days (10.8% vs. 13.1%, p=0.057), symptomatic proximal DVT (2.7% vs. 3.4%, p=0.269), or PE (2.0% vs. 2.4%, p=0.453). The incidence of any DVT (symptomatic, asymptomatic, proximal or calf) was significantly lower for IPC group (16.2% vs. 21.1%, OR=0.72, 95% CI 0.60-0.87, p=0.001). Skin breakdown was more common in IPC group (3.1% vs. 1.4%, OR=2.23, 95% CI 1.313-3.81, p=0.002). At 6 months, the incidence of any DVT remained significantly lower in the IPC group (16.7% vs. 21.7%, OR=0.72, 95% CI 0.60-0.87, p=0.001). The incidence of any DVT, death or PE also remained significantly lower for IPC group (36.6% vs. 43.5%, OR=0.74, 95% CI 0.63-0.86, p&lt;0.0001).</p>
Empfehlung	<p>Low molecular weight heparin (i.e., enoxaparin) should be considered for patients with acute ischemic stroke at high risk of venous thromboembolism; or unfractionated heparin for patients with renal failure</p>
Stärke	<p>A</p>
Begründung	<p>The use of low molecular weight heparins (LMWH) has been shown to be more effective for the prevention of venous thromboembolism compared with unfractionated heparin (UFH) and is associated with a lower risk of serious bleeding events. A Cochrane review [115] included the results from 9 RCTs (n= 3,137) of patients with acute ischemic stroke who were randomized within 14 days of stroke onset to receive LMWHs or heparinoids, or UFH for an average of 10 to 12 days. The odds of DVT occurrence during treatment period were lower in the LMWH/heparinoid group (OR=0.55, 95% CI 0.44 -0.70, p&lt;0.0001). There was no difference between groups in mortality during the treatment period or follow-up, nor in the odds of any ICH/hemorrhagic transformation during treatment (OR= 0.75, 95% CI 0.46- 1.23, p=0.25); however, there was an increased risk of major extracranial hemorrhage associated with the UHF group (OR= 3.79, 95% CI 1.30-11.06, p=0.015). The authors cautioned that the event rates for serious events (pulmonary embolus, death and serious bleeding) were too low to provide reliable estimates of the risk and benefits.</p> <p>In the PREVAIL trial [110], 1,762 patients who had experienced an ischemic stroke within the previous 48 hours and who were immobile with NIHSS (leg) motor scores of <math>\geq 2</math>, were randomized to receive 40 mg enoxaparin subcutaneously once daily or 5000U UFH twice daily with UFH, for 10 days. The risk of all DVT at 14 days was 43%</p>

	<p>lower among patients receiving enoxaparin (10% vs. 18%, RR= 0.57, 95% CI 0.44 to 0.76, p&lt;0.0001). The incidences of all proximal and distal DVT at 14 days were lower among patients receiving enoxaparin (5% vs. 10%, RR= 0.47, 95% CI 0.31 to 0.72, p=0.0003 and 7% vs. 13%, RR= 0.52, 95% CI 0.37 to 0.74, p=0.0002, respectively). There were no differences between groups in the incidence of symptomatic DVT or PE at 14 days (DVT: &lt;1% vs. 1%, RR=0.29, 95% CI 0.06-1.38, p=0.096; PE: &lt;1% vs. 1%, RR= 0.29, 95% CI 0.02-1.39, p=0.059). The protective effects were maintained at day 30, 60 and 90, following treatment. There were no significant differences between groups in any of the bleeding outcomes: total bleeding events, symptomatic ICH, major extracranial hemorrhage, all-cause mortality at days 14 or 90. In subgroup analysis treatment was effective regardless of time to initiation of prophylaxis, diabetes, obesity, previous stroke, stroke severity (NIHSS score <math>\geq 14</math> vs. <math>&lt; 14</math>), gender or age. Using data from the PREVAIL trial, Pineo et al. [116] conducted an economic analysis associated with enoxaparin or UFH use in a hypothetical cohort of 10,000 acutely ill medical inpatients. Although the drug cost was higher (\$260 vs. \$59), enoxaparin was associated with an overall average net savings of \$1096 per patient. The cost savings was highest for patients with more severe strokes (NIHSS score <math>\geq 14</math>). The increased cost of enoxaparin was off-set by the avoidance of additional medical costs associated with reduced event rates of DVT and PE.</p>
	Anmerkung: zwei neuere Cochrane reviews vorhanden [111, 117]

<b>LL</b>	<b>RCP 2016 [10]</b>
Empfehlung	Patients with immobility after acute stroke should be offered intermittent pneumatic compression within 3 days of admission to hospital for the prevention of deep vein thrombosis. Treatment should be continuous for 30 days or until the patient is mobile or discharged, whichever is sooner.
Empfehlung	Patients with immobility after acute stroke should not be routinely given low molecular weight heparin or graduated compression stockings (either full-length or below-knee) for the prevention of deep vein thrombosis
Empfehlung	Patients with ischaemic stroke and symptomatic deep vein thrombosis or pulmonary embolism should receive anticoagulant treatment provided there are no contraindications.
Begründung	CLOTS [106, 107, 113]

**SF 1.1.8: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA ein systematisches Dysphagie-Screening im Vergleich zum Nicht-Screening das funktionelle Outcome?**

<b>LL</b>	<b>LL ESPEN Nutrition 2018, Kapitel 6 [29]</b>
Empfehlung	A formalized screening for dysphagia should be performed in all stroke patients as early as possible and before oral intake
Stärke	B
Begründung	<p>Dysphagia affects at least 50% of patients with ischemic or hemorrhagic stroke [118, 119]. In the acute stage of stroke aspiration pneumonia is the most important complication of dysphagia. Adjusted for other risk factors dysphagia more than doubles the risk for this complication [120].</p> <p>Several studies have demonstrated that a formalized dysphagia screening and assessment is capable to reduce the rate of pneumonia [21] In particular, the prospective registry-based cohort study by Bray et al. has demonstrated in 63,650 stroke patients that any delay in dysphagia screening and comprehensive dysphagia assessment leads to an increase in stroke-associated pneumonia in a strong time-</p>

	dependent manner [121]. Therefore, screening and if necessary assessment for dysphagia should be performed as early as possible. The diagnostic approach starts with a formal aspiration screening, which may be a water swallow test [122-124] or a multi-consistency-test [125-128]
Empfehlung	All stroke patients failing the dysphagia screening or demonstrating symptoms of or risk factors for dysphagia should be evaluated with a more thorough assessment of swallowing function as early as possible.
Stärke	B
Begründung	If a patient fails the screening or demonstrates signs of dysphagia, such as coughing, choking, wet voice, food-residuals in the mouth or pneumonia outside the screening test, a more thorough assessment has to be performed [350,355]. The same is true if the screening is negative, but risk factors for dysphagia such as dysarthria, aphasia, facial palsy, cognitive impairment, decreased level of consciousness and high stroke severity are present [123, 129-132]. The more severe the stroke, the higher is the probability of dysphagia. In fact, a National Institute of Health stroke scale of 10 and above demonstrated a high sensitivity and specificity in predicting dysphagia [360,361]. When it comes to a more comprehensive assessment, a clinical bedside assessment (CBA) performed by a speech and language therapist, a VFS or a FEES can be performed. Since the diagnostic properties of the CBA have been less well explored and questioned recently, instrumental testing should be preferred [133]. A study by Bax et al. could suggest that access to FEES was associated with a significantly reduced rate of pneumonia after stroke [134].

LL	<b>German Nutrition 2013 [21]</b>
Empfehlung	A formalised screening for dysphagia should be performed in all stroke patients
Stärke	B
Begründung	In spite of this evidence, the impact of bed-side dysphagia screening, in particular the accuracy of the WST (Water Swallow Test) has been repeatedly questioned during recent years. Two meta-analyses of Ramsey et al. and Bours et al. suggested that when compared to VFSS (videofluoroscopic swallowing study) or FEES (fiberoptic endoscopic evaluation of swallowing) the sensitivity of the WST for detecting aspiration is markedly below 80% in nearly all reviewed studies [128, 135]. This observation also applies to specificity and negative and positive predictive values [128, 135]. The multiple-consistency test according to the GUSS protocol has been evaluated in one prospective study [126] and performed with a sensitivity of 100% and a specificity of 50% when compared to FEES. Therefore this test seems to be more accurate in detecting dysphagic stroke patients than all versions of the simple WST. The main disadvantage of the GUSS protocol consists in its low specificity due to which dietary recommendations may be more restrained and nasogastric tubes may be inserted more often than actually necessary.
Empfehlung	All stroke patients failing the dysphagia screening should be evaluated with a more thorough assessment of swallowing function
Stärke	B
Begründung	Due to the insufficient sensitivity of most published screening procedures or missing replication studies, stroke patients without pathological findings in the initial bedside testing should be referred to a further swallowing assessment if other known clinical predictors of dysphagia are present, such as a severe neurological deficit, marked dysarthria or aphasia or a distinct facial palsy [129, 131, 132].

Empfehlung	Clinical bedside assessment (CBA): The CBA may be performed by trained personnel, typically a speech language pathologist, according to a standardised protocol
Stärke	C
Empfehlung	The limitations of clinical testing, in particular insufficient detection of silent aspiration and poor information on the efficacy of an intervention imply that a reliable, timely and cost effective instrumental swallow evaluation might be useful in acute stroke patients. Both VFSS and FEES may be used to this end
Stärke	C
Empfehlung	Assessment of dysphagia should be carried out as early as possible
Stärke	CCP
Begründung	The CBA published by Logemann contains 28 items and has been tested for inter- and intra-rater reliability [136]. Alternatively, other standardized protocols may be taken into consideration. VFSS has long been regarded as gold standard in the assessment of dysphagia. VFSS dynamically visualizes the oral, pharyngeal and esophageal phases of swallowing. By using non-ionic contrast agents the risk of pulmonary complications in patients at risk of aspiration is minimized [41]. VFSS provides a comprehensive assessment of swallowing, determining not only whether the patient is aspirating but also why. Furthermore, it allows for experimentation with different textures, postures and manoeuvres suggested to improve the safety and efficiency of the swallow [137]. Penetration and aspiration are ideally graded according to the rating scale of Rosenbek et al. [138]. FEES is an instrumental assessment of swallowing using a flexible nasolaryngoscope which is passed through the nares, over the velum into the pharynx. Recent studies suggest that in patients with acute stroke FEES is a safe, reliable and predictive tool of dysphagia assessment [139-141]. Main advantages of FEES over VFSS, in particular with regard to acute stroke patients, are i) that the assessment can be done at the bedside, ii) that severely handicapped and uncooperative patients may be readily examined, iii) that the lack of radiation exposure enables short-term re-evaluations, and iv) that the saliva of the patients is directly visualized [142, 143]. The main disadvantage of FEES compared to VFSS is that not the whole swallowing act is covered and that intradeglutively, for a short moment the endoscopic view is impaired by the so called "white-out". However, in spite of this weakness of FEES two recent studies suggest that FEES is more sensitive than VFSS in detecting residues, penetration and aspiration [144, 145].
LL	<b>AHA 2018, Kap 4.6 [1]; AHA 2019, Kap 4.7 [11]</b>
Empfehlung	Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is reasonable to identify patients at increased risk for aspiration.
Stärke	Ila, C-LD
Begründung	Dysphagia, a common (37%–78%) complication of acute stroke, is a risk factor for aspiration pneumonia and is associated with higher mortality and worse patient outcomes. The evidence review committee completed a systematic review to determine whether dysphagia screening, compared with no screening or usual care, decreased outcomes of pneumonia, death, or dependency.[68, 146-148] There were insufficient data to determine whether implementation of a dysphagia screening protocol reduces the risk of death or dependency. However, insufficient evidence does not mean that dysphagia screening is ineffective. Joundi et al [149] determined that patients who failed dysphagia screening were older, had a higher rate of multiple comorbidities (including prior stroke and dementia), more often came from a long-term care facility, more often presented with weakness and speech deficits, had a

	lower level of consciousness, and had a higher stroke severity. Patients who failed dysphagia screening were more likely to develop pneumonia (13.1% versus 1.9%), to have more severe disability (52.4% versus 18.0%), and to be discharged to a long-term care institution (14.0% versus 4.3%). Early dysphagia screening can be effective to identify patients at higher risk for aspiration, which is associated with greater risk of pneumonia, even if dysphagia screening was not associated with reduced rates of pneumonia or improvements in death or disability when tested in RCTs.[68, 147, 148]
Empfehlung	It is reasonable for dysphagia screening to be performed by a speech-language pathologist or other trained healthcare provider.
Stärke	Ila; C-LD
Begründung	2016 Rehab-GL
Empfehlung	An endoscopic evaluation is reasonable for those patients suspected of aspiration to verify the presence/absence of aspiration and to determine the physiological reasons for the dysphagia to guide the treatment plan.
Stärke	Ila; B-NR
Begründung	2016 Rehab-GL
<hr/>	
LL	<b>NICE 2019, 10.1 [24]</b>
Empfehlung	On admission, people with acute stroke should have their swallowing screened by an appropriately trained healthcare professional before being given any oral food, fluid or medication.
Stärke	1b++
Empfehlung	If the admission screen indicates problems with swallowing, the person should have a specialist assessment of swallowing, preferably within 24 hours of admission and not more than 72 hours afterwards
Stärke	1b++
Empfehlung	People with suspected aspiration on specialist assessment or who require tube feeding or dietary modification for 3 days should be: <ul style="list-style-type: none"> <li>• reassessed and be considered for instrumental examination</li> <li>• referred for dietary advice.</li> </ul>
Stärke	./.
Empfehlung	In people with dysphagia, food and fluids should be given in a form that can be swallowed without aspiration following specialist assessment of swallowing.
Stärke	./.
Begründung	Swallow screening is useful in determining early management of feeding after stroke, however, it is not very accurate in isolation. The sensitivity and specificity of screening is such that some patients will be judged unsafe to swallow when there is no evidence on instrumental assessment that they are aspirating, and a smaller number will be assessed as safe to swallow when in fact they are not. The GUSS bedside screen appears to be a better predictor than other clinical assessments of aspiration as detected by FEES, but the numbers in this study are small. There is good evidence for a link between dysphagia and poor clinical outcome (chest infection, death, disability, discharge destination, length of stay) reinforcing the need for early detection and management. Although aspiration is clearly associated with worse outcome, there is no evidence that the withdrawal or modification of oral intake prevents chest infection or other adverse outcomes. Research evidence is lacking and would be difficult to obtain, as it would be unethical to give oral food or most fluids to patients who are aspirating although a trial of water in this situation might be possible. No evidence that directly compared FEES vs VF was reviewed. Each instrumental

	assessment has its advantages and disadvantages. VF is most widely available but is limited by practical considerations (the need to sit up and to be able to follow instructions) as well as radiation dosage. FEES is more appropriate for patients who are immobile and for whom VF might be impractical. One limitation of FEES is that the moment of swallowing is not visualised, and therefore provides less neurophysiological information than VF. Both techniques may be difficult to interpret especially by inexperienced practitioners and specialist training is necessary. All assessments only reveal the swallow at one moment in time so all patients need careful monitoring and observation and reassessment when necessary. The group were concerned that patients with persistent dysphagia were at risk of malnutrition and that those patients who remained dysphagic after 3 days should have access to detailed instrumental examination. The patient representatives on the GDG felt that the assessment used should be that which provides the most accurate diagnosis. They also felt that it is important to distinguish whether or not tube feeding is required, and that if tube feeding is required then it is commenced as soon as possible. There was concern from the group that the recommendation was based on relatively little evidence.
<b>LL</b>	<b>Canada 2018, S. 59, S. 103 [8]</b>
Empfehlung	Patient swallowing screen should be completed as early as possible by a practitioner trained to use a validated swallowing screening tool as part of initial assessment, but should not delay decision-making regarding eligibility for acute stroke treatments
Stärke	A
Empfehlung	Ideally swallow screening should be done within 24 hours of hospital arrival, including patients that receive acute stroke treatments
Stärke	C
Empfehlung	Patients should remain NPO (nil per os - no oral intake) until swallowing screen completed for patient safety
Stärke	B
Empfehlung	Oral medications should not be administered until swallowing screen using a validated tool has been completed and found normal; alternate routes such as intravenous and rectal administration should be considered while a patient is NPO
Stärke	B
Empfehlung	Patients found to have abnormal swallowing ability on screening should be referred to a healthcare professional with expertise in swallowing assessments for an in-depth swallowing assessment
Stärke	B
Empfehlung	Interdisciplinary team members should be trained to complete initial swallowing screening for all stroke patients to ensure patients are screened in a timely manner
Stärke	C
Empfehlung	Abnormal results from the initial or ongoing swallowing screens should prompt referral to a speech-language pathologist, occupational therapist, and/or dietitian for more detailed assessment and management of swallowing, nutritional and hydration status
Stärke	C
Begründung	A standardized program for screening, diagnosis and treatment of dysphagia following acute stroke results has been shown to reduce the incidence of pneumonia and feeding tube dependency. Bedside screening may include components related to a patient's level of consciousness, an evaluation of the patient's oral motor

function and oral sensation, as well as the presence of a cough. It may also include trials of fluid. Coughing during and up to one minute following test completion and/or “wet” or hoarse voice are suggestive of an abnormal swallow. Silent aspiration may occur in patients who do not cough or complain of any problems with swallowing or have no wet-sounding voice, highlighting the importance of dysphagia screen for all patients acutely following stroke.

Hinchey et al. [150] evaluated adherence to screening for dysphagia and associated pneumonia among individuals with ischemic stroke in the United States and reported that pneumonia occurred less frequently among those who had received a dysphagia screen (2.4% vs. 5.4%). Similar results were found in a study by Lakshminarayan et al. [151] in which unscreened patients were found to have a greater risk of developing pneumonia than patients who had passed a screen for dysphagia (OR=2.2; 95% CI 1.7-2.7). In contrast to these two studies suggesting that screening is associated with a lower incidence of pneumonia, Masrur et al. [152] reviewed the records of 314,007 patients with ischemic stroke admitted to hospitals participating in the Get-with-the-Guideline Registry. The outcomes of patients who had received a standardized swallowing screen including bedside or instrumental methods, were compared with those of patients who had not been screened. 68.9% patients were screened for dysphagia, while 31.1% were not. Of the 5.7% of patients who developed post-stroke pneumonia within 48 hours of admission, patients who were screened for dysphagia were more likely to develop pneumonia compared with those who did not develop pneumonia (7.5% vs. 68.5%,  $p < 0.001$ ). This finding suggests that patients who were perceived to be at high risk of dysphagia/aspiration may have been screened preferentially compared with patients perceived to be at low risk. To wit, Joundi et al. [149] reported that patients with mild strokes were less likely to be screened compared with those with moderate strokes (adj OR=0.51, 95% CI 0.41-0.64) using data from 6,677 patients included in the Canadian Stroke Registry.

Middleton et al. [56], in a multi-centered cluster RCT including 19 large tertiary care facilities with acute stroke units, randomized 4,198 patients to receive care at institutions that had adopted nursing protocols to identify and manage 3 complications- hyperglycemia, fever and swallowing dysfunction or to a control facility. The dysphagia component included education and training in the use of the ASSIST screening tool. While the intervention was associated with a decreased frequency of death or dependency at 90 days (42% vs. 58%,  $p = 0.002$ ) and swallowing screening was performed more frequently in the intervention group (46% vs. 7%,  $p < 0.0001$ ), there was no difference between groups in the incidence of pneumonia (2% vs. 3%,  $p = 0.82$ ). Using UK registry data, Bray et al [121] reported a higher risk of stroke-associated pneumonia (SAP) with increasing times to dysphagia screening and assessment. The overall incidence of SAP was 8.7% (13.8% for patients not screened, 8.0% for patients who were screened and 14.7% for patients who received a comprehensive assessment). Independent predictors of receiving a dysphagia screen have been reported to include older age, admission to specialized units, the presence of weakness, increased stroke severity, speech difficulties and treatment with thrombolysis [149, 152].

The effectiveness of a variety of treatments for dysphagia management was recently the subject of a Cochrane review [153]. The results from 33 RCTs examining acupuncture, behavioral interventions, drug therapy, neuromuscular electrical stimulation, pharyngeal electrical stimulation, physical stimulation, (thermal, tactile) transcranial direct current stimulation and transcranial magnetic stimulation, were included. Pooling of results was not possible for many of the outcomes due to small



	<p>numbers of studies available evaluating similar interventions/outcomes. Death or dependency at end of trial was the primary outcome, although only two RCTs were included in the pooled result. The results were not significant (OR=1.05, 95% CI 0.63 to 1.75, p=0.86). Acupuncture and behavioural modifications were associated with reduction in the presence of dysphagia at the end of treatment. No significant treatment effect was associated with subgroup analysis by therapy type (behavioral interventions, drug therapy, and electrical stimulation) for the outcome of chest infections.</p>
<b>LL</b>	<b>Australia 2017, Kap 3.9 [6]</b>
<b>Empfehlung</b>	People with acute stroke should have their swallowing screened, using a validated screening tool, by a trained healthcare professional.
<b>Stärke</b>	Weak
<b>Begründung</b>	<p>A nation-wide, registry-based prospective cohort study in England and Wales analysed data from 63,650 patients admitted with acute stroke [121]. The overall incidence of stroke associated pneumonia was 8.7%, and the median time from admission to dysphagia screening was 2.9 hours (IQR 1.3–5.7 hours). They found that patients with the longest delays in dysphagia screening (4th quartile, &gt;= 345 minutes) had a higher risk of stroke-associated pneumonia (OR 1.36, 95%CI 1.20–1.53), compared with the shortest time (1st quartile, 0–79 minutes).</p> <p>Swallow screen test may increase performance in identifying dysphagia.</p> <p>Systematic reviews have found screening assessments vary greatly in terms of their methods, endpoints, and psychometric values. Poorjavad and Jalaie [125] in a recent systematic review concluded that there are four screening tools that have used high-quality methodologies to determine the validity, reliability, sensitivity and specificity when compared with instrumental measures of swallowing function. These four screening tools are the (1) Oral Pharyngeal and Clinical Swallowing Examination, (2) Bedside Aspiration Test, (3) The Gugging Swallowing Screen, and (4) The Toronto Bedside Swallowing Screening Test (TOR-BSST), and all have consistently scored well in terms of sensitivity and specificity.</p> <p>Schepp et al. (2012) [154] had previously conducted a systematic review of swallowing screens for use after acute stroke. They included screening tools and assessments that did not require specialised training and skills and had been validated against a gold standard, and reported validity and reliability data. Only four tools met their criteria, with the TOR-BSST the only overlap with the recent review by [125]. Two of the screening tools had small sample sizes, while the TOR-BSST and Acute Stroke Dysphagia Screen (ASDS) were considered to have sufficient sample sizes. Reliability was high for both of these screening tools, as was sensitivity and NPV, but specificity and PPV values were not as strong. These authors highlight that evidence supporting the impact screening has on morbidity, mortality, and length of hospital stay is still to be produced.</p> <p>Daniels et al. (2012) [155] conducted a systematic review focused on identifying valid items for inclusion in a swallowing screening tool (SST). It was noted that inclusion of a direct assessment of swallowing was associated with high-quality studies. Specifically, they noted that an essential item for inclusion was a water swallow test (WST); with cough and wet voice in response to the WST the essential predictors or aspiration. They did note that most current SST focus on aspiration risk and not dysphagia. The recommendation was for further research to determine the volume of water that should be used in the WST; whether it is an independent screening measure or should occur in conjunction with consideration of non-swallowing items;</p>

	<p>and whether it can predict dysphagia rather than just aspiration. Leder et al (2012) [156] reported on an observational study that suggested that the 90-cc WST (n = 75) and concluded that if 90-cc challenge is passed diet recommendations can be safely made without further objective dysphagia assessment. Martino 2014 [157] reported a high diagnostic performance of using water intake of 10 teaspoons and a lingual motor test.</p> <p>A recent cohort study suggests that swallow frequency rates also have potential as a screening tool that can be used without requiring trained personnel [158]. Based on a cohort of 63 acute stroke patients, a swallowing frequency rate <math>\leq 0.40</math> swallows per minute (SPM) had a sensitivity of 96% and specificity of 68% for identifying dysphagia. As an observational study with a small sample size, this provides low-quality evidence for swallowing frequency as a screening tool.</p>
Empfehlung	All stroke patients who have failed swallow screening or who deteriorate should have a comprehensive assessment of swallowing performed by a speech pathologist.
Stärke	Weak
Begründung	<p>Two systematic reviews have examined a range of bedside swallow assessment for their potential as diagnostic tools, with reference standards being instrumental swallow exams such as fiberoptic endoscopic evaluation of swallowing (FEES) and videofluoroscopy (VFS) [127, 159]. Kertscher et al only included studies with high methodological quality, and identified Volume-Viscosity Swallowing Test and Toronto Bedside Swallowing Screening Test as appropriate screening tools with high sensitivity and acceptable specificity [159]. O'Horo et al found individual studies reporting dysphonia assessments, abnormal pharyngeal sensation assessments, dual axis accelerometry, and 3 oz swallow test to be sensitive tools, but none of them was validated to be consistently sensitive [127].</p> <p>Kjaersgaard et al [160] conducted a randomised controlled trial to determine how a clinical versus instrumental assessment would influence the rate of pneumonia in a group of acquired brain injury patient. Stroke participants represented a large proportion of this group. The comparison was between the Facial-Oral Tract Therapy (FOTT) approach and the instrumental measure FEES. The pneumonia rate was slightly higher for the comparator (FEES) than for those assessed with FOTT. However, there was no statistical comparison and the rates were both quite low in this relatively small sample. Kjaersgaard et al [161] reported on the return to oral intake outcomes for the cohort of participants reported in the 2014 study. They found that the type of initial assessment did not influence the time taken to commence oral intake, nor did it influence the time to full oral intake for those participants able to achieve this during their neurorehabilitation stay.</p> <p>Mortensen and colleagues [162] reported on the diagnostic performance of the Swallowing Assessment of Saliva (SAS) based on FOTT approach. Comparison with FEES indicated that it was able to detect aspiration with a sensitivity of 91% and specificity of 88%. Therefore, the SAS as a bedside assessment tool for aspiration risk is comparable to FEES and is more likely to result in false positives rather than false negatives which is clinically preferable. However, the aim of the SAS was to identify patients at risk of aspiration, rather than to provide a comprehensive evaluation of dysphagia.</p> <p>With respect to the timing of a comprehensive swallowing assessment by a speech-language pathologist, Brady et al [121] demonstrated that there was a strong dose-response relationship between a comprehensive dysphagia assessment and stroke associated pneumonia; the earlier dysphagia was assessed, the lower the risk of pneumonia. Patients with the longest delays in dysphagia assessment (4th quartile</p>

	adjusted OR 2.01, 1.76 to 2.30) had a higher risk of stroke-associated pneumonia, with an absolute increase of pneumonia incidence of 1% per day of delay.
Empfehlung	For stroke survivors with swallowing difficulties, behavioural approaches such as swallowing exercises, environmental modifications, safe swallowing advice, and appropriate dietary modifications should be used early.
Stärke	Strong
Begründung	Geeganage et al [153] undertook a systematic review exploring the impact of a range of interventions seeking to address dysphagia and nutritional support in acute and subacute stroke. Within the range of interventions investigated only 5 were reported to have been focused on randomised controlled trials of behavioural interventions such as swallowing exercises, environmental modifications, safe swallowing advice, and appropriate dietary modifications. Three of the studies compared high and low intensity with or without usual care behavioural interventions, while the remaining 2 studies investigated differing modes of delivering interventions. Overall, behavioural interventions were found to significantly reduce dysphagia at the end of the trials. Bakhtiyari et al [163] conducted a 3-arm randomised controlled trial investigating the optimal time to introduce behavioural intervention for dysphagia, blinding patients to group allocation but not therapists or assessors. All groups were similar at baseline. Findings suggested that early intervention significantly reduced dysphagia and frequency of pneumonia as compared to both the medium and late-onset groups. The early intervention group also required fewer intervention sessions. Combined, the systematic review and recent randomised trial suggest that behavioural interventions can reduce dysphagia, and that earlier intervention is preferable to delayed intervention.

LL	<b>DEGAM 2020, Kap 6.3.5 [16]</b>
Empfehlung	Bei Patienten mit Schluckbeschwerden und/oder pathologischen Screeningbefund sollte ein weiterführendes Assessment der Schluckfunktion angeboten werden
Stärke	B, 2-3
Begründung	Leitlinienmodifikation DGEM [21], SIGN [164]
Empfehlung	Patienten ohne pathologischen Screeningbefund, bei denen aber andere etablierte klinische Prädiktoren für das Vorliegen einer Dysphagie bzw. deren Komplikationen vorhanden sind (wie insbesondere ein insgesamt schweres neurologisches Defizit, eine Dysarthrie, eine Aphasie oder eine ausgeprägte faziale Parese), sollte ebenfalls ein weiterführendes Assessment angeboten werden.
Stärke	B, 2-3
Begründung	Leitlinienmodifikation DGEM [21], SIGN [164]
Empfehlung	Patienten mit einer Dysphagie soll eine oropharyngeale Schluckrehabilitation angeboten werden, die sich aus restituierenden, kompensatorischen und/oder adaptiven Maßnahmen zusammensetzt
Stärke	A, 1 b
Begründung	Leitlinienmodifikation SIGN [164]

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with residual neurological symptoms or signs should remain nil by mouth until screened for dysphagia by a specifically trained healthcare professional.
Begründung	Working Party consensus

Empfehlung	Patients with acute stroke should have their swallowing screened, using a validated screening tool, by a trained healthcare professional within four hours of arrival at hospital and before being given any oral food, fluid or medication.
Begründung	NICE, 2016; Kertscher 2014 [159]; Martino et al, 2014 [157]; Bray et al, 2016 [121]
Empfehlung	Until a safe swallowing method is established, patients with dysphagia after acute stroke should: <ul style="list-style-type: none"> <li>– be immediately considered for alternative fluids;</li> <li>– have a comprehensive specialist assessment of their swallowing;</li> <li>– be considered for nasogastric tube feeding within 24 hours;</li> <li>– be referred to a dietitian for specialist nutritional assessment, advice and monitoring;</li> <li>– receive adequate hydration, nutrition and medication by alternative means.</li> </ul>
Begründung	NICE 2006, 2008; Geegenage et al, 2012
Empfehlung	Patients with swallowing difficulties after acute stroke should only be given food, fluids and medications in a form that can be swallowed without aspiration
Begründung	Consensus

SF 1.1.9: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt und Dysphagie die enterale Ernährung mittels Magensonde im Vergleich zu Nahrungskarenz | parenteraler Ernährung das funktionelle Outcome?

LL	<b>AHA 2018, Kap 4.7 [1]; AHA 2019, Kap 4.8 [11]</b>
Empfehlung	Enteral diet should be started within 7 days of admission after an acute stroke.
Stärke	I, B-R
Empfehlung	For patients with dysphagia, it is reasonable to initially use nasogastric tubes for feeding in the early phase of stroke (starting within the first 7 days) and to place percutaneous gastrostomy tubes in patients with longer anticipated persistent inability to swallow safely (>2–3 weeks).
Stärke	Ila; C-EO
Begründung	The FOOD RCTs (Feed Or Ordinary Diet; phases I–III), completed in 131 hospitals in 18 countries, 235 showed that supplemented diet was associated with an absolute reduction in risk of death of 0.7% and that early tube feeding (within 7 days of admission) was associated with an absolute reduction in risk of death of 5.8% and a reduction in death or poor outcomes of 1.2%. When nasogastric feeding and percutaneous endoscopic gastrostomy feeding were compared, percutaneous endoscopic gastrostomy feeding was associated with an increase in absolute risk of death of 1.0% and an increased risk of death or poor outcomes of 7.8%. The conclusion was that stroke patients should be started on enteral diet within the first 7 days of admission.[165] In 2012, a Cochrane review analyzed 33 RCTs involving 6779 patients to assess the intervention for dysphagia treatment, feeding strategies and timing (early [within 7 days] versus later), fluid supplementation, and the effects of nutritional supplementation on acute and subacute stroke patients.[153] The conclusion was that, although data remained insufficient to offer definitive answers, available information suggested that percutaneous endoscopic gastrostomy feeding and nasogastric tube feeding do not differ in terms of case fatality, death, or dependency, but percutaneous endoscopic gastrostomy is associated with fewer treatment failures (P=0.007), less gastrointestinal bleeding (P=0.007), and higher food delivery (P<.00001).

LL	<b>German Nutrition 2013 [21]</b>
----	-----------------------------------

Empfehlung	Patients with a decreased level of consciousness and mechanical ventilation often require enteral nutrition for a longer period of time and tube feeding can therefore start early
Stärke	C
Begründung	There are no systematic trials investigating this issue. Since it is mandatory to artificially feed patients with a relevant decrease of consciousness, it only remains to be decided whether parenteral or enteral nutrition is superior. There are no systematic evaluations comparing parenteral and enteral nutrition in stroke patients. Based on data in other critical care patients, an advantage of tube feeding in stroke patients can be assumed [20] but an influence on mortality has not yet been proven [166].
Empfehlung	Patients with prolonged severe dysphagia anticipated to last for more than 7 days should receive tube feeding
Stärke	CCP
Begründung	Patients with swallowing difficulties have a high risk for aspiration and aspiration pneumonia as well as for developing malnutrition. Aspiration pneumonia cannot be prevented by tube feeding in the acute phase after stroke [129, 167, 168]. However, the rate of aspiration pneumonia does not increase during enteral nutrition [169]. Thus, the aspiration risk per se does not represent an indication for tube feeding. But patients with persistent dysphagia are also at risk of malnutrition. Since malnutrition worsens the prognosis and leads to an increased rate of complications, it should be avoided [170, 171].
Empfehlung	If a sufficient oral food intake is not possible during the acute phase of stroke, enteral nutrition shall be preferably given via a nasogastric tube
Stärke	A
Empfehlung	If enteral feeding is likely for a longer period of time (> 28 days), a PEG should be chosen and shall be placed in a stable clinical phase (after 14 – 28 days)
Stärke	A
Empfehlung	Mechanically ventilated stroke patients should receive a PEG at an early stage
Stärke	B
Empfehlung	If a nasogastric tube is repeatedly removed accidentally by the patient and if artificial nutrition will probably be necessary for more than 14 days, early placement of a PEG should be considered
Stärke	B
Begründung	Dysphagia due to ischemic cerebral insult resolves within 7–14 days in 73 – 86% of the cases [172, 173]. It is therefore worthwhile to consider an access to enteral nutrition which is less invasive than percutaneous endoscopic gastrostomy at first. At present, only two prospective, randomized, controlled intervention studies exist that compare nasogastric tube feeding and PEG feeding after stroke. In a study by Norton et al. that included 30 stroke patients, 16 patients who were assigned to the PEG-group, had a better nutritional status, lower mortality and shorter hospital stay after 6 weeks of intervention [174]. In the FOOD-study no differences between PEG feeding and nasogastric tube feeding could be found regarding the endpoint “death after six months” in 321 dysphagic stroke patients [165, 169]. But patients with nasogastric tube feeding showed a significantly 7.8% lower risk of the combined end point “death and/or impaired functional status” when compared to patients with early PEG feeding after 6 months. In addition, there was an increase in pressure sores in the PEG-group (p = 0.04). In general, dislodgement of nasogastric tubes and by this poor enteral nutrition is a major concern. Two studies about nasal loops in stroke patients

	demonstrated that nasal loops are safe, well tolerated and effective at delivering full enteral nutrition [175, 176]. A recent randomized controlled trial observed an increase of 17% mean volume of fluid and tube feed given in the nasal loop group without any differences in outcome after 3 months [175]. A randomized study published in 2005 by Kostadima et al. reported that early nutrition (within 24 hours) via PEG in 41 mechanically ventilated patients with stroke or head injury was superior to feeding via nasogastric tube, as it was associated with a lower prevalence of ventilator-associated pneumonia [177]. However, a significant difference in length of stay and mortality could not be found. Conclusions for the treatment of ventilated stroke patients can be drawn from this study, as stroke patients were represented with 61%. In particular in mechanically ventilated stroke patients, in whom prolonged artificial nutrition (> 14 days) is probable, early feeding via PEG should be preferred to nasogastric tube feeding, due to a lower rate of ventilation related pneumonia [166, 177].
<b>LL</b>	<b>NICE 2019, Kap 10.2 [24]</b>
Empfehlung	<p>People with acute stroke who are unable to take adequate nutrition and fluids orally should:</p> <ul style="list-style-type: none"> <li>• receive tube feeding with a nasogastric (NG) tube within 24 hours of admission</li> <li>• be considered for a nasal bridge tube or gastrostomy if they are unable to tolerate an NG tube</li> <li>• be referred to an appropriately trained healthcare professional for detailed nutritional assessment, individualised advice and monitoring.</li> </ul>
Stärke	1++
Begründung	The Feed or Ordinary Diet (FOOD) trial showed no statistically significant difference between early versus late tube feeding with respect to mortality, morbidity, adverse events, disability, quality of life or discharge destination. Although the confidence intervals for the effect of early feeding are wide, meaning that the data are consistent with significant benefit or harm, it was felt by the group to be more biologically plausible to have a small benefit from early tube feeding rather than a negative effect. Better functional outcomes were associated with feeding via NG tube than PEG tube. The increase in GI haemorrhages in the NG group were not reflected in increases in mortality or outcome. The group agreed that NG tube feeding should be the intervention of choice for acute stroke (excluding those receiving palliative care) if it is practical to do so and that nasal bridge tubes or gastrostomy should be the intervention of choice if it is impractical to use a NG tube.
<b>LL</b>	<b>Australia 2017, Kap 6.5.2 [6]</b>
Empfehlung	All stroke patients should be screened for malnutrition at admission and on an ongoing basis (at least weekly) while in hospital
Stärke	Strong
Begründung	<p>Geeganage et al [153] conducted a Cochrane review and compared nutritional supplementation versus no nutritional supplementation in acute stroke patients. There was no significant difference on the outcome of death, death or dependence, and length of hospital stay in the meta-analysis of more than 4000 patients. It should be noted that one study FOOD Trial contributed more than 90% of the patients included in this meta-analysis [165].</p> <p>In terms of energy and protein intake, three studies totalling 174 patients showed significant improvement with nutritional supplementation. However, it should be</p>

	<p>noted there is a very high level of statistical heterogeneity (91%) and all three trials reported are very small. A recent randomised controlled trial of 146 acute stroke patients with dysphagia in China compared nasogastric nutrition and family managed nutrition [178]. Benefits were shown in improved nutritional status, reduced nosocomial infection and lower mortality rates, whereas no significant differences were found in activities of daily living (measured by Barthel Index) and neurological outcomes (measured by modified Rankin Score). This study had high risk of bias (insufficient reporting of methodology) and limited applicability to an Australian setting.</p> <p>Overall, nutrition support improves nutritional status in adults with stroke but the benefits are less clear in death or dependence. On the other hand, the quality of evidence precludes a definitive conclusion.</p>
Empfehlung	For stroke patients who do not recover a functional swallow, nasogastric tube feeding is the preferred method of feeding in the short term
Stärke	Weak
Begründung	<p>Evidence on the comparison between percutaneous endoscopic gastrostomy feeding (PEG) compared to nasogastric tube feeding (NG) comes mainly from a Cochrane review by Geegagane [153] comparing percutaneous endoscopic gastrostomy feeding (PEG) and nasogastric tube feeding (NG). A more recent meta-analysis [179] compared PEG and NG but this meta-analysis was not specific to stroke patients and included patients who required tube feeding regardless of whether they had had a stroke or not.</p> <p>Both meta-analyses showed consistent non-significant differences in critical outcomes of case fatality, death or dependency, length of stay, and chest infection or pneumonia. Indicators of nutritional status such as weight and mid-arm circumferences were also not significantly different. However, the sample sizes in the included trials were generally small (ranging from 21 to 115).</p>
Empfehlung	For stroke patients, there is no preference with regard to continuous pump (meaning using a pump for greater than or equal to 16hrs out of 24hrs for less than or equal to 80ml/hr) feeding versus intermittent bolus feeding (meaning 250-400ml/hr for 4-5times/day) therefore practical issues, cost and patient preferences should guide practice.
Stärke	weak
Begründung	One randomised controlled trial [180] has compared pump feeding undertaken over at least 16 hours of the day to bolus feeding undertaken on at least four to five occasions throughout the day. The study involved 178 patients likely to require nasogastric tube feeding for at least 4 weeks and aged 60 years or older. Most patients were either new or old stroke patients (149/178). Results indicated that compared with bolus feeding, fewer people in the pump feeding group died or developed pneumonia.
LL	<b>LL ESPEN Nutrition 2018, Kapitel 6 [29]</b>
Empfehlung	The available evidence suggests that all stroke patients should be screened for risk of malnutrition on admission to hospital (within 48 h), and the MUST can be used to identify patients who are more likely to benefit from medical nutrition therapy.
Stärke	GPP
Begründung	When compared to a normal nutritional status, malnutrition is associated with a worsened outcome in terms of increased mortality, length of hospital stay and hospitalization costs. The association between nutritional status and mortality was

	analyzed in a large cohort of 3012 patients with a recent stroke enrolled in the Feed Or Ordinary Food (FOOD) trial [181]. The 6-month mortality was higher in the group of 275 patients deemed malnourished, using a variety and often non-validated criteria, than in patients with normal nutritional status (37 vs 20%). These findings were confirmed recently using a formal nutritional screening tool in 543 patients with acute stroke. Using the Malnutrition Universal Screening Tool (MUST) to evaluate the risk of malnutrition within 48 h post stroke, from low to high, the authors found a 6-month mortality rate increasing from 6 to 42% [182].
Empfehlung	Patients with prolonged severe dysphagia after stroke that presumably last for more than 7 days should receive early (not more than 72 h) enteral tube feeding.
Stärke	GPP
Empfehlung	Critically ill stroke patients with decreased level of consciousness that need mechanical ventilation should receive early (not more than 72 h) enteral tube feeding.
Stärke	GPP
Begründung	<p>Around 8.5e29% of stroke patients require tube feeding in the acute phase of stroke [183]. However, it remains unclear what kind of stroke patients can improve their prognosis with enteral feeding [21, 153, 184]. Probably, previously malnourished patients could benefit the more, although this affirmation has not been proved. In the FOOD trial-2 [169], early enteral feeding (within seven days after stroke) was compared with tube feeding initiated after seven days in 859 patients. Early tube feeding reduced mortality in dysphagic patients by 5.8%, compared with the group of "late" initiation, although the differences were not significant. However, the proportion of patients surviving with poor outcome (great disabilities) was higher in the group who started early enteral nutrition, as well as prevalence of gastrointestinal bleeding. It could be speculated that these patients with poor outcome probably would not have survived without enteral nutrition. This study suffers from important limitations in the design. The first is the lack of standardization of nutritional assessment (as previously stated), but probably the most important bias for this question is that patients with a clear indication for early tube feeding were not included, only those in which the attending physician was unsure about the adequate nutritional therapy. Zheng [178] evaluated the impact of early enteral nutrition (within 72 h of admission) on short term prognosis after acute stroke. However, this non-randomized study has serious limitations in the design, as they compared 75 patients admitted to a stroke unit managed with enteral nutrition with 71 patients admitted to the regular ward that received family managed oral nutrition.</p> <p>Critically ill stroke patients with a severe decreased level of consciousness that need mechanical ventilation can benefit from enteral nutrition. In ESPEN Guidelines on enteral nutrition: Intensive care [20], critically ill patients benefit from early medical nutrition therapy (preferably by the enteral route) if they cannot meet their nutritional requirements by the oral route within three days. Although the studies that support this recommendation are not performed specifically in stroke patients, the beneficial effects may be extrapolated to stroke patients. Patients with presumably long duration of dysphagia (more than 7 days) because of the severity of stroke or certain cerebral infarct localizations (as bulbar and brainstem areas) are at nutritional risk and therefore they can benefit from enteral nutrition. In these cases, enteral nutrition should start early, as acquired malnutrition is a negative prognostic factor for outcome in stroke patients [170, 171, 185].</p>
Empfehlung	If enteral feeding is likely necessary for a longer period of time (>28 days), a PEG should be chosen and placed in a stable clinical phase (after 14-28 days).



Stärke	A
Begründung	The only randomized, controlled study evaluating timing of feeding in stroke patients, was the “Early versus Avoid Trial” of the FOOD-study, which was published in 2005 [165, 186]. It was also the study with the biggest sample size (859 patients) addressing this question. After randomization tube feeding was either started as soon as possible or the placement of the tube was delayed for at least seven days. During this period, fluid was given intravenously or subcutaneously. Whether enteral nutrition was given via a PEG tube or a nasogastric tube, was decided by the attending physician. In 429 patients, a nasogastric tube was chosen; only 10 patients received a PEG-tube. The group of patients that started enteral nutrition within 7 days of admission had a reduction in mortality by 5.8%, which was not significant. The proportion of patients surviving with poor outcome was greater in the group with early nutrition (defined as Rankin Score 4 or 5). It could be speculated that these patients with an “impaired outcome” would have died with a delayed start of nutrition. Pneumonia did not occur more often in patients that received early enteral nutrition. Gastrointestinal bleeding occurred more often in early feeding than in delayed feeding. In this study, patients were only included when the attending physician was not sure about the timing of feeding. Nutritional status was not evaluated by standardized screening, but recorded informally by the attending physician. Together with some other limitations of the study, the amount of tube feed given was not documented.

LL	<b>Canada 2018, S. 112 [8]</b>
Empfehlung	An individualized management plan should be developed to address therapy for dysphagia, nutrition needs, and specialized nutrition plans
Stärke	C
Empfehlung	for enteral nutrition support (nasogastric tube feeding) in patients who cannot safely swallow or meet their nutrient and fluid needs orally. The decision to proceed with tube feeding should be made as early as possible after admission, usually within the first three days of admission in collaboration with the patient, family (or substitute decision maker), and interdisciplinary team
Stärke	B
Begründung	For patients who cannot obtain nutrient and fluid needs orally, enteral nutrition may be required. The decision to use enteral support should be made within the first seven days post stroke. The largest trial that addresses both the issues of timing of initiation of enteral feeding and the choice of feeding tube was the FOOD trial [169], which included 1,210 patients admitted within 7 days of stroke from 47 hospitals in 11 countries. In one arm of the trial, patients were randomized to receive either a percutaneous endoscopic gastrostomy (PEG) or nasogastric (NG) feeding tube within 3 days of enrolment into the study. PEG feeding was associated with an absolute increase in risk of death of 1.0% (–10.0 to 11.9, p=0.9) and an increased risk of death or poor outcome of 7.8% (0.0 to 15.5, p=0.05) at 6 months. In the second part of the trial patients were randomized to receive feeds as early as possible or to avoid feeding for 7 days. Early tube feeding was associated with non-significant absolute reductions in the risk of death or poor outcome (1.2%, 95% CI -4.2 to 6.6, p=0.7) and death (15.8%, 95% CI -0.8 to 12.5, p=0.09) at 6 months

LL	<b>DEGAM 2020, Kap 6.3.5 [16]</b>
----	-----------------------------------

Empfehlung	Ist enterale Ernährung voraussichtlich länger erforderlich (>28 Tage), soll, bei nicht palliativer Intention, nach 14-28 Tagen die Anlage einer PEG-Sonde angeboten werden.
Stärke	A, 1 b
Begründung	Leitlinienmodifikation DGEM [21]

SF 1.1.10: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die prophylaktische Gabe eines Antibiotikums im Vergleich zum Verzicht hierauf das funktionelle Outcome?

LL	<b>AHA 2019, Kap 4.11 [11]</b>
Empfehlung	Routine use of prophylactic antibiotics has not been shown to be beneficial
Stärke	III: No benefit; A
Begründung	Two large RCTs demonstrated no effect of preventive antimicrobial therapy on functional outcome. PASS (Preventive Antibiotics in Stroke Study) showed no difference in the primary end point of distribution of functional outcome scores on the mRS score at 3 months (adjusted common OR, 0.95 [95% CI, 0.82–1.09]; P=0.46) despite an overall reduction in the incidence of infection (OR, 0.57 [95% CI, 0.38–0.85]; P=0.005), including reducing the number of urinary tract infections (OR, 0.34 [95% CI, 0.26–0.46]; P<0.001), but no significant decrease in the rate of poststroke pneumonia (OR, 0.91 [95% CI, 0.73–1.13]; P=0.385).[187] In STROKE-INF (Antibiotics to Prevent Infection in Stroke), prophylactic antibiotics did not affect the incidence of the primary end point of poststroke pneumonia (adjusted OR, 1.21 [95% CI, 0.71–2.08]; P=0.489) or the secondary end point of mRS score of 0 to 2 at 90 days (adjusted OR, 0.87 [95% CI, 0.6–1.24]; P=0.448).[188] Three meta-analyses including these trials and other smaller RCTs all demonstrated a reduction in infection but no change in functional outcome.[189-191]

SF 1.1.11: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die prophylaktische Gabe eines Antiepileptikums im Vergleich zum Verzicht hierauf das funktionelle Outcome?

LL	<b>AHA 2018, Kap 5.2 [1]; AHA 2019, Kap 5.2 [11]</b>
Empfehlung	Prophylactic use of anti-seizure drugs is not recommended.
Stärke	III: No Benefit; C-LD
Begründung	Reworded from 2013: The reported incidence of seizures after ischemic infarction varies greatly, with most reports indicating an incidence <10%.[192, 193] An increased incidence of seizures after ischemic infarction is reported in patients with hemorrhagic transformation.[194] A great variance is also reported in the incidence of recurrent and late-onset seizures.[195, 196] With few data available on the efficacy of anticonvulsants in the treatment of seizures in stroke patients, current recommendations are based on the established management of seizures that may complicate any neurological illness. No studies to date have demonstrated a benefit of prophylactic anticonvulsant use after ischemic stroke, and little information exists on indications for the long-term use of anticonvulsants after a seizure.

LL	<b>ESO GL Seizure 2017 [13]</b>
Empfehlung	The presence of only one underpowered RCT does not give any reliable evidence if immediate primary prophylaxis with an antiepileptic drug compared to no treatment prevents occurrence of ASS in ischaemic stroke or intracranial (intracerebral or subarachnoid) haemorrhage. Observational studies show that in most patients with stroke, the risk to develop ASS is very low (approximately 5%). Furthermore, the

	consequences of ASS probably are rather limited. Thus, only a weak recommendation can be made, and we suggest not generally employing primary AED prophylaxis.
Stärke	Very low, weak against
Begründung	One RCT was identified which compared valproate (n=36) to placebo (n=36) administered directly after intracerebral haemorrhage[197]. There was no significant difference between groups regarding prevention of ASS (defined in that study as manifestation within first 14 days). This study was underpowered, prevention of ASS was not one of the primary endpoints. The quality of evidence was downgraded to very low due to the fact that there is only one small RCT and due to serious imprecision of the effect estimate. All other data on ASS are observational, report the incidence of post-stroke ASS, and analyse independent risk factors. Overall incidence for ASS following stroke is low (3–6%). Risk is increased in intracerebral or subarachnoid haemorrhage (10– 16%). Cortical involvement enhances the risk in ischaemic stroke, in particular in haemorrhagic transformation, and primary intracerebral haemorrhage (up to 35%) [198].

LL	<b>Canada 2018, S. 103 [8]</b>
Empfehlung	A single, self-limiting seizure occurring at the onset, or within 24 hours after an ischemic stroke (considered an “immediate” post-stroke seizure) should not be treated with longterm anticonvulsant medications
Stärke	C
Begründung	The incidence of post-stroke seizure ranges from 5%-15%, depending on stroke etiology, severity, and location [199]. Hemorrhagic events and cortical lesions are associated with the highest risk of both first and recurrent seizure. Evidence examining the effectiveness of pharmacological treatment for post- stroke seizures is limited. A recent Cochrane review [200] sought studies including patients of any age recovering from ischemic stroke or ICH, suffering from any seizure type that evaluated antiepileptic drugs compared with a placebo or no drug for the primary and secondary prevention of post stroke seizures. Only a single trial [197] was found. In this trial, 84 patients with spontaneous non-traumatic and non-aneurysmatic ICH were randomized to receive 800 mg/day valproic acid or placebo daily for one month, for primary seizure prophylaxis. At 1 year, there were 15 cases of new seizure. There were no differences in early (within 14 days of randomization) or late (>14 days) seizure between treatment groups (1 vs. 4, p=0.8 and 6 vs. 4, p=0.5, respectively). Van Tuijl et al. [201] planned to recruit 200 patients with lobar ICH or ischemic stroke, with a cortical syndrome and mRS $\geq$ 3 or NIHSS $\geq$ 6. Patients were to be randomized to receive either 1500 mg of levetiracetam daily or placebo, within 2 to 7 days following acute stroke for primary seizure prevention. Treatment was scheduled to continue for 12 weeks. The trial was stopped prematurely due to a failure to recruit sufficient numbers of patients. At the point the trial was stopped, only 16 patients had been recruited over a period of 16 months.

SF 1.1.12: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die Gabe eines Antiepileptikums nach einem ersten epileptischen Anfall im Vergleich zum Verzicht hierauf das funktionelle Outcome?

LL	<b>ESO GL Seizure 2017 [13]</b>
Empfehlung	The absence of RCTs does not give guidance for a recommendation on when and whom to administer secondary AED prophylaxis compared to no treatment for prevention of further ASS (acute symptomatic seizure). Findings from observational

	studies indicate that acute seizure recurrence after one ASS is low (10–20%). Thus, only a weak recommendation can be made, and we suggest not generally employing secondary AED prophylaxis.
Stärke	Very low, weak against
Begründung	No RCTs are available on the question if – in patients who have suffered at least one ASS – immediate secondary prophylaxis with an AED compared to no treatment prevents occurrence of further ASS. Risk of acute recurrence of ASS (within seven days of the same stroke) is 10–20%
Empfehlung	The absence of RCTs does not guide us to make a recommendation if – after an index US (unprovoked seizure)– immediate secondary prophylaxis with an AED should be implemented to prevent occurrence of further unprovoked post-stroke seizures. Findings from observational studies indicate high seizure recurrence risk (70%) after one post-stroke unprovoked seizure. Thus, employing secondary AED prophylaxis after one US needs to be considered.
Stärke	Very low, weak for
Begründung	No RCTs are available on prevention of further unprovoked post-stroke seizures after one index US with vs. without secondary AED prophylaxis. US recurrence risk is reported to be higher than 70% in 10 years [202]. Two RCTs compared efficacy of each two different AED after stroke. In these underpowered trials, seizure freedom rates after 12 months did not differ comparing levetiracetam and carbamazepine[203] and comparing lamotrigine and carbamazepine [204].
Kommentar	Though acute seizure recurrence risk after one post-stroke ASS is low, AED secondary prophylaxis seems to be common in many centres probably to reduce the risk of clinical worsening in the acute setting. The underlying concept of this approach likely is based on pathophysiological considerations such as increased neuronal excitotoxicity, peri-infarct depolarisations, and inflammatory response. <sup>39</sup> These are considered to be risk factors for acute recurrence of epileptic seizures, and therefore clinicians may tend to administer AED. However, the 10-year-risk of an unprovoked seizure after one poststroke ASS is 30% [202]. Being so, we encourage withdrawing AED – if administered after one ASS – after the acute phase
Anmerkung	Die Leitlinie differenziert zwischen symptomatischem (ASS) und unprovokierten (US) Anfällen, mit wegen des unterschiedlichen Rezidivrisikos unterschiedlichen Empfehlungen

LL	<b>AHA 2018, Kap 5.2 [1]; AHA 2019, Kap 5.2 [11]</b>
Empfehlung	Recurrent seizures after stroke should be treated in a manner similar to when they occur with other acute neurological conditions, and anti-seizure drugs should be selected based upon specific patient characteristics
Stärke	I, C-LD
Begründung	Reworded from 2013: The reported incidence of seizures after ischemic infarction varies greatly, with most reports indicating an incidence <10%.[192, 193] An increased incidence of seizures after ischemic infarction is reported in patients with hemorrhagic transformation.[194]A great variance is also reported in the incidence of recurrent and late-onset seizures.[195, 196] With few data available on the efficacy of anticonvulsants in the treatment of seizures in stroke patients, current recommendations are based on the established management of seizures that may complicate any neurological illness. No studies to date have demonstrated a benefit of prophylactic anticonvulsant use after ischemic stroke, and little information exists on indications for the long-term use of anticonvulsants after a seizure.

LL	<b>Canada 2018, S. 56, S: 103 [8]</b>
Empfehlung	Recurrent seizures in patients with ischemic stroke should be treated as per treatment recommendations for seizures in other neurological conditions
Stärke	C
Begründung	The use of antiepileptic medications for the secondary prevention of seizures has also been examined, although placebo-controlled trials are absent. Gilad et al [202] randomized 64 elderly patients admitted to a neurological department after stroke who had experienced a first seizure to receive either lamotrigine (100 mg BID) or carbamazepine (300 mg BID). The number of patients who were seizure free at 12 months was non-significantly higher in the lamotrigine group (23 vs. 14, p=0.06). The total number of adverse events was significantly higher in the carbamazepine group (12 vs. 2, p=0.05), as was the number of withdrawals for adverse events (10 vs. 1, p=0.02).

#### SF 1.2.1: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt die Zuweisung auf eine Stroke Unit im Vergleich zur Behandlung auf einer Normalstation das funktionelle Outcome?

LL	<b>AHA 2018, Kap 4.1 [1]; AHA 2019, Kap 4.1 [11]</b>
Empfehlung	The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation is recommended.
Stärke	I, A
Begründung	Unchanged from 2013: Numerous studies, performed mainly in Europe and Canada, demonstrate the utility of comprehensive stroke units in lessening the rates of mortality and morbidity after stroke. The positive effects persist for years. The benefits from treatment in a stroke unit are comparable to the effects achieved with intravenous administration of rtPA.

LL	<b>Australia 2017, Kap 1.3.5; Kap 3.5 ( [6]</b>
Empfehlung	All stroke patients should be admitted to hospital and be treated in a stroke unit with an interdisciplinary team.
Stärke	Strong
Begründung	<p>There is substantial evidence of benefit from organised inpatient stroke unit care of stroke patients: 44 fewer deaths, 54 fewer deaths or being dependent, and 64 fewer deaths or being under institutional care, with every 1000 stroke patients [205]. The benefit applies to all types of stroke and the full range of stroke severity and patient age. Care must be delivered in the one area/ward as there is little benefit for mobile stroke teams. There is no evidence of harm from admitting stroke patients to a stroke unit [205].</p> <p>A Cochrane review conducted by the Stroke Unit Trialists' Collaboration [205] compared organised stroke unit care to alternative services. The review included 28 RCTs with 5855 participants. Organised stroke unit care was defined as focused care for stroke patients by a multidisciplinary team specialising in stroke management. This included:</p> <ul style="list-style-type: none"> <li>• Stroke wards where care was given in a discrete ward caring exclusively for stroke patients.</li> <li>• Mixed rehabilitation wards with multidisciplinary teams and specialist nursing staff in a ward that does not care exclusively for stroke patients.</li> <li>• Mobile stroke teams that provide care in a variety of settings</li> </ul> <p>Overall, organised stroke unit care significantly reduced mortality compared to conventional care (OR 0.76, 95% CI 0.66 to 0.88), and significantly reduced the odds of death or institutionalisation and death or dependency. Comparisons between</p>

	<p>different kinds of stroke wards generally did not provide strong evidence for particular forms of stroke unit organisation.</p> <p>Sun et al. [206] also carried out a systematic review and meta-analysis comparing acute stroke unit care to conventional care in general medical wards. The 8 trials included in the main analysis were a subset of those included in the Cochrane review for the comprehensive stroke ward subgroup, excluding unpublished data and trials with short observation periods. Analysis of these 8 trials revealed a borderline significant effect on mortality (OR 0.84, 95% CI 0.70 to 1.00). This is a weaker finding than was seen in the Cochrane review. It may be explained by the inclusion of newer and unpublished studies in the 2013 Cochrane review. However, Sun et al. also mention an error in an earlier version of the Cochrane review that appears to be uncorrected in the 2013 review, where the number of deaths in the control group was incorrectly recorded for one trial. This error does raise some questions about the effect reported in the 2013 Cochrane review, suggesting the true effect may be slightly weaker.</p> <p>Chan et al. [207] conducted a systematic review of comparisons between different forms of stroke unit care, i.e. comparisons of acute stroke units, rehabilitation units and comprehensive units which provide both acute care and rehabilitation. There were no randomised controlled trials that directly compared comprehensive stroke units to other forms of stroke unit, so the review included a meta-analysis which used indirect comparisons, a cross-sectional comparison and a 'before-and-after' study. The review found that comprehensive stroke units were associated with decreased death and dependency and shorter length of stay. However, the indirect nature of the evidence means that there is substantial uncertainty about these benefits.</p>
LL	<b>NICE 2019, Kap 7.1 [24]</b>
Empfehlung	All people with suspected stroke should be admitted directly to a specialist acute stroke unit following initial assessment either from the community or accident & emergency (A&E) department
Stärke	2++
Begründung	The relatively low overall mortality rate in the systematic review compared to most unselected hospital-based cohorts may be due to selective entry of patients into trials. It was agreed that observational studies may be more representative of the stroke population as a whole. Three studies demonstrated that patients admitted to a stroke unit received therapeutic interventions and investigations more appropriately and quickly compared to those in a general medical ward. While better processes of care are linked to better outcomes there is currently no definitive trial support that these result in a reduction in mortality and morbidity. The lack of high-quality evidence was noted. There is a need for a randomised trial comparing direct admission to an acute stroke unit vs admission to a medical ward at least while the latter remains standard clinical practice. In the absence of evidence on whether rapid admission to an acute unit reduces mortality, morbidity and length of hospital stay, expert consensus led to the agreement that patients should be admitted where possible directly to an acute stroke unit. Trials outside the acute setting which demonstrate that direct admission improved the processes of care were noted. In the absence of any evidence identified in acute management, the group felt that there needed to be a very good reason not to generalise overall stroke unit results to those in the acute setting. A cost-effectiveness analysis compared stroke units to care by a mobile stroke team on a general ward, or domiciliary care. Although the cost-effectiveness ratio of over £60,000 per QALY gained compared with domiciliary care

	would seem to imply that stroke units are not cost effective, this result must be treated with extreme caution since the one-year time horizon is likely to have dramatically under-estimated both the QALYs gained from averting deaths and the cost savings due to averting dependence. The consensus view of the GDG is that all patients should be directly admitted to a stroke unit.
--	--

<b>LL</b>	<b>Canada 2018, S. 95 [8]</b>
<b>Empfehlung</b>	Patients admitted to hospital with an acute stroke or transient ischemic attack should be treated on an inpatient stroke unit as soon as possible; ideally within 24 hours of hospital arrival
<b>Stärke</b>	A Teil 1, C Teil 2
<b>Begründung</b>	<p>It is now well-established that patients who receive stroke unit care are more likely to survive, return home, and regain independence compared to patients who receive less organized forms of care. Stroke unit care is characterized by an experienced interdisciplinary stroke team, including physicians, nurses, physiotherapists, occupational therapists, speech therapists, among others, dedicated to the management of stroke patients, often located within a geographically defined space. Other features of stroke units include staff members who have an interest in stroke, routine team meetings, continuing education/training, and involvement of caregivers in the rehabilitation process. In an updated Cochrane Review, the Stroke Unit Trialists' Collaboration [205] identified 28 randomized and quasi-randomized trials (n=5,855) comparing stroke unit care with alternative, less organized care (e.g., an acute medical ward). Compared to less organized forms of care, stroke unit care was associated with a significant reduction in the odds of death (OR= 0.81, 95% CI 0.69 to 0.94, p = 0.005), death or institutionalization (OR=0.78, 95% CI 0.68 to 0.89, p = 0.0003), and death or dependency (OR= 0.79, 95% CI 0.68 to 0.90, p = 0.0007) at a median follow-up period of one year. Based on the results from a small number of trials, the authors also reported that the benefits of stroke unit care are maintained for periods up to 5 and 10 years post stroke. Moreover, subgroup analyses demonstrated benefits of stroke unit care regardless of sex, age, or stroke severity. Saposnik et al. [208] investigated the differential impact of stroke unit care on four subtypes of ischemic stroke (cardioembolic, large artery disease, small vessel disease, or other) and reported that stroke unit care was associated with reduced 30-day mortality across all subtypes.</p> <p>To determine if the benefits of stroke unit care demonstrated in clinical trials can be replicated in routine clinical practice, Seenan et al. [209] conducted a systematic review of 25 observational studies (n=42,236) comparing stroke unit care to non-stroke unit care. Stroke unit care was associated with a reduction in the risk of death (OR=0.79, 95% CI 0.73 to 0.86, p&lt;0.001) and of death or poor outcome (OR=0.87, 95% CI=0.80 to 0.95; p=0.002) within one-year of stroke. Similar findings were reported for the outcome of death at one year in a secondary analysis limited to multi-centered trials (OR=0.82, 95% CI 0.77 to 0.87, p&lt;0.001).</p>

<b>LL</b>	<b>RCP 2016 [10]</b>
<b>Empfehlung</b>	People with an acute neurological presentation suspected to be a stroke should be admitted directly to a hyperacute stroke unit which cares predominantly for stroke patients.
<b>Stärke</b>	./.

Begründung	Follows from the evidence concerning the emergency diagnosis and treatment of stroke (Sections 3.4-3.7)
------------	---

### SF 1.2.2: Verbessert bei erwachsenen Patienten mit kürzlicher TIA die Zuweisung auf eine Stroke Unit im Vergleich zur ambulanten Behandlung das funktionelle Outcome?

LL	<b>Australia 2017, Kap 2.5 [6]</b>
Empfehlung	Patients with symptoms that are present or fluctuating at time of initial assessment should be treated as having a stroke and be immediately referred for emergency department and stroke specialist assessment, investigation and reperfusion therapy where appropriate
Stärke	Strong
Begründung	<p>The risk of stroke is greatest in the first few hours and days after a TIA. Two studies in UK and France using historical controls reported an 80% risk reduction in recurrent stroke at 90 days when rapid access clinics to assess, investigate and initiate intensive secondary prevention medications were established [210, 211]. There were no harms identified.</p> <p>The evidence is largely based on non-randomised studies comparing stroke incidence following TIA before and after implementing rapid access TIA management or comparing outcomes to historical controls (Lavalley et al. 2007[25]; Rothwell et al. 2007[26]). This introduces a potential risk of bias that could result in overestimation of the treatment effect without accounting for other factors that may have reduced post-TIA stroke risk over recent years (e.g. more widespread use of cardiovascular risk management at baseline), and the comparators may not represent the true baseline rate of recurrent stroke. However, the large size of effect makes us moderately confident that it was effective in reducing recurrent stroke.</p> <p>One UK study (EXPRESS) measured the rate of recurrent stroke before and after the set-up of a TIA clinic, in which patients with suspected TIA were immediately assessed and treated [211]. The 90-day risk of recurrent stroke in the patients referred to the study clinic was 10.3% (32/310 patients) before the clinic and 2.1% (6/281 patients) after (adjusted hazard ratio 0.20, 95% CI 0.08-0.49; p=0.0001). The reduction in risk was independent of age and sex, and early treatment did not increase the risk of intracerebral haemorrhage or other bleeding. A French study (SOS-TIA) set up a 24/7 rapid TIA clinic attached to a large urban stroke unit hospital [210]. They also found an 80% reduction in 90-day recurrent stroke rate compared to that predicted by the ABCD2tool (1.24% actual vs 5.96% expected risk).</p> <p>Both studies have high methodological quality, but it is questionable if the comparators represent the true rate of recurrent stroke in the population. On the other hand, the large scale of risk reduction still shows that rapid assessment and treatment is likely to be beneficial for patients with suspected TIA.</p>
Empfehlung	In TIA patients, use of the ABCD2risk score in <b>isolation</b> to determine the urgency of investigation may delay recognition of atrial fibrillation and symptomatic carotid stenosis in some patients and should be avoided.
Stärke	weak
Begründung	Several risk scores have been proposed to stratify the risk of recurrent ischaemic events and have sometimes been used as a means of prioritising the urgency of investigation for TIA. However, studies have indicated that the most commonly used risk score (ABCD <sup>2</sup> ) and its more recent adaptations (e.g. ABCD <sup>3</sup> ) classify an important proportion of TIA patients with atrial fibrillation and symptomatic carotid stenosis in



	the "low risk" category, potentially exposing them to detrimental treatment delays and risk of recurrent ischaemic events [212-215]
--	---

LL	<b>Canada 2018, S. 95 [8]</b>
Empfehlung	Patients identified as highest risk should be immediately sent to an emergency department with capacity for advanced stroke care (such as brain imaging on site, and ideally access to acute stroke treatments)
Stärke	C
Begründung	Patients who present within 48 hours of a suspected transient ischemic attack or non-disabling ischemic stroke with the following symptoms are considered at highest risk of first or recurrent stroke: a. transient, fluctuating or persistent unilateral weakness (face, arm and/or leg) [Evidence Level B]; b. transient, fluctuating or persistent language/speech disturbance [Evidence Level B]; c. fluctuating or persistent symptoms without motor weakness or language/speech disturbance (e.g. hemibody sensory symptoms, monocular vision loss, hemifield vision loss, +/- other symptoms suggestive of posterior circulation stroke such as binocular diplopia, dysarthria, dysphagia, ataxia) [Evidence Level B].

LL	<b>DEGAM 2020, S. 17 [16]</b>
Empfehlung	<p>Patienten mit TIA-Symptomatik innerhalb der letzten 48 Stunden sollten umgehend einer Stroke Unit zugewiesen werden.</p> <p>Bei Patienten, bei denen die Symptomatik länger als 14 Tage zurückliegt, ist in der Regel eine ambulante Abklärung ausreichend, die schnellstmöglich, jedoch binnen eines Monats nach Symptombeginn komplettiert werden sollte.</p> <p>Im intermediären Zeitraum sollten Patienten mit vielen Risikofaktoren, hohem ABCD<sup>2</sup>-Score (z. B. ≥4), bekanntem VHF, bekannten Stenosen hirnersorgender Arterien oder früheren kardiovaskulären Erkrankungen einer Stroke Unit zugewiesen werden</p>
Stärke	B, 2b
Begründung	Leitlinienmodifikation: CAN 2015 Hyperacute Stroke, AHA/ASA TIA 2009

LL	<b>RCP 2016 [10]</b>
Empfehlung	People with acute neurological symptoms that resolve completely within 24 hours (i.e. suspected TIA) should be given aspirin 300 mg immediately and assessed urgently within 24 hours by a specialist physician in a neurovascular clinic or on an acute stroke unit.
Stärke	
Begründung	Follows from the evidence concerning TIA diagnosis and treatment (Section 3.2-3.3) Rothwell et al, 2007 [211]; Lavalley et al, 2007 [210]; Giles and Rothwell, 2007 Rothwell et al, 2016 [216]

**SF 1.2.3: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt eine direkte Zuweisung in ein Comprehensive Stroke Center im Vergleich zur Behandlung auf einer Stroke Unit das funktionelle Outcome?**

LL	<b>AHA 2018, Kap 1.3 [1]</b>
Empfehlung	When several IV alteplase-capable hospital options exist within a defined geographic region, the benefit of bypassing the closest to bring the patient to one that offers a

	higher level of stroke care, including mechanical thrombectomy, is uncertain. Further research is needed.
Stärke	IIb, B-NR
Begründung	For prehospital patients with suspected LVO by a stroke severity scale, the Mission: Lifeline Severity-based Stroke Triage Algorithm for EMS30 recommends direct transport to a comprehensive stroke center if the travel time to the comprehensive stroke center is <15 additional minutes compared with the travel time to the closest primary stroke center or acute stroke-ready hospital. However, at this time, there is insufficient evidence to recommend 1 scale over the other or a specific threshold of additional travel time for which bypass of a primary stroke center or acute stroke-ready hospital is justifiable. Given the known impact of delays to IV alteplase on outcomes [217], the known impact of delays to mechanical thrombectomy on outcome,[218] and the anticipated delays in transport for mechanical thrombectomy in eligible patients originally triaged to a nonendovascular center, the Mission: Lifeline algorithm may be a reasonable guideline in some circumstances. Customization of the guideline to optimize patient outcomes will be needed to account for local and regional factors, including the availability of endovascular centers, door in-door out times for nonendovascular stroke centers, interhospital transport times, and DTN and door-to-puncture times.

LL	<b>Canada 2018, Kap 3.4 S. 50; [8]</b>
Empfehlung	Direct transport in many regions involves two considerations: (1) patients who may be eligible for intravenous alteplase may be directed to the closest centre (primary/advanced stroke centre or comprehensive stroke centre) and, (2) patients who are determined to be a likely candidate for endovascular thrombectomy may proceed directly to an EVT-enabled comprehensive stroke centre OR to the primary centre first to rapidly receive intravenous alteplase, and then be considered for transported to the EVT-enabled comprehensive stroke centre.
Stärke	
Begründung	Acute interventions such as thrombolytic therapy are time-sensitive and therefore strategies such as re-directing ambulances to stroke centres to facilitate earlier assessment, diagnosis, and treatment may result in better outcomes.

LL	<b>ESO Prehospital [15]</b>
Empfehlung	There is insufficient evidence that these stroke scales could be useful instruments for selecting stroke patients for direct transport to comprehensive stroke centres.
Stärke	
Begründung	

LL	<b>ESO MT [23]</b>
Empfehlung	The mothership model might be favoured in metropolitan areas, with transportation time to a comprehensive stroke centre of less than 30–45 min and the use of the drip-and-ship model when transportation times are longer (vote: 11/11 experts agree).
Stärke	EO
Begründung	
Empfehlung	In adult patients with large vessel occlusion related acute ischaemic stroke, we recommend treatment in a comprehensive stroke centre.
Stärke	Very low. Strong

Begründung	<p>The literature search did not identify RCTs of MT performed in a comprehensive stroke centre compared with MT performed outside of a comprehensive stroke centre.</p> <p>A recent study based on administrative data assessed mortality rates among 8533 patients admitted for MT in 118 U.S. centres, showing a negative correlation between institutional procedural volume and mortality (<math>r=-0.24</math>, <math>p=0.007</math>) [219]. Numeric cut-offs for institutional procedural volumes that yielded the greatest differences in mortality index were <math>\leq 7</math> procedures per year (low-volume thrombectomy centres) and <math>&gt;35</math> procedures per year (high-volume thrombectomy centres). A lower mortality rate among patients treated with MT who were transferred to high-volume centres compared with those directly admitted to low volume centres was observed (10.0% vs. 20.4%; <math>p=0.005</math>). The authors concluded that the benefit of greater institutional procedural experience may mitigate the delay in reperfusion associated with hospital transfer</p>
------------	--

SF 1.3.1: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine umgehende Schnittbildgebung des Gehirns mit MRT im Vergleich zu einer CT-Untersuchung das funktionelle Outcome?

