Evidenzbericht für die S3-Leitlinie: „Empfehlungen zur Therapie von Patienten mit COVID-19“

AWMF-Registernummer: 113 - 001

Aktueller Stand: Januar 2024

Inhaltsverzeichnis

1 Informationen zum Evidenzbericht

1.1 Autor*innen des Evidenzberichts

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1.2 Federführende Fachgesellschaft(en) der Leitlinie

- Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN)
- Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)
- Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)
- Deutsche Gesellschaft für Infektiologie (DGI)

1.3 Finanzierung der Leitlinie

Die vorliegende Aktualisierung wird unter dem Projekt „S3Cov19live – Living Guideline: Empfehlungen zur Therapie von Patienten mit COVID-19“ (Förderkennzeichen: 01VSF2300) durch den Gemeinsamen Bundesausschuss (Innofonds) für den Zeitraum 01.08.2023 und 31.07.2026 gefördert.

Die Vorgängerversion dieser Leitlinie wurde durch das Projekt CEOsys, das im Rahmen des Nationalen Forschungsnetzwerks der Universitätsmedizin (NaFoUniMedCovid19) durch das Bundesministerium für Bildung und Forschung (BMBF) gefördert wurde, unterstützt; FKZ: 01KX2021. Die Förderung von CEOsys endete zum 31.12.2021.

1.4 Weitere Dokumente zur Leitlinie

- https://register.awmf.org/de/leitlinien/detail/113-001LG
- https://app.magicapp.org/#/guideline/7753

1.5 Abkürzungsverzeichnis

Auf eine Übersetzung englischer Abkürzungen wurde verzichtet.

Abkürzung	Erläuterung
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
EtD	Evidence to Decision Framework
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFNC	High flow Sauerstoff über Nasenbrille
IMV	Invasive mechanische Beatmung

Abkürzung	Erläuterung
JAK	Januskinase (JAK) Inhibitoren
MAGICapp	Making GRADE an Irresistable Choice application
NIV	Nicht-invasive Beatmung
RCT	Randomisiert kontrollierte Studie
RoB	Risk of Bias
ROBINS-I	Risk of bias tool to assess non-randomized studies of interventions
SoC	Standard of Care

2 Geltungsbereich und Zweck der Leitlinie

2.1 Zielsetzung und Zielpopulation der Leitlinie

Diese Leitlinie verfolgt das Ziel, Empfehlungen zur zugrundeliegenden Pathophysiologie, Diagnostik und therapeutischen Strategien bei Patienten mit COVID-19 zu vermitteln. Die Leitlinie wendet sich an alle tätigen Ärzte und weitere Berufsgruppen, die Patienten mit COVID-19 betreuen. Zugleich soll sie als Orientierung für Personen und Organisationen dienen, die direkt oder indirekt mit diesem Thema befasst sind.

2.2 Adressaten der Leitlinie

Adressaten der Leitlinie sind mit der Behandlung von COVID-19 Patienten befasste Ärzte, insbesondere Anästhesisten, Infektiologen, Pneumologen, Gastroenterologen, Kardiologen, Internist*innen, Rheumatolog*innen, Kinderärzte, Nephrologen, Neurologen, Gerinnungsspezialisten, Angiologen, Palliativmediziner*innen, und Experten für Mikrobiologie/Hygiene sowie betroffene Patienten. Die Leitlinie dient zur Information für alle weiteren an der Versorgung Beteiligten.

2.3 Gültigkeitsdauer und Aktualisierungsverfahren

- Datum der letzten inhaltlichen Überarbeitung: 01/2024
- Gültigkeitsdauer der Leitlinie: bis November 2024

3 Zusammensetzung der Leitliniengruppe und Beteiligung von Interessengruppen

3.1 Koordination und Redaktion

- Prof. Dr. Stefan Kluge
- Prof. Dr. Nicole Skoetz

3.2 Beteiligte Fachgesellschaften und Betroffene/Patient*innenvertretung

Fachgesellschaft	Kürzel	Bisherige/r Mandatsträger/in
Patient*innenenvertretende		Reiner Haase
Deutsche Gesellschaft für Neurologie e.V.	DGN	Peter Berlit

Deutscher Rat für Wiederbelebung	GRC	Georg Trummer
Deutsche Gesellschaft für Hygiene und Mikrobiologie e.V.	DGHM	Christian Brandt
Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.	DGKJ	Florian Hoffmann
Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e. V.	DIVI	Uwe Janssens Gernot Marx
Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin	DGIIN	Christian Karagiannidis Stefan Kluge
Deutsche Gesellschaft für Kardiologie – Herz und Kreislaufforschung e.V.	DGK	Alexander Kersten
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten	DGVS	Marcin Krawczyk
Gesellschaft für Thrombose und Hämostaseforschung e.V.	GTH	Florian Langer
Deutsche Gesellschaft für Infektiologie e.V.	DGI	Miriam Stegemann
Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin	DGAI	Gernot Marx Henrik Bracht Gereon Schälte
Deutsche Gesellschaft für Angiologie	DGA	Oliver J. Müller
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin	DGP	Michael Pfeifer Klaus F. Rabe Tobias Welte Michael Westhoff
Deutsche Gesellschaft Für Innere Medizin	DGIM	Marcel Schorrlepp Michael Pfeifer
Deutsche Gesellschaft für Rheumatologie e.V.	DGRh	Christof Specker
Deutsche Gesellschaft für Nephrologie	DGfN	Julia Weinmann-Menke
Deutsche Gesellschaft für Palliativmedizin		Wiebke Nehls

4 Methodisches Vorgehen

4.1 Formulierung der Schlüsselfragen und Priorisierung von Endpunkten

Die Schlüsselfragen wurden im PICO-Format von der Leitliniengruppe zusammengetragen und wichtige therapeutische Fragestellungen nach klinischer Relevanz priorisiert. Die Endpunkte lehnen sich an die Vorgängerversionen der Leitlinie an und wurden von Koordinierenden der Leitlinie noch einmal begutachtet, jedoch nicht formal priorisiert.

4.2 Systematische Recherche, Auswahl der Evidenz

Für die Beantwortung der Schlüsselfragen dieser Leitlinienaktualisierung wurde auf den bisherigen Versionen aufgebaut. Eine erfahrene Informationsspezialistin führte systematische Recherchen pro Schlüsselfrage in verschiedenen relevanten Datenbanken ab dem letzten Suchdatum durch. Zunächst wurden pro festgelegter Schlüsselfrage nach randomisiert-kontrollierten Studien recherchiert. Bei mangelnder Studienlage wurden weitere Recherchen zu Observationsstudien ergänzt. Die einzelnen Literaturrecherchen mit Suchdatum, Flow Charts, Evidenztabellen und Bewertungen sind unter Überschrift 5 pro Schlüsselfrage zusammengefasst.

Sofern keine randomisierten-kontrollierten Studien identifiziert werden konnten, wurden nach Möglichkeit aktuelle, qualitativ hochwertige systematische Übersichtsarbeiten herangezogen. Die Qualitätsbewertung der identifizierten systematischen Übersichtsarbeiten erfolgt mit dem Bewertungsinstrument AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews). Bei hoher methodischer Qualität und inhaltlicher Übereinstimmung der definierten Schlüsselfrage, wurden die eingeschlossenen Einzelstudien in Evidenztabellen extrahiert und die Datensynthese, sofern möglich, für die Erstellung eines Evidenzprofils herangezogen. Bei Abwesenheit aktueller systematischer Reviews von hoher Qualität wurden Recherchen nach kontrollierten nicht-randomisierten Interventionsstudien durchgeführt.

Die identifizierten Studien wurden jeweils im zweistufigen Verfahren von wissenschaftlich Tätigen in enger Kooperation mit erfahrenen Kliniker*innen gesichtet und ausgewählt.

4.3 Datenextraktion und Bewertung des Verzerrungsrisikos

Die identifizierten Studien wurden systematisch in MS Excel Datenextraktionsformulare extrahiert. RCTs wurden mit dem Cochrane Risk of Bias 2 Tool bewertet, nicht-randomisierte Studien wären mit ROBINS-I oder einer ähnlich geeigneten Checkliste bewertet worden. Meta-analysen wurden mit der Software RevMan oder R erstellt.

4.4 Evidenzklassifikation nach GRADE und Evidence-to-Decision Framework

Die Bewertung der Studien erfolgte endpunktbezogen nach der GRADE (Grading of recommendations assessment, development and evaluation) Methodik. In die GRADE Bewertung gehen das Verzerrungsrisiko der einzelnen Studien (randomisierte Studien bewertet mit dem Cochrane Risk of Bias Tool bzw. nichtrandomisierte Studien mit dem ROBINS I Tool) die Heterogenität der Effektschätzer, die Direktheit der untersuchten Patientenpopulation, Intervention, Vergleich bzw. Endpunkte, die Präzision der Effektschätzer und die Wahrscheinlichkeit eines Publikationsbias ein. Die Bewertung ist aus den Evidenztabellen (Summary of findings tables) im Evidenzbericht ersichtlich. Die Qualität der Evidenz (Vertrauen in die Evidenz) wird nach GRADE eingeteilt in hoch/moderat/niedrig/sehr niedrig.

Als Basis für die Empfehlungsformulierung wurden definierte Entscheidungskriterien benutzt, basierend auf dem GRADE Evidence to Decision Framework (EtD). Die Bewertung erfolgte in der MAGICapp unter Benutzung der GRADE EtD Ansicht mit den Kriterien: Nutzen/Schaden, Abwägung/Sicherheit der Evidenz, Wertevorstellungen und Präferenzen von Patienten, Ressourcen, Equity (Zugangs- und Versorgungsgerechtigkeit), Akzeptanz und Machbarkeit. Die Kriterien wurden in vorbereitenden Sitzungen gemeinsam von den evidenzaufarbeitenden Kolleg*innen und Vertreter*innen der Leitliniengruppe bearbeitet. Alle Bewertungen für Kriterien, für die keine systematische recherchierte Evidenz vorlag, erfolgten auf Basis von subjektiven Einschätzungen.

5 Resultate nach Schlüsselfrage

Der Evidenzbericht beinhaltet all die Fragen, die bearbeitet wurden, auch wenn nicht alle Fragestellungen in positiven Empfehlungen resultierten.

5.1 Schlüsselfrage 1: Paxlovid und SoC vs. SoC alone

Autor*innen: Nina Kreuzberger

Es wurde ein systematisches Review zugrunde gelegt, das jeweils eine Studie zu ambulanten und stationären COVID-19 Patient*innen einschloss.

5.1.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.1.1.1 *Evidenzprofil 1: Outpatients*

Population: Outpatients with confirmed SARS-CoV-2 infection (at high risk of disease progression)

Intervention: Nirmatrelvir / ritonavir plus standard of care

Vergleichsintervention: Placebo plus standard of care

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** placebo + SoC	**Absolute Effektschätzer** paxlovid + SoC	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality, day 28	Relatives Risiko: 0.04 (CI 95% 0.0 - 0.68) Basierend auf Daten von 2224 patienter und 1 Studien[1]	**11** pro 1000	**0** pro 1000 Differenz: **11 weniger pro 1000** (CI 95% 11 weniger - 4 weniger)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[2]	Paxlovid plus standard of care may decrease all-cause mortality by day 28.
All-cause mortality, day 90	Relatives Risiko (CI 95% -)	pro 1000	pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at all-cause mortality by day 90.
Admission to hospital or death, day 28	Relatives Risiko: 0.13 (CI 95% 0.07 - 0.27) Basierend auf Daten von 2224 patienter und 1 Studien	**61** pro 1000	**8** pro 1000 Differenz: **53 weniger pro 1000** (CI 95% 57 weniger - 45 weniger)	**Niedrig** Due to serious risk of bias, Due to serious indirectness[3]	Paxlovid plus standard of care may decrease admission to hospital or death by day 28.
Symptom resolution	Relatives Risiko (CI 95% -)	pro 1000	pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at symptom resolution.
Adverse events, any grade during study period	Relatives Risiko: 0.95 (CI 95% 0.82 - 1.1) Basierend auf Daten von 2224 patienter und 1 Studien	**239** pro 1000	**227** pro 1000 Differenz: **12 weniger pro 1000** (CI 95% 43 weniger - 24 mehr)	**Moderat** Due to serious risk of bias[4]	Paxlovid plus standard of care probably has little or no effect on any grade adverse events.
Adverse events, grade 3-4[5] during study period	Relatives Risiko: 0.49 (CI 95% 0.34 - 0.69) Basierend auf Daten von 2224 patienter und 1 Studien	**83** pro 1000	**41** pro 1000 Differenz: **42 weniger pro 1000**	**Niedrig** Due to serious risk of bias, Due to serious imprecision[6]	Paxlovid plus standard of care may decrease the incidence of grade 3 to 4 adverse events.

		(CI 95% 55 weniger - 26 weniger)		
Serious adverse events suring study period	Relatives Risiko: 0.24 (CI 95% 0.15 - 0.41) Basierend auf Daten von 0 patienter und 1 Studien	**66** pro 1000 **16** pro 1000 Differenz: **50 weniger pro 1000** (CI 95% 56 weniger - 39 weniger)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[7]	Paxlovid plus standard of care may decrease the incidence of serious adverse events.
Post COVID19 condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at Post Covid19 condition.
Quality of life	Gemessen mit: Skala: - Höher ist besser	Mittelwert Mittelwert Differenz: **MD null kleiner**		No studies were found that looked at quality of life.

1. Systematic review [40] mit eingeschlossenen Studien: [38] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm.
2. Risiko für Bias: schwerwiegend. inappropriate analysis ((„All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Unzureichende Präzision: schwerwiegend. Low number of events;
3. Risiko für Bias: schwerwiegend. Inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Indirektheit: schwerwiegend. Differences between the outcomes of interest and those reported (COVID-19 related hospitalisation instead of all-cause hospitalisation);
4. Risiko für Bias: schwerwiegend. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status.");
5. undefined
6. Risiko für Bias: schwerwiegend. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
7. Risiko für Bias: schwerwiegend. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Unzureichende Präzision: schwerwiegend. few SAE other than hospitaliation or death;

5.1.1.2 *Evidenzprofil 2: Inpatients*

Population: Hospitalised patients

Intervention: Paxlovid plus standard of care

Vergleichsintervention: Standard of care alone

Endpunkt		Absolute Effektschätzer	Gewissheit der Evidenz	Zusammenfassung

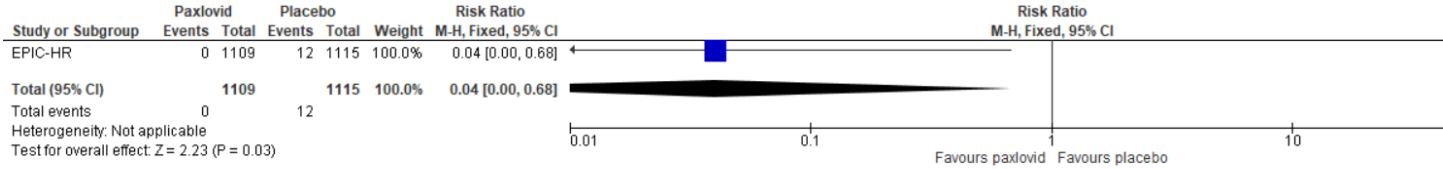
Zeitrahmen	**Ergebnisse und Messwerte**	SoC	Paxlovid + SoC	(Vertrauenswürdigkeit der Evidenz)	
Mortality, day 28	Relatives Risiko: 0.63 (CI 95% 0.21 - 1.86) Basierend auf Daten von 264 patienter und 1 Studien[1] Beobachtzungszeit 28 days	**61** pro 1000	**38** pro 1000 Differenz: **23 weniger pro 1000** (CI 95% 48 weniger - 52 mehr)	**Sehr niedrig** Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether paxlovid plus standard of care decreases or increases mortality by day 28.
IMV or death, day 28	Relatives Risiko (CI 95% -)				No studies were found that looked at need for IMV or death by day 28
Discharged alive	Relatives Risiko (CI 95% -)				No studies were found that looked at the number of participants discharged alive.
Serious adverse events	Relatives Risiko (CI 95% -)				No studies were found that looked at serious adverse events.
Adverse events	Relatives Risiko (CI 95% -)				No studies were found that looked at adverse events.
Post Covid-19 condition	Relatives Risiko (CI 95% -)				No studies were found that looked at post Covid-19 condition.
Quality of life	Gemessen mit: Skala: - Höher ist besser				No studies were found that looked at quality of life.

1. Systematic review [40] mit eingeschlossenen Studien: [39] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
2. Indirektheit: schwerwiegend. Differences between the population of interest and those studied: Atypical hospital population, WHO 2-4; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients;

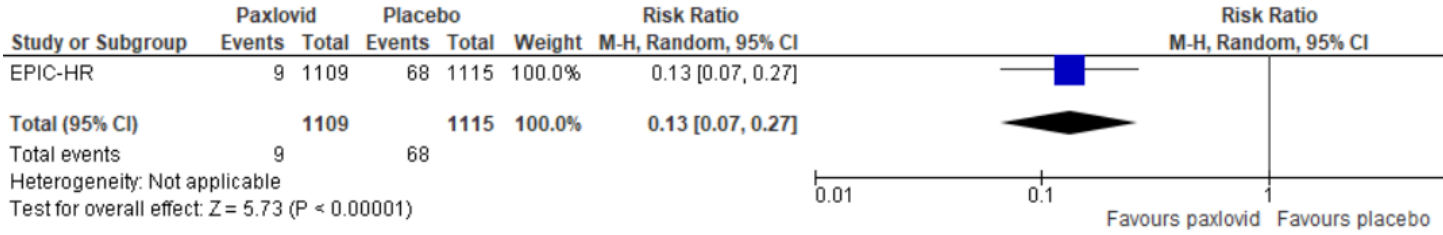
5.1.2 Analysen / Forest Plots

5.1.2.1 *Outpatients*

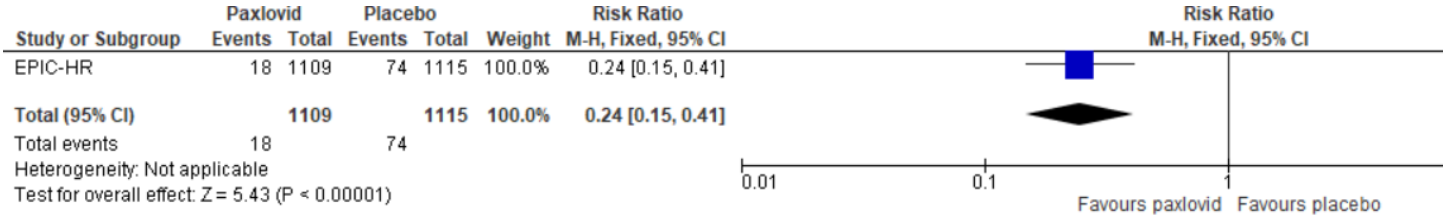
Mortality, day 28



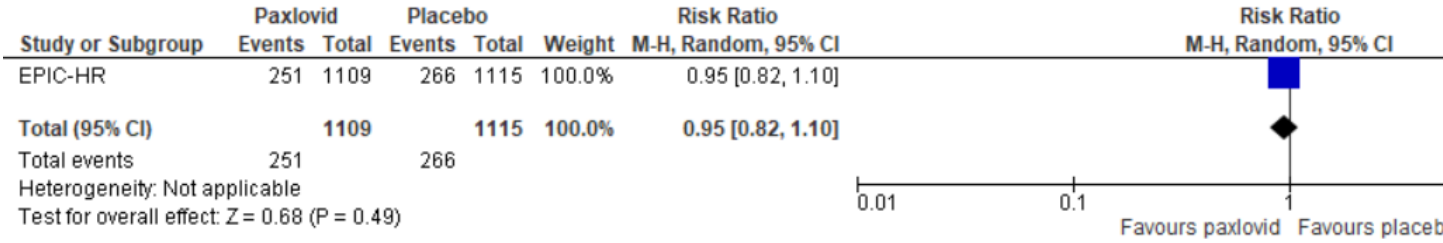
Admission to hospital or death, day 30



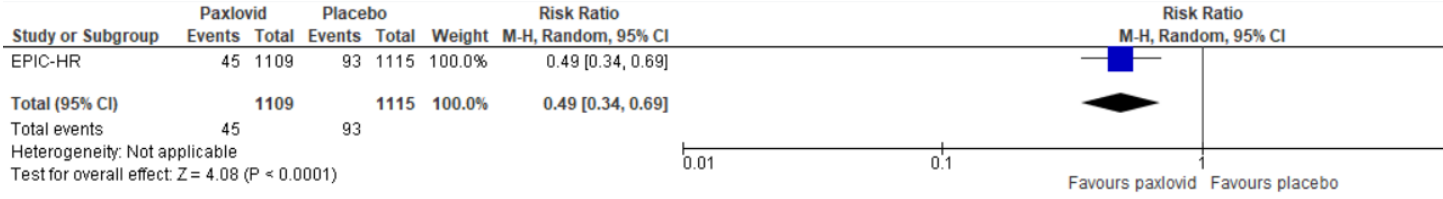
Serious adverse events



Adverse events, any grade

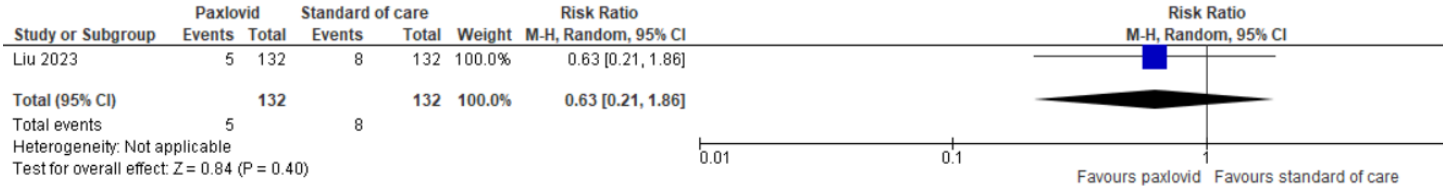


Adverse events, grade 3-4



5.1.2.2 *Inpatients*

Mortality, day 28



5.1.3 Referenzen der eingeschlossenen Studien

5.1.3.1 *RCT-Recherche*

Studien eingeschlossen im Cochrane Review: Reis S, Metzendorf MI, Kuehn R, Popp M, Gagyor I, Kranke P, Meybohm P, Skoetz N, Weibel S. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. Cochrane Database Syst Rev. 2022 Sep 20;9(9):CD015395. doi: 10.1002/14651858.CD015395.pub2. Update in: Cochrane Database Syst Rev. 2023

- Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R, Rusnak JM; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Apr 14;386(15):1397-1408. doi: 10.1056/NEJMoa2118542. Epub 2022 Feb 16. PMID: 35172054; PMCID: PMC8908851.
- Liu J, Pan X, Zhang S, Li M, Ma K, Fan C, Lv Y, Guan X, Yang Y, Ye X, Deng X, Wang Y, Qin L, Xia Z, Ge Z, Zhou Q, Zhang X, Ling Y, Qi T, Wen Z, Huang S, Zhang L, Wang T, Liu Y, Huang Y, Li W, Du H, Chen Y, Xu Y, Zhao Q, Zhao R, Annane D, Qu J, Chen D. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac. 2023 Apr;33:100694. doi: 10.1016/j.lanwpc.2023.100694. Epub 2023 Feb 6. PMID: 36777445; PMCID: PMC9899586.

Keine weiteren RCTs identifiziert.

5.1.3.2 *Kohorten-Recherche*

Nicht weiter verwendet.

5.1.4 Charakteristika der eingeschlossenen Studien

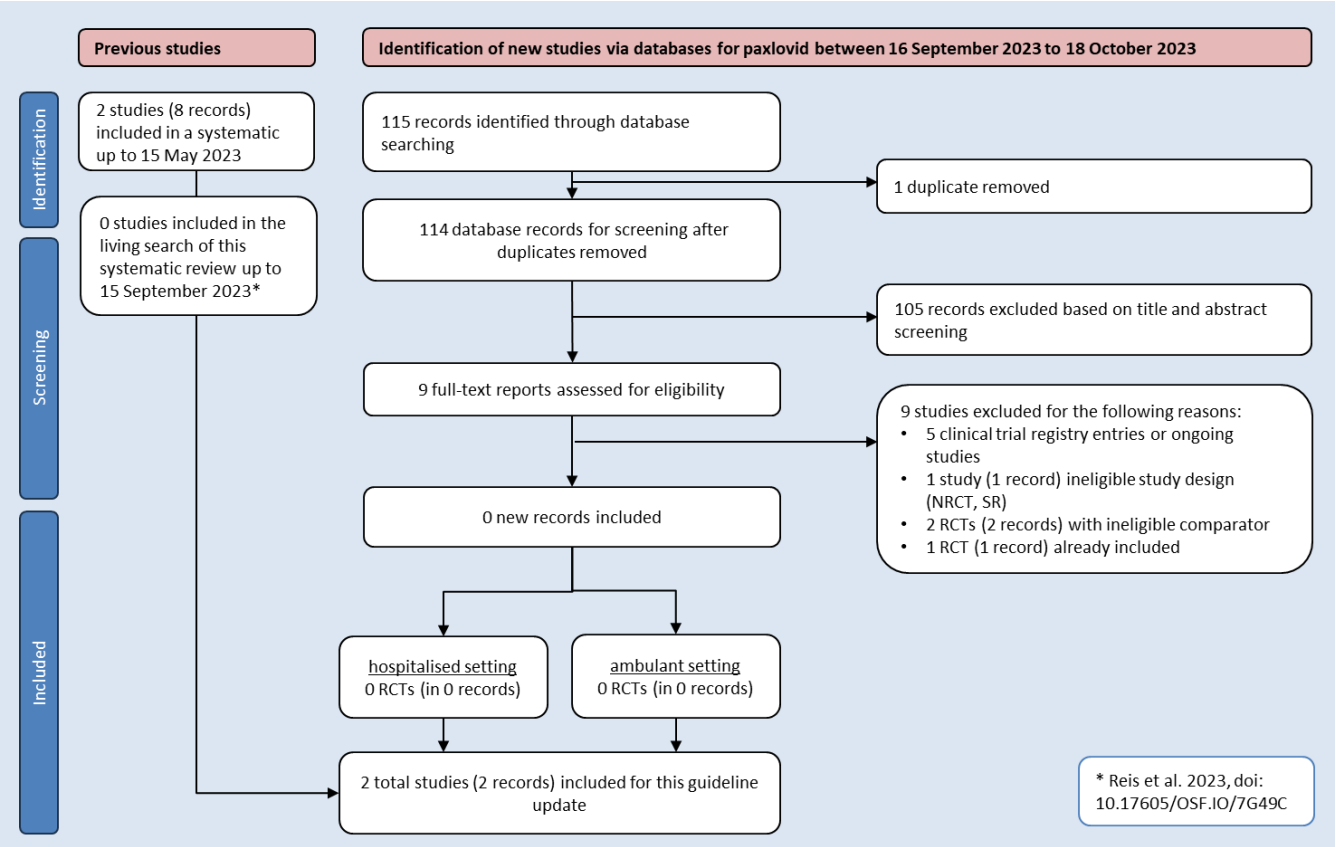
5.1.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodo
Reis 2023 Systematic review with MA	**Study design:** RCTs **Search time frame** From inception to 11 July 2022 **Sources:** ▪ Cochrane COVID-19 Study Register (CCSR)	**Intervention A** Nirmatrelvir/ Ritonavir + standard of care **Intervention B** Placebo, standard of care, or any other intervention	2 studies, one inpatient, one outpatient **Outpatient** *N = 2246* *Recruitment:* 16.07.2021 to 09.12.2021 worldwide *Age (median, range, years)*	**<u>Comparison 1: outpatients</u>** Number of studies: 1 Number of participants: 2246 **Critical outcomes:** ▪ All-cause mortality (at up tp day 28): HR 0.04 (95% CI 0.00 to 0.68) ▪ All-cause mortality (at up tp day 60): not reported ▪ New need for IMV or death within 28 days: not reported ▪ Admission to hospital or death: HR 0.13 (95% CI 0.07 to 0.27)	**Methodologic** **included studi** **using the Risk** *Outpatients:* All outcomes h concern regard due to an inap protocol analy *Inpatients:* No concerns, c outcome. **Evidence syntl**

	(comprises MEDLINE, Embase, clinicaltrials.gov, ICTRP, medRxiv, CENTRAL) ▪ Scopus ▪ WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** ▪ Confirmed SARS-CoV-2 infection ▪ PEP, PrEP nirmatrelvir/ritonavir ▪ Treatment with nirmatrelvir/ritonavir ▪ Any dose	fro treating COVID-19	▪ Exp: 45 (18 to 86) ▪ Plcb: 46.5 (18 to 88) *Sex (% female)* ▪ Exp: 49.5% ▪ Plcb: 48.3% *vaccination status*: 0% *Median time since SO:* ▪ Exp: 3.00 (0.00–7.00) ▪ Plcb: 3.00 (0.00–9.00) *At least one risk factor for severe disease:* All participants **Inpatients** *N = 264* *Recruitment:* 10.04.2022 to 19.05.2022, China *Age (mean, sd years)* ▪ Exp: 71.50 ± 11.61 ▪ Plcb: 69.20 ± 14.43 Sex (% female) ▪ Exp: 45.45% ▪ SoC: 46.97% *vaccination status*: ▪ Exp: 21.21% ▪ SoC: 28.78% *Median time since SO:* ▪ Exp: 3 (1, 5) ▪ SoC: 3 (2, 6) *At least one risk factor for severe disease:* All participants	▪ Serious adverse events at up to day 28: RR 0.24 (95% CI 0.15 to 0.42) ▪ Adverse events (any grade) at up to day 28: RR 0.95 (95% CI 0.82 to 1.10)	▪ ITT, safet (serious) a ▪ Random- case of he applicable study per **GRADE** ▪ Mortality ▪ Admissio death: lo ▪ SAE: Low ▪ AE, any g moderate All outcomes due to seriou admission to downgraded indirectness, imprecsion

5.1.5 Studienselektion: Flow Chart

5.1.5.1 *Flow chart für die RCT-Recherche*



5.1.6 Literaturrecherche

5.1.6.1 *Literaturrecherche für RCTs*

Date of search for all databases: 18.10.2023			
Database/Register	**Search**	**Update Search**	**Update Search**
CCSR	5 references		
WOS (SCI+ECI) ab 06.10.2023 Scopus	110		
Total	**115**		
Total (after deduplication)	**114**		

Grundlage für diese Fragestellung ist das folgende Living systematische Cochrane Review „Nirmatrelvir combined with ritonavir for preventing and treating COVID-19“ mit regelmäßigen Aktualisierungssuchen (verfügbar unter https://osf.io/7g49c/). Für die vorliegende Version wurde das Dokument vom 27.09.2023 mit Suchdatum bis 15.09.2023 genutzt, die Aktualisierungssuche lief zwischen dem 16.09.2023 und dem 18.10.2023.