LL	<b>AHA 2018, Kap 2.2 [1]</b>
Empfehlung	All patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival to hospital. In most cases, noncontrast CT (NCCT) will provide the necessary information to make decisions about acute management.
Stärke	I, B-NR
Begründung	<p>Diagnostic testing is most cost-effective when it leads to a change in treatment that improves outcomes, not just a change in treatment. Although diffusion-weighted magnetic resonance imaging (DW-MRI) is more sensitive than CT for detecting AIS,[220, 221] routine use in all patients with AIS is not cost-effective.[222, 223] NCCT scanning of all patients with acute stroke has been shown to be cost-effective primarily because of the detection of acute ICH and the avoidance of antithrombotic treatment in these patients.[224] In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention.[221, 225, 226]. In some patients with negative NCCT such as those with puzzling clinical presentations or those with uncertain clinical stroke localization for early carotid endarterectomy (CEA) or stenting, demonstration of an area of restricted diffusion on DW-MRI may lead to a change in treatment that improves outcomes. There are inadequate data at this time to establish which patients will benefit from DW-MRI, and more research is needed to determine criteria for its cost-effective use.</p>
Empfehlung	Routine use of magnetic resonance imaging (MRI) to exclude cerebral microbleeds (CMBs) before administration of IV alteplase is not recommended.
Stärke	III: No Benefit; B-NR
Begründung	<p>No RCTs of IV alteplase in AIS with baseline MRI to identify CMBs have been conducted, so no determination of the effect of baseline CMB on the treatment effect of alteplase with CMB is available. Two meta-analyses of the association of baseline CMBs on the risk of sICH after IV alteplase have shown that sICH is more common in patients with baseline CMBs (OR, 2.18; 95% CI, 1.12–4.22; OR, 2.36; 95% CI, 1.21–4.61) [227, 228]. However, sICH in patients with baseline CMBs is not more common (6.1%, 6.5%) [227, 228] than in the NINDS rtPA trial (6.4%).<sup>87</sup> One meta-analysis</p>

	reported that the sICH rate was 40% in patients with >10 CMBs, but this was based on only 6 events in 15 patients, and patients with >10 CMBs constituted only 0.8% of the sample [227].
Empfehlung	Routine use of brain MRI in all patients with AIS is not cost-effective and is not recommended for initial diagnosis or to plan subsequent treatment
Stärke	III: No Benefit; B-NR
Empfehlung	In some patients with AIS, the use of MRI might be considered to provide additional information for initial diagnosis or to plan subsequent treatment, although the effect on outcomes is uncertain.
Stärke	IIb, C-EO
Begründung	Diagnostic testing is cost-effective when it leads to a change in treatment that improves outcomes. NCCT scanning of all patients with acute stroke has been shown to be cost-effective primarily because of the detection of acute ICH and the avoidance of antithrombotic treatment in these patients [224]. In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention [226]. Although DW-MRI is more sensitive than CT for detecting AIS [221], systematic reviews with meta-analyses and decision-analytic modeling have shown that routine use of MRI in all patients with AIS is not cost-effective [222, 223]. Studies of patients with AIS have shown poor or no association between the pattern on ischemic lesions on brain MRI and etiologic classification [229-236]. Specifically, the pattern of acute multiple infarcts in multiple cerebral circulations has a positive likelihood ratio of 1.41 and a negative likelihood ratio of 0.96 for cardioembolic etiologic classification (combined data from 4 studies [230-232, 237] and a positive likelihood ratio of 1.18 and a negative likelihood ratio of 0.98 for subsequent detection of atrial fibrillation on long-term cardiac monitoring (combined data from 2 studies [235, 236]. In some patients with negative NCCT such as those with uncertain clinical stroke localization who are candidates for early CEA or stenting for secondary prevention, demonstration of an area of restricted diffusion on DW-MRI may be helpful in selecting treatment that improves outcomes. However, there are inadequate data at this time to establish which patients will benefit from DW-MRI, and its routine use is not recommended. More research is needed to determine criteria for its cost-effective use.
LL	<b>AHA 2019, Kap 2.2 [11]</b>
Empfehlung	Administration of IV alteplase in eligible patients without first obtaining MRI to exclude cerebral microbleeds (CMBs) is recommended.
Stärke	I, B-NR
Begründung	CMBs are common in patients receiving IV alteplase, occurring in 15% to 27%. <sup>89–94</sup> Such patients were undoubtedly included in the pivotal NINDS and ECASS III trials that established the benefits of IV alteplase treatment [238, 239]. Two meta-analyses of the association of baseline CMBs and the risk of sICH after IV alteplase reported that sICH is more common in patients with baseline CMBs, whereas 2 other meta-analyses and 1 multicenter study did not [227, 228, 240-242]. In 2 studies using ECASS II sICH criteria, the rates in patients with CMBs were 5.8% and 6.5% compared with 5.3% in ECASS III [227, 239, 240]. One study analyzing the risk of sICH in patients with CMBs detected after IV alteplase treatment reported sICH of 5% using the NINDS criteria compared with 6.4% in the NINDS tPA trials treatment [238, 243]. The risk of sICH in patients with >10 CMBs (30%–47%) is consistently reported as significantly greater

	than in those with no CMBs (1%–4.4%). However, these data are based on <50 patients, constituting <2% of these series [227, 240, 242, 243]. No RCTs of IV alteplase in AIS with baseline MRI to identify CMBs have been conducted, so no determination of the effect of baseline CMB on the treatment effect of alteplase with CMB is available. In the absence of direct evidence that IV alteplase provides no benefit or produces harm in eligible patients with CMBs, withholding treatment on the basis of the presence of CMBs could lead to the exclusion of patients who would benefit from treatment.
Empfehlung	For prevention of recurrent stroke, the use of MRI is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention treatments.
Stärke	IIa, C-EO
Begründung	NCCT scanning of patients with acute stroke is effective for the detection of acute ICH and the avoidance of antithrombotic treatment in these patients. <sup>85</sup> In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention [221, 225, 226]. Many RCTs that provide the current best evidence for secondary stroke prevention treatments did not require MRI for patient selection [109, 244-254]. The benefits shown in these RCTs can be expected when the same eligibility criteria are applied without the addition of MRI. DW-MRI is more sensitive than CT for detecting AIS [255, 256], but there are inadequate data at this time to identify which patients will benefit from brain MRI in addition to or instead of NCCT to improve effectiveness of treatment for prevention of recurrent stroke. A systematic review in 2012 identified almost no direct evidence that MRI affects outcome in patients with stroke and limited evidence that MRI affects management [257]. A decision-analytical model of patients with TIA and minor stroke concluded that routine use of MRI did not improve outcome except for patients presenting at >1 week after symptoms to diagnose hemorrhage [222]. Two studies from the 1990s evaluating repeat neuroimaging recommended repeat CT over additional MRI for most clinical situations in AIS with the exceptions of documenting lacunar and infratentorial infarcts, but they did not present evidence of a benefit on outcome for these situations [258, 259]. For instance, 2 situations in which MRI can be useful to select treatments that have been demonstrated by RCTs to improve outcome are (1) patients with carotid stenosis who are potential candidates for carotid revascularization in whom NCCT or neurological examination (eg, pure motor hemiparesis) does not permit accurate localization and (2) patients with patent foramen ovale (PFO) who are potential candidates for mechanical closure
Empfehlung	The effectiveness of routine brain MRI to guide treatment selection for prevention of recurrent stroke is uncertain
Stärke	IIb, B-NR
Begründung	See above
<b>LL</b>	<b>Australia 2017, Kap 7.1 [6]</b>
Empfehlung	All patients with suspected stroke who are candidates for reperfusion therapies should undergo brain imaging immediately. All other suspected stroke patients should have an urgent brain CT or MRI ('urgent' being immediately where facilities are available and preferably within 60 minutes).
Stärke	Strong

Begründung	<p>Ischaemic stroke and intracerebral haemorrhage cannot be reliably differentiated on clinical grounds. Brain imaging with CT or MRI is therefore essential for accurate diagnosis and determination of management. Treatment is time-critical with benefit declining rapidly with passing minutes. Brain imaging should therefore occur immediately for patients who are potential candidates for reperfusion treatments. Rapid confirmation of the diagnosis of stroke facilitates direct access to stroke units, which improves outcomes for all stroke patients and the distinction between intracerebral haemorrhage and ischaemic stroke changes management (e.g. blood pressure and thromboprophylaxis), hence the recommendation that all stroke patients should have brain imaging within 60 minutes of arrival in hospital.</p> <p>Although MRI is more sensitive than non-contrast CT for diagnosis of ischaemic stroke, it may not be immediately accessible, leading to treatment delays [223]. There are also some patients who cannot have MRI due to metallic implants and the cost is greater than CT.</p> <p>The evidence is based on observational studies but this is standard for studies of diagnostic accuracy</p>
Empfehlung	In patients with suspected stroke and TIA, MRI is more sensitive and specific than non-contrast CT and is the preferred modality when diagnostic confirmation is required.
Stärke	Weak
Begründung	<p>MRI is markedly more sensitive than non-contrast CT for diagnosis of ischaemic stroke [223]. Specificity and differentiation of stroke mimics are also better using MRI. This is particularly applicable to minor stroke patients, in whom non-contrast CT is often normal, and some patients with resolved symptoms will have their diagnosis altered from TIA to stroke by the finding of a lesion on diffusion MRI. Patients with diffusion lesions are at higher risk of stroke recurrence. A finding of multi-territory diffusion lesions can indicate pathogenesis (i.e. central embolic source). There are, however, some patients who cannot have MRI due to metallic implants and the cost is greater than CT.</p>
LL	<b>NICE 2019, Kap 6.2, 7.2[24]</b>
Empfehlung	People who have had a suspected TIA who need brain imaging (that is, those in whom vascular territory or pathology is uncertain) should undergo diffusion-weighted MRI except where contraindicated,* in which case computed tomography (CT) scanning should be used.
Stärke	3
Begründung	<p>The evidence reviewed did not specifically compare CT with MR after TIA. However, it is well established that MR is more sensitive than CT in the detection of vascular lesions particularly if performed early. The consensus of the GDG was that where brain scanning was felt to be necessary following TIA, MR with DWI within 24 hours should be performed. For those patients with contraindications or unable to tolerate MR, CT scanning should be used.</p>
Anmerkung	Die LL differenziert sehr klar zwischen TIA/non-disabling stroke und stroke
Empfehlung	<p>Brain imaging should be performed immediately* for people with acute stroke if any of the following apply:</p> <ul style="list-style-type: none"> <li>• indications for thrombolysis or early anticoagulation treatment</li> <li>• on anticoagulant treatment</li> <li>• a known bleeding tendency</li> <li>• a depressed level of consciousness (Glasgow Coma Score (GCS) below 13)</li> </ul>

	<ul style="list-style-type: none"> <li>• unexplained progressive or fluctuating symptoms</li> <li>• papilloedema, neck stiffness or fever</li> <li>• severe headache at onset of stroke symptoms.</li> </ul> <p>For all people with acute stroke without indications for immediate brain imaging, scanning should be performed as soon as possible.**</p>
Stärke	./.
Begründung	<p>No clinical trial was identified to answer this question. However, it is clear that there are some patients in whom urgent scanning will result in immediate changes in clinical management. In the absence of reviewing the evidence on which patients should receive urgent scanning, a consensus was reached by the group. It was agreed that patients who are on anticoagulant therapy, have a known bleeding tendency, a depressed level of consciousness, unexplained progressive or fluctuating symptoms, papilloedema, neck stiffness or fever, severe headache at onset and/or indications for thrombolysis or early anticoagulation should receive immediate (next available slot or within 1 hour; within 1 hour out of hours) brain imaging. This consensus was based on both clinical experience and a recommendation made in the Intercollegiate Stroke Working Party guideline (2004 edition).<sup>29</sup> The GDG felt that immediate imaging of this patient population would result in changes in clinical management. For the remaining acute stroke patients, the clinical consensus of the group was that scanning should be performed as soon as possible (certainly within 24 hours). The health economic evidence supports the cost effectiveness of immediate scanning, although there may be limitations to the UK study because of changes in radiology staff costings. Immediate scanning, whilst cost effective, maybe difficult to implement because of scanning availability.</p>
Anmerkung	<p>*: Within one hour                  **: within 24 hours</p>

LL	<b>Canada 2018, S: 57 [8]</b>
Empfehlung	<p>Outpatient: Patients presenting with suspected acute or recent transient ischemic attack or nondisabling ischemic stroke should undergo an initial assessment that includes brain imaging, non-invasive vascular imaging (including carotid imaging), and 12-lead ECG, and laboratory investigations:</p> <p>a. Brain imaging (CT or MRI) and non-invasive vascular imaging (CTA or MRA from aortic arch to vertex) should be completed as appropriate and within time frames based on triage category and severity described in Section 2.1</p>
Stärke	B
Begründung	<p>MRI is superior to CT scan in terms of diagnostic sensitivity for small strokes and may provide additional information that could guide diagnosis, prognosis, and management decision-making. Decisions regarding MRI scanning should be based on MRI access, availability and timing of appointments.</p>
Empfehlung	<p>Hospital: All patients with suspected acute stroke should undergo brain imaging with non-contrast CT or MRI</p>
Stärke	A
Begründung	<p>Immediate access to brain and vascular imaging is required for all patients arriving to hospital with suspected stroke or TIA. A non-contrast CT scan is considered the imaging standard to be used initially to identify acute ischemic stroke and to rule out intracranial hemorrhage. CT scans are quick to perform, easy to tolerate, and are known to be very reliable for the detection of intracerebral hemorrhage. Early detection of hemorrhage is essential since the presence of blood in the brain or</p>

	subarachnoid space is the main contraindication for the administration of aspirin, anticoagulants and thrombolytic therapy. Early imaging is particularly important for patients who may be potential candidates for thrombolytic therapy, since it has a narrow therapeutic window for administration. Wardlaw et al. (2004) found that a computed tomography (CT) scan for all patients with suspected stroke on admission to hospital was the most cost-effective strategy, despite the increased cost of scans being performed during “off hours”. The higher costs were offset by savings realized through decreased lengths of hospital stay
Empfehlung	All patients with suspected acute ischemic stroke who arrive within 4.5 hours and are potentially eligible for intravenous thrombolysis should undergo immediate brain imaging with non-contrast CT (NCCT) without delay to determine eligibility for thrombolysis
Stärke	A

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with suspected acute stroke should receive brain imaging urgently and at most within 1 hour of arrival at hospital.
Empfehlung	MRI with stroke-specific sequences (diffusion-weighted imaging, T2*) should be performed in patients with suspected acute stroke when there is diagnostic uncertainty
Begründung	Follows from the evidence for emergency stroke treatments in Sections 3.5 and 3.6 Wardlaw et al, 2014 [222]

SF 1.3.2: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine umgehende nicht-invasive Gefäßdiagnostik mit CTA/MRA im Vergleich zur alleinigen Parenchymdiagnostik das funktionelle Outcome?

LL	<b>AHA 2018 Kap 2, Kap 6.2 [1]</b>
Empfehlung	For patients who otherwise meet criteria for EVT, a noninvasive intracranial vascular study is recommended during the initial imaging evaluation of the acute stroke patient, but should not delay IV alteplase if indicated. For patients who qualify for IV alteplase according to guidelines from professional medical societies, initiating IV alteplase before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible.
Stärke	I, A
Begründung	A recent systematic review evaluated the accuracy of prediction instruments for diagnosing LVO [42]. In the setting where confirmed ischemic stroke patients would be assessed by a neurologist or emergency physician in the ED, the authors suggested that the NIHSS is the best of the LVO prediction instruments. According to their metaanalysis, a threshold of $\geq 10$ would provide the optimal balance between sensitivity (73%) and specificity (74%). To maximize sensitivity (at the cost of lower specificity), a threshold of $\geq 6$ would have 87% sensitivity and 52% specificity. However, even this low threshold misses some cases with LVO, whereas the low specificity indicates that false-positives will be common.
Empfehlung	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



Stärke	IIa, C-EO
Begründung	Knowledge of vessel anatomy and presence of extracranial vessel dissections, stenoses, and occlusions may assist in planning endovascular procedures or identifying patients ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature.
Empfehlung	In patients with AIS, routine noninvasive imaging by means of CTA or MRA of the intracranial vasculature to determine the presence of intracranial arterial stenosis or occlusion is not recommended to plan subsequent secondary preventive treatment.
Stärke	III: No Benefit; A
Empfehlung	In some patients with AIS, noninvasive imaging by means of CTA or MRA of the intracranial vasculature to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain
Stärke	IIb; C-EO
Begründung	Intracranial atherosclerosis is associated with a high risk of recurrent stroke, often in the same arterial distribution [260, 261]. There is no RCT evidence that patients with AIS and symptomatic intracranial stenosis should be treated differently from other patients with ischemic stroke of presumed atherosclerotic cause. In the WASID RCT (Warfarin-Aspirin Symptomatic Intracranial Disease), warfarin provided no benefit over aspirin 325 mg/d, even in those who were taking antithrombotics at the time of the qualifying event [262]. The SAMMPRIS study (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) showed no benefit of adding Wingspan stenting to aggressive medical therapy that included aspirin 325 mg/d and clopidogrel 75 mg/d for 90 days after enrolment, again even in those who were taking antithrombotics at the time of qualifying event [263-265]. Compared with pooled historical control subjects from similar patients in WASID, the medical treatment-only group in SAMMPRIS had an almost 2-fold lower risk of any stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery after 30 days. Whether this was the result of dual antiplatelet treatment with aspirin and clopidogrel for 90 days remains to be demonstrated by an RCT [263, 264, 266]. Thus, the added utility and cost-effectiveness of noninvasive imaging CTA or MRA of the intracranial vessels to identify intracranial arterial steno-occlusive disease in guiding validated therapy that will ultimately improve outcomes are unproven. Moreover, MRA and CTA often overestimate the degree of stenosis [267, 268], so any data from the angiographically based WASID or SAMMPRIS RCTs cannot be reliably extrapolated.
LL	<b>AHA 2019 Kap 2, Kap 6.2 [11]</b>
Empfehlung	For prevention of recurrent stroke, the use of intracranial vessel imaging is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention treatments.
Stärke	IIa, C-EO
Begründung	An extensive literature search did not yield adequate data to identify subgroups of patients with AIS for whom information obtained from intracranial vessel imaging will lead to improved outcome. There is no RCT evidence that patients with AIS and symptomatic intracranial stenosis should be treated differently from other patients with ischemic stroke of presumed atherosclerotic cause. In the WASID RCT (Warfarin-Aspirin Symptomatic Intracranial Disease), warfarin provided no benefit over aspirin 325 mg/d, even in those who were taking antithrombotics at the time of the

	qualifying event [262]. The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) showed no benefit of adding Wingspan stenting to aggressive medical therapy that included aspirin 325 mg/d and clopidogrel 75 mg/d for 90 days after enrollment, again even in those who were taking antithrombotics at the time of qualifying event [263-265]. The CHANCE trial, which compared dual antiplatelet treatment with clopidogrel and aspirin and aspirin alone for 21 days in patients with high-risk TIA and minor stroke, showed no evidence of preferential benefit from dual antiplatelet treatment in patients with intracranial arterial stenosis. Compared with pooled historical control subjects in WASID, the medical treatment-only group in SAMMPRIS had an almost 2-fold lower risk of any stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery after 30 days. Whether this was the result of dual antiplatelet treatment with aspirin and clopidogrel for 90 days remains to be demonstrated by an RCT[263, 264, 266].
--	---

LL	<b>Australia 2017, Kap 7.1 [6]</b>
Empfehlung	All patients who would potentially be candidates for endovascular thrombectomy should have vascular imaging from aortic arch to cerebral vertex (CTA or MRA) to establish the presence of vascular occlusion as a target for thrombectomy and to assess proximal vascular access.
Stärke	Strong
Begründung	CT angiography (CTA) is highly accurate and shows the entire vascular tree, which has major advantages in accurately diagnosing stroke aetiology. CTA does involve ionising radiation and iodinated contrast, which may be associated with a low risk of contrast nephropathy in patients with severe pre-existing kidney disease. CTA is a routine part of initial brain imaging at many centres and is essential for patients who may be considered for endovascular thrombectomy. All randomised trials that demonstrated the benefits of endovascular thrombectomy used non-invasive vessel imaging (predominantly CTA) to assess eligibility [269]. The IMS-3 trial did not use CTA and was neutral overall but did demonstrate benefit in the subgroup of patients with demonstrated vessel occlusion [270].

LL	<b>Canada 2018, S. 57 [8]</b>
Empfehlung	Outpatient: Patients presenting with suspected acute or recent transient ischemic attack or nondisabling ischemic stroke should undergo an initial assessment... CTA including extracranial and intracranial vasculature from aortic arch to vertex, which can be performed at the time of initial brain CT, is recommended as an ideal way to assess both the extracranial and intracranial circulation
Stärke	B
Empfehlung	All patients with suspected acute ischemic stroke who arrive within 6 hours and are potentially eligible for endovascular thrombectomy should undergo immediate brain imaging with non-contrast CT and CT angiography (CTA) without delay, from arch-to-vertex including the extra- and intra-cranial circulation, to identify large vessel occlusions eligible for endovascular thrombectomy
Stärke	A
Empfehlung	All patients with suspected ischemic stroke who arrive at 6-24 hours after stroke onset (late presentation and stroke on awakening with unknown onset time) and are potentially eligible for late window endovascular thrombectomy treatment should

	undergo immediate brain imaging with non-contrast CT with CTA and CT perfusion, or MRI with MRA and MRP
Stärke	B
Begründung	<p>CT angiography (CTA) should be performed as part of the initial acute stroke CT imaging protocol. It is fast, simple and helps to identify patients with small core infarcts (ASPECTS 6 or higher) in the anterior circulation, who should be considered for endovascular therapy. Either multiphase or dynamic CTA is recommended over single-phase CTA, as the former can be used to assess for both intracranial arterial occlusion and also pial arterial collateral circulation [271]. Evidence of adequate pial collaterals may predict better response to reperfusion and outcomes in acute ischemic stroke patients [272]. CTA is well-tolerated with a very low risk of allergic reaction or renal impairment from contrast administration, and does not pharmacologically interact with t-PA.</p> <p>CT perfusion (CTP) is another advanced CT imaging modality that can be used to determine infarct core size (based on cerebral blood volume [CBV] maps) and ischemic penumbra (using cerebral blood flow [CBF] or time maps). CTP has been used in recent trials of endovascular therapy to identify patients who were candidates for treatment. In the EXTEND-IA trial [273], inclusion required a 20% mismatch between core infarct and ischemic penumbra identified using CTP. Due to variability in vendor software, specific CBV volume cut-offs for core infarct size is not standardized. The use of CTP for acute stroke patients should be reserved for centres with well-established CTP protocols and experience in interpreting CTP, or the use of quantitative CTP software, and must not substantially delay decisions for acute stroke treatments.</p> <p>While CT scans are recommended for initial brain imaging following stroke, there are cases where magnetic resonance imaging (MRI) with diffusion-weighted sequences (DWI) may be superior. MRI has been shown to be more sensitive in detection of the early changes associated with ischemia, especially in patients with small infarcts. Using the results from 8 studies, Brazzelli et al. [223] reported that the sensitivity of magnetic resonance imaging (MRI) may be higher than CT scans for the identification of ischemic stroke (99% vs. 39%), although the authors questioned the generalizability of their findings. If an MRI is available and performed in place of CT, enhanced imaging in the form of DWI, GRE and FLAIR is indicated. Brunser et al. [274] included 842 patients admitted to the Emergency Department with a suspected ischemic stroke. Diffusion-weighted imaging (DWI) examinations were performed for all patients. For patients with a final diagnosis of stroke, the sensitivity of DWI in detecting ischemic stroke was 90% (95% CI 87.9 to 92.6), and specificity was 97% (95% CI 91.8 to 99.0).</p>
LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with ischaemic stroke who are eligible for endovascular therapy should have a CT angiogram from aortic arch to skull vertex immediately. This should not delay the administration of intravenous thrombolysis
Begründung	Follows from the evidence for emergency stroke treatments in <a href="#">Sections 3.5</a> and <a href="#">3.6</a>

SF 1.3.3: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA das kontinuierliche apparative Monitoring der Herz-Kreislauf- und der Stoffwechsel-Funktion auf der Stroke Unit im Vergleich zum Nicht-Monitoring das funktionelle Outcome?

LL	<b>AHA 2018, Kap 6.3 [1]; AHA 2019, Kap 6.3 [11]</b>
Empfehlung	Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours.
Stärke	I; B-NR
Begründung	2018: In patients with TIA or ischemic stroke and atrial fibrillation detected by ECG at the time or within the preceding 24 months, oral anticoagulation begun within 3 months is superior to aspirin for the prevention of vascular death, stroke, MI, and systemic embolism (HR, 0.60; 95% CI, 0.41–0.87)[275]. 2019: Further support for this unchanged recommendation from the 2013 AIS Guidelines is provided by 2 additional studies published since the 2013 guidelines. Kallmünzer et al [276] prospectively monitored by cardiac telemetry 501 patients with acute stroke (92% with cerebral ischemia) for a median of 73 hours after admission to a dedicated stroke unit. A total of 139 serious arrhythmias were detected in 126 patients (25.1%). Atrial fibrillation accounted for 24 of 139 (17%) of the arrhythmias. Detection of arrhythmia led to direct antiarrhythmic treatment in 77.7%. In that study, 52.2% of all detected arrhythmias occurred within 12 hours and 74.4% within 24 hours after admission. Fernández- Menéndez et al [277] prospectively monitored by cardiac telemetry for a minimum of 48 hours 332 patients admitted to the stroke unit with a diagnosis of ischemic stroke, TIA, or intraparenchymal hemorrhage (90% with cerebral ischemia) admitted within 48 hours of symptom onset. One hundred seventy-four significant cardiac arrhythmias occurred in 98 patients (29.5%). Atrial fibrillation/flutter accounted for 23 of 174 (13%) of the arrhythmias. Thirtythree of 98 (34%) patients were directly treated for the arrhythmia (excluding anticoagulation for atrial fibrillation). Thirty-seven percent of all detected arrhythmias occurred on day 1, 29% on day 2, and 15% on day 3 [277].

LL	<b>Australia 2017, Kap 7.3 [6]</b>
Empfehlung	Initial ECG monitoring should be undertaken for all patients with stroke. The duration and mode of monitoring should be guided by individual patient factors but would generally be recommended for at least the first 24 hours
Stärke	Weak
Begründung	The early phase after stroke can be associated with cardiac complications including arrhythmia, and cardiac monitoring is advised in the initial period.
Empfehlung	Keine Empfehlung zum kontinuierlichen Monitoring gegeben, aber Evidenz beschrieben
Begründung	Ciccone et al. (2013) [278] conducted a Cochrane review assessing whether continuous monitoring of physiological variables affected patients' prognosis of mortality or disability. Three studies were included (N = 354), including two randomised controlled trials and one quasi-RCT where patients were allocated to continuous or intermittent monitoring based on the availability of beds. Continuous monitoring was associated with decreased death and disability at 3 months (OR 0.27, 95% CI 0.13 to 0.56), as well as a non-significant reduction in all-cause mortality. However, the decrease in death and disability was non-significant when excluding the quasi-RCT with high risk of bias. Cardiac complications were also detected

	significantly more often, but comparisons of other outcomes such as dependency, vascular death, and neurological complications showed no significant differences.
<b>LL</b>	<b>RCP 2016 [10]</b>
	Patients with suspected stroke or TIA should be monitored for atrial fibrillation and other arrhythmias
<b>Begründung</b>	Working Party consensus
<b>Empfehlung</b>	Patients with acute stroke should have their clinical status monitored closely, including: <ul style="list-style-type: none"> <li>– level of consciousness</li> <li>– blood glucose;</li> <li>– blood pressure;</li> <li>– oxygen saturation;</li> <li>– hydration and nutrition;</li> <li>– temperature;</li> <li>– cardiac rhythm and rate.</li> </ul>
<b>Begründung</b>	Middleton et al, 2011 [56]

SF 1.3.4: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die regelmäßige neurologische Untersuchung und Erfassung mittels etablierter klinischer Scores im Vergleich zu einer selteneren Kontrolle das funktionelle Outcome?

<b>LL</b>	<b>AHA 2018 Kap 2.1 [1]; AHA 2019 Kap 2.1 [11]</b>
<b>Empfehlung</b>	The use of a stroke severity rating scale, preferably the NIHSS, is recommended.
<b>Stärke</b>	I; B-NR
<b>Begründung</b>	Formal stroke scores or scales such as the NIHSS may be performed rapidly, have demonstrated utility, and may be administered by a broad spectrum of healthcare providers with accuracy and reliability [279, 280]. Use of a standardized scale quantifies the degree of neurological deficit, facilitates communication, helps identify patients for thrombolytic or mechanical intervention, allows objective measurement of changing clinical status, and identifies those at higher risk for complications such as intracerebral hemorrhage (ICH) [256, 281-283].

SF 1.3.5: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine frühzeitige transoesophageale Echokardiografie im Vergleich zur transthorakalen Echokardiografie das funktionelle Outcome?

<b>LL</b>	<b>AHA 2018, Kap 6.3 [1]; AHA 2019, Kap 6.3 [11]</b>
<b>Empfehlung</b>	Routine use of echocardiography in all patients with AIS to plan subsequent secondary preventive treatment is not cost-effective and is not recommended.
<b>Stärke</b>	III: No Benefit; B-NR
<b>Empfehlung</b>	In selected patients with AIS, echocardiography to provide additional information to plan subsequent secondary preventive treatment may be reasonable
<b>Stärke</b>	IIb; B-R
<b>Begründung</b>	Current evidence on cost-effectiveness is insufficient to justify routine use of echocardiography in stroke patients. Those patients with known or newly discovered atrial fibrillation by ECG will benefit from oral anticoagulation regardless of echocardiographic findings. The risk of recurrent stroke associated with most echocardiographic lesions and the efficacy of treatment in reducing that risk are unclear. The estimated yield and accuracy of echocardiography in detecting

	<p>intracardiac thrombus indicate that for unselected patients, transthoracic echocardiography and transesophageal echocardiography will produce at least as many false positive as true-positive diagnoses. Intracardiac thrombus occurs almost exclusively in patients with clinical evidence of heart disease but is rare even in them [284]. Additional research on how to identify patients likely to harbor intracardiac thrombus, on recurrent stroke risk in patients with intracardiac thrombus, and on the efficacy of oral anticoagulation in reducing that risk is needed [284-286]. Five RCTs have evaluated mechanical closure of echocardiographically detected patent foramen ovale to prevent recurrent stroke in patients without obvious cause for their index stroke [287-292]. All 5 suffered from potential bias resulting from unblinded investigators determining which events should be referred for blinded end-point adjudication. Three had many more patients lost to follow-up than stroke end points, making their results unreliable [287, 288, 290, 291]. Of 2 RCTs with 1% lost to follow-up, 1 showed no benefit of closure over antithrombotic therapy alone over a 2-year period of 12 strokes (2.9%) versus 13 strokes (3.1%; P=0.79) [289], and the other showed a reduction in all stroke versus antiplatelet therapy alone over a mean of 5.3 years of 0 versus 14 (P&lt; 0.001) with rates at 5 years of 0% and 5%. There was, however, no change in disabling stroke, 0 versus 1 (P=0.63), over the duration of the trial [292]. These 2 trials had different highly restrictive eligibility criteria, used different closure devices, and had different guidelines for antithrombotic therapy.</p>
LL	<b>AHA 2019, Kap 6.3 [11]</b>
Empfehlung	For prevention of recurrent stroke, the use of echocardiography is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention.
Stärke	Ila, C-EO
Empfehlung	<p>many patients, appropriate evidence-based treatment for secondary prevention can be selected without the use of echocardiography. Many RCTs that provide the current best evidence for secondary prevention treatments did not require echocardiography for patient selection. These include NASCET (North American Symptomatic Carotid Endarterectomy Trial), ECST (European Carotid Surgery Trial), IST, SALT (Swedish Aspirin Low-dose Trial), CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), ESPS2 (European Stroke Prevention Study 2), PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes), CHANCE, PROGRESS (Perindopril Protection Against Recurrent Stroke Study), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), SOCRATES, POINT, and TARDIS (Triple Antiplatelets for Reducing Dependency After Ischaemic Stroke) [109, 244-254, 293]. The benefits shown in these RCTs can be expected when the same eligibility criteria are applied. Those patients with known or newly discovered atrial fibrillation by routine ECG will benefit from oral anticoagulation regardless of echocardiographic findings [275]. Intracardiac thrombus occurs almost exclusively in patients with clinical evidence of heart disease but is rare even in them. Echocardiography for detecting intracardiac thrombus in unselected patients will produce at least as many false-positive as true-positive diagnoses.<sup>351</sup> In large series of patients with AIS who underwent echocardiography, the reported yield of important potentially cardioembolic sources has ranged from 0.2% to 55%.</p> <p>Much of this discrepancy is the result of differences in categorization of cardiac pathology as either pathophysiologically or therapeutically relevant. The efficacy of treatment in reducing the risk of recurrent stroke associated with many of these echocardiographic lesions is unknown, or there is not a treatment that has been shown to be better than standard medical therapy [294-302]. Different authors have</p>

	concluded that routine echocardiography is indicated or contraindicated. Various inconsistent recommendations for selecting which patients with AIS should undergo echocardiography have been made [300, 303-305]. Six RCTs have evaluated mechanical closure of echocardiographically detected PFO to prevent recurrent stroke in patients without an obvious cause for their index stroke [287-292, 306]. These trials had highly restrictive eligibility criteria. They do not support the routine use of echocardiography in all patients with AIS.
<b>LL</b>	<b>Canada 2018, S 58; S. 101 [8]</b>
Empfehlung	Outpatient: Echocardiography could be considered in cases where a stroke mechanism has not been identified
Stärke	C
Empfehlung	Hospital: Echocardiography (2D or TEE) may be considered in patients where a cardiac cause of stroke is suspected, including in young adults and children who present with stroke, and when infectious endocarditis is suspected
Stärke	C
Begründung	<p>The use of a transesophageal echocardiography (TEE) is indicated when there is suspected cardiac embolism involvement. For patients with an unknown cause of stroke following baseline diagnostic assessments, and no contraindications to anticoagulation therapy, TEE was found to identify possible sources of cardiac embolism [307]. In 231 patients with recent stroke (all types) or TIA, TEE was found to perform significantly better than transthoracic echocardiography (TTE) in identifying possible sources of cardiac embolism (55% vs. 39%). Among the 39 patients ≤45 years, a potential cardiac source was identified in 13 patients. Of these, the abnormality was identified by TEE in 10 cases and in 3 cases using TTE. Among 192 patients &gt;45 years, a potential cardiac source of embolism was identified in 59% of patients. TEE confirmed the potential cardiac source in 34 patients, but also detected a potential cardioembolic source in an additional 80 patients.</p> <p>The use of transesophageal echocardiography (TEE) has been shown to be more sensitive compared with transthoracic echocardiography (TTE) for detecting cardiac abnormalities following ischemic stroke or TIA, although it is costlier and less acceptable to patients. Common TEE findings following stroke have included atheromatosis, patent foramen ovale, atrial septal aneurysm, [308, 309]. Marino et al. [308] reported that 42.6% of 263 patients admitted following an acute ischemic stroke had a TEE finding which could explain the etiology of stroke/TIA. De Bruijn et al. [307] included 231 patients with recent stroke (all types) or TIA whose stroke etiology remained in questions following initial ECG, ultrasound assessments and blood tests. All patients had a TEE followed by a TTE and the identification of major and minor cardiac sources of embolism were compared between the two diagnostic tools. A potential cardiac source of embolism was detected in 55% of the patients. Significantly more abnormalities were identified using TEE. A cardiac source was detected in 39% of patients where TEE was positive and the TTE, negative. A major cardiac risk factor was detected based on TEE in 16% of patients. The detection of possible cardiac sources of embolism was statistically significantly greater using TEE compared to TTE in both patients aged ≤45 years and &gt;45 years.</p>
<b>LL</b>	<b>Australia 2017, Kap 7.3 [6]</b>
Empfehlung	Further cardiac investigations should be performed where clarification of stroke aetiology is required after initial investigations. In patients with ischaemic stroke,

	echocardiography should be considered based on individual patient factors. Transoesophageal echocardiography is more sensitive for suspected valvular, left atrial and aortic arch pathology
Stärke	weak
Begründung	<p>Holmes et al. (2014) [295] performed a systematic review comparing diagnostic performance of transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) in the identification of the cardiac source of stroke and TIA (excluding atrial fibrillation). Patent foramen ovale (PFO), atrial septal aneurysm and mitral valve prolapse were the most commonly detected cardiac risk factors. In most cases, TTE and TOE have similar specificity and TTE had lower sensitivity. The reported sensitivity varies widely and therefore one cannot be certain how many patients may be missed due to a low sensitivity. Detection of PFO with TTE, for example, has a sensitivity ranging from 0 to 94% when compared with TOE, with a pooled point estimate of 34%.</p> <p>Tanaka et al. (2014)[310] evaluated the association between the volume of the left atrial appendage measured by real-time threedimensional TOE and presence of paroxysmalatrial fibrillation. The optimal cut-off for left atrial appendage peak flow velocity was 39.0 cm/s (sensitivity, 54.6%; specificity, 89.7%). This may be a promising method for detecting atrial fibrillation, but more studies will be needed to validate its diagnostic performance</p>

SF 1.3.6: Führt bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine mehrtägige Kontrolle des Herzrhythmus auf der Stroke Unit im Vergleich zu einem konventionellen 24Std.-Langzeit-EKG a) zu einer erhöhten Detektionsrate für VHF? oder b) zu einem verbesserten funktionellen Outcome?

LL	<b>AHA 2018, Kap 6.3 [1]</b>
Empfehlung	The clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after AIS is uncertain.
Stärke	IIb; B-R
Empfehlung	In some patients with AIS, prolonged cardiac monitoring to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain.
Stärke	IIb; C-EO
Begründung	<p>With prolonged cardiac monitoring by a variety of techniques, atrial fibrillation is newly detected in nearly a quarter of patients with stroke or TIA [311]. However, in the few RCTs of prolonged cardiac monitoring after stroke with clinical end points, no significant benefit of oral anticoagulation for stroke prevention in such patients has been demonstrated [312-317]. In CRYSTAL AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), at 36 months, atrial fibrillation was detected in 30% of 221 patients with implantable cardiac monitors and in 3% of 220 control subjects (<math>P&lt;0.001</math>), but the occurrence of TIA or ischemic stroke was 9% in the implantable cardiac monitor group and 11% in the control group (<math>P=0.64</math>) [314, 315]. In Find-AFRANDOMISED (Finding Atrial Fibrillation in Stroke–Evaluation of Enhanced and Prolonged Holter Monitoring), atrial fibrillation was detected in 14% of 200 patients with 10-day Holter monitoring at baseline, 3 months, and 6 months versus 5% of 198 patients in the standard care group who had at least 24 hours of rhythm monitoring (<math>P=0.002</math>). There was no significant difference in recurrent stroke at 12 months (3.7% versus 5.4%; <math>P=0.46</math>) [312]. Other smaller studies have also failed to show a difference in outcomes [313, 316, 318]. All of these studies were underpowered for the secondary clinical end points. Thus, the appropriate</p>



	patient selection criteria for prolonged cardiac monitoring and the clinical benefits of doing so remain uncertain at this time. Further randomized trials are planned or ongoing and are needed to clarify best practice.
LL	<b>AHA 2019, Kap 6.3 [11]</b>
Empfehlung	The effectiveness of prolonged cardiac monitoring during hospitalization after AIS to guide treatment selection for prevention of recurrent stroke is uncertain
Stärke	IIb, C-LD
Begründung	<p>In patients with TIA or ischemic stroke and atrial fibrillation detected by routine ECG at the time or within the preceding 24 months, oral anticoagulation begun within 3 months is superior to aspirin for the prevention of vascular death, stroke, MI, and systemic embolism (HR, 0.60 [95% CI, 0.41–0.87]) [275]. With prolonged cardiac monitoring during hospitalization, atrial fibrillation is newly detected in nearly a quarter of patients with stroke or TIA [311]. No RCTs have specifically evaluated the benefit of anticoagulation in patients with brief episodes of subclinical atrial fibrillation detected in hospital after AIS. In CRYSTAL AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), at 36 months, atrial fibrillation was detected in 30% of 221 patients with implantable cardiac monitors and in 3% of 220 control subjects (<math>P&lt;0.001</math>), but the occurrence of TIA or ischemic stroke was 9% in the implantable cardiac monitor group and 11% in the control group (<math>P=0.64</math>) [314, 315]. In Find-AFRANDOMISED (Finding Atrial Fibrillation in Stroke–Evaluation of Enhanced and Prolonged Holter Monitoring), atrial fibrillation was detected in 14% of 200 patients with 10-day Holter monitoring at baseline, 3 months, and 6 months versus 5% of 198 patients in the standard care group who had at least 24 hours of rhythm monitoring (<math>P=0.002</math>). There was no significant difference in recurrent stroke at 12 months (3.7% versus 5.4%; <math>P=0.46</math>) [312]. Other smaller studies have also failed to show a difference in outcomes [313, 316, 318].</p> <p>All of these studies were underpowered for the secondary clinical end points. Randomized trials are ongoing to determine whether oral anticoagulation therapy compared with aspirin reduces the risk of stroke or systemic embolism in patients with permanent pacemakers, defibrillators, or insertable cardiac monitors who have subclinical atrial fibrillation or high-rate episodes and additional risk factors (NCT01938248, NCT02618577).</p>
LL	<b>Australia 2017, Kap 7.3 [6]</b>
Empfehlung	Initial ECG monitoring should be undertaken for all patients with stroke. The duration and mode of monitoring should be guided by individual patient factors but would generally be recommended for at least the first 24 hours.
Stärke	weak
Begründung	<p>There is very limited literature comparing ECG vs continuous monitoring in detection of atrial fibrillation (AF) in acute stroke patients if one considers continuous monitoring as telemetric monitoring only (excluding Holter monitoring). In the single study available [319], 151 patients were included, 73.5% had ischaemic stroke, 18.5% had TIA and 8% had cerebral haemorrhage. A total of 4809.5 monitoring hours were elevated. 35 patients had known AF prior to admission, 6 had AF detected on admission ECG and 10 had AF detected during continuous monitoring.</p> <p>When Holter monitoring is considered as well there is more literature available, but the evidence for the superiority of any particular monitoring method is limited. An observational study by Lazzaro et al. (2012) [320] assessed outcomes for 133 stroke and TIA patients registered prospectively in a stroke registry who received both</p>

	<p>Holter and continuous cardiac telemetry monitoring. Holter monitoring detected significantly more atrial fibrillation (6% vs 0%). However, the small size was small, with a small number of atrial fibrillation cases. In contrast, Douen et al. (2008) [321] studied 144 patients with ischaemic stroke. Atrial fibrillation was detected in 15 patients by serial ECG, but out of the 12 AF cases who also had Holter monitoring, Holter monitoring only identified 6 (50%), suggesting Holter may underestimate atrial fibrillation. Gunalp et al. (2006) [322] had previously found Holter monitoring to be superior to serial ECG for detection of arrhythmias in an observational study of 26 patients with thromboembolic stroke and sinus rhythm. On the basis of these mixed results, there is no clear evidence for the superiority of any particular monitoring method.</p>
Empfehlung	For patients with embolic stroke of uncertain source, longer term ECG monitoring (external or implantable) should be used.
Stärke	Strong
Begründung	<p>To date, there are three high-quality randomised controlled trials investigating the detection of atrial fibrillation with long term ECG monitoring. A meta-analysis by Afzal et al. pooled data and reported OR of 4.54 (95%CI 2.92–7.06) of detecting atrial fibrillation with long-term monitoring compared to routine outpatient follow-up [323]. The three randomised controlled trials reported in the systematic review used different technologies with varying duration of monitoring (7–180 days) and definition of atrial fibrillation (20 seconds to greater than 30 seconds) when compared to "routine practice" which is mostly 24-hr Holter monitoring [323]. A small pilot trial did not find any atrial fibrillation in 21 days of telemetry monitoring or outpatient follow-up and the authors believed it was due to low compliance –patients wore monitors for only 64% of assigned days [324]. Afzal et al. also pooled data from 13 observational studies and found that implantable loop recorders (ILR) detected more atrial fibrillation than wearable devices (23.3% compared to 13.6%) [323].</p>
<b>LL</b>	<b>Canada 2018, S. 101 [8]</b>
Empfehlung	Outpatient: Patients with suspected transient ischemic attack or ischemic stroke should have a 12-lead ECG to assess cardiac rhythm and identify atrial fibrillation or flutter or evidence of structural heart disease (e.g. myocardial infarction, left ventricular hypertrophy)
Stärke	B
Empfehlung	Outpatient: For patients being investigated for an acute embolic ischemic stroke or TIA of undetermined source whose initial short-term ECG monitoring does not reveal atrial fibrillation but a cardioembolic mechanism is suspected, prolonged ECG monitoring for at least 2 weeks is recommended to improve detection of paroxysmal atrial fibrillation in selected patients aged ≥ 55 years who are not already receiving anticoagulant therapy but would be potential anticoagulant candidates
Stärke	A
Empfehlung	Hospital: Patients with suspected transient ischemic attack or ischemic stroke should have a 12-lead ECG to assess cardiac rhythm and identify atrial fibrillation or flutter or evidence of structural heart disease (e.g. myocardial infarction, left ventricular hypertrophy)
Stärke	B
Begründung	An electrocardiogram (ECG) should be performed immediately to identify arrhythmias for all patients with stroke and TIA presenting to the Emergency Department. Atrial fibrillation (AF) is commonly diagnosed post-stroke, and is of

particular concern due to its role in forming emboli. Sposato et al. [311] included the results from 11 studies in which cardiac monitoring was initiated in the ED. An estimated 7.7% of patients, without a history of AF, were newly diagnosed. Suissa et al. [325] included 946 patients with ischemic stroke without history of AF and found that the odds of detection were greatest within the first 24 hours of stroke (OR= 9.82; 95% CI 3.01 to 32.07). Patients who received continuous cardiac monitoring group were more likely to be identified with AF compared with those who received a baseline ECG, 24-hour Holter monitor and additional ECGs when necessary (adj OR= 5.29; 95% CI 2.43 to 11.55). Regardless of the type of monitoring used, the initial ECG will not always detect all cases of AF. In the same study, it was found that ECG monitoring beyond the baseline assessment resulted in the identification of additional cases of AF in 2.3%-14.9% of the population [325]. The use of serial ECG assessments over the first 72 hours following stroke can be an effective means of diagnosing AF. For example, Douen et al. [321] reported there was no significant difference in detection rates between cardiac monitoring groups. AF was identified in 15 new patients using serial ECG and in 9 new patients using a Holter monitor. The majority of these cases were identified within 72 hours (83%).

Detecting atrial fibrillation (AF) after a stroke or TIA is important since it is a major risk factor for subsequent stroke and, once identified, can be effectively treated. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic. Additionally, although many abnormalities can be detected within the first few days of monitoring, prolonged screening may be required to detect others. Flint et al. [326] followed 239 patients with cryptogenic ischemic stroke who underwent outpatient cardiac monitoring using an electrocardiographic loop recorder for 30 days. Paroxysmal atrial fibrillation (PAF) was detected in 26 patients (11.0%; 95% CI: 7.6% to 15.7%) who were previously undiagnosed. While PAF was detected most often (45%) in patients within the first 10 days, 31% were detected from day 11 to 20 and 24%, from day 21 to 30. Suissa et al. [325] included 946 patients with acute ischemic stroke who were previously undiagnosed with AF. Patients were admitted to an intensive stroke unit care that included continuous cardiac monitoring or to a conventional stroke unit care where patients received a baseline ECG, 24-hour Holter monitor and additional ECGs when necessary. Significantly more cases of AF were detected in patients in the continuous cardiac monitoring group (14.9% vs. 2.3%, adj OR=5.29; 95% CI 2.43 to 11.55). The odds of detection were highest within the first 24 hours of monitoring (OR=9.82; 95% CI 3.01 to 32.07). A prospective cohort study that compared the effectiveness of serial ECGs and Holter monitoring for the identification of AF in patients post stroke found that both methods were equally effective in identifying cases that were not present on a baseline assessment [321]. Together, serial ECG's and Holter monitoring identified 18 new cases of AF after baseline ECG assessment in the 144 patients included in the study. The majority (83%) of these cases were identified within 72 hours. A recent systematic review [327] includes the results from 32 studies (5,038 patients) of patients with acute ischemic stroke or TIA who had undergone invasive or non-invasive cardiac monitoring for a minimum of 12 hours following event. The different types of cardiac monitoring evaluated included inpatient cardiac monitoring, 24, 48 & 72hr and 7-day Holter, external loop recorder, invasive cardiac monitoring and mobile cardiac outpatient telemonitoring. The overall detection rate of AF was 11.5% (95% CI 8.9%-14.3%) and was higher in selected (pre-screened or cryptogenic) patients (13.4%, 95% CI 9.0%-18.4%) compared with unselected patients (6.2%, 95% CI 4.4%-8.3%). The detection rate of AF in cryptogenic stroke was 15.9% (95% CI 10.9%-21.6%).

SF 1.3.7: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die duplexsonografische Untersuchung der extra- und intrakraniellen Arterien im Vergleich zur CTA/MRA/DSA die Genauigkeit der ätiologischen Einordnung?

LL	<b>AHA 2018, Kap 6.2 [1]; AHA 2019, Kap 6.2 [11]</b>
Empfehlung	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.
Stärke	I; B-NR
Begründung	Past data have indicated that the risk of recurrent stroke caused by symptomatic carotid stenosis is highest early after the initial event [328-332]. Although there is evidence that early or emergency revascularization via either CEA or carotid angioplasty and stenting may be safe in selected cases [333-335], there are no high-quality prospective data supporting early versus late carotid revascularization in all cases [336]. In cases of nondisabling stroke, a meta-analysis by De Rango et al [331] demonstrates high rates of complications when treated <48 hours after the initial event and no difference in risks when treated between 0 and 7 days and 0 and 15 days. Revascularization between 48 hours and 7 days after initial stroke is supported by the data in cases of nondisabling stroke (mRS score 0–2) [337]. Imaging within 24 hours of admission is feasible and recommended to facilitate CEA/carotid angioplasty and stenting in eligible patients in the 48- to 72-hour window.

LL	<b>Australia 2017, Kap [6]</b>
Empfehlung	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.
Stärke	Strong
Begründung	Carotid imaging is critically important for people with carotid stenosis to identify candidates for endarterectomy which substantially reduces the risk of recurrent stroke in appropriate patients. If carotid imaging using CTA has not already been performed, Doppler ultrasound is widely available and requires no contrast or ionising radiation, but is operator dependent and visualises a relatively small region of the carotid circulation. Contrast-enhanced MR angiography is accurate but less widely available, and gadolinium contrast is contraindicated in kidney disease. People with carotid artery stenosis (CAS) may require carotid endarterectomy and therefore the accuracy of measuring the stenosis is important for indication of the CEA procedure. In the comparison between CT angiography, digital subtraction angiography, Doppler ultrasonography and MR angiography, the strongest correlation coefficient and the best allocation of stenosis into clinical significant groups (<50%, 50–69%, >=70%) was observed for CTA. Netuka concluded that CTA yielded the best accuracy in detection of carotid stenosis provided all axial slices of the stenosis are checked and carefully analysed [338]. In an individual patient data meta-analysis [339] where ultrasonography, CTA, MR angiography and contrast material-enhanced MT angiography were compared to diagnose both severe and moderate symptomatic CAS, contrast-enhanced MR angiography was the most accurate for cases where stenosis was 70–99%. Benefits outweigh harms for both interventions and no issues were identified regarding values and preferences.

LL	<b>Canada 2018 [8]</b>
Empfehlung	Vascular imaging is recommended to identify significant symptomatic extracranial carotid artery stenosis for which patients should be referred for possible carotid revascularization
Stärke	A
Empfehlung	Carotid ultrasound (for extracranial vascular imaging) and MR angiography are acceptable alternatives to CTA, and selection should be based on immediate availability, and patient characteristics
Stärke	C
Begründung	./.

SF 1.5.1: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine frühzeitige antithrombotische Therapie mit ASS im Vergleich zum Verzicht auf eine antithrombotische Therapie das funktionelle Outcome?

LL	<b>AHA 2018, Kap 3.9 [1], AHA 2019, Kap 3.9 [11]</b>
Empfehlung	2018/2019: Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.
Stärke	I, A
Begründung	The safety and benefit of aspirin in the treatment of patients with AIS were established by 2 large clinical trials administering doses between 160 and 300 mg [109, 340]. This has recently been confirmed by a large Cochrane review of aspirin trials [341]. In patients unsafe or unable to swallow, rectal or nasogastric administration is appropriate. Limited data exist on the use of alternative antiplatelet agents in the treatment of AIS. However, in patients with a contraindication to aspirin, administering alternative antiplatelet agents may be reasonable. A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or EVT compared with initiation >24 hours. However, this study may have been subject to selection bias, and the timing of initiation of antiplatelet therapy or anticoagulation should be made on an individual level, balancing risk versus benefit. The recommendation was modified from the previous guideline to remove the specific dosing recommendation, "initial dose is 325 mg," because previous clinical trials supporting its use for AIS included doses of 160 to 300 mg.
Empfehlung	Ticagrelor is not recommended (over aspirin) in the acute treatment of patients with minor stroke.
Stärke	III: No benefit; B-R
Begründung	The recently completed SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA (ABCD2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). With a primary outcome of time to the composite end point of stroke, myocardial infarction (MI), or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89; 95% CI, 0.78–1.01;

	P=0.07) [246]. However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin.
Empfehlung	2018/2019: The administration of the IV glycoprotein IIb/IIIa inhibitor abciximab as medical treatment for AIS is potentially harmful and should not be performed.
Stärke	III: Harm; B-R
Begründung	A recent Cochrane review of IV glycoprotein IIb/IIIa receptor antagonists in the treatment of AIS found that these agents are associated with a significant risk of ICH without a measurable improvement in death or disability [342]. The majority of trial data apply to abciximab, which was studied in the AbESTT trial (A Study of Effectiveness and Safety of Abciximab in Patients With Acute Ischemic Stroke). The phase III trial was terminated early because of an unfavorable risk-benefit analysis [343].
Empfehlung	2018/2019: The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide in the treatment of AIS is not well established
Stärke	IIB; B-R
Begründung	Prospective, randomized, open-label phase II trials of tirofiban [344] and eptifibatide [345] have suggested safety for treatment in patients with AIS. Single-arm studies of eptifibatide as adjunctive therapy to IV alteplase support ongoing RCTs to establish safety and efficacy [346, 347]. Further trials are necessary to clarify the safety and efficacy of this intervention.
Empfehlung	2018/2019: Aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy
Stärke	III: Harm; B-R
Begründung	Recommendation revised from 2013 AIS Guidelines.
<hr/>	
LL	<b>NICE 2019, Kap 8.2 [24]</b>
Empfehlung	All people presenting with acute stroke who have had a diagnosis of primary intracerebral haemorrhage excluded by brain imaging should, as soon as possible but certainly within 24 hours, be given: <ul style="list-style-type: none"> <li>• aspirin 300 mg orally if they are not dysphagic, or</li> <li>• aspirin 300 mg rectally or by enteral tube if they are dysphagic.</li> </ul> Thereafter aspirin 300 mg should be continued until 2 weeks after the onset of stroke symptoms, at which time definitive long-term antithrombotic treatment should be initiated. People being discharged before 2 weeks can be started on long-term treatment earlier.
Stärke	./.
Empfehlung	Any person with acute ischaemic stroke for whom previous dyspepsia associated with aspirin is reported should be given a proton pump inhibitor in addition to aspirin
Stärke	./.
Empfehlung	Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin should be given an alternative antiplatelet agent.
Stärke	./.
Begründung	No RCTs, meta-analyses or systematic reviews were identified that addressed the safety and efficacy of aspirin versus other antiplatelet agents in acute ischaemic stroke. One preliminary pilot study was identified and excluded. The GDG recommended that a research study should be carried out comparing aspirin with other antiplatelet agents singly or in combination, in patients with acute ischaemic stroke and TIA. The review of the safety and efficacy of antiplatelet agents versus

	<p>placebo included some antiplatelet drugs that are not licensed in the UK. These were excluded from the analysis. The GDG agreed that from the evidence presented to it, aspirin should be recommended. It was noted that from the evidence presented, doses of 160–300 mg were reported as being equally effective. The two largest trials recommended that aspirin should be given as soon as possible after haemorrhage had been excluded and within a maximum of 48 hours. One of these studies compared aspirin administration within 0–12 hours with administration within 12–48 hours and found no significant difference. No specific research reviews into methods of delivery were conducted. There is little evidence comparing different methods of aspirin delivery and in most studies it has been administered by a variety of routes. The GDG agreed that aspirin should be delivered by the most clinically appropriate route (oral, rectal or by enteral tube) and that the latter two routes are appropriate for patients with dysphagia. In the two largest RCTs, CAST and IST, aspirin therapy was continued for 2–4 weeks post stroke onset. These RCTs made up to 98% of the data within the Cochrane review and a clinical consensus was agreed by the GDG that aspirin should be continued for 2 weeks. It was noted that there is very little evidence to guide the management of aspirin-intolerant patients. The consensus of the GDG based on clinical experience was that patients who are not truly allergic to aspirin or without contraindications should take aspirin with proton pump inhibitor cover where appropriate. The GDG used the definition of aspirin tolerance used in the NICE vascular disease TA90. Genuine aspirin intolerance was defined as people with proven hypersensitivity to aspirin-containing medicines or history of severe dyspepsia induced by low-dose aspirin. Patients who have not previously tolerated high doses of aspirin may be able to tolerate low-dose aspirin. In patients receiving anticoagulant therapy, there was a significant reduction in the incidence of clinically significant venous thromboembolism and recurrent stroke. However, there was also a significant increase in the number of symptomatic intracranial haemorrhages and extracranial bleeds compared to placebo. Anticoagulant therapy confers no additional benefit over antiplatelet agents in acute stroke (and may be harmful) in the absence of specific indications. It was noted that there was no evidence available on long-term morbidities associated with DVT following stroke. However, the GDG noted that some patients are at higher risk of venous thromboembolism and review at 48 hours should be undertaken. The GDG noted that there is a NICE guideline currently in development which looks at reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.</p>
<b>LL</b>	<b>Australia 2017, Kap 3.10 [6]</b>
Empfehlung	Patients with ischaemic stroke who are not receiving reperfusion therapy should receive antiplatelet therapy as soon as brain imaging has excluded haemorrhage
Stärke	Strong
Begründung	Sandercock et al [341] conducted a systematic review and meta-analysis of immediate oral antiplatelet therapy for acute ischaemic stroke. Eight randomised controlled trials with 41,483 patients were included. The two largest trials, contributing 98% of the data, used 300mg or 160mg aspirin. Aspirin was associated with a small but significant reduction in death or dependence (OR 0.95, 95% CI 0.91 to 0.99) at the end of follow-up (up to 6 months). There were also significant reductions in death and recurrent stroke, as well as a significant increase in symptomatic intracranial haemorrhages that was small in absolute terms due to the low overall risk. The review authors rated the risk of bias as low. Although one of the

	<p>large trials contributing the majority of the data was unblinded, outcomes were self-reported by patients or assessed by a blinded interviewer, and a pilot study suggested that the majority of patients did not remember the treatment they had received at 6-month follow-up.</p> <p>Rothwell et al. [216] conducted an individual patient data analysis of the effects of aspirin on risk of recurrent stroke following TIA or ischaemic stroke. Data for aspirin following acute stroke predominantly came from the two largest trials included in the Sandercock et al [341] review. Time course analysis of the risk of recurrent ischaemic stroke following aspirin treatment was conducted. For patients with mild or moderately severe neurological deficits, there was a non-significant reduction in risk in the first 24 hours following aspirin treatment, with significant reductions by day 2 that remained significant at day 3, days 4-6 and days 7-14. Risks were not significantly different after 14 days.</p>
Empfehlung	Acute antiplatelet therapy should not be given within 24 hours of alteplase administration.
Stärke	Strong against
Begründung	A randomised trial [348] comparing addition of intravenous aspirin to alteplase versus alteplase alone was halted early due to increased numbers of symptomatic intracranial haemorrhage in the aspirin group, with no evidence of benefit on the primary endpoint of a favourable outcome (score of 0-2 on the modified Rankin Scale). Addition of intravenous aspirin to alteplase versus alteplase alone showed no improvements in favourable outcomes (defined as modified Rankin Scale 0–2) and an increase in symptomatic intracranial haemorrhage (28 more per 1000)
<b>LL</b>	<b>Canada 2018, S. 85 [8]</b>
Empfehlung	All acute stroke patients not already on an antiplatelet agent and not receiving alteplase therapy should be given at least 160 mg of acetylsalicylic acid (ASA) immediately as a one-time loading dose after brain imaging has excluded intracranial hemorrhage and after dysphagia screening has been performed and passed
Stärke	A
Empfehlung	Acetylsalicylic acid (81 to 325 mg daily) should then be continued indefinitely or until an alternative antithrombotic regime is started
Stärke	A
Begründung	Aspirin therapy, provided acutely following ischemic stroke, is known to reduce the risk of recurrent (ischemic) stroke. In an updated Cochrane review, Sandercock et al. (2014) identified 8 RCTs (n=41,483 patients) that compared a single oral antiplatelet agent (aspirin, n=3 or ticlopidine, n=2) or a combination of antiplatelet agents (aspirin + dipyridamole and/or heparin, n=2) with control (placebo or no treatment). In 8/10 trials, therapy was initiated within one week following stroke. The dose of aspirin ranged from 160-325 mg/day and treatment duration ranged from 5 days to 3 months following stroke. Two large trials testing aspirin, started within 48 hours of stroke onset, contributed 98% of the data [109, 340]. Antiplatelet therapy was associated with a significant reduction in the odds of being dead or dependent at final follow-up (OR= 0.95, 95% CI 0.91 to 0.99, p= 0.01). Treatment was also associated with a marginally significant reduction in death during treatment (OR= 0.92, 95% CI 0.85 to 1.00, p=0.05) and a significant reduction in the odds of death at a final follow-up (OR=0.92, 95% CI 0.87 to 0.99, p=0.01). Although antiplatelet therapy was associated with a significant increase in the odds of intracerebral hemorrhage (OR=1.23, 95% CI 1.00 to 1.50, p=0.04), a net reduction was reported in the odds of



	any stroke recurrence (i.e., ischemic or hemorrhagic; OR=0.88, 95% CI 0.80 to 0.97). For every 1,000 people treated with aspirin, 13 fewer people would avoid death or dependency, 9 fewer would avoid death and 7 fewer would avoid a recurrent stroke. The results from a patient-level metaanalysis using 3 RCTs, (Rothwell et al. 2016) suggest that the greatest reduction in early stroke recurrence associated with aspirin monotherapy is among patients presenting with mild or moderately disabling stroke. Aspirin therapy was not associated with a significant reduction in stroke recurrence among those with a severe stroke.
Empfehlung	In patients treated with tissue plasminogen activator (alteplase), initiation of antiplatelet agents should be delayed until after the 24-hour post-thrombolysis scan has excluded intracranial haemorrhage
Stärke	B
Begründung	After thrombolysis, a portion of patients may develop reocclusion, which has been attributed to increased platelet aggregation. Therefore, antiplatelet therapy early after alteplase was thought to potentially reduce the risk of reocclusion and thereby improve functional outcome. However, the results from The Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke (ARTIS) Trial suggest that treatment may be associated with harm. Zinkstok & Roos [348] randomized 640 patients to receive 300 mg of aspirin intravenously within 90 minutes of alteplase treatment or standard treatment (no aspirin). At the three-month follow-up, although there was no difference between groups in the odds of a good outcome, defined as mRS score of 0-2 (54% vs. 57.2%, OR=0.91, 95% CI 0.66 to 1.26), the risk of symptomatic ICH was significantly higher among patients in the early aspirin group (RR=2.78, 95% CI 1.01 to 7.63, p=0.04)

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke should be given aspirin 300mg as soon as possible within 24 hours (unless contraindicated): – orally if they are not dysphagic; – rectally or by enteral tube if they are dysphagic. Thereafter aspirin 300 mg daily should be continued until 2 weeks after the onset of stroke at which time long-term antithrombotic treatment should be initiated. Patients being transferred to care at home before 2 weeks should be started on long-term treatment earlier.
Empfehlung	Patients with acute ischaemic stroke reporting previous dyspepsia with an antiplatelet agent should be given a proton pump inhibitor in addition to aspirin.
Empfehlung	Patients with acute ischaemic stroke who are allergic to or intolerant of aspirin should be given an alternative antiplatelet agent (e.g. clopidogrel).
Begründung	Sandercock et al, 2015 [111]; NICE, 2010; Working Party consensus

SF 1.5.2: Führt bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA eine frühzeitige duale antithrombotische Therapie im Vergleich zu einer singulären antithrombotischen Therapie a) zur Reduktion des Risikos früher Schlaganfallrezidive?; b) zu einer veränderten Risiko-Nutzen-Abwägung?; c) zur Verbesserung des funktionellen Outcomes?

LL	<b>AHA 2018 [1]</b>
Empfehlung	In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.

Stärke	Ila, B-R
Begründung	The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled trial conducted in China to study the efficacy of short-term dual antiplatelet therapy begun within 24 hours, clopidogrel plus aspirin for 21 days followed by clopidogrel alone to 90 days, in patients with minor stroke (NIHSS score $\leq 3$ ) or high-risk TIA (ABCD2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score $\geq 4$ ). The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone (hazard ratio [HR], 0.68; 95% CI, 0.57–0.81; $P < 0.001$ ) [244]. A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days [349]. The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the United States, Canada, Europe, and Australia is ongoing [350].
LL	<b>AHA 2019, Kap 3.9 [11]</b>
Empfehlung	In patients presenting with minor non-cardioembolic ischemic stroke (NIHSS score $\leq 3$ ) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.
Stärke	I-A
Begründung	Two independent multicenter, randomized, double-blind, placebo-controlled trials have established the efficacy of short-term dual antiplatelet therapy to prevent recurrent ischemic stroke in patients with minor stroke or high-risk TIA. The CHANCE trial (Clopidogrel in High Risk Patients With Acute Nondisabling Cerebrovascular Events; N=5170) conducted in China studied the efficacy of short-term dual antiplatelet therapy begun within 24 hours in patients with minor stroke (NIHSS score $\leq 3$ ) or high-risk TIA (ABCD2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score $\geq 4$ ). The dosing regimen was clopidogrel at an initial dose of 300 mg followed by 75 mg/d for 90 days plus aspirin at a dose of 75 mg/d for the first 21 days or placebo plus aspirin (75 mg/d for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone: hazard ratio (HR), 0.68 (95% CI, 0.57–0.81; $P < 0.001$ ) [244]. Post hoc analysis found a small but measurable reduction in poor functional outcome (mRS score 2–6) on dual antiplatelet therapy compared with aspirin alone (absolute RR, 1.7% [95% CI, 0.03%–3.42%]; $P = 0.046$ ) [351]. However, a post hoc time-course analysis showed that the benefit in reducing recurrent ischemic stroke compared with the risk of bleeding on dual antiplatelet therapy dissipated after $\approx 10$ days of treatment [352]. A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days [349]. In addition, subgroup analyses found no benefit of clopidogrel plus aspirin in carriers of a CYP2C19 loss-of-function allele [353] or those with a single acute infarction or no infarction compared with those with multiple acute infarctions [354], although these subgroup analyses were likely underpowered. The POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; N=4881) was conducted in North America, Europe, Australia, and New Zealand, with the majority (83%) enrolled in the United States (75% white, 20% black) [245]. Similar

	<p>to CHANCE, the target enrolment population included minor stroke (NIHSS score <math>\leq 3</math>) or high-risk TIA (ABCD2 score <math>\geq 4</math>) within 12 hours of symptom onset. Patients were randomized to either clopidogrel plus aspirin (600-mg loading dose of clopidogrel followed by 75 mg/d from day 2–90) plus open-label aspirin (50–325 mg/d) versus aspirin alone (50–325 mg/d) for 90 days. The primary outcome was a composite of ischemic stroke, myocardial infarction (MI), or death resulting from an ischemic vascular event up to 90 days, with a secondary safety end point of major hemorrhage during the same time period. Compared with aspirin alone, aspirin plus clopidogrel resulted in fewer ischemic events (5% versus 6.5%; HR, 0.75 [95% CI, 0.59–0.95]; <math>P=0.02</math>) but more major hemorrhages (0.9% versus 0.4%; HR, 2.32 [95% CI, 1.10–4.87]; <math>P=0.02</math>). Overall, the beneficial effect of aspirin plus clopidogrel was driven by a reduction in ischemic stroke (HR, 0.72 [95% CI, 0.56–0.92]; <math>P=0.01</math>) and greatest in the first 30 days of treatment from symptom onset (HR, 0.73 [95% CI, 0.56–0.95]; <math>P=0.02</math>). However, the risk of major hemorrhage was greatest after the first 7 days of treatment (HR, 2.69 [95% CI, 1.05–6.86]; <math>P=0.04</math>). There was no significant added benefit of aspirin plus clopidogrel after 30 days of treatment. In addition, in a prespecified analysis of functional outcomes determined by 90-day mRS score <math>\geq 2</math> for new disability, there was no difference between groups (HR, 0.97 [95% CI, 0.82–1.14]; <math>P=0.71</math>).</p>
LL	<b>UK 2018</b> [9], NICE 59 ?? [24]
Empfehlung	We recommend dual antiplatelet therapy over single agent therapy. Start as soon as possible after index event.
Stärke	Strong
Empfehlung	We recommend administering dual antiplatelet therapy for 10-21 days after the index event
Stärke	Strong
Begründung	<p>Systematic review: Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. <i>BMJ</i> 2018 [355]</p> <p>The linked systematic review found three RCTs examining DAPT versus aspirin alone reporting on a total of 10 447 patients [244, 245, 356]. Figure 2 provides an overview of the RCTs and RCT participants. Overall, patients included in these trials were similar to those seen in everyday practice. Mean age varied from 62 to 68.1 years. In the FASTER trial 1/6 of the patients were older than 81 years; in CHANCE 1/4 of patients were over 72; and in POINT 1/4 were over 85. Just over half of participants (52.866.2%) were male.</p> <p>Compared with single antiplatelet therapy,</p> <ul style="list-style-type: none"> <li>• DAPT decreased all (ischaemic and haemorrhagic) non-fatal recurrent stroke (risk ratio 0.70 (95% confidence interval 0.61 to 0.80), high certainty)</li> <li>• DAPT led to small improvements in functional disability (moderate certainty) and quality of life (moderate certainty)</li> <li>• DAPT led to a small, possibly important increase in moderate or major extracranial bleeding (moderate certainty)</li> </ul> <p>Overall, the panel was confident that DAPT, when started within 24 hours of symptom onset and used for 10–21 days:</p>

	<ul style="list-style-type: none"> <li>• Reduces non-fatal recurrent stroke (ischaemic and haemorrhagic) in the first 90 days by 1.9% (high quality evidence)</li> <li>• Reduces the incidence of moderate or severe functional disability by 1.4% (moderate quality evidence)</li> <li>• Reduces the incidence of poor quality of life by 1.3% (moderate quality evidence).</li> </ul> <p>However, DAPT has little or no impact on:</p> <ul style="list-style-type: none"> <li>• All-cause mortality (moderate quality evidence).</li> <li>• Incidence of myocardial infarction or recurrent transient ischaemic attack (moderate quality evidence).</li> </ul> <p>Furthermore, DAPT also has some harms:</p> <ul style="list-style-type: none"> <li>• A small (0.2%), possibly important increase in moderate to major extracranial bleeding events (moderate quality evidence)</li> <li>• A small increase in the risk of minor extracranial bleeding events by 0.7% (high quality evidence)</li> </ul>
--	--

LL	<b>Australia 2017, Kap 3.10 [6]</b>
Empfehlung	Aspirin plus clopidogrel may be used in the short term (first three weeks) in high-risk patients with minor ischaemic stroke or TIA to prevent stroke recurrence.
Stärke	weak
Begründung	A systematic review [357] of trials investigating dual antiplatelet therapy compared to mono antiplatelet included 14 studies with 9012 patients, including the recent CHANCE study that was substantially larger than all previous trials. Dual antiplatelet therapies included aspirin + clopidogrel, aspirin +dipyridamole and cilostazol + aspirin. Dual antiplatelet therapy produced significant reductions in the risk of recurrent stroke (RR 0.69, 95% CI 0.60 to 0.80) and the composite outcome of stroke, TIA, ACS, and all deaths, with no significant increase in major bleeding. Sensitivity analyses that included only the 7 trials that were double-blinded showed similar results. While there was no significant heterogeneity across different dual and mono antiplatelet treatment regimens, the majority of data came from the aspirin + clopidogrel versus aspirin alone comparison investigated in the CHANCE trial. Two subsequent randomised controlled trials [358, 359] compared combined clopidogrel and aspirin treatment to aspirin alone. Both had short follow-up periods, of 14 or 30 days. In both trials, neurological deterioration and recurrent stroke occurred less often in the combined therapy groups, although only one of the studies reported that these differences were statistically significant.
Anmerkung	POINT noch nicht berücksichtigt

LL	<b>Canada 2018, S. 85 [8]</b>
Empfehlung	In very high risk TIA patients or minor stroke of non-cardioembolic origin (NIHSS 0-3), a combination of clopidogrel and acetylsalicylic acid should be given for a duration of 21 to 30 days followed by antiplatelet monotherapy (such as acetylsalicylic acid or clopidogrel alone). Dual antiplatelet therapy should be started as soon as possible after brain imaging, within 24 hours of symptom onset, and ideally within 12 hours.
Stärke	A
Empfehlung	A minimal loading dose of 300 mg Clopidogrel (based on dose in CHANCE) up to 600mg (based on dose used in POINT) and 160 mg of acetylsalicylic acid should be given at the start of treatment
Stärke	A

Begründung	<p>There is some evidence to suggest that dual antiplatelet therapy, provided in the early post-stroke period may help to reduce the risk of recurrent stroke. Geeganage et al. [360] included the results from 12 trials assessing various combinations and doses of other antiplatelet agents, in addition to aspirin. Based on the results from all trials, dual therapy was associated with significantly reduced risks of recurrent stroke (RR=0.67, 95% CI 0.49-0.93, p=0.02), composite of stroke, MI and vascular death (RR=0.75; 95% CI, 0.56 – 0.99, p=0.04), without significant increases in ICH or major bleeding events. In contrast, the results of the TARDIS trial [293] suggest that triple antiplatelet therapy with aspirin, dipyridamole and clopidogrel, does not significantly reduce the risk of recurrent stroke, but does increase the risk of bleeding events. Clopidogrel is indicated for acute management of ischemic stroke in patients who are not tolerant of aspirin. Two major trials, published within the previous 5 years, both with short-term outcomes, were positive. The most recent one, the Platelet-Oriented Inhibition in New TIA &amp; Minor Ischemic Stroke (POINT) Trial [245], enrolled 4,881 patients with recent (within previous 12 hours) minor stroke or TIA from centres located mainly in the United States. Patients were randomized to receive 81 mg aspirin + 75 mg clopidogrel or aspirin + placebo, for 90 days. The risk of ischemic stroke was significantly lower in the clopidogrel group (4.6% vs. 6.3%; HR=0.72, 95% CI 0.56–0.92, p= 0.01), although the risk of major hemorrhage was significantly increased (0.9% vs. 0.4%, HR=2.32, 95% CI 1.10–4.87, p= 0.02). The authors estimated that for every 1,000 patients treated with clopidogrel plus aspirin for 90 days, 15 ischemic strokes would be prevented but 5 major hemorrhages would result. Another positive trial was the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, in which investigators randomized 5,170 patients from China with recent minor ischemic stroke (within previous 24 hours) or high-risk TIA to receive clopidogrel (75 mg/day) plus lowdose ASA (75 mg/day) or clopidogrel placebo plus aspirin for 90 days [244]. Significantly fewer patients in the clopidogrel + aspirin group experienced a stroke within 90 days (Any stroke: 8.2% vs. 11.7%, HR=0.68, 95% CI 0.057-0.81, p&lt;0.001) or an MI, stroke or vascular death stroke (8.4% vs. 11.9%, HR=0.69, 95% CI 0.58- 0.82, p&lt;0.001). There was no difference in (any) bleeding events between groups (2.3% vs. 1.6%, p=0.09). In the Fast Assessment of Stroke and TIA to prevent Stroke Recurrence (FASTER) trial [356], randomized 392 patients presenting with minor stroke or TIA to receive clopidogrel or placebo and simvastatin or placebo within 24 hours of the qualifying event. In the antiplatelet arm of the trial, there were non-significant reductions in the risks of recurrent stroke (7.1% vs. 10.8%, RR=0.7, 95% CI 0.3-1.2, p=0.19) and the composite secondary outcome, which included myocardial infarction and death, associated with clopidogrel use. Clopidogrel use was associated with a significant 3% increase in risk (p=0.03) for symptomatic bleeding events. The addition of dipyridamole to both aspirin and clopidogrel (i.e., triple antiplatelet therapy) to prevent recurrent events within 90 days was found to be associated with increased bleeding events in the TRADIS trial [293], compared with standard antiplatelet therapy using one or two agents. There was no significant difference between groups in the incidence or severity of stroke or TIA. The trial was stopped prematurely due to futility and safety concerns.</p>
------------	---

SF 1.6.1: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt eine frühzeitige Physiotherapie im Vergleich zum Verzicht darauf das funktionelle Outcome?

LL	<b>AHA 2018, Kap 4.11 [1]; AHA 2019, Kap 4.12 [11]</b>
----	--

Empfehlung	High-dose, very early mobilization within 24 hours of stroke onset should not be performed because it can reduce the odds of a favorable outcome at 3 months.
Stärke	III: Harm; B-R
Begründung	The AVERT RCT (A Very Early Rehabilitation Trial) compared high-dose, very early mobilization with standard-of care mobility [361]. High-dose mobilization protocol interventions included the following: Mobilization was begun within 24 hours of stroke onset whereas usual care typically was 24 hours after the onset of stroke; there was a focus on sitting, standing, and walking activity; and there were at least 3 additional out-of-bed sessions compared with usual care. Favorable outcome at 3 months after stroke was defined as an mRS score of 0 to 2. A total of 2104 patients were randomly assigned (1:1). The results of the RCT showed that patients in the highdose, very early mobilization group had less favorable outcomes (46% versus 50%) than those in the usual care group: 8% versus 7% of patients died in the very early mobilization group and 19% versus 20% had a nonfatal serious adverse event with high-dose, very early mobilization.

LL	<b>Canada 2018, S. 102 [8]</b>
Empfehlung	All patients admitted to hospital with acute stroke should have an initial assessment, conducted by rehabilitation professionals, as soon as possible after admission
Stärke	A
Empfehlung	Initial screening and assessment should be commenced within 48 hours of admission by rehabilitation professionals in direct contact with the patient
Stärke	C
Empfehlung	Rehabilitation therapy should begin as early as possible once the patient is determined to be medically able to participate in active rehabilitation
Stärke	A
Begründung	Early mobilization post stroke is intended to reduce the risk of medical complications including deep vein thrombosis, pressure sores, painful shoulders, and respiratory infections. The potential benefits of early mobilization have been examined in several RCTs, with ambiguous results. One of the sources of variability among studies examining the issue, which may account for conflicting results, is differences in treatment contrasts. Early mobilization was defined as early as 12 hours following stroke to as long as 52 hours, while patients in the delayed group were mobilized from time periods ranging from 48 hours to 7 days. Small sample sizes (i.e. under-powered samples sizes) may also have contributed to null findings. In the Akerhus Early Mobilization in Stroke Study (AKEMIS) 65 patients were randomized to a very early mobilization (VEM) group or to a control group following ischemic or hemorrhagic stroke. Patients in both groups received standard stroke unit care. Patients in the VEM group were mobilized as soon as possible (within 24 hours post stroke), while patients in the control group were mobilized between 24 and 48 hours. The median time to first mobilization from stroke onset was significantly shorter for patients in the VEM group (13.1 vs. 33.3 hrs, $p < 0.001$ ); however, there were no significant differences between groups on any of the outcomes of interest, including poor outcome at 3 months (mRS score of 3-6), death or dependency, dependency, or number of complications at 3 months. Diserens et al. [362] randomized 50 patients with ischemic stroke to either an “early mobilization” group who were mobilized out of bed after 52 hour or to a “delayed mobilization” group where patients were mobilized after 7 days. While there were significantly fewer severe complications

among patients in the early mobilization group (8% vs. 47%,  $p < 0.006$ ), there were no significant differences between groups in the numbers of minor complications, neurological deficits, or blood flow modifications.

Several publications are associated with the A Very Early Rehabilitation Trial for Stroke (AVERT) trial. The safety and feasibility of an early mobilization intervention was established by Bernhardt et al. [363] in Phase I. 71 patients were randomized to receive either very early and frequent mobilization (upright, out of bed, activity – 2x/day, for 6 days a week until discharge beginning within 24 hours of stroke), or usual multi-disciplinary stroke team care. There was a non-significant increase in the number of patient deaths in the early mobilization vs. delayed mobilization group at 3 months (21% vs. 9%, absolute risk difference = 12.0%, 95% CI, 4.3% to 28.2%,  $p=0.20$ ). After adjusting for age, baseline NIHSS score and premorbid mRS score, the odds of experiencing a good outcome were significantly higher at 12 months for the VEM group (OR= 8.15, 95% CI 1.61-41.2,  $p<0.01$ ), although not at 3 or 6 months. In AVERT II, examining medical complications associated with very early mobilization (VEM), Sorbello et al. [364] reported there were no differences in the total number of complications between groups. Severe complications or stroke-related complications occurred in 91 patients in the control group compared with 87 in the VEM group. Cumming et al. [365] reported that patients in the VEM group returned to walking significantly sooner than patients in the standard care group (median of 3.5 vs. 7.0 days,  $p=0.032$ ). While there were no differences between groups in proportions of patients who were independent in ADL, or who experienced a good outcome at either 3 or 12 months, VEM group assignment was a significant, independent predictor of independence in ADL at 3 months and of good outcome at both 3 and 12 months. Pooling the results from both the AVERT and VERITAS trials, which used similar protocols for early mobilization, Craig et al. [366] reported that, compared with patients receiving standard care, patients in the VEM group were more likely to be independent in activities of daily living at 3 months (OR= 4.41, 95% CI 1.36-14.32), and were less likely to experience immobility related complications (OR= 0.20, 95%CI 0.10-0.70). The most recent replication of AVERT examined the effectiveness of a protocol of more intensive, early out-of-bed activity.

Bernhardt et al. [367] randomized 2,104 adults (1:1) to receive early mobilization, a task-specific intervention focused on sitting, standing, and walking activity, initiated within 24 hours of stroke onset, or to usual care for 14 days (or until hospital discharge). The median time to first mobilization was significantly earlier in the early mobilization group (18.5 vs. 22.4 hrs,  $p<0.0001$ ). Patients in the early mobilization group received significantly more out of bed sessions (median of 6.5 vs. 3,  $p<0.0001$ ) and received more daily therapy (31 vs. 10 min,  $p<0.0001$ ). However, significantly fewer patients in the early mobilization group had a favourable outcome, the primary outcome, defined as mRS 0-2, at 3 months (46% vs. 50%; adjusted OR=0.73, 95% CI 0.59-0.90,  $p=0.004$ ). There were no significant differences between groups for any of the secondary outcomes (shift in distribution of mRS, time to achieve assisted- free walking over 50m, proportion of patients able to walk unassisted at 3 months, death or serious adverse events), nor were any interactions identified based on pre-specified sub groups for the primary outcome (age, stroke type, stroke severity, administration of t-PA, or geographical region of recruitment). Further analysis of AVERT data [368], controlling for age and stroke severity, suggested that shorter, more frequent mobilization early after acute stroke was associated with improved odds of favorable outcome at 3 months, while increased amount (minutes per day) of mobilization reduced the odds of a good outcome.

LL	<b>Australia 2017, Kap 5.8 [6]</b>
Empfehlung	For stroke patients, starting intensive out-of-bed activities within 24 hours of stroke onset is not recommended.
Stärke	Strong against
Begründung	The AVERT trial reported by Bernhardt et al [367] was a large (N = 2104), multicentre, single-blind randomised trial assessing the efficacy of early mobilisation following stroke. Patients in the intervention group began mobilisation within 24 hours, including sitting, standing and walking activity with at least three out-of-bed sessions compared to usual care. Results showed that patients mobilised early had significantly lower odds of a favourable outcome (modified Rankin Scale score of 0-2) at 3 months (OR 0.73, 95% CI 0.59 to 0.90). The proportion of deaths at 3 months was also non-significantly higher in the early mobilisation group (OR 1.34, 95% 0.93 to 1.93).
Empfehlung	All stroke patients should commence mobilisation (out-of-bed activity) within 48 hours of stroke onset unless otherwise contraindicated (e.g. receiving end-of-life care).
Stärke	strong
Begründung	Lynch et al [369] conducted a systematic review of early physical rehabilitation studies, including 5 randomised controlled trials and 38 cohort studies. Limited evidence was available regarding rehabilitation started within 3 days of stroke, as only a small randomised trial and two cohort studies directly compared the < 3 day period to later rehabilitation. The randomised trial showed significantly fewer serious complications following early rehabilitation, while the cohort studies reported reduced disability and better ADL function. These studies provide insufficient evidence to determine the benefits of early rehabilitation.
Empfehlung	For patients with mild and moderate stroke, frequent, short sessions of out-of-bed activity should be provided, but the optimal timing within the 48-hour post-stroke time period is unclear
Stärke	Weak
Begründung	The AVERT trial reported by Bernhardt et al [367] was a large (N = 2104), multicentre, single-blind randomised trial assessing the efficacy of early mobilisation following stroke. Patients in the intervention group began mobilisation within 24 hours, including sitting, standing and walking activity with at least three out-of-bed sessions compared to usual care. Results showed that patients mobilised early had significantly lower odds of a favourable outcome (modified Rankin Scale score of 0-2) at 3 months (OR 0.73, 95% CI 0.59 to 0.90). The proportion of deaths at 3 months was also non-significantly higher in the early mobilisation group (OR 1.34, 95% 0.93 to 1.93).
LL	<b>NICE 59 Kap 11.1 [24]</b>
Empfehlung	People with acute stroke should be mobilised as soon as possible (when their clinical condition permits) as part of an active management programme on a specialist stroke unit.
Stärke	1++
Empfehlung	People with acute stroke should be helped to sit up as soon as possible (when their clinical condition permits).
Stärke	3



Begründung	There are insufficient data to comment on the safety of very early mobilisation in patients with acute stroke, but there is no evidence that it is harmful. In one study in which no physiotherapy was compared with early mobilisation, patients who received no physiotherapy had worse outcomes but this gives no data on what form of early mobilisation is most effective. Early mobilisation has many potential advantages including reducing the risk of chest infection, preventing DVTs, early access to water and fluids (thus improving hydration) and access to nutrition. The consensus was that these potential advantages outweighed any disadvantages. This was also supported by the patient representatives who felt that early mobilisation was more likely to have a positive psychological effect on the patient and prolonged bed rest was likely to be detrimental to patients with acute stroke. One study examined the effect of nursing patients in specific positions on oxygen saturation. Sitting up resulted in improved oxygen saturations, again supporting the group consensus that early positioning including sitting is of benefit, helping to maintain oxygen saturation above 95% (see section 9.1) and reducing the likelihood of hypostatic pneumonia
------------	---

LL	<b>RCP 2016 [10]</b>
Empfehlung	In the first two weeks after stroke, therapy targeted at the recovery of mobility should consist of frequent, short interventions every day, typically beginning between 24 and 48 hours after stroke onset.
Empfehlung	Patients with difficulty moving after stroke should be assessed as soon as possible within the first 24 hours of onset by an appropriately trained healthcare professional to determine the most appropriate and safe methods of transfer and mobilisation
Empfehlung	Patients with difficulty moving early after stroke who are medically stable should be offered frequent, short daily mobilisations (sitting out of bed, standing or walking) by appropriately trained staff with access to appropriate equipment, typically beginning between 24 and 48 hours of stroke onset. Mobilisation within 24 hours of onset should only be for patients who require little or no assistance to mobilise.
Begründung	AVERT Group, 2015 [361]; Bernhardt et al, 2016 [368], Consensus

### 8.2.3. Synopse der externen Leitlinien zu Kapitel 2

SF 2.1.1: Führt bei Patienten mit Hirninfarkt und einem Zeitfenster von bis zu 4.5h seit Symptombeginn eine systemische Thrombolyse mit Alteplase im Vergleich zur Nicht-Anwendung zu einem besseren funktionellem Ergebnis?

LL	<b>NICE 2019 [24]</b>
Empfehlung	Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults if: <ul style="list-style-type: none"> <li>- treatment is started as soon as possible within 4.5 hours of onset of stroke symptoms and</li> <li>- intracranial haemorrhage has been excluded by appropriate imaging techniques</li> </ul>
Stärke	
Begründung	
Empfehlung	Alteplase should only be administered within a well-organised stroke service with: <ul style="list-style-type: none"> <li>- staff trained in delivering thrombolysis and in monitoring for any associated complications</li> <li>- care up to level 1 and level 2 nursing staff trained in acute stroke and thrombolysis*</li> </ul>

	- immediate access to imaging and re-imaging, and staff appropriately trained to interpret the images.
Empfehlung	Staff in A&E departments, if appropriately trained and supported, can administer alteplase* for the treatment of acute ischaemic stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support.
Empfehlung	Protocols should be in place for the delivery and management of thrombolysis, including post-thrombolysis complications
Begründung	It has been reviewed in detail in NICE Technology Appraisal (TA) 122,70 and thus the evidence has not been reviewed again here.

<b>LL</b>	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke, regardless of age or stroke severity, in whom treatment can be started within 3 hours of known onset should be considered for treatment with alteplase
Stärke	
Begründung	Wardlaw et al, 2012 [370]; Emberson et al, 2014 [371]
Empfehlung	Patients with acute ischaemic stroke under the age of 80 years in whom treatment can be started between 3 and 4.5 hours of known onset should be considered for treatment with alteplase.
Stärke	
Begründung	Wardlaw et al, 2012 [370]; Emberson et al, 2014 [371]
Empfehlung	Alteplase should only be administered within a well-organised stroke service with: <ul style="list-style-type: none"> <li>- processes throughout the emergency pathway to minimise delays to treatment, to ensure that thrombolysis is administered as soon as possible after stroke onset;</li> <li>- staff trained in the delivery of thrombolysis and monitoring for post-thrombolysis complications;</li> <li>- nurse staffing levels equivalent to those required in level 1 or level 2 nursing care with training in acute stroke and thrombolysis;</li> <li>- immediate access to imaging and re-imaging, and staff appropriately trained to interpret the images;</li> <li>- protocols in place for the management of post-thrombolysis complications.</li> </ul>
Stärke	
Begründung	Wardlaw et al, 2012 [370]

<b>Leitlinie</b>	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible.
Stärke	I-A
Begründung	Reworded from 2013
Empfehlung	In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging
Stärke	I B-NR
Begründung	NCCT was the only neuroimaging modality used in the NINDS rt-PA trial and in ECASS III and is therefore sufficient neuroimaging for decisions about IV alteplase in most patients [238, 239]. Multimodal CT and MRI, including diffusion and perfusion imaging, are not necessary when the diagnosis of ischemic stroke is very likely, and their performance may delay time-sensitive administration of IV alteplase. In some cases, particularly when there is substantial diagnostic uncertainty, advanced imaging may be beneficial

Empfehlung	In patients undergoing fibrinolytic therapy, physicians should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction.
Stärke	I, B-NR
Begründung	Reworded from 2013
Empfehlung	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.
Stärke	I, A
Begründung	<p>The safety and efficacy of this treatment when administered within the first 3 hours after stroke onset are solidly supported by combined data from multiple RCTs [370, 372, 373] and confirmed by extensive community experience in many countries [374]. The eligibility criteria for IV alteplase have evolved over time as its usefulness and true risks have become clearer. A recent AHA statement provides a detailed discussion of this topic. Eligibility recommendations for IV alteplase in patients with AIS are summarized in Table 8. The benefit of IV alteplase is well established for adult patients with disabling stroke symptoms regardless of age and stroke severity [375, 376].</p> <p>Because of this proven benefit and the need to expedite treatment, when a patient cannot provide consent (eg, aphasia, confusion) and a legally authorized representative is not immediately available to provide proxy consent, it is justified to proceed with IV alteplase in an otherwise eligible adult patient with a disabling AIS. In a recent trial, a lower dose of IV alteplase (0.6 mg/kg) was not shown to be noninferior to standard-dose IV alteplase for the reduction of death and disability at 90 days [377]</p>
Empfehlung	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility
Stärke	I, B-R
Begründung	One trial (ECASS III) specifically evaluating the efficacy of IV alteplase within 3 and 4.5 hours after symptom onset [239] and pooled analysis of multiple trials testing IV alteplase within various time windows [370, 372, 373] support the efficacy of IV alteplase up to 4.5 hours after symptom onset. ECASS III excluded octogenarians, patients taking warfarin regardless of international normalized ratio, patients with combined history of diabetes mellitus and previous ischemic stroke, and patients with very severe strokes (NIHSS score >25) because of a perceived excessive risk of intracranial hemorrhage in those cases. However, careful analysis of available published data summarized in an AHA/American Stroke Association (ASA) scientific statement indicates that these exclusion criteria from the trial may not be justified in practice.
Empfehlung	Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.
Stärke	Ila, B-NR
Begründung	Idem zu 2015: Notably, because unsuspected thrombocytopenia is rare, [378] clinicians should not await the platelet count results before administering intravenous alteplase to patients with acute stroke unless there is a suspected bleeding abnormality, thrombocytopenia, or coagulopathy. Whether a platelet count

	of 100 000 mm <sup>3</sup> is a justified threshold for withholding intravenous thrombolysis remains unclear.
Empfehlung	IV aspirin should not be administered within 90 minutes after the start of IV alteplase.
Stärke	III: Harm, B-R
Begründung	The ARTIS trial (Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke) compared the effects of very early addition (within 90 minutes) of 300 mg IV aspirin to alteplase with standard treatment with alteplase without IV aspirin [348]. The trial was terminated after 642 of the 800 targeted patients had been enrolled because IV aspirin was associated with an increased risk of symptomatic intracranial hemorrhage (4.3% versus 1.6% in the standard treatment group; RR, 2.78 [95% CI, 1.01–7.63]; P=0.04) and no difference in the rate of favorable functional outcome (mRS score 0–2) at 3 months (54.0% of patients in the aspirin group versus 57.2% of patients in the standard treatment group; RR, 0.94 [95% CI, 0.82–1.09]; P=0.42).
Empfehlung	The risk of antithrombotic therapy (other than IV aspirin) within the first 24 hours after treatment with IV alteplase (with or without mechanical thrombectomy) is uncertain. Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.
Stärke	IIB, B-NR
Begründung	A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or EVT compared with initiation >24 hours. However, this study may have been subject to selection bias, and the timing of the initiation of antiplatelet therapy or anticoagulation should be based on an individual level, balancing risk and benefit [379]
LL	<b>Australia 2017 [6]</b>
Empfehlung	For patients with potentially disabling ischaemic stroke who meet specific eligibility criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered. (Wardlaw et al. 2014 [372]; Emberson et al. 2014 [371])
Stärke	Strong, high LoE
Empfehlung	Thrombolysis should commence as early as possible (within the first few hours) after stroke onset but may be used up to 4.5 hours after onset. (Wardlaw et al. 2014 [372]; Anderson et al. 2016 [377])
Stärke	Strong, high LoE
Begründung	High-quality evidence suggests that the benefits of intravenous alteplase outweigh its harms if given within 4.5 hours in patients satisfying specific criteria (Wardlaw et al. 2014 [372]; Emberson et al. 2014[371]). However, benefits have not been established beyond 4.5 hours. Lower dose alteplase (0.6 mg/kg) did not meet non-inferiority criteria and therefore standard (0.9 mg/kg) dose is recommended (Wardlaw et al. 2014 [37]; Anderson et al. 2016 [40]).  0-3h: An individual patient data meta-analysis conducted by Emberson et al. (2014) [371] included subgroup analyses for patients treated ≤ 3 hours after stroke, > 3 and ≤ 4.5 hours, and > 4.5 hours. It showed that treatment within 3 hours was associated with the greatest improvement in excellent outcomes (mRS of 0 or 1) at 90 days (114 per 1000). Alteplase was associated with increased risk of intracranial haemorrhage within 7 days, which led to death in approximately 2% of patients. Subsequent higher rates of death in the control group meant there was no difference in mortality at 3 months. By 3–6 months the average absolute increase in disability-free survival was

	<p>10% for patients treated within 3.0 h, which includes the impact of symptomatic haemorrhage.</p> <p>A Cochrane review by Wardlaw et al. (2014)[372] included 27 RCTs of thrombolytic agents for the treatment of ischaemic stroke. In most trials, treatment began up to 6 hours after stroke. Death or dependency by the end of follow-up was significantly reduced in the 10 trials using intravenous alteplase (OR 0.84, 95% CI 0.77 to 0.93), although there was significant heterogeneity. A stronger effect was seen when analysing intravenous alteplase given with 3 hours of stroke (OR 0.65, 95% CI 0.54 to 0.80) with no significant heterogeneity.</p> <p>3-4,5h: An individual patient data meta-analysis conducted by Emberson et al. (2014) [371] included subgroup analyses for patients treated ≤ 3 hours after stroke, &gt; 3 and ≤ 4.5 hours, and &gt; 4.5 hours. It showed that treatment with 4.5 hours was associated with the improvement on good stroke outcomes (mRS of 0 or 1) at 90 days (51 per 1000). Alteplase was associated with increased risk of intracranial haemorrhage within 7 days (23 per 1000). Overall, by 3–6 months the average absolute increase in disability free survival was 5% for patients treated between 3.0 and 4.5 hours which includes the effect of intracerebral haemorrhage.</p>
Empfehlung	<p>Thrombolysis should be undertaken in a setting with appropriate infrastructure, facilities and network support (e.g. via telemedicine) including:</p> <ul style="list-style-type: none"> <li>• access to an interdisciplinary acute care team with expert knowledge of stroke management, who are trained in delivery of thrombolysis and monitoring of patients receiving thrombolytic therapy</li> <li>• a streamlined acute stroke assessment workflow (including ambulance pre-notification, code stroke team response and direct transport from triage to CT scan) to minimise treatment delays, and protocols available to guide medical, nursing and allied health acute phase management</li> <li>• immediate access to imaging facilities and staff trained to interpret images</li> <li>• routine data collected in a central register to allow monitoring, benchmarking and improvements of patient outcomes over time for those treated with reperfusion. The patient and caregivers should be involved in the decision to give thrombolysis whenever possible and this discussion of risk and benefit documented in the medical record. However, as a time-critical emergency therapy, thrombolysis should not be delayed if the patient does not have the capacity to consent and there are no legal representatives present. Clinicians should follow local health department policies regarding consent for emergency treatment in patients who are unable to consent for themselves.</li> </ul>
Stärke	Practice Point
LL	<b>Canada 2018 [8]</b>
Empfehlung	All eligible patients with disabling ischemic stroke should be offered intravenous alteplase. Eligible patients are those who can receive intravenous alteplase within 4.5 hours of the onset of stroke symptoms
Stärke	[Evidence Level A]
Empfehlung	<p>All eligible patients should receive intravenous alteplase as soon as possible after hospital arrival [Evidence Level A], with a target door-to-needle time of less than 60 minutes in 90% of treated patients, and a median door-to-needle time of 30 minutes [Evidence Level B].</p> <p>a. Treatment should be initiated as soon as possible after patient arrival and CT scan [Evidence Level B]; every effort should be made to ensure door-to-needle times are routinely monitored and improved [Evidence Level C].</p>

	b. Alteplase should be administered using a dose of 0.9 mg/kg to a maximum of 90 mg total dose, with 10 percent (0.09 mg/kg) given as an intravenous bolus over one minute and the remaining 90 percent (0.81 mg/kg) given as an intravenous infusion over 60 minutes [Evidence Level A].
Stärke	See above
Empfehlung	Hospital inpatients who present with a sudden onset of new stroke symptoms should be rapidly evaluated by a specialist team and provided with access to appropriate acute stroke treatments (including thrombolysis and endovascular thrombectomy)
Stärke	[Evidence Level B].
Empfehlung	Management of complications from alteplase administration: a. For patients with angio-edema, a staged response using antihistamines, glucocorticoids and standard airway management should be used as per local protocol b. There is insufficient evidence to support the routine use of cryoprecipitate, fresh frozen plasma, prothrombin complex concentrates, tranexamic acid, factor VIIa, or platelet transfusions for alteplase - associated bleeding Use of these medications should be decided on an individual case basis.
Stärke	[Evidence Level C].
Begründung	<p>Meta-analyses of the randomized controlled trials of intravenous alteplase for acute ischemic stroke have shown that thrombolytic treatment can reduce the risk of disability and death, despite the risk of serious bleeding. The latest time for alteplase administration after stroke onset remains imprecisely defined, but currently available data show clear evidence of benefit when given up to 4.5 hours after the onset of symptoms. The available evidence demonstrates a strong inverse relationship between treatment delay and clinical outcome; eligible patients should be treated without delay, regardless of when they present within the treatment window.</p> <p>The weight of evidence from many large, international trials over a time frame of 20 years, clearly indicate that treatment with intravenous alteplase reduces the risk of death or disability following ischemic stroke, at 3 to 6 months post treatment. The NINDS trial [238] was one of the earliest, large trials, which was conducted in the USA. Patients were randomized to receive alteplase or placebo within 3 hours of symptom onset. At 3 months, significantly more patients in the rt-PA group had experienced a good outcome (using any one of the study's 4 metrics), with no difference in 90-day mortality between groups. In contrast, patients who received alteplase within 3 to 5 hours in the ATLANTIS trial [256] were no more likely to have a good neurological or functional outcome at 90 days than patients in the placebo group. In the first ECASS trial [380] 620 patients received alteplase or placebo within 6 hours of event. Using intention-to-treat analysis and including the data from 109 patients with major protocol violations, the authors did not report a significant benefit of treatment. The median Barthel Index and modified Rankin scores at 90 days did not differ between groups. In an analysis restricted to patients in the target population, there were differences favouring patients in the alteplase group. In the ECASS II trial [381], there was again no significant difference on any of the primary outcomes. The percentages of patients with a good outcome at day 90 (mRS&lt;2) treated with alteplase and placebo were 40.3% vs. 36.6%, respectively, absolute difference =3.7%, p=0.277. In subgroup analysis of patients treated &lt; 3 hours and 3-6 hours, there were no between-group differences on any of the outcomes. The authors suggested that the reason for the null result may have been that the study was underpowered, since it was powered to detect a 10% difference in the primary outcome, but the observed difference between groups in previous trials was only 8.3%. Finally, in the ECASS III trial [239] 821 patients were randomized within 3 and 4.5 hours of symptom onset.</p>

In this trial, a higher percentage of patients in the alteplase group experienced a favourable outcome, defined as mRS scores <2 (52.4% vs. 45.2%, adjusted OR=1.34, 95% CI 1.02 to 1.76, p=0.04). A higher percentage of patients in the alteplase group also had NIHSS scores of 0 or 1, (50.2% vs. 43.2%, adjusted OR=1.33, 95% CI 1.01 to 1.75, p=0.04). Secondary outcomes of the ECASS III trial were reported by Bluhmki et al. [382]. At 90 days, there were no between-group differences in the percentages of patients with mRS score of 0-2 (59% vs. 53%, p=0.097) or BI score  $\geq$ 85 (60% vs. 56%, p=0.249, but a significantly greater percentage of patients had improved NIHSS scores of  $\geq$ 8 points (58% vs. 51%, p=0.031). In all of the trials described above there was an increased risk of symptomatic ICH associated with treatment with alteplase and in some cases, increased short-term mortality; however, there were no differences between treatment and placebo groups in 90-day mortality.

The Third International Stroke Trial [109], is the largest (n=3,035) and most recent trial of alteplase, in which patients were randomized to receive a standard dose of alteplase (0.9 mg/kg) or placebo. Investigators aimed to assess the risks and benefits of treatment among a broader group of patients, and to determine if particular subgroups of patients might benefit preferentially from treatment. In this trial, 95% of patients did not meet the strict licensing criteria, due to advance age or time to treatment. Unlike all previous, large trials, which excluded them, IST-3 included patients >80 years. In fact, the majority of patients (53%) were >80 years. Approximately one-third of all patients were treated within 0-3 hours, 3.0- 4.5 hours and 4.5-6.0 hours of onset of symptoms. Overall, there was an increase in the risk of death within 7 days in patients who had received alteplase, although there was no difference in 6-month mortality in both crude and adjusted analyses. There was no significant difference in the percentage of patients who were treated with alteplase who were alive and independent (defined as an Oxford Handicap Score of 0-1) at 6 months (37% vs. 35%, adjusted OR=1.13, 95% CI 0.95 to 1.35, p=0.181, although a secondary ordinal analysis suggested a significant, favourable shift in the distribution of OHS scores at 6 months. Significantly improved odds of a good outcome at 6 months were associated with the sub groups of older patients ( $\geq$ 80 years), higher NIHSS scores, higher baseline probability of good outcome and treatment within 3 hours. Fatal or non-fatal symptomatic intracranial hemorrhage within 7 days occurred more frequently in patients in the t-PA group (7% vs. 1%, adjusted OR=6.94, 95% CI 4.07 to 11.8, p<0.0001). The 3-year risk of mortality (2016) was similar between groups (47% vs. 47%, 95% CI 3.6%, 95% CI -0.8 to 8.1); however, patients who received rt-PA had a significantly lower risk of death between 8 days and 3 years (41% vs. 47%; HR= 0.78, 95% CI 0.68-0.90, p=0.007). Although it is known that the optimal timing of administration of intravenous alteplase is <3 hours, debate continues as to the safety and efficacy of treatment provided between 3 and 6 hours post stroke.

The results from a few studies suggest that treatment is still beneficial if provided beyond the 3-hour window. The Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) includes patients who were treated with intravenous alteplase under strict licensing criteria and also those who were thought to be good candidates based on clinical/imaging assessment of the treating facility. Wahlgren et al. [282] used data from a cohort of patients collected from 2002-2007 to compare the outcomes of patients who had been treated with alteplase within 3 hour of symptom onset (n=11,865) and those treated from 3-4.5 hours (n=644). The primary focus of this analysis was to assess treatment safety beyond the 3-hour treatment window. Patients in the <3-hour group had significantly lower initial median NIHSS scores (11 vs. 12, p<0.0001). There were no significant between group differences on any of the outcomes (symptomatic ICH within 24-36 hours, mortality within 3 months, or percentage of patients who were independent

	<p>at 3 months); however, there was a trend towards increased number of patients treated from 3 to 4.5 hours who died (12.7% vs. 12.2%, adjusted OR=1.15, 95% CI 1.00-1.33, p=0.053) and who experienced symptomatic ICH (2.2% vs. 1.6%, adjusted OR=1.32, 95% CI 1.00-1.75, p=0.052). Additional analysis from the SITS-ISTR cohort was conducted to further explore the timing of alteplase treatment (Ahmed et al. 2010). In this study, patients treated within 3 hours (n=21,566) and 3-4.5 hours (n=2,376) of symptom onset between 2007 and 2010, were again compared. Significantly more patients treated from 3-4.5 hours experienced a symptomatic ICH (2.2% vs.1.7%, adjusted OR=1.44, 95% CI 1.05-1.97, p=0.02), and were dead at 3 months (12.0% vs. 12.3%, adjusted OR=1.26, 95% CI 1.07-1.49, p=0.005). Significantly fewer patients treated from 3-4.5 hours were independent at 3 months: (57.5% vs. 60.3%, adjusted OR=0.84, 95% CI 0.75-0.95, p=0.005).</p> <p>Emberson et al. [371] used data from 6,756 patients from 9 major t-PA trials (NINDs a/b, ECASS I/II, III, ATLANTIS a/b, EPITHET, IST-3) to more closely examine the effect of timing of administration. Earlier treatment was associated with the increased odds of a good outcome, defined as an (mRS score of 0-1 (<math>\leq 3.0</math> h: OR=1.75, 95% CI 1.35-2.27 vs. <math>&gt;3</math> to <math>\leq 4.5</math> h: OR=1.26, 95% CI 1.05-1.051 vs. <math>&gt;4.5</math> h: OR=1.15, 95% CI 0.95-1.40). Framed slightly differently, when patient-level data from the same 9 major RCTs were recently pooled, Lees et al. [375] reported that for each patient treated within 3 hours, significantly more would have a better outcome (122/1,000, 95% CI 16-171), whereas for each patient treated <math>&gt;4.5</math> hours, only 20 patients/1,000 (95% CI -31-75, p=0.45) would have a better outcome. Wardlaw et al. (2013), including the results from 12 RCTs (7,012 patients), concluded that for every 1,000 patients treated up to 6 hours following stroke, 42 more patients were alive and independent (mRS<math>&lt;2</math>) at the end of follow-up, despite an increase in early ICH and mortality. The authors also suggested that patients who did not meet strict licensing criteria due to age and timing of treatment (i.e., patients from the IST-3) trial were just as likely to benefit; however, early treatment, within 3 hours of stroke onset, was more effective.</p>
--	--

**SF 2.1.2: Führt bei Patienten über 80 Jahre mit Hirninfarkt, die für eine Thrombolyse in Frage kommen, eine systemische Thrombolyse mit Alteplase im Vergleich zur Thrombolyse bei Patienten  $<80$  Jahren zu einem vergleichbaren klinischen Nutzen der Therapie?**

<b>LL</b>	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke over 80 years in whom treatment can be started between 3 and 4.5 hours of known onset should be considered for treatment with alteplase on an individual basis. In doing so, treating clinicians should recognise that the benefits of treatment are smaller than if treated earlier, but that the risks of a worse outcome, including death, will on average not be increased.
Stärke	
Begründung	Wardlaw et al, 2012 [370]; Emberson et al 2014 [371]
<b>Leitlinie</b>	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	For otherwise medically eligible patients $\geq 18$ y of age, IV alteplase administration within 3 h is equally recommended for patients $\leq 80$ and $>80$ y of age
Stärke	I, A
Begründung	Wie 2015: The benefits of alteplase in stroke patients $\geq 80$ years of age were assessed in 3 randomized trials and 12 observational studies. The most relevant comparison to determine the benefit of intravenous alteplase in older patients is from RCTs because they provide information on clinical outcomes between patients taking alteplase and control subjects in each age strata. In contrast, most observational studies, aimed at monitoring the safety of thrombolytic therapy in the real world, provided only



	<p>comparative information on stroke outcome between patients &gt;80 and those &lt;80 years of age receiving intravenous alteplase (usually lacking non-alteplase-treated patients).</p> <p>Only 3 multicenter, randomized stroke trials included patients <math>\geq 80</math> years [238, 376, 383] recent meta-analysis including 6 randomized trials within a 3-hour time window suggests a benefit in favor of intravenous alteplase for both younger (OR, 1.51; 95% CI, 1.18–1.93) and older (OR, 1.68; 95% CI, 1.20–2.34) patients [370]. Among patients treated within 3 hours, for every 1000 patients 80 years of age, there would be 96 more patients alive and independent at the end of follow-up (28.9% of patients taking tissue-type plasminogen activator versus 19.3% of control subjects; <math>P &lt; 0.003</math>). Similar findings were observed for those &lt;80 years of age (49.6% of patients taking alteplase versus 40.1% of control subjects; <math>P &lt; 0.001</math>), which translates to 95 more patients alive and independent per 1000 people <math>\leq 80</math> years of age treated within 3 hours [370]. Data from observational studies revealed similar results. The largest observational study evaluating the benefits of alteplase by age was the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry (SITS-ISTR) [384].</p>
Empfehlung	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients $\leq 80$ y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score $\leq 25$ , not taking any OACs, and without imaging evidence of ischemic injury involving more than one-third of the MCA territory.
Stärke	I, B-R
Empfehlung	For patients >80 y of age presenting in the 3- to 4.5-h window, IV alteplase is safe and can be as effective as in younger patients.
Stärke	IIa, B-NR
Begründung	<p>Wie 2015: In the pooled analysis of EPITHET and IST-3, 970 subjects &gt;80 years of age were randomized to alteplase versus placebo in the 3- to 6-hour window. Compared with those <math>\leq 80</math> years of age, the likelihood for favorable outcome at 3 months in those treated with alteplase versus those treated with placebo was not different by age; however, the OR for good outcome compared with placebo was not significant (OR, 0.97; 95% CI, 0.73–1.30) and far less than the benefit in patients treated in the 0- to 3-hour window [370]. Data were not presented comparing outcomes by age strata in the 3- to 4.5-hour window alone.</p> <p>Only 2 other studies have evaluated age &gt;80 years specifically in the 3- to 4.5-hour window. In the GWTG-Stroke database, among 1008 patients &gt;80 years of age treated with intravenous alteplase in the extended window, sICH was observed in 8% (versus 6.7% among patients &gt;80 years of age in the &lt;3-hour window; <math>P = 0.11</math>), 19.5% were ambulatory at hospital discharge (versus 17.7% in the &lt;3-hour group; <math>P = 0.08</math>), and 21.2% were discharged home (versus 20.3% in the &lt;3-hour group; <math>P = 0.41</math>) [385]. In a smaller study that compared outcomes after intravenous alteplase in the extended window by age strata of 31 patients &gt;80 years of age, there were 2 patients with sICH (6.5%) compared with 7 of 160 patients (4.4%) &lt;80 years of age (<math>P = 0.64</math>). Not surprisingly, however, in-hospital mortality was higher among those &gt;80 years of age (16.1% versus 3.8%; <math>P = 0.02</math>) [386]. In a study that examined the impact of removing specific exclusions for intravenous alteplase in stroke, if the upper age limit were removed for treatment in the 3- to 4.5-hour window, the percentage of eligible patients would increase from 26% to 29% [387].</p>

SF 2.1.3: Führt bei Patienten mit Hirninfarkt und einem Zeitfenster von 4,5-9 Std. seit Symptombeginn oder unklarem Zeitfenster (z.B. Symptome beim Erwachen) eine Thrombolyse basierend auf

erweiterter Bildgebung und einem CT/MRT-basiert dargestellten Mismatch von Infarktkern und Penumbra im Vergleich zur Nicht-Anwendung zu einem besseren funktionellem Ergebnis?

LL	<b>Australia 2017 [6]</b>
Empfehlung	
Stärke	
Begründung	An individual patient data meta-analysis conducted by Emberson et al. (2014) [371] included subgroup analyses for patients treated $\leq 3$ hours after stroke, $> 3$ and $\leq 4.5$ hours, and $4.5 - 6$ hours. It showed that treatment between $4.5-6$ hours was associated with a small improvement on good stroke outcomes (mRS of 0 or 1) at 90 days (30 per 1000), but also increased risk of fatal intracranial haemorrhage within 7 days (21 per 1000). In this case, it is unclear that the benefits outweigh the potential harms.
Kommentar	Passt aber eigentlich nicht zu der Schlüsselfrage, da es eher um Mismatch-basierte Lyse im erweiterten Zeitfenster geht.

SF 2.1.4: Führt bei Patienten mit Hirninfarkt mit Symptomen beim Erwachen oder einem unbekanntem Zeitfenster und einer Vorstellung innerhalb von 4,5 Std. nach Erkennen der Symptome eine Thrombolyse mit Alteplase basierend auf einem DWI-FLAIR-Mismatch im Vergleich zur Nicht-Anwendung zu einem besseren funktionellen Ergebnis?

Leitlinie	<b>AHA 2019 [11]</b>
Empfehlung	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset $>4.5$ hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR.
Stärke	Ila, B-R
Begründung	The WAKE-UP RCT randomized 503 patients with AIS who awoke with stroke or had unclear time of onset and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the MCA, NIHSS score $>25$ , contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well to symptom recognition was $\approx 7$ hours and to alteplase administration slightly over 10 hours. The primary end point of an mRS score 0 to 1 at 90 days was achieved in 53.3% of the alteplase group and in 41.8% of the placebo group ( $P=0.02$ ). Only 20% had LVO of the intracranial internal carotid or proximal middle cerebral arteries [388].

LL	<b>Canada 2018 [8]</b>
Empfehlung	Keine Empfehlung, aber Text
Stärke	
Begründung	Most recently, the results from the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-Up) trial [388] suggest that highly-selected patients with mild to moderate ischemic strokes and an unknown time of symptom onset, treated with alteplase may also benefit from treatment. Patients in this trial were not eligible for treatment with mechanical thrombectomy and were selected based on a pattern of "DWIFLAIR- mismatch. A significantly higher proportion of patients in the alteplase group had a favourable clinical outcome (mRS 0-1) at 90 days (53.3% vs. 41.8%, adj OR=1.61, 95% CI 1.06-2.36, $p=0.02$ ), although the risk of parenchymal hemorrhage

	type 2 was significantly higher compared with placebo (4% vs. 0.4%, adj OR=10.46, 95% CI 1.32 to 82.77, p=0.03).
--	--

SF 2.1.5: Führt Bei Patienten mit Hirninfarkt und einem Symptombeginn < 4,5 Std. eine Thrombolyse mit Tenecteplase im Vergleich zur Thrombolyse mit Alteplase zu einem besseren funktionellen Ergebnis?

Dieser Abschnitt wurde im Rahmen des Amendments „Oktober 2022“ um die Angaben aus der ESO-Leitlinie zur IV-Thrombolyse ergänzt.

LL	<b>NEU: ESO IVT (2021) [17], PICO 5.1 und PICO 5.2</b>
Empfehlung	For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. Please see paragraph 5.2 for patients eligible for mechanical thrombectomy.
Begründung	A meta-analysis of 5 randomized trials (TNK-S2B, Tenecteplase versus Alteplase for Acute Ischemic Stroke [TAAIS], ATTEST, NOR-TEST, Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke [EXTEND-IA TNK]) suggested that there is enough evidence to conclude that tenecteplase is non-inferior to alteplase for acute ischemic stroke (risk difference for mRS 0–1: 4%, 95% CI: –1% to 8%). However, this result was mostly driven by the inclusion of EXTEND-IA TNK and TAAIS in the meta-analysis, which enrolled only patients with large vessel occlusion as opposed to the other trials.
Empfehlung	For patients with acute ischaemic stroke of <4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg.
Begründung	We have conducted a study-level meta-analysis of EXTEND-IA TNK and the subgroup of patients with complete vessel occlusion in the pooled analysis by Bivard et al..The pooled OR for excellent outcome and better functional outcome were 2.42 (95% CI: 0.73–8.04) and 2.09 (1.16–3.76), respectively.

LL	<b>ESO EST [23]</b>
Empfehlung	Keine Empfehlung, aber Text
Begründung	The superiority of tenecteplase over alteplase in patients eligible for MT has only been shown in a single phase II RCT (EXTEND-IA TNK [389]), in which functional outcome was a pre-specified secondary outcome. The superiority of tenecteplase was shown for better functional outcome (ordinal analysis over the whole range of the mRS), but failed to reach statistical significance for functional independence (mRS ≤2) and excellent outcome (mRS ≤1). The non-inferiority of tenecteplase over alteplase has not been established in other situations [390-394]

Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy
Stärke	IIb, B-R
Begründung	IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) [389]. This multicenter trial randomized 202 patients without previous severe

	disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (P=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; P=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (P=0.23) or 0 to 2 (P=0.06). sICH rates were 1% in both groups.
Empfehlung	Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.
Stärke	IIB, B-R
Begründung	IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase [390-392, 394]. In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion [390]. Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.
Empfehlung	The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.
Stärke	III: No Benefit, B-R
Begründung	Randomized placebo-controlled trials have not shown benefit from the administration of IV streptokinase within 6 hours or desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra, large intracranial artery occlusion, or severe stenosis [372, 395-397]
LL	<b>Canada 2018 [8]</b>
Empfehlung	Keine Empfehlung aber Text
Stärke	
Begründung	Although not yet approved in Canada for the use in stroke, results from several recent studies, indicate that tenecteplase, which has some pharmacokinetic advantages over alteplase, may be non-inferior to alteplase. In the NOR-TEST Logallo et al. [390] recruited 1,100 patients from 13 stroke units. Patients were randomized to receive intravenous tenecteplase 0.4 mg/kg (maximum of 40 mg) or alteplase 0.9 mg/kg (maximum of 90 mg). At 90 days, a similar proportion of patients had an excellent outcome (mRS 0-1, 64% vs. 63%). Similar percentages of patients in each group experienced an ICH within 24-48 hours (9%) and had died by 90 days (5%). Results from the phase II ATTEST Trial, [392] also suggest that tenecteplase is non-inferior to alteplase. In this trial, 104 patients were randomized to receive tenecteplase (0.25 mg/kg, 25 mg max) or alteplase (0.9 mg/kg, 90 mg max) within 4.5 hours of ischemic stroke. Safety and efficacy outcomes were non-significantly different between groups.

SF 2.1.6: Führt bei Patienten mit Hirninfarkt im 4,5 Std. Zeitfenster eine Thrombolyse mit einer reduzierten Dosis von 0,6 mg/kg Körpergewicht im Vergleich zur Standarddosis von 0.9mg/kg Körpergewicht nicht zu einem schlechteren funktionellen Ergebnis?

LL	<b>Australia 2017 [6]</b>
Empfehlung	Lower dose alteplase (0.6 mg/kg) did not meet non-inferiority criteria and therefore standard (0.9 mg/kg) dose is recommended (Wardlaw et al. 2014 [37]; Anderson et al. 2016 [40]).
Begründung	Anderson et al. (2016) [377] compared low-dose (0.6 mg per kilogram body weight) intravenous alteplase to standard dose (0.9 mg per kilogram) in an open-label randomised trial (N = 3310). While previous evidence on intravenous alteplase has suggested that doses of 0.9 mg per kilogram body weight provide benefits in the form of increased survival without disability, the treatment has also been associated with increased intracerebral haemorrhage, particularly in the short term. This risk of intracerebral haemorrhage may be higher in Asian populations. In this trial, low-dose alteplase did not meet non-inferiority criteria compared to standard dose treatment when comparing the primary outcome of modified Rankin scale scores 2–6 (OR 1.09, 95% CI 0.95 to 1.25), where the boundary for non-inferiority was prespecified at 1.14. However, there were significantly fewer symptomatic intracerebral haemorrhages in patients treated with low-dose alteplase (1% for the low-dose group vs 2.1% for the standard dose). The trial included predominantly Asian patients which could limit generalisability, but in subgroup analyses, no significant differences were seen between Asian and non-Asian patients. Median stroke severity (NIHSS 8) was milder than in the major preceding thrombolysis trials. Previous comparisons of dosages, included in a 2013 Cochrane review by Wardlaw et al. [372], provided limited evidence on overall mortality or death and dependency. Only a few small trials reporting these outcomes were included in the review, with results from 5 studies (N = 496) showing a lower number of total deaths in patients given higher-dose alteplase (OR 0.74, 95% 0.37 to 1.52) but no significant differences. Four included trials also showed significantly increased fatal intracranial haemorrhage but the total number of events was low, with 3 out of 4 included trials observing no fatal ICH

LL	<b>Canada 2018 [8]</b>
Empfehlung	Keine Empfehlung, aber Text
Begründung	The standard treatment dose of rt-PA is established to be 0.9 mg/kg, with a maximum dose of 90 mg. The non-inferiority of a lower dose (0.6 mg/kg) was recently examined in the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial [377]. The primary outcome (death or disability at 90 days) occurred in 53.2% of low-dose patients and 51.1% in standard dose patients (OR=1.09, 95% CI 0.95-1.25, p for non-inferiority=0.51), which exceeded the upper boundary set for non-inferiority of 1.14. The risks of death within 90 days or serious adverse events did not differ significantly between groups (low dose vs. standard dose: 8.5% vs. 10.3%; OR=0.80, 95% CI 0.63-1.01, p=0.07 and 25.1% vs. 27.3%; OR=0.89, 95% CI 0.76-1.04, p=0.16, respectively), although the risk of symptomatic ICH was significantly higher in patients that received the standard dose of rt-PA.

SF 2.1.7: Führt bei Patienten mit Hirninfarkt im 4,5 Std. Zeitfenster, die mit Alteplase behandelt werden, eine zusätzliche Behandlung mit Ultraschall (Sonothrombolyse) im Vergleich zur alleinigen systemischen Thrombolyse zu einem besseren funktionellen Ergebnis?

Leitlinie	<b>AHA 2019 [11]</b>
-----------	----------------------

Empfehlung	The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended.
Stärke	III: No benefit; A
Begründung	Since the publication of the 2013 AIS Guidelines, 2 RCTs of sonothrombolysis as adjuvant therapy for IV thrombolysis have shown no clinical benefit. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis (93 patients) or sham (90 patients). Neurological improvement at 24 hours and functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of sICH [398]. CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke) randomized 676 patients with AIS (NIHSS score $\geq 10$ ) who received IV alteplase within 3 or 4.5 hours of symptom onset and randomly allocated to operator independent sonothrombolysis or sham ultrasound [399]. Compared with the control arm, the neurological improvement, death, and serious adverse events in the intervention arm were not statistically different. At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV fibrinolysis.

SF 2.1.8: Führt bei Patienten mit Hirninfarkt im 4,5 Std. Zeitfenster mit leichtem, aber behindernden Defizit oder sich rasch verbessernden Symptomen eine systemische Thrombolyse im Vergleich zur Nicht-Anwendung zu einem besseren funktionellen Ergebnis?

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke, regardless of age or stroke severity, in whom treatment can be started within 3 hours of known onset should be considered for treatment with alteplase.
Begründung	Wardlaw et al, 2012 [370]; Emberson et al, 2014 [371]

Leitlinie	<b>AHA 2019 [11]</b>
Empfehlung	For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.
Stärke	I, B-R
Empfehlung	For otherwise eligible patients with mild disabling stroke symptoms, IV alteplase may be reasonable for patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.
Stärke	IIb, N-R
Empfehlung	For otherwise eligible patients with mild <u>non</u> disabling stroke symptoms (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state
Stärke	III: NO benefit, B-R
Empfehlung	For otherwise eligible patients with mild non-disabling stroke symptoms (NIHSS 0–5), IV alteplase is not recommended for patients who could be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.
Stärke	III: NO benefit; C-LD
Begründung (für alle)	Subgroup analyses of the NINDS rt-PA Trial and IST (International Stroke Trial)-3 with mild stroke defined in various ways have inconsistently shown a benefit for IV alteplase [400-402]. A meta-analysis of 9 trials of IV alteplase in AIS including subjects



	<p>from the NINDS rt-PA trial and IST-3 showed benefit for patients with mild stroke defined as NIHSS score 0 to 4 [371]. In ECASS III, there was no significant interaction of benefit (mRS score 0–1 at 90 days) or safety (sICH or death) with stroke severity when patients were categorized by baseline NIHSS score of 0 to 9, 10 to 19, and &gt;20 [382].</p> <p>In SITS-ISTR (Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry), good functional outcomes (mRS score 0–1 at 90 days) and risk of sICH were similar or the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours [403]. Similarly, in the AHA GWTG registry, good functional outcomes, mortality, and risk of sICH were the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours [404]. These patients were not further categorized by whether their acute neurological deficits were disabling. The PRISMS RCT (A Study of the Safety and Efficacy of Activase [Alteplase] in Patients With Mild Stroke) evaluated IV alteplase in patients with mild (NIHSS score 0–5) AIS whose acute neurological deficits were judged to not interfere with activities of daily living or prevent return to work. There was no benefit of treatment within 3 hours of onset [405].</p>
--	--

SF 2.1.9: Führt bei Patienten mit Hirninfarkt und sehr schweren Symptomen eine systemische Thrombolyse mit Alteplase im Vergleich zur Nicht-Anwendung zu einem besseren funktionellen Ergebnis?

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke, regardless of age or stroke severity, in whom treatment can be started within 3 hours of known onset should be considered for treatment with alteplase.
Begründung	Wardlaw et al, 2012 [370]; Emberson et al, 2014 [371]

Leitlinie	<b>AHA 2019 [11]</b>
Empfehlung	In patients with a hyperdense MCA sign, IV alteplase can be beneficial
Stärke	Ila,B-NR
Begründung	Analyses of data from RCTs of IV alteplase for AIS have shown no statistically significant deleterious interaction on clinical outcomes between alteplase treatment and the hyperdense MCA sign on baseline CT. In the NINDS rt-PA trial, there was no interaction between hyperdense MCA sign and treatment for outcomes at 3 months measured by any of the 4 clinical scales (mRS score 0–1, NIHSS score 0–1, Barthel Index score $\geq 95$ , Glasgow Outcome Scale score 0–1) or for death [406]. In IST-3, no significant interaction of the hyperdense MCA sign with benefit of alteplase measured by the Oxford Handicap Score at 6 months was observed [407, 408].
Empfehlung	For severe stroke, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms.
Stärke	I, A
Begründung	Wie 2015: In an analysis of the predictors of good outcome from the 2 original NINDS alteplase trials, milder stroke severity (NIHSS score <20) was one of the most important predictors of good outcome [409]. However, a significant and independent alteplase treatment effect was also seen for those strokes with an NIHSS score >20 [255]. This has been confirmed in several other analyses, most recently in the IST-3.6 In IST-3, prespecified subgroup analyses of presenting NIHSS found an overall significant difference in treatment effect by NIHSS strata (P=0.003). Overall, the estimated aOR for a good outcome increased with increasing severity, although the individual strata did not reach statistical significance and were not adjusted for time

	to treatment. Although this analysis was not statistically significant, there clearly was not a decreasing response to alteplase in the more severe patients
--	--

SF 2.1.10: Führt bei Thrombolyse-Patienten, die initial einen entgleisten Blutdruck haben (> 185 mmHg syst. und/oder > 110 mmHg diast.) eine Senkung des Blutdrucks unter die genannten Grenzen im Vergleich zur Nicht-Senkung zu einem besseren funktionellen Ergebnis?

LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke otherwise eligible for treatment with alteplase should have their blood pressure reduced to below 185/110 mmHg before treatment
Begründung	Wardlaw et al, 2012 [370]; Consensus

Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their SBP is <185 mm Hg and their diastolic BP is <110 mm Hg before IV fibrinolytic therapy is initiated
Stärke	I, B-R
Begründung	The RCTs of IV alteplase required the BP to be <185 mm Hg systolic and <110 mm Hg diastolic before treatment and <180/105 mm Hg for the first 24 hours after treatment. Options to treat arterial hypertension in patients with AIS who are candidates for immediate reperfusion therapy are given in Table 5. Some observational studies suggest that the risk of hemorrhage after administration of alteplase is greater in patients with higher BPs [410-415] and in patients with more BP variability [416]. The exact BP at which the risk of hemorrhage after IV alteplase increases is unknown. It is thus reasonable to target the BPs used in the RCTs of IV alteplase
Empfehlung	BP should be maintained at <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment.
Stärke	I, B-R
Begründung	ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) randomized 2196 alteplase-eligible patients with AIS and systolic BP (SBP) ≥150 mm Hg to receive intensive target SBP of 130 to 140 mm Hg within 1 hour versus guideline target SBP <180 mm Hg; 1081 were in the intensive group, and 1115 were in the guideline group [417]. Median time from stroke onset to randomization was 3.3 hours. Mean SBP in the intensive group was 144.3 mm Hg, and mean SBP in the guideline group was 149.8 mm Hg. Primary outcome mRS score at 90 days did not differ between the 2 groups. Although fewer patients in the intensive group had ICH, the number of patients with serious adverse events did not differ between the 2 groups. Although intensive BP lowering was observed to be safe, the observed reduction in ICH did not lead to improved clinical outcome compared with guideline treatment.

SF 2.2.1: Führt bei Hirninfarkt-Patienten mit einem proximalen Gefäßverschluss in der vorderen Zirkulation im 6 Std. Zeitfenster nach Symptombeginn eine interventionelle Thrombektomie zusätzlich zur bestmöglichen medizinischen Management im Vergleich zum alleinigen bestmöglichen medizinischen Management zu einem verbesserten funktionellen Ergebnis?

LL	<b>ESO EST [23], PICO 1</b>
Empfehlung	In adults with anterior circulation large vessel occlusion-related acute ischaemic stroke presenting within 6 h after symptom onset, we recommend mechanical thrombectomy plus best medical management – including intravenous thrombolysis



	whenever indicated – over best medical management alone to improve functional outcome.																																																							
Stärke	QoE High, SoR Strong																																																							
Begründung	<table border="1"> <thead> <tr> <th>Studie</th> <th>MT+BMT</th> <th>BMT</th> <th>OR (95%CI)</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>MR CLEAN (2015)</td> <td>76/233</td> <td>51/267</td> <td>2.05 (1.36, 3.09)</td> <td>21.80</td> </tr> <tr> <td>EXTEND IA (2015)</td> <td>25/35</td> <td>14/35</td> <td>3.75 (1.38, 10.17)</td> <td>3.68</td> </tr> <tr> <td>ESCAPE (2015)</td> <td>87/164</td> <td>43/147</td> <td>2.73 (1.71, 4.37)</td> <td>16.64</td> </tr> <tr> <td>SWIFT PRIME (2015)</td> <td>59/98</td> <td>33/93</td> <td>2.75 (1.53, 4.94)</td> <td>10.65</td> </tr> <tr> <td>REVASCAT (2015)</td> <td>45/103</td> <td>29/103</td> <td>1.98 (1.11, 3.53)</td> <td>10.91</td> </tr> <tr> <td>THRACE (2016)</td> <td>106/200</td> <td>85/202</td> <td>1.55 (1.05, 2.30)</td> <td>23.63</td> </tr> <tr> <td>THERAPY (2016)</td> <td>19/50</td> <td>14/46</td> <td>1.40 (0.60, 3.27)</td> <td>5.09</td> </tr> <tr> <td>PISTE (2017)</td> <td>17/33</td> <td>12/30</td> <td>1.59 (0.59, 4.33)</td> <td>3.67</td> </tr> <tr> <td>EASI (2017)</td> <td>19/35</td> <td>14/32</td> <td>1.53 (0.58, 4.01)</td> <td>3.94</td> </tr> <tr> <td><b>Insges. (I<sup>2</sup>=0%; p=0,525)</b></td> <td></td> <td></td> <td><b>2.03 (1.68, 2.46)</b></td> <td><b>100.00</b></td> </tr> </tbody> </table>	Studie	MT+BMT	BMT	OR (95%CI)	%	MR CLEAN (2015)	76/233	51/267	2.05 (1.36, 3.09)	21.80	EXTEND IA (2015)	25/35	14/35	3.75 (1.38, 10.17)	3.68	ESCAPE (2015)	87/164	43/147	2.73 (1.71, 4.37)	16.64	SWIFT PRIME (2015)	59/98	33/93	2.75 (1.53, 4.94)	10.65	REVASCAT (2015)	45/103	29/103	1.98 (1.11, 3.53)	10.91	THRACE (2016)	106/200	85/202	1.55 (1.05, 2.30)	23.63	THERAPY (2016)	19/50	14/46	1.40 (0.60, 3.27)	5.09	PISTE (2017)	17/33	12/30	1.59 (0.59, 4.33)	3.67	EASI (2017)	19/35	14/32	1.53 (0.58, 4.01)	3.94	<b>Insges. (I<sup>2</sup>=0%; p=0,525)</b>			<b>2.03 (1.68, 2.46)</b>	<b>100.00</b>
Studie	MT+BMT	BMT	OR (95%CI)	%																																																				
MR CLEAN (2015)	76/233	51/267	2.05 (1.36, 3.09)	21.80																																																				
EXTEND IA (2015)	25/35	14/35	3.75 (1.38, 10.17)	3.68																																																				
ESCAPE (2015)	87/164	43/147	2.73 (1.71, 4.37)	16.64																																																				
SWIFT PRIME (2015)	59/98	33/93	2.75 (1.53, 4.94)	10.65																																																				
REVASCAT (2015)	45/103	29/103	1.98 (1.11, 3.53)	10.91																																																				
THRACE (2016)	106/200	85/202	1.55 (1.05, 2.30)	23.63																																																				
THERAPY (2016)	19/50	14/46	1.40 (0.60, 3.27)	5.09																																																				
PISTE (2017)	17/33	12/30	1.59 (0.59, 4.33)	3.67																																																				
EASI (2017)	19/35	14/32	1.53 (0.58, 4.01)	3.94																																																				
<b>Insges. (I<sup>2</sup>=0%; p=0,525)</b>			<b>2.03 (1.68, 2.46)</b>	<b>100.00</b>																																																				
Empfehlung	There is a consensus among the Guideline group (11/11 votes) that patients with M2 occlusion fulfilled the inclusion criteria in most randomised trials and therefore mechanical thrombectomy is reasonable in this situation.																																																							
Stärke	EK																																																							
Begründung	In the HERMES collaboration subgroup analysis, the number of patients with an M2 occlusion was 67/818 (8%) in the MT+BMM and 64/828 (8%) in the BMM arms, respectively [269]. The common adjusted OR for better functional outcome was 1.68 (95% CI 0.90–3.14) in this subgroup. This result did not reach statistical significance, but there was no evidence for heterogeneity of treatment effect across occlusion sites ( $p_{\text{interaction}}=0.32$ ) [418]. Of note, MT was significantly associated with functional independence in the subgroup of patients with M2 occlusion (adjusted OR=2.35, 95% CI: 1.07–5.14). No patient with M2 occlusion experienced sICH after MT. Despite these results, we believe that data is insufficient to give a specific evidence-based recommendation for or against MT+BMM in patients with M2 occlusions, especially as some patients probably were misclassified as M1 occlusions and then adjudicated as proximal M2 occlusions [419].																																																							
LL	<b>NICE 2019 [24]</b>																																																							
Empfehlung	Offer thrombectomy as soon as possible and within 6 hours of symptom onset, together with intravenous thrombolysis (if not contraindicated and within the licensed time window), to people who have: <ul style="list-style-type: none"> <li>- acute ischaemic stroke and</li> <li>- confirmed occlusion of the proximal anterior circulation demonstrated by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) taking into account the factors in recommendation 1.4.8 (next)</li> </ul>																																																							
Empfehlung	Take into account the person's overall clinical status and the extent of established infarction on initial brain imaging to inform decisions about thrombectomy. Select people who have (in addition to the factors in recommendations 1.4.5 to 1.4.7): <ul style="list-style-type: none"> <li>- a pre-stroke functional status of less than 3 on the modified Rankin scale and</li> <li>- a score of more than 5 on the National Institutes of Health Stroke Scale (NIHSS).</li> </ul>																																																							
Begründung	Overall, the evidence across time-frames showed that thrombectomy, with or without thrombolysis, improved functional outcome as measured by the modified Rankin scale (mRS) in people last known to be well up to 24 hours previously, compared with usual care. There was also a potential benefit for improved quality of																																																							

	<p>life. However, there was no clinical difference in mortality and there were low rates of symptomatic intracerebral haemorrhage. The committee noted there had been some procedural complications associated with thrombectomy, but agreed that these were outweighed by the benefits of improvement in functional outcome. The committee looked at the results of 2 published cost–utility analyses with a UK NHS perspective. The first estimated that thrombectomy alongside intravenous thrombolysis (when appropriate) is cost effective compared with intravenous thrombolysis alone, when performed within 6 hours of stroke onset (that is, from when a person was last known to be well). The second demonstrated the cost effectiveness of thrombectomy therapy and best medical therapy compared with best medical therapy alone, when performed 6 to 24 hours after stroke onset. Therefore, the committee agreed to recommend thrombectomy up to 24 hours after stroke onset, together with intravenous thrombolysis if within the licensed time window, for people with appropriate clinical and radiological characteristics. Few people presenting between 6 and 24 hours after stroke onset received thrombolysis because this is outside the licensed time window. Therefore, the recommendation for those presenting beyond 6 hours is for thrombectomy alone. The evidence for thrombectomy within 6 hours of symptom onset was from populations selected using computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) to identify proximal anterior circulation occlusions.</p> <p>All the studies followed the PROBE design (prospective, randomized, open-label, controlled trial with blinded outcome evaluation). It is noted that although this is the highest quality of study design suitable for these trials, subjective outcomes (EQ-5D and mRS) have been downgraded due to lack of blinding of the interventions for the patient or care giver. All the trials were in people aged 18 and over, but this was considered similar enough to our protocol of 16 years and over not to warrant a downgrade in evidence quality. The majority of studies were funded by industry. Following the results of MR CLEAN [420] which showed efficacy of thrombectomy, the majority of other trials stopped recruitment. Some conducted planned interim analysis; others state that they are underpowered. A pre-planned subgroup analysis based on time to thrombectomy was performed due to heterogeneity. This resolved the inconsistency and so the results are reported according to the pre-specified subgroups based on time to thrombectomy. The DAWN [421] trial investigated thrombectomy performed 6 - 24 hours after a stroke and the DEFUSE 3 [422] trial had time to treatment of 6 - 16 hours after symptom onset and has also been included in the 6 - 24 hour subgroup. The REVASCAT [423] and ESCAPE [424] trials have been reported individually as thrombectomy was performed within 8 and 12 hours respectively. The remaining studies all performed thrombectomy within 6 hours and have been meta-analysed.</p>
<b>LL</b>	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke should be considered for combination intravenous thrombolysis and intra-arterial clot extraction (using stent retriever and/or aspiration techniques) if they have a proximal intracranial large vessel occlusion causing a disabling neurological deficit (National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) and the procedure can begin (arterial puncture) within 5 hours of known onset.
Begründung	Goyal et al 2016 [269]
Empfehlung	Patients with acute ischaemic stroke and a contraindication to intravenous thrombolysis but not to thrombectomy should be considered for intra-arterial clot extraction (using stent retriever and/or aspiration techniques) if they have a proximal

	intracranial large vessel occlusion causing a disabling neurological deficit (National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) and the procedure can begin (arterial puncture) within 5 hours of known onset.
Begründung	Goyal et al 2016 [269]
<b>Leitlinie</b>	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	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 $\geq$ 18 years; (4) NIHSS score of $\geq$ 6; (5) ASPECTS of $\geq$ 6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.
Stärke	I-A
Begründung	Results from 6 recent randomized trials of mechanical thrombectomy using predominantly stent retriever devices (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE) support COR I, LOE A recommendations for a defined group of patients as described in the 2015 Guidelines [273, 420, 423-426]. A pooled, patient-level analysis from 5 of these studies reported by the HERMES Collaboration showed treatment effect in the subgroup of 188 patients not treated with IV alteplase (cOR, 2.43 [95% CI, 1.30–4.55]); therefore, pretreatment with IV alteplase has been removed from the prior recommendation.
Empfehlung	Direct aspiration thrombectomy as first-pass mechanical thrombectomy is recommended as noninferior to stent retriever for patients who meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age $\geq$ 18 years; (4) NIHSS score of $\geq$ 6; (5) ASPECTS $\geq$ 6; and (6) treatment initiation (groin puncture) within 6 hours of symptom onset.
Stärke	I, B-R
Begründung	Comparative available randomized data has assessed patients primarily in the therapeutic window within 6 hours of onset. The COMPASS (Comparison of Direct Aspiration Versus Stent Retriever as a First Approach) trial randomized patients with (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age $\geq$ 18 years; (4) NIHSS score of $\geq$ 5; (5) ASPECTS $\geq$ 6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset to aspiration thrombectomy or stentriever thrombectomy as first-line technique. Primary outcome was noninferiority of mRS score at 90 days. An mRS score of 0 to 2 was achieved in 69 of 134 (52%) of patients in the aspiration group and 67 of 136 (50%) in the stentriever group, demonstrating noninferiority of aspiration thrombectomy compared with stentriever thrombectomy ( $P_{\text{noninferiority}}=0.0014$ ). No difference in recanalization rates or intracranial hemorrhage was found [427]. The ASTER trial (Contact Aspiration vs Stent Retriever for Successful Revascularization) compared the contact aspiration technique and the standard stent retriever technique as first-line mechanical thrombectomy for successful revascularization within 6 hours among patients with acute anterior circulation ischemic stroke and LVO. Eligibility criteria were different from COMPASS, lacking specification of NIHSS or ASPECTS. Primary outcome was successful revascularization. The proportion of patients with successful revascularization at the end of all interventions was 85.4% (n=164) in the contact aspiration group versus 83.1% (n=157) in the stent retriever group (OR, 1.20 [95% CI, 0.68–2.10]; $P=0.53$ ; difference, 2.4% [95% CI, –5.4 to 9.7]). The secondary clinical end point of mRS score of 0 to 2 at 90 days was achieved by 82 of 181 (45.3%) in the contact aspiration group versus 91 of 182 (50.0%) in the stent retriever group (OR, 0.83 [95% CI, 0.54–1.26]; $P=0.38$ ). Given its superiority design to detect a 15% difference in the primary end point, this trial was not designed to establish noninferiority [428]. The Penumbra Separator 3D Trial compared a 3-D stent retriever

	combined with aspiration to aspiration alone as first-line intracranial mechanical thrombectomy for successful revascularization within 8 hours among patients with AIS (NIHSS score of at least 8) and LVO refractory to or ineligible for IV alteplase in a 1:1 randomized, noninferiority trial with a 15% noninferiority margin. The primary end point of mTICI grade 2 to 3 occurred in 87.2% of the combination group versus 82.3% in the aspiration alone group, meeting the noninferiority criterion of lower 90% confidence bound less than -15%. A 90-day mRS score of aspiration alone group [429]. The trial demonstrated noninferiority of 3-D stent retriever with aspiration versus aspiration alone, using older-generation aspiration technology. The trial was not powered to demonstrate noninferiority in the secondary outcome of 90-day functional independence.
Empfehlung	Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.
Stärke	IIB, N-R
Begründung	In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the direction of treatment effect for mechanical thrombectomy over standard care was favorable in M2 occlusions, but the adjusted cOR was not significant (1.28 [95% CI, 0.51–3.21]) [269]. In patient level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration: SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT) showed that the direction of treatment effect was favorable for mechanical thrombectomy over standard care in M2 occlusions, but the OR and 95% CI were not significant [430]. In an analysis of pooled data from SWIFT (Solitaire With the Intention for Thrombectomy), STAR (Solitaire Flow Restoration Thrombectomy for Acute Revascularization), DEFUSE 2, and IMS III, among patients with M2 occlusions, reperfusion was associated with excellent functional outcomes (mRS score 0–1; OR, 2.2 [95% CI, 1.0–4.7]) [431].
Empfehlung	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)
Stärke	IIB, B-R
Begründung	Wie 2015: keine Begründung, sondern Studienzusammenfassung
Empfehlung	To ensure benefit, reperfusion to mTICI grade 2b/3 should be achieved as early as possible within the therapeutic window.
Stärke	I, A
Begründung	In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), and ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes [218]. Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76–0.93]; ARD, -6.7%) and less functional independence (OR, 0.81 [95% CI, 0.71–0.92]; ARD, -5.2% [95% CI, -8.3 to -2.1]) [218].

LL	<b>Australia 2017 [6]</b>
Empfehlung	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. (Goyal et al. 2016 [269])
Stärke	Strong, High QoE
Begründung	<p>There is clear and high quality evidence of improved functional outcome (229 more patients had functional independence per 1000 stroke patients treated) and lower mortality (44 fewer patients died with every 1000 stroke patients treated), with no evidence of Substantial net benefits of the recommended alternative Endovascular thrombectomy is effective in a broad range of patients without evidence of an effect of age, sex or clinical severity on treatment benefit (Goyal et al. 2016 [269]). The majority of the patients enrolled in the randomised trials had treatment commenced within 6 hours although, in individual patient data meta-analysis, the benefit of thrombectomy extended to at least 7.3 hours (Saver et al. 2016 [218]). increased risk of symptomatic intracerebral haemorrhage (Goyal et al. 2016 [269]).</p> <p>Goyal et al. (2016) [269] conducted an individual patient meta-analysis that pooled results from five recent trials of endovascular thrombectomy. The included trials were different to previously published trials in that they all used CT or magnetic resonance imaging to target large vessel occlusions, emphasised fast treatment, and used second-generation neurothrombectomy devices with better recanalization rates and lower complications. The primary outcome was scores on the modified Rankin scale, analysed using ordinal logistic regression to estimate the odds that intervention would improve mRS scores by 1 or more points. Intervention was shown to increase the odds of improvement significantly (common odds ratio 2.49, 95% CI 1.76 to 3.53). The number needed to treat for one patient to have a reduction of their mRS score of 1 point or more was 2.6. The dichotomous outcome of mRS 0–2 vs 3–6 also showed a significant increase in functional independence (adjusted OR 2.71, 95% CI 2.07 to 3.55). There were no significant effects on 90-day mortality or symptomatic intracranial haemorrhage. The trials were generally of high quality, with blinded outcome assessment, and effects were consistent across trials. A previous meta-analysis by Badhiwala et al. (2015) [432] included the same 5 trials as the Goyal et al. analysis but also included 3 earlier trials. The pooled results showed a significant increase in the odds of a reduction of mRS score (OR 1.56, 95% CI 1.14 to 2.13), and in the odds of functional independence (OR 1.71, 95% CI 1.18 to 2.49), although in both cases the effect appeared to be weaker than the comparable analysis in the Goyal et al. meta-analysis. The stronger effects in the Goyal et al. analysis may result from the newer trials employing improved patient selection and achieving faster, more effective reperfusion as discussed above. There was a significant interaction between functional outcome and year of publication in the Badhiwala et al. analysis.</p>
Empfehlung	For patients with ischaemic stroke caused by occlusion in the M2 segment of the middle cerebral artery, endovascular thrombectomy may be considered based on individual patient and advanced imaging factors.
Stärke	Consensus-based recommendations
LL	<b>Canada 2018 [8]</b>
Empfehlung	Endovascular thrombectomy should be offered within a coordinated system of care including agreements with emergency medical services, access to rapid neurovascular (brain and vascular) imaging, coordination between emergency

	medical services, the Emergency Department, the stroke team and radiology, local expertise in neurointervention, and access to a stroke unit for ongoing management
Stärke	[Evidence Level A].
Empfehlung	Endovascular thrombectomy is indicated in patients based upon imaging selection with noncontrast CT head and CT angiography (including extracranial and intracranial arteries)
Stärke	[Evidence Level A]
Empfehlung	Endovascular thrombectomy is indicated in patients who have received intravenous alteplase and those who are not eligible for intravenous alteplase
Stärke	[Evidence Level A]
Empfehlung	Eligible patients who can be treated with endovascular thrombectomy within 6 hours of symptom onset (i.e., arterial access within 6 hours of onset) should receive endovascular thrombectomy
Stärke	[Evidence Level A]
Begründung	<p>Endovascular treatment for large artery ischemic stroke has clearly demonstrated efficacy with numbers needed to treat (NNT) of approximately four to achieve functional independence at 90 days. Recent data from the DAWN trial [421] suggest the NNT may be as low as three, while pooled results from a series of older trials, indicated the number was higher, closer to five [269]. This therapy has profound impact on patients who suffer the most devastating ischemic strokes; patients who, if left untreated, will place a more significant burden on the healthcare system, long term care and family caregivers.</p> <p>In the largest trial, MR CLEAN [420], included 500 patients who were <math>\geq 18</math> years, with a baseline NIHSS score of 2 or greater, and were treatable within 6 hours of stroke onset. Patients were randomized to receive endovascular treatment with rt-PA or urokinase, and/or mechanical treatment with retrievable stents, which were used in 81.5% of patients, or other available devices, versus best medical management. The median time from stroke onset to groin puncture was 260 minutes. The majority of patients in both groups were treated with intravenous t-PA (87.1% intervention group, 90.6% control group). There was a significant shift in the distribution towards more favourable mRS scores among patients in the intervention group at 90 days (adj common OR=1.67, 95% CI 1.21-2.30). The odds of both a good (mRS 0-2) and excellent (mRS 0-1) recovery at day 90 were also significantly higher among patients in the intervention group (adj OR=2.07, 95% CI 1.07-4.02 and adj OR=2.16, 95% CI 1.39-3.38, respectively). Patients in the intervention group were more likely to show no evidence of intracranial occlusion on follow-up CTA (adj OR=6.88, 95% CI 4.34-10.94, n=394) and to have a lower median final infarct volume (-19 mL, 95% CI 3-34, n=298). At two-year follow-up (van den Berg et al. 2017), the odds of an mRS score of 0-2 remained significantly higher in the intervention group (37.1% vs. 23.9%, adj OR= 2.21, 95% CI 1.30-3.73, p=0.003). The ESCAPE trial [424] enrolled 316 patients <math>\geq 18</math> years, with stroke onset less than 12 hours, a baseline NIHSS score of <math>&gt; 5</math> and moderate-to-good collateral circulation. Patients were randomized to receive endovascular mechanical thrombectomy, using available devices or best medical management. The median time from stroke onset to first reperfusion was 241 minutes. 72.7% of patients in the intervention group and 78.7% of those in the control group received intravenous t-PA. The odds of improvement in mRS scores by 1 point at 90 days were significantly higher among patients in the intervention group (adj OR=3.2, 95% CI 2.0-4.7). The odds of good outcome (mRS score 0-2) at 90 days were also higher in the intervention group (adj OR=1.7, 95% CI 1.3-2.2), as were the odds of a NIHSS score of 0-2 and a Barthel Index score of 95-100 (adj OR=2.1, 95% CI 1.5-3.0 and 1.7, 95% CI 1.3-2.22, respectively). The risk of death was significantly lower</p>

in the intervention group (adj RR=0.5, 95% CI 0.-0.8). In neither MR CLEAN nor ESCAPE, was there an increased risk of symptomatic ICH associated with endovascular therapy. No interaction effects were found in subgroup analyses of age, stroke severity, time to randomization, or baseline ASPECTS in either of the trials. The THRACE trial [425] had broader eligibility criteria and included 414 patients aged 18- 80 years with an occlusion in the intracranial carotid, the MCA (M1) or the upper third of the basilar artery with onset of symptoms <4 hours and NIHSS score of 10-25 at randomization. Patients were randomized to receive dual intravenous rt-PA therapy + intra-arterial mechanical clot retrieval with the Merci, Penumbra, Catch or Solitaire devices or treatment with IV rt-PA only. The median time from symptom onset to thrombectomy was 250 minutes. The odds of achieving mRS score of 0-2 at 90 days were increased significantly in the thrombectomy group (53% vs. 42.1%, OR=1.55, 95% CI 1.05-2.3, p=0.028, NNT=10). There were no significant differences between groups in the number of patients with symptomatic or asymptomatic hemorrhages at 24 hours. Three trials evaluated the efficacy of the use of a specific retriever device (Solitaire FR Revascularization Device). In the EXTEND IA trial [273], there were no inclusion criteria related to stroke severity. Seventy patients  $\geq$ 18 years, with good premorbid function and an anterior circulation acute ischemic stroke, with criteria for mismatch, who could receive intra-arterial treatment within 6 hours of stroke onset, were included. All patients received intravenous rt-PA, while 35 also underwent intra-arterial mechanical clot retrieval. A significantly greater proportion of patients in the endovascular group experienced early neurological improvement (80% vs. 37%, p<0.001), >90% reperfusion without ICH at 24 hours (89% vs. 34%, p<0.001) and were functionally independent at day 90 (71% vs. 40%, p=0.009). The SWIFT-PRIME trial [426] randomized 196 patients, aged 18-80 years with NIHSS scores of 8-29 with a confirmed infarction located in the intracranial internal carotid artery, MCA, or carotid terminus who could be treated within 6 hours of onset of stroke symptom, to receive intravenous rt-PA therapy + intra-arterial mechanical clot retrieval, or rt-PA only. The likelihood of successful reperfusion (>90%) at 27 hours was significantly higher in the endovascular therapy group (82.8% vs. 40.4%, RR=2.05, 95% CI 1.45-2.91, p<0.001) and a significantly higher percentage of patients were independent at day 90 (mRS 0-2) (60.2% vs. 35.5%, RR=1.70, 95% CI 1.23-2.33, p=0.001). Finally, in the REVASCAT trial [423], 206 patients with NIHSS scores of 6 or greater who could be treated within 8 hours of stroke onset were randomized to receive mechanical embolectomy + best medical management or best medical management only, which could include intravenous t-PA (78%). The odds of dramatic neurological improvement at 24 hours were increased significantly in the intervention group (adj OR=5.8, 95% CI 3.0-11.1). The odds for improvement by 1 mRS point at 90 days were increased significantly in the intervention group (adj OR=1.7, 95% CI 1.05-2.8), as were the odds of achieving an mRS score of 0-2 at 90 days (adj OR=2.1, 95% CI 1.1-4.0). At one-year follow-up [433], the proportion of patients who were functionally independent (mRS score 0–2) was significantly higher for patients in the thrombectomy group (44% vs. 30%; OR=1.86, 95% CI 1.01-3.44). No treatment effects were noted based on sub group analyses in either SWIFT-PRIME or REVASCAT, based on age, baseline NIHSS score, site of occlusion, time to randomization, or ASPECTS score. There was no increased risk of symptomatic ICH in any of these trials.

Two trials (THERAPY and PISTE) halted recruitment prematurely following the presentation of the MR CLEAN trial, resulting in much smaller sample sized than planned. These trials generally reported improved outcomes for patients undergoing mechanical thrombectomy, although the smaller sample sizes were not powered to

	<p>meet the primary endpoints. As a result, statistical significance was not always achieved.</p> <p>The results from several meta-analyses, indicated the odds of a favourable outcome were all significantly increased with mechanical thrombectomy. Goyal et al. [269] included the results from 5 trials, using second generation devices. The odds of achieving a mRS score of 0-1 or 0-2 at 90 days were significantly higher for patients in the endovascular group. The NNT for a one-point reduction in mRS was 2.6. Using data from these same trials, Saver et al. [434] conducted pooled analysis to examine the timeframe in which endovascular treatment is associated with benefit. Compared with medical therapy, the odds of better disability outcomes at 90 days associated with endovascular therapy declined with longer time from symptom onset to arterial puncture. The point at which endovascular therapy was not associated with a significantly better outcome was 7 hours and 18 minutes. Campbell et al. [430], included the results of 4 trials in which the Solitaire device was used. Treatment with Solitaire device was associated with both a significantly greater likelihood of independence, and of excellent functional outcome at 90 days compared with best medical management. Flynn et al. [435] included the results from 8 trials and reported that mechanical thrombectomy was associated with significantly higher odds of functional independence (unadjusted OR=2.07, 95% CI 1.70-2.51, p&lt;0.0001). Time series analysis demonstrated robust evidence for a 30% relative benefit for mechanical thrombectomy for this outcome. While there was no evidence that mechanical thrombectomy was associated with increased risks of mortality or symptomatic ICH, robust evidence to demonstrate a 30% relative risk reduction was lacking.</p>
--	--

SF 2.2.2: Führt bei Hirninfarkt-Patienten mit einem proximalen Gefäßverschluss in der vorderen Zirkulation, die sich in einem unklaren aber maximal 24 Stunden bzw. gesichertem max. 24 Std. Zeitfenster befinden und zum Zeitpunkt der Behandlung in einer erweiterten Bildgebung 1) bei schwerer Symptomatik einen kleinen Infarktkern aufweisen und/oder 2) ein CT/MRT-basiert dargestelltes Mismatch von Infarktkern und Penumbra aufweisen eine interventionelle Thrombektomie zusätzlich zum bestmöglichen medizinischen Management im Vergleich zum alleinigen bestmöglichen medizinischen Management zu einem verbesserten funktionellem Ergebnis?

<b>LL</b>	<b>ESO EST [23], PICO 2</b>
Empfehlung	In adults with anterior circulation large vessel occlusion-related acute ischaemic stroke presenting between 6 and 24 h from time last known well and fulfilling the selection criteria of DEFUSE-3* or DAWN**, we recommend mechanical thrombectomy plus best medical management over best medical management alone to improve functional outcome.
Stärke	QoE moderate, SoR strong
Begründung	Two RCTs of endovascular therapy recruited highly selected patients from 6 up to 16 (DEFUSE-3[422]: n=182) or 24 h (DAWN[421]: n=206) after symptom onset or last known well. The inclusion of patients with stroke upon awakening, if otherwise fitting the inclusion criteria, was encouraged. A small number of patients were recruited beyond 6 h in REVASCAT (up to 8 h, n=21) [423] and ESCAPE (up to 12 h, n=49)[424]. Inclusion criteria varied between the trials. DAWN used a stratification by age and National Institutes of Health Stroke Scale (NIHSS) score leading to differing maximum infarct core cut-off volumes measured by imaging software in an automated fashion (>80 years, infarct core up to 20 mL; <80 years and NIHSS 10–19, infarct core up to 30 mL; <80 years and NIHSS 20 or more, infarct core up to 51 mL). DEFUSE-3 allowed a larger core volume (up to 70 mL) but required a perfusion mismatch measured by



	<p>perfusion CT or MRI of more than 1.8 (ratio) and a penumbra volume <math>\geq 15</math> mL, again measured by imaging software in an automated fashion. The median infarct core volume was 8 (75th percentile: 20 mL) and 10 mL (75th percentile: 25 mL) in DAWN and DEFUSE-3, respectively. A large majority of patients enrolled in DAWN or DEFUSE-3 had an unknown time of stroke onset (stroke on awakening or unwitnessed stroke): 88% in DAWN and 64% in DEFUSE-3. It is possible that many of those patients had an actual stroke-onset-to-treatment time within the 6-h time window. The total numbers of IVT patients and M2 occlusions were negligible. There was no blinding of patient or staff for treatment arm in DAWN and DEFUSE-3. However, the primary endpoint (mRS at 90 days) was assessed in a blinded fashion. Each trial was considered to be at low risk of bias.</p> <p>An individual patient data meta-analysis of DAWN, DEFUSE-3 and patients recruited beyond 6 h in ESCAPE and REVASCAT (AURORA Collaboration) was presented at the 2018 ESO Conference. A total of 459 patients were included in this meta-analysis. Compared with BMM alone, MT+BMM was strongly associated with better functional outcome (adjusted common OR 2.77, 95%CI: 1.95–3.94, <math>p &lt; 0.001</math>) and functional independence at three months (mRS <math>\leq 2</math>): 46.7% vs. 16.7%, adjusted OR 4.65 (95% CI: 2.02–10.72, <math>p &lt; 0.001</math>). It should be borne in mind that the vast majority (84.5%) of patients included in the analysis of the AURORA collaboration were included in DAWN and DEFUSE-3. Therefore, the evidence-based recommendations presented for the 6–24 h time window are only based on the results of these two trials.</p>
--	---

LL	<b>NICE 2019 [24]</b>
Empfehlung	<p>Offer thrombectomy as soon as possible to people who were last known to be well between 6 hours and 24 hours previously (including wake-up strokes):</p> <ul style="list-style-type: none"> <li>- who have acute ischaemic stroke and confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA and</li> <li>- if there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume</li> </ul>
Begründung	<p>For thrombectomy undertaken between 6 and 24 hours after stroke onset, the evidence was based on more highly selected populations using CT perfusion, MRI diffusion and MRI perfusion imaging, in addition to identifying a proximal anterior circulation arterial occlusion. Because the effectiveness of thrombectomy is likely to be lower in a less selected population, the committee recommended that, in line with the evidence, imaging such as CT perfusion or diffusion-weighted MRI sequences is performed if presentation is 6 to 24 hours after stroke onset in people being considered for thrombectomy. This would ensure that there is vulnerable but salvageable brain tissue to be targeted for thrombectomy. Although benefit is still seen up to 24 hours after stroke, time is still critical. Therefore, the committee agreed that thrombectomy should be performed as soon as possible.</p>

LL	<b>RCP 2016 [10]</b>
Empfehlung	<p>Patients with acute ischaemic stroke causing a disabling neurological deficit (a National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) may be considered for intraarterial clot extraction (using stent retriever and/or aspiration techniques, with prior intravenous thrombolysis unless contraindicated) beyond an onset-to-arterial puncture time of 5 hours if:</p> <ul style="list-style-type: none"> <li>– a favourable profile on salvageable brain tissue imaging has been proven, in which case treatment up to 12 hours after onset may be appropriate.</li> </ul>
Begründung	Goyal et al 2016 [269]

Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window
Stärke	I-A
Begründung	<p>The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical-core mismatch (a combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority &gt;0.999) [421].</p> <p>The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; P&lt;0.0001) [422].</p> <p>Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy &gt;6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice [421, 422].</p>
Empfehlung	When evaluating patients with AIS within 6 hours of last known normal with LVO and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of $\geq 6$ , selection for mechanical thrombectomy based on CT and CTA or MRI and MRA is recommended in preference to performance of additional imaging such as perfusion studies.
Stärke	I-BR
Begründung	<p>Of the 6 RCTs that independently demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed &lt;6 hours from stroke onset, 4 trials (REVASCAT [Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset], SWIFT PRIME [Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment], EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial], and ESCAPE) [273, 423, 424, 426] used some form of advanced imaging to determine eligibility, whereas 2 (THRACE [Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke] and MR CLEAN) [420, 425] required only NCCT and demonstration of LVO.</p> <p>Because the last 2 studies independently demonstrated benefit in the treated group, the role of additional imaging-based eligibility criteria is not well established and could lead to the exclusion of patients who would benefit from treatment and are therefore not indicated at this time. Further RCTs may be helpful to determine whether advanced imaging paradigms using CTP, CTA, and MRI perfusion and</p>

	diffusion imaging, including measures of infarct core and penumbra, are beneficial for selecting patients for reperfusion therapy who are within 6 hours of symptom onset and have an ASPECTS <6.
Empfehlung	In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.
Stärke	I-A
Empfehlung	In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable
Stärke	Ila, B-R
Begründung (für beide)	<p>The DAWN trial used clinical-core mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in function outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority &gt;0.999) [421]. In DAWN, there were few strokes with witnessed onset (12%).</p> <p>The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; P&lt;0.0001) [422]. Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy &gt;6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice [421, 422].</p>
Empfehlung	In the 6- to 24-hour thrombectomy window evaluation and treatment should proceed as rapidly as possible to ensure access to treatment for the greatest proportion of patients.
Stärke	I, B-R
Begründung	The 6- to 16- and 6- to 24-hour treatment windows trials, which utilized advanced imaging to identify a relatively uniform patient group, showed limited variability of treatment effect with time in these highly selected patients [421, 422]. The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible.
<b>LL</b>	<b>Australia 2017 [6]</b>
Empfehlung	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 between 6-24 hours after they were last known to be well if clinical and CT perfusion or MRI features indicate the presence of salvageable brain tissue. (Nogueira et al. 2017 [71], Albers et al. 2018 [72])
Stärke	Strong

Begründung	Endovascular thrombectomy is effective within 6 hours of stroke onset in a broad range of patients with ICA, proximal (M1) MCA or tandem occlusion of the cervical ICA and intracranial MCA without evidence of an effect of age, sex or clinical severity on treatment benefit (Goyal et al. 2016 [269]). Between 6 and 24 hours after stroke onset, patients with ICA, M1 MCA or tandem occlusion and favourable CT perfusion or MR diffusion imaging benefit from endovascular thrombectomy. The two trials of thrombectomy beyond 6 hours (DAWN and DEFUSE 3) differed in inclusion criteria but DEFUSE 3 criteria (ischemic core <70mL with a mismatch ratio >1.8 and absolute mismatch >15mL) are broader and include virtually all DAWN-eligible patients. Although DAWN extended to 24hr and DEFUSE 3 only to 16hr, there was no evidence of reduced treatment effect over time in either trial and so we have elected not to differentiate between 6-16hr and 16-24hr. Within 6 hours of stroke onset, there is clear and high quality evidence that endovascular thrombectomy improves functional outcome (229 more patients had functional independence per 1000 stroke patients treated) and a trend towards lower mortality (44 fewer patients died per 1000 stroke patients treated), with no evidence of increased risk of symptomatic intracerebral haemorrhage (Goyal et al. 2016 [269]). In the 6-24 hour treatment window, there is clear evidence that endovascular thrombectomy improves functional outcome (319 more patients had functional independence per 1000 stroke patients treated) and a trend towards lower mortality (51 fewer patients died per 1000 stroke patients treated). Symptomatic intracerebral haemorrhage did not differ significantly between the endovascular thrombectomy and standard medical care groups. Only ~9% in either group received intravenous alteplase in DAWN and DEFUSE 3 (Nogueira et al. 2018 [421], Albers et al. 2018 [422]).
LL	<b>Canada 2018 [8]</b>
Empfehlung	Highly selected patients with large vessel occlusion who can be treated with endovascular thrombectomy within 24 hours of symptom onset (i.e., arterial access within 24 hours of onset) and those patients with stroke discovered on awakening should receive endovascular thrombectomy
Stärke	[Evidence Level A]
Begründung	The results of the DAWN [421] and DEFUSE-3 [422] trials suggest that the treatment window for mechanical thrombectomy is wider than previously thought. The DAWN trial included 206 patients, last been known to be well 6 to 24 hours earlier, with no previous disability (mRS 0-1) and who met clinical mismatch criteria who had either failed intravenous t-PA therapy, or for whom its administration was contraindicated, because of late presentation. Patients were randomized to treatment with thrombectomy with Trevo device + medical management or medical management alone. The trial was terminated early after interim analysis when efficacy of thrombectomy was established. The median intervals between the time that a patient was last known to be well and randomization was 12.2 hours in the thrombectomy group and 13.3 hours in the control group. The mean utility weighted mRS score was significantly higher in the thrombectomy group (5.5 vs. 3.4, adj difference =2.0, 95% Cr I 1.1-3.0, prob of superiority >0.999). There were no interactions in sub group analysis (mismatch criteria, sex, age, baseline NIHSS score, occlusion site, interval between time that patient was last known to be well and randomization and type of stroke onset). A significantly higher proportion of patients in the thrombectomy group experienced an early response to treatment, had achieved recanalization at 24 hours and were independent (mRS 0-2) at 90 days (49% vs. 13%, NNT=3). The admission criteria for the DEFUSE-3 trial were broader and included those who had remaining ischemic brain tissue that was not yet infarcted. The median time from stroke onset to randomization was just under 11 hours for

	patients in the endovascular group. A significantly higher proportion of patients in the endovascular group were independent (mRS 0- 2) at 90 days (45% vs. 17%, OR=2.67, 95% CI 1.60–4.48, p<0.001, NNT=4).
--	--

SF 2.2.3: Führt bei Patienten mit Hirninfarkt und einem proximalem Gefäßverschluss, bei denen sowohl eine systemische Thrombolyse als auch eine interventionelle Thrombektomie möglich und empfohlen ist, eine kombinierte Therapie mit systemischer Thrombolyse und interventioneller Thrombektomie im Vergleich zu einer alleinigen interventionellen Thrombektomie zu einem besseren funktionellen Ergebnis?