Cochrane COVID-19 Study Register (CCSR)

Search string: "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

Results available:

Report results

Study characteristics:

1) "Intervention assignment": “Randomised” OR "Unclear"

2) "Study design": "Parallel/Crossover" OR "Unclear" OR

Scopus (via Elsevier)

TITLE-ABS ("PF-08208;07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*)

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") AND PUBYEAR = 2023

AND (LIMIT-TO (DOCTYPE , "ar"))

5.1.6.2 *Literaturrecherche für Kohortenstudien*

Date of search for all databases: 18.10.2023				
Database/Register	**Search**	**Update Search**	**Update Search**	**Update Search**
CCSR	201 references			
Scopus	138			
WHO COVID-19 DB*	150			
Total	**489**			
Total (after deduplication)	**382 (108 included CT.gov und preprints)**			

*The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.

Cochrane COVID-19 Study Register (CCSR)

Search string**:** "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

Results available:

report results

Study characteristics:

1) "Study design": case series/case control/cohort

Scopus (via Elsevier)

TITLE-ABS ("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND TITLE-ABS ((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*)

AND PUBYEAR = 2022 OR PUBYEAR = 2023

AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND ((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*) AND year_cluster:("2022" OR "2023")

5.2 Schlüsselfrage 2: Remdesivir und SoC vs. SoC alone/with Placebo

Autor*innen: Claire Iannizzi

Es wurden insgesamt 12 RCTs identifiziert und eingeschlossen, davon sind 2 RCTs zur milden COVID-19 Erkrankung (ambulante Behandlungssituation) und 10 RCTs zur schweren COVID-19 Erkrankung (stationäre Behandlungssituation). Zudem wurden 18 Kohortenstudien identifiziert, allerdings wurden diese weder bewertet noch die Evidenz aufbereitet.

5.2.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.2.1.1 *PICO 1. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild to moderate disease, according to the WHO clinical progression scale (WHO 2 to 3)*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Remdesivir + Standard of Care

Vergleichsintervention: Standard of Care (with or without placebo)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo or Standard of Care alone	 Remdesivir + SOC	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Time to symptom alleviation at day 14	Hazard ratio: 1.41 (CI 95% 0.73 - 2.72) Basierend auf Daten von 126 patienter und 1 Studien[1]	**250** pro 1000	**333** pro 1000 Differenz: **83 mehr pro 1000** (CI 95% 61 weniger - 293 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision[2]	We are uncertain whether remdesivir increases or decreases time to symptom alleviation.
All-cause mortality at up to day 28[3]	Relatives Risiko (CI 95% -)	pro 1000	**0** pro 1000	**Niedrig** Due to very serious imprecision[4]	There were no events observed, thus it was not possible to determine

	Basierend auf Daten von 562 patienter und 1 Studien	Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)		whether Remdesivir makes a difference in 28-day mortality.
Hospitalization or death by day 28	Relatives Risiko: 0.28 (CI 95% 0.11 - 0.75) Basierend auf Daten von 562 patienter und 1 Studien[5]	**64** pro 1000 **18** pro 1000 Differenz: **46 weniger pro 1000** (CI 95% 57 weniger - 16 weniger)	**Moderat** Due to serious imprecision[6]	Remdesivir probably decreases the rate of hospitalisation or death by day 29.
Adverse events (any grade) at up to day 28	Relatives Risiko: 0.91 (CI 95% 0.76 - 1.1) Basierend auf Daten von 562 patienter und 1 Studien[7]	**463** pro 1000 **421** pro 1000 Differenz: **42 weniger pro 1000** (CI 95% 111 weniger - 46 mehr)	**Moderat** Due to serious imprecision[8]	Remdesivir probably has little or no difference on the risk of adverse events (any grade) at up to day 28.
Serious adverse events at up to day 28	Relatives Risiko: 0.29 (CI 95% 0.12 - 0.72) Basierend auf Daten von 698 patienter und 2 Studien[9]	**60** pro 1000 **17** pro 1000 Differenz: **43 weniger pro 1000** (CI 95% 53 weniger - 17 weniger)	**Niedrig** Due to serious indirectness, Due to serious imprecision[10]	Remdesivir may decrease the risk of serious adverse events at up to day 28.

1. Systematic review [37] . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
2. Risiko für Bias: schwerwiegend. Difference in pre-defined outcome and measurement.; Indirektheit: schwerwiegend. Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); Unzureichende Präzision: schwerwiegend. Low number of patients, Wide confidence intervals, Only data from one study;
3. undefined
4. Unzureichende Präzision: sehr schwerwiegend. Only data from one study, Low number of patients;
5. Systematic review [37] mit eingeschlossenen Studien: Gottlieb 2021 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm
6. Unzureichende Präzision: schwerwiegend. Wide confidence intervals and optimal information size not met. ;
7. Systematic review [37] mit eingeschlossenen Studien: Gottlieb 2021 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm
8. Unzureichende Präzision: schwerwiegend. Only data from one study, Wide confidence intervals;
9. Systematic review [37] mit eingeschlossenen Studien: [75], Jittamala 2023 (PLATCOV), Gottlieb 2021 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm.
10. Indirektheit: schwerwiegend. due to huge overlap with COVID-19 symptoms, already considered in hospitalisation or death; Unzureichende Präzision: schwerwiegend. Low number of patients;

5.2.1.2 *PICO 2. Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Remdesivir + Standard of Care

Vergleichsintervention: Standard of Care (with or without placebo)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** SOC	Remdesivir	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**

All-cause mortality at up to day 28	Relatives Risiko: 0.91 (CI 95% 0.83 - 1.01) Basierend auf Daten von 10171 patienter und 5 Studien[1]	**138** pro 1000 **126** pro 1000 Differenz: **12 weniger pro 1000** (CI 95% 23 weniger - 1 mehr)	**Moderat** Due to serious imprecision[2]	Remdesivir probably makes little or no difference to all-cause mortality at up to day 28.
All-cause mortality at up to day 60	Relatives Risiko: 0.85 (CI 95% 0.69 - 1.05) Basierend auf Daten von 1281 patienter und 1 Studien[3]	**235** pro 1000 **200** pro 1000 Differenz: **35 weniger pro 1000** (CI 95% 73 weniger - 12 mehr)	**Moderat** Due to serious risk of bias[4]	Remdesivir probably makes little or no difference to all-cause mortality up to 60 days.
In-hospital mortality at up to day 150	Relatives Risiko: 0.93 (CI 95% 0.84 - 1.03) Basierend auf Daten von 8275 patienter und 1 Studien[5]	**156** pro 1000 **145** pro 1000 Differenz: **11 weniger pro 1000** (CI 95% 25 weniger - 5 mehr)	**Moderat** Due to serious risk of bias[6]	Remdesivir probably makes little or no difference to in-hospital mortality up to 150 days.
Clinical improvement: participants discharged alive at up to day 28	Relatives Risiko: 1.11 (CI 95% 1.06 - 1.17) Basierend auf Daten von 2514 patienter und 4 Studien[7]	**617** pro 1000 **685** pro 1000 Differenz: **68 mehr pro 1000** (CI 95% 37 mehr - 105 mehr)	**Moderat** Due to serious risk of bias[8]	Remdesivir probably increases the chance of clinical improvement slightly.
Clinical worsening: new need for invasive mechanical ventilation/death at up to day 28	Relatives Risiko: 0.7 (CI 95% 0.52 - 0.94) Basierend auf Daten von 683 patienter und 1 Studien[9]	**253** pro 1000 **177** pro 1000 Differenz: **76 weniger pro 1000** (CI 95% 121 weniger - 15 weniger)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[10]	Remdesivir may decrease the risk of clinical worsening: new need for invasive mechanical ventilation or death at up to day 28.
Time to hospital discharge	Hazard ratio: 1.06 (CI 95% 0.93 - 1.2) Basierend auf Daten von 1225 patienter und 2 Studien[11]	**618** pro 1000 **639** pro 1000 Differenz: **21 mehr pro 1000** (CI 95% 27 weniger - 67 mehr)	**Moderat** Due to serious imprecision[12]	Remdesivir probably increases the chance of clinical improvement slightly.
Adverse events (any grade) at day 28	Relatives Risiko: 1.04 (CI 95% 0.92 - 1.18) Basierend auf Daten von 2498 patienter und 4 Studien[13]	**579** pro 1000 **602** pro 1000 Differenz: **23 mehr pro 1000** (CI 95% 46 weniger - 104 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency[14]	We are very uncertain whether remdesivir increases or decreases the risk for adverse events (any grade).
Serious adverse events at day 28	Relatives Risiko: 0.84 (CI 95% 0.65 - 1.07) Basierend auf Daten von 2498 patienter und 4 Studien[15]	**273** pro 1000 **229** pro 1000 Differenz: **44 weniger pro 1000** (CI 95% 96 weniger - 19 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[16]	Remdesivir may have little or no effect on the risk of serious adverse events.

Quality of life (EQ-VAS)[17]	Basierend auf Daten von 208 patienter und 1 Studien[18]	One study reported the median of the EQ-VAS Quality of life score (patient-reported outcome measure of quality of life on a scale from 0 to 100): Median EQ-VAS was 75.5 (IQR 67.8–85.0) in the remdesivir and 80 (IQR 67.5–86.5) in SoC group (ordered logistic regression OR 0.83, 95% CI 0.49–1.40).	**Sehr niedrig** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness[19]	We are very uncertain whether remdesivir has any effect on quality of life.
Long COVID symptoms[20]	Basierend auf Daten von 208 patienter und 1 Studien[21]	One study reported that regarding the 21 potential long-COVID symptoms they assessed, there were no statistically significant differences between treatment arms.	**Sehr niedrig** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness[22]	We are very uncertain whether remdesivir has any effect on Long COVID symptoms.

1. Systematic review [36] mit eingeschlossenen Studien: Wang 2020, WHO Solidarity Trial Consortium 2022, Mohiuddin 2022, Spinner 2020, Beigel 2020, [41], [41] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
2. Risiko für Bias: keine. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Unzureichende Präzision: schwerwiegend. Because the 95% confidence interval includes both benefits and harms.;
3. Systematic review [36] mit eingeschlossenen Studien: WHO Solidarity Canada 2022 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
4. Risiko für Bias: schwerwiegend. Incomplete and/or missing outcome data;
5. Systematic review [36] mit eingeschlossenen Studien: WHO Solidarity Trial Consortium 2022 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
6. Risiko für Bias: schwerwiegend. Selective outcome reporting;
7. Systematic review [36] mit eingeschlossenen Studien: Wang 2020, WHO Solidarity France 2021, Beigel 2020, Spinner 2020 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
8. Risiko für Bias: schwerwiegend. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
9. Systematic review [36] mit eingeschlossenen Studien: WHO Solidarity France 2021 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
10. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Unzureichende Präzision: schwerwiegend. Low number of patients, Only data from one study;
11. Systematic review [36] . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
12. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
13. Systematic review [36] mit eingeschlossenen Studien: WHO Solidarity France 2021, Spinner 2020, Wang 2020, Beigel 2020 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
14. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, one trial stopped earlier than scheduled, resulting in potential for overestimating benefits, due to inappropriate patient population, due to competing risk of death; Inkonsistenz: schwerwiegend. The magnitude of statistical heterogeneity was high, with I^2 of 68 %. The direction of the effect is not consistent between the included studies.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals and the 95% confidence interval includes the zero effect line;
15. Systematic review [36] mit eingeschlossenen Studien: WHO Solidarity France 2021, Spinner 2020, Wang 2020, Beigel 2020 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
16. Risiko für Bias: schwerwiegend. One trial stopped earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for

performance bias, due to inappropriate patient population, due to competing risk of death, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals and the 95% confidence interval includes both benefits and harms.;

17. EQ-VAS: patient-reported outcome measure of quality of life on a scale from 0 to 100
18. Primary study Referenzen [42].
19. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); Unzureichende Präzision: schwerwiegend. Only data from one study;
20. Infection affected quality of life in the last month as: 0 = No symptoms of infection, 1 = Slight harm, 2 = Moderate harm, 3 = Severe harm
21. Primary study Referenzen [42].
22. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); Unzureichende Präzision: schwerwiegend. Only data from one study;

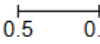
5.2.2 Analysen / Forest Plots

5.2.2.1 *PICO 1. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild to moderate disease, according to the WHO clinical progression scale (WHO 2 to 3)*

All-cause mortality at up to day 28

	Remdesivir and standard care		Standard care (plus/minus placebo)			Risk ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-**
Gottlieb 2021	0	279	0	283		Not estimable	
Total (95% CI)		**279**		**283**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

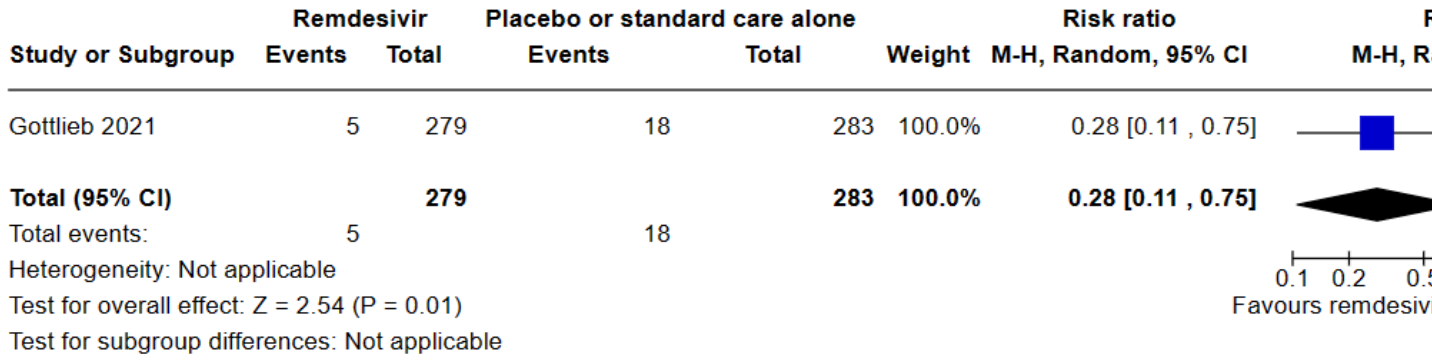


Time to symptom alleviation at day 14

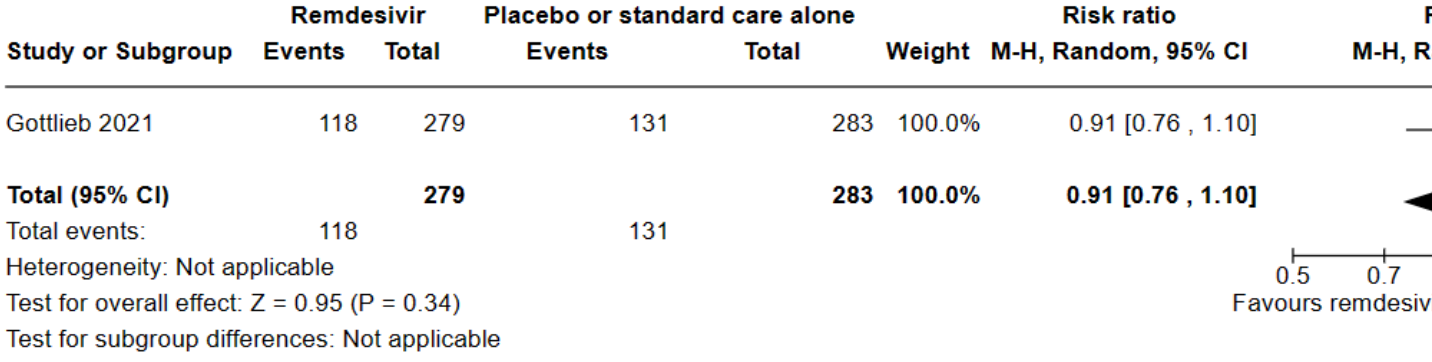
			Remdesivir and standard care	Standard care (plus/minus placebo)		Hazard ratio	
Study or Subgroup	**log[HR]**	**SE**	**Total**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV**
Gottlieb 2021	0.34359	0.332723	66	60	100.0%	1.41 [0.73 , 2.71]	
Total (95% CI)			**66**	**60**	**100.0%**	**1.41 [0.73 , 2.71]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable

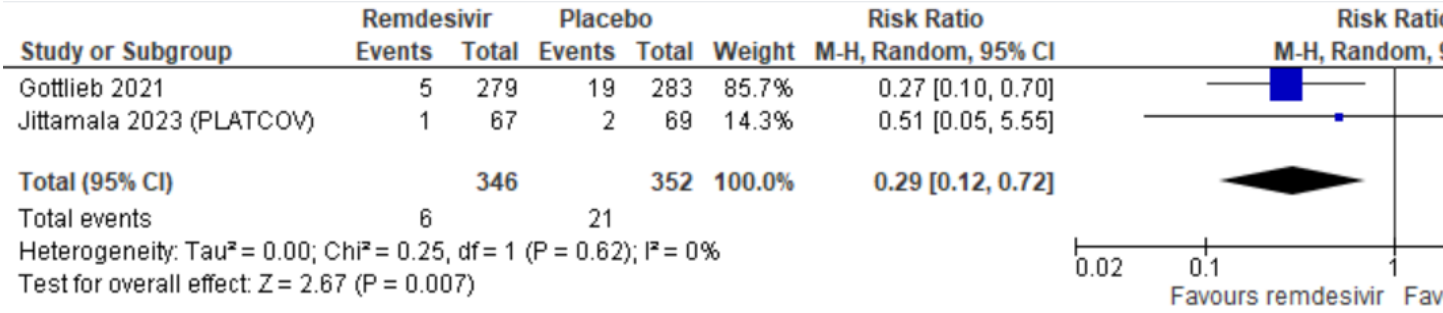
Hospitalization or death by day 28



Adverse events (any grade) at up to day 28

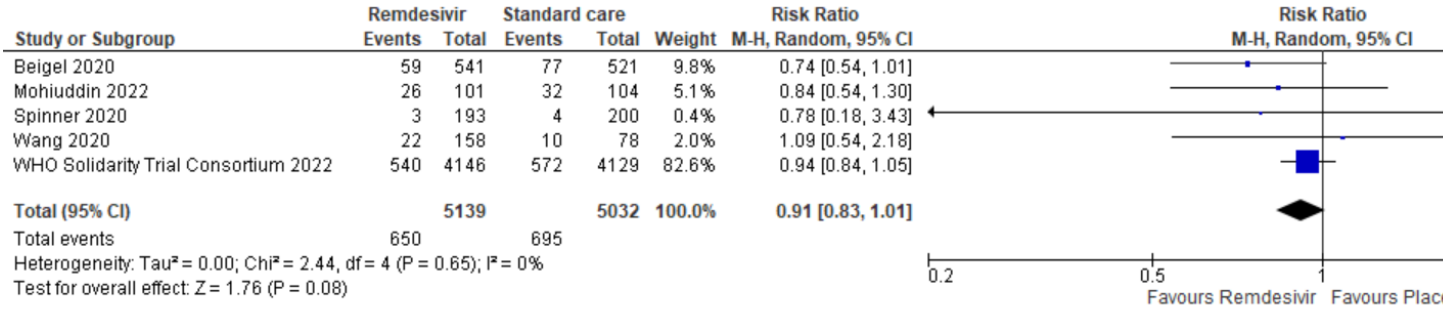


Serious adverse events at up to day 28



5.2.2.2 *PICO 2. Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)*

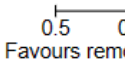
All-cause mortality at up to day 28



All-cause mortality at up to day 60

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
WHO Solidarity Canada 2022	127	634	152	647	100.0%	0.85 [0.69 , 1.05]
Total (95% CI)		**634**		**647**	**100.0%**	**0.85 [0.69 , 1.05]**
Total events:	127		152			

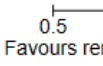
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



In-hospital mortality at up to day 150

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
WHO Solidarity Trial Consortium 2022	602	4146	643	4129	100.0%	0.93 [0.84 , 1.03]
Total (95% CI)		**4146**		**4129**	**100.0%**	**0.93 [0.84 , 1.03]**
Total events:	602		643			

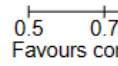
Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable



Clinical improvement: participants discharged alive at up to day 28

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Beigel 2020	357	541	294	521	26.3%	1.17 [1.06 , 1.29]
Spinner 2020	178	193	170	200	48.5%	1.09 [1.01 , 1.17]
Wang 2020	92	150	45	77	4.8%	1.05 [0.84 , 1.32]
WHO Solidarity France 2021	265	414	241	418	20.5%	1.11 [1.00 , 1.24]
Total (95% CI)		**1298**		**1216**	**100.0%**	**1.11 [1.06 , 1.17]**
Total events:	892		750			

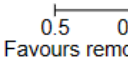
Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)
Test for subgroup differences: Not applicable



Clinical worsening: new need for invasive mechanical ventilation/death at up to day 28

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
WHO Solidarity France 2021	60	339	87	344	100.0%	0.70 [0.52 , 0.94]
Total (95% CI)		**339**		**344**	**100.0%**	**0.70 [0.52 , 0.94]**
Total events:	60		87			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable



Time to hospital discharge

Study or Subgroup	log[HR]	SE	Remdesivir and standard care Total	Standard care (plus/minus placebo) Total	Weight	Hazard ratio IV, Random, 95% CI
Spinner 2020	0.10436	0.107189	193	200	36.5%	1.11 [0.90 , 1.37]
WHO Solidarity France 2021	0.029559	0.08124	414	418	63.5%	1.03 [0.88 , 1.21]
Total (95% CI)			**607**	**618**	**100.0%**	**1.06 [0.93 , 1.20]**

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

0.5
Favours

Adverse events (any grade) at day 28

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Beigel 2020	305	532	323	516	31.0%	0.92 [0.83 , 1.01]
Spinner 2020	113	193	93	200	20.6%	1.26 [1.04 , 1.52]
Wang 2020	102	155	50	78	19.5%	1.03 [0.84 , 1.26]
WHO Solidarity France 2021	241	406	236	418	28.9%	1.05 [0.94 , 1.18]
Total (95% CI)		**1286**		**1212**	**100.0%**	**1.04 [0.92 , 1.18]**
Total events:	761		702			

Heterogeneity: Tau² = 0.01; Chi² = 9.41, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

0.5
Favours remd

Serious adverse events at day 28

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Beigel 2020	130	532	163	516	37.4%	0.77 [0.64 , 0.94]
Spinner 2020	10	193	18	200	9.1%	0.58 [0.27 , 1.22]
Wang 2020	28	155	20	78	16.3%	0.70 [0.43 , 1.17]
WHO Solidarity France 2021	135	406	130	418	37.2%	1.07 [0.88 , 1.30]
Total (95% CI)		**1286**		**1212**	**100.0%**	**0.84 [0.65 , 1.07]**
Total events:	303		331			

Heterogeneity: Tau² = 0.03; Chi² = 7.37, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable

Favours remd

5.2.3 Referenzen der eingeschlossenen Studien

- Grundeis F, Ansems K, Dahms K, Thieme V, Metzendorf M-I, Skoetz N, et al. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev 2023;1(1):CD014962.
- Jittamala P, Schilling WHK, Watson JA, Luvira V, Siripoon T, Ngamprasertchai T, et al. Clinical Antiviral Efficacy of Remdesivir in Coronavirus Disease 2019: An Open-Label, Randomized Controlled Adaptive Platform Trial (PLATCOV). The Journal of infectious diseases 2023;228(10):1318-1325.
- Mohiuddin Chowdhury ATM, Kamal A, Abbas KU, Talukder S, Karim MR, Ali MA, et al. Efficacy and Outcome of Remdesivir and Tocilizumab Combination Against Dexamethasone for the Treatment of Severe COVID-19: A Randomized Controlled Trial. Frontiers in pharmacology 2022;13:690726.