Dieser Abschnitt wurde im Rahmen des Amendments „Oktober 2022“ und die ESO-Leitlinie zur bridging-Therapie ergänzt.

LL	<b>NEU: ESO-bridging 2022 [19]</b>
Empfehlung	For patients directly admitted to a thrombectomy-capable centre for an acute ischaemic stroke ( $\leq 4.5$ hrs of symptom onset) with anterior circulation large vessel occlusion and who are eligible for both treatments, we recommend intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone. Both treatments should be performed as early as possible after hospital arrival. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis, and intravenous thrombolysis should not delay mechanical thrombectomy.
Empfehlung	For patients directly admitted to a thrombectomy-capable centre within 4.5 hours of symptom recognition after wakeup ischaemic stroke caused by anterior circulation large vessel occlusion, we suggest intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone in selected patients.
Empfehlung	For patients admitted to a non-thrombectomy-capable centre for an acute ischaemic stroke ( $\leq 4.5$ hrs of symptom onset) with anterior circulation large vessel occlusion and who are eligible for both treatments, we recommend intravenous thrombolysis followed by rapid transfer to a centre with thrombectomy facilities over omitting intravenous thrombolysis and transfer to a centre with thrombectomy facilities. Intravenous thrombolysis should not delay the transfer to a centre with thrombectomy facilities.
Begründung	Six randomized controlled clinical trials have assessed whether mechanical thrombectomy (MT) alone is non-inferior to intravenous thrombolysis (IVT) plus MT within 4.5 hours of symptom onset in patients with anterior circulation large vessel occlusion (LVO) ischaemic stroke and no contraindication to IVT. We identified two relevant Population, Intervention, Comparator, Outcome (PICO) questions, performed systematic reviews and meta-analyses of the literature, assessed the quality of the available evidence and wrote evidence-based recommendations. Expert opinion was provided if insufficient evidence was available to provide recommendations based on the GRADE approach. For stroke patients with anterior circulation LVO directly admitted to a MT-capable centre ('mothership') within 4.5 hours of symptom onset and eligible for both treatments, we recommend IVT plus MT over MT alone (moderate evidence, strong recommendation). MT should not prevent the initiation of IVT, nor should IVT delay MT. In stroke patients with anterior circulation LVO admitted to a centre without MT facilities and eligible for IVT $\leq 4.5$ hrs and MT, we recommend IVT followed by rapid transfer to a MT capable-centre ('drip-and-ship') in preference to omitting IVT (low evidence, strong recommendation).

	<p>Expert consensus statements on ischaemic stroke on awakening from sleep are also provided. Patients with anterior circulation LVO stroke should receive IVT in addition to MT if they have no contraindications to either treatment.</p> <p>We conducted a study-level random-effects metaanalysis of the six RCTs of MT alone versus IVT plus MT, comprising 2331 patients. Compared with patients randomised to bridging therapy, the pooled unadjusted OR for good outcome in patients randomized to MT alone was 0.93 (95% CI 0.79 to 1.10, <math>p=0.38</math>; <math>I^2=0\%</math>). The corresponding pooled RR and risk difference were 0.96 (95% CI 0.89 to 1.04, <math>p=0.30</math>; <math>I^2=0\%</math>) and -1.9% (95% CI: -5.9% to 2.1%), respectively. Therefore, noninferiority was not met based on our pre-specified 1.3% margin. Importantly though, non-inferiority was also not met based on the maximum clinically acceptable noninferiority margin of 5.0% proposed by MWG members. Similar results were obtained when risk difference was estimated with the random-effects pooled proportion of good outcome in the bridging therapy group (52.8%) and the pooled RR for good outcome (risk difference: -2.1%, 95% CI -6.3% to 2.1%)</p> <p>The common adjusted OR for reduced disability with MT alone was 0.92 (95% CI: 0.80 to 1.07; <math>p=0.27</math>; <math>I^2=0\%</math>; Figure 5). The pooled unadjusted OR for excellent outcome (mRS 0-1 at 90 days) was 0.99 (95% CI; 0.82 to 1.18; <math>p=0.88</math>; <math>I^2=0\%</math>). The rates of all-cause mortality at 90 days were similar in patients randomized to MT alone and bridging therapy (unadjusted pooled OR 1.06, 95% CI: 0.84 to 1.35; <math>p=0.60</math>; <math>I^2=0\%</math>). Successful reperfusion at the end of the endovascular procedure was significantly less frequent in patients randomized to MT alone (unadjusted pooled OR 0.72, 95% CI: 0.57 to 0.92, <math>p=0.01</math>, <math>I^2=0\%</math>).</p> <p>Symptomatic intracerebral haemorrhage did not significantly differ between treatment arms (unadjusted pooled OR 0.77, 95% CI: 0.52–1.13, <math>p=0.18</math>, <math>I^2=0\%</math>) but the occurrence of any ICH was less frequent in patients randomized to MT alone (unadjusted pooled OR 0.80, 95% CI: 0.66–0.96, <math>p=0.02</math>, <math>I^2=10\%</math>).</p>
<b>LL</b>	<b>ESO EST [23], PICO 3</b>
Empfehlung	In large vessel occlusion-related ischaemic stroke patients eligible for both treatments, we recommend intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone. Both treatments should be performed as early as possible after hospital arrival. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis and intravenous thrombolysis should not delay mechanical thrombectomy.
Stärke	QoE very low, SoR Strong
Begründung	MT+IVT vs. MT alone. The literature search did not identify any RCT directly addressing this PICO question. In the pivotal RCTs demonstrating the benefit of endovascular therapy, the experimental treatment arm comprised not only MT but also BMM, including IVT with alteplase in 83% of patients [269]. Therefore, the current standard of care for adults with LVO-related acute ischaemic stroke is MT plus IVT (bridging therapy), if the patient has no contraindications for IVT. The HERMES collaboration individual patient data metaanalysis of the first five RCTs (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT) reported a common OR for a better functional outcome of 2.45 (95% CI: 1.68–3.57) in patients receiving IVT plus MT vs. 2.43 (95% CI: 1.30–4.55) in those receiving MT alone, [269] apparently not suggesting a higher benefit of MT in patients treated with vs. without IVT. This result might be explained by a selection bias, as good responders to IVT might have been less likely to be enrolled in REVASCAT, in which the response to IVT had to be evaluated after

	30 min, [423] and in MR CLEAN, in which the median time between IVT and randomisation was 2 h.[420] A systematic review and meta-analysis of 13 studies allowing the non-randomised comparison of MT+IVT vs. MT alone in adults with anterior circulation LVO-related acute ischaemic stroke suggested a superiority of MT+IVT regarding functional independence (mRS $\leq$ : OR=1.27, 95% CI: 1.05–1.55; $I^2=17\%$ ) [436]. However, this analysis is limited by potential selection bias, confounding by indication and indirectness. Therefore, the QoE was downgraded as very low. Another meta-analysis did not suggest the superiority of MT+IVT vs. MT alone in the subgroup of patients eligible for IVT (OR for mRS $\leq 2$ : 0.93, 95% CI: 0.57–1.49; $I^2=41\%$ ) [437].
Empfehlung	In large vessel occlusion-related ischaemic stroke patients not eligible for intravenous thrombolysis, we recommend mechanical thrombectomy as stand-alone treatment.
Stärke	QoE Low, SoR Strong
Begründung	MT alone in patients not eligible to IVT. The abovementioned results of the HERMES collaboration individual patient data meta-analysis of the five first RCTs suggest that in the subgroup of patients not receiving IVT (n=180), MT was effective as stand-alone therapy as compared to BMM without IVT (OR for functional independence 2.43, 95% CI: 1.30–4.55) [269]. However, this subgroup analysis suffers from very serious indirectness, because the five above-mentioned RCTs were not designed to address the question of the effectiveness and safety of MT in patients with a contraindication to IVT. The reasons for non-eligibility to IVT were likely heterogeneous, including not only patients with a contraindication to IVT (e.g. oral anticoagulation) but mostly patients outside of the 4.5 h time window.
LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke should be considered for combination intravenous thrombolysis and intra-arterial clot extraction (using stent retriever and/or aspiration techniques) if they have a proximal intracranial large vessel occlusion causing a disabling neurological deficit (National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) and the procedure can begin (arterial puncture) within 5 hours of known onset.
Begründung	Goyal et al 2016 [269]
Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	Patients eligible for IV alteplase should receive IV alteplase even if mechanical thrombectomy is being considered
Stärke	I-A
Empfehlung	In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed
Stärke	III: Harm, B-R
Begründung	In pooled patient-level data from 5 trials (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials], which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS score distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; and cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes [217]. Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76–0.93]; ARD, –6.7%) and less functional independence (OR, 0.81

	[95% CI, 0.71–0.92]; ARD, –5.2% [95% CI, –8.3 to –2.1]) but no change in mortality (OR, 1.12 [95% CI, 0.93–1.34]; ARD, 1.5% [95% CI, –0.9 to 4.2])[217]. The REVASCAT trial included a 30-minute period of observation before undertaking EVT. Available data do not directly address the question of whether patients should be observed after IV alteplase to assess for clinical response before pursuing mechanical thrombectomy. However, one can infer that because disability outcomes at 90 days were directly associated with time from symptom onset to arterial puncture, any cause for delay to mechanical thrombectomy, including observing for a clinical response after IV alteplase, should be avoided.
--	---

LL	<b>Australia 2017 [6]</b>
Empfehlung	Eligible stroke patients should receive intravenous thrombolysis while concurrently arranging endovascular thrombectomy, with neither treatment delaying the other. (Goyal et al. 2016 [269])
Stärke	Strong, High QoE
Begründung	As with intravenous thrombolysis, time is brain and earlier removal of occlusion is more likely to lead to improved outcomes. Trials to date have administered intravenous thrombolysis prior to clot retrieval in all eligible patients (Goyal et al. 2016 [55]). However, endovascular thrombectomy is effective in patients with contraindications to intravenous thrombolysis (Goyal et al. 2016 [269]). Goyal et al. (2016) [269] conducted an individual patient meta-analysis that pooled results from five recent trials of endovascular thrombectomy. The overall analysis showed a significant increase in odds of a reduced modified Rankin scale score (OR 2.49, 95% CI 1.76 to 3.53). A prespecified subgroup analysis of patients who had received alteplase treatment found a similar treatment effect (OR 2.45, 95% CI 1.68 to 3.57). There was non-significant heterogeneity ( $p = 0.43$ ) between subgroups receiving or not receiving alteplase, suggesting that the effect of thrombectomy did not differ between the groups. As in the overall analysis, endovascular thrombectomy significantly improved the odds of functional independence and produced no significant differences in 90-day mortality. Palesch et al. (2015) [438] reported 12-month outcomes from an earlier trial of endovascular therapy (IMS III), where all patients (in both the endovascular therapy and control groups) had received intravenous alteplase. At 12 months, the odds of functional independence following endovascular therapy were significantly improved for patients with severe strokes but showed no difference among patients with moderate stroke. However, the more recent trials included in the Goyal et al. analysis had substantially stronger early treatment effect with no heterogeneity across the spectrum of stroke severity. Two-year follow-up from the MR CLEAN trial has been reported in abstract form and demonstrated preserved treatment benefit with an 8% reduction in mortality that was not detected at 3 months.

LL	<b>Canada 2018 [8]</b>
Empfehlung	Patients eligible for intravenous alteplase as well as endovascular thrombectomy should also be treated with intravenous alteplase, which can be initiated while simultaneously preparing the angiography suite for endovascular thrombectomy
Stärke	[Evidence Level A].
Begründung	See above 2.2.1

SF 2.2.4: Führt bei Patienten >80 Jahren mit Hirninfarkt und einem proximalen Gefäßverschluss in der vorderen Zirkulation und den in Fragen 1 und 2 (Kapitel 2.2) beschriebenen Situationen eine



interventionelle Thrombektomie zusätzlich zur bestmöglichen medizinischen Therapie im Vergleich zu einer bestmöglichen medizinischen Therapie allein zu einem besseren funktionellen Ergebnis?

LL	<b>ESO EST [23], PICO 6</b>
Empfehlung	We recommend that patients aged 80 years or more with large vessel occlusion-related acute ischaemic stroke within 6 h of symptom onset should be treated with mechanical thrombectomy plus best medical management, including intravenous thrombolysis whenever indicated. Application of an upper age limit for mechanical thrombectomy is not justified.
Stärke	QoE Moderate, SoR strong
Begründung	Patients aged 80 years or older were allowed to be enrolled in seven RCTs of MT plus BMM vs. BMM alone, but with an upper age limit of 85 years in both REVASCAT and THERAPY [423, 439]. In an individual patient metaanalysis of five RCTs (HERMES Collaboration [269]), 198/1278 (15.5%) patients were aged 80 or more. A clear benefit of MT was observed for those patients, with an adjusted common OR for a better functional outcome of 3.68 (95% CI: 1.95–6.92) and a RR for functional independence (mRS ≤2) of 2.09 (95% CI: 1.03–4.25). There was no evidence of a lower benefit of MT in patients aged 80 years or older compared with younger patients.
Empfehlung	We suggest that patients aged 80 years or more with large vessel occlusion-related acute ischaemic stroke between 6 and 24 h from time last known well should be treated with mechanical thrombectomy plus best medical management if they meet the eligibility criteria of the DEFUSE-3 or DAWN trials
Stärke	QoE low, SoR weak
Begründung	One out of four patients enrolled in DAWN (6–24 h from time last known well) and DEFUSE-3 (6–16 h from time last known well) were 80 years or older [421, 422]. In DAWN, there was no evidence of a lower benefit of MT in patients aged 80 years or older (n=54) compared with younger patients. However, the inclusion criteria for patients aged 80 years or older were more stringent (infarct volume of less than 21 mL and no pre-stroke disability (mRS ≤1)). In that group, the unadjusted OR for functional independence with MT was 13.2 (95% CI: 1.51–114.8). <sup>9</sup> In DEFUSE-3, the upper age limit for inclusion was set at 90 years (with no pre-stroke dependence (mRS ≤2)). There was no evidence of a lower benefit of MT in patients aged 70 years or older compared with younger patients, but no interaction analysis was reported using 80 years as a threshold. Patients aged 80 or older (n=46) treated with MT had an unadjusted OR of 2.86 (95% CI: 0.72–11.37) for functional independence. We conducted a meta-analysis of DAWN and DEFUSE-3, in which MT was significantly associated with functional independence in patients aged 80 or older (OR=4.87; 95% CI: 1.15–20.71; I <sup>2</sup> =29%), but this association failed to reach statistical significance when RR was used as summary measure instead of OR.
Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	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.
Stärke	I-A
Begründung	The HERMES pooled patient-level data also showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years of age (cOR, 3.68 [95% CI, 1.95–6.92]) [269]. In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration [Safety and Efficacy of Solitaire Stent Thrombectomy–Individual

	<p>Patient Data Meta-Analysis of Randomized Trials]: SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT) showed that mechanical thrombectomy had a favorable effect over standard care in patients <math>\geq 80</math> years of age (3.46 [95% CI, 1.58–7.60]) [430].</p> <p>In a meta-analysis of 5 RCTs (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT), there was favorable effect with mechanical thrombectomy over standard care without heterogeneity of effect across patient age subgroups (for patients <math>&lt; 70</math> and <math>\geq 70</math> years of age: OR, 2.41 [95% CI, 1.51–3.84] and 2.26 [95% CI, 1.20–4.26], respectively) [440]. However, the number of patients in these trials who were <math>\geq 90</math> years of age was very small, and the benefit of mechanical thrombectomy over standard care in patients <math>\geq 90</math> years of age is not clear. As with any treatment decision in an elderly patient, consideration of comorbidities and risks should factor into the decision-making for mechanical thrombectomy.</p> <p>KOM: Das ist der gleiche Text wie bei 2.2.1, allerdings gibt es hier eine extra Begründung für das Alter</p>
--	--

SF 2.2.5: Führt bei Patienten mit Hirninfarkt und proximalem Gefäßverschluss eine vollständige Reperfusion (TICI 3) im Vergleich zu einer inkompletten Reperfusion zu einem besseren funktionellen Ergebnis?

LL	<b>ESO EST [23], PICO 11</b>
Empfehlung	For adults with large vessel occlusion-related acute ischaemic stroke, we recommend that interventionalists should attempt a TICI Grade 3 reperfusion, if achievable with reasonable safety.
Stärke	QoE low, SoR strong
Begründung	<p>The literature search did not identify RCTs comparing the effect of attempting a reperfusion result of a TICI Grade 3 vs. TICI Grade 2b. A dedicated systematic review and study-level meta-analysis included 14 studies with available follow-up [441]. Eleven of the 14 studies were retrospective observational studies, while one currently unpublished study examined different degrees of successful reperfusion in the HERMES collaboration of recent endovascular trials. TICI 3 and 2b were achieved in 1131 and 1248 patients, respectively.</p> <p>In the meta-analysis, TICI 3 reperfusion was associated with higher rates of functional independence (mRS <math>\leq 2</math>: OR=1.74, 95% CI: 1.44–2.10), also after including adjusted estimates. Due to the observational design of available studies, the QoE for the present recommendations was considered to be low</p>

Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome
Stärke	I-A
Begründung	<p>Mechanical thrombectomy aims to achieve reperfusion, not simply recanalization. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.<sup>196,197</sup> All recent endovascular trials used the mTICI grade 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to mTICI grade 2b/3 [269]. Earlier trials with less efficient devices showed lower recanalization rates, a factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%). The additional benefit of pursuing mTICI of grade 3 rather than grade 2b deserves further investigation.</p>
Empfehlung	Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be reasonable to achieve mTICI grade 2b/3 angiographic results.

Stärke	IIB, C-LD
Begründung	Intra-arterial fibrinolytic therapy played a limited role in the recent endovascular trials but was used as rescue therapy, not initial treatment. In MR CLEAN, the EVT method was at the discretion of operator, with 40 of 233 treated with alternative stent retrievers to Trevo and Solitaire or intra-arterial alteplase. Details are not available, but no patients were treated with intra-arterial alteplase alone. Twenty-four of 233 (10.3%) had treatment with a second modality. Treatment method had no impact on outcomes in this trial [442]. In THRACE, an intra-arterial lytic was used to a maximum dose of 0.3 mg/kg and allowed to establish goal reperfusion, only after mechanical thrombectomy was attempted. A mean dose of 8.8 mg was administered in 15 of 141 patients receiving mechanical thrombectomy (11%). There was no effect on outcomes compared with mechanical thrombectomy alone.

SF 2.2.6: Führt bei Patienten mit Hirninfarkt, die mit einer interventionellen Thrombektomie behandelt werden eine Behandlung in „conscious sedation“ im Vergleich zu einer Behandlung in Vollnarkose zu einem besseren funktionellen Ergebnis?

LL	<b>ESO EST [23], PICO 13</b>
Empfehlung	We cannot provide recommendations to use general anaesthesia or conscious sedation in patients undergoing mechanical thrombectomy, due to a low quality of evidence and conflicting results between three small single-centre randomised clinical trials and the best available observational evidence. Therefore, we recommend the enrolment of patients in multicentre randomised controlled trials addressing this question.
Stärke	QoE very low, SoR -
Begründung	<p>Three randomised trials of conscious sedation (CS) versus general anaesthesia (GA) in patients receiving MT for acute stroke were identified: SIESTA [443], AnSTROKE [444] and GOLIATH [445]. The trials recruited 128, 90 and 150 patients (N=368 in total), respectively. One hundred and eighty-five patients received CS and 183 patients received GA. The risk of bias in each trial was considered low. There was no blinding of patients or staff for treatment arm but the endpoint of interest for the present meta-analysis (mRS at 90 days) was assessed in a blinded fashion. There was a statistically non-significant trend in favour of GA with a RR for an independent outcome (mRS ≤2) of 0.74 (95% CI: 0.54–1.01, p=0.056; I<sup>2</sup>=37%) and a significant OR of 0.55 (95% CI: 0.34–0.89, p=0.01; I<sup>2</sup>=15%), both analyses showing low heterogeneity. Using the RR as summary measure, the absolute effect was 91 fewer (from 4 more to 162 fewer) patients being dependent or dead for 1000 patients treated. Despite the randomised design of these single centre trials, the overall QoE was downgraded to low, due to serious indirectness and imprecision.</p> <p>The HERMES collaboration performed a pooled analysis of individual patient data from seven RCTs of MT [446], in which the use of GA was either discouraged (ESCAPE and REVASCAT trials) or left at the discretion of the investigators. Two-hundred and thirty-six (30%) of 797 patients who had MT procedures were treated under GA. The protocol for GA or CS was left at the discretion of each investigator. Three-month functional outcome, evaluated in a blinded fashion, was significantly better for patients who did not receive GA versus those who received GA (adjusted common OR for better outcome: 1.53, 95% CI: 1.14–2.04). The proportion of patients with functional independence was also higher in patients treated without GA (50% vs. 40%, adjusted OR=1.65, 95% CI: 1.14–2.38). Still both outcomes were significantly better for patients treated with MT and GA versus patients in the BMM control arms [446]. We consider that this analysis represents the best available observational evidence for the present PICO question, because high-quality data were prospectively collected and monitored in large multicentre trials, allowing adjustment for several</p>

confounders. However, a major limitation of the HERMES data is the high likelihood of confounding by indication. It is likely that patients who underwent GA had more frequently a medically required GA rather than an 'elective' GA. The QoE for the HERMES collaboration analysis was therefore considered very low

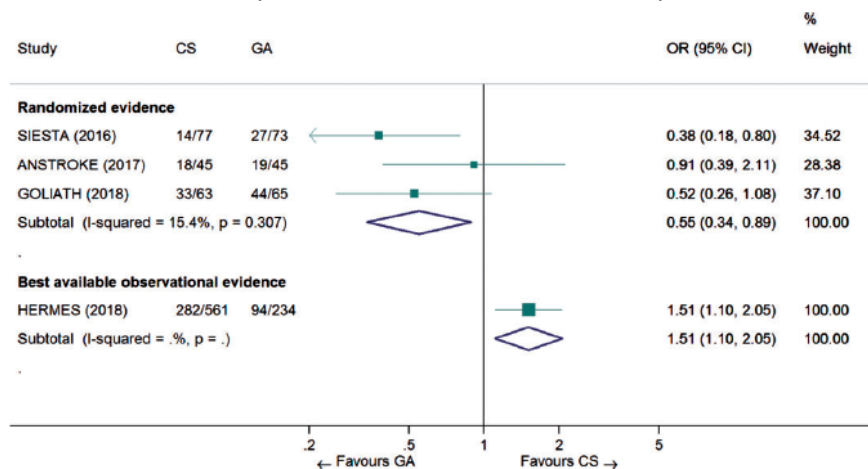


Figure 16. Unadjusted odds ratio for functional independence in patients undergoing conscious sedation (CS) vs. general anaesthesia (GA) for mechanical thrombectomy. Random-effects meta-analysis.

**Statement** We suggest that further randomised multicentric data with less bias should be generated. However, if inclusion of the patient in a randomised controlled trial is not possible, 11/11 experts suggest that local anaesthesia or conscious sedation may be favoured over general anaesthesia, if the patient is able to undergo mechanical thrombectomy without general anaesthesia. On the other hand, general anaesthesia does not need to be avoided if indicated. The decision for or against general anaesthesia should be made rapidly and delays to induction of general anaesthesia should be minimised. We suggest, that according to the three randomised controlled trials, a specialised neuro- anaesthesiological or neurocritical care team should perform the general anaesthesia procedure, whenever possible. Excessive blood pressure drops should be avoided. Adequate monitoring of vital parameters also of patients under conscious sedation or local anaesthesia is advised.

<b>Leitlinie</b>	<b>AHA 2018 [1] AHA 2019 [11]</b>
<b>Empfehlung</b>	It is reasonable to select an anesthetic technique during EVT for AIS on the basis of individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics.
<b>Stärke</b>	Ila, B-R
<b>Begründung</b>	Conscious sedation (CS) was the anesthetic modality widely used during endovascular procedures for acute stroke in the recent endovascular trials (90.9% of ESCAPE, 63% of SWIFT PRIME) with no clear positive or negative impact on outcome. In MR CLEAN, post hoc analysis showed a 51% (95% CI, 31–86) decrease in treatment effect with general anesthesia (GA) compared with CS [447]. In THRACE, 51 of 67 patients receiving GA and 43 of 69 patients receiving CS during acute stroke endovascular procedures achieved mTICI grade 2b/3 (P=0.059) with no impact on functional outcomes (35 of 67 patients with GA and 36 of 74 with CS had an mRS score of 0–2 at 90 days) [425]. Thirty-five of 67 patients with GA and 36 of 74 with CS during acute stroke endovascular procedures had mRS scores of 0 to 2 at 90 days.109 Although several retrospective studies suggest that GA for acute stroke endovascular procedures produces worsening of functional outcomes, the limited available prospective randomized data do not support this. Three small (≤150 participants each) single-center RCTs have compared GA with CS during acute stroke endovascular procedures. All failed to show superiority of GA for the primary end point (2 clinical,

	1 DW-MRI infarct growth), whereas 2 of the 3 showed better outcomes for GA for some of the many secondary clinical end points [443-445]. Until further data are available, either method of procedural sedation for acute stroke endovascular procedures is reasonable.
LL	<b>Canada 2018 [8]</b>
Empfehlung	For endovascular procedures, procedural sedation is generally preferred over general anaesthesia and intubation in most patients when necessary. a. General anaesthesia and intubation is appropriate if medically indicated (e.g. for airway compromise, respiratory distress, depressed level of consciousness, severe agitation, or any other indication determined by the treating physician) and in such cases, excessive and prolonged hypotension and time delays should be avoided
Stärke	[Evidence Level B]
Begründung	Evidence from several trials and meta-analyses have examined the outcomes of patients undergoing mechanical thrombectomy using general anesthesia versus conscious sedation. Generally, the findings indicate that conscious sedation is preferred. Using the results from 7 RCTs including MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, PISTE and THRACE, Campbell et al. [446] performed a patient-level meta-analysis comparing the outcomes of patients randomized to the mechanical thrombectomy groups who had received general anesthesia or non-general anesthesia. The odds of improved outcome using non-general anesthesia were significantly higher in ordinal analysis of mRS scores. The authors estimated for every 100 patients treated under general anesthesia (compared with non-general anesthesia), 18 patients would have worse functional outcome, including 10 who would not achieve functional independence. There was no increased risk of 90-day mortality associated with general anesthesia. The results from a meta-analysis including the results of 22 studies [448], also indicated that conscious sedation (i.e., non-general anesthesia) was associated with better outcomes. The odds of a favorable functional outcome at 90 days were significantly lower for patients who received general anesthesia (OR=0.58; 95% CI, 0.48–0.64), while the odds of 90-day mortality were significantly increased (OR=2.02, 95% CI 1.66–2.45). In contrast to these findings, Löwhagen Hendén et al. [444] reported no significant differences between groups (general anesthesia vs conscious sedation) in the proportion of patients with a good outcome at 3 months (42% vs. 40%, p=1.00), or in the distribution of mRS scores at 90 days. In the SIESTA trial [443], a significantly higher percentage of patients in the general anesthesia group had a good outcome (mRS 0-2) at 3 months (37% vs. 18.2%, p=0.01), compared with conscious sedation.

SF 2.2.7: Führt bei Patienten mit Hirninfarkt, die mit einer interventionellen Thrombektomie behandelt werden, eine Senkung des Blutdrucks unter einen bestimmten Schwellenwert im Vergleich zur Nichtanwendung eines Schwellenwertes zu einem besseren funktionellen Ergebnis?

LL	<b>ESO EST [23], PICO 14</b>
Empfehlung	We suggest to keep blood pressure below 180/105 mmHg during and 24 h after mechanical thrombectomy. No specific blood pressure-lowering drug can be recommended.
Stärke	QoE Very low, SoR weak
Empfehlung	During mechanical thrombectomy systolic blood pressure drops should be avoided.
Stärke	QoE very low; SoR strong
Begründung	Blood pressure (BP) targets, for patients with LVO-related acute ischaemic stroke undergoing MT, were not specifically evaluated in RCTs. Post-hoc analyses from MR CLEAN indicated a U-shaped correlation between baseline systolic blood pressure



	<p>(SBP) and functional outcome [449]. Both low and high baseline SBP were associated with three-month poor functional outcome, whereas higher SBP levels were associated with symptomatic intracranial haemorrhage (adjusted OR=1.25 for every 10 mmHg increment in SBP, 95% CI: 1.09–1.44).</p> <p>Retrospective studies suggest also an association between baseline SBP and mortality following a similar U-shaped correlation. During the first 24 hours following MT, each 10 mmHg increment in SBP is associated with increased three months poor functional outcome (OR=0.70; 95% CI: 0.56–0.87) and mortality (OR=1.49; 95% CI: 1.18–1.88) [450]. Retrospective data support also that achieving a BP goal below 160/90 mmHg is associated with decreased three-month mortality rates (OR=0.08; 95% CI: 0.01–0.54) [451]. Additionally, mean arterial BP falls during MT procedures, as low as 10%, were reported to be a risk factor for poor outcome in patients eligible to MT [452].</p> <p>Interpretation of these pieces of evidence should be done keeping in mind that studied populations are often heterogenous, mixing patients with different reperfusion statuses (i.e. complete vs. incomplete or no reperfusion) and medical histories (e.g. with or without history of hypertension). In fact, the impact of BP reduction may be different considering different patient characteristics.</p> <p>There is no strong evidence to support the use of a specific BP-lowering drug in the setting of MT.</p>
Statement	11/11 experts think that the degree of reperfusion should be taken into account in the choice of a blood pressure target after mechanical thrombectomy, with a lower blood pressure target in case of complete reperfusion.

Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	In patients who undergo mechanical thrombectomy, it is reasonable to maintain the BP at $\leq 180/105$ mm Hg during and for 24 hours after the procedure.
Stärke	Ila, B-NR
Empfehlung	In patients who undergo mechanical thrombectomy with successful reperfusion, it might be reasonable to maintain BP at a level $< 180/105$ mm Hg.
Stärke	IIf, B-NR
Begründung	There are very limited data to guide BP management during and after the procedure in patients who undergo mechanical thrombectomy. RCT data on optimal BP management approaches in this setting are not available. The vast majority of patients enrolled in $< 6$ -hour RCTs received IV alteplase, and the trial protocols stipulated management according to local guidelines with BP $\leq 180/105$ during and for 24 hours after the procedure for these participants. Two trial protocols provided additional recommendations. The ESCAPE protocol states that SBP $\geq 150$ mm Hg is probably useful in promoting and keeping collateral flow adequate while the artery remains occluded and that controlling BP once reperfusion has been achieved and aiming for a normal BP for that individual is sensible. Labetalol or an IV $\beta$ -blocker such as metoprolol in low doses is recommended [424]. The DAWN protocol recommends maintaining SBP $< 140$ mm Hg in the first 24 hours in subjects who are reperfused after mechanical thrombectomy (defined as achieving more than two-thirds MCA territory reperfusion) [421]. Further studies are needed to determine the optimal BP target during and after mechanical thrombectomy.

SF 2.2.8: Führt bei Patienten mit akutem Hirninfarkt und Verschluss von großen Gefäßen der hinteren Zirkulation (A. basilaris, Aa. vertebrales) eine interventionelle Thrombektomie zusätzlich zu einer bestmöglichen medizinischen Therapie im Vergleich zu einer alleinigen bestmöglichen medizinischen Therapie zu einem besseren funktionellen Ergebnis?

LL	<b>ESO EST [23]</b>
----	---------------------

Empfehlung	There is a consensus among the panel (11/11 votes) that in analogy to anterior circulation large vessel occlusion and with regard to the grim natural course of basilar artery occlusions, the therapeutic approach with intravenous thrombolysis plus mechanical thrombectomy should strongly be considered.
Stärke	EK
Begründung	For basilar artery stroke there are currently no published randomised trial results. An international prospective registry of patients with basilar artery occlusion did not suggest the superiority of intraarterial therapy over IVT [453]. However, this study was observational and the intra-arterial therapy group did not only correspond to patients treated with MT, but also to patients treated with intra-arterial thrombolysis or stenting. Furthermore, older generation MT devices were used in most instances.

LL	<b>NICE 2019 [24]</b>
Empfehlung	<p>Consider thrombectomy together with intravenous thrombolysis (where not contraindicated and within the licensed time window) as soon as possible for people last known to be well up to 24 hours previously (including wake-up strokes):</p> <ul style="list-style-type: none"> <li>- who have acute ischaemic stroke and confirmed occlusion of the proximal posterior circulation (that is, basilar or posterior cerebral artery) demonstrated by CTA or MRA and</li> <li>- if there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume</li> </ul>
Begründung	<p>No clinical- or cost-effectiveness evidence was identified for the population with posterior circulation stroke. The committee discussed that prognosis is usually very poor in basilar artery occlusion, with around an 80% mortality. As few as 2 to 5% of people with basilar artery occlusion make a full neurological recovery in the absence of interventions to achieve recanalisation or reperfusion. The committee agreed that the prevalent current practice is to consider intravenous thrombolysis and mechanical thrombectomy. Good outcomes can be achieved even up to 24 hours after stroke onset, which is important because diagnosis can be delayed in this population by a non-focal presentation, a reduced conscious level, or both.</p> <p>The main risk of thrombectomy and thrombolysis in this population is intervening when there is established disabling ischaemic brain injury. For example, if a person with basilar artery occlusion has irreversible bilateral damage to the pons, they may be left with locked-in-syndrome with complete face and body paralysis but clear consciousness, even if the basilar artery is opened. The committee agreed that it is standard practice to perform brain imaging and look for established tissue damage in the brain regions affected by the arterial occlusion, particularly in the brainstem, before intervening. This reduces the number of people surviving with severe neurological disability. Appropriate CT perfusion imaging or diffusion-weighted MRI sequences should be performed to demonstrate that there is salvageable brain tissue and to seek evidence of established injury to functionally critical areas of the posterior circulation.</p> <p>The outlook for this population without intervention is poor, but good outcomes can be achieved with intervention and there is supportive evidence from treating anterior stroke. Therefore, the committee agreed that thrombectomy, and thrombolysis within its licensed indications, should be considered for people with posterior circulation proximal occlusions and without evidence of irreversible infarction who were last known well up to 24 hours previously. This should be done as soon as possible after presentation because better outcomes are likely with earlier intervention.</p>

	No RCT or observational data were found for this stratum that met the protocol criteria. It is noted that the BEST[454] trial, a multicentre randomised outcome blinded trial on acute ischaemic stroke due to basilar artery occlusion, has a published protocol. The trial was due to have finished in March 2018 but no results have yet been published and therefore this trial is not included in the review. The trial authors were contacted for further information but no response was received.
LL	<b>RCP 2016 [10]</b>
Empfehlung	Patients with acute ischaemic stroke causing a disabling neurological deficit (a National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) may be considered for intraarterial clot extraction (using stent retriever and/or aspiration techniques, with prior intravenous thrombolysis unless contraindicated) beyond an onset-to-arterial puncture time of 5 hours if: – <b>the large artery occlusion is in the posterior circulation, in which case treatment up to 24 hours after onset may be appropriate</b>
Begründung	Goyal et al 2016 [269] (Anm: keine wirklich geeignete Referenz)
Leitlinie	<b>AHA 2018 [1] AHA 2019 [11]</b>
Empfehlung	Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.
Stärke	IIb, C-LD
Begründung	Reworded from 2015, dort aber keine Begründung enthalten
LL	<b>Australia 2017 [6]</b>
Empfehlung	In selected stroke patients with occlusion of the basilar artery, endovascular thrombectomy should be undertaken.
Stärke	Strong, LoE Moderate
Begründung	The BASICS study (Schonewille et al. 2009 [453]) assessed a prospective observational registry of patients with symptomatic and radiologically confirmed basilar artery occlusion. 619 patients were included from 48 international centres, receiving either antithrombotic treatment only (AT), primary intravenous thrombolysis (IVT) or intra-arterial therapy (IAT). The intra-arterial therapy available at that time included intra-arterial thrombolysis in 90% of patients and did not include the current generation of stent retriever and aspiration devices that have proven effective in the anterior circulation. Risk of poor outcome (modified Rankin scale score 4–6) was compared between treatments, adjusting for 6 baseline variables including age, National Institutes of Health Stroke Scale score, and time to treatment. Among patients with mild-to-moderate deficit, there were no significant differences between intravenous thrombolysis and antithrombotic treatment (relative risk 0.94, 95% CI 0.60 to 1.45) or intraarterial therapy and antithrombotic treatment (relative risk 1.29, 95% CI 0.97 to 1.72). Patients treated with intra-arterial therapy had higher risk of poor outcome than those treated with intravenous thrombolysis (relative risk 1.49, 95% CI 1.00–2.23). For patients with severe deficit, both intra-arterial therapy and intravenous thrombolysis had non-significantly lower risk of poor outcome than antithrombotic treatment, with no significant difference between IAT and IVT. 72% of patients treated with intraarterial therapy had partial or complete recanalisation of the basilar artery and this was associated with a significantly lower risk of poor outcome (relative risk 0.75, 95% CI 0.66 to 0.85). The study was non-randomised and patients receiving



	<p>intra-arterial therapy had greater baseline stroke severity, potentially increasing the rate of poor outcomes in the IAT group. The covariate adjusted analyses are also unlikely to have fully corrected or baseline differences between treatment groups. Kumar et al. (2015) [455] included 45 observational studies of reperfusion therapies for acute basilar artery occlusion in a metaanalysis. The included studies used either intravenous thrombolysis (IVT) or intra-arterial thrombolysis and/or endovascular therapy (IA/EVT). Recanalisation was associated with a lower risk of death or dependency overall (relative risk 0.67, 95% CI 0.63 to 0.72), although there were indications of significant publication bias. Estimates of relative risk were similar for IVT (0.68) and IA/EVT (0.67). Recanalisation rates were higher with IA/EVT (77%) than IVT (59%), although the review authors noted that a valid comparison between the treatment approaches was not possible given the study design, and that further evidence was required to determine the relative efficacy of the approaches. In the AUST study (Macleod et al. 2005 [455]), 16 patients with basilar or vertebral artery occlusion were randomised to treatment with intra-arterial urokinase or control, with both groups receiving anticoagulant therapy. The trial was halted early due to slow recruitment and urokinase being withdrawn from sale. There was no significant difference in death and disability at 6 months (odds ratio 0.14, 95% CI 0.02 to 1.43). Basilar artery occlusion has a dire prognosis untreated, with high mortality and disability. Meta-analysis of observational data demonstrated clear association between recanalisation and reduced death and dependency (Kumar et al. 2015 [456]). Safety was acceptable (Kumar et al. 2015 [456]). Although randomised trials are ongoing, the effect size of recanalisation and poor natural history justifies pursuit of endovascular thrombectomy (and intravenous thrombolysis in those presenting within 4.5 hours).</p>
--	---

LL	<b>Canada 2018 [8]</b>
Empfehlung	For large artery occlusions in the posterior circulation (e.g. basilar artery occlusion) the decision to treat with endovascular thrombectomy should be based on the potential benefits and risks of the treatment for the individual patient, and made by a physician with stroke expertise in consultation with the patient and/or substitute decision-makers.
Stärke	Evidence Level C

## 8.2.4. Synopse der externen Leitlinien zu Kapitel 3

Schlüsselfrage 3.1.1.: Verbessert bei erwachsenen Patienten ( $\leq 60$  Jahre) mit großem, raumfordernden Hirninfarkt im Stromgebiet der A. cerebri media rechts oder links (supratentoriell) eine Hemikraniectomie innerhalb von 48 Stunden nach Beginn der Schlaganfallsymptome zusätzlich zum konservativen intensivmedizinischen Management a) die Überlebensrate und b) das neurologische Funktionsniveau bei Überleben

Leitlinie	<b>AHA 2019 (Powers et al, 2019) [11]</b>
Empfehlung	Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness attributed to brain swelling as selection criteria.
Stärke	Ila   A
Begründung	Recommendation, COR, and LOE unchanged from 2014 Brain Swelling.
Empfehlung	In patients $\leq 60$ years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion is reasonable.
Stärke	Ila   A
Begründung	Recommendation revised from 2014 Brain Swelling. The pooled results of RCTs demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction in patients $< 60$ years of age, with an absolute risk reduction in mortality of 50% (95% CI, 34–66) at 12 months [457]. These findings were noted despite differences in the clinical trials in terms of inclusion and exclusion criteria, percent of MCA territory involved, and surgical timing [458, 459] At 12 months, moderate disability (ability to walk) or better (mRS score 2 or 3) was achieved in 43% (22 of 51) of the total surgical group and 55% (22 of 40) of survivors compared with 21% (9 of 42; $P=0.045$ ) of the total nonsurgical group and 75% (9 of 12; $P=0.318$ ) of the nonsurgical survivors. At 12 months, independence (mRS score 2) was achieved in 14% (7 of 51) of the total surgical group and 18% (7 of 40) of survivors compared with 2% (1 of 42) of the total nonsurgical group and 8% (1 of 12) of the nonsurgical survivors [457-461].
Leitlinie	<b>NCS GUIDELINES (2015) [3]</b>
Empfehlung	We recommend DHC as a potential therapy to improve survival after LHI regardless of patient age
Stärke	strong recommendation, high quality of evidence
Begründung	There is currently insufficient data to recommend against DHC in LHI patients based on hemispheric dominance
Empfehlung	To achieve the best neurological outcome, we recommend performing DHC within 24–48 h hours of symptom onset and prior to any herniation symptoms
Stärke	strong recommendation, moderate quality of evidence
Begründung	
Empfehlung	We recommend a size of 12 cm as an absolute minimum for DHC. Larger sizes of 14–16 cm seem to be associated with better outcomes
Stärke	strong recommendation, moderate quality of evidence
Begründung	
Empfehlung	We suggest that that lobectomy or duraplasty should only be considered as an individualized treatment option
Stärke	weak recommendation, low quality of evidence
Begründung	

Empfehlung	We suggest that the resection of the temporal muscle should only be considered as an individualized treatment option
Stärke	weak recommendation, low quality of evidence
Begründung	

Leitlinie	<b>Canada (2018) [462]</b>
Empfehlung	Hemicraniectomy should be considered in patients in the early stages of extensive (malignant) middle cerebral artery territory ischemic stroke as a life-saving measure for patients willing to accept a significant risk of living with a degree of disability that may leave them dependent on others for their activities of daily living
Stärke	Evidence Level A for patients age 18 – 60 years
Begründung	<p>The morbidity and mortality for the routine care of patients with malignant hemispheric strokes is higher than other stroke subgroups, and there is evidence to support that, in selected cases, hemicraniectomy may significantly reduce mortality but it could leave people with significant disability and possible dependence for activities of daily living. Consideration for hemicraniectomy must be individualized; there is a strong need for careful clinical consideration and patient selection. Decisions regarding hemicraniectomy involve several members of the multidisciplinary stroke team, including neurology, neurosurgery, intensive care and nursing through a collaborative and coordinated system of care. The benefit of decompressive hemicraniectomy (versus standard medical treatment) early following malignant middle cerebral artery (MCA) infarction in patients &lt;60 years has been evaluated in three major RCTs, all of which had comparable inclusion criteria and primary outcome measures (DESTINY 1, HAMLET and DECIMAL). In the first DESTINY trial [463], which randomized 32 patients to receive either surgical plus medical treatment or to conservative medical treatment only, there was a trend towards more favourable outcome (mRS 0-3) among patients in the surgical arm at 6 months (47% vs. 27%, (p=0.23; OR=2.44, 95% CI 0.55 to 10.83). Thirty-day survival was significantly higher among patients in the surgical arm (88% vs. 47%, OR=6.4, 95% CI 1.35 to 29.2). In the HAMLET trial [464], while there were no differences between groups in the proportion of patients who had experienced either a good (mRS 0-1) or poor (mRS 4-6) outcome at 1 year, surgery was associated with a 38% absolute risk reduction (95% CI 15 to 60, p=0.002) in 1-year mortality. Patients who received decompressive hemicraniectomy had significantly lower mean physical summary scores on the SF-36 Quality of Life scale, compared with those treated with medical care only (29 vs. 36; mean difference = -8, 95% CI -14 to -1, p = 0.02). No significant differences were found between the two treatment groups with respect to the mental summary score of the SF-36 score, mood, or the proportion of patients or carers dissatisfied with treatment. At 3 years follow-up, a significantly lower percentage of patients in the surgical group had died (26% vs. 63%, p=0.002) [465]. In the DECIMAL trial [466], while there was no difference in the number of patients with mRS scores of 0-3 between groups at 6 months, a significantly higher proportion of surgical patients had mRS scores of 0-4 and there was also a survival advantage among patients in the surgical arm. The results from all three trials were pooled in a recent Cochrane review [467], which reported that decompressive hemicraniectomy was associated with a significantly reduced risk of death at the end of follow-up (OR = 0.19, 95% CI 0.09 to 0.37) and the risk of death or severe disability (mRS &gt; 4) at 12 months (OR = 0.26, 95% CI 0.13 to 0.51). Surgery was also associated with a non-significant trend towards increased survival with severe disability (mRS of 4 or 5; OR = 2.45, 95% CI 0.92 to 6.55). No significance between group differences were found for the combined outcome death or moderate disability (mRS 4-6) at the end of follow-up (OR = 0.56, 95% CI 0.27 to 1.15). In a more recent systematic review, which</p>

	included the results from 7 trials, [468], similar findings were reported. The odds of a favourable outcome (mRS 0-3) and survival at 6-12 months were significantly increased for patients in the hemicraniectomy group (OR=2.04, 95% CI 1.03-4.02, p=0.04 and OR=5.56, 95% CI 3.40-9.08, p<0.001, respectively).
Empfehlung	If a potential patient's location is initially outside a comprehensive stroke centre, the patient should have expedited transfer to a tertiary or quaternary centre where advanced stroke care and neurosurgical services are available
Stärke	[Evidence Level C].
Empfehlung	Initiate a discussion with patient, family members and legal decision-maker regarding a potential hemicraniectomy a. Key issues to be discussed with the patient and/or alternate decision-makers include: stroke diagnosis and prognosis if untreated, the risks of surgery, the possible and likely outcomes following surgery including the odds of living with severe disability, and the patient's previously expressed wishes concerning treatment in the event of catastrophic illness and probability of living with severe handicap. b. The discussion with the patient and decision-makers should state more clearly that there is a survival benefit, but an uncertain impact on quality of life and disability. Furthermore that even with treatment, a good outcome (MRS 0-2) is rare.
Stärke	Evidence Level C

Leitlinie	<b>RCP (2016) [10]</b>
Empfehlung	Patients with middle cerebral artery (MCA) infarction who meet the criteria below should be considered for decompressive hemicraniectomy. Patients should be referred to neurosurgery within 24 hours of stroke onset and treated within 48 hours of stroke onset: – pre-stroke modified Rankin Scale score of less than 2; – clinical deficits indicating infarction in the territory of the MCA; – National Institutes of Health Stroke Scale (NIHSS) score of more than 15; – a decrease in the level of consciousness to a score of 1 or more on item 1a of the NIHSS; – signs on CT of an infarct of at least 50% of the MCA territory with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cubic centimetres on diffusion-weighted MRI.
Stärke	
Begründung	The DESTINY II trial of decompressive hemicraniectomy for older patients with severe space-occupying MCA territory infarction has shown a substantial survival benefit for patients over the age of 60 years [469] akin to that seen in young patients [467].

Schlüsselfrage 3.1.2.: Bei erwachsenen Patienten (>60 Jahre) mit großem, raumfordernden Hirninfarkt im Stromgebiet der A. cerebri media rechts oder links (supratentoriell) verbessert eine Hemikraniektomie innerhalb von 48 Stunden nach Beginn der Schlaganfallsymptome zusätzlich zum konservativen intensivmedizinischen Management a) die Überlebensrate und b) das neurologische Funktionsniveau bei Überleben.

Leitlinie	<b>AHA 2019 (Powers et al, 2019) [11]</b>
Empfehlung	In patients >60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion may be considered.
Stärke	IIb   B-R
Begründung	Recommendation revised from 2014 Brain Swelling.

	<p>There is evidence that patients &gt;60 years of age can have a reduction in mortality of ≈50% (76% in the nonsurgical group versus 42% in the surgical group in DESTINY [Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery] II) when decompressive craniectomy for malignant MCA infarction is performed within 48 hours of stroke onset [458, 459] [469-473]. However, functional outcomes in elderly patients seem to be worse than those in patients &lt;60 years of age. At 12 months, moderate disability (able to walk; mRS score 3) was achieved in 6% (3 of 47) of the total surgical group and 11% (3 of 27) of survivors compared with 5% (3 of 22) of the total nonsurgical group and 20% (3 of 15) of the nonsurgical survivors. At 12 months, independence (mRS score ≤2) was not achieved by any survivors in either group.</p>
--	--

<b>Leitlinie</b>	<b>NCS GUIDELINES (2015) [3]</b>
<b>Empfehlung</b>	In patients older than 60 years, we recommend taking in consideration patients and family wishes, since in this age group, DHC can reduce mortality rate but with a higher likelihood of being severely disabled
<b>Stärke</b>	strong recommendation, moderate quality of evidence
<b>Begründung</b>	

<b>Leitlinie</b>	<b>Canada (2018) [462]</b>
<b>Empfehlung</b>	Hemicraniectomy should be considered in patients in the early stages of extensive (malignant) middle cerebral artery territory ischemic stroke as a life-saving measure for patients willing to accept a significant risk of living with a degree of disability that may leave them dependent on others for their activities of daily living
<b>Stärke</b>	Evidence Level B for patients 60 – 80 years
<b>Begründung</b>	<p>The upper age limit for decompressive hemicraniectomy in malignant MCA infarct has been a focus of debate, given that the evidence is conflicting. Using data from 276 patients, obtained from 17 case series McKenna et al. [474] reported that patients 60 years of age and older who underwent surgery had a higher mortality rate and poorer outcome compared with younger patients. In the DECIMAL trial's surgical group, younger age correlated with better outcomes at 6 months (<math>r = 0.64</math>, <math>p &lt; 0.01</math>) [466]. A recent retrospective study investigating decompressive hemicraniectomy in older adults compared the outcomes of individuals aged between 61-70 years and those &gt; 70 years of age [475]. The mortality rate was significantly higher among those in the older cohort (60% vs. 0%, <math>p = 0.01</math>). However, there is also evidence suggesting that older patients also benefit from surgery. Zhao et al [470] randomized 47 patients, aged 18-80 years, 29 of whom were &gt;60-80 years. Decompressive hemicraniectomy within 48 hours of stroke onset was associated with a significant overall reduction in mortality at both 6 (12.5% vs. 60.9 %, <math>p = 0.001</math>) and 12-month follow-up (16.7% vs. 69.6 %, <math>p &lt; 0.001</math>). In the subgroup of older patients, significantly fewer patients in the surgical arm had an unfavourable outcome (mRS 5–6) at 6 months (31.2% vs. 92.3%, ARR=61.1%; 95 % CI 34.1 to 88.0) with similar results reported at one year (ARR = 62.5%; 95% CI 38.8 to 86). Authors from the HAMLET trial reported that there was a trend towards greater benefit of surgery in patients between the ages of 51–60 compared with patients 50 years of age or younger [464]. Most recently, in the DESTINY II trial [469], 112 patients ≥61 years admitted with unilateral MCA infarction were randomized to receive conservative treatment or early surgical intervention. A significantly higher proportion of patients in the surgical group were alive and living without severe disability at 6 months (38% vs.18%, OR=2.91, 95% CI 1.06-7.49, <math>p=0.04</math>). Although no patients in either the surgical or medical care groups had good outcome (mRS score of 0-2) at 6 or 12 months, a significantly higher percentage of</p>

	patients in the surgical group had mRS scores of 3-4 (38% vs. 16%) and a significantly lower percentage had mRS scores of 5-6 (62% vs. 84%).
<b>Leitlinie</b>	<b>RCP (2016) [10]</b>
<b>Empfehlung</b>	Decisions to undertake major life-saving surgery need to be carefully considered on an individual basis, but patients should not be excluded from treatment by age alone.
<b>Stärke</b>	
<b>Begründung</b>	

Schlüsselfrage 3.1.3: Bei erwachsenen Patienten mit großem, raumfordernden Kleinhirnfarkt und klinischer Verschlechterung verbessert eine externe Ventrikeldrainage und eine subokzipitale Kraniotomie mit Erweiterung der Dura zusätzlich zum maximal konservativen Management a) die Überlebensrate und b) das neurologische Funktionsniveau bei Überleben

<b>Leitlinie</b>	<b>AHA 2019 (Powers et al, 2019) [11]</b>
<b>Empfehlung</b>	Ventriculostomy is recommended in the treatment of obstructive hydrocephalus after cerebellar infarction. Concomitant or subsequent decompressive craniectomy may or may not be necessary on the basis of factors such as the size of the infarction, neurological condition, degree of brainstem compression, and effectiveness of medical management.
<b>Stärke</b>	I   C-LD
<b>Begründung</b>	Recommendation revised from 2014 Brain Swelling. Ventriculostomy is a well-recognized effective treatment for the management of acute obstructive hydrocephalus and is often effective in isolation in relieving symptoms, even among patients with acute cerebellar infarction. <sup>289,296</sup> Thus, in patients who develop symptoms of obstructive hydrocephalus from cerebellar infarction, emergency ventriculostomy is a reasonable first step in the surgical management paradigm. If cerebrospinal fluid diversion by ventriculostomy fails to improve neurological function, decompressive suboccipital craniectomy should be performed [461, 476, 477]. Although a risk of upward herniation exists with ventriculostomy alone, it can be minimized with conservative cerebrospinal fluid drainage or subsequent decompression if the cerebellar infarction causes significant swelling and mass effect [461, 477].
<b>Empfehlung</b>	Decompressive suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarction causing neurological deterioration from brainstem compression despite maximal medical therapy. When deemed safe and indicated, obstructive hydrocephalus should be treated concurrently with ventriculostomy.
<b>Stärke</b>	I   B-NR
<b>Begründung</b>	Recommendation revised from 2014 Brain Swelling. The data support decompressive cerebellar craniectomy for the management of acute ischemic cerebellar stroke with mass effect [461, 476, 477]. This surgery is indicated as a therapeutic intervention in cases of neurological deterioration caused by swelling as a result of cerebellar infarction that cannot be otherwise managed with medical therapy or ventriculostomy in the setting of obstructive hydrocephalus [461, 477].
<b>Empfehlung</b>	When considering decompressive suboccipital craniectomy for cerebellar infarction, it may be reasonable to inform family members that the outcome after cerebellar infarct can be good after the surgery.
<b>Stärke</b>	IIb   C-LD

Begründung	Recommendation and COR unchanged from 2014 Brain Swelling. Wording revised and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
------------	---

Leitlinie	<b>Canada (2018) [462]</b>
Empfehlung	Posterior fossa decompression can be considered in selected patients with significant cerebellar stroke with evidence of mass effect and / or hydrocephalus
Stärke	[Evidence Level C]
Begründung	

Schlüsselfrage 3.2.: Bei erwachsenen Patienten mit akutem Hirninfarkt verbessert eine therapeutische Hypothermie zusätzlich zur Standardtherapie a) die Überlebensrate und b) das neurologische Funktionsniveau bei Überleben.

Leitlinie	<b>AHA 2019 (Powers et al, 2019) [11]</b>
Empfehlung	In patients with AIS, the benefit of treatment with induced hypothermia is uncertain.
Stärke	I   C-LD
Begründung	Recommendation revised from 2013 AIS Guidelines. To date, studies of hypothermia in AIS show no benefit in functional outcome and suggest that induction of hypothermia increases the risk of infection, including pneumonia [478-480]. These studies use a variety of methods to induce hypothermia and are small/underpowered, meaning that a benefit for hypothermia in AIS cannot be definitively excluded. A large phase III trial of hypothermia in AIS is ongoing.

Leitlinie	<b>NCS Guidelines (2015) [3]</b>
Empfehlung	We suggest considering hypothermia as a treatment option in patients who are not eligible for surgical intervention
Stärke	weak recommendation, low quality of evidence
Begründung	
Empfehlung	If hypothermia is considered, we suggest a target temperature of 33–36 °C for duration of 24–72 h
Stärke	weak recommendation, low quality of evidence
Begründung	

Leitlinie	<b>ESO Fever (2015) [5]</b>
Empfehlung	In patients with acute ischemic stroke, we do not recommend induction of hypothermia as a means to improve functional outcome and/or survival.
Stärke	QoE very low, SoR weak against
Begründung	Favorable functional outcome was assessed with the mRS at one- to three-months in five studies, and defined as $\leq 1$ in two and $\leq 2$ in three. The analysis included 227 patients and showed no statistically significant difference in favorable functional outcome between patients treated with induction of hypothermia and controls (RR: 0.92, 95% CI: 0.63–1.33), with no sign of heterogeneity (I <sup>2</sup> :0%). The quality of evidence was graded as low because of serious risk of bias and serious imprecision. The funnel plot of the included RCTs is presented in Fig. S6. Mortality was assessed at one- to three-months in all six trials (20–25). The analysis included 252 patients, and there was no statistically significant difference in mortality between patients receiving hypothermia and controls (RR: 1.20, 95% CI: 0.65– 2.22), with no sign of heterogeneity (I <sup>2</sup> : 0%). The quality of evidence was graded as very low because of the serious risk of bias and very serious imprecision

Kommentar	Bezieht sich nicht speziell auf Patienten mit raumfordernem Infarkt, wird daher nicht zur Empfehlungsformulierung verwendet.
-----------	--

Schlüsselfrage 3.3.: Bei erwachsenen Patienten mit akutem Hirninfarkt und einer durch Hirnödem bedingten klinischen Verschlechterung verbessert die intravenöse Gabe von osmotisch wirksamen Arzneimitteln zusätzlich zur Standardtherapie a) die Überlebensrate und b) das neurologische Funktionsniveau bei Überleben

Leitlinie	<b>AHA 2019 (Powers et al, 2019) [11]</b>
Empfehlung	Use of osmotic therapy for patients with clinical deterioration from brain swelling associated with cerebral infarction is reasonable.
Stärke	Ila   C-LD
Begründung	Recommendation reworded for clarity from 2014 Brain Swelling. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Empfehlung	We suggest using osmolar gap instead of serum osmolality to guide mannitol dosing and treatment duration
Stärke	weak recommendation, low quality of evidence

Leitlinie	<b>NCS GUIDELINES (2015) [3]</b>
Empfehlung	We recommend using mannitol and hypertonic saline for reducing brain edema and tissue shifts in LHI only when there is clinical evidence of cerebral edema
Stärke	strong recommendation, moderate quality of evidence
Begründung	
Empfehlung	We suggest using osmolar gap instead of serum osmolality to guide mannitol dosing and treatment duration
Stärke	weak recommendation, low quality of evidence
Begründung	
Empfehlung	Hypertonic saline dosing should be guided by serum osmolality and serum sodium
Stärke	Strong recommendation, moderate quality of evidence
Begründung	
Empfehlung	We recommend using mannitol cautiously in patients with acute renal impairment
Stärke	strong recommendation, moderate quality of evidence
Begründung	
Empfehlung	We recommend using hypertonic saline cautiously in patients with volume overload states (i.e., heart failure, cirrhosis, etc.,) since this agent will expand intravascular volume
Stärke	strong recommendation, high quality of evidence
Begründung	

Leitlinie	<b>Canada (2018) [462]</b>
Empfehlung	Patients with suspected elevation in intracranial pressure may be managed according to institutional protocols (e.g, administration of hyperosmolar therapy, head of bed elevation)
Stärke	[Evidence Level C]
Begründung	



### 8.3. SUCHALGORITHMEN UND ERGEBNIS DER SYSTEMATISCHEN SUCHE NACH ÜBERSICHTSARBEITEN ODER EINZELSTUDIEN

SF 1.1.13: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA ein systematisches Delir-Screening und ggfs. Delir-Behandlung im Vergleich zur konventionellen Therapie das funktionelle Outcome?

Datum der Evidenzgewinnung 07.09.2020

#### MedLine

A) Suchterm: ((delir\* or confus\*) AND (thera\* or preven\* or screen\*)) AND (stroke)

Filter: systematic review

Treffer: 28

Ausschluss nach Beurteilung von Titel/Abstract: 23

Verblieben: 3

**#01**: Mansutti I, Saiani L, Palese A. Detecting delirium in patients with acute stroke: a systematic review of test accuracy. BMC Neurol. 2019 Dec 2;19(1):310. doi: 10.1186/s12883-019-1547-4. PMID: 31791260; PMCID: PMC6889202.

**#02**: Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: a systematic review and meta-analysis. Stroke. 2012 Mar;43(3):645-9. doi: 10.1161/STROKEAHA.111.643726. Epub 2012 Jan 19. PMID: 22267831.

**#03**: Carin-Levy G, Mead GE, Nicol K, Rush R, van Wijck F. Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. J Neurol. 2012 Aug;259(8):1590-9. doi: 10.1007/s00415-011-6383-4. Epub 2012 Jan 11. PMID: 22234842.

Eine weitere Übersichtsarbeit wurde bei der Textbewertung gefunden

**#04**: Shaw RC, Walker G, Elliott E, Quinn TJ. Occurrence Rate of Delirium in Acute Stroke Settings: Systematic Review and Meta-Analysis. Stroke. 2019 Nov;50(11):3028-3036. doi: 10.1161/STROKEAHA.119.025015. Epub 2019 Sep 26. PMID: 31554501.

B) Suchterm: ((delir\* or confus\*) AND (thera\* or preven\* or screen\*)) AND (stroke) and (random\*)

Filter: ./.

Treffer: 108

Ausschluss nach Beurteilung von Titel/Abstract: 107

Verblieben: 1

**#05**: Rice KL, Bennett MJ, Berger L, Jennings B, Eckhardt L, Fabré-LaCoste N, Houghton D, Vidal G, Gropen T, Diggs E, Barry E, St John J, Mathew S, Egger A, Ryan S, Egger R, Galarneau D, Gaines K, Ely EW. A Pilot Randomized Controlled Trial of the Feasibility of a Multicomponent Delirium Prevention Intervention Versus Usual Care in Acute Stroke. J Cardiovasc Nurs. 2017 Jan/Feb;32(1):E1-E10. doi: 10.1097/JCN.0000000000000356. PMID: 27306854.

C) Suchterm: (delir\* or confus\*) AND (screen\*) AND (stroke)

Filter: ./.

Treffer: 112

Ausschluss nach Beurteilung von Titel/Abstract und Duplikation zu A) und B): 104

Verblieben: 8

**#06**: Boßelmann C, Zurluh J, Stefanou MI, Stadler V, Weber Y, Lerche H, Poli S, Ziemann U, Mengel A. Delirium Screening in Aphasic Patients With the Intensive Care Delirium Screening Checklist (ICDSC): A Prospective Cohort Study. Front Neurol. 2019 Nov 12;10:1198. doi: 10.3389/fneur.2019.01198. PMID: 31781026; PMCID: PMC6861445.

**#07:** Klimiec E, Dziedzic T, Kowalska K, Szyper A, Pera J, Potoczek P, Slowik A, Klimkowicz-Mrowiec A. PROspective Observational POLish Study on post-stroke delirium (PROPOLIS): methodology of hospital-based cohort study on delirium prevalence, predictors and diagnostic tools. BMC Neurol. 2015 Jun 19;15:94. doi: 10.1186/s12883-015-0351-z. PMID: 26084453; PMCID: PMC4472262.

**#08:** Infante MT, Pardini M, Balestrino M, Finocchi C, Malfatto L, Bellelli G, Mancardi GL, Gandolfo C, Serrati C. Delirium in the acute phase after stroke: comparison between methods of detection. Neurol Sci. 2017 Jun;38(6):1101-1104. doi: 10.1007/s10072-017-2832-x. Epub 2017 Feb 1. PMID: 28150101.

**#09:** von Hofen-Hohloch J, Awissus C, Fischer MM, Michalski D, Rumpf JJ, Classen J. Delirium Screening in Neurocritical Care and Stroke Unit Patients: A Pilot Study on the Influence of Neurological Deficits on CAM-ICU and ICDSC Outcome. Neurocrit Care. 2020 Mar 20. doi: 10.1007/s12028-020-00938-y. Epub ahead of print. PMID: 32198728.

**#10:** Mitasova A, Kostalova M, Bednarik J, Michalcakova R, Kasperek T, Balabanova P, Dusek L, Vohanka S, Ely EW. Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM- ICU). Crit Care Med. 2012 Feb;40(2):484-90. doi: 10.1097/CCM.0b013e318232da12. PMID: 22001583.

**#11:** Lees R, Corbet S, Johnston C, Moffitt E, Shaw G, Quinn TJ. Test accuracy of short screening tests for diagnosis of delirium or cognitive impairment in an acute stroke unit setting. Stroke. 2013 Nov;44(11):3078-83. doi: 10.1161/STROKEAHA.113.001724. Epub 2013 Aug 29. PMID: 23988641.

**#12:** Carin-Levy G, Nicol K, van Wijck F, Mead G, McVittie C. Identifying and Responding to Delirium in Acute Stroke: Clinical Team Members' Understandings. Qual Health Res. 2020 Sep 24;1049732320959295. doi: 10.1177/1049732320959295. Epub ahead of print. PMID: 32969764.

**#13:** Nakamizo T, Kanda T, Kudo Y, Sugawara E, Hashimoto E, Okazaki A, Usuda M, Nagai T, Hara H, Johkura K. Development of a clinical score, PANDA, to predict delirium in stroke care unit. J Neurol Sci. 2020 Aug 15;415:116956. doi: 10.1016/j.jns.2020.116956. Epub 2020 May 30. PMID: 32505010.

#### Cochrane library

Suchterm: stroke in Title Abstract Keyword AND delirium in Title Abstract Keyword

Treffer: 1 („Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults“)

Bewertung: Nach Beurteilung von Title und Abstract als nicht passend bewertet

#### AWMF-Leitlinien

Stichwortsuche Delir und Schlaganfall

Treffer: 46

Ausschluss nach Beurteilung des Titels: 45

Verblieben: S3-Leitlinie Analgesie, Sedierung und Delirmanagement in der Intensivmedizin (Registrierungsnummer: 001-012)

#### Bewertung:

Die S3-Leitlinie kann verwendet werden, insbes. da es um eine Deutsche LL handelt.

<b>Studie (review)</b>	<b>#01:</b> Mansutti I, Saiani L, Palese A. Detecting delirium in patients with acute stroke: a systematic review of test accuracy. BMC Neurol. 2019 Dec 2;19(1):310
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	
<b>I. Beschreibung des Reviews</b>	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Systematische Literatursuche in mehreren Datenbanken. (a) diagnostic test accuracy studies; (b) evaluating tools detecting delirium among patients with acute stroke; (c) written in English; and (d) published up to September 2018.	

2. Welche Interventionen sind betrachtet/untersucht worden?  
 Insgesamt wurden vier Studien mit variabler Qualität gefunden, die hauptsächlich zwei Werkzeuge beschrieben: (1) der 4-Assessment Test for delirium (4AT), der eine Sensitivität von 90,2 bis 100% und eine Spezifität von 64,5 bis 86% aufweist; und (2) der Confusion Assessment Method-Intensive Care Unit (CAM-ICU) mit einer Sensitivität von 76% (95%CI 55-91) und einer Spezifität von 98% (95%CI 93-100). Weitere Instrumente wurden untersucht:  
 Abbreviated Mental Test-10,  
 Abbreviated Mental Test short form,  
 Clock Drawing Test,  
 Cognitive Examination abgeleitet von der NIHSS und der GCS  
 Die vom multidisziplinären Team beantwortete Frage - "Hat dieser Patient kognitive Probleme" – wurde ebenfalls einem Validierungsprozess unterzogen

3. Welche Zielkriterien (Endpunkte) wurden bestimmt? The included studies were assessed in their quality by using the Quality Assessment of Diagnostic Accuracy Studies-2

4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.

5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? n.a.

II. Interne Validität	Ja	Nein
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
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?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	

**Gesamtbeurteilung** ++

**III. Ergebnisse**

**Table 3** Delirium detection tools emerged from the included studies: comparison in the diagnostic test accuracy properties documented

Tool	Author, year (reference)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)	Internal consistency (Cronbach $\alpha$ )	Accuracy % (95% CI)	Interrater reliability (K)	Likelihood ratio	AUC	Gold standard considered
4AT	Infante et al., 2017 [20]	90.2 <sup>b</sup>	64.5 <sup>b</sup>							0.82 <sup>d</sup>	DSM-V criteria
		96.4 <sup>c</sup>	76.7 <sup>c</sup>							0.88 <sup>b</sup>	
	Kutlubaeve et al., 2016 [21]	93	86	86	85.6	0.80				0.89	DSM-IV criteria
	Lees et al., 2013 [22]	100 (74–100)	82 (72–89)	43	100						
CAM-ICU		100 <sup>a</sup> (72–100)	83 <sup>a</sup> (73–88)								CAM
	Mitasova et al., 2012 [8]	76 (55–91)	98 (93–100)	91 (70–99)	94 (88–98)		94 <sup>d</sup> (88–97)	0.94 (0.83–1.00)	0.47(0.27–0.83)		DSM-IV criteria
AMT-10	Lees et al., 2013 [22]	75 (43–95)	61 (51–71)	21	95						CAM
AMT-4	Lees et al., 2013 [22]	83 (52–98)	61 (51–71)	23	96						CAM
CDT	Lees et al., 2013 [22]	67 (22–96)	38 (28–49)	7	95						CAM
COG4	Lees et al., 2013 [22]	70 (35–93)	44 (35–55)	13	92						CAM
GCS	Lees et al., 2013 [22]	17 (2–48)	81 (71–88)	11	88						CAM
"Does this patient has cognitive issues?" <sup>e</sup>	Lees et al., 2013 [22]	58 (28–85)	85 (76–92)	35	93						CAM

<sup>a</sup>subgroup analysis, excluding patients with severe aphasia (n = 7; over 111 patients included); <sup>b</sup>at the admission; <sup>c</sup>after 7 days; <sup>d</sup>considered as ratio: true-positives + true-negatives/true positives + false-positives + true-negatives + false-negatives; <sup>e</sup>the single question was asked to healthcare professionals of the multidisciplinary team  
 4AT: 4-Assessment Test for delirium, AMT: Abbreviated Mental Test, AUC Area Under the Curve, CAM: Confusion Assessment Method, CAM-ICU: Confusion Assessment Method for the Intensive Care Unit, CDT: Clock Drawing Test, CI: Confidence of Interval, COG4: cognitive examination derived from National Institutes of Health Stroke Scale (NIHSS), DSM: Diagnostic and Statistical Manual of mental disorders, GCS: Glasgow Coma Scale.

**IV. Ableitbare Empfehlung**

Bisher wurden einige wenige Studien veröffentlicht, um die Genauigkeit von Werkzeugen in ihrer Fähigkeit zu testen das Delirium nach einem Schlaganfall zu erkennen; von den verfügbaren Instrumenten sind die 4AT und die CAM-ICU am häufigsten untersucht worden.

Die Forschung hat gerade erst damit begonnen, die Herausforderung der Erkennung und sinnvollen Bewertung neu erworbener Delire bei Schlaganfallpatienten. Daher sind mehr Studien erforderlich, um das Wissen zu verbessern und eine robuste Auswahl des nützlichsten Instruments, das in dieser Population eingesetzt werden kann

<b>Studie (review)</b>	#02: Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in acute stroke: a systematic review and meta-analysis. Stroke. 2012 Mar;43(3):645-9.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? following inclusion criteria: (1) the study was designed as an observational study or case series; (2) stroke is defined as ischemic, hemorrhagic, transient ischemic attack, or subarachnoid hemorrhage (3) delirium was either the presenting symptom or developed within 10 days of admission (acute phase of stroke); (4) reported the number of affected patients in each group; (5) reported at least 1 outcome of interest; and (6) the study was written in English		
2. Welche Interventionen sind betrachtet/untersucht worden? keine		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Delirinzidenz, Mortalität, Disability, length of stay, Hospitalisierung		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Alter zwischen 57 und 80 J.		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Bei den meisten Studien Stroke Unit		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
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?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		
Systematic review zur Bestimmung des Outcomes von Schlaganfallpatienten mit Delir, geht aber weder auf Diagnose noch Therapie ein. Von 78 in Frage kommenden Studien erfüllten 10 Studien (n=2004 Patienten) die Einschlusskriterien. Schlaganfall-Patienten mit Delir hatte eine höhere stationäre Sterblichkeit (OR, 4,71; 95% CI, 1,85-11,96) und eine höhere Sterblichkeit nach 12 Monaten (OR, 4,91; 95% CI, 3,18 -7,6) im Vergleich zu nicht-deliranten Patienten. Patienten mit Delirium neigten auch dazu, länger im Krankenhaus zu bleiben, im Vergleich zu denen ohne Delir (mittlerer Unterschied, 9,39 Tage; 95% KI, 6,67-12,11) und wurden mit größerer Wahrscheinlichkeit in ein Pflegeheim oder andere Einrichtungen entlassen (OR, 3,39; 95% CI, 2,21-5,21).		
<b>IV. Ableitbare Empfehlung</b>		
Schlaganfallpatienten mit Entwicklung eines Delirs haben ungünstige Ergebnisse, insbesondere eine höhere Mortalität, längere Krankenhausaufenthalte und ein höheres Maß an Abhängigkeit nach der Entlassung. Früherkennung und Prävention von Delirium kann die Ergebnisse bei Schlaganfallpatienten verbessern		

<b>Studie (review)</b>	#03: Carin-Levy G, Mead GE, Nicol K, Rush R, van Wijck F. Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. J Neurol. 2012 Aug;259(8):1590-9.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? We included cross-sectional studies, longitudinal studies, cohort studies case control studies and case series		
2. Welche Interventionen sind betrachtet/untersucht worden? The incidence of delirium, the patient-related factors associated with its development, and the association between developing delirium and outcome		
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 Studiensumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	n.a.	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
<p>The incidence of delirium in acute stroke ranged from 2.3–66%, with our meta-analysis random effects approach placing the rate at 26% (95% CI 19–33%). Of the 11 studies reporting risk factors for delirium, increased age, aphasia, neglect or dysphagia, visual disturbance and elevated cortisol levels were associated with the development of delirium in at least one study.</p> <p>The outcomes associated with the condition are increased morbidity and mortality. Delirium is found in around 26% of stroke patients. Difference in diagnostic and screening procedures could explain the wide variation in frequency of delirium. There are a number of factors that may predict the development of the condition.</p>		
<b>IV. Ableitbare Empfehlung</b>		
älterer review der keine Kennzahlen zu einzelnen Skalen beinhaltet, aber eine Übersicht über mögliche Risikofaktoren gibt		

<b>Studie (review)</b>	#04: Shaw RC, Walker G, Elliott E, Quinn TJ. Occurrence Rate of Delirium in Acute Stroke Settings: Systematic Review and Meta-Analysis. Stroke. 2019 Nov;50(11):3028-3036.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? We searched multiple cross-disciplinary electronic databases using a prespecified search strategy, complemented by hand searching.		
2. Welche Interventionen sind betrachtet/untersucht worden? keine		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? We compared delirium occurrence using random-effects models to describe summary estimates. We assessed risk of bias using the Newcastle-Ottawa tool, incorporating this in sensitivity analyses. We performed subgroup analyses for delirium diagnostic method (confusion assessment method scoring, clinical diagnosis, other), duration and timing of delirium assessment (>1 or <1 week), and performed meta-regression based on the year of publication.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Schlaganfall in den letzten 6 Wochen, 41 bis 1072 Patienten, Alter 57-79 Jahre, 30-67% Frauen,		
5. Was waren die Charakteristika des Studiensumfelds (Setting, z.B. Praxis, Klinik)? n.a.		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
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?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		

Of 8822 titles, we included 32 papers (6718 participants) in the quantitative analysis. Summary estimate for occurrence of delirium was 25% (95% CI, 20%–30%; moderate quality evidence). Limiting to studies at low risk of bias (22 studies, 4422 participants), the occurrence rate was 23% (95% CI, 17%–28%). Subgroup summary estimates suggest that delirium occurrence may vary with assessment method: confusion assessment method, 21% (95% CI, 16%–27%); clinical diagnosis, 27% (95% CI, 19%–38%); other, 32% (95% CI, 22%–43%) but not with duration and timing of assessment. Meta-regression suggested decline in occurrence of delirium comparing historical to more recent studies (slope, 0.03 [SE, 0.004];  $P < 0.0001$ ).

#### IV. Ableitbare Empfehlung

Delirium is common, affecting 1 in 4 acute stroke patients. Reported rates of delirium may be dependent on assessment method. knapper Vergleich von CAM mit DSM.

<b>Studie (RCT)</b>	#05: Rice KL, Bennett MJ, Berger L, Jennings B, Eckhardt L, Fabré-LaCoste N, Houghton D, Vidal G, Gropen T, Diggs E, Barry E, St John J, Mathew S, Egger A, Ryan S, Egger R, Galarneau D, Gaines K, Ely EW. A Pilot Randomized Controlled Trial of the Feasibility of a Multicomponent Delirium Prevention Intervention Versus Usual Care in Acute Stroke. J Cardiovasc Nurs. 2017 Jan/Feb;32(1):E1-E10.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung der Studie</b>			
1. Welche Intervention wurde untersucht? randomisiert übliche Behandlung oder Delir-Behandlung.			
2. Welche Zielkriterien (Endpunkte) wurden bestimmt? This pilot study assessed the feasibility of (1) enrollment within the 48-hour window when delirium risk is greatest, (2) measuring cognitive function using the Montreal Cognitive Assessment, (3) delivering interventions 7 days per week, and (4) determining delirium incidence in stroke-related cognitive dysfunction			
3. Wie viele Studienteilnehmer (insgesamt und pro Studienarm, bzw. Gruppe)? 125			
4. Wie war die Studienpopulation definiert? Patients admitted with ischemic and hemorrhagic strokes and 50 years or older, English speaking, and without delirium			
5. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 66 Jahre, 43% Frauen (ungleich zwischen den Gruppen verteilt), 78% Infarkte			
6. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Stroke Unit			
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? 514 gescreent, 134 randomisiert, 8 Patienten der Interventionsgruppe widerriefen Einwilligung, 1 Pat der Standardgruppe lost 2 follow up			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
8. Wurden die Probanden den Gruppen randomisiert zugeordnet?		X	
9. Waren die Probanden und Untersucher bezüglich der Zuordnung verblindet?			X
10. Wurde die Randomisierung geheim gehalten (allocation concealment)?			X
11. Wurde ein prospektives Design verwendet?		X	
12. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?		X	
13. Waren Interventions- und Kontrollgruppe zu Studienbeginn vergleichbar?			X
14. Wurden die Zielkriterien der Studie eindeutig definiert und adäquat erhoben?		X	
15. Wurden die Gruppen, mit Ausnahme der Prüf-Intervention, gleich behandelt?		X	
16. Wurden Nebenwirkungen dokumentiert?			X
17. Wurden alle Probanden in der Gruppe ausgewertet, der sie ursprünglich zugeordnet waren (intention-to-treat-Regel)		X	
18. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X	
<b>Gesamtbeurteilung</b>		<b>+</b>	
<b>III. Ergebnisse</b>			
Studie bei 125 Schlaganfall-Patienten (Infarkt oder ICB), über 50J. ohne Delir bei Aufnahme, randomisiert übliche Behandlung oder Delir-Behandlung. Aphasische Patienten wurden ausgeschlossen!			
<b>IV. Ableitbare Empfehlung</b>			

Neben der üblichen Stroke Unit Behandlung (Flüssigkeit, Physiotherapie, Ergotherapie, Logopädie) wurde die Interventionsgruppe täglich zweimal von Freiwilligen aktiviert, mit dem Ziel verbale, sensorische und motorische Tätigkeiten durchzuführen. Außerdem wurde täglich die Medikation anhand von zwei Skalen auf anticholinerge Effekte überprüft. 14 Freiwillige führten 360 Behandlungen bei der Behandlungs-Gruppe durch. Insgesamt kam es zu 10 Delirfällen (8). Die Delir-Inzidenz betrug 5,1% in der Interventionsgruppe und 10,6% in der Standardgruppe, wobei diese Quoten in dem Manuskript gar nicht angegeben wurden. Schlussfolgerung des Manuskripts war, dass es möglich ist, so ein Studienplan umzusetzen.

<b>Studie (Dx)</b>	#06: Boßelmann C, Zurluh J, Stefanou MI, Stadler V, Weber Y, Lerche H, Poli S, Ziemann U, Mengel A. Delirium Screening in Aphasic Patients With the Intensive Care Delirium Screening Checklist (ICDSC): A Prospective Cohort Study. Front Neurol. 2019 Nov 12;10:1198.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung der Studie</b>		
1.	Welche diagnostische Intervention wurde untersucht? The index test, ICDSC, was compared with the DSM-V diagnostic criteria as reference standard.	
2.	Wie viele Studienteilnehmer (insgesamt und pro Studienarm, bzw. Gruppe)? 346	
3.	Wie war die Studienpopulation definiert? Erwachsene Pat., konsekutiv nach Aufnahme auf die Stroke Unit in Tübingen. Exclusion criteria were: (i) a duration of stay in the Stroke Unit of <24 h; (ii) a Richmond Agitation-Sedation Scale (RASS) level of -5 or -4 for the majority (>50%) of the stay; (iii) patients on mechanical ventilation or in shock; (iv) diagnosis of delirium or exposure to benzodiazepines on admission; (v) an incomplete record of the National Institutes of Health Stroke Scale (NIHSS), RASS and ICDSC during the stay.	
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)? Stroke Unit Therapie	
6.	Mit welchem Referenztest wurde der Prüftest verglichen? DSM-V	
7.	Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? 1737 gescreent, 346 geeignet. Alter 75J., ca 50% Frauen, NIHSS 3,6-12,3 (ohne und mit Aphasie)	
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1.	X	
2.	X	
3.	X	
4.	X	
5.	X	
6.	X	
7.		X
8.		?
9.		X
10.		X
11. a)	X	
b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?		
12.	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
Delirium was present in 83 out of 231 (36%) patients with aphasia and 32 out of 115 (27.8%) patients without aphasia (p = 0.132). For patients without aphasia, sensitivity and specificity at the established cut-off value of >/= 4 points were 100% and 78%, respectively. For patients with aphasia, the test demonstrated inferior performance, with a sensitivity and specificity of 98% and 55%, respectively. It was necessary to increase the cut-off value to >/= 5 points. Through this, sensitivity was 90% (95% CI, 81.9–95.8%) and specificity was 75% (95% CI, 67.2–81.8%). The degree of agreement to the DSM-V criteria was “substantial” (Cohen’s k = 0.61).		

IV. Ableitbare Empfehlung	
prospektive Studie zur Evaluierung der Intensive Care Delirium Screening Checklist (ICDSC), gibt Schwellwerte an in Abhängigkeit des Vorhandenseins einer Aphasie	
<b>Studie (Dx)</b>	#07: Klimiec E, Dziedzic T, Kowalska K, Szyper A, Pera J, Potoczek P, Slowik A, Klimkowicz-Mrowiec A. PRospective Observational POLish Study on post-stroke delirium (PROPOLIS): methodology of hospital-based cohort study on delirium prevalence, predictors and diagnostic tools. BMC Neurol. 2015 Jun 19;15:94..
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Protokoll-Paper einer prospektiven Studie aus 2015, in dem als Studienziel auch die Validierung von Screening-Skalen erwähnt wird. Eine getrennte Suche nach Ergebnissen (Autor, Acronym) ergab fünf Arbeiten, keiner davon beschäftigt sich mit Testgüte der Screening-Tools. [NZV].
III. Ergebnisse	
IV. Ableitbare Empfehlung	

<b>Studie (Dx)</b>	#08: Infante MT, Pardini M, Balestrino M, Finocchi C, Malfatto L, Bellelli G, Mancardi GL, Gandolfo C, Serrati C. Delirium in the acute phase after stroke: comparison between methods of detection. Neurol Sci. 2017 Jun;38(6):1101-1104.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Vergleich in einer prospektiven Studie den 4AT mit dem DSM-V. Am Aufnahmetag betrug die Sensitivität 90,2% und die Spezifität 64,5%, an Tag 7 war die Sensitivität 96,4% und die Spezifität 76,7%. [NZV, Berücksichtigt in #01 und #04].
III. Ergebnisse	
IV. Ableitbare Empfehlung	
./.	

<b>Studie (Dx)</b>	#09: von Hofen-Hohloch J, Awissus C, Fischer MM, Michalski D, Rumpf JJ, Classen J. Delirium Screening in Neurocritical Care and Stroke Unit Patients: A Pilot Study on the Influence of Neurological Deficits on CAM-ICU and ICDSC Outcome. Neurocrit Care. 2020 Mar 20.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
I. Beschreibung der Studie			
1.	Welche diagnostische Intervention wurde untersucht? CAM-ICU and ICDSC		
2.	Wie viele Studienteilnehmer (insgesamt und pro Studienarm, bzw. Gruppe)? 123		
3.	Wie war die Studienpopulation definiert? Over a period of 1 month, all patients admitted to a neurocritical care and stroke unit at a single academic center		
4.	Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Alter 69J., 57% Männer, 3,2% ICB		
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)?		
II. Interne Validität		Ja	Nein
8.	Wurde ein prospektives Design verwendet?	X	
9.	Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?	X	
10.	Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert	X	



11. War die Studienpopulation repräsentativ	X	
12. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validen Referenztest („Gold-Standard“) verglichen?	X	
13. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
14. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?	X	
15. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?		X
16. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?		X
17. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		X
18. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht? b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?	X	
19. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>++</b>

**III. Ergebnisse**

Twenty-three patients (18.7%) were diagnosed with delirium according to the clinical evaluation. Delirium incidence amounted to 23.6% (CAM-ICU) and 26.8% (ICDSC). Sensitivity and specificity of both screening tools were 66.9% and 93.3% for CAM-ICU and 69.9% and 93.9% for ICDSC, respectively. Patients identified with delirium by either CAM-ICU or ICDSC presented a higher proportion of neurological deficits such as impaired consciousness, expressive aphasia, impaired language comprehension, and hemineglect. Subsequently, generalized estimating equations identified a significant association between impaired consciousness (as indexed by Richmond Agitation and Sedation Scale) and a positive delirium assessment with both CAM-ICU and ICDSC, while impaired language comprehension and hemineglect were only associated with a positive CAM-ICU result.

**IV. Ableitbare Empfehlung**

Monozentrische Studie bei 123 Patienten. Es wurden nicht nur Schlaganfallpatienten eingeschlossen. Bei 23 Patienten (18,7%) wurde nach der klinischen Bewertung ein Delir diagnostiziert. Die Delir-Inzidenz anhand der CAM-ICU betrug 23,6% und anhand der ICDSC 26,8%. Sensitivität und Spezifität beider Screening-Instrumente lagen bei 66,9% und 93,3% für CAM-ICU und 69,9% bzw. 93,9% für die ICDSC. Patienten, bei denen entweder mit der CAM-ICU oder der ICDSC ein Delir identifiziert wurde, hatten einen höheren Anteil neurologischer Defizite wie Bewusstseinsstörungen, expressive Aphasie, gestörtes Sprachverständnis oder Hemineglect

<b>Studie (Dx)</b>	<b>#10:</b> Mitasova A, Kostalova M, Bednarik J, Michalcakova R, Kasperek T, Balabanova P, Dusek L, Vohanka S, Ely EW. Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM- ICU). Crit Care Med. 2012 Feb;40(2):484-90.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Monozentrische Studie zur Evaluation der tschechischen Version der CAM-ICU bei 129 Patienten. Verglichen mit dem Goldstandard (DSM-IV) betrug die Sensitivität 76% (95%CI 55-91) und die Spezifität 98% (95%CI 93-100) [Berücksichtigt in #01 und #04]
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

<b>Studie (Dx)</b>	<b>#11:</b> Lees R, Corbet S, Johnston C, Moffitt E, Shaw G, Quinn TJ. Test accuracy of short screening tests for diagnosis of delirium or cognitive impairment in an acute stroke unit setting. Stroke. 2013 Nov;44(11):3078-83..
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Berücksichtigt in #01 und #04
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (Dx)</b>	<b>#12:</b> Carin-Levy G, Nicol K, van Wijck F, Mead G, McVittie C. Identifying and Responding to Delirium in Acute Stroke: Clinical Team Members' Understandings. Qual Health Res. 2020 Sep 24:..
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Qualitative Forschung anhand von Interviews bei 15 Therapeuten auf Stroke Units. INsbes. wurden Schwierigkeiten bei der Erkennung hypoaktiver Delire deutlich. Keine statistische Bewertung von Delir-Diagnose-/Screening Skalen
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

<b>Studie (Dx)</b>	<b>#13:</b> Nakamizo T, Kanda T, Kudo Y, Sugawara E, Hashimoto E, Okazaki A, Usuda M, Nagai T, Hara H, Johkura K. Development of a clinical score, PANDA, to predict delirium in stroke care unit. J Neurol Sci. 2020 Aug 15;415:.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	geht um einen Prädiktionsscore, nicht um Erkennung selber, dieses wurde anhand der ICDS definiert
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

SF 1.3.3: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA das kontinuierliche apparative Monitoring der Herz-Kreislauf- und der Stoffwechsel-Funktion auf der Stroke Unit im Vergleich zum Nicht-Monitoring das funktionelle Outcome?

Datum der Evidenzgewinnung 20.11.2020

#### MedLine

Suchterm: „'stroke unit' AND monitoring

Filter: systematic review OR randomized controlled trial, 10 years

Treffer: 19

Ausschluss nach Beurteilung von Titel/Abstract: 16

Verblieben:3 (#01, #02, #03)

#### Web of Science

Suchterm: „'stroke unit' AND monitoring

Filter: review

Treffer: 21

Ausschluss nach Beurteilung von Titel/Abstract: 20

Ausschluss von Doubletten: 1 (#01)

Verblieben: 0

#### Cochrane library

Seit dem 2013 publizierten review wurde kein neueres herausgegeben.

#### Gefundene Literatur zum Monitoring auf der Stroke Unit

**#01:** Ciccone A, Celani MG, Chiamonte R, Rossi C, Righetti E. Continuous versus intermittent physiological monitoring for acute stroke. Cochrane Database Syst Rev. 2013 May 31;(5):CD008444. doi: 10.1002/14651858.CD008444.pub2. PMID: 23728675.

**#02:** Urimubenshi G, Langhorne P, Cadilhac DA, Kagwiza JN, Wu O. Association between patient outcomes and key performance indicators of stroke care quality: A systematic review and meta-analysis. Eur Stroke J. 2017 Dec;2(4):287-307. doi: 10.1177/2396987317735426. Epub 2017 Oct 5. PMID: 31008322; PMCID: PMC6453192.

**#03:** Middleton S, McElduff P, Drury P, D'Este C, Cadilhac DA, Dale S, Grimshaw JM, Ward J, Quinn C, Cheung NW, Levi C. Vital sign monitoring following stroke associated with 90-day independence: A secondary analysis of the QASC cluster randomized trial. Int J Nurs Stud. 2019 Jan;89:72-79. doi: 10.1016/j.ijnurstu.2018.09.014. Epub 2018 Sep 27. PMID: 30342326.

### Bewertung

#01 ist das Cochrane-review, das bereits beschrieben wurde

<b>Studie (review)</b>	#02: Urimubenshi G, Langhorne P, Cadilhac DA, Kagwiza JN, Wu O. Association between patient outcomes and key performance indicators of stroke care quality: A systematic review and meta-analysis. Eur Stroke J. 2017 Dec;2(4):287-307.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	In dem review wurden zahlreiche sog. „key performance indicators“ (KPI) und ihre Auswirkung auf Morbidität, Mortalität und Length of stay untersucht. Das apparative Monitoring auf der Stroke Unit gehörte nicht dazu
<b>III. Ergebnisse</b>	
./.	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (RCT)</b>	#03: Middleton S, McElduff P, Drury P, D'Este C, Cadilhac DA, Dale S, Grimshaw JM, Ward J, Quinn C, Cheung NW, Levi C. Vital sign monitoring following stroke associated with 90-day independence: A secondary analysis of the QASC cluster randomized trial. Int J Nurs Stud. 2019 Jan;89:72-79.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Dies ist die sekundäre Analyse von Daten des QASC Studie, einer Studie in 19 australischen Kliniken. Untersucht wurde der Einfluss von Fiebermanagement, Hyperglykämie-management und Dysphagiescreening auf das Outcome. Das apparative Monitoring war nicht Thema
<b>III. Ergebnisse</b>	
./.	
<b>IV. Ableitbare Empfehlung</b>	
./.	

SF 1.3.4: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die regelmäßige neurologische Untersuchung und Erfassung mittels etablierter klinischer Scores im Vergleich zu einer selteneren Kontrolle das funktionelle Outcome?

Datum der Evidenzgewinnung 22.11.2020

### MedLine

Suchterm: „neurolog\* exam\* AND ‘stroke unit’“

Filter: Clinical trial OR Meta-Analysis OR Randomized Controlled Trial OR Review OR Systematic Review

Treffer: 82

Ausschluss nach Beurteilung von Titel/Abstract: 82

Verblieben: 0

### Web of Science

Suchterm: „neurolog\* exam\* AND ‘stroke unit’“

Filter: review

Treffer: 6

Ausschluss nach Beurteilung von Titel/Abstract: 6

Verblieben: 0

### **Cochrane library**

./.

SF 1.3.8: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt oder TIA die zusätzliche Untersuchung des Herzens mittels CT/MRT ergänzend zur Echokardiografie die Genauigkeit der ätiologischen Einordnung?

Datum der Evidenzgewinnung 14.12.2020

### **MedLine**

Suchterm: stroke AND cardia\* and (CT or MRI)

Filter: Systematic Review OR Meta-Analysis, 10 years

Treffer: 54

Ausschluss nach Beurteilung von Titel/Abstract: 53

Verblieben: 1 (#01)

Suchterm: cardia\* AND thromb\* AND (CT or MRI)

Filter: Systematic Review OR Meta-Analysis, 10 years

Treffer: 34

Ausschluss nach Beurteilung von Titel/Abstract: 30

Ausschluss von Doubletten der 1. Suche: 1

Verblieben: 4 (#02-#04)

Bei der Suche in den Referenzen eine weitere gefunden (#05)

Suchterm: stroke AND cardiac AND CT AND (thrombus OR thrombotic OR cardioembolic OR thrombi)

Filter: 10 years

Treffer: 222

Ausschluss nach Beurteilung von Titel/Abstract: 210

Ausschluss von Doubletten der 1. und 2. Suche: 1

Verblieben: 11 (#06-#16)

Suchterm: stroke AND cardiac AND MRI AND (thrombus OR thrombotic OR cardioembolic OR thrombi)

Filter: 10 years

Treffer: 401

Ausschluss nach Beurteilung von Titel/Abstract: 396

Ausschluss von Doubletten der 1. und 2. Suche: 2

Verblieben: 3 (#17-#19)

### **Gefundene Literatur um kardialen CT/MRT**

**#01:** Groeneveld NS, Guglielmi V, Leeflang MMG, Matthijs Boekholdt S, Nils Planken R, Roos YBWEM, Majoie CBLM, Coutinho JM. CT angiography vs echocardiography for detection of cardiac thrombi in ischemic stroke: a systematic review and meta- analysis. J Neurol. 2020 Jun;267(6):1793-1801. doi: 10.1007/s00415-020-09766-8. Epub 2020 Mar 5. Erratum in: J Neurol. 2020 Oct;267(10):3119. PMID: 32140869; PMCID: PMC7293690.

**#02:** Aimo A, Kollia E, Ntritsos G, Barison A, Masci PG, Figliozzi S, Klettas D, Stamatelopoulos K, Delialis D, Emdin M, Georgiopoulos G. Echocardiography versus computed tomography and cardiac magnetic resonance for the detection of left heart thrombosis: a systematic review and meta-analysis. Clin Res Cardiol. 2020 Sep 13. doi: 10.1007/s00392-020-01741-7. Epub ahead of print. PMID: 32920662.

**#03:** Vira T, Pechlivanoglou P, Connelly K, Wijeyesundera HC, Roifman I. Cardiac computed tomography and magnetic resonance imaging vs. transoesophageal echocardiography for diagnosing left atrial appendage thrombi. *Europace*. 2019 Jan 1;21(1):e1-e10. doi: 10.1093/europace/euy142. PMID: 29961869.

**#04:** Roifman I, Connelly KA, Wright GA, Wijeyesundera HC. Echocardiography vs. Cardiac Magnetic Resonance Imaging for the Diagnosis of Left Ventricular Thrombus: A Systematic Review. *Can J Cardiol*. 2015 Jun;31(6):785-91. doi: 10.1016/j.cjca.2015.01.011. Epub 2015 Jan 24. PMID: 25913472.

**#05:** Zou H, Zhang Y, Tong J, Liu Z. Multidetector computed tomography for detecting left atrial/left atrial appendage thrombus: a meta-analysis. *Intern Med J*. 2015 Oct;45(10):1044-53. doi: 10.1111/imj.12862. PMID: 26178177.

**#06:** Apfaltrer G, Lavra F, De Cecco CN, Varga-Szemes A, van Assen M, Mastrodicasa D, Scarabello M, Eid MH, Griffith LP, Nance JW, Litwin SE, Saba L, Schoepf UJ. Predictive Value of Cardiac CT Angiography, Cardiac MRI, and Transthoracic Echocardiography for Cardioembolic Stroke Recurrence. *AJR Am J Roentgenol*. 2020 Sep 16. doi: 10.2214/AJR.20.23903. Epub ahead of print. PMID: 32936016.

**#07:** Yan S, Ying Z, Quan H, Yi C, Min L. Potential Role of 2-Phase Cardiac CT in Patients With Embolic Stroke of Unterterminated Source. *Am J Med*. 2020 Jun;133(6):e290-e293. doi: 10.1016/j.amjmed.2019.11.019. Epub 2019 Dec 20.

**#08:** Resen MS, Poulsen MB, Overgaard K, Rasmussen RS, Soja AMB, Nilsson B, Kristensen MO, Kruuse C, Ulriksen PS. Cardiovascular computed tomography versus transoesophageal echocardiography after cryptogenic ischaemic stroke - a pilot study of 12 patients. *J Int Med Res*. 2020 Jan;48(1):300060518764220. doi: 10.1177/0300060518764220. Epub 2018 May 30. PMID: 29848127; PMCID: PMC7287197.

**#09:** Popkirov S, Schlegel U, Weber W, Kleffner I, Altenbernd J. Cardiac Imaging Within Emergency CT Angiography for Acute Stroke Can Detect Atrial Clots. *Front Neurol*. 2019 Apr 10;10:349. doi: 10.3389/fneur.2019.00349. PMID: 31024438; PMCID: PMC6467937.

**#10:** Yeo LLL, Holmin S, Andersson T, Lundström E, Gopinathan A, Lim EL, Leong BSH, Kuan WS, Ting E, Tan BYQ, Eide SE, Tay ELK. Nongated Cardiac Computed Tomographic Angiograms for Detection of Embolic Sources in Acute Ischemic Stroke. *Stroke*. 2017 May;48(5):1256-1261. doi: 10.1161/STROKEAHA.117.016903. Epub 2017 Apr 6. PMID: 28386043.

**#11:** Hur J, Choi BW. Cardiac CT Imaging for Ischemic Stroke: Current and Evolving Clinical Applications. *Radiology*. 2017 Apr;283(1):14-28. doi: 10.1148/radiol.2016152043. PMID: 28318443.

**#12:** Ajlan AM, Bagdadi RR, Alama MN, Ayoub O. Impact of Implementing Cardiac CT in Evaluating Patients Suspected of Cardioembolic Stroke. *J Comput Assist Tomogr*. 2016 May-Jun;40(3):380-6. doi: 10.1097/RCT.0000000000000369. PMID: 26854417.

**#13:** Sipola P, Hedman M, Onatsu J, Turpeinen A, Halinen M, Jäkälä P, Vanninen R. Computed tomography and echocardiography together reveal more high-risk findings than echocardiography alone in the diagnostics of stroke etiology. *Cerebrovasc Dis*. 2013;35(6):521-30. doi: 10.1159/000350734. Epub 2013 Jun 25. PMID: 23817231.

**#14:** Pagán RJ, Parikh PP, Mergo PJ, Gerber TC, Mankad R, Freeman WD, Shapiro BP. Emerging role of cardiovascular CT and MRI in the evaluation of stroke. *AJR Am J Roentgenol*. 2015 Feb;204(2):269-80. doi: 10.2214/AJR.14.13051. PMID: 25615749.

**#15:** Hur J, Kim YJ, Lee HJ, Nam JE, Ha JW, Heo JH, Chang HJ, Kim HS, Hong YJ, Kim HY, Choe KO, Choi BW. Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. *Stroke*. 2011 Sep;42(9):2471-7. doi: 10.1161/STROKEAHA.110.611293. Epub 2011 Jul 14. PMID: 21757676.

**#16:** Bousset L, Cakmak S, Wintermark M, Nighoghossian N, Loffroy R, Coulon P, Derex L, Cho TH, Douek PC. Ischemic stroke: etiologic work-up with multidetector CT of heart and extra- and intracranial

arteries. Radiology. 2011 Jan;258(1):206-12. doi: 10.1148/radiol.10100804. Epub 2010 Nov 9. PMID: 21062925.

**#17:** Mohammad Y, Alhoqbani T, Alfaqih R, Altamimi L, Alotaibi A, AlMousa A, El Shaer F, Al-Hussain F. Cardiovascular MRI: A valuable tool to detect cardiac source of emboli in cryptogenic ischemic strokes. Brain Behav. 2020 Jun;10(6):e01620. doi: 10.1002/brb3.1620. Epub 2020 Apr 18. PMID: 32304360; PMCID: PMC7303393.

**#18:** Yaghi S, Liberman AL, Atalay M, Song C, Furie KL, Kamel H, Bernstein RA. Cardiac magnetic resonance imaging: a new tool to identify cardioaortic sources in ischaemic stroke. J Neurol Neurosurg Psychiatry. 2017 Jan;88(1):31-37. doi: 10.1136/jnnp-2016-314023. Epub 2016 Sep 22. PMID: 27659922.

**#19:** Hoey ET, Mankad K, Al-Chalabi H, Rosa S. The emerging role of cardiovascular MRI for suspected cardioembolic stroke. Clin Radiol. 2013 Feb;68(2):107-16. doi: 10.1016/j.crad.2012.07.003. Epub 2012 Aug 28. PMID: 22939694.

### Bewertung:

<b>Review</b>	<b>#01:</b> Groeneveld NS, Guglielmi V, Leeflang MMG, Matthijs Boekholdt S, Nils Planken R, Roos YBWEM, Majoie CBLM, Coutinho JM. CT angiography vs echocardiography for detection of cardiac thrombi in ischemic stroke: a systematic review and meta-analysis. J Neurol. 2020 Jun;267(6):1793-1801. doi: 10.1007/s00415-020-09766-8. Epub 2020 Mar 5. Erratum in: J Neurol. 2020 Oct;267(10):3119. PMID: 32140869; PMCID: PMC7293690.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? had a randomized controlled trial or a cross-sectional diagnostic accuracy study design (cohort or case control with a minimum population size of 20 patients).		
2. Welche Interventionen sind betrachtet/untersucht worden? (1) performed cardiac CTA as well as echocardiography (TEE or TTE); (2) in patients with ischemic stroke or transient ischemic attack (TIA)		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? cardiac CTA was considered the index test and echocardiography the reference standard The primary endpoint was diagnostic yield, defined as proportion of patients with <b>a cardiac thrombus</b> on CTA or echocardiography. The secondary endpoint was diagnostic accuracy, defined as sensitivity and specificity of cardiac CTA compared to echocardiography.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 20-314 Patienten; Mean Age 52-69y, Männer 66%		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? unklar		
<b>II. Interne Validität</b>		<b>Ja</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		

14 were included (all single center cohort studies), with data on 1568 patients.  
 In ten studies that compared CTA to TEE, CTA detected cardiac thrombi in 87/1385 (6.3%) patients versus 68/1385 (4.9%) on TEE ( $p < 0.001$ ). Pooled sensitivity and specificity of CTA versus TEE were 86.0% (95% CI 65.6–95.2) and 97.4% (95% CI 95.0–98.7), respectively  
 In four studies comparing CTA to TTE, CTA detected thrombi in 23/183 (12.5%) patients versus 12/183 (6.6%) on TTE ( $p = 0.010$ ).

**IV. Ableitbare Empfehlung**

CTA may be a promising alternative to echocardiography for detection of cardiac thrombi in patients with ischemic stroke, especially now that CTA is standard care for patient selection for endovascular treatment. However, studies were too heterogeneous and of insufficient methodological quality to draw firm conclusions. Large, prospective studies on this topic are warranted.

<b>Review</b>	#02: Aimo A, Kollia E, Ntritsos G, Barison A, Masci PG, Figliozzi S, Klettas D, Stamatiopoulos K, Delialis D, Emdin M, Georgiopoulos G. Echocardiography versus computed tomography and cardiac magnetic resonance for the detection of left heart thrombosis: a systematic review and meta-analysis. Clin Res Cardiol. 2020 Sep 13. doi: 10.1007/s00392-020-01741-7. Epub ahead of print. PMID: 32920662.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Fall-Kontroll-Studien
2. Welche Interventionen sind betrachtet/untersucht worden?  
 a) meta-analysis concerned the diagnostic accuracy of TTE versus DE-CMR for the detection of LV thrombosis  
 b) meta-analysis the diagnostic accuracy of CT versus TEE for LA thrombosis
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? For each study, values of sensitivity and specificity for the diagnostic accuracy of TTE versus the gold standard (DE-CMR) in LV, or for CT versus the gold standard (TEE) in LA were retrieved.
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 64-402 Patienten; Mean age 56-67 years, 52-85% Männer
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? unk

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

**III. Ergebnisse**

Six studies were included in the first meta-analysis (TTE vs. CMR for LV thrombosis). Pooled sensitivity and specificity values were 62% [95%CI 37–81%] and 97% (95%CI 94–99%). The shape of the hierarchical summary receiver operating characteristic (HSROC) curve and the area under the curve (AUC) of 0.96 suggested a high accuracy.  
 Ten studies were included in the second meta-analysis (CT versus TEE for LAA thrombosis). The pooled values of sensitivity and specificity were 97% (95% CI, 77–100%) and 94% (95% CI, 87–98%). The pooled diagnostic odds ratio (DOR) was 500 (95% CI, 52–4810), and the pooled likelihood ratios (LR + and LR-) were 17% (95% CI, 7–40%) and 3% (95% CI, 0–28%). The shape of the HSROC curve and 0.99 AUC suggested a high accuracy of CT vs. TEE.

**IV. Ableitbare Empfehlung**

TTE is a fair alternative to DE-CMR for the identification of LV thrombi, while CT has a good accuracy compared to TEE for the detection of LAA thrombosis  
 Letzteres passt zu unserer SF

<b>Review</b>	#03: Vira T, Pechlivanoglou P, Connelly K, Wijeysondera HC, Roifman I. Cardiac computed tomography and magnetic resonance imaging vs. transoesophageal echocardiography for diagnosing left atrial appendage thrombi. Europace. 2019 Jan 1;21(1):e1-e10. doi: 10.1093/europace/euy142. PMID: 29961869.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Studies were selected if they were comparative studies involving at least two of the three modalities of interest (CCT, CMR, and/or TOE).		
2. Welche Interventionen sind betrachtet/untersucht worden? CCT to TOE and CMR to TOE We performed a pre-specified subgroup meta-analysis to estimate the pooled performance of early and delayed image acquisition protocols for CCT vs. TOE across the selected studies		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Sensitivität, Spezifität, ROC		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Mean Age 51-76 years; 19-82% Men		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		
Cardiac computed tomography demonstrated sensitivity and specificity of 0.99 [95%CI 0.93–1.00] and 0.94 (CI 0.90–0.97) respectively vs. TOE. A subgroup analysis comparing early vs. delayed protocol showing no significant differences in sensitivity (P-value= 0.17) however improved specificity of the delayed imaging protocols (P-value= 0.04). Cardiac magnetic resonance imaging demonstrated sensitivity and specificity of 0.80 (CI 0.63–0.91) and 0.98 (CI 0.97–0.99), respectively when compared to TOE. There was no significant difference in sensitivity or specificity between CMR and CCT (P-values 0.996 and 0.484, respectively)		
<b>IV. Ableitbare Empfehlung</b>		
Cardiac computed tomography and CMR had good to excellent sensitivity and specificity vs. TOE. Further, there was no significant difference in the sensitivity and specificity of CCT vs. CMR, suggesting that both modalities can be considered reasonable alternatives to TOE in the identification of LAA thrombi. Cardiac magnetic resonance imaging may be especially beneficial when TOE and CCT cannot be performed		

<b>Review</b>	#04: Roifman I, Connelly KA, Wright GA, Wijeysondera HC. Echocardiography vs. Cardiac Magnetic Resonance Imaging for the Diagnosis of Left Ventricular Thrombus: A Systematic Review. Can J Cardiol. 2015 Jun;31(6):785-91. doi: 10.1016/j.cjca.2015.01.011. Epub 2015 Jan 24. PMID: 25913472.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>JA</b>	
Begründung	Zu alt, und vergleicht nur MRT mit TTE	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? The initial search was limited to studies reporting on subjects 19 years of age and to those written in the English language. No other initial exclusion criteria were used.		
2. Welche Interventionen sind betrachtet/untersucht worden? TTE, MRT		
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 Studientumfelds (Setting, z.B. Praxis, Klinik)? 24-200 Pat., age mean 56-62 y.		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
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?		
<b>Gesamtbeurteilung</b>	-	
<b>III. Ergebnisse</b>		
Our results suggest that late gadolinium enhancement CMR imaging is the most accurate modality for the detection of LV thrombi (sensitivity 88%, specificity 99%), followed by cine-CMR imaging		
<b>IV. Ableitbare Empfehlung</b>		

<b>Review</b>	#05: Zou H, Zhang Y, Tong J, Liu Z. Multidetector computed tomography for detecting left atrial/left atrial appendage thrombus: a meta-analysis. Intern Med J. 2015 Oct;45(10):1044-53. doi: 10.1111/imj.12862. PMID: 26178177.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Fall-Kontroll-Studien		
2. Welche Interventionen sind betrachtet/untersucht worden? (i) both TEE and MDCT were examined in 1 week, (ii) TEE is the reference standard, (iii) the exact true-positive (TP) and false-negative (FN) and false-positive (FP) and true-negative (TN) data can be extracted from the study and (iv) prospective study.		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Pooled sensitivities (SEN), specificities (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), area under the curve (AUC), symmetric receiver operator characteristics and their 95% confidence interval (95% CI) were calculated		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? N=31-402; Mean age 64-5 y.,		
5. Was waren die Charakteristika des Studientumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	++	
<b>III. Ergebnisse</b>		
Fifteen prospective clinical controlled trials with 2540 patients fulfilled the inclusion criteria. The pooled sensitivities (SEN): 0.957; pooled specificities (SPE): 0.917; pooled positive likelihood ratio (PLR): 22.017; pooled negative likelihood ratio (NLR): 0.060; pooled diagnostic odds ratio (DOR): 437.43; the area under the curve (AUC): 0.9883; Q*-value: 0.9544. However, in the abovementioned indexes, the heterogeneities were statistically significant between studies (P < 0.05, inconsistency index (I2) > 50%).		
In a sub-analysis of studies in which delayed imaging, electrocardiogram (ECG) gating and heart rate control were performed, not only the diagnostic accuracy, but also the heterogeneities were significantly improved (pooled SEN 0.991; pooled SPE 0.989; pooled PLR 60.768; pooled NLR 0.034; pooled DOR 2561.7; AUC 0.9972; Q*-value 0.9806; all the indexes' P-value were greater than 0.05 and the I2 were 0%, except for SPE, I2 = 54.6%).		

<b>IV. Ableitbare Empfehlung</b>
For patients with TEE intolerance or contraindications, MDCT may be an alternative method, especially when the delayed imaging, ECG gating and heart rate control were performed

<b>Review</b>	<b>#14:</b> Pagán RJ, Parikh PP, Mergo PJ, Gerber TC, Mankad R, Freeman WD, Shapiro BP. Emerging role of cardiovascular CT and MRI in the evaluation of stroke. AJR Am J Roentgenol. 2015 Feb;204(2):269-80. doi: 10.2214/AJR.14.13051. PMID: 25615749.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Cohort studies
2. Welche Interventionen sind betrachtet/untersucht worden? (1) echocardiography (TTE or TEE), CT, MRI; (2) in patients with suspected cardiogenic ischemic stroke or TIA.
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? (1) Evaluation of left atrial appendage thrombus (i), left ventricular thrombus (ii), intracardiac masses (iii), valvular disease (iv), paradoxical emboli (v), aortic atheroma (vi); (2) potential complications and costs.
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? (i) 43-2955 patients, (ii) 31 patients, CT to echocardiography, (iv) 37 patients with endocarditis, comparison CT to TEE, (v) 20-152 patients, comparison CT to TEE as reference.
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? Clinic

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

**III. Ergebnisse**

(i) SEN: 70-100%, SPE: 77.9-94%, NPV: 92-100% accurate detection of LAA thrombus; (ii) SEN: 94%, SPE: 97% accurate detection of LV thrombus; (iii) CT and MRI are excellent methods for assessing a mass; (iv) SEN: 97%, SPE: 88%, PPV: 97%, NPV: 88% for detection of vegetation, abscess or pseudoaneurysm; MRI no systematically study; (v) SEN: 67-73%, SPE: 86-98% in detection of PFO in CT; (vi) High diagnostic utility of CTA in the evaluation of aortic atheromatous disease.

<b>IV. Ableitbare Empfehlung</b>
Cardiovascular CT angiography and MRI have growing potential compared with conventional cardiovascular echography.

<b>Review</b>	<b>#18:</b> Yaghi S, Liberman AL, Atalay M, Song C, Furie KL, Kamel H, Bernstein RA. Cardiac magnetic resonance imaging: a new tool to identify cardioaortic sources in ischaemic stroke. J Neurol Neurosurg Psychiatry. 2017 Jan;88(1):31-37. doi: 10.1136/jnnp-2016-314023. Epub 2016 Sep 22. PMID: 27659922.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Randomised trials, comparative studies and case series.		
2. Welche Interventionen sind betrachtet/untersucht worden? (1) cardiac MRI (CMR) as well as echocardiography (TEE or TTE); (2) in patients with ischemic stroke or TIA.		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Detection of several potential embolic cardioaortic sources.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 26-4792 patients		
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? Clinical		
<b>II. Interne Validität</b>		
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss klar definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
There is a potential role for CMR in the diagnostic evaluation of patients with cryptogenic stroke to identify potential aetiologies such as cardiac thrombi, cardiac tumours, aortic arch disease and other rare cardiac anomalies.		
<b>IV. Ableitbare Empfehlung</b>		
CMR is a non-invasive modality that can help identify potential mechanisms in cryptogenic stroke and patients who may be targeted for enrolment into clinical trials comparing anticoagulation to antiplatelet therapy in secondary stroke prevention.		

<b>Review</b>	#19: Hoey ET, Mankad K, Al-Chalabi H, Rosa S. The emerging role of cardiovascular MRI for suspected cardioembolic stroke. Clin Radiol. 2013 Feb;68(2):107-16. doi: 10.1016/j.crad.2012.07.003. Epub 2012 Aug 28. PMID: 22939694.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>JA</b>
Begründung	Zu alt
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Review</b>	#11: Hur J, Choi BW. Cardiac CT Imaging for Ischemic Stroke: Current and Evolving Clinical Applications. Radiology. 2017 Apr;283(1):14-28. doi: 10.1148/radiol.2016152043. PMID: 28318443.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>JA</b>
Begründung	Keine SR, sondern nur normaler review-Artikel
<b>III. Ergebnisse</b>	
LA or left ventricular thrombus (SEN: 96-100%, SPE: 92-99%, PPV: 41, 92%, NPV: 99, 100%), Intraatrial septal abnormalities (SEN: 73.1%, SPE: 98.4%, PPV: 90.5%, NPV: 94.7%), compared to TEE.	
<b>IV. Ableitbare Empfehlung</b>	
Cardiac CT is a very useful and powerful modality for the detection of cardioembolic sources, as well as risk assessment in patients with stroke. Cardiac CT is a reliable alternative imaging modality to TEE for the evaluation of cardioembolic sources in patients with ischemic stroke, avoiding the discomfort and risks associated with TEE.	

<b>Original research</b>	#06: Apfaltrer G, Lavra F, De Cecco CN, Varga-Szemes A, van Assen M, Mastrodicasa D, Scarabello M, Eid MH, Griffith LP, Nance JW, Litwin SE, Saba L, Schoepf UJ. Predictive Value of Cardiac CT Angiography, Cardiac MRI, and Transthoracic Echocardiography for Cardioembolic Stroke Recurrence. AJR Am J Roentgenol. 2020 Sep 16. doi: 10.2214/AJR.20.23903. Epub ahead of print. PMID: 32936016.	
Bearbeiter	Olav Jansen, Patrick Langguth	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung der Studie</b>		
1. Welche diagnostische Intervention wurde untersucht (Prüftest)? (1) performed cardiac CTA or MRI as well as TTE; (2) in patients with ischemic stroke		
2. Wie viele Studienteilnehmer wurden eingeschlossen? 151 patients;		
3. Wie war die Studienpopulation definiert? a) Einschlusskriterien: if previous findings are ambiguous or if there is high suspicion of cardiac embolus b) Ausschlusskriterien: kein imaging		
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? mean age 62.4 years, 53% male		
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? hospital		
6. Mit welchem Referenztest wurde der Prüftest verglichen? TTE, 76 cCTA, 75 CMRT		
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? a) Im zu prüfenden diagnostischen Test b) Im Referenztest		
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?		X
2. Wurden die Ein- und Ausschlusskriterien eindeutig definiert?		X
3. Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?		X
4. War die Studienpopulation repräsentativ?	X	
5. Wurde der zu prüfende diagnostische Test mit einem adäquaten, validen Referenztest („Gold-Standard“) verglichen?		X
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?		X
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?	X	
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?	X	
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?	X	
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?	X	
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>+</b>	
<b>III. Ergebnisse</b>		
Sensitivity, specificity, PPV and NPV were: 33.3%, 93.7%, 50.0%, and 88.2% for cCTA; 14.3%, 80.3%, 14.3%, and 80.3% for CMR; 14.3%, 83.6%, 16.7%, 80.9% for TTE in the CMR group, and 8.3%, 93.7%, 20.0% and 84.5% for TTE in the cCTA group. Accuracy was not different ( $p > 0.05$ ) between cCTA (0.63, 95% CI [0.49, 0.77]), CMR (0.53, 95% CI [0.42, 0.63]), TTE in CMR group (0.51, 95% CI [0.40, 0.61], and TTE in cCTA group (0.51, 95% CI [0.42, 0.59]).		
<b>IV. Ableitbare Empfehlung</b>		
CTA, CMR, and TTE all showed comparable high specificity and NPV for stroke recurrence. cCTA and CMR may be useful alternatives to TTE. cCTA may be preferred given its better detection of left atrial and left ventricular thrombi.		

<b>Original research</b>	#07: Yan S, Ying Z, Quan H, Yi C, Min L. Potential Role of 2-Phase Cardiac CT in Patients With Embolic Stroke of Unterterminated Source. Am J Med. 2020 Jun;133(6):e290-e293. doi: 10.1016/j.amjmed.2019.11.019. Epub 2019 Dec 20.	
Bearbeiter	Olav Jansen, Patrick Langguth	
Ausschluss	<b>JA</b>	
Begründung	Kein Vergleich mit anderen Methoden, nur CT	
<b>III. Ergebnisse</b>		
Positive cardiac findings were found in 21/74 (28.4%).		

<b>IV. Ableitbare Empfehlung</b>
Two-phase cardiac CT is a useful tool for stroke etiology evaluation, providing diagnostic information in a quarter of patients with ESUS.

<b>Original research</b>	<b>#08:</b> Resen MS, Poulsen MB, Overgaard K, Rasmussen RS, Soja AMB, Nilsson B, Kristensen MO, Kruse C, Ulriksen PS. Cardiovascular computed tomography versus transoesophageal echocardiography after cryptogenic ischaemic stroke - a pilot study of 12 patients. J Int Med Res. 2020 Jan;48(1):300060518764220. doi: 10.1177/0300060518764220. Epub 2018 May 30. PMID: 29848127; PMCID: PMC7287197.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>JA</b>
Begründung	Geringe Patientenzahl von 10 mit beiden Modalitäten.

<b>III. Ergebnisse</b>
Thrombi were not detected in any patients. Patent foramen ovale was visualized in five patients by TEE, while cardiovascular CT only identified three.
<b>IV. Ableitbare Empfehlung</b>
The sensitivity for detecting patent foramen ovale was considerably lower for cardiovascular CT than for TEE, however the cardiovascular CT revealed several other very important clinical findings.

<b>Original research</b>	<b>#09:</b> Popkirov S, Schlegel U, Weber W, Kleffner I, Altenbernd J. Cardiac Imaging Within Emergency CT Angiography for Acute Stroke Can Detect Atrial Clots. Front Neurol. 2019 Apr 10;10:349. doi: 10.3389/fneur.2019.00349. PMID: 31024438; PMCID: PMC6467937.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>JA</b>
Begründung	Kein Vergleich mit Alternativmethoden, z.B. TEE

<b>I. Beschreibung der Arbeit</b>
<b>III. Ergebnisse</b>
-
<b>IV. Ableitbare Empfehlung</b>
Intracardiac clots can be detected on extended emergency CCTA before they are potentially dissolved by thrombolysis or flushed into the circulation.

<b>Original research</b>	<b>#10:</b> Yeo LLL, Holmin S, Andersson T, Lundström E, Gopinathan A, Lim EL, Leong BSH, Kuan WS, Ting E, Tan BYQ, Eide SE, Tay ELK. Nongated Cardiac Computed Tomographic Angiograms for Detection of Embolic Sources in Acute Ischemic Stroke. Stroke. 2017 May;48(5):1256-1261. doi: 10.1161/STROKEAHA.117.016903. Epub 2017 Apr 6. PMID: 28386043.
Bearbeiter	Olav Jansen, Patrick Langguth
Ausschluss	<b>NEIN</b>
Begründung	

<b>I. Beschreibung der Studie</b>		
1. Welche diagnostische Intervention wurde untersucht (Prüftest)? (1) performed cardiac CTA as well as echocardiography (TEE or TTE); n patients with ischemic stroke		
2. Wie viele Studienteilnehmer wurden eingeschlossen?		
3. Wie war die Studienpopulation definiert? a) Einschlusskriterien: $\geq$ 21J, AIS, Rekanalisation geplant und daher CTA, die aufs Herz ausgedehnt wurde b) Ausschlusskriterien: CTA Kontraindikation		
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? mean age 63 years, 65% male		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? hospital		
6. Mit welchem Referenztest wurde der Prüftest verglichen? TTE		
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? a) Im zu prüfenden diagnostischen Test ? b) Im Referenztest		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?	X	

2. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?	X	
3. Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?	X	
4. War die Studienpopulation repräsentativ?	X	
5. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validen Referenztest („Gold-Standard“) verglichen?	X	
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?		X
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?	X	
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?	X	
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		X
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?		X
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		
3/20 patients had abnormal findings. Echocardiography did not identify any further sources of cardioembolic stroke not diagnosed from CTA imaging.		
<b>IV. Ableitbare Empfehlung</b>		
This study confirms the feasibility and value of a composite CTA protocol as described above that allows evaluation of the heart for potential cardiac sources of embolism and ascending aorta together with the mandatory imaging of the caroticovertebral circulation. Such a protocol allows maximal returns of a scan that is already part of most acute stroke protocols with minimal additional risk and resource cost to the patient.		

<b>Original research</b>	#12: Ajlan AM, Bagdadi RR, Alama MN, Ayoub O. Impact of Implementing Cardiac CT in Evaluating Patients Suspected of Cardioembolic Stroke. J Comput Assist Tomogr. 2016 May-Jun;40(3):380-6. doi: 10.1097/RCT.0000000000000369. PMID: 26854417.	
Bearbeiter	Olav Jansen, Patrick Langguth	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung der Studie</b>		
1. Welche diagnostische Intervention wurde untersucht (Prüftest)? Cardia CT		
2. Wie viele Studienteilnehmer wurden eingeschlossen? 47		
3. Wie war die Studienpopulation definiert? a) Einschlusskriterien: retrospektiv, carCT gemacht, Stroke b) Ausschlusskriterien: kein carCT		
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 52J, 25 Männer		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? hospital		
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		
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?		X
2. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?		X
3. Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?		X
4. War die Studienpopulation repräsentativ?		X
5. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validen Referenztest („Gold-Standard“) verglichen?	X	
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?		X
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?		X
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?		X
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		X

11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?		X
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		-
<b>III. Ergebnisse</b>		
Cardiac CT showed findings of major embolic potential in 21%, none of which were documented in echocardiography reports. Two cases (4%) with findings of major embolic potential where identified on echocardiography but not on CT. Computed tomography of 13 patients (28%) showed 16 potentially significant stroke-unrelated findings.		
<b>IV. Ableitbare Empfehlung</b>		
Implementing cardiac CT in assessing patients suspected of cardioembolic stroke added value to echocardiographic evaluation, by detecting major embolic potential findings.		

<b>Original research</b>	#13: Sipola P, Hedman M, Onatsu J, Turpeinen A, Halinen M, Jäkälä P, Vanninen R. Computed tomography and echocardiography together reveal more high-risk findings than echocardiography alone in the diagnostics of stroke etiology. Cerebrovasc Dis. 2013;35(6):521-30. doi: 10.1159/000350734. Epub 2013 Jun 25. PMID: 23817231.	
Bearbeiter	Olav Jansen, Patrick Langguth	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung der Studie</b>		
1. Welche diagnostische Intervention wurde untersucht (Prüftest)?		
2. Wie viele Studienteilnehmer wurden eingeschlossen? 140		
3. Wie war die Studienpopulation definiert?		
a) Einschlusskriterien: (1) stroke/TIA with suspicion of cardiogenic source by a neurologist, or (2) age <50 years and stroke/ TIA of undetermined origin because cardioembolism is the most frequent etiology in these patient		
b) Ausschlusskriterien: Exclusion criteria were: atrial fibrillation (AF) on electrocardiogram on admittance because cardiac imaging will not affect the decision to start anticoagulant treatment, inability to obtain informed consent from the patient or from the patient's legally authorized representative if the patient was incapable of providing informed consent; previous allergic reaction to iodinated contrast media; renal insufficiency (serum creatinine >140 µmol/l, >1.58 mg/dl); pregnancy, and age <18 years.		
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 60 Jahre, 95 Männer		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? hospital		
6. Mit welchem Referenztest wurde der Prüftest verglichen? TTE		
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)?		
a) Im zu prüfenden diagnostischen Test ?		
b) Im Referenztest		
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?	X	
2. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?	X	
3. Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?	X	
4. War die Studienpopulation repräsentativ?		
5. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validen Referenztest („Gold-Standard“) verglichen?	X	
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?	X	
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?	X	
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?		X
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		X
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?	X	
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		

Combined use of CACC-CT and TTE/TEE was more sensitive than TTE/TEE alone for detecting patients with at least one cardiac or aortic high-risk finding (sensitivity 91 vs. 41%,  $p < 0.001$ ; specificity 98 vs. 99%; overall accuracy 97 vs. 90%).

#### IV. Ableitbare Empfehlung

Cardiac CT and TTE/TEE alone show limited accuracy for the diagnostics of stroke etiology. Therefore, cardiac CT could be a valuable tool in patients with cryptogenic stroke despite standard stroke diagnostics.

<b>Original research</b>	#15: Hur J, Kim YJ, Lee HJ, Nam JE, Ha JW, Heo JH, Chang HJ, Kim HS, Hong YJ, Kim HY, Choe KO, Choi BW. Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. Stroke. 2011 Sep;42(9):2471-7. doi: 10.1161/STROKEAHA.110.611293. Epub 2011 Jul 14. PMID: 21757676.	
Bearbeiter	Olav Jansen, Patrick Langguth	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung der Studie</b>		
1. Welche diagnostische Intervention wurde untersucht (Prüftest)? Dual-Enhanced Cardiac CT		
2. Wie viele Studienteilnehmer wurden eingeschlossen? 83		
3. Wie war die Studienpopulation definiert?		
a) Einschlusskriterien: . High risk factors for thrombus formation were defined as follows: (1) persistent atrial fibrillation (AF) confirmed by electrocardiography <sup>12,13</sup> ; (2) valve disease assessed by echocardiography, <sup>14 –16</sup> including mitral stenosis (at least moderate in severity), previous mitral valve surgery (valve replacement or repair), or severe aortic regurgitation; (3) left ventricular dysfunction <sup>17</sup> defined as severe systolic dysfunction (ejection fraction 30%) or cardiomyopathy with moderate systolic dysfunction (ejection fraction 40%); or (4) history of AF documented by 12-lead electrocardiography before the index TEE examination		
b) Ausschlusskriterien: contrast allergie, poor renal function		
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 62,6 Jahre, 56 Männer		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? hospital		
6. Mit welchem Referenztest wurde der Prüftest verglichen? TEE		
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)?		
a) Im zu prüfenden diagnostischen Test ? n.a.		
b) Im Referenztest		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?	X	
2. Wurden die Ein- und Ausschlusskriterien eindeutig definiert?	X	
3..Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?	X	
4. War die Studienpopulation repräsentativ?	X	
5.. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validenReferenztest („Gold-Standard“) verglichen?	X	
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?		X
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?		X
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?		X
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		X
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?	X	
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>+</b>	
<b>III. Ergebnisse</b>		
Sensitivity and specificity of CT for the detection of thrombi and circulatory stasis in the left atrial appendage were 96% (95% CI, 78% to 99%), and 100% (95% CI, 92% to 100%).		
<b>IV. Ableitbare Empfehlung</b>		
Dual-enhanced cardiac CT with prospective electrocardiographic gating is a noninvasive and sensitive modality for detecting left atrial appendage thrombus with an acceptable radiation dose.		



<b>Original research</b>	#16: Bousset L, Cakmak S, Wintermark M, Nighoghossian N, Loffroy R, Coulon P, Derex L, Cho TH, Douek PC. Ischemic stroke: etiologic work-up with multidetector CT of heart and extra- and intracranial arteries. Radiology. 2011 Jan;258(1):206-12. doi: 10.1148/radiol.10100804. Epub 2010 Nov 9. PMID: 21062925.		
<b>Bearbeiter</b>	Olav Jansen, Patrick Langguth		
<b>Ausschluss</b>	NEIN		
<b>Begründung</b>			
<b>I. Beschreibung der Studie</b>			
1. Welche diagnostische Intervention wurde untersucht (Prüftest)? Multidetector CT des Herzens			
2. Wie viele Studienteilnehmer wurden eingeschlossen? 46 Dup, 39 TEE			
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)? 63 J, 83% Männer, 48% Hypertonus			
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? hospital			
6. Mit welchem Referenztest wurde der Prüftest verglichen? TTE/TEE, DUP/MRA			
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? a) Im zu prüfenden diagnostischen Test ? ./. b) Im Referenztest			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?		X	
2. Wurden die Ein- und Ausschlusskriterien eindeutig definiert?			X
3. Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?		X	
4. War die Studienpopulation repräsentativ?		X	
5. Wurde der zu prüfende diagnostische Test mit einem adäquaten, validen Referenztest („Gold-Standard“) verglichen?		X	
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?		X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?			X
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?			X
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?			X
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?			X
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?		X	
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X	
<b>Gesamtbeurteilung</b>		+	
<b>III. Ergebnisse</b>			
a) CT having sensitivity and specificity for the detection of cardiac sources of 72% (18 of 25 cases; 95% CI: 50.6%, 87.9%) and 95% (20 of 21 cases; 95% CI: 76.1%, 99.8%). b) CT having sensitivity and specificity for the detection of major arterial atheroma of 100% (all 24 cases; 95% CI: 85.7%, 100%) and 91% (20 of 22 cases; 95% CI: 70.8%, 98.9%) These results led to a correct multidetector CT-based classification for 38 (83%) of the 46 patients and a $\kappa$ value of 0.78, corresponding to good agreement between the two techniques.			
<b>IV. Ableitbare Empfehlung</b>			
Multidetector CT is a promising tool for etiologic assessment of ischemic stroke, although the identification of minor cardiac sources with this examination requires the establishment of robust criteria.			

<b>Original research</b>	#17: Mohammad Y, Alhoqbani T, Alfaqih R, Altamimi L, Alotaibi A, AlMousa A, El Shaer F, Al-Hussain F. Cardiovascular MRI: A valuable tool to detect cardiac source of emboli in cryptogenic ischemic strokes. Brain Behav. 2020 Jun;10(6):e01620. doi: 10.1002/brb3.1620. Epub 2020 Apr 18. PMID: 32304360; PMCID: PMC7303393.	
<b>Bearbeiter</b>	Olav Jansen, Patrick Langguth	
<b>Ausschluss</b>	NEIN	
<b>Begründung</b>		
<b>I. Beschreibung der Studie</b>		

1. Welche diagnostische Intervention wurde untersucht (Prüftest)? Cardiovascular MRI		
2. Wie viele Studienteilnehmer wurden eingeschlossen? 24		
3. Wie war die Studienpopulation definiert? a) Einschlusskriterien: TEE was reserved to the patients whose stroke remains cryptogenic despite the above stroke workup and cardiac embolic source was highly suspected. All patients who were scheduled for TEE were also arranged to have a noncontrast CMR b) Ausschlusskriterien: non-cryptoge infarction		
4. Was waren die Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Mittleres Alter 62J, 54% Männer		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? hospital		
6. Mit welchem Referenztest wurde der Prüftest verglichen? TEE		
7. Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? a) Im zu prüfenden diagnostischen Test ?n.a. b) Im Referenztest		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Wurde ein prospektives Studiendesign verwendet?	X	
2. Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?		X
3. Wurden die Studienteilnehmer aus der durch die Ein-/bzw. Ausschlusskriterien definierten Population konsekutiv oder randomisiert rekrutiert?	X	
4. War die Studienpopulation repräsentativ?	X	
5. Wurde der zu prüfende diagnostische Test mit einem ein adäquaten, validen Referenztest („Gold-Standard“) verglichen?	X	
6. Wurde der Referenztest unabhängig vom Prüftestergebnis durchgeführt?	X	
7. Waren die Beurteiler des Prüftests gegenüber den Ergebnissen des Referenztests verblindet?		X
8. Wurden Prüf- und Referenztest zeitnah aufeinander folgend durchgeführt?	X	
9. Wurden die Testergebnisse für alle Studienteilnehmer angegeben?	X	
10. Wurde der Umgang mit nicht-eindeutigen Befunden beschrieben?		X
11. a) Wurden Zahlenangaben zur Genauigkeit des Prüftests gemacht- b) wenn nein, lassen sich diese errechnen (4-Felder-Tafel vollständig abbildbar)?	X	
12. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		
The accuracy of cardiovascular MRI to detect aortic atheroma, atrial septal aneurysm or left ventricular thrombus was great; 96%, 95.83%, and 100%, respectively.		
<b>IV. Ableitbare Empfehlung</b>		
In patients with cryptogenic stroke, cardiovascular MRI is comparable to transesophageal echocardiogram in detecting cardiac and aortic source of emboli.		

SF 1.4.1: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt die Stimulation des Ganglion sphenopalatinum im Vergleich zur konventionellen Therapie ohne Stimulation das funktionelle Outcome?

Datum der Evidenzgewinnung 06.09.2020

#### MedLine

A) Suchterm: „stroke AND sphenopal\* AND stimulat\*“

Filter: systematic review

Treffer: 0

In der folgenden Arbeit #01 ist aber eine gemeinsame Auswertung mit #03 enthalten.

B) Suchterm: „stroke AND sphenopal\* AND stimulat\*“

Filter: randomized clinical trials

Treffer: 2 (#1-#2)

Beim Lesen der Arbeiten wurde eine weitere Studie gefunden (#03)

#### Web of Science

C) Suchterm: „stroke AND sphenopal\* stimulat\*“

Filter: review

Treffer: 8

Ausschluss nach Beurteilung von Titel/Abstract: 7

Verblieben: 1 (#04)

### Gefundene Literatur zur Stimulation des Ganglion sphenopalatinum

**#01:** Bornstein NM, Saver JL, Diener HC, Gorelick PB, Shuaib A, Solberg Y, Thackeray L, Savic M, Janelidze T, Zarqua N, Yarnitsky D, Molina CA; ImpACT-24B investigators. An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial. *Lancet*. 2019 Jul 20;394(10194):219-229. doi: 10.1016/S0140-6736(19)31192-4. Epub 2019 May 24. PMID: 31133406.

**#02:** Khurana D, Kaul S, Schneider D, Csanyi A, Adam I, Ichaporia NR, Griewing B, Csiba L, Valikovics A, Puri V, Diener HC, Schwab S, Hetzel A, Bornstein N; ImpACT-1 Study Group. Implant for Augmentation of Cerebral Blood Flow Trial-1 (ImpACT-1). A single-arm feasibility study evaluating the safety and potential benefit of the Ischemic Stroke System for treatment of acute ischemic stroke. *PLoS One*. 2019 Jul 3;14(7):e0217472. doi: 10.1371/journal.pone.0217472. PMID: 31269025; PMCID: PMC6609146.

**#03:** Bornstein NM, Saver JL, Diener HC, et al. Sphenopalatine Ganglion Stimulation to Augment Cerebral Blood Flow [published online ahead of print, 2019 May 23]. *Stroke*. 2019; 50:2108-2117. doi:10.1161/STROKEAHA.118.024582

**#04:** Hosseini MB, Saver JL Mechanisms of action of acute and subacute sphenopalatine ganglion stimulation for ischemic stroke. *International Journal of Stroke* 2020

### Bewertung:

Die drei Arbeiten #01 - #03 stammen aus der gleichen Arbeitsgruppe und wurden vom gleichen Sponsor unterstützt. Die zweite Arbeit (Khurana 2019) ist eine einarmige Sicherheitsstudie. Bewertung folgt als Tabelle

#04 ist eine Übersichtsarbeit, in der über die Wirkung spekuliert wird.

### Tabellarische Zusammenfassung und Bewertung

Referenz	Bornstein 2019 (doi:10.1161/STROKEAHA.118.024582) ImpACT-24A	Khurana 2019 (PMID: 31269025) ImpACT-1	Bornstein 2019 (PMID: 31133406) ImpACT-24B
Referenz	[481]	[482]	[483]
Studientyp	RCT, doppelblind, sham-kontrolliert, multinational	Einarmige Studie, multinational	RCT, doppelblind, sham-kontrolliert, multinational
Teilnehmeranzahl (Gruppenverteilung)	Gesamt 303 (SPG-Stim.: 153; Sham: 100)	Gesamt 98	Gesamt 1078 (SPG-Stim.: 555; Sham. 523)
Einschlusskriterien	Alter 18-85J; NIHSS 7-18 24 Std Zeitfenster Infarkt vordere Zirkulation	Alter 18-85J; NIHSS 7-20 24 Std Zeitfenster Infarkt vordere Zirkulation	Männer 40-89J. Frauen 40-85J NIHSS 7-18 Infarkt vordere Zirkulation 8-24Std Zeitfenster

<b>Ausschlusskriterien (Wesentliche)</b>	ICB, >2/3 Inf., Lakune, Posteriorinf., Rekanalisationstherapie	ICB, >2/3 Inf., Lakune, Posteriorinf., TIA, pRS >2, Schlaganfall <6M, unkontrollierte Hypertonie,	ICB, >2/3 Inf., Lakune, Posteriorinf., Sopor/Koma, pRS >1, Schlaganfall <6M, bekannte AVM oder intrakran. Aneurysma, epileptischer Anfall, unkontrollierte Hypertonie, Rekanalisationstherapie
<b>Pat.-Charakteristika</b>	Altersmedian 73J., 52,6% Frauen, NIHSS-median 11, Zeitfenster Median 18,6Std	Altersmedian 56,8J., 34,7% Frauen, NIHSS-MW 12,2 Zeitfenster MW 18,6Std	Altersmedian 70J., 49% Frauen, NIHSS-median 12, Zeitfenster Median 19,9Std
<b>Drop out Rate</b>	24 Patienten (6 vor der Implantation, 18 unvollständige Prozeduren)	Kein Device erhalten: 6 Kein FU: 3 Für die Effektivitätsanalyse 14 Pat. ausgeschlossen	78 Pat. erhielten keine Behandlung und wurden aus der mITT ausgeschlossen 6 Patienten waren lost to FU
<b>Intervention</b>	SPG-Stimulation via bettseitigem minimal-invasivem Eingriff. 5 Tage jeweils 4 Std.	SPG-Stimulation mit dem "Ischemic Stroke System" der Fa. BrainsGate Ltd.	SPG-Stimulation via bettseitigem minimal-invasivem Eingriff. 5 Tage jeweils 4 Std.
<b>Kontrolle</b>	Echte oder Sham-Stimulation über externes Steuergerät	Keine	Echte oder Sham-Stimulation über externes Steuergerät
<b>Zielgröße(n)</b>	pEP: Anteil von Patienten mit besser als erwartetem Behinderungsergebnisse (mRS@3M) in den SPG-Stimulations. im Vergleich zur Sham-Gruppe (gleitende Dichotomie-Analyse).  sEP: pEP bei Pat. mit Aphasie, erhebliche neurologische Verbesserung @3M (ENI), Lebensqual. (SIS-16) @3M, mRS 0-2@3M  savEP: SAEs, neurologische Verschlechterung, Implantations-Komplikationen, Mortalität	pEP (savEP): Mortalität, SAEs, prozedurale oder Decive-Komplikationen, Notwendigkeit die Behandlung abzubrechen  sEP: mRS-Shift, mRS@3M 0-2, NIHSS, Barthel-Indes	pEP: Anteil von Patienten mit besser als erwartetem Behinderungsergebnisse (mRS@3M) in den SPG-Stimulations. im Vergleich zur Sham-Gruppe (gleitende Dichotomie-Analyse).  sEP: mRS 0-2@3M, Lebensqual. (SIS-16) @3M, Infarktwachstum @d5  savEP: SAEs, stimulations-assoziierte SAEs, neurologische Verschlechterung, Mortalität

<b>Hauptergebnis (pEP)</b>	SPG vs sham 49,7% vs 40,0%, OR 1,48 (95%CI 0,89-2,47)  Abhängigkeit von Schlaganfall-Lokalisation wurde gefunden (bei kortikalen Infarkten OR 2,70 (95%CI 1,08-6,73))	Mortalität 12,2% SAE-Quote 23,5%	SPG vs-sham 49% vs 45%; OR 1,14 (95%CI 0,89-1,46)  Bei Beteiligung des Cortex OR 1,48 (95%CI 1,05-2,10)
<b>Nebenergebnis (sEP)</b>	ENI OR 1,37; 95%CI 0,81-2,33) Aphasie Pat: OR 1,80 (95%CI 0,84-3,88) SIS-16: OR 1,16 (0,74-1,83) mRS 0-2:OR 1,05 (95%CI 0,63-1,75)	Vergleich mit historische NINDS-Daten ergab Vorteile für die SPG-Stimulation	mRS 0-2: OR 1,10 (0,86-1,41) SIS-16: Dif -3,0 (-1,8-7,8)
<b>Sicherheit</b>	Keine Unterschiede in Sicherheit (OR 0,78; 95%CI 0,47-1,30) oder Mortalität (12,9% vs. 15,8%; OR 0,78; 95%CI 0,40-1,54)	= pEP	Keine Unterschiede in Sicherheit (OR 1,10 95%CI 0,84-1,43) oder Mortalität (14,2% vs. 12,3%; OR 1,17; 95%CI 0,82-1,68)
<b>Autoreninterpretation</b>	SPG-Stimulation im 24 Std ZF sicher, nicht überlegem. Größere Studie gerechtfertigt und notwendig	Das Implantationsverfahren und die SPG-Stimulation, waren sicher und tolerierbar. Die Ergebnisse erfordern eine randomisierte Folgestudie	Die SPG-Stimulation ist sicher für Patienten mit akutem ischämischen Schlaganfall 8-24 h nach Beginn, die für eine Rekanalisationstherapie nicht in Frage kommen. Obwohl sie keine Signifikanz erreichen, unterstützen die Ergebnisse der Studie, dass bei Patienten mit kortikaler Beteiligung das funktionelle Ergebnis wahrscheinlich verbessert werden kann
<b>Kommentar</b>	Studie wegen technischer Weiterentwicklung vorzeitig abgebrochen	Studie über 10 Jahre nach Einschluss des letzten Patienten publiziert. Der Vergleich mit den NINDS Daten ist durch erhebliche Unterschiede der Basisdaten erschwer	Primärer Endpunkt nicht positiv  Bisher keine Daten zu Rekanalisationspatienten vorliegend

EC: Ausschlusskriterien, FU: Follow Up, IC: Einschlusskriterien, MW: Mittelwert; mITT: modifizierte intention to treat; mRS: modifizierte Rankins-Skala; pEP: primärer Endpunkt, pRS: prämorbid Rankins-Skala; RCT: Randomisierte klinische Studie, sEP: sekundäre Endpunkte; savEP: Sicherheitsendpunkt, SAE: serious adverse event

SF 1.6.1: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt eine frühzeitige Physiotherapie im Vergleich zum Verzicht darauf das funktionelle Outcome?

Datum der Evidenzgewinnung 30.09.2020

**MedLine**

A) Suchterm: (physiotherapy OR "physio therap\*") AND (acute stroke)

Filter: systematic review, last 10 years

Treffer: 487

Ausschluss nach Beurteilung von Titel/Abstract: 484

Verblieben: 3 (#01-#03)

B) Suchterm: (physiotherapy OR "physio therap\*") AND (acute stroke) AND early

Filter: systematic review, last 10 years

Treffer: 31

Ausschluss nach Beurteilung von Titel/Abstract: 26

Ausschluss von Duplikaten aus der vorherigen Suche: 2

Verblieben: 3 (#04-#06)

**Web of Science**

C) Suchterm: (physiotherapy OR "physio therap\*") AND (acute stroke) AND early

Filter: review, 2010-2020

Treffer: 3

Ausschluss nach Beurteilung von Titel/Abstract: 1

Verblieben: 2 (#07-#08)

**Cochrane library**

D) Suchterm: physiotherapy stroke

Treffer: 21

Ausschluss nach Beurteilung von Titel/Abstract: 20

Verblieben: 1 (#09)

Suchterm: early mobilisation stroke

Treffer: 6

Ausschluss nach Beurteilung von Titel/Abstract: 5

Verblieben: 1 (#10)

**AWMF-Leitlinien**

Stichwortsuche: Physiotherapie Schlaganfall

Filter: Treffergenauigkeit  $\geq 20\%$

Treffer: 11

Ausschluss nach Beurteilung vom Titel: 8

Verblieben: 3 (#11-#13)

**Gefundene Literatur zum Thema Physiotherapie:**

**#01:** Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014 Feb 4;9(2):e87987. doi: 10.1371/journal.pone.0087987. PMID: 24505342; PMCID: PMC3913786.

**#02:** D'Anci KE, Uhl S, Oristaglio J, Sullivan N, Tsou AY. Treatments for Poststroke Motor Deficits and Mood Disorders: A Systematic Review for the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Guidelines for Stroke Rehabilitation. Ann Intern Med. 2019 Dec 17;171(12):906-915. doi: 10.7326/M19-2414. Epub 2019 Nov 19. PMID: 31739315

**#03:** Hayward KS, Kramer SF, Thijs V, Ratcliffe J, Ward NS, Churilov L, Jolliffe L, Corbett D, Cloud G, Kaffenberger T, Brodtmann A, Bernhardt J, Lannin NA. A systematic review protocol of timing, efficacy

and cost effectiveness of upper limb therapy for motor recovery post-stroke. Syst Rev. 2019 Jul 25;8(1):187. doi: 10.1186/s13643-019-1093-6. PMID: 31345263; PMCID: PMC6657039.

**#04:** Schröder J, Truijen S, Van Crieking T, Saeys W. Feasibility and effectiveness of repetitive gait training early after stroke: A systematic review and meta-analysis. J Rehabil Med. 2019 Feb 1;51(2):78-88. doi: 10.2340/16501977-2505. PMID: 30516821.

**#05:** Lynch E, Hillier S, Cadilhac D. When should physical rehabilitation commence after stroke: a systematic review. Int J Stroke. 2014 Jun;9(4):468-78. doi: 10.1111/ij.s.12262. Epub 2014 Mar 18. PMID: 24636633.

**#06:** Rethnam V, Langhorne P, Churilov L, Hayward KS, Herisson F, Poletto SR, Tong Y, Bernhardt J. Early mobilisation post-stroke: a systematic review and meta- analysis of individual participant data. Disabil Rehabil. 2020 Jul 16:1-8. doi: 10.1080/09638288.2020.1789229. Epub ahead of print. PMID: 32673130. Nur Abstract zu bekommen

**#07:** Knecht S, Hesse S, Oster P Rehabilitation After Stroke. Deutsches Ärzteblatt International 2011; 108(36):600-U29. PMID: 21966318

**#08:** Serrada I, McDonnell MN, Hillier SL What is current practice for upper limb rehabilitation in the acute hospital setting following stroke? A systematic review. Neurorehabilitation 2016; 39(3):431-8

**#09:** Pollock A, Baer G, Campbell P et al. Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database Syst Rev 2014; (4):CD001920

**#10:** Langhorne P, Collier JM, Bate PJ, Thuy MNT, Bernhardt J. Very early versus delayed mobilisation after stroke. Cochrane Database of Systematic Reviews 2018. DOI 10.1002/14651858.CD006187.pub3

**#11:** S3-Leitlinie Rehabilitative Therapie bei Armparese nach Schlaganfall der DGNR (AWMF-Register-Nr. 080-001).

**#12:** S3-Leitlinie Schlaganfall der DEGAM (AWMF Register-Nr. 053-011)

**#13:** S2k-Leitlinie Rehabilitation von sensomotorischen Störungen (AWMF Register-Nr. 030-123).

**Bewertung:**

<b>Studie (review)</b>	<b>#01:</b> Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014 Feb 4;9(2):e87987
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs
2. Welche Interventionen sind betrachtet/untersucht worden? Physiotherapie := „therapeutic modalities frequently used in physical therapy specialty by physical therapists or physiotherapists to promote, maintain, or restore the physical and physiological well-being of an individual“ Die Behandlungen wurden unterteilt in: (1) interventions related to gait and mobility-related functions and activities, including novel methods focusing on efficient resource use, such as circuit class training and caregivermediated exercises; (2) interventions related to arm-hand activities; (3) interventions related to activities of daily living; (4) interventions related to physical fitness; and ( (5) other interventions which could not be classified into one of the other categories. In addition, attention was paid to (6) intensity of practice and (7) neurological treatment approaches.
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? „The primary outcomes were at the body functions and activities and participation levels, while secondary outcomes included contextual factors“

4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.		
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? n.a.		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
<p>The search yielded 467 RCTs (N = 25373; median PEDro score 6 [IQR 5–7]), identifying 53 interventions. No adverse events were reported. Strong evidence was found for significant positive effects of 13 interventions related to gait, 11 interventions related to arm-hand activities, 1 intervention for ADL, and 3 interventions for physical fitness. Summary Effect Sizes (SEs) ranged from 0.17 (95%CI 0.03–0.70; I2 = 0%) for therapeutic positioning of the paretic arm to 2.47 (95%CI 0.84–4.11; I2 = 77%) for training of sitting balance. There is strong evidence that a higher dose of practice is better, with SEs ranging from 0.21 (95%CI 0.02–0.39; I2 = 6%) for motor function of the paretic arm to 0.61 (95%CI 0.41–0.82; I2 = 41%) for muscle strength of the paretic leg. Subgroup analyses yielded significant differences with respect to timing poststroke for 10 interventions. Neurological treatment approaches to training of body functions and activities showed equal or unfavorable effects when compared to other training interventions. Main limitations of the present review are not using individual patient data for meta-analyses and absence of correction for multiple testing. Remarkably, only three RCTs started their intervention within the first days poststroke, despite evidence that most patients are physical inactive early poststroke.</p>		
<b>IV. Ableitbare Empfehlung</b>		
<p>There is strong evidence for PT interventions favoring intensive high repetitive task-oriented and task-specific training in all phases poststroke. Effects are mostly restricted to the actually trained functions and activities. Nur wenige Studien zur Akuttherapie, kein signifikante Interaction des timing</p>		

<b>Studie (review)</b>	#02: D'Anci KE, Uhl S, Oristaglio J, Sullivan N, Tsou AY. Treatments for Poststroke Motor Deficits and Mood Disorders: A Systematic Review for the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Guidelines for Stroke Rehabilitation. Ann Intern Med. 2019 Dec 17;171(12):906-915
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Review fokussierte sich auf Studien im ambulanten setting, also nicht die Stroke Unit Akutbehandlung
<b>I. Beschreibung des Reviews</b>	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? SR, RCTs	
2. Welche Interventionen sind betrachtet/untersucht worden? Interventions included therapies for rehabilitation of motor deficits and behavioral health interventions for poststroke mood disorders	
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Critical outcomes included functional independence measures, ADLs, gait speed or velocity, performance measures, return to work, validated depression or anxiety measures, and quality of life. Only data from outcomes measured by using validated instruments were abstracted.	
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.	
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? outpatient	
<b>III. Ergebnisse</b>	
<p>Most interventions (for example, SSRIs, mental practice, mirror therapy) did not improve motor function. High-quality evidence did not support use of fluoxetine to improve motor function. Moderate-quality evidence supported use of cardiorespiratory training to improve maximum walking speed and repetitive task training or transcranial direct current stimulation to improve activities of daily living (ADLs). Low-quality evidence supported use of robotic arm training to improve ADLs.</p>	



<b>IV. Ableitbare Empfehlung</b>
./.

<b>Studie (review)</b>	<b>#03:</b> Hayward KS, Kramer SF, Thijs V, Ratcliffe J, Ward NS, Churilov L, Jolliffe L, Corbett D, Cloud G, Kaffenberger T, Brodtmann A, Bernhardt J, Lannin NA. A systematic review protocol of timing, efficacy and cost effectiveness of upper limb therapy for motor recovery post-stroke. Syst Rev. 2019 Jul 25;8(1):187
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Publikation des Protokolls eines SR

<b>III. Ergebnisse</b>
------------------------

<b>IV. Ableitbare Empfehlung</b>
./.

<b>Studie (review)</b>	<b>#04:</b> Schröder J, Truijen S, Van Criekinge T, Saeys W. Feasibility and effectiveness of repetitive gait training early after stroke: A systematic review and meta-analysis. J Rehabil Med. 2019 Feb 1;51(2):78-88.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Die untersuchten Studien schlossen die Patienten im Mittel nach 9-26 Tagen ein, also nicht während der Stroke Unit Phase

<b>I. Beschreibung des Reviews</b>
------------------------------------

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs
2. Welche Interventionen sind betrachtet/untersucht worden? The focus here is on the early rehabilitation phase, defined as the first 3 months post-stroke, i.e. the period during which most gait recovery gains are observed. Studies initiating gait training within a mean of at most 31 days post-stroke were included, to guarantee that the investigated population was exposed to the intervention within this time-window.
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? All included studies had to include the ability to walk independently (primary outcome) as an outcome measure. Secondary gait-related outcomes were included, such as motor impairments of the affected leg and different measures on walking performance.
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)?

<b>III. Ergebnisse</b>
------------------------

Fifteen randomized controlled trials were included. Repetitive training can safely be provided through body weight support and locomotor assistance from therapists or a robotic device. No difference in drop-out rates was reported despite the demanding nature of the intervention. The metaanalysis yielded significant, but small, effects on walking independence and endurance. Training with end-effector robots appears most effective.

<b>IV. Ableitbare Empfehlung</b>
./.

<b>Studie (review)</b>	<b>#05:</b> Lynch E, Hillier S, Cadilhac D. When should physical rehabilitation commence after stroke: a systematic review. Int J Stroke. 2014 Jun;9(4):468-78.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

<b>I. Beschreibung des Reviews</b>
------------------------------------

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? we included 5 randomized controlled trials and 38 cohort studies

2. Welche Interventionen sind betrachtet/untersucht worden? The aims of this systematic review were to determine when it is best to commence physical rehabilitation post-stroke. Specifically:		
1. To update: What are the effects on mortality, function and complications when physical rehabilitation is commenced 'early' i.e. within seven days of stroke?		
2. When sustained rehabilitation is not provided by an acute SU, what are the effects of earlier transfer to a designated rehabilitation ward/hospital?		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Outcomes of interest in this review were differences in the health and functional outcomes of people with stroke		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.		
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? Acute und comprehensive (reha) stroke units		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
<p>Three RCTs used similar protocols to commence physical rehabilitation early on SUs, and compared this to usual SU care in Australia, United Kingdom and Norway. Overall, 159 people with stroke were included in early (versus usual SU care) rehabilitation trials. We found a trend for fewer deaths in the usual care group which was mobilized 24–48 h post stroke [P = 0.06, OR 2.58 (95% CI 0.98–6.79)]. At 3 months there was no significant difference between groups in BI [P = 0.23, OR 1.20 (95% CI – 0.77–3.18)]. The likelihood of having a good outcome and experiencing no complications within 3 months following stroke was similar between groups, (P = 0.66 and P = 0.82 respectively).</p> <p>One RCT provided evidence that commencing physical rehabilitation 3 days compared to 7 days after stroke resulted in significantly fewer serious complications, and did not influence cerebral blood flow</p>		
<b>IV. Ableitbare Empfehlung</b>		
<p>From this review we have found that the current research is very limited regarding the ideal time point at which to commence physical rehabilitation and the benefits of commencing physical rehabilitation early. Further, the studies included in our review had several limitations including study design, small sample sizes and the ability to fully account for factors that may influence the associations with health outcomes. This review highlights that further well-designed research is needed.</p> <p>There is some evidence that physical rehabilitation should commence within 3 days of stroke, but the benefits of commencing physical rehabilitation within 24 h of stroke remain unclear.</p>		

<b>Studie (review)</b>	<b>#06:</b> Rethnam V, Langhorne P, Churilov L, Hayward KS, Herisson F, Poletto SR, Tong Y, Bernhardt J. Early mobilisation post-stroke: a systematic review and meta- analysis of individual participant data. Disabil Rehabil. 2020 Jul 16:1-8.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Nur als Abstract erhältlich, Autoren idem zu #10
<b>III. Ergebnisse</b>	
Nur Abstract zu bekommen	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (review)</b>	<b>#07:</b> Knecht S, Hesse S, Oster P Rehabilitation After Stroke. Deutsches Ärzteblatt International 2011; 108(36):600-U29.
Bearbeiter	Peter A. Ringleb

Ausschluss	<b>JA</b>
Begründung	Kein systematisches review
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (review)</b>	<b>#08:</b> Serrada I, McDonnell MN, Hillier SL What is current practice for upper limb rehabilitation in the acute hospital setting following stroke? A systematic review. Neurorehabilitation 2016; 39(3):431-8
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Das review hatte das Ziel herauszubekommen wieviel Zeit für PT und / oder OT zur Reha des Armes verwendet wird, nicht ob das was nutzt
<b>I. Beschreibung des Reviews</b>	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Studies were eligible if they were <u>observational studies</u> of adults with a confirmed diagnosis and within 4 weeks post-stroke; receiving Physiotherapy (PT) and/or Occupational Therapy (OT);	
2. Welche Interventionen sind betrachtet/untersucht worden? PT/OT	
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? included amount of therapy time devoted to UL and/or types of interventions	
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.	
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)?	
<b>III. Ergebnisse</b>	
From the 94 studies reviewed, seven studies involving 3236 participants met the inclusion criteria. Pooled results indicated that 7.9 min/day (21.4%) of a total 36.7 min/day combined PT and OT session was devoted to UL therapy.	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (review)</b>	<b>#09:</b> Pollock A, Baer G, Campbell P et al. Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database Syst Rev 2014; (4):CD001920		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung des Reviews</b>			
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs			
2. Welche Interventionen sind betrachtet/untersucht worden? physical rehabilitation approaches aimed at promoting the recovery of function or mobility in adult participants with a clinical diagnosis of stroke.			
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Outcomes included measures of independence in activities of daily living (ADL), motor function, balance, gait velocity and length of stay.			
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.			
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? n.a.			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X	
2. Ist die Literatursuche angemessen beschrieben?		X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?			X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X	

<b>Gesamtbeurteilung</b>	<b>++</b>
<b>III. Ergebnisse</b>	
<p>We included a total of 96 studies (10,401 participants) in this review. More than half of the studies (50/96) were carried out in China. Generally, the studies were heterogeneous, and many were poorly reported.</p> <p>Physical rehabilitation was found to have a beneficial effect, as compared with no treatment, on functional recovery after stroke (27 studies, 3423 participants; standardised mean difference (SMD) 0.78, 95% confidence interval (CI) 0.58 to 0.97, for Independence in ADL scales), and this effect was noted to persist beyond the length of the intervention period (nine studies, 540 participants; SMD 0.58, 95% CI 0.11 to 1.04). Subgroup analysis revealed a significant difference based on dose of intervention (P value &lt; 0.0001, for independence in ADL), indicating that a dose of 30 to 60 minutes per day delivered five to seven days per week is effective. This evidence principally arises from studies carried out in China. Subgroup analyses also suggest significant benefit associated with a shorter time since stroke (P value 0.003, for independence in ADL).</p> <p>We found physical rehabilitation to be more effective than usual care or attention control in improving motor function (12 studies, 887 participants; SMD 0.37, 95% CI 0.20 to 0.55), balance (five studies, 246 participants; SMD 0.31, 95% CI 0.05 to 0.56) and gait velocity (14 studies, 1126 participants; SMD 0.46, 95% CI 0.32 to 0.60). Subgroup analysis demonstrated a significant difference based on dose of intervention (P value 0.02 for motor function), indicating that a dose of 30 to 60 minutes delivered five to seven days a week provides significant benefit. Subgroup analyses also suggest significant benefit associated with a shorter time since stroke (P value 0.05, for independence in ADL).</p> <p>No one physical rehabilitation approach was more (or less) effective than any other approach in improving independence in ADL (eight studies, 491 participants; test for subgroup differences: P value 0.71) or motor function (nine studies, 546 participants; test for subgroup differences: P value 0.41). These findings are supported by subgroup analyses carried out for comparisons of intervention versus no treatment or usual care, which identified no significant effects of different treatment components or categories of interventions.</p>	
<b>IV. Ableitbare Empfehlung</b>	
<p>Physical rehabilitation, comprising a selection of components from different approaches, is effective for recovery of function and mobility after stroke. Evidence related to dose of physical therapy is limited by substantial heterogeneity and does not support robust conclusions.</p> <p>No one approach to physical rehabilitation is any more (or less) effective in promoting recovery of function and mobility after stroke.</p>	

<b>Studie (review)</b>	#10: Langhorne P, Collier JM, Bate PJ, Thuy MNT, Bernhardt J. Very early versus delayed mobilisation after stroke. Cochrane Database of Systematic Reviews 2018.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung des Reviews</b>			
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Randomised controlled trials (RCTs) of people with acute stroke,			
2. Welche Interventionen sind betrachtet/untersucht worden? comparing an intervention group that started out-of-bed mobilisation within 48 hours of stroke, and aimed to reduce time-to-first mobilisation, with or without an increase in the amount or frequency (or both) of mobilisation activities, with usual care, where time-to-first mobilisation was commenced later			
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Death oder dependence, poor outcome			
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.			
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? acute stroke unit			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X	
2. Ist die Literatursuche angemessen beschrieben?		X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X	

<b>Gesamtbeurteilung</b>	<b>++</b>
<b>III. Ergebnisse</b>	
<p>We included nine RCTs with 2958 participants; one trial provided most of the information (2104 participants). The median (range) delay to starting mobilisation after stroke onset was 18.5 (13.1 to 43) hours in the VEM group and 33.3 (22.5 to 71.5) hours in the usual care group.</p> <p>Primary outcome data were available for 2542 of 2618 (97.1%) participants randomized and followed up for a median of three months. VEM probably led to similar or slightly more deaths and participants who had a poor outcome, compared with delayed mobilisation (51% versus 49%; odds ratio (OR) 1.08, 95% confidence interval (CI) 0.92 to 1.26; P = 0.36; 8 trials; moderate-quality evidence). Death occurred in 7% of participants who received delayed mobilisation, and 8.5% of participants who received VEM (OR 1.27, 95% CI 0.95 to 1.70; P = 0.11; 8 trials, 2570 participants; moderate-quality evidence), and the effects on experiencing any complication were unclear (OR 0.88; 95% CI 0.73 to 1.06; P = 0.18; 7 trials, 2778 participants; low-quality evidence). Analysis using outcomes collected only at three-month follow-up did not alter the conclusions.</p> <p>The mean ADL score (measured at end of follow-up, with the 20-point Barthel Index) was higher in those who received VEM compared with the usual care group (mean difference (MD) 1.94, 95% CI 0.75 to 3.13, P = 0.001; 8 trials, 9 comparisons, 2630/2904 participants (90.6%); low quality evidence), but there was substantial heterogeneity (93%). Effect sizes were smaller for outcomes collected at three-month follow up, rather than later.</p> <p>The mean length of stay was shorter in those who received VEM compared with the usual care group (MD -1.44, 95% CI -2.28 to -0.60, P = 0.0008; 8 trials, 2532/2618 participants (96.7%); low-quality evidence). Confidence in the answer was limited by the variable definitions of length of stay. The other secondary outcome analyses (institutionalisation, extended activities of daily living, quality of life, walking ability, patient mood) were limited by lack of data.</p> <p>Sensitivity analysis by intervention characteristics: analyses restricted to trials where the mean VEM time-to-first mobilisation was less than 24 hours, showed an odds of death of 1.35 (95% CI 0.99 to 1.83; P = 0.06; IO = 25%; 5 trials). Analyses restricted to the trials that clearly reported a more prolonged out-of-bed activity showed a similar primary outcome (OR 1.14; 0.96 to 1.35; P = 0.13; IO = 28%; 5 trials), and odds of death (OR 1.27; 0.93 to 1.73; P = 0.13; IO = 0%; 4 trials) to the main analysis.</p>	
<b>IV. Ableitbare Empfehlung</b>	
<p>VEM, which usually involved first mobilisation within 24 hours of stroke onset, did not increase the number of people who survived or made a good recovery after their stroke. VEM may have reduced the length of stay in hospital by about one day, but this was based on low-quality evidence. Based on the potential hazards reported in the single largest RCT, the sensitivity analysis of trials commencing mobilisation within 24 hours, and the NMA, there was concern that VEM commencing within 24 hours may carry an increased risk, at least in some people with stroke. Given the uncertainty around these effect estimates, more detailed research is still required.</p>	

**#11:** Enthält weniger Empfehlungen zum timing: Soweit der klinische Zustand des Patienten es erlaubt, sollte ein früher Beginn der Rehabilitation der Armmotorik innerhalb weniger Tage nach dem Schlaganfall erfolgen (Evidenz niedrig [da kein RCT mit frühem vs. spätem Beginn], Einschätzung der Effekte: sehr niedrige Qualität; Empfehlungsgrad B [klinische Plausibilität]; starker Konsens). Wird bei subakuten Schlaganfallpatienten eine Beschleunigung der Armaktivitäten angestrebt, dann sollen werktägliche Behandlungsintensitäten von mindestens 30 Minuten zum Einsatz kommen (Evidenz 1b, Einschätzung der Effekte: hohe Qualität; Empfehlungsgrad A; starker Konsens).