- Nevalainen OPO, Horstia S, Laakkonen S, Rutanen J, Mustonen JMJ, Kalliala IEJ, et al. Effect of remdesivir post hospitalization for COVID-19 infection from the randomized SOLIDARITY Finland trial. Nature communications 2022;13(1):6152.

5.2.4 Charakteristika der eingeschlossenen Studien

5.2.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

5.2.4.2 *PICO 1. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild to moderate disease, according to the WHO clinical progression scale (WHO 2 to 3)*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodis
Grundeis, 2023a Systematic review with MA	**Study design** Living systematic review **Search time frame** Inception of each database to 31.05.2022 **Sources:** ▪ Cochrane COVID-19 Study Register (CCSR) (PubMed, Embase, ClinicalTrials, WHO ICTRP, medRxiv, CENTRAL) ▪ Web of Science Clarivate (Science Citation Index Expanded, Emerging Sources Citation Index) ▪ WHO COVID-19 Global literature on coronavirus disease	**Intervention A** ▪ Remdesivir and standard care for the treatment of SARS-CoV-2 infection **Intervention B** ▪ Standard care (plus/minus placebo). ▪ Standard care in both arms should be similar.	1 study on 562 patients **Descriptive statistics:** Setting: outpatient Age: mean age 50 years, included adolescents younger than 18 Gender: 52.10% male Severity of illness at beginning: mild	**Comparison X:** NUMBER OF STUDIES: 1 NUMBER OF PARTICIPANTS: 562 **Critical outcomes:** ▪ All-cause mortality (at up to day 28): no events observed, therefore not estimable N=562 in 1 RCT) ▪ Clinical improvement: symptom alleviation at up to day 14: 250 per 1000 in comparison group, Difference: 61 fewer to 289 more (HR 1.41, CI 95% 0.73 to 2.71, N=126 in 1 RCT, very low certainty) ▪ Clinical worsening: admission to hospital or death at up to day 28: 64 per 1000 in comparison group, Difference: 57 fewer to 16 fewer (RR 0.28, CI 95% 0.11 to 0.75, N=562 in 1 RCT, moderate certainty) ▪ Quality of life: nicht berichtet ▪ Serious adverse events at up to day 28: 67 per 1000 in comparison group, Difference: 60 fewer to 20 fewer (RR 0.27, CI 95% 0.10 to 0.70, N=562 in 1 RCT, low certainty) ▪ Adverse events (any grade) at up to day 28: 463 per 1000 in comparison group, Difference: 111 fewer to 46 more (RR 0.91, CI 95% 0.76 to 1.10, N=562 in 1 RCT, moderate certainty) **Additional outcomes:**	**Methodologica** **included studi** **using GRADE t** **Evidence synth** ▪ ITT, safety (serious) a ▪ Random-e due to het populatio **GRADE** ▪ All-cause to day 28: ▪ Clinical im symptom to day 14: risk of bia imprecisio ▪ Clinical wo admission death at u moderate imprecisio ▪ Serious ad low due to (wide CIs) ▪ Adverse e grade): m imprecisio

	Eligibility criteria **Study type:** randomized controlled trials ▪ **Participants:** adults with a confirmed diagnosis of COVID-19 (as described in the study) without exclusion of any studies based on gender, ethnicity, disease severity, or setting. ▪ The review excluded studies evaluating remdesivir against other coronavirus diseases such as SARS or MERS, or other viral diseases, such as ebola. ▪ If studies enrolled populations with or exposed to mixed viral diseases, the review authors had planned to only include these if study authors provided			▪ Severity: Non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19	

	subgroup data for SARS-CoV-2 infection.				

5.2.4.2.1 PICO 2. Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodis
Grundeis, 2023b Systematic review with MA	**Study design** Living systematic review **Search time frame** Inception of each database to 31.05.2022 **Sources:** ▪ Cochrane COVID-19 Study Register (CCSR) (PubMed, Embase, ClinicalTrials, WHO ICTRP, medRxiv, CENTRAL) ▪ Web of Science Clarivate (Science Citation Index Expanded, Emerging Sources Citation Index) ▪ WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** **Study type:** randomized controlled trials	**Intervention A** ▪ Remdesivir and standard care for the treatment of SARS-CoV-2 infection **Intervention B** ▪ Standard care (plus/minus placebo). ▪ Standard care in both arms should be similar.	8 studies on 10656 patients **Descriptive statistics:** Setting: hospitalized Age: mean age 60.9 years Gender: 65.0% male Severity of illness at beginning: moderate – high/critical	**Comparison X:** NUMBER OF STUDIES: 8 NUMBER OF PARTICIPANTS: 10656 **Critical outcomes:** ▪ All-cause mortality (at up to day 28): 108 per 1000 in comparison group, Difference: 8 fewer per 1000 (RR 0.93, CI 95% 0.81 to 1.06, N=7142 in 4 RCTs, I^2 = 0%, moderate certainty) ▪ All-cause mortality (at up to day 60): 235 per 1000 in comparison group, Difference: 35 fewer per 1000 (RR 0.85, CI 95% 0.69 to 1.05, N=1281 in 1 RCT, moderate certainty) ▪ In-hospital mortality (at up to day 150): 156 per 1000 in comparison group, Difference: 11 fewer per 1000 (RR 0.93, CI 95% 0.84 to 1.03, N=8275 in 1 RCT, moderate certainty) ▪ Clinical improvement participants discharges alive (at up to day 28): 617 per 1000 in comparison group, Difference: 68 more per 1000 (RR 1.11, CI 95% 1.06 to 1.17, N=2514 in 4 RCTs, I^2 = 0%, moderate certainty) ▪ Clinical worsening: new need for IMV or death within 28 days: 544 per 1000 in comparison group, Difference: 135 fewer per 1000 (HR 0.67, CI 95% 0.54 to 0.82, N=1734 in 2 RCTs, I^2 = 0%, moderate certainty) ▪ Adverse events (any grade) at up to day 28: 579 per 1000 in comparison	**Methodologica** **included studi** **using GRADE t** **Evidence synth** ▪ ITT, safety (serious) a ▪ Random-e due to het populatio **GRADE** ▪ All-cause to day 28: to impreci ▪ All-cause to day 60: to impreci informatio reached) ▪ In-hospita moderate of bias (se reporting) ▪ Clinical im participan alive: mod high risk o blinding) ▪ Clinical wo need for I moderate of bias (no

	Participants: ▪ adults with a confirmed diagnosis of COVID-19 (as described in the study) without exclusion of any studies based on gender, ethnicity, disease severity, or setting. ▪ The review excluded studies evaluating remdesivir against other coronavirus diseases such as SARS or MERS, or other viral diseases, such as ebola ▪ If studies enrolled populations with or exposed to mixed viral diseases, the review authors had planned to only include these if study authors provided subgroup data for SARS-CoV-2 infection.			group, Difference: 23 more per 1000 (RR 1.04, CI 95% 0.92 to 1.18, N=2498 in 4 RCTs, I^2 = 68%, low certainty) ▪ Serious adverse events at up to day 28: 273 per 1000 in comparison group, Difference: 44 fewer per 1000 (RR 0.84, CI 95% 0.65 to 1.07, N=2498 in 4 RCT, I^2 = 59%, low certainty) **Additional outcomes:** ▪ All-cause mortality, time to event: HR 0.88, 95% CI 0.67 to 1.16, N=6513 in 2 RCTs, I^2 = 57%) ▪ Quality of life: not reported ▪ Adverse events grade 3 to 4, at up to day 28: 39 fewer per 1000 (RR 0.92, 95% CI 0.84 to 1.01, N=2498 in 4 RCTs, I^2 = 0%) ▪ Ventilator-free days: mean difference 1.90, 95% CI 0.61 to 3.19; P value = 0.004; N=1281 in 1 RCT	▪ Serious ad low die to (wide CIs) bias (no b ▪ Adverse e grade): lo imprecisio high risk o blinding)

5.2.4.3 *Charakteristika der zusätzlich eingeschlossenen Studien*

5.2.4.3.1 Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Jittamala 2023 (PLATCOV) RCT Platform trial	**Sample size:** N = 131 pts. (337 pts. Planned: 136 Remdesivir or SOC alone and 201 for other interventions) **Enrolment period:** 30.09.2021 to 10.06.2022 (remdesivir enrollment was stopped as the prespecified success margin had been reached) **Inclusion criteria:** ▪ Previously healthy adults aged between 18 and 50 years if they had had early symptomatic COVID-19 (i.e., reported symptoms for ≤4 days), oxygen saturation ≥96%, were unimpeded in activities of daily living, and gave fully informed consent. ▪ SARS-CoV-2 positivity was defined either as a nasal lateral flow antigen test that became positive within 2 minutes (STANDARD Q COVID-19 Ag Test, SD Biosensor, Suwon-si, Korea) or a positive polymerase chain reaction (PCR) test within the previous 24 hours with a cycle threshold value <25 (all viral gene targets), both suggesting high viral loads. **Days since symptom onset (mean, SD):** ▪ Exp: 2.4 (0.8) ▪ Ctrl: 2.2 (0.7) **<u>Characteristics</u>** **Age (mean, SD)** ▪ Exp: 30.1 (8.2)	**Experimental:** ▪ intravenous remdesivir plus optimized standard of care (SOC) ▪ Dose: over 60 minutes (reconstituted & added to 250 mL 0.9% saline) in an initial adult dose of 200 mg, followed by 100 mg once daily for 4 days to complete a 5-day course ▪ N = 67 **Control:** ▪ optimized standard of care (SOC) alone ▪ N = 64	Viral clearance: expressed as a slope coefficient and estimated under a Bayesian hierarchical linear model fitted to the daily log10 viral load measurements between days 0 and 7 (18 measurements per patient), using weakly informative priors and treating non-detectable viral loads (cycle threshold value ≥40) as left censored	Relative to the control arm, of oropharyngeal virus in pat randomized to remdesivir wa faster (95% CrI, 18%–73%; pr of >12.5% acceleration: 0.99 The median estimated viral c half-lives under the linear mo 12.8 (range, 4.8–50.0) hours remdesivir arm and 18.0 (ran 46.7) hours in the contempo control arm
			All cause hospitalization for clinical deterioration (day 28)	Not reported
			Adverse events >/= grade 3	Exp: 1/67 Ctrl: 3/69
			Serious adverse events	Exp: 1/67 Ctrl: 3/69 Two patients in the control a in the remdesivir arm had asymptomatic raised creatin phosphokinase levels (>10 ti upper limit of normal) attribu COVID-19–related skeletal m damage. There were no trea related SAEs.

	▪ Ctrl: 30.1 (6.5) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR			

5.2.4.3.2 Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Nevalainen 2022 (Solidarity Finland) RCT, NCT04978259	**Sample size:** N baseline = 208 pts. (208 pts. planned) N after 1 years = 181 **Enrolment period:** ▪ 23 July 2020 to 27 January 2021 **Inclusion criteria:** ▪ Adult patients, 18 years and older ▪ Laboratory-confirmed SARS-CoV-2 infection ▪ Admitted to the hospital ward or the intensive care unit (ICU) ▪ Patient provides written informed consent prior to initiation of the study OR close relative/legal representative provides written informed consent prior to initiation of the study according to the presumed will of the patient when patient is unable to give consent. ▪ No anticipated transfer within 72 hours to a non-study hospital <u>**Characteristics baseline**</u> **Age (mean, SD)** ▪ Exp: 57.2 (13.5) ▪ Ctrl: 59.7 (13.2) **Severity** ▪ Rdv: 26% WHO 4, 74% >/=WHO 5 (any oxygen), 10.5% >/=WHO6 (ICU)	**Experimental:** ▪ intravenous remdesivir plus optimized standard of care (SOC) ▪ Dose: 200 mg on 1st day and 100 mg per day until discharge or for a maximum duration of 10 days ▪ N = 114 **Control:** ▪ optimized standard of care (SOC) alone ▪ N = 94 N mortality analysis = 191 (Exp. 103, Ctrl. 88) included in mortality analysis N 1 year follow-up analyses = 181 (Exp. 98, Ctrl. 83) (mind. eine Dosis und ausgewertet)	All-cause mortality (at up to 1 year follow-p)	RR 0.82 (0.25 – 2.76) Exp : 5/98 (4.4%) Ctrl :5/83 (5.3%);
			Recovering from COVID-19 infection	RR 0.94 (0.47–1.90) Exp : 85% Ctrl : 86%
			Clinical worsening: new need if IMV or death	Not reported
			Admission to ICU or death	Not reported
			Adverse events: Fatique	No or slight fatigue (1–2): Exp: 74 (75.5) Ctrl: 60 (72.2) Moderate or severe fatigue (3 RR 0.88 (0.54 – 1.44) Exp: 24 (24.5) Ctrl: 23 (27.7)
			Excertional dyspnea	RR 0.61 (0.20 – 1.85) Exp : 5% Ctrl : 8%
			Long COVID symptoms	Narrative: Regarding the 2 long-COVID symptoms, ther statistically significant between treatment arms
			QoL (median EQ-VAS)	OR 0.83 (0.49 – 1.40) Exp:75.5 (IQR 67.8–85.0) Ctrl: 80 (IQR 67.5–86.5) in SoC
			QoL (EQ-5D-5L)	Mobility, walking: RR 1.03, 95% CI 0.54–1.96 Self-care, washing or dressing RR 0.51, 95% CI 0.13–2.08 Usual activities, e.g., wo housework, family or leisure a RR 0.71, 95% CI0.32–1.55 Pain or discomfort: RR 0.85 (0.44 – 1.63) Anxiety or depression: RR 1.27 (0.47 – 3.42)

	▪ Ctrl: 21% WHO4, 79% >/=WHO 5 (any oxygen), 11.7% >/=WHO6 (ICU) **Received dexamethasone** ▪ Exp: 79 (69.3) ▪ Ctrl: 72 (76.6) **<u>Characteristics after 1 years</u>** **Age (mean, SD)** ▪ Exp: 57.7 (12.9) ▪ Ctrl: 59.4 (13.0) **Severity** ▪ Exp: 25.5% WHO 4, 74.5% <WHO 5 (any oxygen), 10.2% <WHO6 (in ICU) ▪ Crtl: 18.1% WHO4, 81.9% <WHO 5 (any oxygen), 12% <WHO6 (in ICU) **Received dexamethasone** ▪ Exp: 69 (70.4) ▪ Ctrl: 61 (73.5) ***<u>Comorbidities</u>*** **<u>(baseline pop)</u>** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes n (%):**			

	▪ Exp: 20 (17.5) ▪ Ctrl: 16 (17.0) **BMI (mean, SD)** ▪ Exp: 31.5 (6.35) ▪ Ctrl: 29.6 (6.0) **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR ***Comorbidities* (after 1 year pop)** **Diabetes n (%):** ▪ Exp: 25 (25.5) ▪ Ctrl: 15 (18.1) **BMI (mean, SD)** ▪ Exp: 31.7 (6.09) ▪ Ctrl: 29.9 (6.01)			

Mohiuddin 2022 RCT, NCT04678739	**Sample size:** N = 208 pts. randomized (291 pts. planned) **Enrolment period:** NR Bangladesh **Inclusion criteria:** ▪ Severe COVID-19 patients require hospitalization under HDU/ICU. The SARS-CoV-2 infection will be confirmed by RT PCR / CT Chest in every case. 16 Years to 80 Years (Child, Adult, Older Adult) **Exclusion Criteria:** ▪ Participants with uncontrolled clinical status who were hospitalized from the before. ▪ Contraindication / possible drug interaction. ▪ Participants who have any severe and/or uncontrolled medical conditions like, Severe ischemic heart disease, epilepsy, malignancy, Pulmonary/renal/hepatic disease, AIDS, Pulmonary TB, pregnancy, Corpulmonale, and etc. **Time since symptom onset (median, range):** ▪ NR **<u>Characteristics</u>** **Age (mean, SD)** ▪ Exp: 56.24 ± 15 ▪ Ctrl: 57.04 ± 15.15	**Experimental:** ▪ Remdesivir 100 IV Infusion as a lyophilized powder ▪ Dose: 5 mg/kg (<40 kg) or 200 mg (>40 kg) on day 1 and then 2.5 mg/kg (<40 kg) or 100 mg (>40 kg) daily] + tocilizumab [8 mg/kg up to 800 mg highest 12 h apart ▪ N = 104/101 (3 withdraw themselves from the study) **Control:** ▪ dexamethasone 6 mg/day ▪ N = 101 N 205= (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	Exp: 26/101 (25.74%) Ctrl: 32/104 (30.76%)
			Time to Clinical Improvement (TTCI):	Exp: 9.41 ± 5.38; 3–32 days Ctrl: 14.21 ± 5.694; 6–28 day
			Duration of ICU Stay (mean, SD)	Exp : 7.68 ± 5.45; 1–27 days Ctrl : 10.59 ± 5.453; 2–42 da
			Time to Recovery	Exp: 9.41 ± 5.38; 3–32 days Ctrl : 14.21 ± 5.694; 6–28 da
			Hospital stay/duration of hospitalisation	Exp : 10.02 ± 6.277; 1–35 da Ctrl : 14.48 ± 8.882; 3–42 da
			Rate of daily Supplemental Oxygen Use	Not reported
			Time to Clinical Failure	Exp: 6.88 ± 6.139; 1–27 days Ctrl: 10.38 ± 12.27; 3–42 day
			Adverse events	Not reported

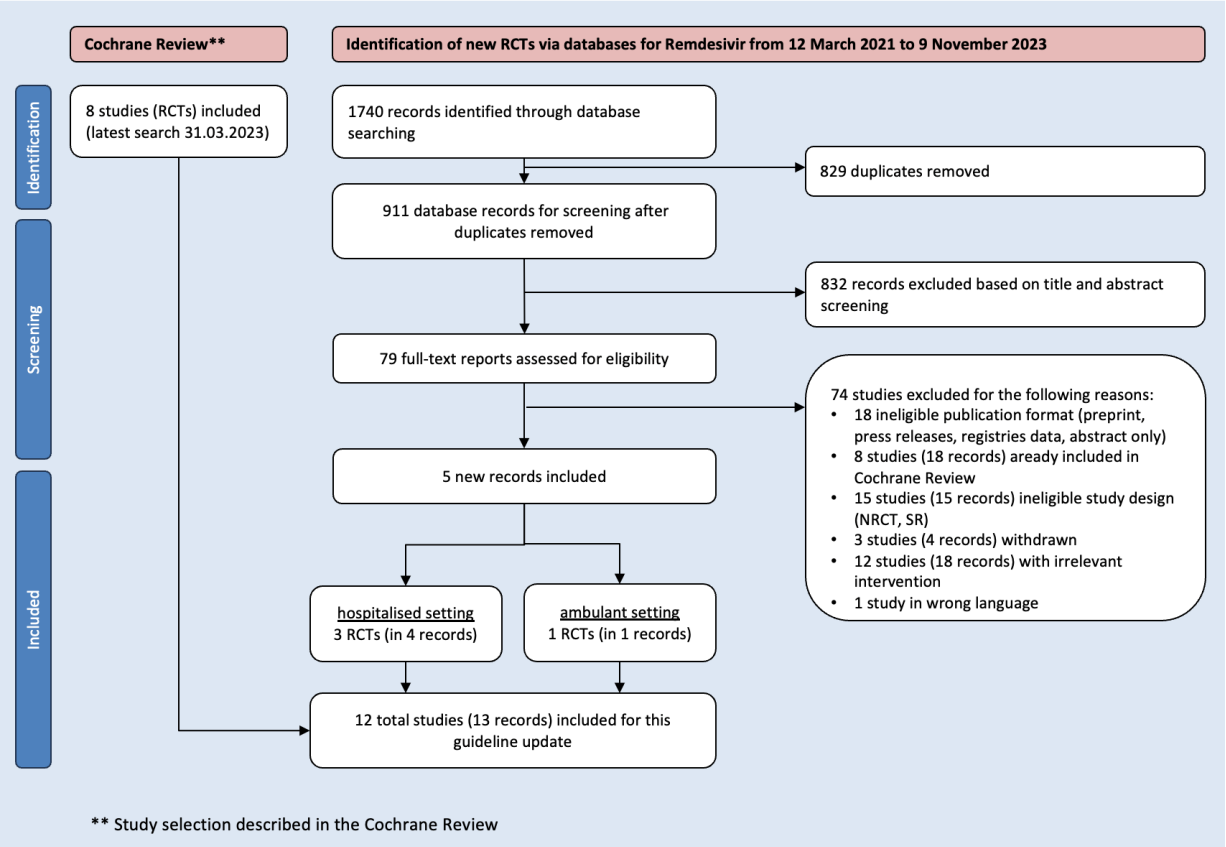
	Severity: ICU patients ***<u>Comorbidities</u>*** **Any** ▪ Exp: 61 (58.7%) ▪ Ctrl: 46 (44.2%) **Diabetes:** ▪ Exp: NR ▪ Ctrl: NR **BMI (mean, SD)** ▪ Exp: 23.6± 5.6 ▪ Ctrl: 22.9 ± 5.8 **Hypertension (MAP(Mean arterial pressure in mm of Hg))** ▪ Exp: 86.16 ± 13.55 ▪ Ctrl: 86.26±12.19 **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR		QoL	Not reported

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Sarham, 2022 RCT	**Sample size:** N = 108 pts. (108 pts. planned) **Enrolment period:** 01.10.2020 to 10.03.2021 Egypt **Inclusion criteria:** ▪ Patients included in the study who admitted to intensive care unit with confirmed COVID-19 infection through polymerase chain reaction (PCR); after one week of home isolation or after 7 days of inpatient isolation with significant clinical manifestation of systematic hyper inflammation defined as rapid deterioration in oxygen saturation (SaO2) for less than 92% at ambient air or respiratory rate (RR) for more than 30, or PaO2/FiO2 ratio for less than 250; or in radiological findings of CT chest according to CO-RADS classification defined as worsening of lung involvement as an increase in the number and /or expansion of	**Experimental (TCZ-RMV):** ▪ intravenous remdesivir + Tocilizumab (400 mg–800 mg every 24 h for only two doses) ▪ Dose: 200 mg on day 1 followed by 100 mg per day infused over 60 min for 5 days ▪ N = 52 **Control (TCZ-HCQ):** ▪ IV Tocilizumab 400 mg–800 mg every 24 h for only two doses and hydroxychloroquine 400 mg twice daily at day 1 then 200 mg twice daily for 5 days ▪ N = 56 N = 108 (mind. eine Dosis und ausgewertet)	All-cause mortality (no time indication)	Exp: 15 (28.8%) Ctrl: 12 (21.4%), p= 0.06
			Clinical improvement: discharged alive (day 30)	Not reported
			Patient discharge after improvememt (no time indication)	Exp: 37 (71.2%) Ctrl: 44 (78.6%), p= 0.4
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Therapeutic failure	Exp: 16 (30.8%) Ctrl: 15 (26.8%)
			Length of hospitalization (days)	Exp: 8 (5−12) Ctrl: 10 (6−16), p= 0.4
			Adverse events	Not reported
			QoL	Not reported

	pulmonary areas of consolidation, need for increased FiO2 to maintain stable O2 saturation or worsening O2 saturation of >3% with steady FiO2, as well as elevation on inflammatory marker C-reactive protein (CRP, ≥100 mg/L) or ferritin (≥900 ng/mL) and lactate dehydrogenase (LDH, >220 U/L) **Time since symptom onset (median, range): NR** **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 61(52−70) ▪ Ctrl: 53(46−68) **Severity** ▪ Exp: 9(17.3%): Supplemental oxygen at entry = WHO 5-6 ▪ Crl: 49(87.5%): Supplemental oxygen at entry = WHO 5-6 ▪ Exp: 43(82.7%): Mechanical ventilation need = WHO 7 ▪ Crl: 25(44.6%): Mechanical ventilation need = WHO 7 ▪ Crl: 44(78.6%): ICU admission >WHO 5 ▪ Exp: 50(96.2%): ICU admission >WHO 5 ***<u>Comorbidities</u>*** **Any** *(2 or more comorbidities)* ▪ Exp: 26(50%) ▪ Ctrl: 30(53.6%) **Diabetes:**			

	▪ Exp: 25(48.1%) ▪ Ctrl: 26(46.4%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: ▪ Ctrl: **Hypertension** ▪ Exp: 29(55.8%) ▪ Ctrl: 37(66.1%) **Cardiovascular disease** *Ischemic heart disease* ▪ Exp: 7(13.5%) ▪ Ctrl: 16(28.6%) *Heart failure* ▪ Exp: 1(1.9%) ▪ Ctrl: 3(5.4%) **Lung diseases** *Asthma* ▪ Exp: 4(7.7%) ▪ Ctrl: 10(17.9%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: 3(5.8%) ▪ Ctrl: 2(3.6%)			

5.2.5 Studienselektion: Flow Chart



5.2.6 Literaturrecherche

Für Cochrane Review und LL COVID

Database/Register	Search 12.03.2021	Update Search 09.10.2023
CCSR	**156 references** (109 studies)	**583 references (295 studies)**
Scopus	**329**	**871**
WHO COVID-19 DB*	**323**	**340**
Total	**808**	***1740***
Total (after deduplication)	**724**	***911 (zusätzlich noch 115 preprints, 148 trial registry entries***

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Für Ceosys nur in CCSR bis 12.03.2021

Für COVID LL bis 09.10.2023

Suchstrategien:

Cochrane COVID-19 Study Register

Search string:

remdesivir* OR GS5734 OR "GS 5734" OR veklury*

Study characteristics:

1) "Intervention assignment": "Randomised" OR "Unclear"
2) "Study design": "Parallel/Crossover" OR "Unclear" OR "Other"

Scopus Seit 09.10.2023 anstatt von Web of Science

TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS (remdesivir* OR gs5734 OR "GS 5734" OR veklury*)

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

AND PUBYEAR > 2019 AND PUBYEAR < 2024 AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(remdesivir* OR GS5734 OR "GS 5734" OR veklury) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

5.2.6.1 *Literaturrecherche für Kohortenstudien*

Database	Search 31.08.2022, update search 12.10.2023	
CCSR	246	785 references of 759 studies
WOS (SCI+ECI) ab 12.10.23 Scopus	204	443
WHO COVID-19 DB*	219	249
Total	669	1447
Total (after deduplication)	513	825

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued*

Cochrane COVID-19 Study Register

Search strings:

remdesivir* or GS5734 or "GS 5734" or "GS-5734" or veklury

results available: report results

study design: case series/case control/cohort; created: 1 Jan '22 - 12 Oct '23

Web of Science (Core Collection) – Science Citation Index und Emerging Sources Citation Index

Search strings:

#1 TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#2 (TI=((remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*))) OR AB=((remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*))

#3 (TI=((control AND (group* OR study)))) OR AB=((control AND (group* OR study)))

#4 (TI=(((time AND factors) OR program OR survey* OR ci OR cohort OR comparative stud* OR evaluation studies OR follow-up*))) OR AB=(((time AND factors) OR program OR survey* OR ci OR cohort OR comparative stud* OR evaluation studies OR follow-up*))

#5 #1 AND #2 AND (#3 OR #4) and 2022 (Publication Years)

Scopus (via Elsevier) ab 12.10.2023

TITLE-ABS (remdesivir* OR gs5734 OR "GS 5734" OR "GS-5734" OR veklury) AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") AND TITLE-ABS ((control AND study) OR group* OR (time AND factors) OR program OR survey* OR ci OR cohort OR comparative AND stud* OR evaluation AND studies OR follow-up*) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023)) AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

Search I:

(remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*)

AND

(control AND study) OR group OR groups)

Search II:

(remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*)

AND

((time AND factors) OR program OR survey* OR cohort OR comparative stud* OR evaluation studies OR follow-up*)
In search field: Title, abstract, subject and limit to year 2022 and 2023

5.3 Schlüsselfrage 3a.1) systemische Kortikosteroide und SoC vs. SoC

Autor*innen: Caroline Hirsch

Es gab 11 RCTs mit 8252 Teilnehmenden.