Bei fortbestehenden funktionellen Defiziten (Kriterium 1) und der individuellen Dokumentation von funktionellen Verbesserungen unter Therapie (bzw. auch funktionellen Verschlechterungen nach deren Absetzung) (Kriterium 2) sollten zur Erreichung individueller Therapieziele auch im chronischen Stadium Maßnahmen spezifischer Armrehabilitation durchgeführt werden; wöchentlich 90 - 270 Minuten strukturiertes repetitives Training von Schulter-, Ellenbogen-, sowie Handgelenks- und Fingerbewegungen bei mittelschwerer bis schwerer Armlähmung, ggf. unterstützt durch (EMG-getriggerte) Elektrostimulation oder funktionelles aufgabenbezogenes Training mit wiederkehrenden Behandlungsphasen (und Pausen) sollten zur Verbesserung der Armaktivitäten im Alltag durchgeführt (Evidenz 2b, Einschätzung der Effekte: mittlere Qualität; Empfehlungsgrad B; starker Konsens).

Basiert im Wesentlichen auf einer randomisierten Studie von Kwakkel et al., 1999, 2002 mit wenigen Patienten (n=101 bzw. 86 nach 1 Jahr).

**#12:** Enthält keine Empfehlungen mit Bezug zum timing von Physiotherapie

**#13:** Enthält – methodenbedingt – keine Evidenzgrade oder Empfehlungsstärken. Wenige Empfehlungen und keine zum timing.

**SF 1.6.2:** [Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt eine frühzeitige Ergotherapie im Vergleich zum Verzicht darauf das funktionelle Outcome?](#)

Evidenzgewinnung am 30.09.2020

#### **MedLine**

Suchterm: (occupational therapy) AND (acute stroke)

Filter: systematic review, last 10 years

Treffer: 125

Ausschluss nach Beurteilung von Titel/Abstract: 121

Ausschluss von Doubletten der obigen Suche: 1

Verblieben: 3 (#01-#03)

#### **Web of Science**

Suchterm: (occupational therapy) AND (acute stroke)

Filter: review, 2000-2020

Treffer: 24

Ausschluss nach Beurteilung von Titel/Abstract: 22

Ausschluss von Doubletten der obigen Suche: 2

Verblieben: 0

#### **Cochrane library**

Suchterm: "occupational therapy" AND stroke

Treffer: 9

Ausschluss nach Beurteilung von Titel/Abstract: 9

Verblieben: 0

#### **AWMF-Leitlinien**

Stichwortsuche: Ergotherapie Schlaganfall

Filter: Treffergenauigkeit  $\geq 20\%$

Treffer: 9

Ausschluss nach Beurteilung von Titel/Abstract: 6

Ausschluss von Doubletten der obigen Suche: 3

Verblieben: 0

#### **Gefundene Literatur zum Thema Ergotherapie:**

**#01:** Wattchow KA, McDonnell MN, Hillier SL. Rehabilitation Interventions for Upper Limb Function in the First Four Weeks Following Stroke: A Systematic Review and Meta-Analysis of the Evidence. Arch Phys Med Rehabil. 2018 Feb;99(2):367-382. doi: 10.1016/j.apmr.2017.06.014. Epub 2017 Jul 20. PMID: 28734936.

**#02:** Kringle EA, Barone Gibbs B, Campbell G, McCue M, Terhorst L, Kersey J, Skidmore ER. Influence of Interventions on Daily Physical Activity and Sedentary Behavior after Stroke: A Systematic Review. PM R. 2020 Feb;12(2):186-201. doi: 10.1002/pmrj.12222. Epub 2019 Jul 22. PMID: 31329372.

**#03:** Allison R, Shenton L, Bamforth K, Kilbride C, Richards D. Incidence, Time Course and Predictors of Impairments Relating to Caring for the Profoundly Affected arm After Stroke: A Systematic Review. Physiother Res Int. 2016 Dec;21(4):210-227. doi: 10.1002/pri.1634. Epub 2015 May 25. PMID: 26015292; PMCID: PMC5157782.

**Bewertung:**

<b>Studie (review)</b>	#01: Wattchow KA, McDonnell MN, Hillier SL. Rehabilitation Interventions for Upper Limb Function in the First Four Weeks Following Stroke: A Systematic Review and Meta-Analysis of the Evidence. Arch Phys Med Rehabil. 2018 Feb;99(2):367-382.	
Bearbeiter	Andreas Harloff	
Ausschluss	NEIN	
Begründung	Qualitativ gutes systematic review	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? In das Review wurden 83 randomisiert-kontrollierte und 21 nicht-randomisierte Studien aufgenommen. Jede Art von interventioneller Studien mit einer Untersuchung vor und nach der Intervention (=Ergotherapie) wurde eingeschlossen. Fallserien wurden ausgeschlossen		
2. Welche Interventionen sind betrachtet/untersucht worden? Insgesamt wurden 21 verschiedene Therapien zur Behandlung von Defiziten der oberen Extremität untersucht, die im Review im Einzelnen definiert bzw. erklärt werden. Vergleichstherapien waren a) die übliche Behandlung (diese wurde aber in der Regel schlecht definiert in den Studien) oder Standard-Ergotherapie zur Behandlung eines Defizits der oberen Extremität b) Scheinbehandlung oder c) eine andere Technik.		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Funktion der oberen Extremität von Patienten in den ersten vier Wochen nach Schlaganfall. Endpunkte waren jede Art der Messung der Einschränkung oder Aktivität der oberen Extremität (outcome measure scales), die im Review aber nicht genauer definiert sind		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung), die im Review aufgeführt werden, waren folgende: es wurden nur Erwachsene eingeschlossen; es wurden Patienten eingeschlossen, die innerhalb von vier Wochen nach Schlaganfall (jeder Art); mit einem Defizit der oberen Extremität behandelt wurden Basisdaten der Patienten sind im Review nicht aufgezählt		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
<ul style="list-style-type: none"> <li>Für die modifizierte constraint-induced Bewegungstherapie (mCIMT) und das Aufgaben-spezifische Training gab es einen ausreichenden (sufficient) level of evidence, um die routinemäßige Anwendung zu empfehlen.</li> <li>Für Biofeedbackmethoden und die elektrische Stimulation gab es einen ausreichenden (sufficient) level of evidence, um diese als Zusatztherapien der üblichen Behandlung (usual care) zu empfehlen.</li> <li>Für 16 Therapien (air splints, bilateral arm-training, circuit class therapy, interventions for somatosensory functions, Kinesio tape, mechanical arm trainer, medication, mirror box therapy, music therapy, passive movement, reflex inhibiting/immobilization, robotics, shoulder strapping/orthosis, static positional stretches, strength training, virtual reality training/videogaming) gab es einen unzureichenden level of evidence, um die Anwendung in der üblichen Behandlung zu empfehlen oder davon abzuraten.</li> <li>Für die Bobath-Therapie gab es einen ausreichenden level of evidence, um von der Therapie als Routineverfahren (routine use) abzuraten.</li> </ul>		
<b>IV. Ableitbare Empfehlung</b>		

Patienten mit akutem Schlaganfall sollten in den ersten 28 Tagen nach Ereignis zur Verbesserung der Funktion der oberen Extremität die modifizierte constraint use Bewegungstherapie und/oder Aufgaben-spezifische Therapie erhalten. Wirkungsvolle und daher ebenfalls empfehlenswerte ergänzende Verfahren sind die Biofeedbackmethode und die elektrische Stimulation. Die Bobath-Therapie sollte als Routineverfahren nicht angewendet werden. Die aktuelle Evidenz reicht nicht aus, um die Routineanwendung der anderen Therapieformen zu empfehlen oder von ihnen abzuraten.  
 Weitere qualitativ hochwertige Studien sollten durchgeführt werden, um den Effekt einzelner Therapieformen für die Verbesserung der Funktion der oberen Extremität bei Schlaganfallpatienten in der Akutphase zu untersuchen.

<b>Studie (review)</b>	#02: Kringle EA, Barone Gibbs B, Campbell G, McCue M, Terhorst L, Kersey J, Skidmore ER. Influence of Interventions on Daily Physical Activity and Sedentary Behavior after Stroke: A Systematic Review. PM R. 2020 Feb;12(2):186-201.		
Bearbeiter	A. Harloff		
Ausschluss	<b>JA</b>		
Begründung	Bei diesem systematic Review wurden vor allem chronische Schlaganfallpatienten untersucht. Nur bei einer von 31 Studien wurden akute Schlaganfallpatienten eingeschlossen (siehe Table 1 3. Spalte, chronicity). Bei 2-3 gab es keine Angabe, zu welchem Zeitpunkt nach Schlaganfall die Patienten eingeschlossen wurden. Somit ist das Review nicht geeignet für unsere Fragestellung.		
<b>I. Beschreibung des Reviews</b>			
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 Studenumfelds (Setting, z.B. Praxis, Klinik)?			
<b>II. Interne Validität</b>			
	<b>Ja</b>	<b>Nein</b>	
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?			
<b>Gesamtbeurteilung</b>	<b>++</b>	<b>+</b>	<b>--</b>
<b>III. Ergebnisse</b>			
<b>IV. Ableitbare Empfehlung</b>			

<b>Studie (review)</b>	#03: Allison R, Shenton L, Bamforth K, Kilbride C, Richards D. Incidence, Time Course and Predictors of Impairments Relating to Caring for the Profoundly Affected arm After Stroke: A Systematic Review. Physiother Res Int. 2016 Dec;21(4):210-227.		
Bearbeiter	A. Harloff		
Ausschluss	<b>JA</b>		
Begründung	"The purpose of this review was to identify the incidence and natural course of pain, spasticity, contracture and difficulty with passive care in the profoundly affected arm and to identify potential predictors of difficulty caring for the arm or these related impairments."  Es gibt also keine Intervention, die untersucht wurde, so dass das Review nicht passt für unsere PICO-Frage		
<b>I. Beschreibung des Reviews</b>			
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)?			
<b>II. Interne Validität</b>			
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?			
<b>Gesamtbeurteilung</b>			++ + + --
<b>III. Ergebnisse</b>			
<b>IV. Ableitbare Empfehlung</b>			

SF 1.6.3: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt eine frühzeitige logopädische Behandlung im Vergleich zum Verzicht darauf das funktionelle Outcome?

Datum der Evidenzgewinnung 30.09.2020

**MedLine**

A) Suchterm: (logopedic or logopaedic or speech therapy) and (acute stroke)

Filter: systematic review

Treffer: 61

Ausschluss nach Beurteilung von Titel/Abstract: 47

Ausgeschlossen wurden auch Arbeiten, bei denen es um Dysphagie oder um die Behandlung von Kindern ging

Verblieben: 14

Ausschluss von Aktualisierungen: 8

Verblieben: 6 (#01-#06)

B) Suchterm: (logopedic or logopaedic or speech therapy) and (acute stroke)

Filter: Randomized clinical trial, published within 10 years

Treffer: 111

Ausschluss nach Beurteilung von Titel/Abstract: 107

Verblieben: #08-#11

Davon berichten zwei Manuskripte über das Design der VERSE-Studie, die als #12 addiert wurde und ein Manuskript über das Design der Rotterdam Aphasia Therapy Study-3, die als #13 addiert wurde.

**Web of Science**

Suchterm: ((logopedic or logopaedics) or speech therapy) and (acute stroke)

Filter: review

Treffer: 33

Ausschluss nach Beurteilung von Titel/Abstract: 31

Ausgeschlossen wurden auch Arbeiten, bei denen es um Dysphagie oder um die Behandlung von Kindern ging

Ausschluss nicht englischer/deutscher Artikel: 1

Verblieben: 1 (#07)

**Cochrane library**

Suchterm: Speech therapy

Treffer: 61

Ausschluss nach Beurteilung von Titel/Abstract: 59

Verblieben: 2 (die beiden in der MedLine-Suche gefundenen Cochrane Reviews #01 und #02)

### **AWMF-Leitlinien**

Stichwortsuche: Logopädie

Treffer: 1

Ausschluss nach Beurteilung des Titels: 1

Verblieben: 0

### **Gefundene Literatur zum Thema Logopädie:**

**#01:** Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev.* 2016 Jun 1;(6):CD000425. doi: 10.1002/14651858.CD000425.pub4. PMID: 27245310.

**#02:** Mitchell C, Bowen A, Tyson S, Butterfint Z, Conroy P. Interventions for dysarthria due to stroke and other adult-acquired, non-progressive brain injury. *Cochrane Database Syst Rev.* 2017 Jan 25;1(1):CD002088. doi: 10.1002/14651858.CD002088.pub3. PMID: 28121021; PMCID: PMC6464736.

**#03:** Stephens M. The Effectiveness of Speech and Language Therapy for Poststroke Aphasia. *Am J Nurs.* 2017 Nov;117(11):19. doi: 10.1097/01.NAJ.0000526741.00314.d9. PMID: 29076848.

**#04:** Chiaramonte R, Pavone P, Vecchio M. Speech rehabilitation in dysarthria after stroke, a systematic review of the studies. *Eur J Phys Rehabil Med.* 2020 May 19. doi: 10.23736/S1973-9087.20.06185-7. Epub ahead of print. PMID: 32434313.

**#05:** Cherney LR, Patterson JP, Raymer A, Frymark T, Schooling T. Evidence-based systematic review: effects of intensity of treatment and constraint-induced language therapy for individuals with stroke-induced aphasia. *J Speech Lang Hear Res.* 2008 Oct;51(5):1282-99. doi: 10.1044/1092-4388(2008/07-0206). PMID: 18812489.

**#06:** Greener J, Enderby P, Whurr R, Grant A. Treatment for aphasia following stroke: evidence for effectiveness. *Int J Lang Commun Disord.* 1998;33 Suppl:158-61. doi: 10.3109/13682829809179414. PMID: 10343683.

**#07:** Cherney LR, Patterson JP, Raymer AM Intensity of Aphasia Therapy: Evidence and Efficacy. *Current Neurology and Neuroscience Reports* 2011; 11(6):560-9

**#08:** Godecke E, Armstrong EA, Rai T, Middleton S, Ciccone N, Whitworth A, Rose M, Holland A, Ellery F, Hankey GJ, Cadilhac DA, Bernhardt J. A randomized controlled trial of very early rehabilitation in speech after stroke. *Int J Stroke.* 2016 Jul;11(5):586-92. doi: 10.1177/1747493016641116. Epub 2016 May 5. PMID: 27151156.

**#09:** Godecke E, Rai T, Cadilhac DA, Armstrong E, Middleton S, Ciccone N, Whitworth A, Rose ML, Holland A, Ellery F, Hankey GJ, Bernhardt J; VERSE Collaboration. Statistical analysis plan (SAP) for the Very Early Rehabilitation in Speech (VERSE) after stroke trial: an international 3-arm clinical trial to determine the effectiveness of early, intensive, prescribed, direct aphasia therapy. *Int J Stroke.* 2018 Oct;13(8):863-880. doi: 10.1177/1747493018790055. Epub 2018 Oct 1. PMID: 30270762.

**#10:** Nouwens F, Dippel DW, de Jong-Hagelstein M, Visch-Brink EG, Koudstaal PJ, de Lau LM; RATS-3 investigators. Rotterdam Aphasia Therapy Study (RATS)-3: "The efficacy of intensive cognitive-linguistic therapy in the acute stage of aphasia"; design of a randomised controlled trial. *Trials.* 2013 Jan 23;14:24. doi: 10.1186/1745-6215-14-24. PMID: 23343197; PMCID: PMC3560268.

**#11:** Shrubsole K, Worrall L, Power E, O'Connor DA. The Acute Aphasia IMplementation Study (AAIMS): a pilot cluster randomized controlled trial. *Int J Lang Commun Disord.* 2018 Sep;53(5):1021-1056. doi: 10.1111/1460-6984.12419. Epub 2018 Aug 5. PMID: 30079573.

**#12:** Godecke E, Armstrong E, Rai T, Ciccone N, Rose ML, Middleton S, Whitworth A, Holland A, Ellery F, Hankey GJ, Cadilhac DA, Bernhardt J; VERSE Collaborative Group. A randomized control trial of

intensive aphasia therapy after acute stroke: The Very Early Rehabilitation for SpEEch (VERSE) study. Int J Stroke. 2020 Oct 6:1747493020961926. doi: 10.1177/1747493020961926. Epub ahead of print. PMID: 33019888.

**#13:** Nouwens F, de Lau LM, Visch-Brink EG, van de Sandt-Koenderman WM, Lingsma HF, Goosen S, Blom DM, Koudstaal PJ, Dippel DW. Efficacy of early cognitive-linguistic treatment for aphasia due to stroke: A randomised controlled trial Rotterdam Aphasia Therapy Study-3). Eur Stroke J. 2017 Jun;2(2):126-136. doi:10.1177/2396987317698327. Epub 2017 Mar 10. PMID: 29900407; PMCID: PMC5992741.

**Bewertung:**

<b>Studie (review)</b>	#01: Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev. 2016 Jun 1;(6):CD000425.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs		
2. Welche Interventionen sind betrachtet/untersucht worden? comparing SLT (a formal intervention that aims to improve language and communication abilities, activity and participation) versus no SLT; social support or stimulation (an intervention that provides social support and communication stimulation but does not include targeted therapeutic interventions); or another SLT intervention (differing in duration, intensity, frequency, intervention methodology or theoretical approach).		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Functional communication, receptive language, expressive language		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? n.a.		
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
<p>We included 57 RCTs (74 randomised comparisons) involving 3002 participants in this review (some appearing in more than one comparison). Twenty-seven randomised comparisons (1620 participants) assessed SLT versus no SLT; SLT resulted in clinically and statistically significant benefits to patients' functional communication (standardised mean difference (SMD) 0.28, 95% confidence interval (CI) 0.06 to 0.49, P = 0.01), reading, writing, and expressive language, but (based on smaller numbers) benefits were not evident at follow up. Nine randomised comparisons (447 participants) assessed SLT with social support and stimulation; meta-analyses found no evidence of a difference in functional communication, but more participants withdrew from social support interventions than SLT. Thirty-eight randomised comparisons (1242 participants) assessed two approaches to SLT. Functional communication was significantly better in people with aphasia that received therapy at a high intensity, high dose, or over a long duration compared to those that received therapy at a lower intensity, lower dose, or over a shorter period of time. The benefits of a high intensity or a high dose of SLT were confounded by a significantly higher dropout rate in these intervention groups. Generally, trials randomised small numbers of participants across a range of characteristics (age, time since stroke, and severity profiles), interventions, and outcomes.</p> <p>Das Review beinhaltet auch einen Abschnitt zum Vergleich early vs delayed SLT (Zeitraum nicht näher beschrieben). Für diesen Vergleich konnten 4 Studien ausgewählt werden. Es konnte kein Hinweis auf einen Unterschied bzgl. funktioneller Kommunikation, Sprachverständnis, expressiver Sprache, Schweregrad der Aphasie. Diese Arbeit</p>		

beschäftigt sich jedoch mit der ambulanten Unterstützung von Aphasikern mit der elektronischen Sprachhilfe B.A.Bar und umfasste gerade einmal 18 Patienten.

#### IV. Ableitbare Empfehlung

Our review provides evidence of the effectiveness of SLT for people with aphasia following stroke in terms of improved functional communication, reading, writing, and expressive language compared with no therapy. There is some indication that therapy at high intensity, high dose or over a longer period may be beneficial. High-intensity and high dose interventions may not be acceptable to all.

Basierend im Wesentlichen auf einer Studie (Nobis-Bosch 2010) konnte keinen Vorteil einer frühen Logopädie in Bezug auf Kommunikation, expressiver und perzeptiver Sprache oder Aphasieschwere detektiert werden. Diese Studie ist aber nicht repräsentativ für die hier untersuchte Fragestellung

<b>Studie (review)</b>	<b>#02:</b> Mitchell C, Bowen A, Tyson S, Butterfint Z, Conroy P. Interventions for dysarthria due to stroke and other adult-acquired, non-progressive brain injury. Cochrane Database Syst Rev. 2017 Jan 25;1(1):CD002088.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

#### I. Beschreibung des Reviews

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs
2. Welche Interventionen sind betrachtet/untersucht worden? dysarthria interventions
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)?

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

#### III. Ergebnisse

We included five small trials that randomised a total of 234 participants. Two studies were assessed as low risk of bias; none of the included studies were adequately powered. Two studies used an attention control and three studies compared to an alternative intervention, which in all cases was one intervention versus usual care intervention. Four studies included only people with stroke; one included mostly people with stroke, but also those with brain injury. Three studies delivered interventions in the first few months after stroke; two recruited people with chronic dysarthria. Three studies evaluated behavioural interventions, one investigated acupuncture and another transcranial magnetic stimulation. One study included people with dysarthria within a broader trial of people with impaired communication. Our primary analysis of a persisting (three to nine months post-intervention) effect at the activity level of measurement found no evidence in favour of dysarthria intervention compared with any control (SMD 0.18, 95% CI -0.18 to 0.55; 3 trials, 116 participants, GRADE: low quality,  $I^2 = 0\%$ ). Findings from sensitivity analysis of studies at low risk of bias were similar, with a slightly wider confidence interval and low heterogeneity (SMD 0.21, 95% CI -0.30 to 0.73,  $I^2 = 32\%$ ; 2 trials, 92 participants, GRADE: low quality). Subgroup analysis results for stroke were similar to the primary analysis because few non-stroke participants had been recruited to trials (SMD 0.16, 95% CI -0.23 to 0.54,  $I^2 = 0\%$ ; 3 trials, 106 participants, GRADE: low quality).

Similar results emerged from most of the secondary analyses. There was no evidence of a persisting effect at the impairment (SMD 0.07, 95% CI -0.91 to 1.06,  $I^2 = 70\%$ ; 2 trials, 56 participants, GRADE: very low quality) or participation level (SMD -0.11, 95% CI -0.56 to 0.33,  $I^2 = 0\%$ ; 2 trials, 79 participants, GRADE: low quality) but substantial heterogeneity on the former. Analyses of immediate post-intervention outcomes provided no evidence of any short-term benefit on activity (SMD 0.29, 95% CI -0.07 to 0.66,  $I^2 = 0\%$ ; 3 trials, 117 participants, GRADE: very low quality); or participation (SMD -0.24, 95% CI -0.94 to 0.45; 1 study, 32 participants) levels of measurement.

There was a statistically significant effect favouring intervention at the immediate, impairment level of measurement (SMD 0.47, 95% CI 0.02 to 0.92, P = 0.04, I<sup>2</sup> = 0%; 4 trials, 99 participants, GRADE: very low quality) but only one of these four trials had a low risk of bias.

#### IV. Ableitbare Empfehlung

We found no definitive, adequately powered RCTs of interventions for people with dysarthria. We found limited evidence to suggest there may be an immediate beneficial effect on impairment level measures; more, higher quality research is needed to confirm this finding.

Although we evaluated five studies, the benefits and risks of interventions remain unknown and the emerging evidence justifies the need for adequately powered clinical trials into this condition.

<b>Studie (review)</b>	#03: Stephens M. The Effectiveness of Speech and Language Therapy for Poststroke Aphasia. Am J Nurs. 2017 Nov;117(11):19	
Bearbeiter	Peter A. Ringleb	
Ausschluss	JA	
Begründung	Ist eine Zusammenfassung der Daten aus #01 für Pflegepersonal	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs		
2. Welche Interventionen sind betrachtet/untersucht worden? SLT		
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 Studenumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
<b>III. Ergebnisse</b>		
<b>IV. Ableitbare Empfehlung</b>		
./.		

<b>Studie (review)</b>	#04: Chiamonte R, Pavone P, Vecchio M. Speech rehabilitation in dysarthria after stroke, a systematic review of the studies. Eur J Phys Rehabil Med. 2020 May 19	
Bearbeiter	Peter A. Ringleb	
Ausschluss	JA	
Begründung	Fasst die unterschiedlichen Techniken zusammen, macht keine Aussagen zu Wirksamkeit	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs, case series, case reports, observational studies		
2. Welche Interventionen sind betrachtet/untersucht worden? Rehabilitation speech therapy zur Dysarthrie Behandlung		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Clinical assessments, diagnostic scales, and acoustic analysis		
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 Studiumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>	--	
<b>III. Ergebnisse</b>		

<b>IV. Ableitbare Empfehlung</b>
./.

<b>Studie (review)</b>	<b>#05:</b> Cherney LR, Patterson JP, Raymer A, Frymark T, Schooling T. Evidence-based systematic review: effects of intensity of treatment and constraint-induced language therapy for individuals with stroke-induced aphasia. J Speech Lang Hear Res. 2008 Oct;51(5):1282-99
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Enthält keine Auswertungen zum Therapiezeitpunkt

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? N.a.
2. Welche Interventionen sind betrachtet/untersucht worden? constraint-induced language therapy (CILT)
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Language impairment, communication activity
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? n.a.

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>	--	

**III. Ergebnisse**

**IV. Ableitbare Empfehlung**

./.
-----

<b>Studie (review)</b>	<b>#06:</b> Greener J, Enderby P, Whurr R, Grant A. Treatment for aphasia following stroke: evidence for effectiveness. Int J Lang Commun Disord. 1998;33 Suppl:158-61.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Älteres Review für die Cochrane-Collaboration, abgelöst durch #01

**III. Ergebnisse**

**IV. Ableitbare Empfehlung**

./.
-----

<b>Studie (review)</b>	<b>#07:</b> Cherney LR, Patterson JP, Raymer AM Intensity of Aphasia Therapy: Evidence and Efficacy. Current Neurology and Neuroscience Reports 2011; 11(6):560-9
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Kein systematic review

**III. Ergebnisse**

**IV. Ableitbare Empfehlung**

./.
-----

<b>Studie (RCT)</b>	<b>#08:</b> Godecke E, Armstrong EA, Rai T, Middleton S, Ciccone N, Whitworth A, Rose M, Holland A, Ellery F, Hankey GJ, Cadilhac DA, Bernhardt J. A randomized controlled trial of very early rehabilitation in speech after stroke. Int J Stroke. 2016 Jul;11(5):586-92.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Methodenpaper von #12
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (RCT)</b>	<b>#09:</b> Godecke E, Rai T, Cadilhac DA, Armstrong E, Middleton S, Ciccone N, Whitworth A, Rose ML, Holland A, Ellery F, Hankey GJ, Bernhardt J; VERSE Collaboration. Statistical analysis plan (SAP) for the Very Early Rehabilitation in Speech (VERSE) after stroke trial: an international 3-arm clinical trial to determine the effectiveness of early, intensive, prescribed, direct aphasia therapy. Int J Stroke. 2018 Oct;13(8):863-880.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Methodenpaper von #12
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (RCT)</b>	<b>#10:</b> Nouwens F, Dippel DW, de Jong-Hagelstein M, Visch-Brink EG, Koudstaal PJ, de Lau LM; RATS-3 investigators. Rotterdam Aphasia Therapy Study (RATS)-3: "The efficacy of intensive cognitive-linguistic therapy in the acute stage of aphasia"; design of a randomised controlled trial. Trials. 2013 Jan 23;14:24
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Methodenpaper
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (RCT)</b>	<b>#11:</b> Shrubsole K, Worrall L, Power E, O'Connor DA. The Acute Aphasia IMplementation Study (AAIMS): a pilot cluster randomized controlled trial. Int J Lang Commun Disord. 2018 Sep;53(5):1021-1056.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Eine Studie an LogopädInnen und weniger an Patienten. Diese Studie testete die Durchführbarkeit, Akzeptanz und potenzielle Wirksamkeit einer individualisierten Umsetzungsstrategie zur Verbesserung der Umsetzung von Evidenz durch Logopäden in zwei Praxisbereichen: aphasiefreundliche Informationsbereitstellung und gemeinsame Zielsetzung,
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	
./.	

<b>Studie (RCT)</b>	#12: Godecke E, Armstrong E, Rai T, Ciccone N, Rose ML, Middleton S, Whitworth A, Holland A, Ellery F, Hankey GJ, Cadilhac DA, Bernhardt J; VERSE Collaborative Group. A randomized control trial of intensive aphasia therapy after acute stroke: The Very Early Rehabilitation for SpEech (VERSE) study. Int J Stroke. 2020 Oct 6.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung der Studie</b>			
8.	Welche Intervention wurde untersucht? intensive aphasia therapy, beginning within 14 days after stroke. randomized to receive usual care (direct usual care aphasia therapy), or one of two higher intensity regimens (20 sessions of either non-prescribed (usual care-plus or prescribed (VERSE) direct aphasia therapy)		
9.	Welche Zielkriterien (Endpunkte) wurden bestimmt? improvement of communication on the Western Aphasia Battery-Revised Aphasia Quotient (AQ) at 12 weeks after stroke		
10.	Wie viele Studienteilnehmer (insgesamt und pro Studienarm, bzw. Gruppe)? n=81 usual care, n=82 usual care-plus, n=83 VERS.		
11.	Wie war die Studienpopulation definiert? Einschlusskriterien: >=18J, admitted to hospital with an acute stroke within 14 days after onset, acute aphasia (Score <93.7 on the Aphasia Quotient of the Revised Western Aphasia Battery (WAB-R AQ), medical stable, could maintain a wakeful alert for >30min, normal or corrected hearing and vision Ausschlusskriterien: pre-existing aphasia, dementia, progressive neurological disease, head injury, neurosurgery, depression		
12.	Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Alter 76J MW, NIHSS 8-9; Frauen ca 50%, 52% Hypertonie, 26% KHK, 29% VHF, 13% Diabetes		
13.	Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Krankenhäuser in Australien und Neuseeland		
14.	Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? Bei Einschluss: von 3477 Pat. mit akuter Aphasie waren 2611 nicht geeignet und 620 konnten aus verschiedenen Gründen nicht eingeschlossen werden Bei Auswertung 12% (14 verstorben, 15 withdrew/unwell)		
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
19.	Wurden die Probanden den Gruppen randomisiert zugeordnet?	X	
20.	Waren die Probanden und Untersucher bezüglich der Zuordnung verblindet?	X	
21.	Wurde die Randomisierung geheim gehalten (allocation concealment)?	X	
22.	Wurde ein prospektives Design verwendet?	X	
23.	Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?	X	
24.	Waren Interventions- und Kontrollgruppe zu Studienbeginn vergleichbar?	X	
25.	Wurden die Zielkriterien der Studie eindeutig definiert und adäquat erhoben?	X	
26.	Wurden die Gruppen, mit Ausnahme der Prüf-Intervention, gleich behandelt?	X	
27.	Wurden Nebenwirkungen dokumentiert?	X	
28.	Wurden alle Probanden in der Gruppe ausgewertet, der sie ursprünglich zugeordnet waren (intention-to-treat-Regel)		X
29.	Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>++</b>	
<b>III. Ergebnisse</b>			
At 12 weeks after stroke, the primary outcome was assessed in 217 participants (88%); 14 had died, 9 had withdrawn, and 6 were too unwell for assessment. Communication recovery was 50.3% (95% CI 45.7–54.8) in the high intensity group (n=147) and 52.1% (95% CI 46.1–58.1) in the usual care group (n=70; difference -1.8, 95% CI -8.7–5.0). There was no difference between groups in non-fatal or fatal adverse events (p=0.72).			
<b>IV. Ableitbare Empfehlung</b>			
Early, intensive aphasia therapy did not improve communication recovery within 12 weeks post stroke compared to usual care.			



<b>Studie (RCT)</b>	#13: Nouwens F, de Lau LM, Visch-Brink EG, van de Sandt-Koenderman WM, Lingsma HF, Goosen S, Blom DM, Koudstaal PJ, Dippel DW. Efficacy of early cognitive-linguistic treatment for aphasia due to stroke: A randomised controlled trial (Rotterdam Aphasia Therapy Study-3). Eur Stroke J. 2017 Jun;2(2):126-136.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung der Studie</b>			
1.	Welche Intervention wurde untersucht? Stroke patients with first-ever aphasia were randomised within 2 weeks of onset to either 4 weeks of early intensive cognitive-linguistic treatment (1 h/day) or no language treatment. Patients in die intervention group were to receive at least 1 h of CLT every day of the week for a period of 4 weeks. The hour of treatment could be delivered in more than one session per day, if preferable		
2.	Welche Zielkriterien (Endpunkte) wurden bestimmt? Primary outcome was the score on the Amsterdam-Nijmegen Everyday Language Test, measuring everyday verbal communication, 4 weeks after randomisation		
3.	Wie viele Studienteilnehmer (insgesamt und pro Studienarm, bzw. Gruppe)? 80 Pat. für Intervention und 72 Patienten usual care		
4.	Wie war die Studienpopulation definiert? Einschlusskriterien: aphasia after stroke, shortened Token Test Score <29 OR Goodglass Aphasia Severity Rating Scale <5; Treatment possible <2weeks after stroke onset; Age 18-85y; Language near-native Dutch, Life expectancy > 6 month Ausschlusskriterien: pre-existing aphasia, SAH, SDH, severe dysarthria, dementia, severe dyslexia, severe visual problems, recent psychiatric history		
5.	Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Alter 66J MW, 56% male, 80% Hirninfarkt,		
6.	Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Krankenhaus in Niederlanden		
7.	Wie waren die Teilnehmerquoten (%-Angabe oder Angabe der Anzahl der drop-out-Fälle)? Bei Einschluss: 15 Patienten wurden nach Randomisierung ausgeschlossen (14 refusal, 1 serious illness) Bei Auswertung: 10 Patienten konnten nicht ausgewertet werden (9 refusal, 1 serious illness)		
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
8.	Wurden die Probanden den Gruppen randomisiert zugeordnet?	X	
9.	Waren die Probanden und Untersucher bezüglich der Zuordnung verblindet?		X
10.	Wurde die Randomisierung geheim gehalten (allocation concealment)?		X
11.	Wurde ein prospektives Design verwendet?	X	
12.	Wurden die Ein-/ und Ausschlusskriterien eindeutig definiert?	X	
13.	Waren Interventions- und Kontrollgruppe zu Studienbeginn vergleichbar?	X	
14.	Wurden die Zielkriterien der Studie eindeutig definiert und adäquat erhoben?	X	
15.	Wurden die Gruppen, mit Ausnahme der Prüf-Intervention, gleich behandelt?	X	
16.	Wurden Nebenwirkungen dokumentiert?		X
17.	Wurden alle Probanden in der Gruppe ausgewertet, der sie ursprünglich zugeordnet waren (intention-to-treat-Regel)	X	
18.	Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>+</b>	
<b>III. Ergebnisse</b>			
Median treatment intensity in the intervention-group was 24.5 h. The adjusted difference between groups in mean Amsterdam-Nijmegen Everyday Language Test-scores 4 weeks after randomisation was 0.39, 95% confidence interval: [-2.70 to 3.47], p=0.805. No statistically significant differences were found at 3 and 6 months after randomisation either.			
<b>IV. Ableitbare Empfehlung</b>			
Four weeks of intensive cognitive-linguistic treatment initiated within 2 weeks of stroke is not more effective than no language treatment for the recovery of post-stroke aphasia. Our results exclude a clinically relevant effect of very early cognitive-linguistic treatment on everyday language			

SF 2.1.3: Führt bei Patienten mit Hirninfarkt und einem Zeitfenster von 4,5-9 Std. seit Symptombeginn oder unklarem Zeitfenster (z.B. Symptome beim Erwachen) eine Thrombolyse basierend auf erweiterter Bildgebung und einem CT/MRT-basiert dargestellten Mismatch von Infarktkern und Penumbra im Vergleich zur Nicht-Anwendung zu einem besseren funktionellem Ergebnis?

SF 2.1.4: Führt bei Patienten mit Hirninfarkt mit Symptomen beim Erwachen oder einem unbekanntem Zeitfenster und einer Vorstellung innerhalb von 4,5 Std. nach Erkennen der Symptome eine Thrombolyse mit Alteplase basierend auf einem DWI-FLAIR-Mismatch im Vergleich zur Nicht-Anwendung zu einem besseren funktionellen Ergebnis?

Datum der Evidenzgewinnung 08.12.2020

#### **A) MedLine**

Suchterm: stroke AND (thromboly\* or alteplase) AND (exten\* or mismatch)

Filter: Systematic Review OR Meta-Analysis, 5 years

Treffer: 23

Ausschluss nach Beurteilung von Titel/Abstract: 20

Verblieben: 3 (#01-#03)

#### **Web of Science**

Suchterm: stroke AND (thromboly\* or alteplase) AND (exten\* or mismatch)

Filter: review, 2016-2020

Treffer: 89

Ausschluss nach Beurteilung von Titel/Abstract: 87

Ausschluss von Treffern der MedLine-Suche: 2

Verblieben: 0

#### **Cochrane library**

Suchterm: stroke AND thrombolysis AND mismatch

Treffer: 0

#### **B) MedLine**

Suchterm: stroke AND (thromboly\* or alteplase) AND (wake\* or unknown)

Filter: Systematic Review OR Meta-Analysis, 5 years

Treffer: 15

Ausschluss nach Beurteilung von Titel/Abstract: 10

Ausschluss von Doubletten (2.1.3): 3

Verblieben: 2 (#04-#05)

#### **Web of Science**

Suchterm: stroke AND (thromboly\* or alteplase) AND (wake\* or unknown)

Filter: review, 2016-2020

Treffer: 39

Ausschluss nach Beurteilung von Titel/Abstract: 36

Ausschluss von Doubletten (2.1.3): 2

Verblieben: 1 (#06)

#### **Gefundene Literatur:**

**#01**: Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendzus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, Leys D, Molina C, Wijeratne T, Curtze S, Dewey HM, Barber PA, Butcher KS, De Silva DA, Bladin CF, Yassi N, Pfaff JAR, Sharma G, Bivard A, Desmond PM, Schwab S, Schellinger PD, Yan B, Mitchell PJ, Serena J, Toni D, Thijs V, Hacke W, Davis SM, Donnan GA; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet. 2019 Jul 13;394(10193):139-147. doi:

10.1016/S0140-6736(19)31053-0. Epub 2019 May 22. Erratum in: Lancet. 2020 Jun 20;395(10241):1906. PMID: 31128925.

**#02:** Tsivgoulis G, Katsanos AH, Malhotra K, Sarraj A, Barreto AD, Köhrmann M, Krogias C, Ahmed N, Caso V, Schellinger PD, Alexandrov AV. Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. Neurology. 2020 Mar 24;94(12):e1241-e1248. doi: 10.1212/WNL.0000000000008904. Epub 2019 Dec 31. PMID: 31892636.

**#03:** Thomalla G, Boutitie F, Ma H, Koga M, Ringleb P, Schwamm LH, Wu O, Bendszus M, Bladin CF, Campbell BCV, Cheng B, Churilov L, Ebinger M, Endres M, Fiebich JB, Fukuda-Doi M, Inoue M, Kleinig TJ, Latour LL, Lemmens R, Levi CR, Leys D, Miwa K, Molina CA, Muir KW, Nighoghossian N, Parsons MW, Pedraza S, Schellinger PD, Schwab S, Simonsen CZ, Song SS, Thijs V, Toni D, Hsu CY, Wahlgren N, Yamamoto H, Yassi N, Yoshimura S, Warach S, Hacke W, Toyoda K, Donnan GA, Davis SM, Gerloff C; Evaluation of unknown Onset Stroke thrombolysis trials (EOS) investigators. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. Lancet. 2020 Nov 14;396(10262):1574-1584. doi: 10.1016/S0140-6736(20)32163-2. Epub 2020 Nov 8. PMID: 33176180.

**#04:** Luan D, Zhang Y, Yang Q, Zhou Z, Huang X, Zhao S, Yuan L. Efficacy and Safety of Intravenous Thrombolysis in Patients with Unknown Onset Stroke: A Meta-Analysis. Behav Neurol. 2019 Sep 3;2019:5406923. doi: 10.1155/2019/5406923. PMID: 31565095; PMCID: PMC6745097.

**#05:** Zhu RL, Xu J, Xie CJ, Hu Y, Wang K. Efficacy and Safety of Thrombolytic Therapy for Stroke with Unknown Time of Onset: A Meta-Analysis of Observational Studies. J Stroke Cerebrovasc Dis. 2020 May;29(5):104742. doi:10.1016/j.jstrokecerebrovasdis.2020.104742. Epub 2020 Feb 29. PMID: 32127258.

**#06:** Roaldsen, M. B., Lindekleiv, H., Mathiesen, E. B., & Berge, E. (2018). Recanalisation therapies for wake-up stroke. Cochrane Database Syst Rev, 8, CD010995. doi:10.1002/14651858.CD010995.pub2

**Bewertung:**

<b>Studie (review)</b>	<b>#01:</b> Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, Leys D, Molina C, Wijeratne T, Curtze S, Dewey HM, Barber PA, Butcher KS, De Silva DA, Bladin CF, Yassi N, Pfaff JAR, Sharma G, Bivard A, Desmond PM, Schwab S, Schellinger PD, Yan B, Mitchell PJ, Serena J, Toni D, Thijs V, Hacke W, Davis SM, Donnan GA; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4-5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet. 2019 Jul 13;394(10193):139-147. Epub 2019 May 22. Erratum in: Lancet. 2020 Jun 20;395(10241):1906.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	
<b>I. Beschreibung des Reviews</b>	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs	
2. Welche Interventionen sind betrachtet/untersucht worden? Trials of intravenous alteplase versus placebo in adults (aged ≥18 years) with hemispheric ischaemic stroke more than 4.5 h after stroke onset or wake-up stroke who had pretreatment imaging with CT perfusion or perfusion-diffusion MRI were eligible for inclusion.	
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? primary outcome was the proportion of patients with excellent functional outcome (mRS score 0–1 at 3 months, adjusted for pretreatment clinical severity (NIHSS score) and age. Secondary outcomes were functional improvement (≥1 point reduction in mRS score [ordinal shift analysis]), with mRS categories 5 and 6 merged, at 3 months, functional independence (mRS score 0–2) at 3 months, and early neurological improvement (reduction of ≥8 points on NIHSS or reaching NIHSS score 0–1) at 72 h. All secondary outcomes were adjusted for pretreatment NIHSS score and age. Safety outcomes were symptomatic intracerebral haemorrhage defined as parenchymal haemorrhage type 2	

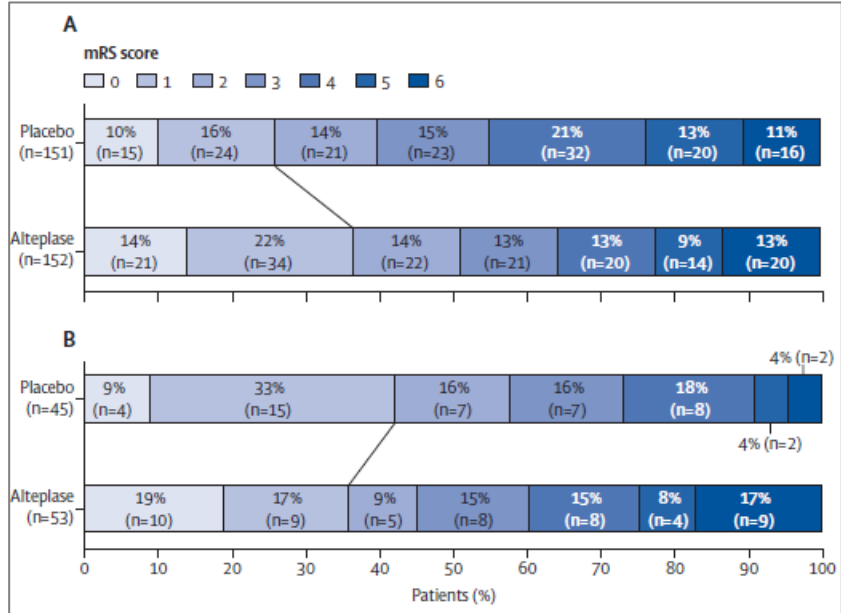
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)?  
 414 Patienten, age 72-32y, 57% men, NIHSS 10-12; 56% Australien, 33% Europa, 11% Asien. 4,5-6 Std 24-27%; 6-9 Std 24%, unknown 12-11%, CTperfusion 47%, MR-Perfusion 53%

5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Stroke Units in Australien, Ostasien oder Europa

II. Interne Validität	Ja	Nein
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

**III. Ergebnisse**

We identified three trials that met eligibility criteria: EXTEND, ECASS4-EXTEND, and EPITHET. Of the 414 patients included in the three trials, 213 (51%) were assigned to receive alteplase and 201 (49%) were assigned to receive placebo. Overall, 211 patients in the alteplase group and 199 patients in the placebo group had mRS assessment data at 3 months and thus were included in the analysis of the primary outcome. 76 (36%) of 211 patients in the alteplase group and 58 (29%) of 199 patients in the placebo group had achieved excellent functional outcome at 3 months (adjusted odds ratio [OR] 1.86, 95% CI 1.15–2.99, p=0.011). Symptomatic intracerebral haemorrhage was more common in the alteplase group than the placebo group (ten [5%] of 213 patients vs one [ $<1\%$ ] of 201 patients in the placebo group; adjusted OR 9.7, 95% CI 1.23–76.55, p=0.031). 29 (14%) of 213 patients in the alteplase group and 18 (9%) of 201 patients in the placebo group died (adjusted OR 1.55, 0.81–2.96, p=0.66).



A: mit automatischer Mismatch-Analyse, B ohne automatische Mismatch-Analyse

**IV. Ableitbare Empfehlung**

Patients with ischaemic stroke 4-5–9 h from stroke onset or wake-up stroke with salvageable brain tissue who were treated with alteplase achieved better functional outcomes than did patients given placebo. The rate of symptomatic intracerebral haemorrhage was higher with alteplase, but this increase did not negate the overall net benefit of thrombolysis.

This pooled analysis provides strong evidence in support of thrombolysis for patients with favourable perfusion imaging 4-5–9 h after stroke, including patients with wake-up stroke.

In der Subgruppe ohne automatische Mismatchanalyse gab es keine Vorteil zugunsten Alteplase

<b>Studie (review)</b>	#02: Tsivgoulis G, Katsanos AH, Malhotra K, Sarraj A, Barreto AD, Köhrmann M, Krogias C, Ahmed N, Caso V, Schellinger PD, Alexandrov AV. Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. Neurology. 2020 Mar 24;94(12):e1241-e1248..	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Nur RCTs		
2. Welche Interventionen sind betrachtet/untersucht worden? We included patients with AIS who were >18 years of age and receiving treatment with IV alteplase (0.9 mg/kg) either in the setting of unknown symptom onset time (wake-up strokes) or presenting >4.5 hours from symptom onset selected by advanced baseline neuroimaging with either CT or MRI.		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? 3-month favourable functional outcome (FFO; modified Rankin Scale [mRS] scores 0–1), 3-month functional independence (FI; mRS scores 0–2), 3-month all-cause mortality, 3-month functional improvement (assessed with ordinal analysis on the mRS scores), symptomatic intracranial hemorrhage		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Age 65-76J, NIHSS-d0 6-17, CoreVol 2-17ml, WUS 65-100%		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Klinik		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		
<p>We identified 4 eligible randomized clinical trials (859 total patients).</p> <p>In unadjusted analyses, IVT was associated with a higher likelihood of 3-month FFO (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.12–1.96), FI (OR 1.42, 95% CI 1.07–1.90), sICH (OR 5.28, 95% CI 1.35–20.68), and CR (OR 3.29, 95% CI 1.90–5.69), with no significant difference in the odds of all-cause mortality risk at 3 months (OR 1.75, 95% CI 0.93–3.29). In the adjusted analyses, IVT was also associated with higher odds of 3-month FFO (adjusted OR [ORadj] 1.62, 95% CI 1.20–2.20), functional improvement (ORadj 1.42, 95% CI 1.11–1.81), and sICH (ORadj 6.22, 95% CI 1.37–28.26). There was no association between IVT and FI (ORadj 1.61, 95% CI 0.94–2.75) or all-cause mortality (ORadj 1.75, 95% CI 0.93–3.29) at 3 months.</p> <p>No evidence of heterogeneity was evident in any of the analyses (<math>I^2 = 0</math>).</p>		
<b>IV. Ableitbare Empfehlung</b>		
IVT in patients with AIS with unknown symptom onset time or elapsed time from symptom onset >4.5 hours selected with advanced neuroimaging results in a higher likelihood of CR and functional improvement at 3 months despite the increased risk of sICH		
<b>V. Kommentar</b>		
Differenziert nicht zwischen extended und unklar. Macht es daher etwas schwierig, die Ergebnisse auf die SF zu übertragen		

<b>Studie (review)</b>	#03: Thomalla G, Boutitie F, Ma H, Koga M, Ringleb P, Schwamm LH, Wu O, Bendszus M, Bladin CF, Campbell BCV, Cheng B, Churilov L, Ebinger M, Endres M, Fiebach JB, Fukuda-Doi M, Inoue M, Kleinig TJ, Latour LL, Lemmens R, Levi CR, Leys D, Miwa K, Molina CA, Muir KW, Nighoghossian N, Parsons MW, Pedraza S, Schellinger PD, Schwab S, Simonsen CZ, Song SS, Thijs V, Toni D, Hsu CY, Wahlgren N, Yamamoto H, Yassi N, Yoshimura S, Warach S, Hacke W, Toyoda K, Donnan GA, Davis SM, Gerloff C; Evaluation of unknown Onset Stroke thrombolysis trials (EOS) investigators. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. Lancet. 2020 Nov 14;396(10262):1574-1584.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung	Kann für SF 2.1.4 verwendet werden	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Nur RCTs with more than 20 patients enrolled		
2. Welche Interventionen sind betrachtet/untersucht worden? intravenous alteplase versus standard of care or placebo in adults (≥18 years), with acute ischaemic stroke and unknown time of symptom onset, using advanced brain imaging with either penumbral imaging (ie, perfusion-diffusion MRI or perfusion CT) or MRIbased tissue-clocking (ie, DWI-FLAIR mismatch)		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? The prespecified primary outcome was a favourable outcome defined by a score of mRS 0-1 @d90. Secondary outcomes were functional improvement across the entire mRS (ie, mRS shift analysis) at 90 days and independent outcome (mRS 0-2) Safety outcomes were death, severe disability or death (mRS score 4–6), symptomatic ICH-SITS.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 843 Pat, age 68,5 J . 62% Männer, Median NIHSS 7, 85% MRT, 24% LVO		
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? Klinik		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>++</b>
<b>III. Ergebnisse</b>		
Of 249 identified abstracts, four trials met our eligibility criteria for inclusion: WAKE-UP, EXTEND, THAWS, and ECASS-4. The four trials provided individual patient data for 843 individuals, of whom 429 (51%) were assigned to alteplase and 414 (49%) to placebo or standard care. A favourable outcome occurred in 199 (47%) of 420 patients with alteplase and in 160 (39%) of 409 patients among controls (adjusted odds ratio [OR] 1.49 [95% CI 1.10–2.03]; p=0.011), with low heterogeneity across studies (I <sup>2</sup> =27%). Alteplase was associated with a significant shift towards better functional outcome (adjusted common OR 1.38 [95% CI 1.05–1.80]; p=0.019), and a higher odds of independent outcome (adjusted OR 1.50 [1.06–2.12]; p=0.022). In the alteplase group, 90 (21%) patients were severely disabled or died (mRS score 4–6), compared with 102 (25%) patients in the control group (adjusted OR 0.76 [0.52–1.11]; p=0.15). 27 (6%) patients died in the alteplase group and 14 (3%) patients died among controls (adjusted OR 2.06 [1.03–4.09]; p=0.040). The prevalence of symptomatic intracranial haemorrhage was higher in the alteplase group than among controls (11 [3%] vs two [1%], adjusted OR 5.58 [1.22–25.50]; p=0.024).		
<b>IV. Ableitbare Empfehlung</b>		
In patients who have had a stroke with unknown time of onset with a DWI-FLAIR or perfusion mismatch, intravenous alteplase resulted in better functional outcome at 90 days than placebo or standard care. A net benefit was observed for all functional outcomes despite an increased risk of symptomatic intracranial haemorrhage. Although there were more deaths with alteplase than placebo, there were fewer cases of severe disability or death		

<b>Studie (review)</b>	#04: Luan D, Zhang Y, Yang Q, Zhou Z, Huang X, Zhao S, Yuan L. Efficacy and Safety of Intravenous Thrombolysis in Patients with Unknown Onset Stroke: A Meta-Analysis. Behav Neurol. 2019 Sep 3;2019:5406923.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	Ja	
Begründung	Inhomogene Patientenselektion, teils mit Perfusions-Mismatch, teils mit DWI-FLAIR-Mismatch	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCT, OS		
2. Welche Interventionen sind betrachtet/untersucht worden? Systemische Thrombolyse bei Patienten im unklaren Zeitfenster (WakeUp)		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Treatment efficacy was measured at two levels: discharge and 90-day post charge, defined as good outcome (mRS 0-2) and mortality. Therapy safety was assessed using the development of ICH and sICH.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? given		
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? n.a.		
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		(?)
<b>Gesamtbeurteilung</b>		-
<b>III. Ergebnisse</b>		
<b>IV. Ableitbare Empfehlung</b>		

<b>Studie (review)</b>	#05: Zhu RL, Xu J, Xie CJ, Hu Y, Wang K. Efficacy and Safety of Thrombolytic Therapy for Stroke with Unknown Time of Onset: A Meta-Analysis of Observational Studies. J Stroke Cerebrovasc Dis. 2020 May;29(5):104742.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	JA	
Begründung	Methodische Mängel, inhomogene Studienpopulation	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational studies		
2. Welche Interventionen sind betrachtet/untersucht worden? Lyse bei stroke with unknown time of onset (UTOS) im Vergleich zu konservativen Therapie oder Lyse bei bekanntem Onset (KOS)		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? mRS 0-2, sICH, Mortality 3 months		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.		
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? hospital		
<b>II. Interne Validität</b>		
	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X

6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		-
<b>III. Ergebnisse</b>		
<b>IV. Ableitbare Empfehlung</b>		
Inhomogene Studien mit verschiedenen Selektionsverfahren, keine verallgemeinerbare Schlussfolgerungen		

<b>Studie (review)</b>	#06: Roaldsen, M. B., Lindekleiv, H., Mathiesen, E. B., & Berge, E. (2018). Recanalisation therapies for wake-up stroke. Cochrane Database Syst Rev, 8, CD010995.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Konnte die WakeUp-Studie (Thomalla et al 2019) noch nicht einschließen, daher nicht aktuell genug, um die SF adäquat zu beantworten

<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational studies		
2. Welche Interventionen sind betrachtet/untersucht worden? Lyse bei stroke with unknown time of onset (UTOS) im Vergleich zu konservativen Therapie oder Lyse bei bekanntem Onset (KOS)		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? mRS 0-2, sICH, Mortality 3 months		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? hospital		

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
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?		
<b>Gesamtbeurteilung</b>		
<b>III. Ergebnisse</b>		
<b>IV. Ableitbare Empfehlung</b>		
There is insufficient evidence from randomised controlled trials for recommendations concerning recanalisation therapies for wake- up stroke. Results from ongoing trials will hopefully establish the efficacy and safety of such therapies		

[SF 2.1.5: Führt bei Patienten mit Hirninfarkt und einem Symptombeginn bis zu 4,5h eine Thrombolyse mit Tenecteplase im Vergleich zur Thrombolyse mit Alteplase zu einem besseren funktionellen Ergebnis?](#)

Diese Schlüsselfrage wurde im Rahmen des Amendments Oktober 2022 neu bearbeitet. Dafür erfolgte eine erneute systematischer Evidenzgewinnung am 24.05.2022. Die Evidenztafeln der Version 5.0 wurden entfernt.

**MedLine**

Suchterm: (stroke tenecteplase alteplase) AND (("2018/01/01"[Date - Publication] : "3000"[Date - Publication])

Filter: systematic review OR Meta-Analysis, 10 years

Treffer: 14

Ausschluss nach Beurteilung von Titel/Abstract: 6



Verblieben: 6

## Gefundene Literatur

No	Referenz	Ok
#01	Thelengana A, Radhakrishnan DM, Prasad M, Kumar A, Prasad K. Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. <i>Acta Neurol Belg.</i> 2019 Sep;119(3):359-367. doi: 10.1007/s13760-018-0933-9. Epub 2018 May 4. PMID: 29728903.	Ja
#02	Oliveira M, Fidalgo M, Fontão L, Antão J, Marques S, Afreixo V, Gregório T. Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis. <i>Am J Emerg Med.</i> 2021 Apr;42:31-37. doi: 10.1016/j.ajem.2020.12.026. Epub 2020 Dec 24. PMID: 33440328.	Ja
#03	Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Hassan M, Bachuwa G, Al Qasmi M, Bhatt DL. Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. <i>J Thromb Thrombolysis.</i> 2018 Nov;46(4):440-450. doi: 10.1007/s11239-018-1721-3. PMID: 30117036.	Ja
#04	Burgos AM, Saver JL. Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. <i>Stroke.</i> 2019 Aug;50(8):2156-2162. doi: 10.1161/STROKEAHA.119.025080. Epub 2019 Jul 18. PMID: 31318627.	Ja
#05	Dumitrascu OM, Newman NJ, Biousse V. Thrombolysis for Central Retinal Artery Occlusion in 2020: Time Is Vision! <i>J Neuroophthalmol.</i> 2020 Sep;40(3):333-345. doi: 10.1097/WNO.0000000000001027. PMID: 32739995.	Nein
#06	Katsanos AH, Safouris A, Sarraj A, Magoufis G, Leker RR, Khatri P, Cordonnier C, Leys D, Shoamanesh A, Ahmed N, Alexandrov AV, Tsvigoulis G. Intravenous Thrombolysis With Tenecteplase in Patients With Large Vessel Occlusions: Systematic Review and Meta-Analysis. <i>Stroke.</i> 2021 Jan;52(1):308-312. doi: 10.1161/STROKEAHA.120.030220. Epub 2020 Dec 4. PMID: 33272127.	Ja
#07	Potla N, Ganti L. Tenecteplase vs. alteplase for acute ischemic stroke: a systematic review. <i>Int J Emerg Med.</i> 2022 Jan 4;15(1):1. doi: 10.1186/s12245-021-00399-w. PMID: 34983359; PMCID: PMC8903524.	Nein
#08	Chen G, Bai C, Zhu Z, Li J, Shao S. Effectiveness and safety of different doses of tenecteplase in the treatment of acute ischemic stroke: A protocol for systematic review and meta-analysis. <i>Medicine (Baltimore).</i> 2021 Jan 22;100(3):e23805. doi: 10.1097/MD.00000000000023805. PMID: 33545944; PMCID: PMC7837936.	Nein
#09	Moussaddy A, Demchuk AM, Hill MD. Thrombolytic therapies for ischemic stroke: Triumphs and future challenges. <i>Neuropharmacology.</i> 2018 May 15;134(Pt B):272-279. doi: 10.1016/j.neuropharm.2017.11.010. Epub 2018 Mar 3. PMID: 29505787.	Nein
#10	Shen T, Zhou J, Zhao Y. Efficacy and safety of different doses of tenecteplase for the treatment of acute ischemic stroke: A protocol for a systematic review and network meta-analysis. <i>Medicine (Baltimore).</i> 2020 Dec 4;99(49):e23379. doi: 10.1097/MD.00000000000023379. PMID: 33285721; PMCID: PMC7717732.	Nein
#11	Katsanos AH, Psychogios K, Turc G, Sacco S, de Sousa DA, De Marchis GM, Palaiodimou L, Filippou DK, Ahmed N, Sarraj A, Menon BK, Tsvigoulis G. Off-Label Use of Tenecteplase for the Treatment of Acute Ischemic Stroke: A Systematic Review and Meta-analysis. <i>JAMA Netw Open.</i> 2022 Mar 1;5(3):e224506. doi: 10.1001/jamanetworkopen.2022.4506. PMID: 35357458; PMCID: PMC8972028.	Ja
#12	Yogendrakumar V, Churilov L, Mitchell PJ, Kleinig TJ, Yassi N, Thijs V, Wu TY, Shah DG, Ng FC, Dewey HM, Wijeratne T, Yan B, Desmond PM, Parsons MW, Donnan GA, Davis SM, Campbell BCV; EXTEND-IA TNK Investigators. Safety and Efficacy of Tenecteplase in Older Patients With Large Vessel Occlusion: A Pooled Analysis of the EXTEND-IA TNK	Nein

	Trials. Neurology. 2022 Mar 22;98(12):e1292-e1301. doi: 10.1212/WNL.0000000000013302. Epub 2022 Jan 11. PMID: 35017305.	
#13	Ng FC, Churilov L, Yassi N, Kleinig TJ, Thijs V, Wu T, Shah D, Dewey H, Sharma G, Desmond P, Yan B, Parsons M, Donnan G, Davis S, Mitchell P, Campbell B. Prevalence and Significance of Impaired Microvascular Tissue Reperfusion Despite Macrovascular Angiographic Reperfusion (No-Reflow). Neurology. 2022 Feb 22;98(8):e790-e801. doi: 10.1212/WNL.0000000000013210. Epub 2021 Dec 14. PMID: 34906976.	Nein
#14	Bahadori M, Mowla A. Re: Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis. Am J Emerg Med. 2022 May;55:185-186. doi: 10.1016/j.ajem.2021.05.079. Epub 2021 Jun 1. PMID: 34116894; PMCID: PMC9010854.	Nein

## Bewertung

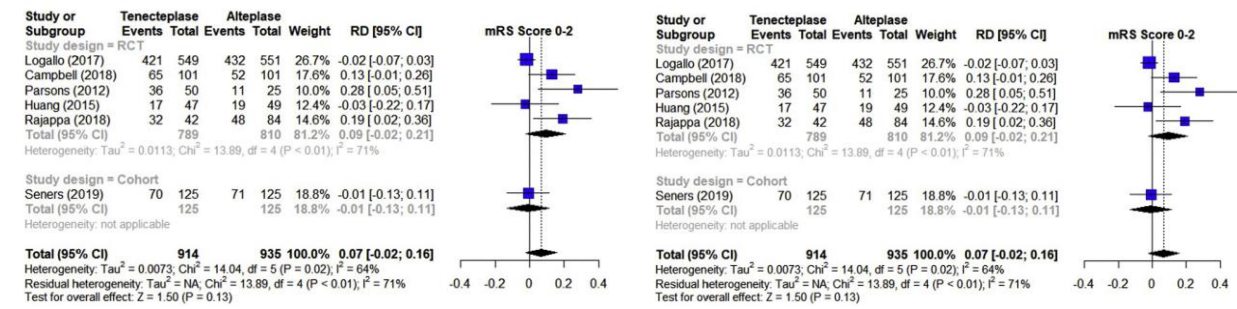
<b>Studie</b>	#01: Thelengana A, Radhakrishnan DM, Prasad M, Kumar A, Prasad K. Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. Acta Neurol Belg. 2019 Sep;119(3):359-367. doi: 10.1007/s13760-018-0933-9. Epub 2018 May 4. PMID: 29728903.	
<b>Berücksichtigen</b>	Ja	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Studies on adult patients with acute ischemic stroke were <b>included</b> . Studies in which intravenous tenecteplase was studied as an interventional drug were included. Studies comparing intravenous tenecteplase with intravenous alteplase were included Studies were <b>excluded</b> if they had compared alteplase with tenecteplase dose 0.1 mg/kg alone		
2. Welche Interventionen sind betrachtet/untersucht worden? Tenecteplase vs. Alteplase IVT IS		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? We considered six main outcomes:(1) early major neurological improvement (Improvement in National Institutes of Health Stroke Scale score, NIHSS of $\geq 8$ points within 24 h); (2) Excellent functional outcome (modified Rankin Scale score, mRS of 0–1 at 90 days), (3) Good functional outcome (mRS of 0–2 at 90 days); (4) Any intracranial haemorrhage; (5) Symptomatic intracranial haemorrhage; (6) Death (mortality at 90 days).		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Von 263 Treffern blieben 4 Studien übrig (Haley 2010; Parson 2012, Huang 2015; Logallo 2017), tabellarische Übersicht auf S 362. 1334 Patienten (>80% aus Logallo 2017): Alter ca 70J, 60% männlich, baseline NIHSS um 7, OTT 130 min. 15% mimics		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	+	

<b>III. Ergebnisse</b>
There was no significant difference between tenecteplase and alteplase in excellent functional outcome at 90 days, good functional outcome at 90 days, any intracerebral haemorrhage, symptomatic intracerebral haemorrhage or mortality at 90 days. Our meta-analysis found tenecteplase to be significantly favouring one outcome: early major neurological improvement (RR1,56 95%CI 1,00-2,43).
<b>IV. Schlussfolgerung der Autoren</b>
In dieser Meta-Analyse zeigte Tenecteplase eine ähnliche Wirksamkeit und Sicherheit wie Alteplase und war wahrscheinlich bei einem Ergebnis überlegen: bei der frühen deutlichen neurologischen Verbesserung. Andere Ergebnisse unterschieden sich nicht zwischen den Tenecteplase- und Alteplase-Gruppen.

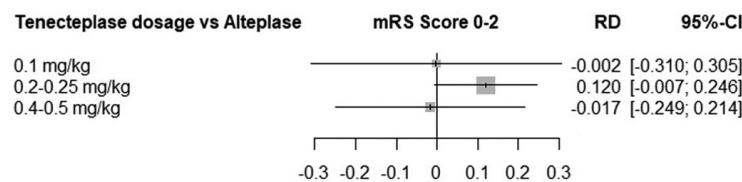
<b>Studie</b>	#02: Oliveira M, Fidalgo M, Fontão L, Antão J, Marques S, Afreixo V, Gregório T. Tenecteplase for thrombolysis in stroke patients: Systematic review with meta- analysis. Am J Emerg Med. 2021 Apr;42:31-37. doi: 10.1016/j.ajem.2020.12.026. Epub 2020 Dec 24. PMID: 33440328.	
<b>Berücksichtigen</b>	Ja	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Studies were eligible for inclusion if they were original studies comparing tenecteplase with alteplase in human adult patients undergoing thrombolysis for acute ischemic stroke. Both experimental and observational studies were included.		
2. Welche Interventionen sind betrachtet/untersucht worden? IV-Alteplase vs. IV-Tenecteplase in IS		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? The efficacy outcomes of interest were functional status at three months, early neurological improvement and recanalization. The safety outcomes of interest were intracranial haemorrhage (ICH), symptomatic ICH (sICH) and 3-month mortality. The definitions of good and excellent functional outcome were a modified Rankin scale score of 0–2 and 0–1 respectively.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 8 Studien wurden ausgewählt, 6 RCT, 2 observationel, alle Dosierungen von 0,1-0,4mg/kg, 4 ohne und 4 mit endovaskulären Schlaganfalltherapie (Tabelle S 32).		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		
<b>Gesamtbeurteilung</b>	+	

**III. Ergebnisse**

Tenecteplase demonstrated an increase in recanalization rate (ARD = 0.11, 95% CI [0.01;0.20], NNT = 9) and early neurological improvement (ARD = 0.10, 95% CI [0.02;0.17], NNT = 10). Tenecteplase also demonstrated an increase in good (ARD = 0.07, 95% CI [-0.02;0.16]) as well as excellent functional outcome (ARD = 0.03, 95% CI [-0.01;0.08]), but these differences were not statistically significant. Heterogeneity was high for all analysis except excellent functional outcome. However, when analysis was restricted to randomized trials, heterogeneity was non-significant except good functional outcome (I<sup>2</sup> = 71%).



**Splittet auch nach Dosierungen auf**



**IV. Schlussfolgerung der Autoren**

Tenecteplase ist eine gute Alternative zu Alteplase für die Thrombolyse bei akuten ischämischen Schlaganfällen. Neben seinem günstigeren pharmakokinetischen Profil, das eine Bolusverabreichung ermöglicht, ist es wirksamer bei der Öffnung verschlossener Gefäße und zeigt eine höhere Rate an frühen neurologischen Verbesserungen.

<b>Studie</b>	#03: Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Hassan M, Bachuwa G, Al Qasmi M, Bhatt DL. Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. J Thromb Thrombolysis. 2018 Nov;46(4):440-450. doi: 10.1007/s11239-018-1721-3. PMID: 30117036.	
<b>Berücksichtigen</b>	Ja	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? The study design was an RCT, (2) The trial included patients undergoing thrombolysis with tenecteplase versus alteplase, and (3) The trial evaluated clinical and/or imaging outcomes.		
2. Welche Interventionen sind betrachtet/untersucht worden? IV Alteplase vs. IV Tenecteplase in IS		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Efficacy: ENI, mRS d90, Reperfusion (TICI) Safety: mRS 4-6 d90; sICH (SITS), mortality		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 5 RTCs (Campbell 2018, Logallo 2017, Huang 2015, Parsons 2012, Haley 2010),		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	

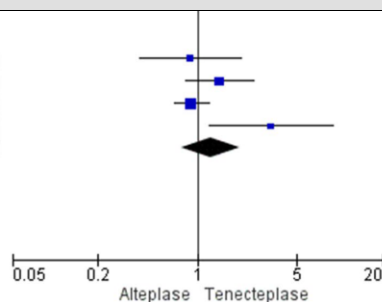
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>+</b>

### III. Ergebnisse

#### 1.1.5 Functional independence (modified Rankin Scale 0-2)

ATTEST 2015	17	47	19	49	18.8%	0.89 [0.39, 2.05]
EXTEND-IA TNK 2018	52	101	43	101	27.7%	1.43 [0.82, 2.49]
NOR-TEST 2017	421	549	432	551	38.8%	0.91 [0.68, 1.20]
Parsons 2012	36	50	11	25	14.8%	3.27 [1.20, 8.92]
<b>Subtotal (95% CI)</b>		<b>747</b>		<b>726</b>	<b>100.0%</b>	<b>1.24 [0.78, 1.98]</b>

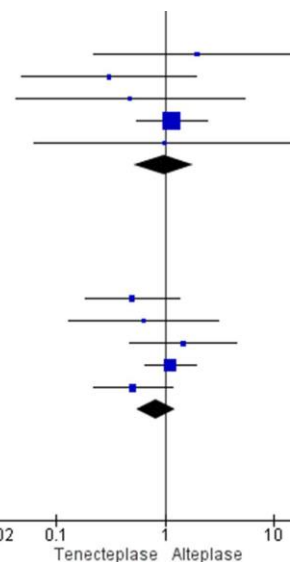
Total events 526 505  
 Heterogeneity: Tau<sup>2</sup> = 0.13; Chi<sup>2</sup> = 7.32, df = 3 (P = 0.06); I<sup>2</sup> = 59%  
 Test for overall effect: Z = 0.90 (P = 0.37)



#### 1.2.3 Symptomatic intracerebral hemorrhage

Haley 2010	5	81	1	31	8.1%	1.97 [0.22, 17.60]	2010
Parsons 2012	2	50	3	25	11.3%	0.31 [0.05, 1.96]	2012
ATTEST 2015	1	52	2	51	6.6%	0.48 [0.04, 5.47]	2015
NOR-TEST 2017	15	549	13	551	68.9%	1.16 [0.55, 2.47]	2017
EXTEND-IA TNK 2018	1	101	1	101	5.0%	1.00 [0.06, 16.21]	2018
<b>Subtotal (95% CI)</b>		<b>833</b>		<b>759</b>	<b>100.0%</b>	<b>0.98 [0.52, 1.83]</b>	

Total events 24 20  
 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 2.43, df = 4 (P = 0.66); I<sup>2</sup> = 0%  
 Test for overall effect: Z = 0.07 (P = 0.94)



#### 1.2.4 Mortality

Haley 2010	12	81	8	31	15.6%	0.50 [0.18, 1.37]	2010
Parsons 2012	4	50	3	25	6.8%	0.64 [0.13, 3.10]	2012
ATTEST 2015	8	47	6	49	12.5%	1.47 [0.47, 4.61]	2015
NOR-TEST 2017	29	549	26	551	42.8%	1.13 [0.65, 1.94]	2017
EXTEND-IA TNK 2018	10	101	18	101	22.2%	0.51 [0.22, 1.16]	2018
<b>Subtotal (95% CI)</b>		<b>828</b>		<b>757</b>	<b>100.0%</b>	<b>0.83 [0.54, 1.26]</b>	

Total events 63 61  
 Heterogeneity: Tau<sup>2</sup> = 0.03; Chi<sup>2</sup> = 4.59, df = 4 (P = 0.33); I<sup>2</sup> = 13%  
 Test for overall effect: Z = 0.88 (P = 0.38)

### IV. Schlussfolgerung der Autoren

Bei Patienten mit akutem ischämischen Schlaganfall ist die einmalige Verabreichung von Tenecteplase mit höheren Rekanalisationsraten und einer frühen neurologischen Besserung verbunden als Alteplase, ohne signifikante Unterschiede bei den Endpunkten nach 3 Monaten oder dem Sicherheitsprofil. Darüber hinaus wird Tenecteplase 0,25 mg/kg mit besseren bildgebungsbasierten Ergebnissen und höheren Funktionsniveaus als Alteplase in Verbindung gebracht, ohne dass ein erhöhtes Risiko für intrazerebrale Blutungen oder Mortalität besteht (was mRS 0-1 aber nicht 0-2 betrifft).

<b>Studie</b>	#04: Burgos AM, Saver JL. Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. Stroke. 2019 Aug;50(8):2156-2162. doi: 10.1161/STROKEAHA.119.025080. Epub 2019 Jul 18. PMID: 31318627.
<b>Berücksichtigen</b>	Ja

### I. Beschreibung des Reviews

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)?  
 RCT,

2. Welche Interventionen sind betrachtet/untersucht worden? TNK vs ALTEPLASE bei IS im 6 Std ZF		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? The primary efficacy end point analyzed was disability-free outcome (modified Rankin Scale [mRS] score, 0–1) at 3 months poststroke. Additional efficacy outcomes were functional independence (mRS, 0–2) at 3 months and reduced level of disability overall 7 mRS levels (shift analysis) at 3 months. Safety outcomes were symptomatic intracranial hemorrhage (sICH) and mortality.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 5 RTCs gefunden (Haley 2010; Parson 2012; Huang 2015; Logallo 2017; Campbell 2018): 1585 Patienten (828 TNK, 757 rtPA), mean age 70.8J, 59% male, mean NIHSS 7, mean tw 148 Min.		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		x
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
For the primary end point, crude cumulative rates of disability-free (modified Rankin Scale score, 0–1) 3 m outcome were TNK 57.9% versus ALT 55.4%. Informal, random-effects meta-analysis, the risk difference was 4% (95% CI, -1% to 8%). The lower 95% CI bound fell well within the prespecified noninferiority margin (6,5%). Similar results were seen for the additional efficacy end points: functional independence (modified Rankin Scale score, 0–2): crude TNK 71.9% versus ALT 70.5%, risk difference 2% (95% CI, -3% to 6%); and modified Rankin Scale shift analysis, common odds ratio 1.21 (95% CI, 0.93–1.57). For safety end points, lower event rates reduced power, but point estimates were also consistent with noninferiority		
<b>IV. Schlussfolgerung der Autoren</b>		
TNK ist nicht-unterlegen der Behandlung mit ALT bei akutem ischämischen Schlaganfall		

<b>Studie</b>	#05: Dumitrascu OM, Newman NJ, Biousse V. Thrombolysis for Central Retinal Artery Occlusion in 2020: Time Is Vision! J Neuroophthalmol. 2020 Sep;40(3):333-345. doi: 10.1097/WNO.0000000000001027. PMID: 32739995.	
<b>Berücksichtigen</b>	Nein, geht nicht um cerebrale Ischämien	
<b>I. Beschreibung des Reviews</b>		
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)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
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?		
<b>Gesamtbeurteilung</b>		
<b>III. Ergebnisse</b>		
<b>IV. Schlussfolgerung der Autoren</b>		

<b>Studie</b>	#06: Katsanos AH, Safouris A, Sarraj A, Magoufis G, Leker RR, Khatri P, Cordonnier C, Leys D, Shoamanesh A, Ahmed N, Alexandrov AV, Tsvigoulis G. Intravenous Thrombolysis With Tenecteplase in Patients With Large Vessel Occlusions: Systematic Review and Meta-Analysis. Stroke. 2021 Jan;52(1):308-312. doi: 10.1161/STROKEAHA.120.030220. Epub 2020 Dec 4. PMID: 33272127.	
<b>Berücksichtigen</b>	Ja	
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs reporting outcomes of AIS patients with		
2. Welche Interventionen sind betrachtet/untersucht worden? confirmed LVO randomized to intravenous thrombolytic treatment with either tenecteplase or alteplase		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? The primary outcome of interest was the odds of favorable functional outcome defined as a mRS score of 0 to 2 at 3 months. Secondary outcomes of interest included the odds of (1) excellent outcome defined as 3-month mRS scores of 0 or 1, (2) 3-month all-cause mortality, (3) 3-month functional improvement (assessed with ordinal logistic regression analysis on the per 1-point decline in the ordinal mRS score at 3 months), (4) any intracranial hemorrhage (ICH), (5) symptomatic ICH (6) successful recanalization, and (7) early neurological improvement		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 4 RCTs (Bivard 2017;Parsons 2012; Campbell 2018; Kvistad 2019) including a total of 433 patients		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	+	
<b>III. Ergebnisse</b>		

Patients with confirmed LVO receiving tenecteplase had higher odds of successful recanalization (odds ratio, 3.05 [95% CI, 1.73–5.40]), higher odds of mRS scores of 0 to 2 (odds ratio, 2.06 [95% CI, 1.15–3.69]) and functional improvement (common odds ratio, 1.84 [95% CI, 1.18–2.87]) at 3 months compared with patients with confirmed LVO receiving alteplase.

Outcomes	No. of participants (studies); follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Effect with alteplase	Effect difference with TNK
SR	315 (3 studies); before EVT	⊕⊕⊕○ Moderate*	OR, 3.05 (1.73–5.40)	227 per 1000	245 more per 1000 (109 more to 385 more)
mRS 0–2	277 (2 studies); 3 mo	⊕⊕⊕○ Moderate†	OR, 2.06 (1.15–3.69)	500 per 1000	173 more per 1000 (35 more to 287 more)
mRS 0–1	433 (4 studies); 3 mo	⊕⊕⊕○ Moderate‡	OR, 1.49 (0.95–2.32)	368 per 1000	97 more per 1000 (12 fewer to 207 more)
Functional improvement	315 (3 studies); 3 mo	⊕⊕⊕○ Moderate*	cOR, 1.84 (1.18–2.87)	...	...
ENI	395 (3 studies); 72 h	⊕○○○ Very low*‡§	OR, 1.09 (0.37–3.16)	510 per 1000	22 more per 1000 (232 fewer to 257 more)
Mortality	395 (3 studies); 3 mo	⊕⊕○○ Low*‡	OR, 0.93 (0.31–2.80)	130 per 1000	8 fewer per 1000 (86 fewer to 165 more)
Symptomatic ICH	395 (3 studies); 48 h	⊕⊕○○ Low*‡	OR, 0.66 (0.19–2.23)	31 per 1000	10 fewer per 1000 (25 fewer to 36 more)
Any ICH	395 (3 studies); 48 h	⊕⊕○○ Low*‡	OR, 0.87 (0.35–2.17)	115 per 1000	13 fewer per 1000 (71 fewer to 105 more)

#### IV. Schlussfolgerung der Autoren

Bei Patienten mit akutem ischämischem Schlaganfall mit LVO, die eine intravenöse Thrombolyse mit Tenecteplase erhalten, sind Rekanalisation und die klinischen Ergebnisse signifikant besser als bei Patienten, die intravenöse Alteplase erhalten

SF 2.1.10: Führt bei Thrombolyse-Patienten, die initial einen entgleisten Blutdruck haben (>185mmHg syst. und/oder >110 mmHg diast.) eine Senkung des Blutdrucks unter die genannten Grenzen im Vergleich zur Nicht-Senkung zu einem besseren funktionellen Ergebnis?

Datum der Evidenzgewinnung 08.12.2020

#### MedLine

Suchterm: stroke AND (thromboly\* or alteplase) AND “blood pressure”

Filter: Systematic Review OR Meta-Analysis, 10 years

Treffer: 12

Ausschluss nach Beurteilung von Titel/Abstract: 9

Verblieben: 3 (#01-#03)

#### Web of Science

Suchterm: stroke AND (thromboly\* or alteplase) AND “blood pressure”

Filter: review, 2011-2020

Treffer: 80

Ausschluss nach Beurteilung von Titel/Abstract: 77

Ausschluss von Treffern der Medline-Suche: 3

Verblieben: 0

#### Gefundene Literatur:

**#01**: Teng RSY, Tan BYQ, Miny S, Syn NL, Ho AFW, Ngiam NJH, Yeo LLL, Choong AM, Sharma VK. Effect of Pretreatment Blood Pressure on Outcomes in Thrombolysed Acute Ischemic Stroke Patients: A Systematic Review and Meta-analysis. J Stroke Cerebrovasc Dis. 2019 Apr;28(4):906-919. doi: 10.1016/j.jstrokecerebrovasdis.2018.12.008. Epub 2019 Jan 3. PMID: 30612890.



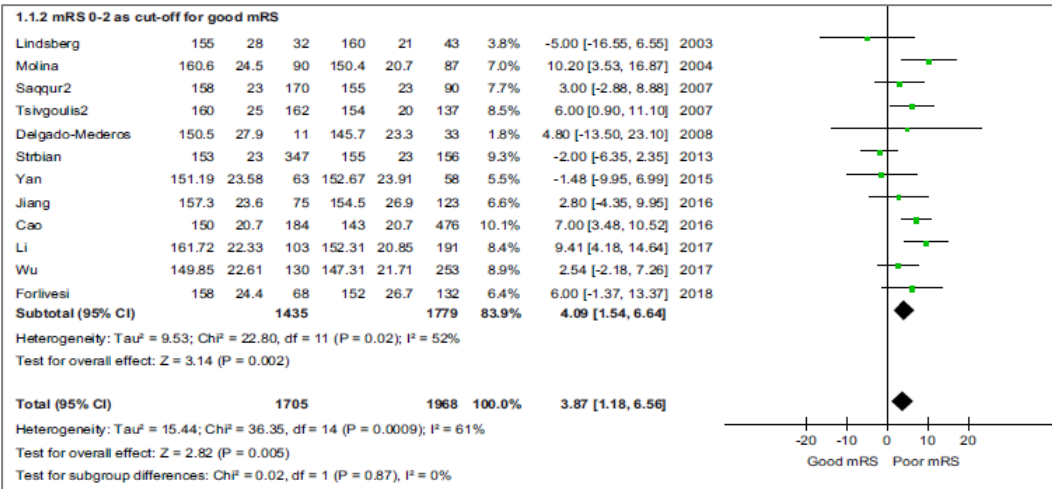
**#02:** Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikilidou M, Schellinger PD, Alexandrov AW, Alexandrov AV, Tsvigoulis G. Association of Elevated Blood Pressure Levels with Outcomes in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. J Stroke. 2019 Jan;21(1):78-90. doi: 10.5853/jos.2018.02369. Epub 2019 Jan 31. PMID: 30732443; PMCID: PMC6372893.

**#03:** Lei Z, Li S, Hu S, Ren L. Effects of Baseline Systolic Blood Pressure on Outcome in Ischemic Stroke Patients with Intravenous Thrombolysis Therapy: A Systematic Review and Meta-Analysis. Neurologist. 2020 May;25(3):62-69. doi: 10.1097/NRL.000000000000267. PMID: 32358463.

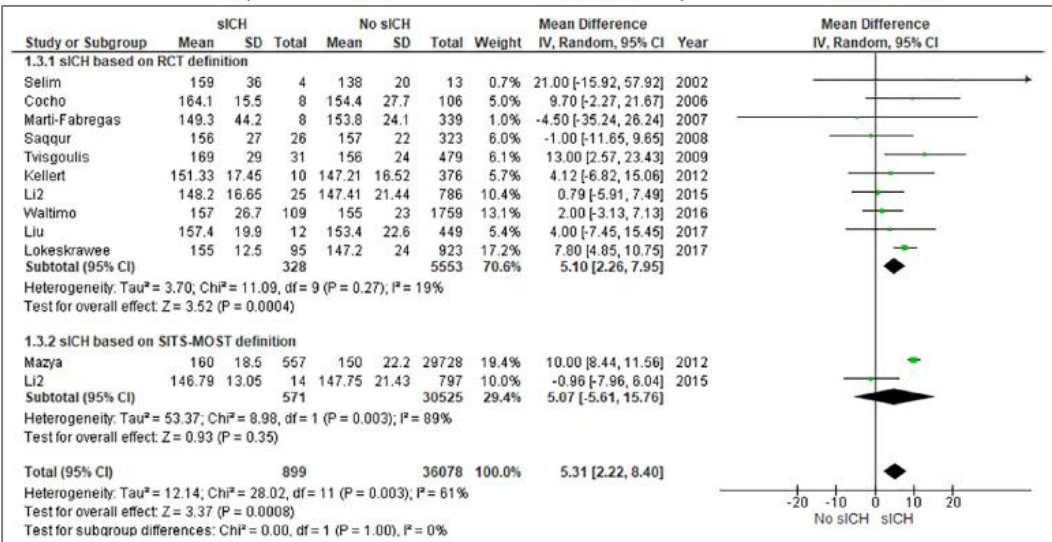
### Beurteilung

<b>Studie (review)</b>	<b>#01:</b> Teng RSY, Tan BYQ, Miny S, Syn NL, Ho AFW, Ngiam NJH, Yeo LLL, Choong AM, Sharma VK. Effect of Pretreatment Blood Pressure on Outcomes in Thrombolysed Acute Ischemic Stroke Patients: A Systematic Review and Meta-analysis. J Stroke Cerebrovasc Dis. 2019 Apr;28(4):906-919.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung des Reviews</b>			
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational cohort studies			
2. Welche Interventionen sind betrachtet/untersucht worden? (1) Subjects were diagnosed as AIS and, (2) Subjects received IV-tPA. From randomized controlled trials that compared thrombolytic therapy and a placebo, only data from the thrombolytic therapy arm was extracted (3) Studies had to report pretreatment systolic and/or diastolic BP values, in terms of mean and standard deviation.			
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? mRS; sICH			
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? N.a.			
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? Da thrombolysed, hospital			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X	
2. Ist die Literatursuche angemessen beschrieben?		X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X	
<b>Gesamtbeurteilung</b>		<b>++</b>	
<b>III. Ergebnisse</b>			

Of 2181 studies screened, 26 studies, involving 38,937 subjects, met inclusion criteria. Higher prethrombolysis systolic BP was significantly-associated with poorer 90-day functional outcome (Mean difference 3.87 mmHg; 95% confidence interval [CI] 1.18-6.56)



and increased incidence of sICH (Mean difference 5.31; 95% CI 2.22-8.40).



When studies were stratified by different cut-offs for functional outcome (mRS 0-1 versus 0-2) and definitions of sICH used (Randomized controlled trials or SITS-MOST), there was no significant difference in mean difference between the subgroups.

#### IV. Ableitbare Empfehlung

higher prethrombolysis systolic BP is associated with poorer functional outcomes and increased incidence of symptomatic intracranial hemorrhage in thrombolysed acute ischemic stroke patients. This supports the case for more aggressive lowering of BP prior to thrombolysis. Perhaps, large well designed prospective studies and randomized trials are required to establish the optimal pretreatment BP targets for a safer and effective systemic thrombolysis.

Eine konkrete Grenze ist nicht ermittelt worden

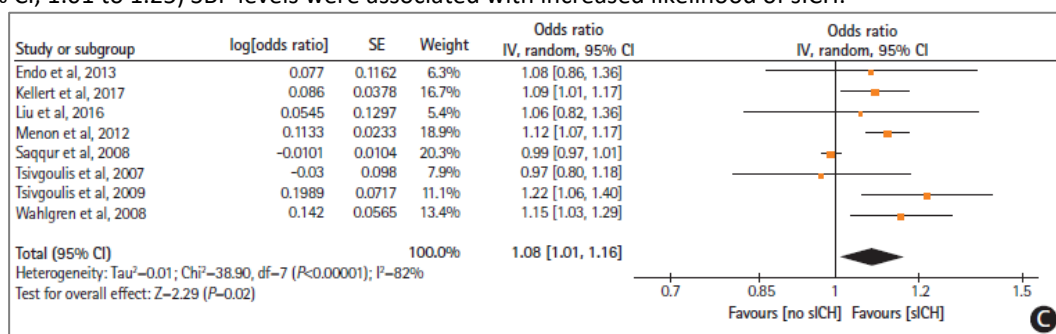
Studie (review)	#02: Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikilidou M, Schellinger PD, Alexandrov AW, Alexandrov AV, Tsivgoulis G. Association of Elevated Blood Pressure Levels with Outcomes in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. J Stroke. 2019 Jan;21(1):78-90
Bearbeiter	Peter A. Ringleb
Ausschluss	NEIN
Begründung	
<b>I. Beschreibung des Reviews</b>	

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational studies excluded studies that reported (1) outcomes not reported as per our inclusion criteria such as parenchymal hematoma or asymptomatic intracranial hemorrhage, (2) treatment with intra-arterial thrombolysis, mechanical thrombectomy, or systemic thrombolysis using agents other than alteplase, (3) descriptive data for BP levels reported as median values, (4) studies reporting mean arterial pressure levels instead of SBP or DBP levels, and (5) case report
2. Welche Interventionen sind betrachtet/untersucht worden? studies that investigated the association of acute BP levels with clinical outcomes in AIS patients treated with IVT.
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? : 3-month favorable functional outcome (defined as modified Rankin Scale [mRS] scores 0–1), 3-month functional independence (defined as mRS-scores of 0–2), 3-month mortality, sICH according to the definitions of included studies, tPA-induced recanalization (in AIS patients with proximal intracranial occlusions) according to the definitions of included studies
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Wurde für jede Studie einzeln angegeben (Suppl. Table 3), Mean age 45-75J.; NIHSS 10-17; Female 26-53%
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? da ICT wohl hospital

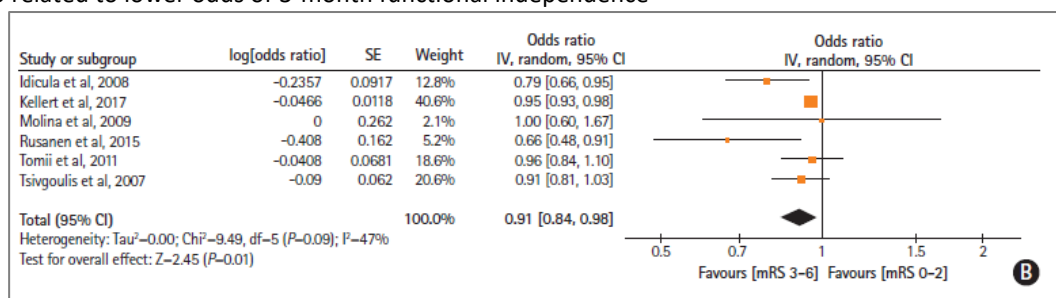
II. Interne Validität	Ja	Nein
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

**III. Ergebnisse**

s We identified 26 studies comprising 56,513 patients. Higher pre- (P=0.02) and posttreatment (P=0.006) SBP levels were observed in patients with sICH. Patients with 3-month functional independence had lower post-treatment (P<0.001) SBP whereas trended towards lower pre-treatment (P=0.06) SBP. In adjusted analyses, elevated pre- (ORadj, 1.08; 95% confidence interval [CI], 1.01 to 1.16) and post-treatment (ORadj, 1.13; 95% CI, 1.01 to 1.25) SBP levels were associated with increased likelihood of sICH.



Increasing pre- (ORadj, 0.91; 95% CI, 0.84 to 0.98) and post-treatment (ORadj, 0.70; 95% CI, 0.57 to 0.87) SBP values were also related to lower odds of 3-month functional independence



<b>IV. Ableitbare Empfehlung</b>			
We found that elevated BP levels adversely impact AIS outcomes in patients receiving IVT. Future randomized-controlled clinical trials will provide definitive data on the aforementioned association			
<b>Studie (review)</b>	#03: Lei Z, Li S, Hu S, Ren L. Effects of Baseline Systolic Blood Pressure on Outcome in Ischemic Stroke Patients with Intravenous Thrombolysis Therapy: A Systematic Review and Meta-Analysis. Neurologist. 2020 May;25(3):62-69.		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>JA</b>		
Begründung	Nur als Abstract verfügbar		
<b>I. Beschreibung des Reviews</b>			
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 Studiensettings (Setting, z.B. Praxis, Klinik)?			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
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?			
<b>Gesamtbeurteilung</b>		<b>++</b>	
<b>III. Ergebnisse</b>			
Eleven studies involving a total of 33,263 patients were included. Pooled data suggested that the odds of good outcome was decreased by 7% per 10 mm Hg increase in baseline SBP (odds ratio=0.93; 95% confidence interval: 0.91-0.94; P<0.001). Patients with higher baseline SBP were more likely to have intracranial hemorrhage (odds ratio=1.12 per 10 mm Hg increase; 95% confidence interval: 1.08-1.16, P<0.001).			
<b>IV. Ableitbare Empfehlung</b>			
This study suggested that lower baseline SBP may be positively associated with a greater chance of good outcome and less chance of intracranial hemorrhage. However, this effect was reliable only when the baseline SBP was within a certain range, which has not been explicitly stated. Therefore, more well-designed studies are needed to define the optimal baseline SBP			

SF 2.2.7: Führt bei Patienten mit Hirninfarkt, die mit einer interventionellen Thrombektomie behandelt werden, eine Senkung des Blutdrucks unter einen bestimmten Schwellenwert im Vergleich zur Nichtanwendung eines Schwellenwertes zu einem besseren funktionellen Ergebnis?

Datum der Evidenzgewinnung am 12.12.2020

#### MedLine

Suchterm: stroke AND (endovasc\* OR thrombec\*) AND "blood pressure"

Filter: Systematic Review OR Meta-Analysis, 10 years

Treffer: 16

Ausschluss nach Beurteilung von Titel/Abstract: 13

Verblieben: 3 (#01-#03)

## Web of Science

Suchterm: stroke AND (endovasc\* OR thrombec\*) AND "blood pressure"

Filter: review, 2011-2020

Treffer: 84

Ausschluss nach Beurteilung von Titel/Abstract: 81

Ausschluss von Treffern der Medline-Suche: 3

Verblieben: 0

## Gefundene Literatur:

#01: Maier B, Fahed R, Khoury N, Guenego A, Labreuche J, Taylor G, Blacher J, Zuber M, Lapergue B, Blanc R, Piotin M, Mazighi M. Association of Blood Pressure During Thrombectomy for Acute Ischemic Stroke With Functional Outcome: A Systematic Review. Stroke. 2019 Oct;50(10):2805-2812. doi: 10.1161/STROKEAHA.119.024915. Epub 2019 Aug 29. PMID: 31462188.

#02: Qin J, Zhang Z. Prognostic significance of early systolic blood pressure variability after endovascular thrombectomy and intravenous thrombolysis in acute ischemic stroke: A systematic review and meta-analysis. Brain Behav. 2020 Oct 14:e01898. doi: 10.1002/brb3.1898. Epub ahead of print. PMID: 33280273.

#03: Maier B, Delvoye F, Labreuche J, Escalard S, Desilles JP, Redjem H, Hébert S, Smajda S, Ciccio G, Lapergue B, Blanc R, Piotin M, Mazighi M. Impact of Blood Pressure After Successful Endovascular Therapy for Anterior Acute Ischemic Stroke: A Systematic Review. Front Neurol. 2020 Oct 29;11:573382. doi: 10.3389/fneur.2020.573382. PMID: 33193021; PMCID: PMC7659685.

## Beurteilung

<b>Studie (review)</b>	#01: Maier B, Fahed R, Khoury N, Guenego A, Labreuche J, Taylor G, Blacher J, Zuber M, Lapergue B, Blanc R, Piotin M, Mazighi M. Association of Blood Pressure During Thrombectomy for Acute Ischemic Stroke With Functional Outcome: A Systematic Review. Stroke. 2019 Oct;50(10):2805-2812.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational cohort studies: (1) study patients with AIS due to anterior circulation LVO (ie, middle cerebral artery or intracranial internal carotid artery); (2) >90% of the study patients treated with MT (with or without intravenous thrombolysis) using first or second-generation stent retriever and/or thromboaspiration;		
2. Welche Interventionen sind betrachtet/untersucht worden? Blutdruckmanagement bei EST bei LVO in der vorderen Zirkulation		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? functional outcome assessment at 3 months using the modified Rankin Scale		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 1037 Patienten, keine Basisdaten angegeben		
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? Hospital		
<b>II. Interne Validität</b>		
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	

<b>Gesamtbeurteilung</b>	+
<b>III. Ergebnisse</b>	
<p>Nine studies were included, for a total of 1037 patients. The heterogeneity in findings with respect to BP monitoring and studied parameters precluded a meta-analysis. Mean arterial pressure was the most frequently reported parameter to describe BP variability during MT, and systolic BP was the main parameter used to define periprocedural BP targets.</p> <p>Five studies suggested an association between 3 types of BP drops as predictors of poor functional outcome at 3 months: &gt;40% drop in mean arterial pressure compared with baseline (odds ratio=2.8; [1.09–7.19]; P=0.032), lowest mean arterial pressure before recanalization (odds ratio=1.28; [1.01–1.62] per 10 mm Hg drop below 100 mm Hg; P=0.04), and MAP drops (odds ratio=4.38; [1.53–12.6] for drops &gt;10%).</p> <p>Four studies did not show an association between BP during MT and functional outcome, including 3 studies with strict periprocedural systolic BP targets (within a 140–180 mm Hg). Three of the latter 4 studies had strict periprocedural BP targets (SBP between 140–160 mm Hg,13,15 SBP ≥140 mm Hg and MAP ≥70 mmHg14),</p>	
<b>IV. Ableitbare Empfehlung</b>	
<p>BP drops during MT seem to be associated with worse functional outcome and seem to be best described by MAP drops with MAP thresholds &lt;70 to 80 mm Hg or MAP drops from baseline between 10% to 40% carrying predictive weight for poor outcome;</p> <p>strict control of periprocedural BP with SBP targets ranging from 140 to 180 mm Hg seems not to affect functional outcome.</p> <p>Having reviewed this literature, it is our conviction that periprocedural BP targets for MT should be tailored and customized to the patient's clinical history, (hypertension, diabetes mellitus, and other medical history), and stroke characteristics (site of occlusion, collateral status, ASPECTS), instead of a one size fits all approach</p>	

<b>Studie (review)</b>	#02: Qin J, Zhang Z. Prognostic significance of early systolic blood pressure variability after endovascular thrombectomy and intravenous thrombolysis in acute ischemic stroke: A systematic review and meta-analysis. Brain Behav. 2020 Oct 14:e01898
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational cohort studies		
2. Welche Interventionen sind betrachtet/untersucht worden? early systolic blood pressure variability (SBPV) after endovascular thrombectomy (EVT) and intravenous thrombolysis (IVT)		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? mRS, sICH		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a		
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? hospital		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	+	
<b>III. Ergebnisse</b>		
<p>Increased early SBPV after EVT was significantly associated with worse functional outcome in AIS (OR = 1.42, 95% CI 1.02 to 1.99, I2 = 82.4%, p value of Q test &lt; .001), whereas no significant associations were indicated between SBPV after IVT and functional outcome, symptomatic intracerebral hemorrhage (sICH) in AIS [functional outcome: RR = 1.08, 95% CI 0.96 to 1.22, I2 = 0.0%, p value of Q test = 0.793; sICH: RR = 2.40, 95% CI 0.71 to 8.03, I2 = 78.2%, p value of Q test = 0.01].</p>		

**IV. Ableitbare Empfehlung**  
 these studies provide evidence that increased early SBPV after EVT is related to worse longer-term functional outcome in AIS, but the association is not significant in AIS patients treated with IVT. In addition, further prospective and large-scale study is essential to explore the factors affecting the association between early SBPV and functional outcome. Furthermore, individualized BP management strategies were essential for AIS patients after EVT or IVT.

<b>Studie (review)</b>	#03: Maier B, Delvoye F, Labreuche J, Escalard S, Desilles JP, Redjem H, Hébert S, Smajda S, Ciccio G, Lapergue B, Blanc R, Piotin M, Mazighi M. Impact of Blood Pressure After Successful Endovascular Therapy for Anterior Acute Ischemic Stroke: A Systematic Review. Front Neurol. 2020 Oct 29;11:
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Observational cohort studies, (1) patients with AIS consecutive to anterior LVO; (2) >90% of the study patients treated with EVT (with or without intravenous thrombolysis) using first or second generation devices; (3) systematic BP monitoring after EVT;
2. Welche Interventionen sind betrachtet/untersucht worden? EVT (with or without intravenous thrombolysis) using first or second generation devices mit successful recanalization (mTICI2b-3)
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? sICH, mTS
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? n.a.
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? hospital

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

### III. Ergebnisse

Five studies were included in the present analysis. Despite a significant heterogeneity among studies which precluded a meta-analysis, systolic BP (SBP) was the most frequently used parameter to describe BP.

#### Functional outcome

Among the three studies with specific post-EVT BP targets, two specifically assessed BP parameters with functional outcome after successful EVT. In these studies, steady BP parameters consisted of an intensive BP control (SBP < 140 mmHg), which was associated with higher odds of good functional outcome compared with guideline-recommended BP targets (SBP < 180 mmHg), while mean SBP > 130 mmHg (OR = 2.66 [1.11–6.41]) was associated with poor outcome. Two studies without specific post-EVT BP targets evaluated the association between dynamic BP parameters and functional outcome. In these studies, SBP reduction (OR = 0.97, [0.95–0.98]), maximum SBP (OR = 0.90, [0.85–0.95]) and SBP range (OR = 0.91, [0.86–0.96]) were associated with a higher odds of poor functional outcome. Only the association between SBP reduction and functional outcome differed according to the specific reperfusion status [i.e., mTICI 2B vs. mTICI 3. SBP reduction was inversely associated with poor functional outcome in patients with mTICI 3 but not in mTICI 2B patients. The reperfusion status did not modify the association between maximum SBP and SBP range with functional outcome.

Four studies evaluated the post-EVT BP impact on recanalized patients solely, with only one specifically addressing the impact of a TICI 2B vs. 2C. Interestingly, SBP reduction was inversely associated with worse outcomes in TICI 3 patients but not in TICI 2B patients, pointing to the potential value of BP management according to the exact TICI.

#### sICH:

Among the studies with strict BP targets after successful EVT, only one dynamic BP parameter was associated with higher odds of sICH: time rate of SBP (OR = 1.71, [1.01–2.9]) no steady BP parameters were associated with sICH in studies with BP control after successful EVT. There was no significant association between these BP goals and the odds of sICH.

### IV. Ableitbare Empfehlung

BP post-EVT seems to be associated with worse functional outcomes and sICH. However, given the important heterogeneity depicted among the included studies, no decisive conclusion can be made from this systematic review, thus underlying the urgent need of randomized controlled trials evaluating this question.

SF 3.2: Verbessert bei erwachsenen Patienten mit akutem Hirninfarkt eine therapeutische Hypothermie zusätzlich zur Standardtherapie a) die Überlebensrate und b) das neurologische Funktionsniveau bei Überleben.

Datum der Evidenzgewinnung 05.12.2020

#### MedLine

A) Suchterm: malignant and (infarction or stroke) and hypothermia

Filter: systematic review

Treffer: 2

Ausschluss nach Beurteilung von Titel/Abstract: 0

Verblieben: 2

**#01:** Chen Z, Zhang X, Liu C. Outcomes of therapeutic hypothermia in patients treated with decompressive craniectomy for malignant Middle cerebral artery infarction: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2020 Jan;188:105569. doi: 10.1016/j.clineuro.2019.105569. Epub 2019 Oct 23. PMID: 31710882

**#02:** Kuczynski AM, Ospel JM, Demchuk AM, Goyal M, Mitha AP, Almekhlafi MA. Therapeutic Hypothermia in Patients with Malignant Ischemic Stroke and Hemispheric Craniectomy-A Systematic Review and Meta-analysis. World Neurosurg. 2020 Sep;141:e677-e685. doi: 10.1016/j.wneu.2020.05.277. Epub 2020 Jun 19. PMID: 32569760



**Bewertung:**

<b>Studie</b>	#01: Chen Z, Zhang X, Liu C. Outcomes of therapeutic hypothermia in patients treated with decompressive craniectomy for malignant Middle cerebral artery infarction: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2020 Jan;188:105569.	
Bearbeiter	Ch. Hametner	
Ausschluss	<b>Nein</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? articles were prospective observational studies, retrospective observational studies, or randomized control trials (RCT)		
2. Welche Interventionen sind betrachtet/untersucht worden? comparing the efficacy of combined DC and TH therapy for malignant MCA infarction treatment		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? the outcomes measured were all-cause mortality or neurological outcomes.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Mean age 49 bis 62 J, Target T 33-35°, Sonst nichts berichtet		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? INTensivstationen		
<b>II. Interne Validität</b>		
	Ja	Nein
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
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?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
Patient data was analyzed for a total of 289 patients from four selected studies and two abstracts. Compared to DC alone, combining DC and TH had a tendency to reduce short-term mortality (RR=0.52, 95% CI 0.26 to 1.05, P=0.07, I2=0%) but had no significant effects on long-term mortality (RR=1.26, 95% CI 0.58 to 2.76, P=0.56, I2=68%) or neurological outcomes (RR=0.81, 95% CI 0.53 to 1.24, P=0.34, I2=30%).		
<b>IV. Ableitbare Empfehlung</b>		
Using TH in tandem with DC did not show definite short- or long-term survival benefits in our study, but may tend to reduce the short-term mortality of patients with malignant MCA infarction		

<b>Studie</b>	#02: Kuczynski AM, Ospel JM, Demchuk AM, Goyal M, Mitha AP, Almekhlafi MA. Therapeutic Hypothermia in Patients with Malignant Ischemic Stroke and Hemicraniectomy-A Systematic Review and Meta-analysis. World Neurosurg. 2020 Sep;141:e677-e685.	
Bearbeiter	Ch. Hametner	
Ausschluss	<b>Nein</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? >10 patients, had a control group, and reported the method(s) of cooling employed. We excluded studies that did not report clinical outcomes or complications.		
2. Welche Interventionen sind betrachtet/untersucht worden? "stroke" AND "hypothermia" AND "hemicraniectomy."		

3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Primary outcome was good functional outcome at follow-up (modified Rankin Scale [mRS] 0e2). Secondary outcomes included overall complications including intracerebral hemorrhage (symptomatic, asymptomatic); hemorrhagic transformation; hematoma formation; herniation; cerebral edema; pneumonia; cardiac complications (e.g., hypotension/hypertension, bradycardia/ tachycardia, arrhythmia); and mortality.		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Age 49-62J, Frauen 26%-50%, NIHSS 18-21.		
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? Intensivstationen		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
Five studies (n=269 patients; n=130 TH, n=139 controls) were included, 4 of which were prospective (n=2 randomized controlled trials). Median achieved body temperature of TH was 33.6C (range 33°C-35°C). Median modified Rankin Scale at the study completion was similar between TH and controls (RR 1.08, 95% CI 0.56-2.07, P=0.8). Three studies reported individual patient modified Rankin Scale outcomes demonstrated a shift toward worse outcomes with TH (unadjusted common odds ratio 1.74; 95% CI 1.05e2.88, P=0.01). Overall complications were similar between groups (RR 1.20, 95% CI 0.70-2.05, random effects Five studies (n=269 patients; n=130 TH, n=139 controls) were included, 4 of which were prospective (n[2 randomized controlled trials). Median achieved body temperature of TH was 33.6C (range 33°C-35°C). Median modified Rankin Scale at the study completion was similar between TH and controls (RR 1.08, 95% CI 0.56-2.07, P=0.8). Three studies reported individual patient modified Rankin Scale outcomes demonstrated a shift toward worse outcomes with TH (unadjusted common odds ratio 1.74; 95% CI 1.05-2.88, P=0.01). Overall complications were similar between groups (RR 1.20, 95% CI 0.70=2.05, random effects		
<b>IV. Ableitbare Empfehlung</b>		
Clinical and functional outcomes were not overall different between patients undergoing systemic TH and controls following DHC despite the shift toward worse outcomes with TH observed in some studies.		

#### Kapitel 4: Geschlechtsspezifische Unterschiede in der Schlaganfall Akutbehandlung

##### MedLine

A) Suchterm: stroke AND (gender or sex) AND (treatment or thera\*)

Filter: systematic review, meta-analysis, 10 years

Treffer: 295

B) Suchterm: stroke AND (gender or sex) AND (difference OR aspec\*)

Filter: systematic review, meta-analysis, 10 years

Treffer: 257

Ausschluss von Duplikaten: 242

Ausschluss nach Beurteilung von Titel/Abstract: 230

Verblieben: 12 (#01-#12)

##### WebOfScience

Suchterm: stroke AND (gender or sex) AND (Treatment or thera\*)

Filter: review, 2011-2020

Treffer: 356

Ausschluss nach Beurteilung von Titel/Abstract/Duplikaten: 350

Verblieben: 6 (#13-#18)

#01: Chalos V, de Ridder IR, Lingsma HF, Brown S, van Oostenbrugge RJ, Goyal M, Campbell BCV, Muir KW, Guillemin F, Bracard S, White P, Dávalos A, Jovin TG, Hill MD, Mitchell PJ, Demchuk AM, Saver JL, van Zwam WH, Dippel DWJ; HERMES Collaborators. Does Sex Modify the Effect of Endovascular Treatment for Ischemic Stroke? *Stroke*. 2019 Sep;50(9):2413-2419. doi: 10.1161/STROKEAHA.118.023743. Epub 2019 Aug 15. PMID: 31412753; PMCID: PMC6727933.

#02: Liu M, Li G, Tang J, Liao Y, Li L, Zheng Y, Guo T, Kang X, Yuan M. The Influence of Sex in Stroke Thrombolysis: A Systematic Review and Meta-Analysis. *J Clin Neurol*. 2018 Apr;14(2):141-152. doi: 10.3988/jcn.2018.14.2.141. PMID: 29629522; PMCID: PMC5897195.

#03: Sheth SA, Lee S, Warach SJ, Gralla J, Jahan R, Goyal M, Nogueira RG, Zaidat OO, Pereira VM, Siddiqui A, Lutsep H, Liebeskind DS, McCullough LD, Saver JL. Sex Differences in Outcome After Endovascular Stroke Therapy for Acute Ischemic Stroke. *Stroke*. 2019 Sep;50(9):2420-2427. doi: 10.1161/STROKEAHA.118.023867. Epub 2019 Aug 15. PMID: 31412752; PMCID: PMC6710145.

#04: Strong B, Lisabeth LD, Reeves M. Sex differences in IV thrombolysis treatment for acute ischemic stroke: A systematic review and meta-analysis. *Neurology*. 2020 Jul 7;95(1):e11-e22. doi: 10.1212/WNL.0000000000009733. Epub 2020 Jun 10. PMID: 32522796.

#05: Langhorne P, Ramachandra S; Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. *Cochrane Database Syst Rev*. 2020 Apr 23;4(4):CD000197. doi: 10.1002/14651858.CD000197.pub4. PMID: 32324916; PMCID: PMC7197653.

#06: Wallach JD, Sullivan PG, Trepanowski JF, Steyerberg EW, Ioannidis JP. Sex based subgroup differences in randomized controlled trials: empirical evidence from Cochrane meta-analyses. *BMJ*. 2016 Nov 24;355:i5826. doi: 10.1136/bmj.i5826. PMID: 27884869; PMCID: PMC5122320.

#07: Giralt D, Domingues-Montanari S, Mendioroz M, Ortega L, Maisterra O, Perea-Gainza M, Delgado P, Rosell A, Montaner J. The gender gap in stroke: a meta-analysis. *Acta Neurol Scand*. 2012 Feb;125(2):83-90. doi: 10.1111/j.1600-0404.2011.01514.x. Epub 2011 Jun 8. PMID: 21649609.

#08: Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017. *Circulation*. 2020 Feb 18;141(7):540-548. doi: 10.1161/CIRCULATIONAHA.119.043594. Epub 2020 Feb 17. PMID: 32065763.

#09: Phan HT, Reeves MJ, Blizzard CL, Thrift AG, Cadilhac DA, Sturm J, Otahal P, Rothwell P, Bejot Y, Cabral NL, Appelros P, Körv J, Vibo R, Minelli C, Gall SL. Sex Differences in Severity of Stroke in the INSTRUCT Study: a Meta-Analysis of Individual Participant Data. *J Am Heart Assoc*. 2019 Jan 8;8(1):e010235. doi: 10.1161/JAHA.118.010235. PMID: 30590965; PMCID: PMC6405721.

#10: Potisopha W, Vuckovic KM, DeVon HA, Park CG, Hershberger PE. Sex Differences in Prehospital Delay in Patients With Acute Stroke: A Systematic Review. *J Cardiovasc Nurs*. 2020 Nov/Dec;35(6):E77-E88. doi: 10.1097/JCN.0000000000000715. PMID: 32649376. **Nur Abstract**

#11: Stroebele N, Müller-Riemenschneider F, Nolte CH, Müller-Nordhorn J, Bockelbrink A, Willich SN. Knowledge of risk factors, and warning signs of stroke: a systematic review from a gender perspective. *Int J Stroke*. 2011 Feb;6(1):60-6. doi: 10.1111/j.1747-4949.2010.00540.x. PMID: 21205242.

#12: Zhou G, Nie S, Dai L, Wang X, Fan W. Sex differences in stroke case fatality: a meta-analysis. *Acta Neurol Scand*. 2013 Jul;128(1):1-8. doi: 10.1111/ane.12091. Epub 2013 Feb 15. PMID: 23410179.

#13: Arnao V, Acciarresi M, Cittadini E et al. Stroke incidence, prevalence and mortality in women worldwide. *International Journal of Stroke* 2016; 11(3):287-301

#14 Berglund A, Schenck-Gustafsson K, von Euler M Sex differences in the presentation of stroke. Maturitas 2017; 99:47-50c

#15: Bushnell C, Howard VJ, Lisabeth L et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. Lancet neurology 2018; 17(7):641-50

#16 Colsch R, Lindseth G Unique Stroke Symptoms in Women: A Review. Journal of Neuroscience Nursing 2018; 50(6):336-42

#17 Poorthuis MHF, Algra AM, Algra A et al. Female- and Male-Specific Risk Factors for Stroke A Systematic Review and Meta-analysis. Jama Neurology 2017; 74(1):75-81

#18 Sohrabji F, Park MJ, Mahnke AH Sex Differences in Stroke Therapies. Journal of Neuroscience Research 2017; 95(1-2):681-91

**Zusätzlich an der Literaturverzeichnisse dieser Arbeiten gefunden und für relevant befundet**

#20: Mainz J, Andersen G, Valentin JB, Gude MF, Johnsen SP. Disentangling Sex Differences in Use of Reperfusion Therapy in Patients With Acute Ischemic Stroke. Stroke. 2020 Aug;51(8):2332-2338. doi: 10.1161/STROKEAHA.119.028589. Epub 2020 Jul 9. PMID: 32640943.

#21 Falsetti L, Viticchi G, Buratti L et al. From head to toe: Sex and gender differences in the treatment of ischemic cerebral disease. Pharmacol Res 2017; 121:240-50

**Bewertung:**

<b>Studie (review)</b>	#01: Chalos V, de Ridder IR, Lingsma HF, Brown S, van Oostenbrugge RJ, Goyal M, Campbell BCV, Muir KW, Guillemin F, Bracard S, White P, Dávalos A, Jovin TG, Hill MD, Mitchell PJ, Demchuk AM, Saver JL, van Zwam WH, Dippel DWJ; HERMES Collaborators. Does Sex Modify the Effect of Endovascular Treatment for Ischemic Stroke? Stroke. 2019 Sep;50(9):2413-2419.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Die Daten der HERMES Gruppe		
2. Welche Interventionen sind betrachtet/untersucht worden? EST vs OMT		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? mRS, TICl, infarctsize, mortality, ICH		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? We included 1762 patients in the analyses, of whom 833 (47%) were women. Frauen 70, Männer 66J, Männer häufiger Raucher, Frauen bessere Kollaterale, sonst keine Unterschiede		
5. Was waren die Charakteristika des Studiensettings (Setting, z.B. Praxis, Klinik)? Klinik		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>+</b>
<b>III. Ergebnisse</b>		
Functional independence (modified Rankin Scale score, 0–2) at 90 days was reached by 318 women (39%) and 364 men (39%). The effect of EVT on the ordinal modified Rankin Scale was similar in women (adjusted common odds ratio [acOR], 2.13; 95% CI, 1.47–3.07) and men (acOR, 2.16; 95% CI, 1.59–2.96), with a P for interaction of 0.926		

<b>IV. Ableitbare Empfehlung</b>
Sex does not influence clinical outcome after EVT and does not modify treatment effect of EVT. Therefore, sex should not be a consideration in the selection of patients for EVT

<b>Studie (review)</b>	<b>#02:</b> Liu M, Li G, Tang J, Liao Y, Li L, Zheng Y, Guo T, Kang X, Yuan M. The Influence of Sex in Stroke Thrombolysis: A Systematic Review and Meta-Analysis. J Clin Neurol. 2018 Apr;14(2):141-152
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs or original observational cohort studies
2. Welche Interventionen sind betrachtet/untersucht worden? investigated the influence of sex difference in the response to thrombolysis in stroke
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? mRS; Recanalization (TIMI), sICH
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Age
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)?

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	

**III. Ergebnisse**

Sixteen reports involving 60,159 patients were available for analysis. The female patients were a 0.89-fold [95% confidence interval (CI)=0.87–0.90, p<0.001], 0.89-fold (95% CI=0.87–0.91, p<0.001), and 1.24-fold (95% CI=1.11–1.36, p<0.001) more likely to obtain good, excellent, and poor functional outcomes, respectively, with no significant difference in the complications of symptomatic intracranial hemorrhage among the sexes [risk ratios (RR)=0.99, 95% CI=0.92–1.07, p=0.81] after thrombolysis treatment.

**IV. Ableitbare Empfehlung**

This study has demonstrated that females often exhibit a worse outcome than males after intravenous thrombolysis (IVT), whereas no relevant sex differences were found in outcome or recanalization after IAT, with safety regarding hemorrhage complications from thrombolysis being the same for the sexes. However, IVT should not be withheld from female stroke patients solely based on their sex before the findings are confirmed in further large-scale research.

<b>Studie (review)</b>	<b>#03:</b> Sheth SA, Lee S, Warach SJ, Gralla J, Jahan R, Goyal M, Nogueira RG, Zaidat OO, Pereira VM, Siddiqui A, Lutsep H, Liebeskind DS, McCullough LD, Saver JL. Sex Differences in Outcome After Endovascular Stroke Therapy for Acute Ischemic Stroke. Stroke. 2019 Sep;50(9):2420-2427.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? RCTs mit Solitaire Stent
2. Welche Interventionen sind betrachtet/untersucht worden? EST mit Solitaire
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? differences in DALYs, mRS
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 175 Männer, 214 Frauen; Age 64-69 J., NIHSS 17, Frauen mehr VHF (45 vs 30%) sonst Baseline idem
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? hospital

<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	+	
<b>III. Ergebnisse</b>		
<p>There were no differences between females vs. males in rate of substantial reperfusion (TICI 2b/3, 87% vs. 83%, p=0.37), onset to reperfusion time (294 vs. 302 mins, p=0.46). Despite older ages (69 vs. 64, p&lt;0.001) and higher rate of atrial fibrillation (45% vs. 30%, p=0.002) for females compared to males, adjusted rates of functional independence at 90 days were similar (odds ratio, 1.0; 95% CI, 0.6–1.6). After adjusting for age at presentation and stroke severity, females had more years of optimal life (DALYs) following EST, 10.6 vs. 8.5 years (p&lt;0.001).</p>		
<b>IV. Ableitbare Empfehlung</b>		
<p>Despite greater age and higher rate of atrial fibrillation, females experienced comparable functional outcomes and greater years of optimal life after intervention compared to males.</p>		

<b>Studie (review)</b>	#04: Strong B, Lisabeth LD, Reeves M. Sex differences in IV thrombolysis treatment for acute ischemic stroke: A systematic review and meta-analysis. Neurology. 2020 Jul 7;95(1):e11-e22.
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	

<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Cohort studies		
2. Welche Interventionen sind betrachtet/untersucht worden? Iv thrombolysis		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Iv treatment rate		
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)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	++	
<b>III. Ergebnisse</b>		
<p>Twenty-four eligible studies were identified during this 10-year period. The summary unadjusted OR based on 17 studies with data on all ischemic stroke patients was 0.87 (95%CI 0.82–0.93), indicating that women had 13% lower odds of receiving IV rtPA treatment than men. However, substantial between-study variability existed. Lower treatment odds in women were also observed in 7 studies that provided data on the subgroup of patients eligible for IV rtPA treatment, although the summary OR of 0.95 (95% CI, 0.88–1.02) was not statistically significant. Examination of time trends across 33 studies published between 2000 and 2018 found evidence that the sex difference had narrowed in more recent years</p>		
<b>IV. Ableitbare Empfehlung</b>		
<p>Although there is considerable variability in the findings of individual studies, pooled data from recent studies show that women with acute stroke are less likely to be treated with IV thrombolysis compared with men. However, the size of this difference has narrowed compared to studies published before 2008.</p>		

<b>Studie (review)</b>	<b>#05:</b> Langhorne P, Ramachandra S; Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. Cochrane Database Syst Rev. 2020 Apr 23;4(4)
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	
<b>III. Ergebnisse</b>	
Das ist das Cochrane-review, das bereits Basis der SF zur Stroke Unit Therapie war. Es enthält eine Geschlechtsauswertung in Bezug auf das schlechte Outcome (Seite 22)	
<b>IV. Ableitbare Empfehlung</b>	
Kein Geschlechtsunterschied der Stroke Unit Therapie in Bezug auf	

<b>Studie (review)</b>	<b>#06:</b> Wallach JD, Sullivan PG, Trepanowski JF, Steyerberg EW, Ioannidis JP. Sex based subgroup differences in randomized controlled trials: empirical evidence from Cochrane meta-analyses. BMJ. 2016 Nov 24;355:i5826.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Cochrane reviews		
2. Welche Interventionen sind betrachtet/untersucht worden? To evaluate the frequency, validity, and relevance of statistically significant ( $P < 0.05$ ) sex-treatment interactions in randomized controlled trials in Cochrane meta-analyses		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? sex-treatment interactions		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? N.a.		
5. Was waren die Charakteristika des Studenumfelds (Setting, z.B. Praxis, Klinik)? N.a.		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	+	
<b>III. Ergebnisse</b>		
Among the 41 reviews with relevant data, there were 109 separate treatment-outcome analyses ("topics"). Among the 109 topics, eight (7%) had a statistically significant sex-treatment interaction.		
Of the 162 individual randomized controlled trials that included both sexes, 15 (9%) had a statistically significant sex-treatment interaction.		
Of four topics where the first published randomized controlled trial had a statistically significant sex-treatment interaction, no meta-analyses that included other randomized controlled trials retained the statistical significance and no meta-analyses showed statistical significance when data from the first published randomized controlled trial were excluded. Of the eight statistically significant sex-treatment interactions from the overall analyses, only three were discussed by the CDSR reviewers for a potential impact on different clinical management for males compared with females. None of these topics had a sex-treatment interaction that influenced treatment recommendations in recent guidelines.		
<b>IV. Ableitbare Empfehlung</b>		
Statistically significant sex-treatment interactions are only slightly more frequent than what would be expected by chance and there is little evidence of subsequent corroboration or clinical relevance of sex-treatment interactions		

<b>Studie (review)</b>	#07: Giralt D, Domingues-Montanari S, Mendioroz M, Ortega L, Maisterra O, Perea- Gainza M, Delgado P, Rosell A, Montaner J. The gender gap in stroke: a meta- analysis. Acta Neurol Scand. 2012 Feb;125(2):83-90	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)?		
2. Welche Interventionen sind betrachtet/untersucht worden? Multiple		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Sex differences		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? N.a.		
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? N.a.		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X
<b>Gesamtbeurteilung</b>		<b>+</b>
<b>III. Ergebnisse</b>		
Women were globally older than men (+5.2 years) and suffered more hypertension (P = 0.017) and atrial fibrillation (P < 0.001), although they were less likely to drink alcohol (P < 0.001), smoke cigarettes (P < 0.001), present hyperlipidemia (P = 0.033) or diabetes (P = 0.003) than men. Baseline stroke severity was not different between genders. Women suffered more cardioembolic strokes, while men had more atherothrombotic strokes. Moreover, women were less likely to receive stroke-related treatments, such as antiplatelets (P < 0.001), statins (P < 0.001), and tPA (P < 0.001) than men. Although meta-regression did not identify age or stroke etiology as sources of heterogeneity, caution should be taken as that analysis was possible only for gender differences in secondary prevention with antiplatelets because of limited data for other end points.		
<b>IV. Ableitbare Empfehlung</b>		
Gender differences have been identified on the risk factors profile and diagnostic and therapeutic management of patients with ischemic stroke. Active measures should thus be taken to avoid bias in clinical practice		

<b>Studie (review)</b>	#08: Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017. Circulation. 2020 Feb 18;141(7):540-548.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Abgeschlossene Studien bei Clinicaltrials.gov erfasst		
2. Welche Interventionen sind betrachtet/untersucht worden? Acht verschiedene Krankheitsbilder mit multiplen Interventionen		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Frauenanteil		
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? Kein durchschnittswerte, gruppenangabe, 87 Stroke Studien		
5. Was waren die Charakteristika des Studiumfelds (Setting, z.B. Praxis, Klinik)? N.a		
<b>II. Interne Validität</b>		<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X



3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		<b>+</b>
<b>III. Ergebnisse</b>		
<p>We identified 740 completed cardiovascular trials including a total of 862 652 adults, of whom 38.2% were women[484] The median female-to-male ratio of each trial was 0.51 (25<sup>th</sup> quartile, 0.32; 75<sup>th</sup> quartile, 0.90) overall and varied by age group (1.02 in ≤55 year old group versus 0.40 in the 61- to 65-year-old group), disease type (0.34 for acute coronary syndrome versus 3.20 for pulmonary hypertension), Women were represented at a rate lower than their share in the respective disease population (PPR&lt;0.8) for stroke (PPR=0.73)</p>		
<b>IV. Ableitbare Empfehlung</b>		
Among cardiovascular trials in the current decade, men still predominate overall, but the representation of women varies with disease and trial characteristics, and has improved in stroke and heart failure trials		

<b>Studie (review)</b>	<b>#09:</b> Phan HT, Reeves MJ, Blizzard CL, Thrift AG, Cadilhac DA, Sturm J, Otahal P, Rothwell P, Bejot Y, Cabral NL, Appelros P, Kõrv J, Vibo R, Minelli C, Gall SL. Sex Differences in Severity of Stroke in the INSTRUCT Study: a Meta-Analysis of Individual Participant Data. J Am Heart Assoc. 2019 Jan 8;8(1)
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Kein SR
<b>III. Ergebnisse</b>	
The pooled unadjusted female:male RR for severe ischemic stroke was 1.35 (95% CI 1.24–1.46). The sex difference in severity was attenuated after adjustment for age, pre-stroke dependency, and atrial fibrillation but remained statistically significant (pooled RRadjusted 1.20, 95% CI 1.10–1.30)	
<b>IV. Ableitbare Empfehlung</b>	
women present with more severe ischemic stroke than men and the difference is partly explained by their older age, greater pre-stroke dependency, and higher prevalence of atrial fibrillation compared with men.	

<b>Studie (review)</b>	<b>#10:</b> Potisopha W, Vuckovic KM, DeVon HA, Park CG, Hershberger PE. Sex Differences in Prehospital Delay in Patients With Acute Stroke: A Systematic Review. J Cardiovasc Nurs. 2020 Nov/Dec;35(6):E77-E88. doi: 10.1097/JCN.0000000000000715. PMID: 32649376
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Volltext nicht erhältlich, von Seiten des Abstracts auch nicht unbedingt notwendig, Thema ausreichend in #15 bearbeitet
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

<b>Studie (review)</b>	<b>#11:</b> Stroebele N, Müller-Riemenschneider F, Nolte CH, Müller-Nordhorn J, Bockelbrink A, Willich SN. Knowledge of risk factors, and warning signs of stroke: a systematic review from a gender perspective. Int J Stroke. 2011 Feb;6(1):60-6. doi: 10.1111/j.1747-4949.2010.00540.x. PMID: 21205242
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	
<b>I. Beschreibung des Reviews</b>	

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? cross-sectional, cohort, and case-control studies, clinical trials, metaanalysis, and systematic reviews with adult human subjects		
2. Welche Interventionen sind betrachtet/untersucht worden? Einige		
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 Studenumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?		X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>+</b>	
<b>III. Ergebnisse</b>		
Twenty-two studies were reviewed including 20 cross-sectional and two pretest-posttest design surveys. Overall, better stroke knowledge was observed in women compared with men in the majority of the studies although there is a general lack of knowledge in both genders. Four out of 18 studies reported better risk factor knowledge and eight out of 15 studies reported better knowledge in stroke warning signs in women compared with men. Women tended to know more evidence-based stroke risk factors than men.		
<b>IV. Ableitbare Empfehlung</b>		
Stroke knowledge among different populations and both in men and women is suboptimal.		

<b>Studie (review)</b>	#12: Zhou G, Nie S, Dai L, Wang X, Fan W. Sex differences in stroke case fatality: a meta-analysis. Acta Neurol Scand. 2013 Jul;128(1):1-8.	
Bearbeiter	Peter A. Ringleb	
Ausschluss	<b>NEIN</b>	
Begründung		
<b>I. Beschreibung des Reviews</b>		
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Populations based or RCT		
2. Welche Interventionen sind betrachtet/untersucht worden? keine		
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Stroke fatality		
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 Studiumfelds (Setting, z.B. Praxis, Klinik)?		
<b>II. Interne Validität</b>	<b>Ja</b>	<b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X	
2. Ist die Literatursuche angemessen beschrieben?	X	
3. Wurde die Qualität der gefundenen Studien ermittelt?	X	
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	<b>++</b>	
<b>III. Ergebnisse</b>		
Thirty-six population-based studies, together with three randomized clinical trials (RCTs), were included in the present study. For the pooled group, there was an overall hazard risk of 1.13 for women compared with men. A hazard risk of 1.27 was observed for women in RCTs subgroup and 1.12 for women in population-based subgroup. The regression analysis found no significant correlation between methodological variables and heterogeneity.		

IV. Ableitbare Empfehlung	
Due to the limited data about sex differences in stroke case fatality, the findings should be treated cautiously as preliminary. More large multicenter clinical trials should be performed to verify the reliability of the results	
<b>Studie (review)</b>	<b>#13:</b> Arnao V, Acciarresi M, Cittadini E et al. Stroke incidence, prevalence and mortality in women worldwide. International Journal of Stroke 2016; 11(3):287-301
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Weltweite Daten, kaum aus Deutschland
I. Beschreibung des Reviews	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? the standard definition of stroke (WHO) was used,	
2. Welche Interventionen sind betrachtet/untersucht worden? any age-specific epidemiologic parameter of interest (i.e. stroke incidence, prevalence, disease specific mortality, relative risk of mortality) was reported and (3) any review articles on population- or community-based incidence and prevalence studies have been included	
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 Studientumfelds (Setting, z.B. Praxis, Klinik)?	
III. Ergebnisse	
IV. Ableitbare Empfehlung	

<b>Studie (review)</b>	<b>#14:</b> Berglund A, Schenck-Gustafsson K, von Euler M Sex differences in the presentation of stroke. Maturitas 2017; 99:47-50c		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
I. Beschreibung des Reviews			
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Any			
2. Welche Interventionen sind betrachtet/untersucht worden? Papers about stroke, symptoms and/or presentation, gender, written in English			
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Symptommhäufigkeit			
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? N.a.			
5. Was waren die Charakteristika des Studientumfelds (Setting, z.B. Praxis, Klinik)? N.a.			
II. Interne Validität		Ja	Nein
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X	
2. Ist die Literatursuche angemessen beschrieben?		X	
3. Wurde die Qualität der gefundenen Studien ermittelt?			X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X	
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?			X
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?			X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?		X	
<b>Gesamtbeurteilung</b>		+	
III. Ergebnisse			

Stroke symptoms	Finding [reference]
Severity	Higher in women [19,28,37,49-51]
Non-traditional symptoms	More common in women [35,36,52-54]
Symptoms more common in women	Impaired consciousness [34,35,49-55] Altered mental status [23,35,52,53] Paralysis [49] Dysphasia [49,50,53] Generalized weakness [35,53] Dysphagia[49] Urine incontinence [49,50]
Symptoms more common in men	Dysarthria [50] Diplopia [53] Sensory loss [50,53] Ataxia [50,53] Balance/walking/dizziness [54]
Conflicting findings	Visual disturbance [50,53]

**IV. Ableitbare Empfehlung**  
Non-traditional stroke symptoms are reported to be more common in women, who are thereby at risk of delayed recognition of stroke and treatment delay

<b>Studie (review)</b>	#15: Bushnell C, Howard VJ, Lisabeth L et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. Lancet neurology 2018; 17(7):641-50
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	Kein SR, aber sehr informativ und umfassend, zahlreiche Referenzen auf Primärliteratur

**I. Beschreibung des Reviews**

1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Kein SR
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)?

<b>II. Interne Validität</b>	Ja	Nein
1. Ist die Fragestellung angemessen und klar eingegrenzt?		X
2. Ist die Literatursuche angemessen beschrieben?		X
3. Wurde die Qualität der gefundenen Studien ermittelt?		X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?		X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X	
6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?		X
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>	+	

**III. Ergebnisse**

Kein SR aber sehr ausführliche Übersicht.  
seven were designed to specifically examine sex differences,4,14-16,20,22,23 and only four4,15,24,18 found a sex difference in the use of emergency medical services  
Several studies have shown an increased prevalence of non-traditional stroke symptoms and signs in women compared with men (table 2).  
Enthält Angaben zur rtPA Eignung und Gabefrequenz, d2nt und outcome  
Wiederholt die HERMES EVT Auswertun

**IV. Ableitbare Empfehlung**  
Thus, non-traditional stroke symptoms might be more common in women than in men

<b>Studie (review)</b>	<b>#16:</b> Colsch R, Lindseth G Unique Stroke Symptoms in Women: A Review. Journal of Neuroscience Nursing 2018; 50(6):336-42
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Nur Abstract erhältlich, ausreichend in #15 abgehandelt
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

<b>Studie (review)</b>	<b>#17:</b> Poorthuis MHF, Algra AM, Algra A et al. Female- and Male-Specific Risk Factors for Stroke A Systematic Review and Meta-analysis. Jama Neurology 2017; 74(1):75-81
Bearbeiter	Peter A. Ringleb
Ausschluss	JA
Begründung	Enthält nur Angaben zu Risikofaktoren, wenig mit unserer LL zu tun
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

<b>Studie (review)</b>	<b>#18:</b> Sohrabji F, Park MJ, Mahnke AH Sex Differences in Stroke Therapies. Journal of Neuroscience Research 2017; 95(1-2):681-91
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>JA</b>
Begründung	Keine SR, bisschen was zu rtPA (bereits ausreichend) und dann zu kortikaler Stimulation, Stammzellen...
<b>III. Ergebnisse</b>	
<b>IV. Ableitbare Empfehlung</b>	

<b>Studie (review)</b>	<b>#20:</b> Mainz J, Andersen G, Valentin JB, Gude MF, Johnsen SP. Disentangling Sex Differences in Use of Reperfusion Therapy in Patients With Acute Ischemic Stroke. Stroke. 2020 Aug;51(8):2332-2338
Bearbeiter	Peter A. Ringleb
Ausschluss	<b>NEIN</b>
Begründung	
<b>I. Beschreibung des Reviews</b>	
1. Welche Studientypen wurden eingeschlossen (RCT, Kohortenstudien, Fall-Kontroll-Studien)? Nationwide public registries aus Dänemark	
2. Welche Interventionen sind betrachtet/untersucht worden? EST in Dänemark	
3. Welche Zielkriterien (Endpunkte) wurden bestimmt? Delays	
4. Was waren die wichtigsten Charakteristika der Studienpopulation (Basisvariablen -z.B., Alter, Schweregrad der Erkrankung, Geschlechtsverteilung; Risiken- z.B. relevante Begleiterkrankung)? 5356 Pats, 43§ Frauen, 77,9 vs 71,6 J., SSS 44 vs 48, VHF 23,7% vs 19,5%	
5. Was waren die Charakteristika des Studienumfelds (Setting, z.B. Praxis, Klinik)? Dänische Krankenhäuser	
<b>II. Interne Validität</b>	<b>Ja</b> <b>Nein</b>
1. Ist die Fragestellung angemessen und klar eingegrenzt?	X
2. Ist die Literatursuche angemessen beschrieben?	X
3. Wurde die Qualität der gefundenen Studien ermittelt?	X
4. Wurden Kriterien zum Ein- und Ausschluss von Studien für die Bewertung im Review definiert?	X
5. Berücksichtigt der Review alle relevanten positiven und negativen Effekte der untersuchten Intervention/en?	X

6. War es sinnvoll, die für diesen Review ausgewählten Studien miteinander zu kombinieren?	X	
7. Rechtfertigen die Ergebnisse die Schlussfolgerungen?	X	
<b>Gesamtbeurteilung</b>		+
<b>III. Ergebnisse</b>		
A total of 5356 stroke events fulfilled the inclusion criteria. Women (26.6%) were less likely to receive IVT than men (30.2 %), corresponding to an unadjusted odds ratio of 0.84 (95% CI, 0.74–0.95). In addition, women experienced a 20 minutes longer median time delay from stroke symptom onset to stroke unit arrival than men. Adjusting for onset-to-door time only appeared to have a limited effect on the sex differences in use of intravenous thrombolysis, whereas the odds ratio was 1.06 (95% CI, 0.93–1.21) when adjusting for age at stroke, stroke severity, and cohabitation status. No sex difference was observed for the use of thrombectomy.		
<b>IV. Ableitbare Empfehlung</b>		
Women received less reperfusion therapy than men and had a longer time delay from symptom onset to stroke unit arrival, primarily due to a longer delay from symptom onset to emergency medical services call. These differences appeared to be due to the higher age and the higher proportion of women living alone at the time of the stroke.		

<b>Studie (review)</b>	#21: Falsetti L, Viticchi G, Buratti L et al. From head to toe: Sex and gender differences in the treatment of ischemic cerebral disease. Pharmacol Res 2017; 121:240-50		
Bearbeiter	Peter A. Ringleb		
Ausschluss	<b>NEIN</b>		
Begründung			
<b>I. Beschreibung des Reviews</b>			
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)?			
<b>II. Interne Validität</b>		<b>Ja</b>	<b>Nein</b>
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?			
<b>Gesamtbeurteilung</b>			+
<b>III. Ergebnisse</b>			
<b>IV. Ableitbare Empfehlung</b>			

**8.4. TABELLARISCHE ÜBERSICHT DER ÄNDERUNGEN ZU AMENDMENT 1**

Folgende Abschnitte wurden im Rahmen des Amendments „Oktober 2022“ modifiziert. Angegeben sind jeweils die Kapitel- bzw. Abschnittsnummer und die Seitenangabe mit Bezug auf die ältere Version 5 oder die aktuelle Version 5.1.

<b>Dokument</b>	<b>Verändertes Kapitel</b>	<b>Seite (V5.0)</b>	<b>Seite (V5.1)</b>
Langfassung 030-046l	Autoren	2	2
	1. Was gibt es Neues?	3	3
	2. Die wichtigsten Empfehlungen auf einen Blick	-	5
	7.1.3. Systemische Thrombolysen mit anderen Substanzen	92ff	92ff
	7.2.2. Bridging-Therapie	107ff	112ff
	11. Methodik der Leitlinienentwicklung	132	140
	12. Erklärung von Interessen und Umgang mit potenziellen Interessenkonflikten	133	141
	13. Gültigkeit und Aktualisierung	134	142
	15. Literatur	138	144
Kurzfassung 030-046k	Autoren	1	1
	1.1. Was gibt es Neues?	4	4
	3.1.3. Systemische Thrombolysen mit anderen Substanzen	21	21
	3.2.2. Bridging-Therapie	23	23
	7. Literatur	29ff	30ff
Methodenbericht 030-046m	2. Zusammensetzung der Leitliniengruppe, Beteiligung von Interessensgruppen	5	5
	3.1.1. Formulierung der Schlüsselfragen	14	14
	3.1.2. Auswahl der Evidenz	14	15
	3.1.3. Verwendung existierender Leitlinien, inkl. Tabelle 4 und Tabelle 5	15	16
	3.1.4. Systematische Literaturrecherche	16	17
	3.2.3. Formale Konsensusfindung inkl. Tabelle 10	21ff	22ff
	4.2. Externe Begutachtung	23	24
	5.2. Darlegung von und Umgang mit potenziellen Interessenkonflikten	23ff	24ff
	6. Verbreitung und Implementierung	25	26
	7. Gültigkeit und Aktualisierung	26	27
	8.1. Interessenanzeige der Autoren	27f	28f
	8.2.3. Synopse der externen Leitlinien, SF 2.1.5	121ff	122ff
	8.2.3. Synopse der externen Leitlinien, SF 2.2.3	138ff	140ff
	8.3. Suchalgorithmen und Ergebnis der systematischen Suche nach Übersichtsarbeiten oder Einzelstudien, SF 2.1.5	212ff	215ff
	8.4 Tabellarische Übersicht der Änderungen zu Amendment 1	./.	246
	8.5. Literatur	240ff	247ff
Patientenversion 030-046p	5.4.1. Systemische Thrombolysetherapie	12	12

## 8.5. LITERATUR

1. Powers WJ, Rabinstein AA, Ackerson T et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018; 49(3):e46-e110. doi: 10.1161/STR.000000000000158
2. Wahlgren N, Moreira T, Michel P et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke* 2016; 11(1):134-47. doi: 10.1177/1747493015609778
3. Torbey MT, Bösel J, Rhoney DH et al. Evidence-based guidelines for the management of large hemispheric infarction : a statement for health care professionals from the Neurocritical Care Society and the German Society for Neuro-intensive Care and Emergency Medicine. *Neurocrit Care* 2015; 22(1):146-64. doi: 10.1007/s12028-014-0085-6
4. Powers WJ, Derdeyn CP, Biller J et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2015; 46(10):3020-35. doi: 10.1161/STR.0000000000000074
5. Ntaios G, Dziedzic T, Michel P et al. European Stroke Organisation (ESO) guidelines for the management of temperature in patients with acute ischemic stroke. *Int J Stroke* 2015; 10(6):941-9. doi: 10.1111/ijvs.12579
6. Australian National Stroke Foundation. Clinical Guidelines for Stroke Management Chapter 1 to 8. Available from: [informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017](http://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017); Stand: 12.01.2020
7. Casaubon LK, Boulanger JM, Blacchiere D et al. Canadian Stroke Best Practice Recommendations: Hyperacute Stroke Care Guidelines, Update 2015. *Int J Stroke* 2015; 10(6):924-40. doi: 10.1111/ijvs.12551
8. Boulanger JM, Butcher K, Gubitza G et al. Canadian Stroke Best Practice Recommendations Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care. Available from: [www.strokebestpractices.ca/recommendations/acute-stroke-management](http://www.strokebestpractices.ca/recommendations/acute-stroke-management); Stand: 20.02.2019
9. Prasad K, Siemieniuk R, Hao Q et al. Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: a clinical practice guideline. *BMJ* 2018; 363:k5130. doi: 10.1136/bmj.k5130
10. Royal College of Physicians. National clinical guideline for stroke(fifth edition). Stand: 30.05.2017
11. Powers WJ, Rabinstein AA, Ackerson T et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2019; 50(12):e344-e418. doi: 10.1161/STR.0000000000000211
12. Dennis M, Caso V, Kappelle LJ et al. European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke. *Eur Stroke J* 2016; 1(1):6-19. doi: 10.1177/2396987316628384
13. Holtkamp M, Beghi E, Benninger F et al. European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. *Eur Stroke J* 2017; 2(2):103-15. doi: 10.1177/2396987317705536
14. Fuentes B, Ntaios G, Putaala J et al. European Stroke Organisation (ESO) guidelines on glycaemia management in acute stroke. *Eur Stroke J* 2018; 3(1):5-21. doi: 10.1177/2396987317742065
15. Kobayashi A, Czlonkowska A, Ford GA et al. European Academy of Neurology and European Stroke Organization consensus statement and practical guidance for pre-hospital management of stroke. *Eur J Neurol* 2018; 25(3):425-33. doi: 10.1111/ene.13539



16. Mader FM, Schwenke R. Schlaganfall - S3-Leitlinie. Available from: <https://www.awmf.org/leitlinien/detail/II/053-011.html>; Stand: 06.05.2020
17. Berge E, Whiteley W, Audebert H et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *European Stroke Journal* 2021; doi: 10.1177/2396987321989865
18. Fonseca AC, Merwick Á, Dennis M et al. European Stroke Organisation (ESO) guidelines on management of transient ischaemic attack. *European Stroke Journal* 2021; doi: 10.1177/2396987321992905
19. Turc G, Tsvigoulis G, Audebert HJ et al. European Stroke Organisation - European Society for Minimally Invasive Neurological Therapy expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion. *Eur Stroke J* 2022; 7(1):I-XXVI. doi: 10.1177/23969873221076968
20. Kreyman KG, Berger MM, Deutz NE et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006; 25(2):210-23. doi: 10.1016/j.clnu.2006.01.021
21. Wirth R, Smoliner C, Jager M et al. Guideline clinical nutrition in patients with stroke. *Exp Transl Stroke Med* 2013; 5(1):14. doi: 10.1186/2040-7378-5-14
22. NICE. Mechanical clot retrieval for treating acute ischaemic stroke. Available from: [nice.org.uk/guidance/ipg548](https://www.nice.org.uk/guidance/ipg548); Stand: 20.02.2019
23. Turc G, Bhogal P, Fischer U et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic Stroke Endorsed by Stroke Alliance for Europe (SAFE). *Eur Stroke J* 2019; 4(1):6-12. doi: 10.1177/2396987319832140
24. NICE. Acute stroke. Available from: <http://pathways.nice.org.uk/pathways/stroke>; Stand: 17.02.2019
25. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007; 38(3):1091-6. doi: 10.1161/01.STR.0000258355.23810.c6
26. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J* 1957; 2(5):200-15. doi: 10.1177/003693305700200504
27. von Kummer R, Broderick JP, Campbell BC et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. *Stroke* 2015; 46:2981-6. doi: 10.1161/STROKEAHA.115.010049
28. OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Oxford Centre for Evidence-Based Medicine. Available from: <https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf>; Stand: 17.02.2019
29. Burgos R, Breton I, Cereda E et al. ESPEN guideline clinical nutrition in neurology. *Clin Nutr* 2018; 37(1):354-96. doi: 10.1016/j.clnu.2017.09.003
30. Ntaios G, Bornstein NM, Caso V et al. The European Stroke Organisation Guidelines: a standard operating procedure. *Int J Stroke* 2015; 10 Suppl A100:128-35. doi: 10.1111/ijls.12583
31. Berglund A, Svensson L, Wahlgren N et al. Face Arm Speech Time Test use in the prehospital setting, better in the ambulance than in the emergency medical communication center. *Cerebrovasc Dis* 2014; 37(3):212-6. doi: 10.1159/000358116
32. De Luca A, Giorgi Rossi P, Villa GF et al. The use of Cincinnati Prehospital Stroke Scale during telephone dispatch interview increases the accuracy in identifying stroke and transient ischemic attack symptoms. *BMC Health Serv Res* 2013; 13:513. doi: 10.1186/1472-6963-13-513
33. Bray JE, Johnson R, Trobbiani K et al. Australian public's awareness of stroke warning signs improves after national multimedia campaigns. *Stroke* 2013; 44(12):3540-3. doi: 10.1161/STROKEAHA.113.002987
34. Rasura M, Baldereschi M, Di Carlo A et al. Effectiveness of public stroke educational interventions: a review. *Eur J Neurol* 2014; 21(1):11-20. doi: 10.1111/ene.12266

35. Advani R, Naess H, Kurz M Mass Media Intervention in Western Norway Aimed at Improving Public Recognition of Stroke, Emergency Response, and Acute Treatment. *J Stroke Cerebrovasc Dis* 2016; 25(6):1467-72. doi: 10.1016/j.jstrokecerebrovasdis.2016.02.026
36. Watkins CL, Leathley MJ, Jones SP et al. Training emergency services' dispatchers to recognise stroke: an interrupted time-series analysis. *BMC Health Serv Res* 2013; 13:318. doi: 10.1186/1472-6963-13-318
37. Lima FO, Silva GS, Furie KL et al. Field Assessment Stroke Triage for Emergency Destination: A Simple and Accurate Prehospital Scale to Detect Large Vessel Occlusion Strokes. *Stroke* 2016; 47(8):1997-2002. doi: 10.1161/STROKEAHA.116.013301
38. Teleg MS, Ver Hage A, Carter J et al. Stroke vision, aphasia, neglect (VAN) assessment-a novel emergent large vessel occlusion screening tool: pilot study and comparison with current clinical severity indices. *J Neurointerv Surg* 2017; 9(2):122-6. doi: 10.1136/neurintsurg-2015-012131
39. Hastrup S, Damgaard D, Johnsen SP et al. Prehospital Acute Stroke Severity Scale to Predict Large Artery Occlusion: Design and Comparison With Other Scales. *Stroke* 2016; 47(7):1772-6. doi: 10.1161/STROKEAHA.115.012482
40. Katz BS, McMullan JT, Sucharew H et al. Design and validation of a prehospital scale to predict stroke severity: Cincinnati Prehospital Stroke Severity Scale. *Stroke* 2015; 46(6):1508-12. doi: 10.1161/STROKEAHA.115.008804
41. Nazliel B, Starkman S, Liebeskind DS et al. A brief prehospital stroke severity scale identifies ischemic stroke patients harboring persisting large arterial occlusions. *Stroke* 2008; 39(8):2264-7. doi: 10.1161/STROKEAHA.107.508127
42. Smith EE, Kent DM, Bulsara KR et al. Accuracy of Prediction Instruments for Diagnosing Large Vessel Occlusion in Individuals With Suspected Stroke: A Systematic Review for the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke. *Stroke* 2018; 49(3):e111-e22. doi: 10.1161/STR.0000000000000160
43. Whiteley WN, Wardlaw JM, Dennis MS et al. Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: a cross-sectional study. *J Neurol Neurosurg Psychiatry* 2011; 82(9):1006-10. doi: 10.1136/jnnp.2010.235010
44. Jiang HL, Chan CP, Leung YK et al. Evaluation of the Recognition of Stroke in the Emergency Room (ROSIER) scale in Chinese patients in Hong Kong. *PLoS One* 2014; 9(10):e109762. doi: 10.1371/journal.pone.0109762
45. Brandler ES, Sharma M, Sinert RH et al. Prehospital stroke scales in urban environments: a systematic review. *Neurology* 2014; 82(24):2241-9. doi: 10.1212/WNL.0000000000000523
46. Roffe C, Nevatte T, Sim J et al. Effect of Routine Low-Dose Oxygen Supplementation on Death and Disability in Adults With Acute Stroke: The Stroke Oxygen Study Randomized Clinical Trial. *JAMA* 2017; 318(12):1125-35. doi: 10.1001/jama.2017.11463
47. Ali K, Warusevitane A, Lally F et al. The stroke oxygen pilot study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke--effect on key outcomes at six months. *PLoS One* 2014; 8(6):e59274. doi: 10.1371/journal.pone.0059274
48. Ronning OM, Guldvog B Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* 1999; 30(10):2033-7. doi: 10.1161/01.str.30.10.2033
49. Pountain SJ, Roffe C Does routine oxygen supplementation in patients with acute stroke improve outcome? *BMJ* 2012; 345:e6976. doi: 10.1136/bmj.e6976
50. Roffe C, Ali K, Warusevitane A et al. The SOS pilot study: a RCT of routine oxygen supplementation early after acute stroke--effect on recovery of neurological function at one week. *PLoS One* 2011; 6(5):e19113. doi: 10.1371/journal.pone.0019113
51. Rowat AM, Dennis MS, Wardlaw JM Hypoxaemia in acute stroke is frequent and worsens outcome. *Cerebrovasc Dis* 2006; 21(3):166-72. doi: 10.1159/000090528
52. Bosson N, Gausche-Hill M, Koenig W Implementation of a titrated oxygen protocol in the out-of-hospital setting. *Prehosp Disaster Med* 2014; 29(4):403-8. doi: 10.1017/S1049023X14000570
53. Grensemann J, Fuhrmann V, Kluge S Oxygen Treatment in Intensive Care and Emergency Medicine. *Dtsch Arztebl Int* 2018; 115(27-28):455-62. doi: 10.3238/arztebl.2018.0455

54. Gray CS, Hildreth AJ, Sandercock PA et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet neurology* 2007; 6(5):397-406. doi: 10.1016/S1474-4422(07)70080-7
55. Cryer PE, Davis SN, Shamon H Hypoglycemia in diabetes. *Diabetes care* 2003; 26(6):1902-12. doi: 10.2337/diacare.26.6.1902
56. Middleton S, McElduff P, Ward J et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet* 2011; 378(9804):1699-706. doi: 10.1016/S0140-6736(11)61485-2
57. Drury P, Levi C, McInnes E et al. Management of fever, hyperglycemia, and swallowing dysfunction following hospital admission for acute stroke in New South Wales, Australia. *Int J Stroke* 2014; 9(1):23-31. doi: 10.1111/ijvs.12194
58. Bellolio MF, Gilmore RM, Ganti L Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; (1):CD005346. doi: 10.1002/14651858.CD005346.pub4
59. Ntaios G, Papavasileiou V, Bargiota A et al. Intravenous insulin treatment in acute stroke: a systematic review and meta-analysis of randomized controlled trials. *Int J Stroke* 2014; 9(4):489-93. doi: 10.1111/ijvs.12225
60. National Institute for Health and Clinical Excellence. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). In: Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update), Hrsg. National Institute for Health and Clinical Excellence: Guidance. London 2008.
61. Yong M, Kaste M Dynamic of hyperglycemia as a predictor of stroke outcome in the ECASS-II trial. *Stroke* 2008; 39(10):2749-55. doi: 10.1161/STROKEAHA.108.514307
62. Rosso C, Corvol JC, Pires C et al. Intensive versus subcutaneous insulin in patients with hyperacute stroke: results from the randomized INSULINFARCT trial. *Stroke* 2012; 43(9):2343-9. doi: 10.1161/STROKEAHA.112.657122
63. Jauch EC, Saver JL, Adams HP, Jr. et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44(3):870-947. doi: 10.1161/STR.0b013e318284056a
64. Fang Y, Zhang S, Wu B et al. Hyperglycaemia in acute lacunar stroke: a Chinese hospital-based study. *Diab Vasc Dis Res* 2013; 10(3):216-21. doi: 10.1177/1479164112459663
65. Uyttenboogaart M, Koch MW, Stewart RE et al. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. *Brain* 2007; 130(Pt 6):1626-30. doi: 10.1093/brain/awm087
66. Nurmi J, Lindsberg PJ, Happola O et al. Strict glucose control after acute stroke can be provided in the prehospital setting. *Acad Emerg Med* 2011; 18(4):436-9. doi: 10.1111/j.1553-2712.2011.01020.x
67. Harbison J, Hossain O, Jenkinson D et al. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. *Stroke* 2003; 34(1):71-6. doi: 10.1161/01.str.0000044170.46643.5e
68. Drury P, Levi C, D'Este C et al. Quality in Acute Stroke Care (QASC): process evaluation of an intervention to improve the management of fever, hyperglycemia, and swallowing dysfunction following acute stroke. *Int J Stroke* 2014; 9(6):766-76. doi: 10.1111/ijvs.12202
69. Saxena M, Young P, Pilcher D et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. *Intensive care medicine* 2015; 41(5):823-32. doi: 10.1007/s00134-015-3676-6
70. Den Hertog HM, van der Worp HB, Tseng MC et al. Cooling therapy for acute stroke. *Cochrane Database Syst Rev* 2009; (1):CD001247. doi: 10.1002/14651858.CD001247.pub2
71. den Hertog HM, van der Worp HB, van Gemert HM et al. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet neurology* 2009; 8(5):434-40. doi:
72. Prasad K, Krishnan PR Fever is associated with doubling of odds of short-term mortality in ischemic stroke: an updated meta-analysis. *Acta neurologica Scandinavica* 2010; 122(6):404-8. doi: 10.1111/j.1600-0404.2010.01326.x

73. Frank B, Fulton RL, Weimar C et al. Use of paracetamol in ischaemic stroke patients: evidence from VISTA. *Acta neurologica Scandinavica* 2013; 128(3):172-7. doi: 10.1111/ane.12094
74. de Ridder IR, den Hertog HM, van Gemert HM et al. PAIS 2 (Paracetamol [Acetaminophen] in Stroke 2): Results of a Randomized, Double-Blind Placebo-Controlled Clinical Trial. *Stroke* 2017; 48(4):977-82. doi: 10.1161/STROKEAHA.116.015957
75. Ovesen C, Brizzi M, Pott FC et al. Feasibility of endovascular and surface cooling strategies in acute stroke. *Acta neurologica Scandinavica* 2013; 127(6):399-405. doi: 10.1111/ane.12059
76. Harris B, Andrews PJ, Murray GD et al. Systematic review of head cooling in adults after traumatic brain injury and stroke. *Health technology assessment (Winchester, England)* 2012; 16(45):1-175. doi: 10.3310/hta16450
77. Saini M, Saqqur M, Kamruzzaman A et al. Effect of hyperthermia on prognosis after acute ischemic stroke. *Stroke* 2009; 40(9):3051-9. doi: 10.1161/STROKEAHA.109.556134
78. Boysen G, Christensen H Stroke severity determines body temperature in acute stroke. *Stroke* 2001; 32(2):413-7. doi: 10.1161/01.str.32.2.413
79. Stead LG, Gilmore RM, Vedula KC et al. Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology* 2006; 66(12):1878-81. doi: 10.1212/01.wnl.0000219628.78513.b5
80. Schrader J, Luders S, Kulschewski A et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke* 2003; 34(7):1699-703. doi: 10.1161/01.STR.0000075777.18006.89
81. Robinson TG, Potter JF, Ford GA et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet neurology* 2010; 9(8):767-75. doi: 10.1016/S1474-4422(10)70163-0
82. Potter JF, Robinson TG, Ford GA et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet neurology* 2009; 8(1):48-56. doi: 10.1016/S1474-4422(08)70263-1
83. Investigators ET Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet* 2015; 385(9968):617-28. doi: 10.1016/S0140-6736(14)61121-1
84. Horn J, de Haan RJ, Vermeulen M et al. Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke* 2001; 32(2):461-5. doi: 10.1161/01.str.32.2.461
85. He J, Zhang Y, Xu T et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA* 2014; 311(5):479-89. doi: 10.1001/jama.2013.282543
86. Lee M, Ovbiagele B, Hong KS et al. Effect of Blood Pressure Lowering in Early Ischemic Stroke: Meta-Analysis. *Stroke* 2015; 46(7):1883-9. doi: 10.1161/STROKEAHA.115.009552
87. Bath PM, Krishnan K Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2014; (10):CD000039. doi: 10.1002/14651858.CD000039.pub3
88. Geeganage C, Bath PM Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2008; (4):CD000039. doi: 10.1002/14651858.CD000039.pub2
89. Geeganage C, Bath PM Vasoactive drugs for acute stroke. *Cochrane Database Syst Rev* 2010; (7):CD002839. doi: 10.1002/14651858.CD002839.pub2
90. Geeganage CM, Bath PM Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension* 2009; 54(4):775-81. doi: 10.1161/HYPERTENSIONAHA.109.133538
91. Castillo J, Leira R, Garcia MM et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke* 2004; 35(2):520-6. doi: 10.1161/01.STR.0000109769.22917.B0
92. Shaw L, Price C, McLure S et al. Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST): results from the pilot randomised controlled trial. *Emerg Med J* 2014; 31(12):994-9. doi: 10.1136/emermed-2013-202536