5.3.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Systemic corticosteroids + Standard of care

Vergleichsintervention: Standard of Care (plus/minus Placebo)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Standard of Care (plus/minus Placebo)	**Absolute Effektschätzer** Systemic corticosteroids + Standard of care	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality up to 30 days	Relatives Risiko: 0.9 (CI 95% 0.84 - 0.97) Basierend auf Daten von 7898 patienter und 9 Studien[1]	**273** pro 1000	**246** pro 1000 Differenz: **27 weniger pro 1000** (CI 95% 44 weniger - 8 weniger)	**Moderat** Due to serious risk of bias[2]	Systemic corticosteroids likely reduce the all-cause mortality up to 30 days.
All-cause mortality up to 120 days	Relatives Risiko: 0.74 (CI 95% 0.23 - 2.34) Basierend auf Daten von 485 patienter und 3 Studien[3]	**402** pro 1000	**297** pro 1000 Differenz: **105 weniger pro 1000** (CI 95% 310 weniger - 539 mehr)	**Niedrig** Due to serious inconsistency, Due to serious risk of bias[4]	Systemic corticosteroids may reduce all-cause mortality up to 120 days.
Clinical improvement: Discharged alive	Relatives Risiko: 1.36 (CI 95% 0.95 - 1.96) Basierend auf Daten von 6786 patienter und 3 Studien[5]	**620** pro 1000	**843** pro 1000 Differenz: **223 mehr pro 1000** (CI 95% 31 weniger - 595 mehr)	**Niedrig** Due to serious inconsistency, Due to serious risk of bias[6]	Systemic corticosteroids may increases the outcome discharged alive.
Clinical worsening: New need for IMV or death	Relatives Risiko: 0.92 (CI 95% 0.84 - 1.01) Basierend auf Daten von 5586 patienter und 2 Studien[7]	**282** pro 1000	**259** pro 1000 Differenz: **23 weniger pro 1000** (CI 95% 45 weniger - 3 mehr)	**Niedrig** Due to serious risk of bias, Due to serious inconsistency[8]	Systemic corticosteroids may decrease the outcome new need for IMV or death.

Ventilator-free days	Gemessen mit: Mean difference Skala: - Höher ist besser Basierend auf Daten von 299 patienter und 1 Studien[9]	**4** daysMittelwert **6.6** daysMittelwert Differenz: **MD 2.6 mehr** (CI 95% 0.67 mehr - 4.53 mehr)	**Niedrig** Due to serious imprecision and due to serious risk of bias[10]	Systemic corticosteroids may increase ventilator-free days.
Serious adverse events during treatment	Basierend auf Daten von 678 patienter und 2 Studien[11]	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. Therefore, we only present descriptive statistics with effects below 1 in favour of corticosteroids: Angus 2020 shock-dependent hydrocortisone: RR 4.11 (95% CI 0.23, 72.98); Angus 2020 fixed-dose hydrocortisone: RR 1.43 (95% CI 0.16, 12.49); Tomazini 2020: RR 0.54 (95% CI 0.19, 1.59).	**Sehr niedrig** Due to very serious risk of bias, serious imprecision.[12]	We are uncertain whether systemic corticosteroids increase or reduce the number of serious adverse events.
Adverse events during treatment	Basierend auf Daten von 660 patienter und 5 Studien[13]	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. We only present descriptive statistics with effects below 1 in favour of corticosteroids: Corral-Gudino 2021: RR 11.60 (95% CI 1.62, 83.03); Dequin 2020: RR 0.77 (95% CI 0.59, 1.00); Edalatifard 2020: RR 0.82 (95% CI 0.12, 5.48); Tang 2021: RR 0.63 (95% CI 0.22, 1.76); Tomazini 2020: RR 0.69 (95% CI 0.50, 0.96).	**Sehr niedrig** Due to very serious risk of bias, serious imprecision[14]	We are uncertain whether systemic corticosteroids increase or reduce the number of adverse events.
Hospital-acquired infections during treatment	Basierend auf Daten von 660 patienter und 5 Studien[15]	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. We present descriptive statistics only: Corral-Gudino 2021: RR 4.14 (95% CI 0.51, 33.49); Dequin 2020: RR 0.77 (95% CI 0.59, 1.00); Edalatifard 2020: RR 2.49 (95% CI 0.11, 58.74); Tang 2021: RR 2.00 (95% CI 0.19, 21.24); Tomazini 2020: RR 0.75 (95% CI 0.52, 1.09).	**Sehr niedrig** Due to very serious risk of bias, serious imprecision[16]	We are uncertain whether systemic corticosteroids increase or reduce the number of hospital-acquired infections.

1. Systematic review . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [5].
2. Risiko für Bias: schwerwiegend. We downgraded for risk of bias for deviation from intended interventions (Angus 2020; Horby 2021; Jeronimo 2020; Tomazini 2020), for selective reporting (Corral-Gudino 2021; Dequin 2020; Jamaati 2021), for missing information about the allocation concealment (Corral-Gudino 2021), for baseline differences (Jamaati 2021).;
3. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [5].
4. Risiko für Bias: schwerwiegend. Edalatifard 2020: no information about the allocation concealment, deviation from the intended intervention (17%), no SAP and protocol available; Jeronimo 2020: deviations from the intended intervention and selective reporting; Inkonsistenz: schwerwiegend. I^2 = 79%;
5. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [5].

6. Risiko für Bias: schwerwiegend. No information about the allocation concealment (Edalatifard 2020), protocol deviations (Edalatifard 2020, Horby 2021, Tomazini 2020), selective reporting (Edalatifard 2020); Inkonsistenz: schwerwiegend. I^2 = 81%;
7. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [5].
8. Risiko für Bias: schwerwiegend. Protocol deviations (Angus 2020, Horby 2021); Inkonsistenz: schwerwiegend. I^2 = 72%;
9. Primary study . Baseline/Vergleichsintervention Systematic review . Referenzen [5].
10. Risiko für Bias: schwerwiegend. We downgraded because of risk of bias through deviation from intended interventions (Tomazini 2020; 1 point).; Unzureichende Präzision: schwerwiegend. imprecision (broad confidence interval, low number of evaluated participants, 1 point).;
11. Primary study Referenzen [5].
12. Risiko für Bias: sehr schwerwiegend. We downgraded for risk of bias for deviations from intended interventions (Angus 2020; Tomazini 2020), missing adjustment for competing risk (Angus 2020; Tomazini 2020; 2 points), selective outcome reporting: 2 out 10 studies including the largest, Horby 2021, did not report this major safety outcome (downgrade 1 point).; Unzureichende Präzision: schwerwiegend. Imprecision (fewer than 500 events, downgrade 1 point);
13. Primary study Referenzen [5].
14. Risiko für Bias: sehr schwerwiegend. We downgraded because of risk of bias mainly through deviation from intended intervention (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020) and selection of adverse events usually associated with steroids (Corral-Gudino 2021; Edalatifard 2020; Tang 2021, 2 points). selective outcome reporting (only 5 out of 10 reported this established safety outcome, 1 point); Unzureichende Präzision: schwerwiegend. Imprecision (fewer than 500 events, 1 point),;
15. Primary study Referenzen [5].
16. Risiko für Bias: sehr schwerwiegend. We downgraded because of risk of bias mainly from deviation from intended interventions (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), missing pre-specification of its definition (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021, 2 points). selective outcome reporting (only 5 out of 10 reported this established safety outcome, 1 point); Unzureichende Präzision: schwerwiegend. Imprecision (fewer than 500 events, 1 point).;

5.3.2 Analysen / Forest Plots

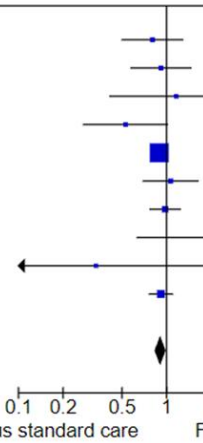
Mortality, day 30

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Angus 2020 (1)	37	141	17	52	2.5%	0.80 [0.50 , 1.29]
Angus 2020 (2)	41	137	16	49	2.5%	0.92 [0.57 , 1.48]
Corral-Gudino 2021	7	35	5	29	0.5%	1.16 [0.41 , 3.27]
Dequin 2020	11	76	20	73	1.3%	0.53 [0.27 , 1.02]
Horby 2021	482	2104	1110	4321	64.8%	0.89 [0.81 , 0.98]
Jamaati 2021	16	25	15	25	3.0%	1.07 [0.69 , 1.65]
Jeronimo 2020	79	209	80	207	9.5%	0.98 [0.77 , 1.25]
Munch A 2021	6	16	2	14	0.3%	2.63 [0.63 , 10.98]
Tang 2021	0	43	1	43	0.1%	0.33 [0.01 , 7.96]
Tomazini 2020	85	151	91	148	15.7%	0.92 [0.76 , 1.11]
Total (95% CI)		**2937**		**4961**	**100.0%**	**0.90 [0.84 , 0.97]**
Total events:	764		1357			

Heterogeneity: Tau² = 0.00; Chi² = 6.58, df = 9 (P = 0.68); I² = 0%

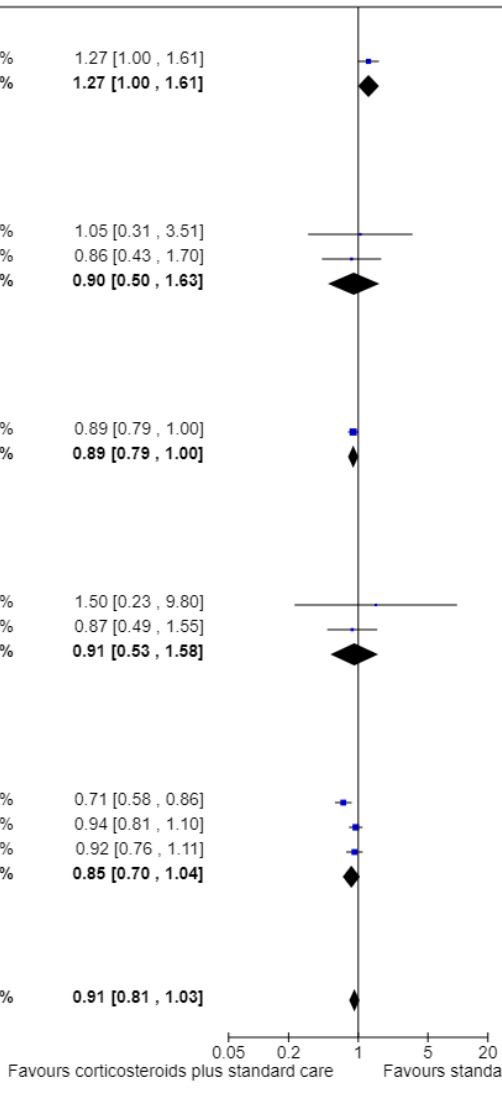
Test for overall effect: Z = 2.64 (P = 0.008)

Test for subgroup differences: Not applicable



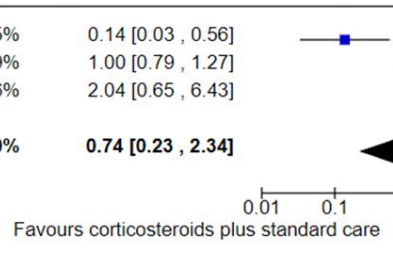
Subgruppenanalyse: Respiratory support, Mortality day 30

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
2.1.1 No oxygen						
Horby 2021	89	501	145	1034	13.6%	1.27 [1.00 , 1.61]
Subtotal (95% CI)		**501**		**1034**	**13.6%**	**1.27 [1.00 , 1.61]**
Total events:	89		145			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						
2.1.2 Low-flow oxygen only						
Corral-Gudino 2021	5	31	4	26	0.9%	1.05 [0.31 , 3.51]
Jeronimo 2020	8	16	7	12	2.7%	0.86 [0.43 , 1.70]
Subtotal (95% CI)		**47**		**38**	**3.7%**	**0.90 [0.50 , 1.63]**
Total events:	13		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
2.1.3 NIV, high-flow, and low-flow oxygen combined						
Horby 2021	298	1279	682	2604	23.8%	0.89 [0.79 , 1.00]
Subtotal (95% CI)		**1279**		**2604**	**23.8%**	**0.89 [0.79 , 1.00]**
Total events:	298		682			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
2.1.4 NIV or high-flow oxygen only						
Corral-Gudino 2021	2	4	1	3	0.4%	1.50 [0.23 , 9.80]
Jeronimo 2020	18	98	19	90	3.7%	0.87 [0.49 , 1.55]
Subtotal (95% CI)		**102**		**93**	**4.1%**	**0.91 [0.53 , 1.58]**
Total events:	20		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
2.1.5 Invasive ventilation						
Horby 2021	95	324	283	683	17.2%	0.71 [0.58 , 0.86]
Jeronimo 2020	53	66	57	67	20.3%	0.94 [0.81 , 1.10]
Tomazini 2020	85	151	91	148	17.3%	0.92 [0.76 , 1.11]
Subtotal (95% CI)		**541**		**898**	**54.8%**	**0.85 [0.70 , 1.04]**
Total events:	233		431			
Heterogeneity: Tau² = 0.02; Chi² = 7.46, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**2470**		**4667**	**100.0%**	**0.91 [0.81 , 1.03]**
Total events:	653		1289			
Heterogeneity: Tau² = 0.01; Chi² = 14.60, df = 8 (P = 0.07); I² = 45%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 7.59, df = 4 (P = 0.11), I² = 47.3%						



Mortality, day 120

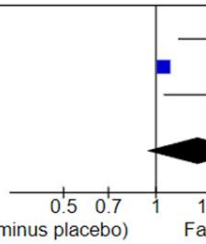
Study or Subgroup	corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Edalatifard 2020	2	34	12	28	26.5%	0.14 [0.03 , 0.56]
Jeronimo 2020	80	194	82	199	42.9%	1.00 [0.79 , 1.27]
Munch A 2021	7	16	3	14	30.6%	2.04 [0.65 , 6.43]
Total (95% CI)		**244**		**241**	**100.0%**	**0.74 [0.23 , 2.34]**
Total events:	89		97			
Heterogeneity: Tau² = 0.80; Chi² = 9.35, df = 2 (P = 0.009); I² = 79%						
Test for overall effect: Z = 0.52 (P = 0.60)						
Test for subgroup differences: Not applicable						



Clinical improvement: discharged alive

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Edalatifard 2020	32	34	16	28	31.4%	1.65 [1.18 , 2.29]
Horby 2021	1416	2104	2748	4321	42.5%	1.06 [1.02 , 1.10]
Tomazini 2020	42	151	25	148	26.1%	1.65 [1.06 , 2.56]
Total (95% CI)		**2289**		**4497**	**100.0%**	**1.36 [0.95 , 1.96]**
Total events:	1490		2789			

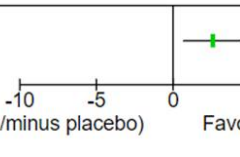
Heterogeneity: Tau² = 0.08; Chi² = 10.55, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



Ventilator-free days

Study or Subgroup	Corticosteroids plus standard care Mean	SD	Total	Standard care (plus/minus placebo) Mean	SD	Total	Mean difference IV, Random, 95% CI
Tomazini 2020	6.6	9.9504	151	4	6.7715	148	2.60 [0.67 , 4.53]

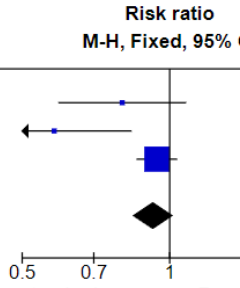
Risk of bias legend
(A) Bias arising from the randomization process



Clinical worsening: new need for IMV or death

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Angus 2020 (1)	42	70	18	24	3.8%	0.80 [0.59 , 1.08]
Angus 2020 (2)	23	50	19	24	3.6%	0.58 [0.40 , 0.84]
Horby 2021	462	1780	1003	3638	92.6%	0.94 [0.86 , 1.03]
Total (95% CI)		**1900**		**3686**	**100.0%**	**0.92 [0.84 , 1.01]**
Total events:	527		1040			

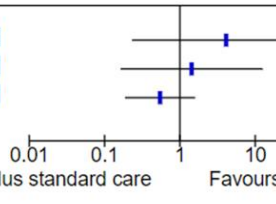
Heterogeneity: Chi² = 7.26, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable



Serious adverse events

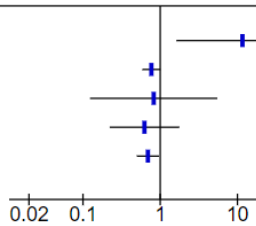
Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Risk ratio M-H, Random, 95% CI
Angus 2020 (1)	5	141	0	52	4.11 [0.23 , 72.98]
Angus 2020 (2)	4	137	1	49	1.43 [0.16 , 12.49]
Tomazini 2020	5	151	9	148	0.54 [0.19 , 1.59]

Footnotes
(1) Angus 2020 intervention arm: shock-dependent hydrocortisone
(2) Angus 2020 intervention arm: fixed-dose hydrocortisone



Adverse events

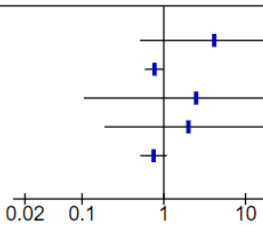
Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Risk ratio M-H, Random, 95% CI
Corral-Gudino 2021	14	35	1	29	11.60 [1.62 , 83.03]
Dequin 2020	40	76	50	73	0.77 [0.59 , 1.00]
Edalatifard 2020	2	34	2	28	0.82 [0.12 , 5.48]
Tang 2021	5	43	8	43	0.63 [0.22 , 1.76]
Tomazini 2020	41	151	58	148	0.69 [0.50 , 0.96]



Risk of bias legend
(A) Bias arising from the randomization process

Hospital-acquired infections

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Risk ratio M-H, Random, 95% CI
Corral-Gudino 2021	5	35	1	29	4.14 [0.51 , 33.49]
Dequin 2020	40	76	50	73	0.77 [0.59 , 1.00]
Edalatifard 2020	1	34	0	28	2.49 [0.11 , 58.74]
Tang 2021	2	43	1	43	2.00 [0.19 , 21.24]
Tomazini 2020	36	151	47	148	0.75 [0.52 , 1.09]



Risk of bias legend
(A) Bias arising from the randomization process

5.3.3 Referenzen der eingeschlossenen Studien

- Wagner C, Griesel M, Mikolajewska A, Metzendorf MI, Fischer AL, Stegemann M, et al. (2022). Systemic corticosteroids for the treatment of COVID-19: Equity-related analyses and update on evidence. Cochrane Database of Systematic Reviews(11). doi:10.1002/14651858.CD014963.pub2

5.3.4 Charakteristika der eingeschlossenen Studien

5.3.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

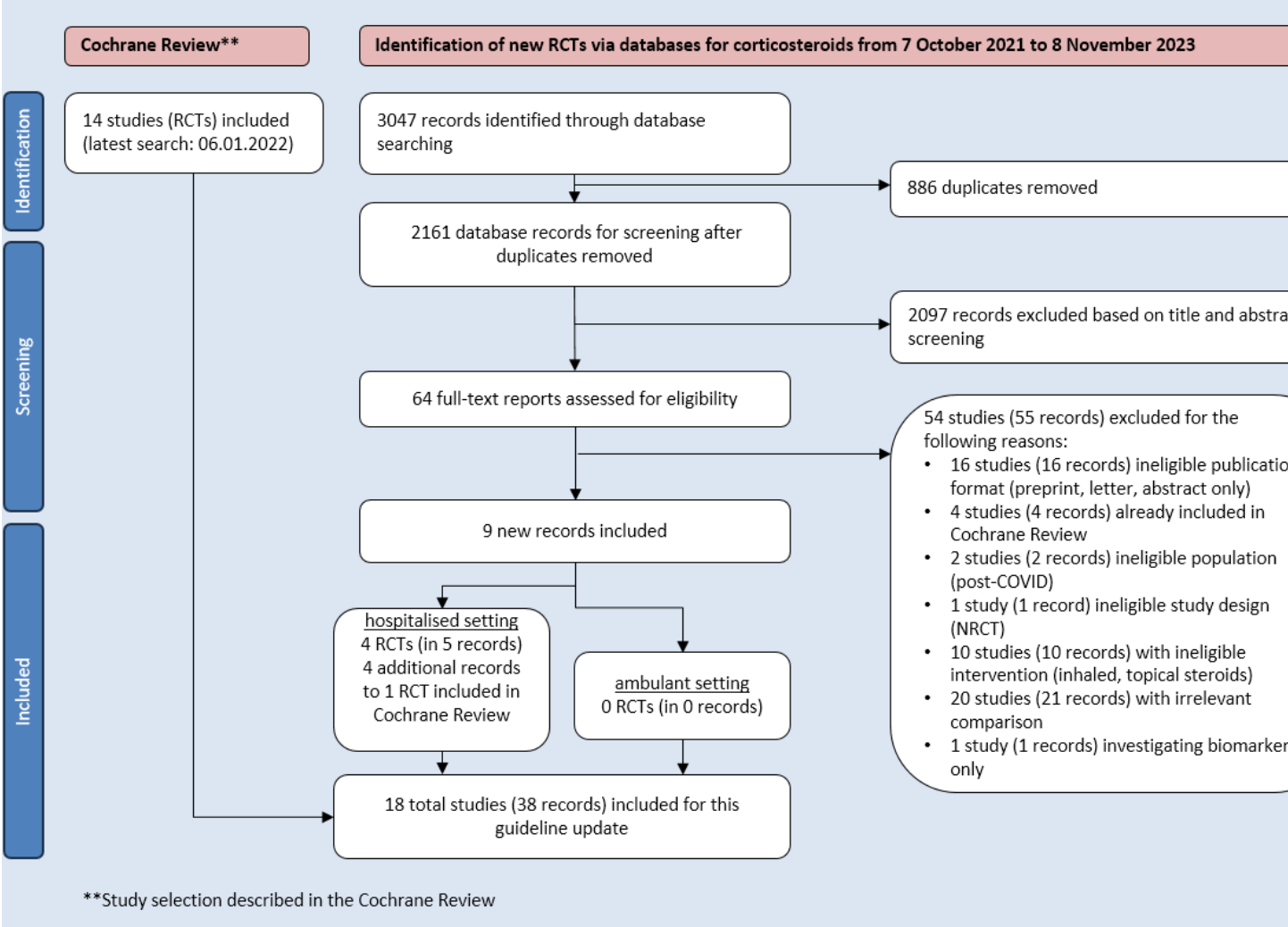
Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodol
Wagner 2022 Systematic review with MA	**Study design** **Search time frame** Inception of each database to 6 January 2022 **Sources:** Cochrane COVID-19 Study	**Intervention A** Systemic corticosteroids **Intervention B** Standard of care + / - placebo	11 studies on 8019 patients **Descriptive statistics:** NR	**Comparison systemic corticosteroids vs. standard of care (+ / - placebo)** Number of studies: 11 Number of participants: 8019 **Critical outcomes:** ▪ All-cause mortality (at up to day 30): 274 per 1000 in SoC group, Difference 28 per 1000 (RR 0.90, CI 95% 0.84 to 0.97, N = 7898 in 9 RCTs, I^2 = 0%)	**Methodologica** **included studi** **using RoB 2 to** Some concerns bias **Evidence synth** ▪ ITT ▪ Random-e and in rar

	Register (CCSR) comprising: - MEDLINE (PubMed) - Embase.com - ClinicalTrials.gov - WHO International Clinical Trials Registry Platform (ICTRP) - medRxiv - Cochrane Central Register of Controlled Trials (CENTRAL) Web of Science Core Collection (Clarivate) - Science Citation Index Expanded (1945 to present) - Emerging Sources Citation Index (2015 to present) WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** - hospitalised individuals with unknown vaccination status and a confirmed			▪ All-cause mortality (at up to day 60): NR ▪ All-cause mortality at up to longest follow-up (day 120): 402 per 1000 in SoC group, Difference 104 per 1000 (RR 0.74, CI 95% 0.23 to 2.34, N = 485 in 3 RCTs, I^2 = 0%) ▪ Clinical improvement participants discharged alive at up to day 28: 620 per 1000 in SoC group, Difference 44 per 1000 (RR 1.07, CI 95% 1.03 to 1.11, N = 6786 in 3 RCTs) Clinical worsening: new need for IMV or death within 28 days: 282 per 1000 in SoC group, Difference 22 per 1000 (RR 0.92, CI 95% 0.84 to 1.01, N = 5586 in 2 RCTs) ▪ Admission to ICU or death: NR ▪ Serious adverse events at up to day 28: Angus 2020 shock-dependent hydrocortisone: RR 4.11 (95% CI 0.23 to 72.98); Angus 2020 fixed-dose hydrocortisone: RR 1.43 (95% CI 0.16 to 12.49); Tomazini 2020: RR 0.54 (95% CI 0.19 to 1.59), N = 678 in 2 RCTs ▪ Adverse events (any grade) at up to day 28: Edalatifard 2020: RR 0.82 (95% CI 0.12 to 5.48); Tang 2021: RR 0.63 (95% CI 0.22 to 1.76); Tomazini 2020: RR 0.99 (95% CI 0.89 to 1.10), N = 447 in 3 RCTs ▪ Hospital-acquired infections: Corral-Gudino 2021: RR 4.14 (95% CI 0.51 to 33.49); Dequin 2020: RR 0.90 (95% CI 0.60 to 1.34); Tang 2021: RR 2.00 (95% CI 0.19 to 21.24); Tomazini 2020: RR 0.75 (95% CI 0.50 to 1.15), N = 598 in 4 RCTs ▪ Quality of life: NR **Additional outcomes:** Invasive fungal infections: Corral-Gudino 2021: RR 2.50 (95% CI 0.11 to 59.15), N = 64 in 1 RCT	effects mo small stud receive ex weight **GRADE** ▪ Mortality, moderate ▪ Mortality, low ▪ Clinical im discharge ▪ Serious ad very low ▪ Adverse e ▪ Hospital-a infections

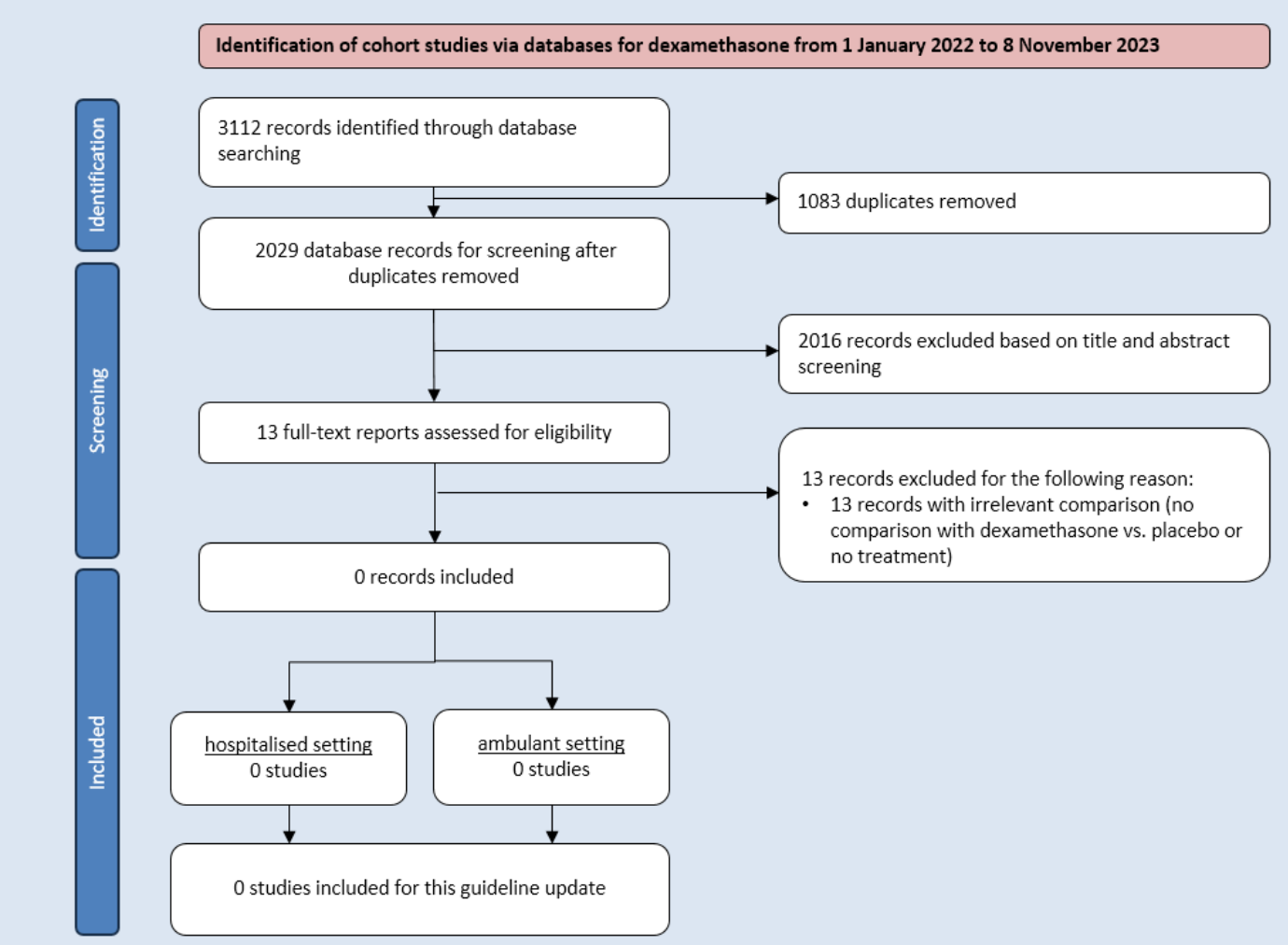
	diagnosis of symptomatic COVID-19; any age, sex, or ethnicity **Study type:** RCTs				

5.3.5 Studienselektion: Flow chart 5a

5.3.5.1 *Flow Chart 3a für die RCT-Recherche*



5.3.5.2 *Flow Chart 3a für die Kohorten-Recherche*



5.3.6 Literaturrecherche 5a

5.3.6.1 *Litraturrecherche für RCTs*

Date of search for all databases: 03.03.2021, update 07.10.2021, update 06.10.2023			
Database/Register	Search	Update Search	Update Search
CCSR	250 references (169 studies)	357 references (233 studies)	1065 references (562 studies)
WOS (SCI+ECI) ab 06.10.2023 Scopus	305	390	1441
WHO COVID-19 DB*	573	650	541
Total	1128	*1397*	*3047*
Total (after deduplication)	1029	*1029+398=1427*	*2164 (include 487 Preprint, clinical trial records)*

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023.*

Since June 2023, manual updates to the database have been discontinued.

Cochrane COVID-19 Study Register

Search string:

corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosон* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR Emmetipi OR esameton* OR firmacort OR medlon* OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone Or precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR Komed OR Nutracort OR Proctocort OR Rectoid OR Hydrocort OR locoid OR Solu-Glyc

Study characteristics:

1) "Intervention assignment": "Randomised"; "Quasi-Randomised" OR "Unclear"
2) "Study design": "Parallel/Crossover" OR "Unclear"

Scopus Seit 06.10.2023 anstatt von Web of Science

TITLE-ABS (corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosон* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR emmetipi OR esameton* OR firmacort OR medlon*

OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone OR precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR maxidex OR dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR komed OR nutracort OR proctocort OR rectoid OR hydrocort OR locoid OR solu-glyc)
AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")
AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023))

WHO COVID-19 Global literature on coronavirus disease

(corticosteroid* OR corticoid* OR prednis* OR hydrocorti* OR methylpredni* OR deltahydrocorti* OR dehydrocorti* OR dexameth* OR desameth*) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

5.3.6.2 *Literaturrecherche für Kohortenstudien*

Intervention Dexamethason

Zeitraum ab 01.01.2022

Date of search for all databases: 08.11.2023		
Database/Register	Search	Update Search
CCSR	2151 (1881 studies)	
Scopus	789	
WHO COVID-19 DB*	172	

Total	3112	
Total (after deduplication)	2029	

Cochrane COVID-19 Study Register

Search string:

corticosteroid* OR corticoid* OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak

5.4 Schlüsselfrage 3a.2) hohe Dosis Dexamethason (12 mg oder höher) vs. niedrige Dosis Dexamethason (6 bis 8 mg)

Autor*innen: Caroline Hirsch

Es gab 7 RCTs mit 3784 Teilnehmenden.

5.4.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: High-dose dexamethasone (12 mg or higher)

Vergleichsintervention: Low-dose dexamethasone (6-8 mg)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Low-dose dexamethasone (6-8 mg)	 High-dose dexamethasone (12 mg or higher)	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality up to 30 days	Relatives Risiko: 1.18 (CI 95% 0.81 - 1.72) Basierend auf Daten von 2648 patienter und 5 Studien[1] Beobachtzungszeit up to 30 days	**200** pro 1000	**236** pro 1000 Differenz: **36 mehr pro 1000** (CI 95% 38 weniger - 144 mehr)	**Sehr niedrig** Due to very serious inconsistency, Due to serious imprecision, Due to serious risk of bias[2]	We are uncertain whether high-dose dexamethasone (12mg or higher) increases or decreases all-cause mortality up to 30 days compared to low-dose dexamethasone
All-cause mortality up to 60 days	Relatives Risiko: 1.19 (CI 95% 0.71 - 2.01) Basierend auf Daten von 863 patienter und 3 Studien[3]	**217** pro 1000	**258** pro 1000 Differenz: **41 mehr pro 1000** (CI 95% 63 weniger - 219 mehr)	**Sehr niedrig** Due to serious inconsistency, Due to serious imprecision, Due to serious risk of bias[4]	We are uncertain whether high-dose dexamethasone (12mg or higher) increases or decreases all-cause mortality up to 60 days compared to low-dose dexamethasone

	Beobachtzungszeit up to 60 days			
All-cause mortality up to longest follow-up	Relatives Risiko: 0.87 (CI 95% 0.74 - 1.04) Basierend auf Daten von 963 patienter und 1 Studien[5] Beobachtzungszeit up to 180 days	**386** pro 1000 **336** pro 1000 Differenz: **50 weniger pro 1000** (CI 95% 100 weniger - 15 mehr)	**Moderat** Due to serious imprecision[6]	High-dose dexamethasone (12mg or higher) probably decreases all-cause mortality up to 180 days compared to low-dose dexamethasone
Clinical improvement: discharged alive up to 30 days	Relatives Risiko: 0.97 (CI 95% 0.93 - 1.02) Basierend auf Daten von 1472 patienter und 2 Studien[7] Beobachtzungszeit up to 30 days	**831** pro 1000 **806** pro 1000 Differenz: **25 weniger pro 1000** (CI 95% 58 weniger - 17 mehr)	**Moderat** Due to serious risk of bias[8]	High-dose dexamethasone (12mg or higher) probably has little or no difference on the number of participants discharged alive up to 30 days compared to low-dose dexamethasone
Clinical worsening: new need for IMV or death up to 30 days	Relatives Risiko: 1.52 (CI 95% 1.18 - 1.97) Basierend auf Daten von 1272 patienter und 1 Studien[9] Beobachtzungszeit up to 30 days	**131** pro 1000 **199** pro 1000 Differenz: **68 mehr pro 1000** (CI 95% 24 mehr - 127 mehr)	**Moderat** Due to serious imprecision[10]	High-dose dexamethasone (12mg or higher) probably increases the number of participants with new need for IMV or death up to 30 days compared to low-dose dexamethasone
Admission to ICU or death up to 30 days	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at admission to ICU or death up to 30 days
Post COVID-19 condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post COVID-19 condition
Serious adverse events[11] during treatment	Basierend auf Daten von 1080 patienter und 2 Studien[12] Beobachtzungszeit during treatment	We did not perform meta-analyses because of high risk of bias arising from the missing adjustment for competing risk of death. We present descriptive data only: Munch 2021b: RR 0.80 (95% CI 0.60 to 1.07); Maskin 2021: RR 1.05 (95% CI 0.88 to 1.25).	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[13]	We are uncertain whether high-dose dexamethasone (12mg or higher) increases or decreases serious adverse events during treatment compared to low-dose dexamethasone
Adverse events any grade[14] during treatment	Basierend auf Daten von 644 patienter und 2 Studien[15] Beobachtzungszeit during treatment	We did not perform meta-analyses because of high risk of bias arising from the missing adjustment for competing risk of death. We present descriptive data only: Bouadma 2022: RR 0.99 (95% CI 0.90 to 1.09); Maskin 2021: RR 1.02 (95% CI 0.96 to 1.08).	**Niedrig** Due to serious risk of bias, Due to serious imprecision[16]	High-dose dexamethasone (12 mg or higher) may have little or no difference on adverse events any grade during treatment compared to low-dose dexamethasone

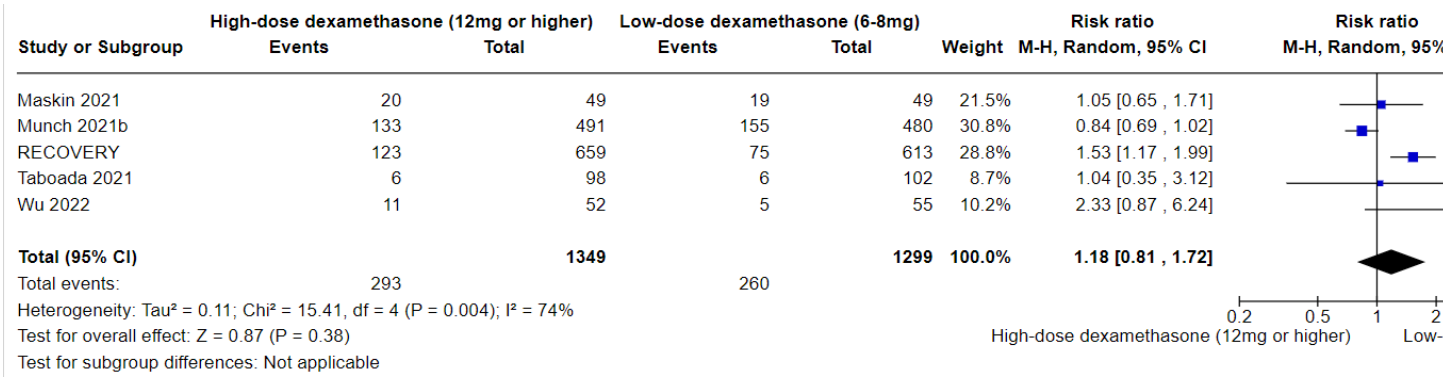
Hospital acquired infections during treatment	Basierend auf Daten von 1626 patienter und 3 Studien[17] Beobachtzungszeit during treatment	We did not perform meta-analyses because of high risk of bias arising from the missing adjustment for competing risk of death. We present descriptive data only: Bouadma 2022: RR 1.10 (95% CI 0.82 to 1.44); Maskin 2021: RR 0.89 (95% CI 0.70 to 1.14); Munch 2021b: RR 0.80 (95% CI 0.56 to 1.14).	**Niedrig** Due to serious risk of bias, Due to serious imprecision[18]	High-dose dexamethasone (12mg or higher) may have little or no difference on hospital acquired infections during treatment compared to low-dose dexamethasone
Quality of life	Basierend auf Daten von 963 patienter und 1 Studien[19] Beobachtzungszeit at 180 days	We did not perform meta-analysis because data were reported as median (IQR) and adjusted mean differences. We present descriptive data only. Granholm 2022: EQ-5D-5L* value index 0.80 (0 to 0.97) vs. 0.68 (0 to 0.92), adjusted mean difference 0.06 (99% CI -0.01 to 0.12); EQ VAS* 65 (0 to 90) vs. 55 (0 to 55) adjusted mean difference 4 (99% CI -3 to 4) *higher values indicate better quality of life; adjusted for stratification variables (being trial site, age below 70 years and the use of invasive mechanical ventilation at baseline)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[20]	High-dose dexamethasone (12mg or higher) may have little or no difference on quality of life at 180 days compared to low-dose dexamethasone

1. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [4]. [6]. [5].
2. Risiko für Bias: schwerwiegend. no information about allocation concealment (Taboada 2021), protocol deviations (Maskin 2021); Inkonsistenz: sehr schwerwiegend. The magnitude of statistical heterogeneity was high, with I^2: 74%., The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies, Point estimates vary widely; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
3. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [5]. [1].
4. Risiko für Bias: schwerwiegend. no information about allocation concealment (Taboada 2021); Inkonsistenz: schwerwiegend. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was moderate, with I^2: 55%.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
5. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [2].
6. Unzureichende Präzision: schwerwiegend. Only data from one study;
7. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [5]. [4].
8. Risiko für Bias: schwerwiegend. no information about allocation concealment (Taboada 2021);
9. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [4].
10. Unzureichende Präzision: schwerwiegend. Only data from one study;
11. undefined
12. Systematic review Referenzen [5].
13. Risiko für Bias: schwerwiegend. due to missing adjustment for competing risk of death; Unzureichende Präzision: sehr schwerwiegend. due to very low number of events/participants;
14. undefined
15. Primary study Referenzen [1]. [5].
16. Risiko für Bias: schwerwiegend. due to missing adjustment for competing risk of death; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
17. Primary study Referenzen [1]. [5].

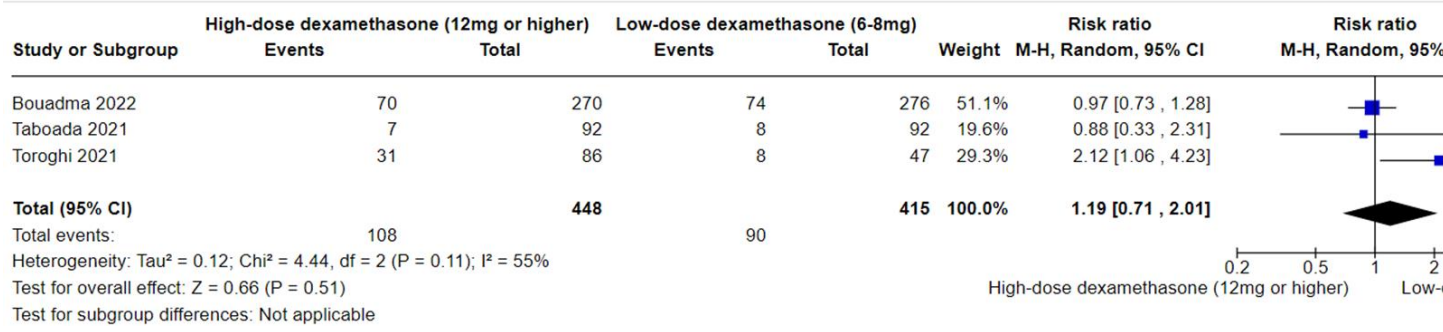
18. Risiko für Bias: schwerwiegend. missing adjustment for competing risk of death, protocol deviations, measurement of the outcome, no information about the allocation concealment; Indirektheit: schwerwiegend.
19. Primary study Referenzen [2].
20. Risiko für Bias: schwerwiegend. missing data multiply imputed; Unzureichende Präzision: schwerwiegend. Only data from one study;

5.4.2 Analysen / Forest Plots

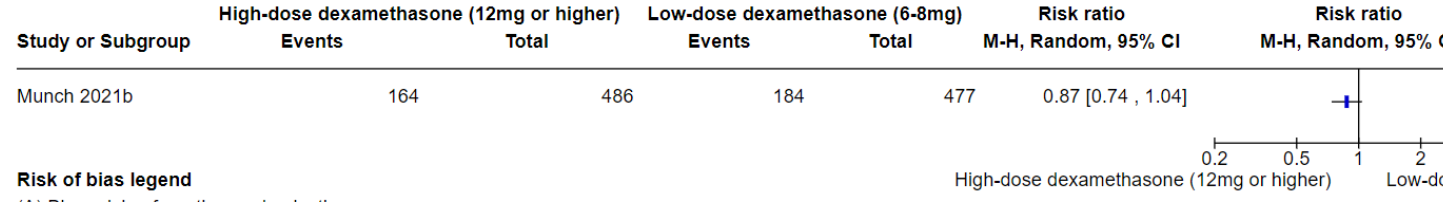
Mortality, day 30



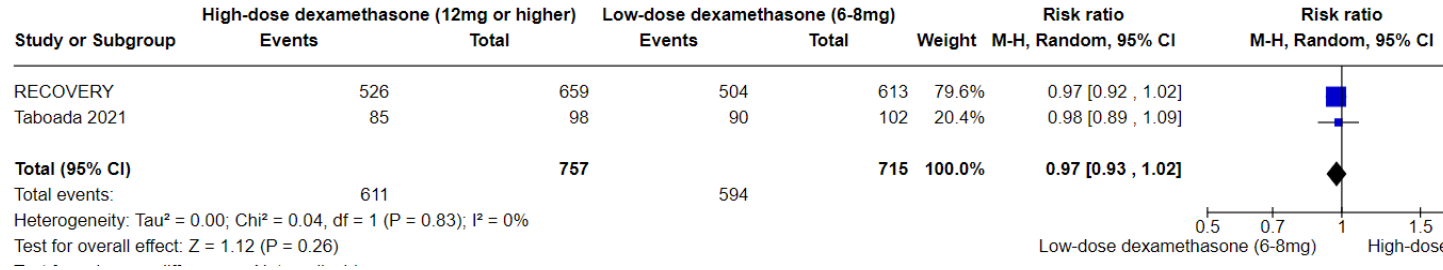
Mortality, day 60



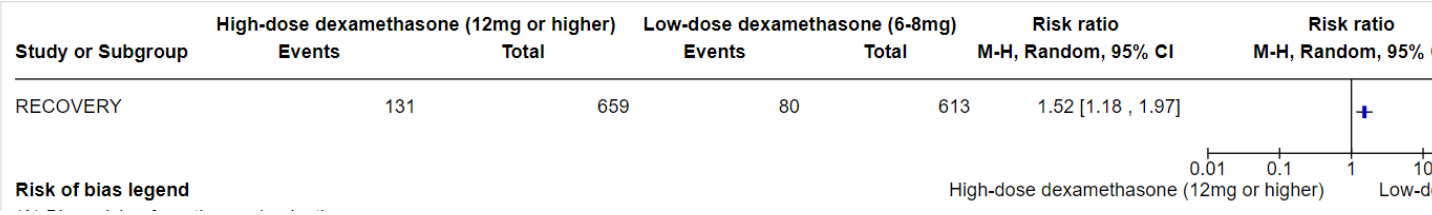
Mortality, day 180



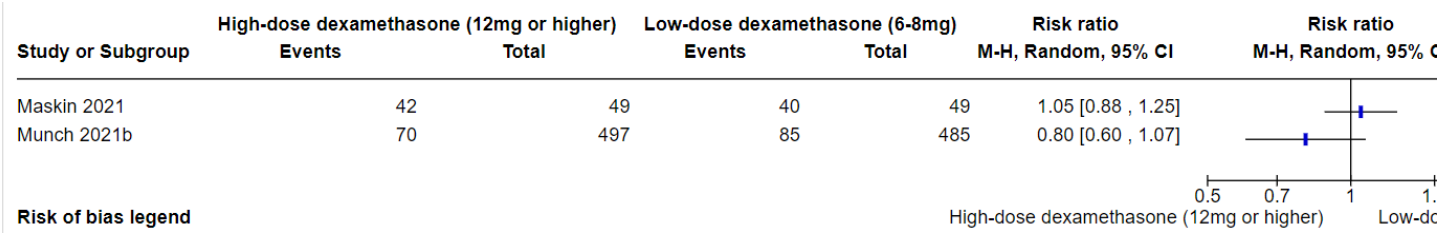
Clinical improvement: discharged alive, day 30



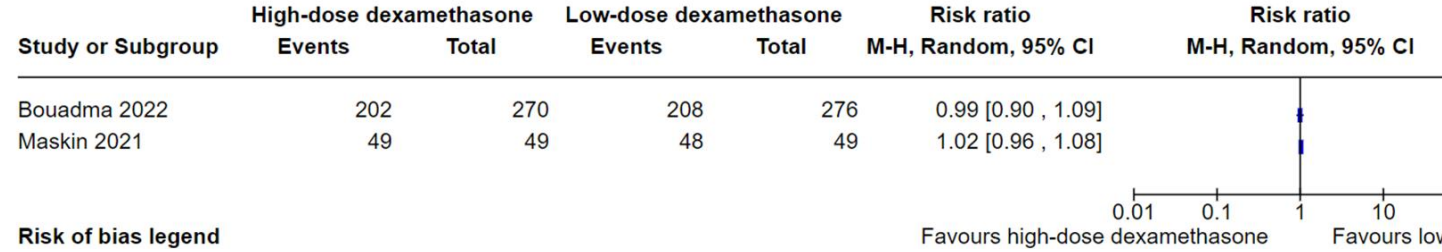
Clinical worsening: new need for IMV or death, day 30



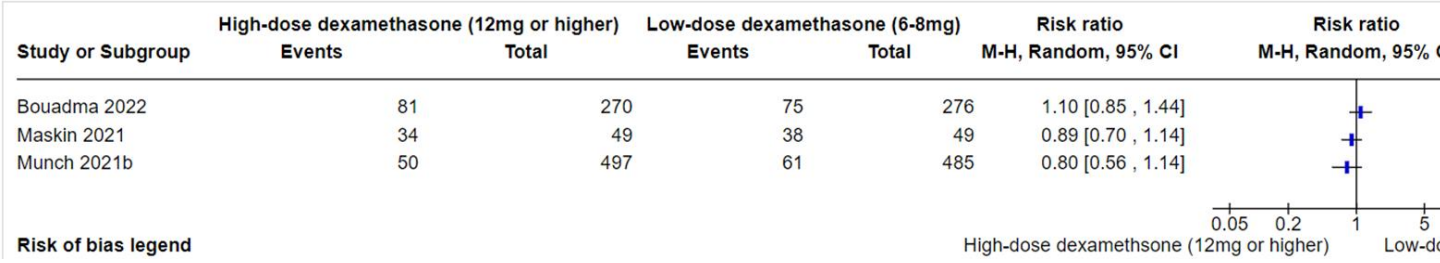
Serious adverse events



Adverse events



Hospital-acquired infections



5.4.3 Referenzen der eingeschlossenen Studien

- Bouadma L, Mekontso-Dessap A, Burdet C, Merdji H, Poissy J, Dupuis C, Guitton C, et al. (2022). High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: the COVIDICUS Randomized Clinical Trial. JAMA Internal Medicine, 182(9), 906-916. doi:10.1001/jamainternmed.2022.2168
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- Maskin LP, Bonelli I, Olarte GL, Palizas F, Jr., Velo AE, Lurbet MF, Lovazzano P, Kotsias S, Attie S, Lopez Saubidet I, Baredes ND, Setten M and Rodriguez PO (2021). High- Versus Low-Dose Dexamethasone for the Treatment of COVID-19-Related Acute Respiratory Distress Syndrome: A Multicenter, Randomized Open-Label Clinical Trial. J Intensive Care Med: 8850666211066799.