93. Ankolekar S, Fuller M, Cross I et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). *Stroke* 2013; 44(11):3120-8. doi: 10.1161/STROKEAHA.113.001301
94. Bath PM, Scutt P, Appleton JP et al. Baseline characteristics of the 1149 patients recruited into the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) randomized controlled trial. *Int J Stroke* 2019; 14(3):298-305. doi: 10.1177/1747493018816451
95. Investigators R- Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet* 2019; 393(10175):1009-20. doi: 10.1016/S0140-6736(19)30194-1
96. Muscari A, Bianchi G, Forti P et al. A comparison of risk factors as predictors of cardiovascular and non-cardiovascular mortality in the elderly people--relevance of N-terminal pro-B-type natriuretic peptide and low systolic blood pressure. *Int J Clin Pract* 2013; 67(11):1182-91. doi: 10.1111/ijcp.12195
97. Manning LS, Mistri AK, Potter J et al. Short-term blood pressure variability in acute stroke: post hoc analysis of the controlling hypertension and hypotension immediately post stroke and continue or stop post-stroke antihypertensives collaborative study trials. *Stroke* 2015; 46(6):1518-24. doi: 10.1161/STROKEAHA.115.009078
98. Leonardi-Bee J, Bath PM, Phillips SJ et al. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002; 33(5):1315-20. doi: 10.1161/01.str.0000014509.11540.66
99. Stead LG, Gilmore RM, Decker WW et al. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. *Neurology* 2005; 65(8):1179-83. doi: 10.1212/01.wnl.0000180939.24845.22
100. Wohlfahrt P, Krajcoviechova A, Jozifova M et al. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. *J Hypertens* 2015; 33(2):339-45. doi: 10.1097/HJH.0000000000000414
101. Okumura K, Ohya Y, Maehara A et al. Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens* 2005; 23(6):1217-23. doi: 10.1097/01.hjh.0000170385.76826.4a
102. Vemmos KN, Tsivgoulis G, Spengos K et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004; 255(2):257-65. doi: 10.1046/j.1365-2796.2003.01291.x
103. Visvanathan A, Dennis M, Whiteley W Parenteral fluid regimens for improving functional outcome in people with acute stroke. *Cochrane Database Syst Rev* 2015; (9):CD011138. doi: 10.1002/14651858.CD011138.pub2
104. Collaboration CT, Dennis M, Sandercock PA et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet* 2009; 373(9679):1958-65. doi: 10.1016/S0140-6736(09)60941-7
105. Muir KW, Watt A, Baxter G et al. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *QJM : monthly journal of the Association of Physicians* 2000; 93(6):359-64. doi: 10.1093/qjmed/93.6.359
106. Collaboration CT Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med* 2010; 153(9):553-62. doi: 10.7326/0003-4819-153-9-201011020-00280
107. Collaboration CT, Dennis M, Sandercock P et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet* 2013; 382(9891):516-24. doi: 10.1016/S0140-6736(13)61050-8
108. Prasad BK, Banerjee AK, Howard H Incidence of deep vein thrombosis and the effect of pneumatic compression of the calf in elderly hemiplegics. *Age Ageing* 1982; 11(1):42-4. doi: 10.1093/ageing/11.1.42
109. International Stroke Trial (IST) Collaborative Group The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *International Stroke Trial Collaborative Group. Lancet* 1997; 349(9065):1569-81. doi:

110. Sherman DG, Albers GW, Bladin C et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet* 2007; 369(9570):1347-55. doi: 10.1016/S0140-6736(07)60633-3
111. Sandercock PA, Counsell C, Kane EJ Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev* 2015; (3):CD000024. doi: 10.1002/14651858.CD000024.pub4
112. Whiteley WN, Adams HP, Jr., Bath PM et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet neurology* 2013; 12(6):539-45. doi: 10.1016/S1474-4422(13)70079-6
113. Dennis M, Sandercock P, Graham C et al. The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial: a randomised controlled trial to determine whether or not intermittent pneumatic compression reduces the risk of post-stroke deep vein thrombosis and to estimate its cost-effectiveness. *Health technology assessment (Winchester, England)* 2015; 19(76):1-90. doi: 10.3310/hta19760
114. Naccarato M, Chiodo Grandi F, Dennis M et al. Physical methods for preventing deep vein thrombosis in stroke. *Cochrane Database Syst Rev* 2010; (8):CD001922. doi: 10.1002/14651858.CD001922.pub3
115. Sandercock PA, Counsell C, Kamal AK Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev* 2008; (4):CD000024. doi: 10.1002/14651858.CD000024.pub3
116. Pineo G, Lin J, Stern L et al. Economic impact of enoxaparin versus unfractionated heparin for venous thromboembolism prophylaxis in patients with acute ischemic stroke: a hospital perspective of the PREVAIL trial. *J Hosp Med* 2012; 7(3):176-82. doi: 10.1002/jhm.968
117. Sandercock PA, Leong TS Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. *Cochrane Database Syst Rev* 2017; 4:CD000119. doi: 10.1002/14651858.CD000119.pub4
118. Suntrup S, Warnecke T, Kemmling A et al. Dysphagia in patients with acute striatocapsular hemorrhage. *Journal of neurology* 2012; 259(1):93-9. doi: 10.1007/s00415-011-6129-3
119. Martino R, Foley N, Bhogal S et al. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke* 2005; 36(12):2756-63. doi: 10.1161/01.STR.0000190056.76543.eb
120. Hoffmann S, Malzahn U, Harms H et al. Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke. *Stroke* 2012; 43(10):2617-23. doi: 10.1161/STROKEAHA.112.653055
121. Bray BD, Smith CJ, Cloud GC et al. The association between delays in screening for and assessing dysphagia after acute stroke, and the risk of stroke-associated pneumonia. *J Neurol Neurosurg Psychiatry* 2017; 88(1):25-30. doi: 10.1136/jnnp-2016-313356
122. Brodsky MB, Suiter DM, Gonzalez-Fernandez M et al. Screening Accuracy for Aspiration Using Bedside Water Swallow Tests: A Systematic Review and Meta-Analysis. *Chest* 2016; 150(1):148-63. doi: 10.1016/j.chest.2016.03.059
123. Maeshima S, Osawa A, Hayashi T et al. Elderly age, bilateral lesions, and severe neurological deficit are correlated with stroke-associated pneumonia. *J Stroke Cerebrovasc Dis* 2014; 23(3):484-9. doi: 10.1016/j.jstrokecerebrovasdis.2013.04.004
124. DePippo KL, Holas MA, Reding MJ Validation of the 3-oz water swallow test for aspiration following stroke. *Arch Neurol* 1992; 49(12):1259-61. doi: 10.1001/archneur.1992.00530360057018
125. Poorjavad M, Jalaie S Systemic review on highly qualified screening tests for swallowing disorders following stroke: Validity and reliability issues. *J Res Med Sci* 2014; 19(8):776-85. doi: 10.1016/j.jstrokecerebrovasdis.2013.04.004
126. Trapl M, Enderle P, Nowotny M et al. Dysphagia bedside screening for acute-stroke patients: the Gugging Swallowing Screen. *Stroke* 2007; 38(11):2948-52. doi: 10.1161/STROKEAHA.107.483933
127. O'Horo JC, Rogus-Pulia N, Garcia-Arguello L et al. Bedside diagnosis of dysphagia: a systematic review. *J Hosp Med* 2015; 10(4):256-65. doi: 10.1002/jhm.2313
128. Ramsey DJ, Smithard DG, Kalra L Early assessments of dysphagia and aspiration risk in acute stroke patients. *Stroke* 2003; 34(5):1252-7. doi: 10.1161/01.STR.0000066309.06490.B8
129. Dziewas R, Ritter M, Schilling M et al. Pneumonia in acute stroke patients fed by nasogastric tube. *J Neurol Neurosurg Psychiatry* 2004; 75(6):852-6. doi: 10.1136/jnnp.2003.019075

130. Dziewas R, Stogbauer F, Ludemann P Risk factors for pneumonia in patients with acute stroke. *Stroke* 2003; 34(8):e105. doi: 10.1161/01.STR.0000083465.17164.AB
131. Falsetti P, Acciai C, Palilla R et al. Oropharyngeal dysphagia after stroke: incidence, diagnosis, and clinical predictors in patients admitted to a neurorehabilitation unit. *J Stroke Cerebrovasc Dis* 2009; 18(5):329-35. doi: 10.1016/j.jstrokecerebrovasdis.2009.01.009
132. Sellars C, Bowie L, Bagg J et al. Risk factors for chest infection in acute stroke: a prospective cohort study. *Stroke* 2007; 38(8):2284-91. doi: 10.1161/STROKEAHA.106.478156
133. Carnaby-Mann G, Lenius K The bedside examination in dysphagia. *Phys Med Rehabil Clin N Am* 2008; 19(4):747-68, viii. doi: 10.1016/j.pmr.2008.05.008
134. Bax L, McFarlane M, Green E et al. Speech-language pathologist-led fiberoptic endoscopic evaluation of swallowing: functional outcomes for patients after stroke. *J Stroke Cerebrovasc Dis* 2014; 23(3):e195-200. doi: 10.1016/j.jstrokecerebrovasdis.2013.09.031
135. Bours GJ, Speyer R, Lemmens J et al. Bedside screening tests vs. videofluoroscopy or fibreoptic endoscopic evaluation of swallowing to detect dysphagia in patients with neurological disorders: systematic review. *Journal of advanced nursing* 2009; 65(3):477-93. doi: 10.1111/j.1365-2648.2008.04915.x
136. Logemann JA, Veis S, Colangelo L A screening procedure for oropharyngeal dysphagia. *Dysphagia* 1999; 14(1):44-51. doi: 10.1007/PL00009583
137. Ekberg O, Olsson R Dynamic radiology of swallowing disorders. *Endoscopy* 1997; 29(6):439-46. doi: 10.1055/s-2007-1004248
138. Rosenbek JC, Robbins JA, Roecker EB et al. A penetration-aspiration scale. *Dysphagia* 1996; 11(2):93-8. doi: 10.1007/BF00417897
139. Dziewas R, Warnecke T, Olenberg S et al. Towards a basic endoscopic assessment of swallowing in acute stroke - development and evaluation of a simple dysphagia score. *Cerebrovasc Dis* 2008; 26(1):41-7. doi: 10.1159/000135652
140. Warnecke T, Ritter MA, Kroger B et al. Fiberoptic endoscopic Dysphagia severity scale predicts outcome after acute stroke. *Cerebrovasc Dis* 2009; 28(3):283-9. doi: 10.1159/000228711
141. Warnecke T, Teismann I, Oelenberg S et al. The safety of fiberoptic endoscopic evaluation of swallowing in acute stroke patients. *Stroke* 2009; 40(2):482-6. doi: 10.1161/STROKEAHA.108.520775
142. Langmore SE Evaluation of oropharyngeal dysphagia: which diagnostic tool is superior? *Curr Opin Otolaryngol Head Neck Surg* 2003; 11(6):485-9. doi: 10.1097/00020840-200312000-00014
143. Leder SB, Sasaki CT, Burrell MI Fiberoptic endoscopic evaluation of dysphagia to identify silent aspiration. *Dysphagia* 1998; 13(1):19-21. doi: 10.1007/PL00009544
144. Kelly AM, Drinnan MJ, Leslie P Assessing penetration and aspiration: how do videofluoroscopy and fiberoptic endoscopic evaluation of swallowing compare? *The Laryngoscope* 2007; 117(10):1723-7. doi: 10.1097/MLG.0b013e318123ee6a
145. Kelly AM, Leslie P, Beale T et al. Fibreoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? *Clin Otolaryngol* 2006; 31(5):425-32. doi: 10.1111/j.1749-4486.2006.01292.x
146. Smith EE, Kent DM, Bulsara KR et al. Effect of Dysphagia Screening Strategies on Clinical Outcomes After Stroke: A Systematic Review for the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke. *Stroke* 2018; 49(3):e123-e8. doi: 10.1161/STR.000000000000159
147. Miles A, Zeng IS, McLauchlan H et al. Cough reflex testing in Dysphagia following stroke: a randomized controlled trial. *J Clin Med Res* 2013; 5(3):222-33. doi: 10.4021/jocmr1340w
148. Rai N, Prasad K, Bhatia R et al. Development and implementation of acute stroke care pathway in a tertiary care hospital in India: A cluster-randomized study. *Neurol India* 2016; 64 Suppl:S39-45. doi: 10.4103/0028-3886.178038
149. Joundi RA, Martino R, Saposnik G et al. Predictors and Outcomes of Dysphagia Screening After Acute Ischemic Stroke. *Stroke* 2017; 48(4):900-6. doi: 10.1161/STROKEAHA.116.015332
150. Hinchey JA, Shephard T, Furie K et al. Formal dysphagia screening protocols prevent pneumonia. *Stroke* 2005; 36(9):1972-6. doi: 10.1161/01.STR.0000177529.86868.8d

151. Lakshminarayan K, Tsai AW, Tong X et al. Utility of dysphagia screening results in predicting poststroke pneumonia. *Stroke* 2010; 41(12):2849-54. doi: 10.1161/STROKEAHA.110.597039
152. Masrur S, Smith EE, Saver JL et al. Dysphagia screening and hospital-acquired pneumonia in patients with acute ischemic stroke: findings from Get with the Guidelines--Stroke. *J Stroke Cerebrovasc Dis* 2013; 22(8):e301-9. doi: 10.1016/j.jstrokecerebrovasdis.2012.11.013
153. Geeganage C, Beavan J, Ellender S et al. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev* 2012; 10:CD000323. doi: 10.1002/14651858.CD000323.pub2
154. Schepp SK, Tirschwell DL, Miller RM et al. Swallowing screens after acute stroke: a systematic review. *Stroke* 2012; 43(3):869-71. doi: 10.1161/STROKEAHA.111.638254
155. Daniels SK, Anderson JA, Willson PC Valid items for screening dysphagia risk in patients with stroke: a systematic review. *Stroke* 2012; 43(3):892-7. doi: 10.1161/STROKEAHA.111.640946
156. Leder SB, Suiter DM, Warner HL et al. Success of recommending oral diets in acute stroke patients based on passing a 90-cc water swallow challenge protocol. *Top Stroke Rehabil* 2012; 19(1):40-4. doi: 10.1310/tsr1901-40
157. Martino R, Maki E, Diamant N Identification of dysphagia using the Toronto Bedside Swallowing Screening Test (TOR-BSST(c)): are 10 teaspoons of water necessary? *Int J Speech Lang Pathol* 2014; 16(3):193-8. doi: 10.3109/17549507.2014.902995
158. Crary MA, Carnaby GD, Sia I et al. Spontaneous swallowing frequency has potential to identify dysphagia in acute stroke. *Stroke* 2013; 44(12):3452-7. doi: 10.1161/STROKEAHA.113.003048
159. Kertscher B, Speyer R, Palmieri M et al. Bedside screening to detect oropharyngeal dysphagia in patients with neurological disorders: an updated systematic review. *Dysphagia* 2014; 29(2):204-12. doi: 10.1007/s00455-013-9490-9
160. Kjaersgaard A, Nielsen LH, Sjolund BH Randomized trial of two swallowing assessment approaches in patients with acquired brain injury: Facial-Oral Tract Therapy versus Fiberoptic Endoscopic Evaluation of Swallowing. *Clinical rehabilitation* 2014; 28(3):243-53. doi: 10.1177/0269215513500057
161. Kjaersgaard A, Nielsen LH, Sjolund BH Factors affecting return to oral intake in inpatient rehabilitation after acquired brain injury. *Brain Inj* 2015; 29(9):1094-104. doi: 10.3109/02699052.2015.1022883
162. Mortensen J, Jensen D, Kjaersgaard A A validation study of the Facial-Oral Tract Therapy Swallowing Assessment of Saliva. *Clinical rehabilitation* 2016; 30(4):410-5. doi: 10.1177/0269215515584381
163. Bakhtiyari J, Sarraf P, Nakhostin-Ansari N et al. Effects of early intervention of swallowing therapy on recovery from dysphagia following stroke. *Iran J Neurol* 2015; 14(3):119-24. doi:
164. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: identification and management of dysphagia. Stand: 03.11.2014
165. Dennis M, Lewis S, Cranswick G et al. FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health technology assessment (Winchester, England)* 2006; 10(2):iii-iv, ix-x, 1-120. doi: 10.3310/hta10020
166. Braunschweig CL, Levy P, Sheean PM et al. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr* 2001; 74(4):534-42. doi: 10.1093/ajcn/74.4.534
167. Mamun K, Lim J Role of nasogastric tube in preventing aspiration pneumonia in patients with dysphagia. *Singapore Med J* 2005; 46(11):627-31. doi:
168. Finucane TE, Bynum JP Use of tube feeding to prevent aspiration pneumonia. *Lancet* 1996; 348(9039):1421-4. doi: 10.1016/S0140-6736(96)03369-7
169. Dennis MS, Lewis SC, Warlow C et al. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet* 2005; 365(9461):764-72. doi: 10.1016/S0140-6736(05)17983-5
170. Finestone HM, Greene-Finestone LS, Wilson ES et al. Prolonged length of stay and reduced functional improvement rate in malnourished stroke rehabilitation patients. *Arch Phys Med Rehabil* 1996; 77(4):340-5. doi: 10.1016/s0003-9993(96)90081-7



171. Gariballa SE, Parker SG, Taub N et al. Influence of nutritional status on clinical outcome after acute stroke. *Am J Clin Nutr* 1998; 68(2):275-81. doi: 10.1093/ajcn/68.2.275
172. Gordon C, Hewer RL, Wade DT Dysphagia in acute stroke. *Br Med J (Clin Res Ed)* 1987; 295(6595):411-4. doi: 10.1136/bmj.295.6595.411
173. Smithard DG, O'Neill PA, England RE et al. The natural history of dysphagia following a stroke. *Dysphagia* 1997; 12(4):188-93. doi: 10.1007/PL00009535
174. Norton B, Homer-Ward M, Donnelly MT et al. A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. *BMJ* 1996; 312(7022):13-6. doi: 10.1136/bmj.312.7022.13
175. Beavan J, Conroy SP, Harwood R et al. Does looped nasogastric tube feeding improve nutritional delivery for patients with dysphagia after acute stroke? A randomised controlled trial. *Age Ageing* 2010; 39(5):624-30. doi: 10.1093/ageing/afq088
176. Anderson MR, O'Connor M, Mayer P et al. The nasal loop provides an alternative to percutaneous endoscopic gastrostomy in high-risk dysphagic stroke patients. *Clin Nutr* 2004; 23(4):501-6. doi: 10.1016/j.clnu.2003.09.008
177. Kostadima E, Kaditis AG, Alexopoulos EI et al. Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients. *Eur Respir J* 2005; 26(1):106-11. doi: 10.1183/09031936.05.00096104
178. Zheng T, Zhu X, Liang H et al. Impact of early enteral nutrition on short term prognosis after acute stroke. *J Clin Neurosci* 2015; 22(9):1473-6. doi: 10.1016/j.jocn.2015.03.028
179. Gomes CA, Jr., Andriolo RB, Bennett C et al. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. *Cochrane Database Syst Rev* 2015; (5):CD008096. doi: 10.1002/14651858.CD008096.pub4
180. Lee JS, Kwok T, Chui PY et al. Can continuous pump feeding reduce the incidence of pneumonia in nasogastric tube-fed patients? A randomized controlled trial. *Clin Nutr* 2010; 29(4):453-8. doi: 10.1016/j.clnu.2009.10.003
181. Food Trial Collaboration Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. *Stroke* 2003; 34(6):1450-6. doi: 10.1161/01.STR.0000074037.49197.8C
182. Gomes F, Emery PW, Weekes CE Risk of Malnutrition Is an Independent Predictor of Mortality, Length of Hospital Stay, and Hospitalization Costs in Stroke Patients. *J Stroke Cerebrovasc Dis* 2016; 25(4):799-806. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.017
183. Broadley S, Croser D, Cottrell J et al. Predictors of prolonged dysphagia following acute stroke. *J Clin Neurosci* 2003; 10(3):300-5. doi: 10.1016/s0967-5868(03)00022-5
184. Gomes F, Hookway C, Weekes CE et al. Royal College of Physicians Intercollegiate Stroke Working Party evidence-based guidelines for the nutritional support of patients who have had a stroke. *J Hum Nutr Diet* 2014; 27(2):107-21. doi: 10.1111/jhn.12185
185. Yoo SH, Kim JS, Kwon SU et al. Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. *Arch Neurol* 2008; 65(1):39-43. doi: 10.1001/archneurol.2007.12
186. Dennis MS, Lewis SC, Warlow C et al. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *Lancet* 2005; 365(9461):755-63. doi: 10.1016/S0140-6736(05)17982-3
187. Westendorp WF, Vermeij JD, Zock E et al. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. *Lancet* 2015; 385(9977):1519-26. doi: 10.1016/S0140-6736(14)62456-9
188. Kalra L, Irshad S, Hodsoll J et al. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet* 2015; 386(10006):1835-44. doi: 10.1016/S0140-6736(15)00126-9
189. Liu L, Xiong XY, Zhang Q et al. The Efficacy of Prophylactic Antibiotics on Post-Stroke Infections: An Updated Systematic Review and Meta-Analysis. *Scientific reports* 2016; 6:36656. doi: 10.1038/srep36656

190. Vermeij JD, Westendorp WF, Dippel DW et al. Antibiotic therapy for preventing infections in people with acute stroke. *Cochrane Database Syst Rev* 2018; 1:CD008530. doi: 10.1002/14651858.CD008530.pub3
191. Zheng F, Spreckelsen NV, Zhang X et al. Should preventive antibiotics be used in patients with acute stroke? A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2017; 12(10):e0186607. doi: 10.1371/journal.pone.0186607
192. Kilincer C, Asil T, Utku U et al. Factors affecting the outcome of decompressive craniectomy for large hemispheric infarctions: a prospective cohort study. *Acta Neurochir (Wien)* 2005; 147(6):587-94; discussion 94. doi: 10.1007/s00701-005-0493-7
193. Burn J, Dennis M, Bamford J et al. Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. *BMJ* 1997; 315(7122):1582-7. doi: 10.1136/bmj.315.7122.1582
194. Alberti A, Paciaroni M, Caso V et al. Early seizures in patients with acute stroke: frequency, predictive factors, and effect on clinical outcome. *Vasc Health Risk Manag* 2008; 4(3):715-20. doi: 10.1186/1745-2912-4-3-715
195. Camilo O, Goldstein LB Seizures and epilepsy after ischemic stroke. *Stroke* 2004; 35(7):1769-75. doi: 10.1161/01.STR.0000130989.17100.96
196. Awada A, Omojola MF, Obeid T Late epileptic seizures after cerebral infarction. *Acta neurologica Scandinavica* 1999; 99(5):265-8. doi: 10.1111/j.1600-0404.1999.tb00674.x
197. Gilad R, Boaz M, Dabby R et al. Are post intracerebral hemorrhage seizures prevented by anti-epileptic treatment? *Epilepsy Res* 2011; 95(3):227-31. doi: 10.1016/j.eplepsyres.2011.04.002
198. Labovitz DL, Hauser WA, Sacco RL Prevalence and predictors of early seizure and status epilepticus after first stroke. *Neurology* 2001; 57(2):200-6. doi: 10.1212/wnl.57.2.200
199. Gilad R Management of seizures following a stroke: what are the options? *Drugs Aging* 2012; 29(7):533-8. doi: 10.2165/11631540-000000000-00000
200. Sykes L, Wood E, Kwan J Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. *Cochrane Database Syst Rev* 2014; (1):CD005398. doi: 10.1002/14651858.CD005398.pub3
201. van Tuijl JH, van Raak EP, de Krom MC et al. Early treatment after stroke for the prevention of late epileptic seizures: a report on the problems performing a randomised placebo-controlled double-blind trial aimed at anti-epileptogenesis. *Seizure* 2011; 20(4):285-91. doi: 10.1016/j.seizure.2010.12.012
202. Hesdorffer DC, Benn EK, Cascino GD et al. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* 2009; 50(5):1102-8. doi: 10.1111/j.1528-1167.2008.01945.x
203. Consoli D, Bosco D, Postorino P et al. Levetiracetam versus carbamazepine in patients with late poststroke seizures: a multicenter prospective randomized open-label study (EpiC Project). *Cerebrovasc Dis* 2012; 34(4):282-9. doi: 10.1159/000342669
204. Gilad R, Sadeh M, Rapoport A et al. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. *Clin Neuropharmacol* 2007; 30(4):189-95. doi: 10.1097/WNF.0b013e3180333069
205. Stroke Unit Trialists' Collaboration Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Systematic Reviews* 2013; (9):CD000197. doi: 10.1002/14651858.CD000197.pub3
206. Sun Y, Paulus D, Eyssen M et al. A systematic review and meta-analysis of acute stroke unit care: what's beyond the statistical significance? *BMC Med Res Methodol* 2013; 13:132-42. doi: 10.1186/1471-2288-13-132
207. Chan DK, Cordato D, O'Rourke F et al. Comprehensive stroke units: a review of comparative evidence and experience. *Int J Stroke* 2013; 8(4):260-4. doi: 10.1111/j.1747-4949.2012.00850.x
208. Saposnik G, Hassan KA, Selchen D et al. Stroke unit care: does ischemic stroke subtype matter? *Int J Stroke* 2011; 6(3):244-50. doi: 10.1111/j.1747-4949.2011.00604.x
209. Seenan P, Long M, Langhorne P Stroke units in their natural habitat: systematic review of observational studies. *Stroke* 2007; 38(6):1886-92. doi: 10.1161/STROKEAHA.106.480871
210. Lavalley PC, Meseguer E, Abboud H et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet neurology* 2007; 6(11):953-60. doi: 10.1016/S1474-4422(07)70248-X

211. Rothwell PM, Giles MF, Chandratheva A et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007; 370(9596):1432-42. doi: 10.1016/S0140-6736(07)61448-2
212. Wardlaw JM, Brazzelli M, Chappell FM et al. ABCD2 score and secondary stroke prevention: meta-analysis and effect per 1,000 patients triaged. *Neurology* 2015; 85(4):373-80. doi: 10.1212/WNL.0000000000001780
213. Sanders LM, Srikanth VK, Blacker DJ et al. Performance of the ABCD2 score for stroke risk post TIA: meta-analysis and probability modeling. *Neurology* 2012; 79(10):971-80. doi: 10.1212/WNL.0b013e31825f9d02
214. Galvin R, Geraghty C, Motterlini N et al. Prognostic value of the ABCD(2) clinical prediction rule: a systematic review and meta-analysis. *Fam Pract* 2011; 28(4):366-76. doi: 10.1093/fampra/cmr008
215. Merwick A, Albers GW, Amarenco P et al. Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet neurology* 2010; 9(11):1060-9. doi: 10.1016/S1474-4422(10)70240-4
216. Rothwell PM, Algra A, Chen Z et al. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* 2016; 388(10042):365-75. doi: 10.1016/S0140-6736(16)30468-8
217. Saver JL, Fonarow GC, Smith EE et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA* 2013; 309(23):2480-8. doi: 10.1001/jama.2013.6959
218. Saver JL, Goyal M, van der Lugt A et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. *JAMA* 2016; 316(12):1279-88. doi: 10.1001/jama.2016.13647
219. Rinaldo L, Brinjikji W, Rabinstein AA Transfer to High-Volume Centers Associated With Reduced Mortality After Endovascular Treatment of Acute Stroke. *Stroke* 2017; 48(5):1316-21. doi: 10.1161/STROKEAHA.116.016360
220. Hwang DY, Silva GS, Furie KL et al. Comparative sensitivity of computed tomography vs. magnetic resonance imaging for detecting acute posterior fossa infarct. *J Emerg Med* 2012; 42(5):559-65. doi: 10.1016/j.jemermed.2011.05.101
221. Chalela JA, Kidwell CS, Nentwich LM et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet* 2007; 369(9558):293-8. doi: 10.1016/S0140-6736(07)60151-2
222. Wardlaw J, Brazzelli M, Miranda H et al. An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. *Health technology assessment (Winchester, England)* 2014; 18(27):1-368, v-vi. doi: 10.3310/hta18270
223. Brazzelli M, Sandercock PA, Chappell FM et al. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. *Cochrane Database Syst Rev* 2009; (4):CD007424. doi: 10.1002/14651858.CD007424.pub2
224. Wardlaw JM, Seymour J, Cairns J et al. Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke* 2004; 35(11):2477-83. doi: 10.1161/01.STR.0000143453.78005.44
225. Heidenreich JO, Hsu D, Wang G et al. Magnetic resonance imaging results can affect therapy decisions in hyperacute stroke care. *Acta Radiol* 2008; 49(5):550-7. doi: 10.1080/02841850801958320
226. Barber PA, Hill MD, Eliasziw M et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry* 2005; 76(11):1528-33. doi: 10.1136/jnnp.2004.059261
227. Tsvigoulis G, Zand R, Katsanos AH et al. Risk of Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis in Patients With Acute Ischemic Stroke and High Cerebral Microbleed Burden: A Meta-analysis. *JAMA Neurol* 2016; 73(6):675-83. doi: 10.1001/jamaneurol.2016.0292
228. Charidimou A, Shoamanesh A, International M-MI Clinical relevance of microbleeds in acute stroke thrombolysis: Comprehensive meta-analysis. *Neurology* 2016; 87(15):1534-41. doi: 10.1212/WNL.0000000000003207

229. Sudacevski V, Bertrand C, Chadenat ML et al. Predictors of Occult Atrial Fibrillation in One Hundred Seventy-One Patients with Cryptogenic Transient Ischemic Attack and Minor Stroke. *J Stroke Cerebrovasc Dis* 2016; 25(11):2673-7. doi: 10.1016/j.jstrokecerebrovasdis.2016.07.014
230. Favilla CG, Ingala E, Jara J et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. *Stroke* 2015; 46(5):1210-5. doi: 10.1161/STROKEAHA.114.007763
231. Bernstein RA, Di Lazzaro V, Rymer MM et al. Infarct Topography and Detection of Atrial Fibrillation in Cryptogenic Stroke: Results from CRYSTAL AF. *Cerebrovasc Dis* 2015; 40(1-2):91-6. doi: 10.1159/000437018
232. Rabinstein AA, Fugate JE, Mandrekar J et al. Paroxysmal atrial fibrillation in cryptogenic stroke: a case-control study. *J Stroke Cerebrovasc Dis* 2013; 22(8):1405-11. doi: 10.1016/j.jstrokecerebrovasdis.2013.05.013
233. Depuydt S, Sarov M, Vandendries C et al. Significance of acute multiple infarcts in multiple cerebral circulations on initial diffusion weighted imaging in stroke patients. *J Neurol Sci* 2014; 337(1-2):151-5. doi: 10.1016/j.jns.2013.11.039
234. Braemswig TB, Usnich T, Albach FN et al. Early new diffusion-weighted imaging lesions appear more often in stroke patients with a multiple territory lesion pattern. *Stroke* 2013; 44(8):2200-4. doi: 10.1161/STROKEAHA.111.000810
235. Cho AH, Kim JS, Jeon SB et al. Mechanism of multiple infarcts in multiple cerebral circulations on diffusion-weighted imaging. *Journal of neurology* 2007; 254(7):924-30. doi: 10.1007/s00415-006-0397-3
236. Roh JK, Kang DW, Lee SH et al. Significance of acute multiple brain infarction on diffusion-weighted imaging. *Stroke* 2000; 31(3):688-94. doi: 10.1161/01.str.31.3.688
237. Novotny V, Thomassen L, Waje-Andreassen U et al. Acute cerebral infarcts in multiple arterial territories associated with cardioembolism. *Acta neurologica Scandinavica* 2017; 135(3):346-51. doi: 10.1111/ane.12606
238. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333(24):1581-7. doi:
239. Hacke W, Kaste M, Bluhmki E et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359(13):1317-29. doi: 10.1056/NEJMoa0804656
240. Zand R, Tsvigoulis G, Singh M et al. Cerebral Microbleeds and Risk of Intracerebral Hemorrhage Post Intravenous Thrombolysis. *J Stroke Cerebrovasc Dis* 2017; 26(3):538-44. doi: 10.1016/j.jstrokecerebrovasdis.2016.11.127
241. Wang S, Lv Y, Zheng X et al. The impact of cerebral microbleeds on intracerebral hemorrhage and poor functional outcome of acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *Journal of neurology* 2017; 264(7):1309-19. doi: 10.1007/s00415-016-8339-1
242. Charidimou A, Turc G, Oppenheim C et al. Microbleeds, Cerebral Hemorrhage, and Functional Outcome After Stroke Thrombolysis. *Stroke* 2017; 48(8):2084-90. doi: 10.1161/STROKEAHA.116.012992
243. Chacon-Portillo MA, Llinas RH, Marsh EB Cerebral microbleeds shouldn't dictate treatment of acute stroke: a retrospective cohort study evaluating risk of intracerebral hemorrhage. *BMC neurology* 2018; 18(1):33. doi: 10.1186/s12883-018-1029-0
244. Wang Y, Wang Y, Zhao X et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013; 369(1):11-9. doi: 10.1056/NEJMoa1215340
245. Johnston SC, Easton JD, Farrant M et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med* 2018; 379(3):215-25. doi: 10.1056/NEJMoa1800410
246. Johnston SC, Amarenco P, Albers GW et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med* 2016; 375(1):35-43. doi: 10.1056/NEJMoa1603060
247. SALT Collaborative Group Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group. *Lancet* 1991; 338(8779):1345-9. doi:

248. PROGRESS Collaborative Group Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358(9287):1033-41. doi:
249. Sacco RL, Diener HC, Yusuf S et al. Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke. *N Engl J Med* 2008; 359(12):1238-51. doi:
250. CAPRIE Steering Committee A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348(9038):1329-39. doi:
251. Diener H, Cunha L, Forbes C et al. European Stroke Prevention Study 2: Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143:1-13. doi:
252. Amarenco P, Bogousslavsky J, Callahan A, 3rd et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355(6):549-59. doi:
253. The European Carotid Surgery Trialists' Collaborative Group Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998; 351(9113):1379-87. doi:
254. The North American Symptomatic Carotid Endarterectomy Trial Collaborators Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med* 1991; 325(7):445-53. doi:
255. NINDS-Study Group Generalized Efficacy of t-PA for Acute Stroke. Subgroup Analysis of the NINDS t-PA Stroke Trial. *Stroke* 1997; 28(11):2119-25. doi:
256. Adams HP, Jr., Davis PH, Leira EC et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999; 53(1):126-31. doi: 10.1212/wnl.53.1.126
257. Burke JF, Gelb DJ, Quint DJ et al. The impact of MRI on stroke management and outcomes: a systematic review. *J Eval Clin Pract* 2013; 19(6):987-93. doi: 10.1111/jep.12011
258. Schneider LB, Libman RB, Kanner R Utility of repeat brain imaging in stroke. *AJNR Am J Neuroradiol* 1996; 17(7):1259-63. doi:
259. Ertl-Wagner B, Brandt T, Seifart C et al. Diagnostic and therapeutic consequences of repeat brain imaging and follow-up vascular imaging in stroke patients. *AJNR Am J Neuroradiol* 1999; 20(1):37-42. doi:
260. Jung JM, Kang DW, Yu KH et al. Predictors of recurrent stroke in patients with symptomatic intracranial arterial stenosis. *Stroke* 2012; 43(10):2785-7. doi: 10.1161/STROKEAHA.112.659185
261. Turan TN, Maida L, Cotsonis G et al. Failure of antithrombotic therapy and risk of stroke in patients with symptomatic intracranial stenosis. *Stroke* 2009; 40(2):505-9. doi: 10.1161/STROKEAHA.108.528281
262. Chimowitz MI, Lynn MJ, Howlett-Smith H et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005; 352(13):1305-16. doi: 10.1056/NEJMoa043033
263. Lutsep HL, Barnwell SL, Larsen DT et al. Outcome in patients previously on antithrombotic therapy in the SAMMPRIS trial: subgroup analysis. *Stroke* 2015; 46(3):775-9. doi: 10.1161/STROKEAHA.114.007752
264. Derdeyn CP, Chimowitz MI, Lynn MJ et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet* 2014; 383(9914):333-41. doi: 10.1016/S0140-6736(13)62038-3
265. Chimowitz MI, Lynn MJ, Derdeyn CP et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011; 365(11):993-1003. doi: 10.1056/NEJMoa1105335
266. Chaturvedi S, Turan TN, Lynn MJ et al. Do Patient Characteristics Explain the Differences in Outcome Between Medically Treated Patients in SAMMPRIS and WASID? *Stroke* 2015; 46(9):2562-7. doi: 10.1161/STROKEAHA.115.009656
267. Liebeskind DS, Kosinski AS, Saver JL et al. Computed Tomography Angiography in the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Study. *Interv Neurol* 2014; 2(4):153-9. doi: 10.1159/000360952

268. Feldmann E, Wilterdink JL, Kosinski A et al. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. *Neurology* 2007; 68(24):2099-106. doi: 10.1212/01.wnl.0000261488.05906.c1
269. Goyal M, Menon BK, van Zwam WH et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387(10029):1723-31. doi: 10.1016/S0140-6736(16)00163-X
270. Broderick JP, Palesch YY, Demchuk AM et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; 368(10):893-903. doi: 10.1056/NEJMoa1214300
271. Menon BK, d'Este CD, Qazi EM et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. *Radiology* 2015; 275(2):510-20. doi: 10.1148/radiol.15142256
272. Christoforidis GA, Mohammad Y, Kehagias D et al. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol* 2005; 26(7):1789-97. doi:
273. Campbell BC, Mitchell PJ, Kleinig TJ et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. *N Engl J Med* 2015; 372(11):1009-18. doi: 10.1056/NEJMoa1414792
274. Brunser AM, Hoppe A, Illanes S et al. Accuracy of diffusion-weighted imaging in the diagnosis of stroke in patients with suspected cerebral infarct. *Stroke* 2013; 44(4):1169-71. doi: 10.1161/STROKEAHA.111.000527
275. EAFT (European Atrial Fibrillation Trial) Study Group Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; 342(8882):1255-62. doi:
276. Kallmünzer B, Breuer L, Kahl N et al. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors--a systematic, prospective analysis. *Stroke* 2012; 43(11):2892-7. doi: 10.1161/STROKEAHA.112.664318
277. Fernández-Menéndez S, García-Santiago R, Vega-Primo A et al. Cardiac arrhythmias in stroke unit patients. Evaluation of the cardiac monitoring data. *Neurologia* 2016; 31(5):289-95. doi: 10.1016/j.nrl.2015.03.013
278. Ciccone A, Celani MG, Chiamonte R et al. Continuous versus intermittent physiological monitoring for acute stroke. *Cochrane Database of Systematic Reviews* 2013; (5):CD008444. doi: 10.1002/14651858.CD008444.pub2
279. Josephson SA, Hills NK, Johnston SC NIH Stroke Scale reliability in ratings from a large sample of clinicians. *Cerebrovasc Dis* 2006; 22(5-6):389-95. doi: 10.1159/000094857
280. Lyden P, Raman R, Liu L et al. National Institutes of Health Stroke Scale certification is reliable across multiple venues. *Stroke* 2009; 40(7):2507-11. doi: 10.1161/STROKEAHA.108.532069
281. Frankel MR, Morgenstern LB, Kwiatkowski T et al. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurology* 2000; 55(7):952-9. doi: 10.1212/wnl.55.7.952
282. Wahlgren N, Ahmed N, Eriksson N et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MONitoring Study (SITS-MOST). *Stroke* 2008; 39(12):3316-22. doi: 10.1161/STROKEAHA.107.510768
283. Fonarow GC, Saver JL, Smith EE et al. Relationship of national institutes of health stroke scale to 30-day mortality in medicare beneficiaries with acute ischemic stroke. *J Am Heart Assoc* 2012; 1(1):42-50. doi: 10.1161/JAHA.111.000034
284. Meenan RT, Saha S, Chou R et al. Effectiveness and cost-effectiveness of echocardiography and carotid imaging in the management of stroke. *Evid Rep Technol Assess (Summ)* 2002; (49):1-10. doi:
285. McNamara RL, Lima JA, Whelton PK et al. Echocardiographic identification of cardiovascular sources of emboli to guide clinical management of stroke: a cost-effectiveness analysis. *Ann Intern Med* 1997; 127(9):775-87. doi: 10.7326/0003-4819-127-9-199711010-00001
286. Meenan RT, Saha S, Chou R et al. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. *Med Decis Making* 2007; 27(2):161-77. doi: 10.1177/0272989X06297388

287. Carroll JD, Saver JL, Thaler DE et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013; 368(12):1092-100. doi: 10.1056/NEJMoa1301440
288. Søndergaard L, Kasner SE, Rhodes JF et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med* 2017; 377(11):1033-42. doi: 10.1056/NEJMoa1707404
289. Furlan AJ, Reisman M, Massaro J et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012; 366(11):991-9. doi: 10.1056/NEJMoa1009639
290. Meier B, Kalesan B, Mattle HP et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013; 368(12):1083-91. doi: 10.1056/NEJMoa1211716
291. Saver JL, Carroll JD, Thaler DE et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. *N Engl J Med* 2017; 377(11):1022-32. doi: 10.1056/NEJMoa1610057
292. Mas JL, Derumeaux G, Guillon B et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. *N Engl J Med* 2017; 377(11):1011-21. doi: 10.1056/NEJMoa1705915
293. Bath PM, Woodhouse LJ, Appleton JP et al. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. *Lancet* 2018; 391(10123):850-9. doi: 10.1016/S0140-6736(17)32849-0
294. Menon BK, Coulter JI, Bal S et al. Acute ischaemic stroke or transient ischaemic attack and the need for inpatient echocardiography. *Postgrad Med J* 2014; 90(1066):434-8. doi: 10.1136/postgradmedj-2013-132220
295. Holmes M, Rathbone J, Littlewood C et al. Routine echocardiography in the management of stroke and transient ischaemic attack: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)* 2014; 18(16):1-176. doi: 10.3310/hta18160
296. McGrath ER, Paikin JS, Motlagh B et al. Transesophageal echocardiography in patients with cryptogenic ischemic stroke: a systematic review. *American heart journal* 2014; 168(5):706-12. doi: 10.1016/j.ahj.2014.07.025
297. Zhang L, Harrison JK, Goldstein LB Echocardiography for the detection of cardiac sources of embolism in patients with stroke or transient ischemic attack. *J Stroke Cerebrovasc Dis* 2012; 21(7):577-82. doi: 10.1016/j.jstrokecerebrovasdis.2011.01.005
298. Schaer B, Sticherling C, Lyrer P et al. Cardiological diagnostic work-up in stroke patients--a comprehensive study of test results and therapeutic implications. *Eur J Neurol* 2009; 16(2):268-73. doi: 10.1111/j.1468-1331.2008.02413.x
299. Douen A, Pageau N, Medic S Usefulness of cardiovascular investigations in stroke management: clinical relevance and economic implications. *Stroke* 2007; 38(6):1956-8. doi: 10.1161/STROKEAHA.106.477760
300. Wolber T, Maeder M, Atefy R et al. Should routine echocardiography be performed in all patients with stroke? *J Stroke Cerebrovasc Dis* 2007; 16(1):1-7. doi: 10.1016/j.jstrokecerebrovasdis.2006.07.002
301. Homma S, Thompson JL, Pullicino PM et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012; 366(20):1859-69. doi: 10.1056/NEJMoa1202299
302. Massie BM, Collins JF, Ammon SE et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009; 119(12):1616-24. doi: 10.1161/CIRCULATIONAHA.108.801753
303. Kapral MK, Silver FL Preventive health care, 1999 update: 2. Echocardiography for the detection of a cardiac source of embolus in patients with stroke. Canadian Task Force on Preventive Health Care. *CMAJ* 1999; 161(8):989-96. doi:
304. Secades S, Martin M, Corros C et al. Diagnostic yield of echocardiography in stroke: should we improve patient selection? *Neurologia* 2013; 28(1):15-8. doi: 10.1016/j.nrl.2012.03.002
305. Ahmad O, Ahmad KE, Dear KB et al. Echocardiography in the detection of cardioembolism in a stroke population. *J Clin Neurosci* 2010; 17(5):561-5. doi: 10.1016/j.jocn.2009.09.016
306. Lee PH, Song JK, Kim JS et al. Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. *J Am Coll Cardiol* 2018; 71(20):2335-42. doi: 10.1016/j.jacc.2018.02.046

307. de Bruijn SF, Agema WR, Lammers GJ et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke* 2006; 37(10):2531-4. doi: 10.1161/01.STR.0000241064.46659.69
308. Marino B, Jaiswal A, Goldberg S et al. Impact of transesophageal echocardiography on clinical management of patients over age 50 with cryptogenic stroke and normal transthoracic echocardiogram. *J Hosp Med* 2016; 11(2):95-8. doi: 10.1002/jhm.2484
309. Katsanos AH, Giannopoulos S, Frogoudaki A et al. The diagnostic yield of transesophageal echocardiography in patients with cryptogenic cerebral ischaemia: a meta-analysis. *Eur J Neurol* 2016; 23(3):569-79. doi: 10.1111/ene.12897
310. Tanaka K, Koga M, Sato K et al. Three-dimensional analysis of the left atrial appendage for detecting paroxysmal atrial fibrillation in acute ischemic stroke. *Int J Stroke* 2014; 9(8):1045-51. doi: 10.1111/ijs.12268
311. Sposato LA, Cipriano LE, Saposnik G et al. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet neurology* 2015; 14(4):377-87. doi: 10.1016/S1474-4422(15)70027-X
312. Wachter R, Gröschel K, Gelbrich G et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF RANDOMISED): an open-label randomised controlled trial. *Lancet neurology* 2017; 16(4):282-90. doi: 10.1016/S1474-4422(17)30002-9
313. Gladstone DJ, Spring M, Dorian P et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; 370(26):2467-77. doi: 10.1056/NEJMoa1311376
314. Brachmann J, Morillo CA, Sanna T et al. Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: Three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. *Circ Arrhythm Electrophysiol* 2016; 9(1):e003333. doi: 10.1161/CIRCEP.115.003333
315. Sanna T, Diener HC, Passman RS et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; 370(26):2478-86. doi: 10.1056/NEJMoa1313600
316. Martin DT, Bersohn MM, Waldo AL et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *European heart journal* 2015; 36(26):1660-8. doi: 10.1093/eurheartj/ehv115
317. Higgins P, MacFarlane PW, Dawson J et al. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. *Stroke* 2013; 44(9):2525-31. doi: 10.1161/STROKEAHA.113.001927
318. Higgins P, Dawson J, MacFarlane PW et al. Predictive value of newly detected atrial fibrillation paroxysms in patients with acute ischemic stroke, for atrial fibrillation after 90 days. *Stroke* 2014; 45(7):2134-6. doi: 10.1161/STROKEAHA.114.005405
319. Kurka N, Bobinger T, Kallmunzer B et al. Reliability and limitations of automated arrhythmia detection in telemetric monitoring after stroke. *Stroke* 2015; 46(2):560-3. doi: 10.1161/STROKEAHA.114.007892
320. Lazzaro MA, Krishnan K, Prabhakaran S Detection of atrial fibrillation with concurrent holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis* 2012; 21(2):89-93. doi: 10.1016/j.jstrokecerebrovasdis.2010.05.006
321. Douen AG, Pageau N, Medic S Serial electrocardiographic assessments significantly improve detection of atrial fibrillation 2.6-fold in patients with acute stroke. *Stroke* 2008; 39(2):480-2. doi: 10.1161/STROKEAHA.107.492595
322. Gunalp M, Atalar E, Coskun F et al. Holter monitoring for 24 hours in patients with thromboembolic stroke and sinus rhythm diagnosed in the emergency department. *Adv Ther* 2006; 23(6):854-60. doi: 10.1007/BF02850206
323. Afzal MR, Gunda S, Waheed S et al. Role of Outpatient Cardiac Rhythm Monitoring in Cryptogenic Stroke: A Systematic Review and Meta-Analysis. *Pacing and clinical electrophysiology : PACE* 2015; 38(10):1236-45. doi: 10.1111/pace.12688
324. Kamel H, Navi BB, Eljovich L et al. Pilot randomized trial of outpatient cardiac monitoring after cryptogenic stroke. *Stroke* 2013; 44(2):528-30. doi: 10.1161/STROKEAHA.112.679100



325. Suissa L, Lachaud S, Mahagne MH Optimal timing and duration of continuous electrocardiographic monitoring for detecting atrial fibrillation in stroke patients. *J Stroke Cerebrovasc Dis* 2013; 22(7):991-5. doi: 10.1016/j.jstrokecerebrovasdis.2012.01.015
326. Flint AC, Banki NM, Ren X et al. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke* 2012; 43(10):2788-90. doi: 10.1161/STROKEAHA.112.665844
327. Kishore A, Vail A, Majid A et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* 2014; 45(2):520-6. doi: 10.1161/STROKEAHA.113.003433
328. Strömberg S, Nordanstig A, Bentzel T et al. Risk of early recurrent stroke in symptomatic carotid stenosis. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 2015; 49(2):137-44. doi: 10.1016/j.ejvs.2014.11.004
329. Johansson EP, Arnerlov C, Wester P Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. *Int J Stroke* 2013; 8(4):220-7. doi: 10.1111/j.1747-4949.2012.00790.x
330. Marnane M, Ni Chroinin D, Callaly E et al. Stroke recurrence within the time window recommended for carotid endarterectomy. *Neurology* 2011; 77(8):738-43. doi: 10.1212/WNL.0b013e31822b00cf
331. De Rango P, Brown MM, Chaturvedi S et al. Summary of Evidence on Early Carotid Intervention for Recently Symptomatic Stenosis Based on Meta-Analysis of Current Risks. *Stroke* 2015; 46(12):3423-36. doi: 10.1161/STROKEAHA.115.010764
332. Ois A, Cuadrado-Godia E, Rodriguez-Campello A et al. High risk of early neurological recurrence in symptomatic carotid stenosis. *Stroke* 2009; 40(8):2727-31. doi: 10.1161/STROKEAHA.109.548032
333. Adachi K, Sadato A, Hayakawa M et al. Acute carotid artery stenting in symptomatic high-grade cervical carotid artery stenosis. *Neurosurg Rev* 2017; 40(1):45-51. doi: 10.1007/s10143-016-0737-4
334. Azzini C, Gentile M, De Vito A et al. Very Early Carotid Endarterectomy After Intravenous Thrombolysis. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 2016; 51(4):482-6. doi: 10.1016/j.ejvs.2015.11.006
335. Kazandjian C, Kretz B, Lemogne B et al. Influence of the type of cerebral infarct and timing of intervention in the early outcomes after carotid endarterectomy for symptomatic stenosis. *Journal of vascular surgery* 2016; 63(5):1256-61. doi: 10.1016/j.jvs.2015.10.097
336. Vasconcelos V, Cassola N, da Silva EM et al. Immediate versus delayed treatment for recently symptomatic carotid artery stenosis. *Cochrane Database Syst Rev* 2016; 9:CD011401. doi: 10.1002/14651858.CD011401.pub2
337. Ferguson GG, Eliasziw M, Barr HW et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. *Stroke* 1999; 30(9):1751-8. doi: 10.1161/01.str.30.9.1751
338. Netuka D, Belsan T, Broulikova K et al. Detection of carotid artery stenosis using histological specimens: a comparison of CT angiography, magnetic resonance angiography, digital subtraction angiography and Doppler ultrasonography. *Acta Neurochir (Wien)* 2016; 158(8):1505-14. doi: 10.1007/s00701-016-2842-0
339. Chappell FM, Wardlaw JM, Young GR et al. Carotid artery stenosis: accuracy of noninvasive tests--individual patient data meta-analysis. *Radiology* 2009; 251(2):493-502. doi: 10.1148/radiol.2512080284
340. CAST (Chinese Acute Stroke Trial) Collaborative Group CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet* 1997; 349(9066):1641-9. doi:
341. Sandercock PA, Counsell C, Tseng MC et al. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; (3):CD000029. doi: 10.1002/14651858.CD000029.pub3
342. Ciccone A, Motto C, Abraha I et al. Glycoprotein IIb/IIIa inhibitors for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; (3):CD005208. doi: 10.1002/14651858.CD005208.pub3
343. Adams HP, Jr., Effron MB, Torner J et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in

- Emergency Treatment of Stroke Trial (AbESTT-II). *Stroke* 2008; 39(1):87-99. doi: 10.1161/STROKEAHA.106.476648
344. Siebler M, Hennerici MG, Schneider D et al. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. *Stroke* 2011; 42(9):2388-92. doi: 10.1161/STROKEAHA.110.599662
345. Pancioli AM, Broderick J, Brott T et al. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: the CLEAR stroke trial. *Stroke* 2008; 39(12):3268-76. doi: 10.1161/STROKEAHA.108.517656
346. Adeoye O, Sucharew H, Khoury J et al. Recombinant tissue-type plasminogen activator plus eptifibatide versus recombinant tissue-type plasminogen activator alone in acute ischemic stroke: propensity score-matched post hoc analysis. *Stroke* 2015; 46(2):461-4. doi: 10.1161/STROKEAHA.114.006743
347. Adeoye O, Sucharew H, Khoury J et al. Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke-Full Dose Regimen Stroke Trial. *Stroke* 2015; 46(9):2529-33. doi: 10.1161/STROKEAHA.115.010260
348. Zinkstok SM, Roos YB, investigators A Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet* 2012; 380(9843):731-7. doi: 10.1016/S0140-6736(12)60949-0
349. Wang Y, Pan Y, Zhao X et al. Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial: One-Year Outcomes. *Circulation* 2015; 132(1):40-6. doi: 10.1161/CIRCULATIONAHA.114.014791
350. Johnston SC, Easton JD, Farrant M et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke* 2013; 8(6):479-83. doi: 10.1111/ij.s.12129
351. Wang X, Zhao X, Johnston SC et al. Effect of clopidogrel with aspirin on functional outcome in TIA or minor stroke: CHANCE substudy. *Neurology* 2015; 85(7):573-9. doi: 10.1212/WNL.0000000000001844
352. Pan Y, Jing J, Chen W et al. Risks and benefits of clopidogrel-aspirin in minor stroke or TIA: Time course analysis of CHANCE. *Neurology* 2017; 88(20):1906-11. doi: 10.1212/WNL.0000000000003941
353. Wang Y, Zhao X, Lin J et al. Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. *JAMA* 2016; 316(1):70-8. doi: 10.1001/jama.2016.8662
354. Jing J, Meng X, Zhao X et al. Dual Antiplatelet Therapy in Transient Ischemic Attack and Minor Stroke With Different Infarction Patterns: Subgroup Analysis of the CHANCE Randomized Clinical Trial. *JAMA Neurol* 2018; 75(6):711-9. doi: 10.1001/jamaneurol.2018.0247
355. Hao Q, Tampi M, O'Donnell M et al. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ* 2018; 363:k5108. doi: 10.1136/bmj.k5108
356. Kennedy J, Hill MD, Ryckborst KJ et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet neurology* 2007; 6(11):961-9. doi: 10.1016/S1474-4422(07)70250-8
357. Wong KS, Wang Y, Leng X et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. *Circulation* 2013; 128(15):1656-66. doi: 10.1161/CIRCULATIONAHA.113.003187
358. He F, Xia C, Zhang JH et al. Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke. *J Clin Neurosci* 2015; 22(1):83-6. doi: 10.1016/j.jocn.2014.05.038
359. Yi X, Lin J, Wang C et al. A comparative study of dual versus monoantiplatelet therapy in patients with acute large-artery atherosclerosis stroke. *J Stroke Cerebrovasc Dis* 2014; 23(7):1975-81. doi: 10.1016/j.jstrokecerebrovasdis.2014.01.022
360. Geeganage CM, Diener HC, Algra A et al. Dual or mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack: systematic review and meta-analysis of randomized controlled trials. *Stroke* 2012; 43(4):1058-66. doi: 10.1161/STROKEAHA.111.637686

361. AVERT Trial Collaboration group Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015; 386(9988):46-55. doi: 10.1016/S0140-6736(15)60690-0
362. Diserens K, Moreira T, Hirt L et al. Early mobilization out of bed after ischaemic stroke reduces severe complications but not cerebral blood flow: a randomized controlled pilot trial. *Clinical rehabilitation* 2012; 26(5):451-9. doi: 10.1177/0269215511425541
363. Bernhardt J, Dewey H, Thrift A et al. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. *Stroke* 2008; 39(2):390-6. doi: 10.1161/STROKEAHA.107.492363
364. Sorbello D, Dewey HM, Churilov L et al. Very early mobilisation and complications in the first 3 months after stroke: further results from phase II of A Very Early Rehabilitation Trial (AVERT). *Cerebrovasc Dis* 2009; 28(4):378-83. doi: 10.1159/000230712
365. Cumming TB, Thrift AG, Collier JM et al. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. *Stroke* 2011; 42(1):153-8. doi: 10.1161/STROKEAHA.110.594598
366. Craig LE, Bernhardt J, Langhorne P et al. Early mobilization after stroke: an example of an individual patient data meta-analysis of a complex intervention. *Stroke* 2010; 41(11):2632-6. doi: 10.1161/STROKEAHA.110.588244
367. Bernhardt J, English C, Johnson L et al. Early mobilization after stroke: early adoption but limited evidence. *Stroke* 2015; 46(4):1141-6. doi: 10.1161/STROKEAHA.114.007434
368. Bernhardt J, Churilov L, Ellery F et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology* 2016; 86(23):2138-45. doi: 10.1212/WNL.0000000000002459
369. Lynch E, Hillier S, Cadilhac D When should physical rehabilitation commence after stroke: a systematic review. *Int J Stroke* 2014; 9(4):468-78. doi: 10.1111/ijvs.12262
370. Wardlaw JM, Murray V, Berge E et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012; 379(9834):2364-72. doi: 10.1016/S0140-6736(12)60738-7
371. Emberson J, Lees KR, Lyden P et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; 384(9958):1929-35. doi: 10.1016/S0140-6736(14)60584-5
372. Wardlaw JM, Murray V, Berge E et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; (7):CD000213. doi: 10.1002/14651858.CD000213.pub3
373. Hacke W, Donnan G, Fieschi C et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; 363(9411):768-74. doi: 10.1016/S0140-6736(04)17117-2
374. Wahlgren N, Ahmed N, Davalos A et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; 369(9558):275-82. doi: 10.1016/S0140-6736(07)61381-2
375. Lees KR, Emberson J, Blackwell L et al. Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes: A Pooled Analysis of 9 Trials. *Stroke* 2016; 47(9):2373-9. doi: 10.1161/STROKEAHA.116.013644
376. IST-3 collaborative group, Sandercock P, Wardlaw JM et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012; 379(9834):2352-63. doi: 10.1016/S0140-6736(12)60768-5
377. Anderson CS, Robinson T, Lindley RI et al. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. *N Engl J Med* 2016; 374(24):2313-23. doi: 10.1056/NEJMoa1515510
378. Cucchiara BL, Jackson B, Weiner M et al. Usefulness of checking platelet count before thrombolysis in acute ischemic stroke. *Stroke* 2007; 38(5):1639-40. doi: 10.1161/STROKEAHA.106.480889
379. Jeong HG, Kim BJ, Yang MH et al. Stroke outcomes with use of antithrombotics within 24 hours after recanalization treatment. *Neurology* 2016; 87(10):996-1002. doi: 10.1212/WNL.0000000000003083

380. Hacke W, Kaste M, Fieschi C et al. Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Stroke. *JAMA* 1995; 274(13):1017-25. doi:
381. Hacke W, Kaste M, Fieschi C et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998; 352(9136):1245-51. doi:
382. Bluhmki E, Chamorro A, Davalos A et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet neurology* 2009; 8(12):1095-102. doi:
383. Davis SM, Donnan GA, Parsons MW et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet neurology* 2008; 7(4):299-309. doi:
384. Ford GA, Ahmed N, Azevedo E et al. Intravenous alteplase for stroke in those older than 80 years old. *Stroke* 2010; 41(11):2568-74. doi: 10.1161/STROKEAHA.110.581884
385. Cronin CA, Sheth KN, Zhao X et al. Adherence to Third European Cooperative Acute Stroke Study 3- to 4.5-hour exclusions and association with outcome: data from Get with the Guidelines-Stroke. *Stroke* 2014; 45(9):2745-9. doi: 10.1161/STROKEAHA.114.005443
386. Cronin CA, Shah N, Morovati T et al. No increased risk of symptomatic intracerebral hemorrhage after thrombolysis in patients with European Cooperative Acute Stroke Study (ECASS) exclusion criteria. *Stroke* 2012; 43(6):1684-6. doi: 10.1161/STROKEAHA.112.656587
387. Rudd AG, Hoffman A, Grant R et al. Stroke thrombolysis in England, Wales and Northern Ireland: how much do we do and how much do we need? *J Neurol Neurosurg Psychiatry* 2011; 82(1):14-9. doi: 10.1136/jnnp.2009.203174
388. Thomalla G, Simonsen CZ, Boutitie F et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *N Engl J Med* 2018; 379(7):611-22. doi: 10.1056/NEJMoa1804355
389. Campbell BCV, Mitchell PJ, Churilov L et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *N Engl J Med* 2018; 378(17):1573-82. doi: 10.1056/NEJMoa1716405
390. Logallo N, Novotny V, Assmus J et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet neurology* 2017; 16(10):781-8. doi: 10.1016/S1474-4422(17)30253-3
391. Haley EC, Jr., Thompson JL, Grotta JC et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke* 2010; 41(4):707-11. doi: 10.1161/STROKEAHA.109.572040
392. Huang X, Cheripelli BK, Lloyd SM et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet neurology* 2015; 14(4):368-76. doi: 10.1016/S1474-4422(15)70017-7
393. Huang X, MacIsaac R, Thompson JL et al. Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials. *Int J Stroke* 2016; 11(5):534-43. doi: 10.1177/1747493016641112
394. Parsons M, Spratt N, Bivard A et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012; 366(12):1099-107. doi: 10.1056/NEJMoa1109842
395. Hacke W, Furlan AJ, Al-Rawi Y et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet neurology* 2009; 8(2):141-50. doi:
396. Hacke W, Albers G, Al-Rawi Y et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): A Phase II MRI-Based 9-Hour Window Acute Stroke Thrombolysis Trial With Intravenous Desmoteplase. *Stroke* 2005; 36(1):66-73. doi:
397. Albers GW, von Kummer R, Truelsen T et al. Safety and efficacy of desmoteplase given 3-9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (DIAS-3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet neurology* 2015; 14(6):575-84. doi: 10.1016/S1474-4422(15)00047-2

398. Nacu A, Kvistad CE, Naess H et al. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study): Randomized Controlled Contrast-Enhanced Sonothrombolysis in an Unselected Acute Ischemic Stroke Population. *Stroke* 2017; 48(2):335-41. doi: 10.1161/STROKEAHA.116.014644
399. Alexandrov AV, Kohrmann M, Soenne L et al. Safety and efficacy of sonothrombolysis for acute ischaemic stroke: a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet neurology* 2019; 18(4):338-47. doi: 10.1016/S1474-4422(19)30026-2
400. Ingall TJ, O'Fallon WM, Asplund K et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke* 2004; 35(10):2418-24. doi: 10.1161/01.STR.0000140891.70547.56
401. National Institute of Neurological Disorders Stroke rt PASSG Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience. *Ann Emerg Med* 2005; 46(3):243-52. doi: 10.1016/j.annemergmed.2005.02.013
402. Khatri P, Tayama D, Cohen G et al. Effect of Intravenous Recombinant Tissue-Type Plasminogen Activator in Patients With Mild Stroke in the Third International Stroke Trial-3: Post Hoc Analysis. *Stroke* 2015; 46(8):2325-7. doi: 10.1161/STROKEAHA.115.009951
403. Ahmed N, Wahlgren N, Grond M et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke: an updated analysis from SITS-ISTR. *Lancet neurology* 2010; 9(9):866-74. doi: 10.1016/S1474-4422(10)70165-4
404. Romano JG, Smith EE, Liang L et al. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the Get With the Guidelines-Stroke registry. *JAMA Neurol* 2015; 72(4):423-31. doi: 10.1001/jamaneurol.2014.4354
405. Khatri P, Kleindorfer DO, Devlin T et al. Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial. *JAMA* 2018; 320(2):156-66. doi: 10.1001/jama.2018.8496
406. Qureshi AI, Ezzeddine MA, Nasar A et al. Is IV tissue plasminogen activator beneficial in patients with hyperdense artery sign? *Neurology* 2006; 66(8):1171-4. doi: 10.1212/01.wnl.0000208407.69544.5a
407. group ISTc Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet neurology* 2015; 14(5):485-96. doi: 10.1016/S1474-4422(15)00012-5
408. Mair G, von Kummer R, Morris Z et al. Effect of alteplase on the CT hyperdense artery sign and outcome after ischemic stroke. *Neurology* 2016; 86(2):118-25. doi: 10.1212/WNL.0000000000002236
409. Demchuk AM, Tanne D, Hill MD et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. *Neurology* 2001; 57:474-80. doi:
410. Waltimo T, Haapaniemi E, Surakka IL et al. Post-thrombolytic blood pressure and symptomatic intracerebral hemorrhage. *Eur J Neurol* 2016; 23(12):1757-62. doi: 10.1111/ene.13118
411. Endo K, Kario K, Koga M et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA Registry. *Stroke* 2013; 44(3):816-8. doi: 10.1161/STROKEAHA.112.681007
412. Wu W, Huo X, Zhao X et al. Relationship between Blood Pressure and Outcomes in Acute Ischemic Stroke Patients Administered Lytic Medication in the TIMS-China Study. *PLoS One* 2016; 11(2):e0144260. doi: 10.1371/journal.pone.0144260
413. Toni D, Ahmed N, Anzini A et al. Intravenous thrombolysis in young stroke patients: results from the SITS-ISTR. *Neurology* 2012; 78(12):880-7. doi: 10.1212/WNL.0b013e31824d966b
414. Perini F, De Boni A, Marcon M et al. Systolic blood pressure contributes to intracerebral haemorrhage after thrombolysis for ischemic stroke. *J Neurol Sci* 2010; 297(1-2):52-4. doi: 10.1016/j.jns.2010.06.025
415. Butcher K, Christensen S, Parsons M et al. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. *Stroke* 2010; 41(1):72-7. doi: 10.1161/STROKEAHA.109.563767

416. Liu K, Yan S, Zhang S et al. Systolic Blood Pressure Variability is Associated with Severe Hemorrhagic Transformation in the Early Stage After Thrombolysis. *Transl Stroke Res* 2016; 7(3):186-91. doi: 10.1007/s12975-016-0458-6
417. Anderson CS, Huang Y, Lindley RI et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet* 2019; 393(10174):877-88. doi: 10.1016/S0140-6736(19)30038-8
418. Roman LS, Menon BK, Blasco J et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet neurology* 2018; 17(10):895-904. doi: 10.1016/S1474-4422(18)30242-4
419. Goyal M, Menon BK, Krings T et al. What constitutes the M1 segment of the middle cerebral artery? *J Neurointerv Surg* 2016; 8(12):1273-7. doi: 10.1136/neurintsurg-2015-012191
420. Berkhemer OA, Fransen PS, Beumer D et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372(1):11-20. doi: 10.1056/NEJMoa1411587
421. Nogueira RG, Jadhav AP, Haussen DC et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med* 2018; 378(1):11-21. doi: 10.1056/NEJMoa1706442
422. Albers GW, Marks MP, Kemp S et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med* 2018; 378(8):708-18. doi: 10.1056/NEJMoa1713973
423. Jovin TG, Chamorro A, Cobo E et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; 372(24):2296-306. doi: 10.1056/NEJMoa1503780
424. Goyal M, Demchuk AM, Menon BK et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; 372(11):1019-30. doi: 10.1056/NEJMoa1414905
425. Bracard S, Ducrocq X, Mas JL et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet neurology* 2016; 15(11):1138-47. doi: 10.1016/S1474-4422(16)30177-6
426. Saver JL, Goyal M, Bonafe A et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015; 372(24):2285-95. doi: 10.1056/NEJMoa1415061
427. Turk AS, 3rd, Siddiqui A, Fifi JT et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet* 2019; 393(10175):998-1008. doi: 10.1016/S0140-6736(19)30297-1
428. Lapergue B, Blanc R, Gory B et al. Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER Randomized Clinical Trial. *JAMA* 2017; 318(5):443-52. doi: 10.1001/jama.2017.9644
429. Nogueira RG, Frei D, Kirmani JF et al. Safety and Efficacy of a 3-Dimensional Stent Retriever With Aspiration-Based Thrombectomy vs Aspiration-Based Thrombectomy Alone in Acute Ischemic Stroke Intervention: A Randomized Clinical Trial. *JAMA Neurol* 2018; 75(3):304-11. doi: 10.1001/jamaneurol.2017.3967
430. Campbell BC, Hill MD, Rubiera M et al. Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials. *Stroke* 2016; 47(3):798-806. doi: 10.1161/STROKEAHA.115.012360
431. Lemmens R, Hamilton SA, Liebeskind DS et al. Effect of endovascular reperfusion in relation to site of arterial occlusion. *Neurology* 2016; 86(8):762-70. doi: 10.1212/WNL.0000000000002399
432. Badhiwala JH, Nassiri F, Alhazzani W et al. Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. *JAMA* 2015; 314(17):1832-43. doi: 10.1001/jama.2015.13767
433. Davalos A, Cobo E, Molina CA et al. Safety and efficacy of thrombectomy in acute ischaemic stroke (REVASCAT): 1-year follow-up of a randomised open-label trial. *Lancet neurology* 2017; 16(5):369-76. doi: 10.1016/S1474-4422(17)30047-9
434. Saver JL, Goyal M, Hill MD et al. Time to Endovascular Thrombectomy for Acute Stroke-Reply. *JAMA* 2017; 317(11):1175-6. doi: 10.1001/jama.2017.0373
435. Flynn D, Francis R, Halvorsrud K et al. Intra-arterial mechanical thrombectomy stent retrievers and aspiration devices in the treatment of acute ischaemic stroke: A systematic review and meta-analysis with trial sequential analysis. *Eur Stroke J* 2017; 2(4):308-18. doi: 10.1177/2396987317719362

436. Mistry EA, Mistry AM, Nakawah MO et al. Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: A Meta-Analysis. *Stroke* 2017; 48(9):2450-6. doi: 10.1161/STROKEAHA.117.017320
437. Kaesmacher J, Mordasini P, Arnold M et al. Direct mechanical thrombectomy in tPA-ineligible and -eligible patients versus the bridging approach: a meta-analysis. *J Neurointerv Surg* 2019; 11(1):20-7. doi: 10.1136/neurintsurg-2018-013834
438. Palesch YY, Yeatts SD, Tomsick TA et al. Twelve-Month Clinical and Quality-of-Life Outcomes in the Interventional Management of Stroke III Trial. *Stroke* 2015; 46(5):1321-7. doi: 10.1161/STROKEAHA.115.009180
439. Mocco J, Zaidat OO, von Kummer R et al. Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone. *Stroke* 2016; 47(9):2331-8. doi: 10.1161/STROKEAHA.116.013372
440. Bush CK, Kurimella D, Cross LJ et al. Endovascular Treatment with Stent-Retriever Devices for Acute Ischemic Stroke: A Meta-Analysis of Randomized Controlled Trials. *PLoS One* 2016; 11(1):e0147287. doi: 10.1371/journal.pone.0147287
441. Kaesmacher J, Dobrocky T, Heldner MR et al. Systematic review and meta-analysis on outcome differences among patients with TIC12b versus TIC13 reperfusions: success revisited. *J Neurol Neurosurg Psychiatry* 2018; 89(9):910-7. doi: 10.1136/jnnp-2017-317602
442. Dippel DW, Majoie CB, Roos YB et al. Influence of Device Choice on the Effect of Intra-Arterial Treatment for Acute Ischemic Stroke in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). *Stroke* 2016; 47(10):2574-81. doi: 10.1161/STROKEAHA.116.013929
443. Schönenberger S, Uhlmann L, Hacke W et al. Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial. *JAMA* 2016; 316(19):1986-96. doi: 10.1001/jama.2016.16623
444. Löwhagen Henden P, Rentzos A, Karlsson JE et al. Hypotension During Endovascular Treatment of Ischemic Stroke Is a Risk Factor for Poor Neurological Outcome. *Stroke* 2015; 46(9):2678-80. doi: 10.1161/STROKEAHA.115.009808
445. Simonsen CZ, Yoo AJ, Sorensen LH et al. Effect of General Anesthesia and Conscious Sedation During Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol* 2018; 75(4):470-7. doi: 10.1001/jamaneurol.2017.4474
446. Campbell BCV, van Zwam WH, Goyal M et al. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. *Lancet neurology* 2018; 17(1):47-53. doi: 10.1016/S1474-4422(17)30407-6
447. Berkhemer OA, van den Berg LA, Fransen PS et al. The effect of anesthetic management during intra-arterial therapy for acute stroke in MR CLEAN. *Neurology* 2016; 87(7):656-64. doi: 10.1212/WNL.0000000000002976
448. Brinjikji W, Pasternak J, Murad MH et al. Anesthesia-Related Outcomes for Endovascular Stroke Revascularization: A Systematic Review and Meta-Analysis. *Stroke* 2017; 48(10):2784-91. doi: 10.1161/STROKEAHA.117.017786
449. Mulder M, Ergezen S, Lingsma HF et al. Baseline Blood Pressure Effect on the Benefit and Safety of Intra-Arterial Treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands). *Stroke* 2017; 48(7):1869-76. doi: 10.1161/STROKEAHA.116.016225
450. Maier B, Gory B, Taylor G et al. Mortality and Disability According to Baseline Blood Pressure in Acute Ischemic Stroke Patients Treated by Thrombectomy: A Collaborative Pooled Analysis. *J Am Heart Assoc* 2017; 6(10)doi: 10.1161/JAHA.117.006484
451. Goyal N, Tsvigoulis G, Pandhi A et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. *Neurology* 2017; 89(6):540-7. doi: 10.1212/WNL.0000000000004184

452. Whalin MK, Halenda KM, Haussen DC et al. Even Small Decreases in Blood Pressure during Conscious Sedation Affect Clinical Outcome after Stroke Thrombectomy: An Analysis of Hemodynamic Thresholds. *AJNR Am J Neuroradiol* 2017; 38(2):294-8. doi: 10.3174/ajnr.A4992
453. Schonewille WJ, Wijman CA, Michel P et al. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. *Lancet neurology* 2009; 8(8):724-30. doi: 10.1016/S1474-4422(09)70173-5
454. Liu X, Xu G, Liu Y et al. Acute basilar artery occlusion: Endovascular Interventions versus Standard Medical Treatment (BEST) Trial-Design and protocol for a randomized, controlled, multicenter study. *Int J Stroke* 2017; 12(7):779-85. doi: 10.1177/1747493017701153
455. Macleod MR, Davis SM, Mitchell PJ et al. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. *Cerebrovasc Dis* 2005; 20(1):12-7. doi: 10.1159/000086121
456. Kumar G, Shahripour RB, Alexandrov AV Recanalization of acute basilar artery occlusion improves outcomes: a meta-analysis. *J Neurointerv Surg* 2015; 7(12):868-74. doi: 10.1136/neurintsurg-2014-011418
457. Vahedi K, Hofmeijer J, Jüttler E et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet neurology* 2007; 6(3):215-22. doi:
458. Maciel CB, Sheth KN Malignant MCA Stroke: an Update on Surgical Decompression and Future Directions. *Curr Atheroscler Rep* 2015; 17(7):40. doi: 10.1007/s11883-015-0519-4
459. Yang MH, Lin HY, Fu J et al. Decompressive hemicraniectomy in patients with malignant middle cerebral artery infarction: A systematic review and meta-analysis. *Surgeon* 2015; 13(4):230-40. doi: 10.1016/j.surge.2014.12.002
460. Alexander P, Heels-Ansdell D, Siemieniuk R et al. Hemicraniectomy versus medical treatment with large MCA infarct: a review and meta-analysis. *BMJ Open* 2016; 6(11):e014390. doi: 10.1136/bmjopen-2016-014390
461. Agarwalla PK, Stapleton CJ, Ogilvy CS Craniectomy in acute ischemic stroke. *Neurosurgery* 2014; 74 Suppl 1:S151-62. doi: 10.1227/NEU.0000000000000226
462. Boulanger JM, Lindsay MP, Gubitz G et al. Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. *Int J Stroke* 2018; 13(9):949-84. doi: 10.1177/1747493018786616
463. Jüttler E, Schwab S, Schmiedek P et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. *Stroke* 2007; 38(9):2518-25. doi:
464. Hofmeijer J, Kappelle LJ, Algra A et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet neurology* 2009; 8(4):326-33. doi:
465. Geurts M, van der Worp HB, Kappelle LJ et al. Surgical decompression for space-occupying cerebral infarction: outcomes at 3 years in the randomized HAMLET trial. *Stroke* 2013; 44(9):2506-8. doi: 10.1161/STROKEAHA.113.002014
466. Vahedi K, Vicaut E, Mateo J et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke* 2007; 38(9):2506-17. doi: 10.1161/STROKEAHA.107.485235
467. Cruz-Flores S, Berge E, Whittle IR Surgical decompression for cerebral oedema in acute ischaemic stroke. *Cochrane Database Syst Rev* 2012; 1:CD003435. doi: 10.1002/14651858.CD003435.pub2
468. Qureshi AI, Ishfaq MF, Rahman HA et al. Hemicraniectomy versus Conservative Treatment in Large Hemispheric Ischemic Stroke Patients: A Meta-analysis of Randomized Controlled Trials. *J Stroke Cerebrovasc Dis* 2016; 25(9):2209-14. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.053
469. Jüttler E, Unterberg A, Woitzik J et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med* 2014; 370(12):1091-100. doi: 10.1056/NEJMoa1311367



470. Zhao J, Su YY, Zhang Y et al. Decompressive hemicraniectomy in malignant middle cerebral artery infarct: a randomized controlled trial enrolling patients up to 80 years old. *Neurocrit Care* 2012; 17(2):161-71. doi: 10.1007/s12028-012-9703-3
471. Yu JW, Choi JH, Kim DH et al. Outcome following decompressive craniectomy for malignant middle cerebral artery infarction in patients older than 70 years old. *J Cerebrovasc Endovasc Neurosurg* 2012; 14(2):65-74. doi: 10.7461/jcen.2012.14.2.65
472. Suyama K, Horie N, Hayashi K et al. Nationwide survey of decompressive hemicraniectomy for malignant middle cerebral artery infarction in Japan. *World Neurosurg* 2014; 82(6):1158-63. doi: 10.1016/j.wneu.2014.07.015
473. Sundseth J, Sundseth A, Jacobsen EA et al. Predictors of early in-hospital death after decompressive craniectomy in swollen middle cerebral artery infarction. *Acta Neurochir (Wien)* 2017; 159(2):301-6. doi: 10.1007/s00701-016-3049-0
474. McKenna A, Wilson CF, Caldwell SB et al. Functional outcomes of decompressive hemicraniectomy following malignant middle cerebral artery infarctions: a systematic review. *Br J Neurosurg* 2012; 26(3):310-5. doi: 10.3109/02688697.2012.654835
475. Inamasu J, Kaito T, Watabe T et al. Decompressive hemicraniectomy for malignant hemispheric stroke in the elderly: comparison of outcomes between individuals 61-70 and >70 years of age. *J Stroke Cerebrovasc Dis* 2013; 22(8):1350-4. doi: 10.1016/j.jstrokecerebrovasdis.2013.02.008
476. Mostofi K Neurosurgical management of massive cerebellar infarct outcome in 53 patients. *Surg Neurol Int* 2013; 4:28-32. doi: 10.4103/2152-7806.107906
477. Raco A, Caroli E, Isidori A et al. Management of acute cerebellar infarction: one institution's experience. *Neurosurgery* 2003; 53(5):1061-5; discussion 5-6. doi: 10.1227/01.neu.0000088766.34559.3e
478. Piironen K, Tiainen M, Mustanoja S et al. Mild hypothermia after intravenous thrombolysis in patients with acute stroke: a randomized controlled trial. *Stroke* 2014; 45(2):486-91. doi: 10.1161/STROKEAHA.113.003180
479. Geurts M, Petersson J, Brizzi M et al. COOLIST (Cooling for Ischemic Stroke Trial): A Multicenter, Open, Randomized, Phase II, Clinical Trial. *Stroke* 2017; 48(1):219-21. doi: 10.1161/STROKEAHA.116.014757
480. Lyden P, Hemmen T, Grotta J et al. Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2). *Stroke* 2016; 47(12):2888-95. doi: 10.1161/STROKEAHA.116.014200
481. Bornstein NM, Saver JL, Diener HC et al. Sphenopalatine Ganglion Stimulation to Augment Cerebral Blood Flow. *Stroke* 2019; 50:2108-17. doi: 10.1161/STROKEAHA.118.024582
482. K Die AWMF erfasst und publiziert die Leitlinien der Fachgesellschaften mit ImpACT-1 (ImpACT-1) größtmöglicher Sorgfalt - dennoch kann die AWMF für die Richtigkeit des Inhalts keine Verantwortung übernehmen. **Insbesondere bei Dosierungsangaben sind stets die Angaben der Hersteller zu beachten!** *Stroke* 2019; 50:2108-17. doi: 10.1371/journal.pone.0211192
483. B Sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial. *Lancet* 2019; 394(10194):219-29. doi: 10.1016/S0140-6736(19)31192-4
484. Jin X, Chandramouli C, Allocco B et al. Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017. *Circulation* 2020; 141(7):540-8. doi: 10.1161/CIRCULATIONAHA.119.043594

**Versionsnummer:** 5.1  
**Erstveröffentlichung:** 05/2002  
**Überarbeitung von:** 05/2021  
**Nächste Überprüfung geplant:** 05/2024

Die AWMF erfasst und publiziert die Leitlinien der Fachgesellschaften mit größtmöglicher Sorgfalt - dennoch kann die AWMF für die Richtigkeit des Inhalts keine Verantwortung übernehmen. **Insbesondere bei Dosierungsangaben sind stets die Angaben der Hersteller zu beachten!**

**Autorisiert für elektronische Publikation: AWMF online**

06.06.2024: Gültigkeit der Leitlinie nach inhaltlicher Überprüfung durch das Leitliniensekretariat verlängert bis 09.05.2026