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5.4.4 Charakteristika der eingeschlossenen Studien

5.4.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodol
Wagner 2022 Systematic review with MA	**Study design** **Search time frame** Inception of each database to 6 January 2022	**Intervention A** high-dose dexamethason e (12 mg or higher) **Intervention B** low-dose dexamethason	4 studies on 1383 patients **Descriptive statistics:** NR	**<u>Comparison high-dose dexamethasone (12 mg or higher) vs. low-dose dexamethasone (6 mg to 8 mg):</u>** Number of studies: 4 Number of participants: 1383 **Critical outcomes:**	**Methodologica included studi using RoB 2 to** Some concerns bias **Evidence synth**

	Sources: Cochrane COVID-19 Study Register (CCSR) comprising: - MEDLINE (PubMed) - Embase.com - ClinicalTrials.gov - WHO International Clinical Trials Registry Platform (ICTRP) - medRxiv - Cochrane Central Register of Controlled Trials (CENTRAL) Web of Science Core Collection (Clarivate) - Science Citation Index Expanded (1945 to present) - Emerging Sources Citation Index (2015 to present) WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** - hospitalised individuals with unknown	e (6 mg to 8 mg)		▪ All-cause mortality (at up to day 30): 285 per 1000 in low-dose group, Difference 37 per 1000 (RR 0.87, CI 95% 0.73 to 1.04, N = 1269 in 3 RCTs, I^2 = 0%) ▪ All-cause mortality (at up to day 60): NR ▪ All-cause mortality at up to longest follow-up (day 120): 329 per 1000 in low-dose group, Difference 23 per 1000 (RR 0.93, CI 95% 0.79 to 1.08, N = 1383 in 4 RCTs, I^2 = 0%) ▪ Clinical improvement participants discharged alive at up to day 28: 882 per 1000 in low-dose group, Difference 17 per 1000 (RR 0.98, CI 95% 0.89 to 1.09, N = 200 in 1 RCT) ▪ Clinical worsening: new need for IMV or death within 28 days: NR ▪ Admission to ICU or death: NR ▪ Serious adverse events at up to day 28: Munch 2021b: RR 0.80 ▪ (95% CI 0.60 to 1.07); Maskin 2021: RR 1.05 (95% CI 0.88 to 1.25: RR 1.02 (95% CI 0.96 to 1.08), N = 1080 in 2 RCTs ▪ Adverse events (any grade) at up to day 28: Maskin 2021: RR 1.02 (95% CI 0.96 to 1.08), N = 98 in 1 RCT ▪ Hospital-acquired infections: Maskin 2021: RR 0.89 (95% CI 0.70 to 1.14); Munch 2021b: RR 0.80 (95% CI 0.56 to 1.14), N = 1080 in 2 RCTs ▪ Quality of life: NR **Additional outcomes:** ▪ Invasive fungal infections: Munch 2021b: RR 0.70 (95% CI 0.36 to 1.34); Maskin 2021: RR 1.00 (95% CI 0.21 to 4.71), N = 1080 in 2 RCTs	▪ ITT ▪ Random-e and in rar effects mo small stud receive ex weight **GRADE** ▪ Mortality, ▪ Mortality, low ▪ Clinical im discharge ▪ Serious ad very low ▪ Adverse e ▪ Hospital-a infections

	vaccination status and a confirmed diagnosis of symptomatic COVID-19; any age, sex, or ethnicity **Study type:** RCTs				

5.4.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Bouadma 2022 COVIDICUS Triple-blinded RCT	**Sample size:** N = 550 (1:1) randomised to standard of care dexamethasone or high-dose dexamethasone ▪ 6 mg standard of care dexamethasone + an additional dose of 14 mg from day 1 to 5, then 4 mg from day 6 to day 10: N = 270 ▪ 6 mg daily + placebo: N = 276 **Enrolment period:** 10.04.2020 to 17.09.2020 France **Inclusion criteria:** ▪ adults aged at least 18 years admitted to an ICU within the last 48 hours for confirmed or highly suspected COVID-19 ▪ with AHRF (defined as arterial partial pressure of oxygen, [PaO2] < 70 mm Hg, transcutaneous oxygen saturation as measured by pulse oximetry [SpO2] < 90% on room air, tachypnea with > 30 breaths/min, labored breathing, respiratory distress, or need for O2 flow ≥ 6 L/min) ▪ who could receive any available treatment targeting COVID-19 ▪ those with ongoing IMV at inclusion or with anatomical factors precluding the use of nasal cannula, hypercapnia	**Experimental:** ▪ intravenous dexamethasone ▪ 6 mg standard of care dexamethasone + an additional dose of 14 mg from day 1 to 5, then 4 mg from day 6 to day 10 ▪ N = 270 **Control:** ▪ Intravenous dexamethasone ▪ Dose: 6 mg + placebo ▪ N = 276 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	Not reported
			All-cause mortality (day 60)	RR: 0.97 (0.73 to 1.28) High-dose dexa: 70/270 Low-dose dexa: 74/276
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	RR: 0.99 (0.90 to 1.09) High-dose dexa: 202/270 Low-dose dexa: 208/276
			Hospital-acquired infections	RR: 1.10 (0.85 to 1.44) High-dose dexa: 81/270 Low-dose dexa: 75/276
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	indicating noninvasive ventilation (PaCO2 ≥50 mm Hg), or intolerance at admission to any of the oxygenation strategies, ie, the IMV population were R11only eligible to the dexamethasone randomization **Time since symptom onset (median, range):** ▪ Exp: 9 (7-11) ▪ Ctrl: 9 (6-11) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 68.1 (IQR 60.1 to 72.9) ▪ Ctrl: 66.3 (IQR 58.9 to 73.8) ***<u>Comorbidities</u>*** **Any** ▪ Exp: 79,3% ▪ Ctrl: 82,2% **Diabetes** ▪ Exp: 34,8% ▪ Ctrl: 39,1% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 40,7% ▪ Ctrl: 58% **Hypertension** ▪ Exp: 53% ▪ Ctrl: 58% **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ <u>Cancer</u> ▪ Exp: 12.2% ▪ Ctrl: 10.1% ▪ <u>SOT</u> ▪ Exp: 1.1% ▪ Ctrl: 2.9%			

	Malignancy ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
RECOVERY Open-label RCT	**Sample size:** N = 1272 (1:1) randomised to usual care plus higher dose Corticosteroids or usual care alone ▪ oral or intravenous dexamethasone 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days: N = 659 ▪ 6 mg daily: N = 613 **Enrolment period:** 25.05.2021 to 13.05.2022 Africa, Asia, UK **Inclusion criteria:** ▪ aged at least 18 years ▪ clinically suspected or laboratory-confirmed SARS-CoV-2 infection, ▪ clinical evidence of hypoxia (ie, receiving oxygen with or without other forms of respiratory support, or with oxygen saturations <92% on room air) ▪ no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial **Time since symptom onset (median, range):** ▪ Exp: 7 (4-10) ▪ Ctrl: 7 (4-10) **<u>Characteristics</u>** **Age (median, IQR)**	**Experimental:** ▪ oral or intravenous dexamethasone ▪ Dose: 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days ▪ N = 659 **Control:** ▪ oral or intravenous dexamethasone ▪ Dose: 6 mg ▪ N = 613 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.53 (1.17 to 1.99) High-dose dexa: 123/659 Low-dose dexa: 75/613
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	RR: 0.97 (0.92 to 1.02) High-dose dexa: 526/659 Low-dose dexa: 504/613
			Clinical worsening: new need for IMV or death (day 30)	RR: 1.52 (1.18 to 1.97) High-dose dexa: 131/659 Low-dose dexa: 80/613
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Exp: 60.2 ▪ Ctrl: 62.1 ***<u>Comorbidities</u>*** **Any** ▪ Exp: 51% ▪ Ctrl: 50% **Diabetes** ▪ Exp: 20% ▪ Ctrl: 19% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 28% ▪ Ctrl: 27% **Lung diseases** ▪ Exp: 20% ▪ Ctrl: 22% **Immunosuppressed** <u>HIV</u> ▪ Exp: < 1% ▪ Ctrl: < 1% **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: 3% ▪ Ctrl: 3%			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Wu 2022 Open-label RCT	**Sample size:** N = 107 (1:1) randomised to treatment with dexamethasone 20 mg daily compared with dexamethasone 6 mg daily ▪ dexamethasone 20 mg daily: N = 52 ▪ 6 mg daily: N = 55 **Enrolment period:** 21.01.2021 to 04.03.2022 US **Inclusion criteria:** ▪ aged at least 18 years ▪ PCR-confirmed COVID-19 infection on admission ▪ needing supplemental oxygen administered via nasal cannula, face mask, high-flow nasal cannula, or positive pressure ventilation (noninvasive or invasive) **Time since symptom onset (median, range):** ▪ Exp: NR ▪ Ctrl: NR **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 56.1	**Experimental:** ▪ Dose: 20 mg daily for five days, followed by 10 mg daily for five days ▪ N = 52 **Control:** ▪ Dose: 6 mg ▪ N = 55 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 2.33 (0.87 to 6.24) High-dose dexa: 11/52 Low-dose dexa: 5/55
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Ctrl: 57.9 ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes** ▪ Exp: 25% ▪ Ctrl: 32.7% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 38.5% ▪ Ctrl: 32.7% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 19.2% ▪ Ctrl: 36.4% **Lung diseases** ▪ Exp: 15.4% ▪ Ctrl: 16.4% **Immunosuppressed** <u>Cancer</u> ▪ Exp: 9.6% ▪ Ctrl: 3.6% **Malignancy** ▪ Exp: 9.6 ▪ Ctrl: 3.6 **Kidney disease** ▪ Exp: 7.7% ▪ Ctrl: 14.6%			

5.4.5 **Studienselektion:** siehe 5.5.6

5.4.6 **Literaturrecherche:** siehe 5.5.7

5.5 Schlüsselfrage 3a.3) gewichtsbasierte Dosis Dexamethason vs. niedrige Dosis Dexamethason

Autor*innen: Caroline Hirsch

Es gab 1 RCT mit 142 Teilnehmenden.

5.5.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Weight-based dexamethasone (0.2 mg/kg)

Vergleichsintervention: Low-dose dexamethasone (6-8 mg)

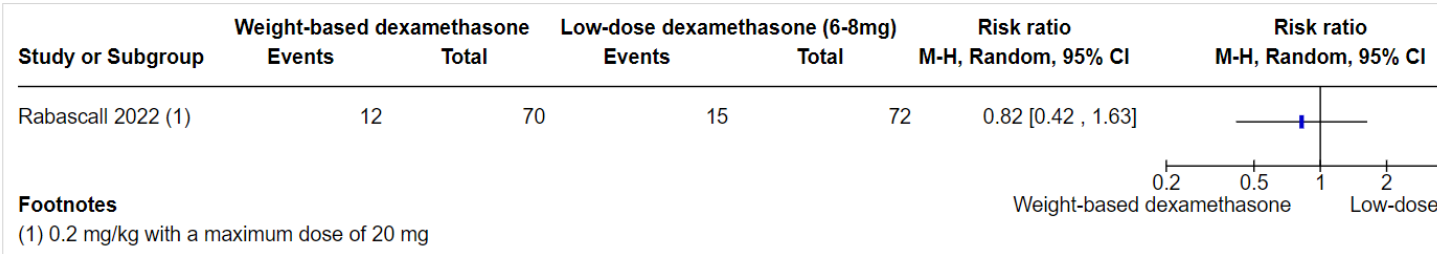
Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Low-dose dexamethasone (6-8 mg)	 Weight-based dexamethasone	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality up to 30 days	Relatives Risiko: 0.82 (CI 95% 0.42 - 1.63) Basierend auf Daten von 142 patienter und 1 Studien[1] Beobachtungszeit up to 30 days	**208** pro 1000	**171** pro 1000 Differenz: **37 weniger pro 1000** (CI 95% 121 weniger - 131 mehr)	**Niedrig** Due to very serious imprecision[2]	Weight-based dexamethasone may decrease all-cause mortality up to 30 days compared to low-dose dexamethasone
All-cause mortality up to 60 days	Relatives Risiko (CI 95% -)	pro 1000	**0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)		No studies were found that looked at all-cause mortality up to 60 days
All-cause mortality up to longest follow-up	Relatives Risiko (CI 95% -)	pro 1000	**0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)		No studies were found that looked at all-cause mortality up to longest follow-up
Clinical worsening: new need for IMV or death up to 30 days	Relatives Risiko (CI 95% -)	pro 1000	pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at new need for IMV or death up to 30 days
Clinical improvement: discharged alive up to 30 days	Relatives Risiko: 1.08 (CI 95% 0.92 - 1.28) Basierend auf Daten von 142 patienter und 1 Studien[3] Beobachtungszeit up to 30 days	**764** pro 1000	**825** pro 1000 Differenz: **61 mehr pro 1000** (CI 95% 61 weniger - 214 mehr)	**Moderat** Due to serious imprecision[4]	Weight-based dexamethasone probably increases the number of participants discharged alive up to day 30 compared to low-dose dexamethasone
Admission to ICU or death[5]	Relatives Risiko (CI 95% -)	pro 1000	pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at admission to ICU or death up to 30 days
Serious adverse events[6] during treatment	Relatives Risiko (CI 95% -)	pro 1000	pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at serious adverse events up to 30 days

Adverse events any grade[7] during treatment	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at adverse events any grade up to 30 days
Hospital acquired infections[8] during treatment	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at hospital acquired infections up to 30 days
Post COVID-19 condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post COVID-19 condition
Quality of life	Gemessen mit: Skala: -	Mittelwert Mittelwert		No studies were found that looked at quality of life

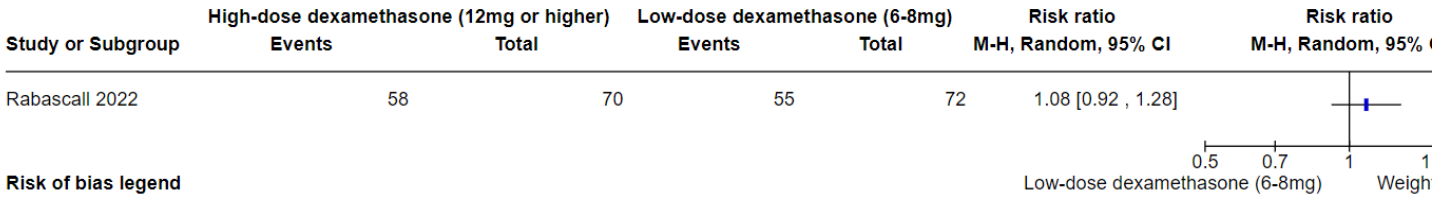
1. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3].
2. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Only data from one study;
3. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3].
4. Unzureichende Präzision: schwerwiegend. Only data from one study;
5. up to 30 days
6. undefined
7. undefined
8. undefined

5.5.2 Analysen / Forest Plots

Mortality, day 30



Clinical improvement: discharged alive, day 30



5.5.3 Referenzen der eingeschlossenen Studien

- Rabascall C, Lou BX, Dhar S, Hasan Z, Fryman C, Izard S, et al. (2022). Randomized Open Investigation Determining Steroid Dose in Severe COVID-19: the ROIDS-Dose Clinical Trial. Cureus, 14(11), e31086. doi:10.7759/cureus.31086

5.5.4 Charakteristika der eingeschlossenen Studien

5.5.4.1 *Charakteristika der eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Rabascall 2022 Open-label RCT	**Sample size:** N = 142 (1:1) randomised to dexamethasone 0.2 mg/kg intravenously daily, 6 mg daily ▪ 0.2 mg/kg intravenously daily: N = 70 ▪ 6 mg daily: N = 72 **Enrolment period:** 19.03.2021 to 28.12.2021 USA **Inclusion criteria:** ▪ adults ≥18 years of age ▪ positive SARS-CoV-2 polymerase chain reaction test ▪ required oxygen supplementation or had a documented oxygen saturation of less than 94% **Time since symptom onset (median, range):** ▪ NR ("data were not collected regarding the timing of initiation of corticosteroid therapy in relation to symptom onset") **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp:55.46 (SD 15.11) ▪ Ctrl: 57.22 (SD 15.18)	**Experimental:** ▪ intravenous dexamethasone ▪ Dose: 0.2 mg/kg with a maximum dose of 20 mg ▪ N = 70 **Control:** ▪ Intravenous dexamethasone ▪ Dose: 6mg ▪ N = 72 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.82 (0.42 to 1.63) Weight-based dexa: 12/70 Low-dose dexa: 15/72
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	RR: 1.08 (0.92 to 1.28) Weight-based dexa: 58/70 Low-dose dexa: 55/72
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	Comorbidities **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes** ▪ Exp: NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

5.5.5 **Studienselektion:** siehe 5.5.6

5.5.6 **Literaturrecherche:** siehe 5.5.7

5.6 Schlüsselfrage 3b) inhalative Steroide und SoC vs. SoC

Autor*innen: Marius Goldkuhle

Die verfügbare Evidenz umfasst 6 RCTs mit insgesamt 3824 eingeschlossenen Teilnehmern.

5.6.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: All adult patients (with or without risk factors for COVID-19) with positive PCR test for SARS-CoV-2

Intervention: inhaled corticosteroid

Vergleichsintervention: placebo and/or standard of care

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** placebo and/or standard of care	 inhaled corticosteroid	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality Up to 30 days	Relatives Risiko: 0.55 (CI 95% 0.21 - 1.42) Basierend auf Daten von 3824 patienter und 6 Studien	**6** pro 1000	**3** pro 1000 Differenz: **3 weniger pro 1000** (CI 95% 5 weniger - 3 mehr)	**Sehr niedrig** Due to serious indirectness, Due to very serious imprecision[1]	We are uncertain whether inhaled corticosteroids reduce all-cause mortality up to 30 days.
Admission to hospital or death Up to 30 days	Relatives Risiko: 0.77 (CI 95% 0.57 - 1.02) Basierend auf Daten von 3717 patienter und 5 Studien	**55** pro 1000	**42** pro 1000 Differenz: **13 weniger pro 1000** (CI 95% 24 weniger - 1 mehr)	**Niedrig** Due to serious indirectness, Due to serious imprecision[2]	Inhaled corticosteroids may reduce the risk of admission to hospital or death up to day 30.
Symptom resolution Up to 14 days	Relatives Risiko: 1.01 (CI 95% 0.82 - 1.25) Basierend auf Daten von 2401 patienter und 4 Studien	**481** pro 1000	**486** pro 1000 Differenz: **5 mehr pro 1000** (CI 95% 87 weniger - 120 mehr)	**Niedrig** Due to serious risk of bias, Due to serious indirectness[3]	Inhaled corticosteroids probably improve symptom resolution up to day 14 slightly.
Serious adverse events	Relatives Risiko: 0.54 (CI 95% 0.18 - 1.61) Basierend auf Daten von 2863 patienter und 2 Studien	**6** pro 1000	**3** pro 1000 Differenz: **3 weniger pro 1000** (CI 95% 5 weniger - 4 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[4]	We are uncertain whether inhaled corticosteroids increase serious adverse events.
Adverse events	Relatives Risiko: 0.72 (CI 95% 0.51 - 1.01) Basierend auf Daten von 1880 patienter und 3 Studien	**73** pro 1000	**53** pro 1000 Differenz: **20 weniger pro 1000** (CI 95% 36 weniger - 1 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision[5]	We are uncertain whether inhaled corticosteroids increase adverse events.
Time to symptom resolution	Gemessen mit: Skala: - Niedriger ist besser Basierend auf Daten von 353 patienter und 2 Studien	**12.1** DaysMittelwert	**9.97** DaysMittelwert Differenz: **MD 2.13 weniger** (CI 95% 3.90 weniger - 0.35 weniger)	**Sehr niedrig** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision[6]	We are uncertain whether inhaled corticosteroids decrease the time to symptom resolution.
Quality of life At day 28	Gemessen mit: WHO-5 Well-Being Questionnaire Skala: 0 - 100 Höher ist besser Basierend auf Daten von 1434 patienter und 2 Studien	**52** PercentMittelwert	**54.6** PercentMittelwert Differenz: **MD 2.60 mehr** (CI 95% 0.02 mehr - 5.18 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias[7]	We are uncertain whether inhaled corticosteroids increase quality of life at day 28.

1. Risiko für Bias: keine. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor

proportion of vaccinated individuals in included trials); Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals;

2. Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials); Unzureichende Präzision: schwerwiegend. Wide confidence intervals;

3. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials);

4. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals;

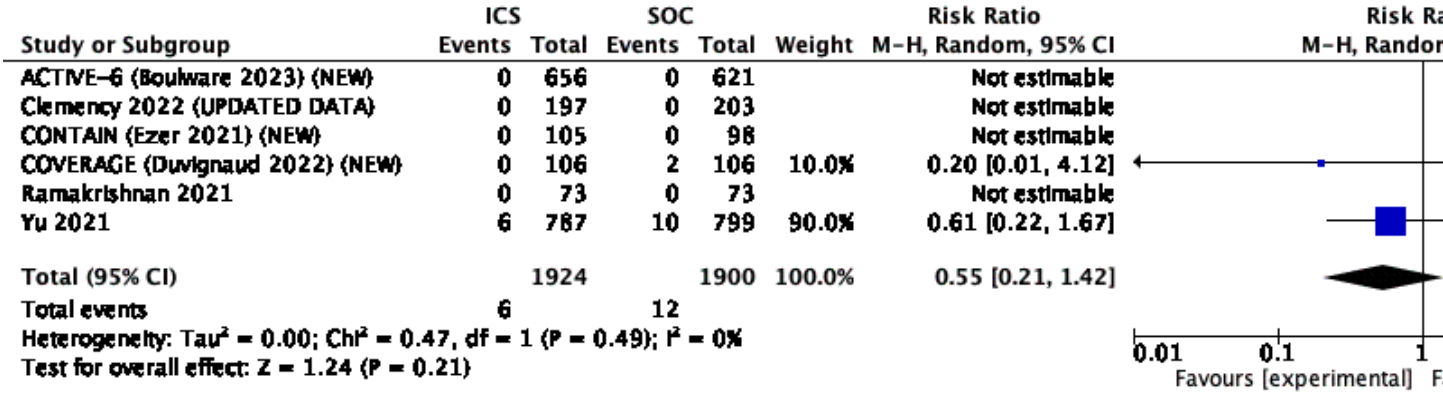
5. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;

6. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inkonsistenz: schwerwiegend. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2:... %.; Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).;

7. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).; Unzureichende Präzision: schwerwiegend. Only data from one study, Wide confidence intervals;

5.6.2 Analysen / Forest Plots

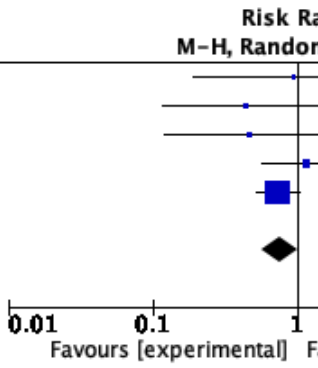
All-cause mortality



Admission to hospital or death

Study or Subgroup	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIVE-6 (Boulware 2023) (NEW)	3	656	3	621	3.3%	0.95 [0.19, 4.67]
Clemency 2022 (UPDATED DATA)	3	197	7	203	4.6%	0.44 [0.12, 1.68]
CONTAIN (Ezer 2021) (NEW)	3	105	6	98	4.5%	0.47 [0.12, 1.82]
COVERAGE (Duvignaud 2022) (NEW)	14	106	12	106	15.9%	1.17 [0.57, 2.40]
Yu 2021	52	787	75	838	71.7%	0.74 [0.53, 1.04]
Total (95% CI)		1851		1866	100.0%	0.77 [0.57, 1.02]
Total events	75		103			

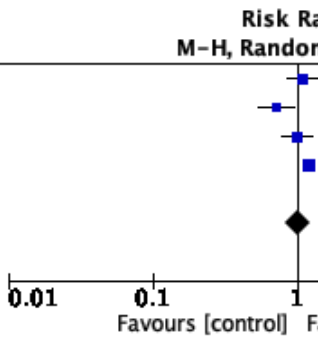
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.58$, $df = 4$ ($P = 0.63$); $I^2 = 0\%$
Test for overall effect: $Z = 1.82$ ($P = 0.07$)



Symptom resolution

Study or Subgroup	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio M-H, Random, 95% CI
Clemency 2022 (UPDATED DATA)	81	197	76	203	23.5%	1.10 [0.86, 1.40]
CONTAIN (Ezer 2021) (NEW)	44	105	57	98	21.3%	0.72 [0.54, 0.95]
COVERAGE (Duvignaud 2022) (NEW)	57	106	57	106	23.1%	1.00 [0.78, 1.28]
Yu 2021	462	787	390	799	32.1%	1.20 [1.10, 1.32]
Total (95% CI)		1195		1206	100.0%	1.01 [0.82, 1.25]
Total events	644		580			

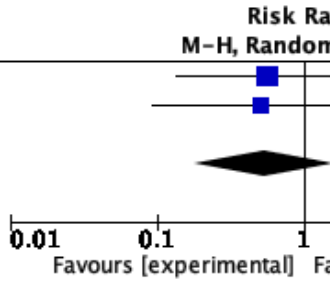
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 12.59$, $df = 3$ ($P = 0.006$); $I^2 = 76\%$
Test for overall effect: $Z = 0.11$ ($P = 0.91$)



Serious adverse events

Study or Subgroup	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIVE-6 (Boulware 2023) (NEW)	3	656	5	621	58.5%	0.57 [0.14, 2.37]
Yu 2021	2	787	4	799	41.5%	0.51 [0.09, 2.76]
Total (95% CI)		1443		1420	100.0%	0.54 [0.18, 1.61]
Total events	5		9			

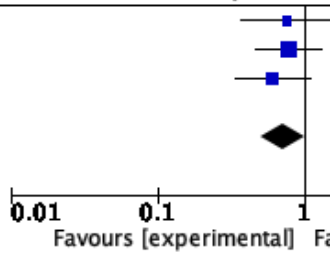
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, $df = 1$ ($P = 0.92$); $I^2 = 0\%$
Test for overall effect: $Z = 1.10$ ($P = 0.27$)



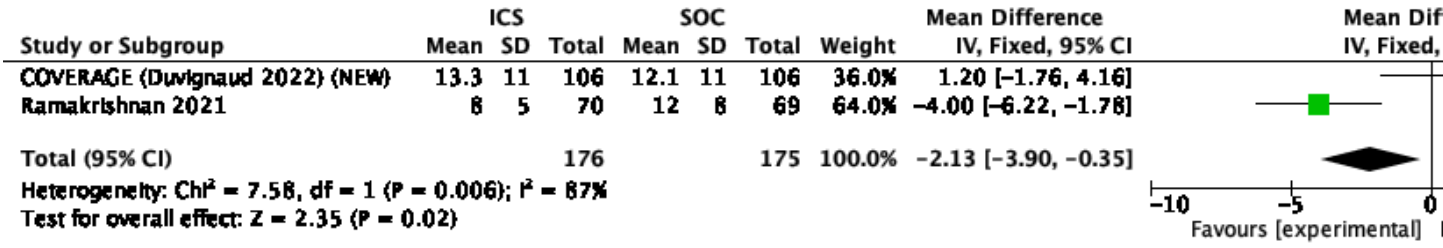
Adverse events

Study or Subgroup	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIVE-6 (Boulware 2023) (NEW)	13	656	16	621	22.4%	0.77 [0.37, 1.59]
Clemency 2022 (UPDATED DATA)	22	197	29	203	43.7%	0.78 [0.47, 1.31]
CONTAIN (Ezer 2021) (NEW)	15	105	23	98	33.8%	0.61 [0.34, 1.10]
Total (95% CI)		958		922	100.0%	0.72 [0.51, 1.01]
Total events	50		68			

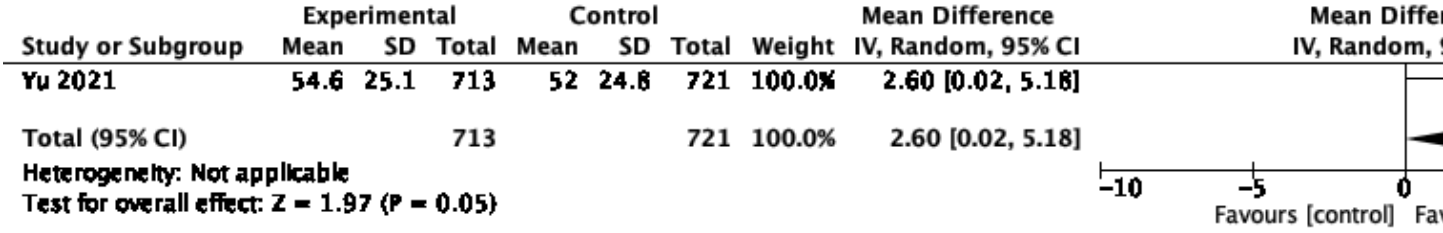
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.44$, $df = 2$ ($P = 0.80$); $I^2 = 0\%$
Test for overall effect: $Z = 1.91$ ($P = 0.06$)



Time to symptom resolution



Quality of life



5.6.3 Referenzen der eingeschlossenen Studien

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5.6.4 Charakteristika der eingeschlossenen Studien

5.6.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodis
Griesel, 2022 Systematic review with MA	**Study design** **Search time frame** Inception of each database to 07.10.2021 **Sources:** ▪ Cochrane COVID-19 Study Register (CENTRAL, MEDLINE; EMBASE; ClinicalTrials.gov,), WHO International Clinical Trials Registry Platform, medRxiv) ▪ • Web of Science Core Collection (Clarivate), from 1 January 2020 ▪ Onwards (Science Citation Index Expanded ▪ Emerging Sources Citation Index, ▪ WHO COVID-19 Global literature on	**Intervention A** Inhaled corticosteroids plus standard care **Intervention B** Standard care (with or without placebo)	3 studies on 3607 patients included in quantitative synthesis **Descriptive statistics:** ▪ Age: in two studies all participants were adults, in one study the participants had to be at least 12 years old (mean age: 43.3 (SD 16.89)) ▪ Sex: NR ▪ Comorbidities: the most common morbidities in the studies were asthma or arterial hypertension	**Comparison X:** Number of studies: 3 Number of participants: 3607 **Critical outcomes:** ▪ All-cause mortality (at up tp day 30): risk of corticosteroids 6 per 1000 vs. risk of standard care 9 per 1000; RR 0.61 (0.22 – 1.67) (3 studies, n = 2132) ▪ All-cause mortality (at up tp day 60): NR ▪ In-hospital mortality at up to longest follow-up: ▪ Clinical worsening: new need for IMV or death within 28 days: ▪ Clinical improvement participants discharges alive at up to day 28: ▪ Serious adverse events during study period: risk of corticosteroids 3 per 1000 vs. risk of standard care 5 per 1000; RR 0.51 (0.09 – 2.76) (1 study, n = 1586) ▪ Adverse events (any grade) at up to day 30: risk of corticosteroids 30 per 1000 vs. risk of standard care 34 per 1000; RR 0.88 (0.30 – 2.58) (1 study, n = 400) **Additional outcomes:** ▪ Symptom resolution at day 14: risk of corticosteroids 553 per 1000 vs. risk of standard care 465 per 1000; RR 1.19 (1.09 – 1.30) (2 studies, n = 1986) ▪ Admission to hospital or death at up to day 30: risk of corticosteroids 57 per 1000 vs. risk of standard care 79 per 1000; RR 0.72 (0.51 – 0.99) (2 studies, n = 2025)	**Methodologica** **included studi** **using GRADE t** **Evidence synth** ▪ Random-e **GRADE** ▪ All-cause (downgra to very se (very low events, wi ▪ In-hospita ▪ Clinical wo ▪ Clinical im ▪ Serious ad very low (three leve serious im low numb wide CI) a bias ▪ Adverse e (downgra due to ser and seriou ▪ Symptom ▪ admission death: mo (Downgra due to ser (low numb participan optimal in would be participan

	coronavirus disease **Eligibility criteria** **Study type:** RCTs as full-text publications or preprint articles, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes **Participants:** people with a confirmed diagnosis of COVID-19 and moderate-to-severe disease and people with a confirmed diagnosis of asymptomatic SARS-CoV-2 infection or mild COVID-19			▪ Infections during study period: risk of corticosteroids 30 per 1000 vs. risk of standard care 34 per 1000; RR 0.88 (0.30. – 2.58) (1 study, n = 400)	▪ Infections (downgra due to ver imprecisio

5.6.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Clemency, 2021 RCT	**Sample size:** N = 400 pts. (1:1) randomized to MDI or placebo (400 pts. planned) **Enrolment period:** 11.06.2020 to 03.11.2020 **Inclusion criteria:** ▪ ≥ 12 years ▪ Positive SARS-CoV-2 molecular antigen diagnostic sample obtained during the previous 72h ▪ not hospitalized or under consideration for hospitalization ▪ oxygen ▪ saturation level ≥ 93% on room air ▪ able to demonstrate successful use of an MDI at least 1 of the following symptomsof COVID-19: fever, cough, or dyspnea. **Time since symptom onset (median, range):**	**Experimental:** ▪ ciclesonide MDI plus standard supportive care ▪ Dose: 160 µg per actuation, for a total of 2 actuations (AM and PM) twice a day (total daily dose, 640 µg) for 30 days ▪ N = 197 **Control:** ▪ Placebo MDI twice a day plus standard supportive care (for 30 days) ▪ N = 203	All-cause mortality (29 days)	Exp: 0/197 Ctrl: 0/203
			Admission to hospital or death (30 days)	OR 0.45 (0.11-1.84) **Exp: 3/197** **Ctrl: 7/203**
			Symptom resolution: all initial symptoms resolved (day 14)	OR 1.19 (0.78-1.81) Exp: 81/197 Ctrl: 76/203 At 30 days: 139 vs. 129 (OR 1 1.97))
			Adverse events	Exp: 22/197 Ctrl: 203

	▪ **NR** **<u>Characteristics</u>** **Age (mean, IQR)** ▪ Exp: 43.7 (SD: 17.53; IQR: 13 – 87) ▪ Ctrl: 42.9 (SD: 16.28; IQR: 14 – 83) **Vaccination status** ▪ NR **Country** ▪ US ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes (Type 2):** ▪ Exp: 22/197 (11.2%) ▪ Ctrl: 8/203 (3.9%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: mean BMI under obesity ▪ Ctrl: mean BMI 30.0 (SD: 6.87) **Hypertension** ▪ Exp: 47/197 (23.9%) ▪ Ctrl: 42/203 (20.7%) **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases (Asthma)** ▪ Exp: 18/197 (9.1%) ▪ Ctrl: 8/203 (3.9%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR			

	▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Boulware, 2023 (ACTIVE-6) RCT	**Sample size:** N = 1407 pts. Randomized to fluticasone furoate or placebo (planned number of pts. NR) **Enrolment period:** 06.08.2021 to 09.02.2022 **Inclusion criteria:** ▪ Age ≥ 30 years old ▪ Confirmed SARS-CoV-2 infection by any authorized or approved polymerase chain reaction (PCR) or antigen test collected within 10 days of screening ▪ Two or more current symptoms of acute infection for ≤7 days. ▪ Symptoms include the following: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills,	**Experimental:** ▪ Inhaled fluticasone furoate ▪ Dose: 200 µg (packaged as 1 blister) once daily for 14 days ▪ N = 715 (656 included in analysis) **Control:** ▪ matched placebo inhaler or contributing placebo (matched placebo for a different active study drug, with data from those groups "contributing" to the pooled analyses) ▪ Dose: matched placebo once daily for 14 days or ivermectin-matched placebo for 3 days or fluvoxamine-matched placebo for 14 days ▪ N = 692 (621 included in analysis)	All-cause mortality (28 days)	Exp: 0/656 Ctrl: 0/621
			Admission to hospital or death (28 days)	HR 1.9 (0.8 to 3.5) **Exp: 3/656** **Ctrl: 3/621**
			Serious adverse events (28 days)	Exp: 3/656 Ctrl: 5/621
			Adverse events (28 days)	Exp: 13/656 Ctrl: 16/621
			Time to symptom resolution	HR 1.01 (0.89 to 1.14)

	headache, sore throat, nasal symptoms, new loss of sense of taste or smell **Time since symptom onset (median, range):** ▪ NR **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 45 (37-55) ▪ Ctrl: 46 (38 – 56) **Vaccination status** <u>Not vaccinated</u> ▪ Exp: 220 (33.5%) ▪ Ctrl: 211 (34.0%) <u>Vaccinated – 1 dose</u> ▪ Exp: 8 (1.2%) ▪ Ctrl: 11 (1.8%) <u>Vaccinated – 2+ doses</u> ▪ Exp: 428 (65.2%) ▪ Ctrl: 399 (64.3%) **Country** ▪ US ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes** ▪ Exp: 56/640 (3.9%) ▪ Ctrl: 65/606 (10.7%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 260/656 (39.6%) ▪ Ctrl: 239/620 (38.5%) **Hypertension**			

	▪ Exp: 156/640 (24.4%) ▪ Ctrl: 169/606 (27.9%) **Cardiovascular disease (Heart disease)** ▪ Exp: 25/640 (3.9%) ▪ Ctrl: 33/606 (5.4%) **Lung diseases** <u>COPD</u> ▪ Exp: 7/640 (1.1%) ▪ Ctrl: 11/606 (1.8%) <u>Asthma</u> ▪ Exp: 76/640 (11.9%) ▪ Ctrl: 86/606 (14.2%) **Immunosuppressed** <u>Cancer</u> ▪ Exp: 20/640 (3.0%) ▪ Ctrl: 23/606 (3.7%) **Malignancy** ▪ Exp: 20/640 (3.0%) ▪ Ctrl: 23/606 (3.7%) **Kidney disease** ▪ Exp: 6/640 (0.9%) ▪ Ctrl: 4/606 (0.7%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Duvignaud, 2022 (COVERAGE) RCT	**Sample size:** N = 217 pts. (1:1) Randomized to ciclesonid or Azinc Vitality (planned number of pts. NR) **Enrolment period:** 29.12.2020 to 23.06.2021 **Inclusion criteria:** ▪ Clinical picture suggestive of COVID-19 ≤ 7 days old ▪ Positive test for acute SARS-CoV-2 ▪ No criteria for hospitalization or acute oxygen therapy ▪ Age ≥ 60 years or between 50 and 59 years of age plus presence of at least one of the following risk factors: HTA under treatment, Obesity, Diabetes, Ischemic heart disease, Heart failure,	**Experimental:** ▪ Inhaled ciclesonide (Alvesco) ▪ Dose: 160 mg, two puffs twice a day using an inhalation chamber (640 mg of ciclesonide per day) for 10 days ▪ N = 110 **Control:** ▪ Azinc Vitality (a combination of vitamins and trace elements) ▪ Dose: 2 pills per day for 10 days ▪ N = 107	All-cause mortality (28 days)	Exp: 0/106 Ctrl: 2/106
			Admission to hospital or death (28 days)	Exp: 14/106 Ctrl: 12/106
			Symptom resolution: all initial symptoms resolved (14 days)	Exp: 57/106 Ctrl: 57/106
			Time to symptom resolution	Exp: 79/106 (mean 13.3, SD Ctrl: 78/106 (mean 12.1, SD

	History of stroke, COPD, Stage 3 chronic kidney disease, Solid tumours or haematological malignancies (within the last 5 years), ▪ Immunodeficiency, **Time since symptom onset (median, range):** ▪ Exp: 4 days (3 – 5) ▪ Ctrl: 4 days (3 – 6) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 62 (58 – 67) ▪ Ctrl: 63 (59 – 70) **Vaccination status** <u>Not vaccinated</u> ▪ Exp: NR ▪ Ctrl: NR <u>Vaccinated – 1 dose</u> ▪ Exp: 13 ▪ Ctrl: 15 <u>Vaccinated – 2+ doses</u> ▪ Exp: 1 ▪ Ctrl: 1 **Country** ▪ France ***<u>Comorbidities</u>*** **Any** ▪ Exp: 84/110 (76.4%) ▪ Ctrl: 73/107 (68.2%)			

	Diabetes ▪ Exp: 17/110 (15.5%) ▪ Ctrl: 16/107 (15.0%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 33/110 (30.0%) ▪ Ctrl: 31/107 (29.0%) **Hypertension** ▪ Exp: 51/110 (46.4%) ▪ Ctrl: 38/107 (35.5%) **Cardiovascular disease** ischemic heart disease ▪ Exp: 4/110 (3.6%) ▪ Ctrl: 7/107 (6.5%) Cardiac insufficiency ▪ Exp: 2/110 (1.8%) ▪ Ctrl: 3/107 (2.8%) **Lung diseases (COPD)** ▪ Exp: 3/110 (2.7%) ▪ Ctrl: 4/107 (3.7%) **Immunosuppressed** HIV ▪ Exp: 0/110 (0.0%) ▪ Ctrl: 1/107 (0.95) **Malignancy (solid tumour or heamatlogical malignancy <5y)** ▪ Exp: 7/110 (6.4%) ▪ Ctrl: 6/107 (5.6%) **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

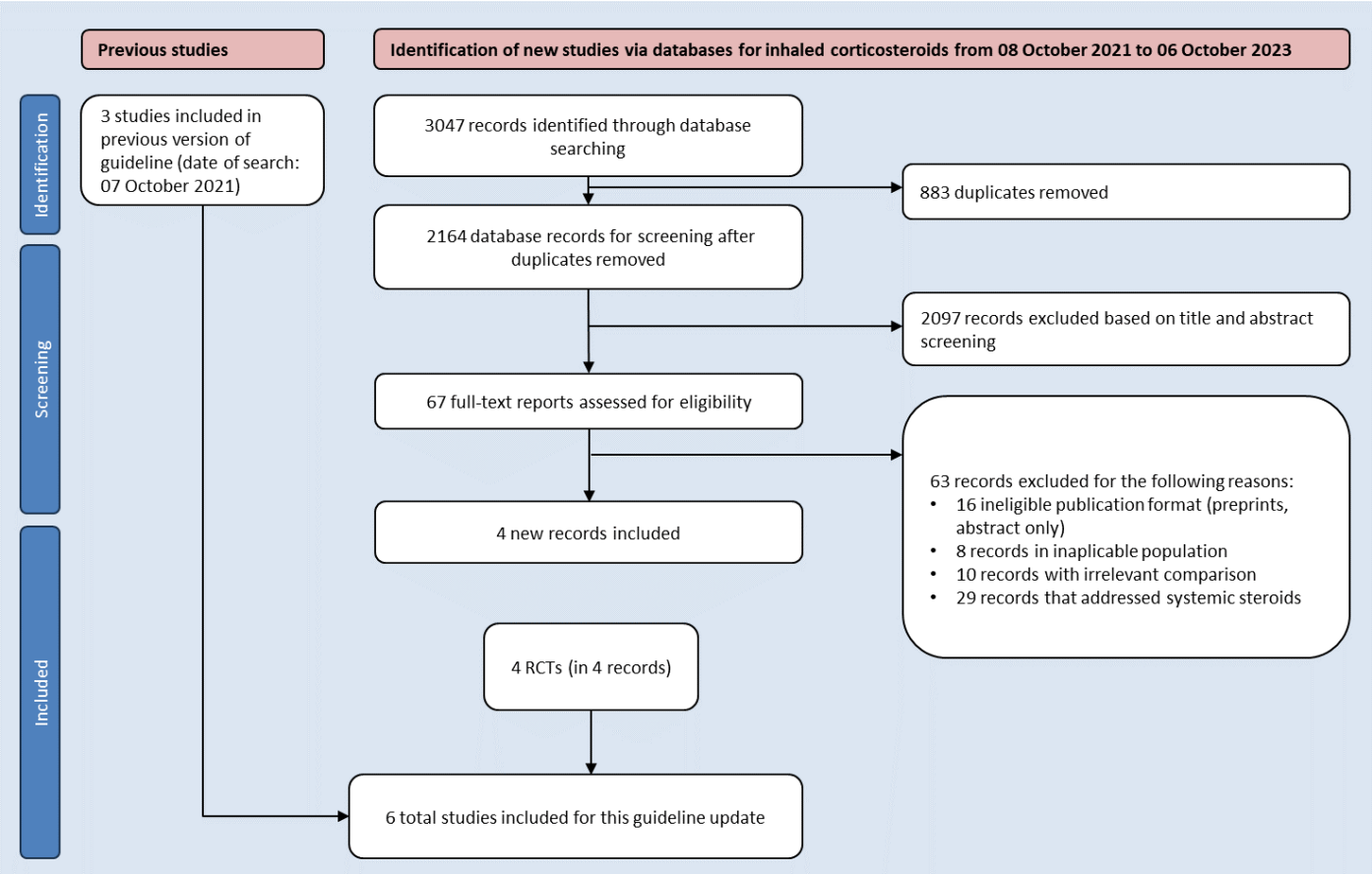
Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ezer, 2021 (CONTAIN) RCT	**Sample size:** N = 2015 pts. (1:1) Randomized to ciclesonide or placebo (XX pts. planned) **Enrolment period:** Quebec: 15.09.2020 to 08.06.2021 Ontario: 09.02.2021 to 08.06.2021 British Columbia: 22.03.2021 to 08.06.2021 **Inclusion criteria:** ▪ ≥ 18 years of age ▪ Symptomatic COVID-19 disease (fever, cough, OR shortness of breath) AND confirmed diagnosis with PCR+ SARS-CoV-2 within <= 5 days of enrolment* ▪ At least one of the following symptoms: ○ Fever >38C by self-report ○ "dry cough" or "wet cough" by self-report ○ Shortness of breath	**Experimental:** ▪ Inhaled and intranasal ciclesonide ▪ Dose: 1200 µg (divided twice daily) along with 200 µg/day of intranasal ciclesonide for 14 days ▪ N = 108 **Control:** ▪ Inhaled and intranasal placebo ▪ Dose: Same dosing schedule as the Experimental ▪ N = 107	All-cause mortality (29 days	Exp: 0 Ctrl: 0
			Admission to hospital or death (14 days)	**adjusted RD 2.3 (−3.0 to 7.6** **Exp: 3/105** **Ctrl: 7/98**
			Symptom resolution: all initial symptoms resolved (14 days)	adjusted RD 9.1 (−4.6 to 22.8 Exp: 44/105 Ctrl: 57/98
			Adverse events	"Side effects" (e.g., headache throat irritation) Exp: 15/105 Ctrl: 23/98

	Time since symptom onset (median, range): ▪ **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 35 (27 -47) ▪ Ctrl: 35 (27 – 45) **Vaccination status** ▪ Exp: no vaccination (exclusion criteria) ▪ Ctrl: no vaccination (exclusion criteria) **Country** ▪ Canada ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes** ▪ Exp: 1/105 (1.0%) ▪ Ctrl: 4/98 (4.0%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: 7/105 (7.0%) ▪ Ctrl: 5/98 (5.0%) **Cardiovascular disease (ischaemic heart disease)** ▪ Exp: 0/105 (0.0%) ▪ Ctrl: 1/98 (1.0%) **Lung diseases (Asthma)** ▪ Exp: 4/105 (4.0%) ▪ Ctrl: 6/98 (6.0%) **Immunosuppressed** <u>Active cancer</u> ▪ Exp: 1/105 (1.0%) ▪ Ctrl: 1/98 (1.0%) **Malignancy (Active cancer)** ▪ Exp: 1/105 (1.0%)			

	▪ Ctrl: 1/98 (1.0%) **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

5.6.5 Studienselektion: Flow Chart 5b

5.6.5.1 *Flow Chart 3b*



5.6.6 **Literaturrecherche:** siehe 5.5.7

5.7 Schlüsselfrage 4a: Tocilizumab und SoC vs. SoC alone

Autor*innen: Caroline Hirsch

Es gab 14 RCTs mit 7597 Teilnehmenden.

5.7.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Tocilizumab + Standard of Care

Vergleichsintervention: Standard of Care (plus/minus Placebo)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Standard of Care (plus/minus Placebo)	 Tocilizumab + Standard of Care	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality up to 30 days	Relatives Risiko: 0.88 (CI 95% 0.81 - 0.96) Basierend auf Daten von 6482 patienter und 9 Studien[1] Beobachtzungszeit up to 30 days	**302** pro 1000	**266** pro 1000 Differenz: **36 weniger pro 1000** (CI 95% 57 weniger - 12 weniger)	**Niedrig** Due to serious inconsistency, Due to serious imprecision[2]	Tocilizumab + standard of care may decrease all-cause mortality up to 30 days compared to standard of care alone
All-cause mortality up to 60 days	Relatives Risiko: 0.92 (CI 95% 0.71 - 1.21) Basierend auf Daten von 1265 patienter und 3 Studien[3] Beobachtzungszeit up to 60 days	**149** pro 1000	**137** pro 1000 Differenz: **12 weniger pro 1000** (CI 95% 43 weniger - 31 mehr)	**Moderat** Due to serious imprecision[4]	Tocilizumab + standard of care probably has little or no difference on all-cause mortality up to 60 days compared to standard of care alone
All-cause mortality up to 180 days	Relatives Risiko: 0.9 (CI 95% 0.77 - 1.05) Basierend auf Daten von 1181 patienter und 1 Studien[5] Beobachtzungszeit up to 180 days	**400** pro 1000	**360** pro 1000 Differenz: **40 weniger pro 1000** (CI 95% 92 weniger - 20 mehr)	**Niedrig** Due to very serious imprecision[6]	Tocilizumab + standard of care may decrease all-cause mortality up to 180 days compared to standard of care alone
Clinical improvement: time to discharged alive	Hazard ratio: 1.22 (CI 95% 1.13 - 1.32) Basierend auf Daten von 4566 patienter und 2 Studien[7]	**458** pro 1000	**526** pro 1000 Differenz: **68 mehr pro 1000** (CI 95% 41 mehr - 96 mehr)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[8]	Tocilizumab + standard of care may improve time to discharged alive compared to standard of care alone (baseline risk from Rosas 2021)
Clinical improvement: discharged alive[9] up to 30 days	Relatives Risiko: 1.17 (CI 95% 0.95 - 1.43) Basierend auf Daten von 438 patienter und 1 Studien[10] Beobachtzungszeit up to 30 days	**458** pro 1000	**536** pro 1000 Differenz: **78 mehr pro 1000** (CI 95% 23 weniger - 197 mehr)	**Niedrig** Due to very serious imprecision[11]	Tocilizumab + standard of care may increase the number of participants discharged alive up to 30 days compared to standard of care alone
Clinical worsening: new need for IMV or death up to 30 days	Relatives Risiko: 0.82 (CI 95% 0.76 - 0.89) Basierend auf Daten von 4865 patienter und 5 Studien[12] Beobachtzungszeit up to 30 days	**368** pro 1000	**302** pro 1000 Differenz: **66 weniger pro 1000** (CI 95% 88 weniger - 40 weniger)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[13]	Tocilizumab + standard of care may decrease the number of participants with new need for IMV or death up to 30 days compared to standard of care alone

Admission to ICU or death up to 30 days	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at admission to ICU or death
Serious adverse events up to 30 days	Relatives Risiko: 0.9 (CI 95% 0.76 - 1.07) Basierend auf Daten von 1758 patienter und 8 Studien[14] Beobachtungszeit up to 30 days	**231** **208** pro 1000 pro 1000 Differenz: **23 weniger pro 1000** (CI 95% 55 weniger - 16 mehr)	**Sehr niedrig** Due to serious inconsistency, Due to serious imprecision, Due to serious risk of bias[15]	We are uncertain whether tocilizumab + standard of care increases or decreases the number of participants with serious adverse events up to 30 days compared to standard of care alone
Serious adverse events[16] 60 to 90 days	Relatives Risiko: 0.9 (CI 95% 0.76 - 1.07) Basierend auf Daten von 1662 patienter und 4 Studien[17] Beobachtungszeit 60 to 90 days	**178** **160** pro 1000 pro 1000 Differenz: **18 weniger pro 1000** (CI 95% 43 weniger - 12 mehr)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[18]	Tocilizumab + standard of care may have little or no difference on serious adverse events 60 to 90 days compared to standard of care alone
Adverse events up to 30 days	Relatives Risiko: 1.1 (CI 95% 0.91 - 1.33) Basierend auf Daten von 1758 patienter und 8 Studien[19] Beobachtungszeit up to 30 days	**471** **518** pro 1000 pro 1000 Differenz: **47 mehr pro 1000** (CI 95% 42 weniger - 155 mehr)	**Sehr niedrig** Due to serious imprecision, Due to serious inconsistency, Due to serious risk of bias[20]	We are uncertain whether tocilizumab + standard of care increases or decreases the number of participants with adverse events up to 30 days compared to standard of care alone
Adverse events 60 to 90 days	Relatives Risiko: 0.98 (CI 95% 0.9 - 1.06) Basierend auf Daten von 907 patienter und 3 Studien[21] Beobachtungszeit 60 to 90 days	**687** **673** pro 1000 pro 1000 Differenz: **14 weniger pro 1000** (CI 95% 69 weniger - 41 mehr)	**Niedrig** Due to serious imprecision, Due to serious risk of bias[22]	Tocilizumab + standard of care may have little or no difference on adverse events 60 to 90 days compared to standard of care alone
Hospital-acquired infections up to 60 days	Relatives Risiko: 0.82 (CI 95% 0.59 - 1.13) Basierend auf Daten von 438 patienter und 1 Studien[23] Beobachtungszeit up to 60 days	**497** **408** pro 1000 pro 1000 Differenz: **89 weniger pro 1000** (CI 95% 204 weniger - 65 mehr)	**Niedrig** Due to very serious imprecision[24]	Tocilizumab + standard of care may decrease hospital-acquired infections up to 60 days compared to standard of care alone
Post COVID-19 condition[25]	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post COVID-19 condition
Quality of life	Gemessen mit: EQ VAS	**68.5** **69.1** Mittelwert Mittelwert	**Niedrig**	Tocilizumab + standard of care may have little or no

	Skala: 0 - 100 Höher ist besser Basierend auf Daten von 332 patienter und 1 Studien[26] Beobachtzungszeit at 180 days	Differenz: **MD 0.60 Größer** (CI 95% 4.43 kleiner - 5.63 Größer)	Due to serious risk of bias, Due to serious imprecision[27]	difference on quality of life at 180 days compared to standard of care alone

1. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [8]. [7]. [30]. [13]. [29]. [28]. [16]. [32]. [31].
2. Inkonsistenz: schwerwiegend. The direction of the effect is not consistent between the included studies; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
3. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [12]. [14]. [30].
4. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
5. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [9].
6. Unzureichende Präzision: sehr schwerwiegend. Only data from one study, Wide confidence intervals;
7. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [10]. [16]. [13].
8. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
9. undefined
10. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
11. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Only data from one study;
12. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [30]. [12]. [16]. [15]. [7].
13. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
14. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [32]. [31]. [13]. [29]. [35]. [7]. [28].
15. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inkonsistenz: schwerwiegend. The direction of the effect is not consistent between the included studies; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
16. undefined
17. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [30]. [8]. [13]. [10].
18. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
19. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [32]. [7]. [35]. [31]. [13]. [29]. [12]. [28].
20. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inkonsistenz: schwerwiegend. The direction of the effect is not consistent between the included studies, The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
21. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [10]. [30]. [13].

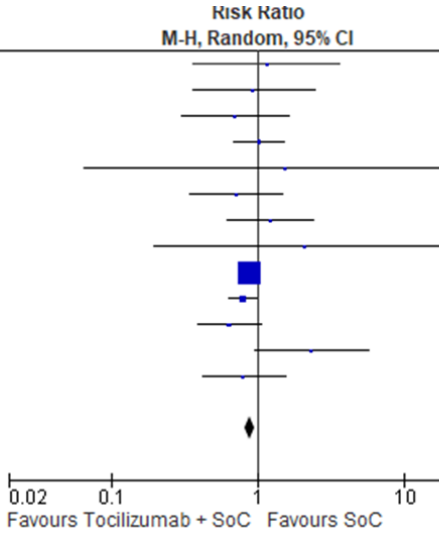
22. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
23. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
24. Unzureichende Präzision: sehr schwerwiegend. Only data from one study, Wide confidence intervals;
25. undefined
26. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [9].
27. Risiko für Bias: schwerwiegend. Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Unzureichende Präzision: schwerwiegend. Only data from one study;

5.7.2 Analysen / Forest Plots

Mortality, day 30

Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BACC-Bay (Stone 2020)	9	161	4	82	0.4%	1.15 [0.36, 3.61]
CORIMUNO-TOCI 1 (Hermine 2021)	7	63	8	67	0.6%	0.93 [0.36, 2.42]
CORIMUNO-TOCI 2 (Hermine 2022a)	8	49	10	43	0.8%	0.70 [0.30, 1.62]
COVACTA (Rosas 2021)	58	294	28	144	3.5%	1.01 [0.68, 1.52]
COVIDSTORM (Broman 2022)	1	57	0	29	0.1%	1.55 [0.07, 36.95]
COVINTOC (Soin 2021)	11	91	15	88	1.1%	0.71 [0.34, 1.46]
EMPACTA (Salama 2021)	26	249	11	128	1.3%	1.22 [0.62, 2.38]
RCT-TCZ (Salvarani 2021)	2	60	1	63	0.1%	2.10 [0.20, 22.56]
RECOVERY (Horby 2021)	621	2022	729	2094	74.9%	0.88 [0.81, 0.96]
REMA-CAP (Gordon 2021)	98	350	142	397	12.7%	0.78 [0.63, 0.97]
Rutgers 2022	21	174	34	180	2.3%	0.64 [0.39, 1.06]
TOCIBRAS (Veiga 2021)	14	65	6	64	0.7%	2.30 [0.94, 5.61]
TOCIDEX (Hermine 2022b)	15	224	19	226	1.4%	0.80 [0.42, 1.53]
Total (95% CI)		**3859**		**3605**	**100.0%**	**0.87 [0.81, 0.94]**
Total events	891		1007			

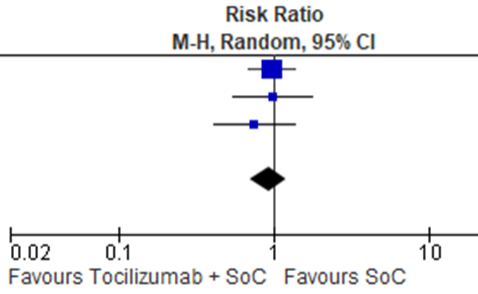
Heterogeneity: Tau² = 0.00; Chi² = 10.07, df = 12 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.48 (P = 0.0005)



Mortality, day 60

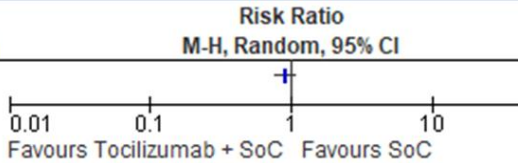
Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
COVACTA (Rosas 2021)	72	295	36	143	59.3%	0.97 [0.69, 1.37]
EMPACTA (Salama 2021)	29	250	15	127	20.8%	0.98 [0.55, 1.76]
TOCIDEX (Hermine 2022b)	17	224	23	226	19.9%	0.75 [0.41, 1.36]
Total (95% CI)		**769**		**496**	**100.0%**	**0.92 [0.71, 1.21]**
Total events	118		74			

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)



Mortality, day 180

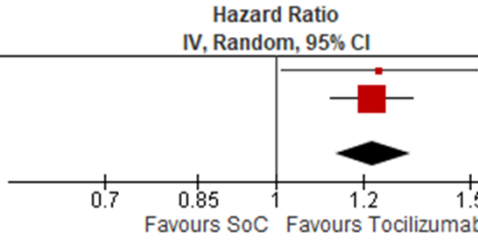
Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
REMA-CAP (Gordon 2021)	298	831	140	350	0.90 [0.77, 1.05]



Clinial improvement: time to discharged alive, day 30

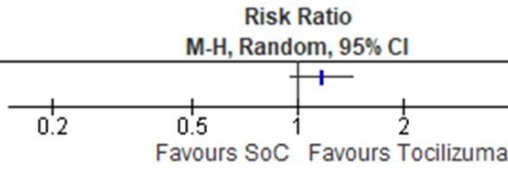
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CORIMUNO-TOCI 2 (Hermine 2022a)	0.2151	0.1047	14.8%	1.24 [1.01, 1.52]
RECOVERY (Horby 2021)	0.1989	0.0436	85.2%	1.22 [1.12, 1.33]
Total (95% CI)			**100.0%**	**1.22 [1.13, 1.32]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.00 (P < 0.00001)



Clinial improvement: discharged alive, day 30

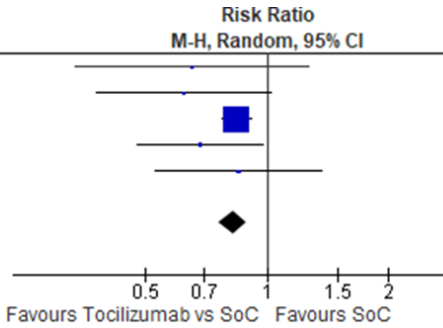
Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
COVACTA (Rosas 2021)	157	294	66	144	1.17 [0.95, 1.43]



Clinial worsening: new need for IMV or death, day 30

Study or Subgroup	Tocilizumab vs SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CORIMUNO-TOCI 1 (Hermine 2021)	11	63	18	67	1.4%	0.65 [0.33, 1.27]
EMPACTA (Salama 2021)	29	249	24	128	2.5%	0.62 [0.38, 1.02]
RECOVERY (Horby 2021)	619	1754	754	1800	88.6%	0.84 [0.77, 0.92]
Rutgers 2022	37	174	56	180	4.8%	0.68 [0.48, 0.98]
TOCIDEX (Hermine 2022b)	27	224	32	226	2.7%	0.85 [0.53, 1.37]
Total (95% CI)		**2464**		**2401**	**100.0%**	**0.82 [0.76, 0.89]**
Total events	723		884			

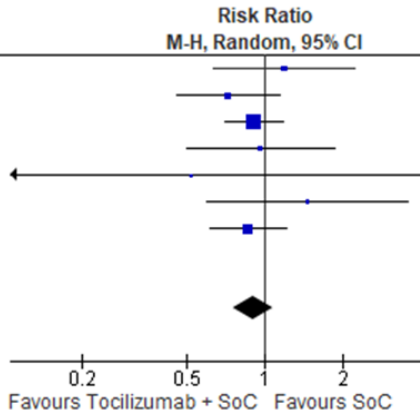
Heterogeneity: Tau² = 0.00; Chi² = 3.07, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 4.80 (P < 0.00001)



Serious adverse events, day 30

Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BACC-Bay (Stone 2020)	28	161	12	82	7.4%	1.19 [0.64, 2.21]
CORIMUNO-TOCI 1 (Hermine 2021)	20	64	29	67	13.9%	0.72 [0.46, 1.14]
COVACTA (Rosas 2021)	103	295	55	143	42.7%	0.91 [0.70, 1.18]
COVINTOC (Soin 2021)	15	91	15	88	6.7%	0.97 [0.50, 1.86]
RCT-TCZ (Salvarani 2021)	1	60	2	63	0.5%	0.53 [0.05, 5.64]
TOCIBRAS (Veiga 2021)	11	67	7	62	3.7%	1.45 [0.60, 3.51]
TOCIDEX (Hermine 2022b)	48	224	56	226	25.1%	0.86 [0.62, 1.21]
Wang 2020	0	34	0	31		Not estimable
Total (95% CI)		**996**		**762**	**100.0%**	**0.90 [0.76, 1.07]**
Total events	226		176			

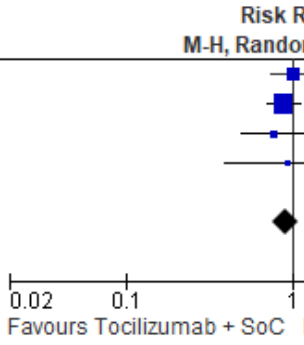
Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 6 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)



Serious adverse events, 60 to 90 days

Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CORIMUNO-TOCI 2 (Hermine 2022a)	31	49	27	43	29.0%	1.01 [0.74, 1.38]
COVACTA (Rosas 2021)	116	295	64	143	53.6%	0.88 [0.70, 1.11]
EMPACTA (Salama 2021)	38	250	25	127	13.6%	0.77 [0.49, 1.22]
REMA-CAP (Gordon 2021)	9	353	11	402	3.8%	0.93 [0.39, 2.22]
Total (95% CI)		**947**		**715**	**100.0%**	**0.90 [0.76, 1.07]**
Total events	194		127			

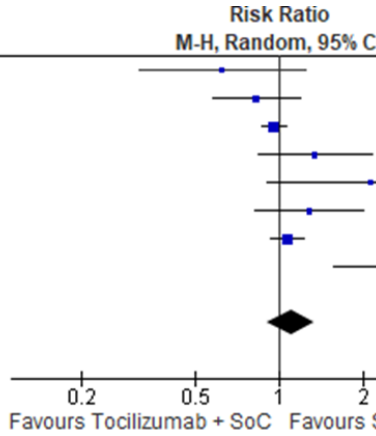
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)



Adverse events, day 30

Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BACC-Bay (Stone 2020)	16	161	13	82	6.2%	0.63 [0.32, 1.24]
CORIMUNO-TOCI 1 (Hermine 2021)	28	63	36	67	14.2%	0.83 [0.58, 1.18]
COVACTA (Rosas 2021)	228	295	116	143	25.3%	0.95 [0.86, 1.05]
COVINTOC (Soin 2021)	30	91	22	89	10.5%	1.33 [0.84, 2.13]
RCT-TCZ (Salvarani 2021)	14	60	7	63	4.5%	2.10 [0.91, 4.84]
TOCIBRAS (Veiga 2021)	29	67	21	62	11.2%	1.28 [0.82, 1.99]
TOCIDEX (Hermine 2022b)	147	224	139	226	23.7%	1.07 [0.93, 1.23]
Wang 2020	20	34	5	31	4.3%	3.65 [1.56, 8.54]
Total (95% CI)		**995**		**763**	**100.0%**	**1.10 [0.91, 1.33]**
Total events	512		359			

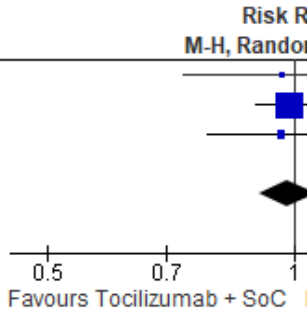
Heterogeneity: Tau² = 0.04; Chi² = 20.82, df = 7 (P = 0.004); I² = 66%
Test for overall effect: Z = 0.96 (P = 0.34)



Adverse events, 60 to 90 days

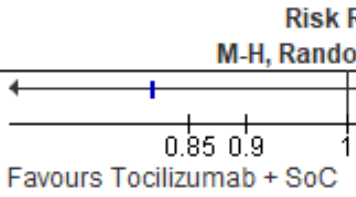
Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CORIMUNO-TOCI 2 (Hermine 2022a)	33	49	30	43	8.6%	0.97 [0.73, 1.27]
COVACTA (Rosas 2021)	240	295	118	143	75.8%	0.99 [0.90, 1.08]
EMPACTA (Salama 2021)	127	250	67	127	15.7%	0.96 [0.78, 1.18]
Total (95% CI)		**594**		**313**	**100.0%**	**0.98 [0.90, 1.06]**
Total events	400		215			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)



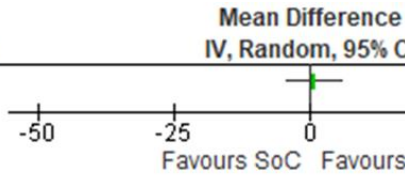
Hospital-acquired infections, day 60

Study or Subgroup	Tocilizumab + SoC Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
COVACTA (Rosas 2021)	71	295	42	143	0.82 [0.59, 1.13]



Quality of life, day 180 (EQ VAS)

Study or Subgroup	Tocilizumab + SoC Mean	SD	Total	SoC Mean	SD	Total	Mean Difference IV, Random, 95% CI
REMA-CAP (Gordon 2021)	69.1	22.6	235	68.5	20.7	97	0.60 [-4.43, 5.63]



5.7.3 Referenzen der eingeschlossenen Studien

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5.7.4 Charakteristika der eingeschlossenen Studien

5.7.4.1 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Broman, 2022 COVIDSTORM RCT, NCT04577534	**Sample size:** N = 88 pts. (90 pts. planned) **Enrolment period:** 12.08.2020 to 16.06.2021 Finland **Inclusion criteria:** ▪ Written consent obtained ▪ Hospitalized with COVID-19 ▪ Age >18 y ▪ SARS-CoV-2 PCR positive ▪ Peripheral oxygen saturation < 93% on ambient airor respiratory rate >30/min ▪ At least 2 of 4: Interleukin-6 >11.8 ng/L(2 xULN); Ferritin >300 mg/L in women or >800 mg/L in men(2 x ULN); D-dimer >1.5 mg/L; C-reactive protein >40 mg/L **Time since symptom onset (median, range):** ▪ Exp: 10 (4 to 18) ▪ Ctrl: 10 (4 to 18) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 63.2 (59.4 to 70.9)	**Experimental:** ▪ Intravenous tocilizumab plus standard of care ▪ Dose: single infusion dependent on body weight (400 mg for <60 kg, 600 mg for 60 to 90 kg, and 800 mg for > 90 kg) ▪ N = 59 **Control:** ▪ Standard of Care (subcutaneous low-molecular weight heparin and glucocorticoids) ▪ N = 29 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.55 (0.07 to 36.95) Tocilizumab: 1/57 SoC: 0/29
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Ctrl: 65.4 (57.6 to 70.5) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 26.3% ▪ Ctrl: 20.7% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 60.7% ▪ Ctrl: 69% **Hypertension** ▪ Exp: 38.6% ▪ Ctrl: 20.7% **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** Asthma ▪ Exp: 15.8% ▪ Ctrl: 10.3% COPD ▪ Exp: 3.5% ▪ Ctrl: 3.5% **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: 10.5% ▪ Ctrl: 13.8% **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Gordon, 2021 REMAP-CAP RCT, NCT02735707	**Sample size:** N = 826 pts. Randomized (including N = 48 Sarilumab) (pts. Planned: not reported) **Enrolment period:** 09.03.2020 to 19.11.2020 United Kingdom **Inclusion criteria:** ▪ Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (Covid-19) infection ▪ Severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an ICU ▪ Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur **Time since symptom onset (median, range):** ▪ NR **<u>Characteristics</u>** **Age (mean, IQR)** ▪ Exp: 61.4 – 63.4	**Experimental:** ▪ Intravenous tocilizumab ▪ Dose: (8 mg/kg infusion, maximum 800 mg), a 2nd infusion could be administered 12 to 24 hours after the 1st at the discretion of the treating clinician. 29% received a 2nd dose. Treatment initiated within 24 hours after starting organ support in the ICU ▪ Cointervention: Steroid use at baseline or any time during the study in > 80% of participants. Remdesivir use was recorded in 33% (265/807) of patients ▪ N = 366 **Control:** ▪ standard of care ▪ N = 412	All-cause mortality (day 30)	RR: 0.78 (0.63 to 0.97) Tocilizumab: 98/350 SoC: 142/397
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	RR: 0.90 (0.77 to 1.05) Tocilizumab: 298/831 SoC: 140/350
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Mean difference 0.60 (-4.43 to Tocilizumab: mean 69.1 (SD 2 SoC: mean 68.5 (SD 20.7)
			Post COVID-19 condition	Not reported

	▪ Ctrl: 61.1 ***<u>Comorbidities</u>*** **Any** ▪ Exp**:** NR ▪ Ctrl: NR **Diabetes:** ▪ Exp**:** NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: median BMI 30.5 (29.2 in Sarilumab): 337/353 (39/48 in Sarilumab) ▪ Ctrl: median BMI 30.9: 377/402 **Hypertension** ▪ Exp**:** NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp**:** NR ▪ Ctrl: NR **Lung diseases** ▪ Exp**:** NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp**:** NR ▪ Ctrl: NR **Malignancy** ▪ Exp**:** NR ▪ Ctrl: NR **Kidney disease** ▪ Exp**:** NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Hermine, 2021 CORIMUNO-TOCI 1 RCT, NCT04331808; EudraCT: 2020-001246-18	**Sample size:** N = 131 pts. Randomized (pts. Planned: not reported) **Enrolment period:** 31.03.2020 to 18.04.2020 France **Inclusion criteria:** ▪ Confirmed SARS-CoV-2 infection (positive on rRT-PCR and/or typical chest CT scan); ▪ requiring more than 3L/min of oxygen; ▪ WHO progression scale = 5 ▪ no NIV or High flow **Time since symptom onset (median, range):** ▪ Exp: 10 days (7-13) ▪ Ctrl: 10 days (8-13) **<u>Characteristics</u>** **Age (median, IQR)** Exp: 64.0 (75.1-74.3) ▪ Ctrl: 63.3 (75.1-72.3) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 20/61 (33%)	**Experimental:** ▪ Tocilizumab ▪ Dose: (8 mg/kg infusion) on day 1, an additional fixed dose of 400 mg IV on day 3 at physician discretion. ▪ N = 64 **Control:** ▪ standard of care alone (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants; provided at the discretion of the clinicians) ▪ N = 67 **Cointervention:** ▪ Steroids at baseline or any time during the study: Tocilizumab: 21 (33%), Standard care: 41 (61%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.93 (0.36 to 3.61) Tocilizumab: 7/63 SoC: 8/67
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.65 (0.33 to 1.27) Tocilizumab: 11/63 SoC: 18/67
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 0.72 (0.46 to 1.14) Tocilizumab: 20/64 SoC: 29/67
			Adverse events, any grade (day 30)	RR: 0.83 (0.58 to 1.18) Tocilizumab: 28/63 SoC: 36/67
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Ctrl: 20/67 (30%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: median BMI under obesity ▪ Ctrl: median BMI under obesity **Hypertension** ▪ Exp: NR ▪ Ctrl:NR **Cardiovascular disease (chronic cardiac disease)** ▪ Exp: 20/61 (33%) ▪ Ctrl: 20/67 (34%) **Lung diseases** chronic pulmonary disease (not asthma) ▪ Exp: 3/61 (5%) ▪ Ctrl: 3/67 (5%) Asthma ▪ Exp: 5/61 (8%) ▪ Ctrl: 3/67 (5%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy (Active malignant neoplasm)** ▪ Exp: 4/61 (7%) ▪ Ctrl: 5/67 (8%) **Kidney disease (chronic stage 1-3 or dialysis)** ▪ Exp: 5/61 (8%) ▪ Ctrl: 13/67 (19%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Hermine, 2022a CORIMUNO-TOCI 2 RCT, NCT04324047	**Sample size:** N = 97 pts. (120 pts. planned) **Enrolment period:** 31.03.2020 to 18.04.2020 France **Inclusion criteria:** ▪ confirmed SARS-CoV-2 infection (positive on reverse transcriptase-PCR and/or typical chest computed tomography scan) ▪ moderate, severe or critical pneumonia (O2 >3 L·min−1, WHO-CPS score ⩾5 **Time since symptom onset (median, range):** ▪ Exp: 11 (9 to 15) ▪ Ctrl: 11 (9 to 14) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 63.2 (59.4 to 70.9) ▪ Ctrl: 65.4 (57.6 to 70.5) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 41%	**Experimental:** ▪ Intravenous tocilizumab plus standard of care ▪ Dose: 8 mg/kg on day 1; additional administration of 400 mg on day 3 at discretion of the treating physician ▪ N = 51 **Control:** ▪ Standard of care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants provided at the discretion of clinicians) ▪ N = 46 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.70 (0.30 to 1.62) Tocilizumab: 8/49 SoC: 10/43
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: time-to-discharged alive (day 30)	HR: 1.24 (1.01 to 1.52)
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 90)	RR: 1.01 (0.74 to 1.38) Tocilizumab: 31/49 SoC: 27/43
			Adverse events, any grade (day 90)	RR: 0.97 (0.73 to 1.27) Tocilizumab: 33/49 SoC: 30/43
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Ctrl: 29% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 29% ▪ Ctrl: 32% **Lung diseases** Asthma ▪ Exp: 6% ▪ Ctrl: 5% COPD ▪ Exp: 6% ▪ Ctrl: 10% **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: 2% ▪ Ctrl: 2% **Kidney disease** ▪ Exp: 6% ▪ Ctrl: 7%			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Hermine, 2022b TOCIDEX RCT, NCT04476979	**Sample size:** N = 453 pts. (660 pts. planned) **Enrolment period:** 24.06.2020 to 18.05.2021 France **Inclusion criteria:** ▪ Patients with confirmed SARS CoV-2 infection (positive PCR and/or typical chest CT-scan) ▪ with moderate and severe pneumopathy requiring oxygen (>3 L/min) but without ventilation support (NIV), high flow or MV, WHO class 5 according to the WHO 10 points- Clinical Progression Scale (CPS) for COVID-19 pneumopathy **Time since symptom onset (median, range):** ▪ Exp: 9 (7 to 11) ▪ Ctrl: 9 (7 to 11) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 63.6 (53 to 73) ▪ Ctrl: median 63.2 (54 to 73)	**Experimental:** ▪ intravenous tocilizumab plus dexamethasone ▪ Dose: single dose 8mg/kg ▪ N = 226 **Control:** ▪ Intravenous dexamethasone ▪ N = 227 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.80 (0.42 to 1.53) Tocilizumab: 15/224 SoC: 19/226
			All-cause mortality (day 60)	RR: 0.75 (0.41 to 1.36) Tocilizumab: 17/224 SoC: 23/226
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.85 (0.53 to 1.37) Tocilizumab: 27/224 SoC: 32/226
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 0.86 (0.62 to 1.21) Tocilizumab: 48/224 SoC: 56/226
			Adverse events, any grade (day 30)	RR: 1.07 (0.93 to 1.23) Tocilizumab: 147/224 SoC: 139/226
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	<u>Comorbidities</u> **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 25% ▪ Ctrl: 22% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: 36% ▪ Ctrl: 38% **Cardiovascular disease** ▪ Exp: 14% ▪ Ctrl: 17% **Lung diseases** Asthma ▪ Exp: 11% ▪ Ctrl: 6% Chronic pulmonary disease ▪ Exp: 6% ▪ Ctrl: 8% **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: 4% ▪ Ctrl: 5% **Kidney disease** ▪ Exp: 9% ▪ Ctrl: 5%			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Horby, 2021 RECOVERY RCT, NCT04381936	**Sample size:** N = 4116 pts. randomized (pts. Planned: not reported) **Enrolment period:** 23.04.2020 – 42.01.2021 UK **Inclusion criteria:** ▪ Hospitalised adults patients (including pregnant women) with clinically suspected or laboratory-confirmed SARS-CoV-2 infection ▪ Hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy); evidence of systemic inflammation (C reactive protein (CRP) ≥ 75 mg/L) ▪ No medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial **Time since symptom onset (median, range):** ▪ NR **<u>Characteristics</u>**	**Experimental:** ▪ Tocilizumab ▪ Dose: 800 mg if weight > 90 kg; 600 mg if weight > 65 and ≤ 90 kg; 400 mg if weight > 40 and ≤ 65 kg; 8 mg/kg if weight ≤ 40 kg); a 2nd infusion could be administered 12 to 24 hours after the 1st ▪ N = 2022 **Control:** ▪ standard of care ▪ N = 2091 **Cointerventions:** ▪ Steroid use at baseline or any time during the study: Tocilizumab: 1664 (82%); Standard care: 1721 (82%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.88 (0.81 to 0.96) Tocilizumab: 621/2022 SoC: 729/2094
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: time-to-discharged alive (day 30)	HR: 1.22 (1.12 to 1.33)
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.84 (0.77 to 0.92) Tocilizumab: 619/1754 SoC: 754/1800
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	Age (mean, IQR) ▪ 63.3 ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Rosas, 2021 COVACTA RCT, NCT04320615	**Sample size:** N = 452 pts. randomized (pts. Planned: not reported) **Enrolment period:** 03.04.2020 to 28.05.2020 Europe and North America (Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, the United Kingdom, and the United States) **Inclusion criteria:** ▪ Patients 18 years or older ▪ severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or CT were enrolled ▪ blood oxygen saturation ≤ 93% or partial pressure of oxygen/fraction of inspired oxygen < 300 mm/Hg ▪ Patients were excluded if the treating physician determined that	**Experimental:** ▪ Tocilizumab ▪ Dose: 8 mg/kg infusion, maximum 800 mg), a second infusion could be administered 8 to 24 hours after the first ▪ N = 301 **Control:** ▪ placebo ▪ N = 151 **Cointerventions:** ▪ Steroid use at baseline or any time during the study: Tocilizumab: 57 (19%), Placebo: 41 (28%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.01 (0.68 to 1.52) Tocilizumab: 58/294 SoC: 28/144
			All-cause mortality (day 60)	RR: 0.97 (0.69 to 1.37) Tocilizumab: 72/295 SoC: 36/143
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	RR: 1.17 (0.95 to 1.43) Tocilizumab: 157/294 SoC: 66/144
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 0.91 (0.70 to 1.18) Tocilizumab: 103/295 SoC: 55/143
			Serious adverse events (day 60)	RR: 0.88 (0.70 to 1.11) Tocilizumab: 116/295 SoC: 64/143
			Adverse events, any grade (day 30)	RR: 0.95 (0.86 to 1.05) Tocilizumab: 228/295 SoC: 116/143
			Adverse events, any grade (day 60)	RR: 0.99 (0.90 to 1.08) Tocilizumab: 240/295 SoC: 118/143
			Hospital-acquired infections (day 60)	RR: 0.82 (0.59 to 1.13) Tocilizumab: 71/295 SoC: 42/143
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	death was imminent and inevitable within 24 hours or if they had active tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2. **Time since symptom onset (median, range):** ▪ Exp: 11.0 (1.0 – 49.0) ▪ Ctrl: 10.0 (2.0-50.0) **<u>Characteristics</u>** **Age (mean, IQR)** ▪ Exp: 60.9 ▪ Ctrl: 60.6 ***<u>Comorbidities</u>*** **Any** ▪ Exp: 231/294 (78.6%) ▪ Ctrl: 124/144 (86.1%) **Diabetes:** ▪ Exp: 105/294 (35.7%) ▪ Ctrl: 62/144 (43.1%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 63/294 (21.4%) ▪ Ctrl: 27/144 (18.8%) **Hypertension** ▪ Exp: 178/294 (60.5%) ▪ Ctrl: 94/144 (65.3%) **Cardiovascular disease** ▪ Exp: 88/294 (29.9%)			

	▪ Ctrl: 94/144 (65.3%) **Lung diseases (chronic)** ▪ Exp: 49/294 (16.7%) ▪ Ctrl: 22/144 (15.3%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Rutgers, 2022 RCT, trialregister.nl/trial/8504	**Sample size:** N = 354. (pts. planned: NR) **Enrolment period:** 06.04.2020 to 12.01.2021 Netherlands **Inclusion criteria:** ▪ 18 years or older, capable of providing informed consent and had SARS-CoV-2 infection confirmed by nasopharyngeal swab polymerase chain reaction ▪ Patients were required to be admitted to a ward ▪ have at least one of the following signs compatible with hyperinflammatio: 1) need for supplemental oxygen (inspired by the ASTCT consensus grade 2 for CRS, generally matching a saturation < 94%) [10] and/or 2) ferritin >2000ug/l or a doubling of serum ferritin in 20–48 hrs	**Experimental:** ▪ intravenous tocilizumab plus standard of care ▪ Dose: single dose 8mg/kg ▪ N = 174 **Control:** ▪ Standard of care ▪ N = 180 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.64 (0.39 to 1.06) Tocilizumab: 21/174 SoC: 34/180
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.68 (0.48 to 0.98) Tocilizumab: 37/174 SoC: 56/180
			Admission to ICU or death	Not reported
			Serious adverse events	Not reported
			Adverse events, any grade	Not reported
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	Time since symptom onset (median, range): ▪ Exp: NR ▪ Ctrl: NR **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 67 (60 to 74) ▪ Ctrl: 66 (56 to 74) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 31% ▪ Ctrl: 32% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Salama, 2021 EMPACTA RCT, NCT04372186	**Sample size:** N = 388 pts. Randomized (pts. Planned: not reported) **Enrolment period:** Not reported US, Mexico, Kenya, South Africa, Peru, or Brazil **Inclusion criteria:** ▪ Patients ≥18 years of age ▪ Hospitalized with Covid-19 pneumonia confirmed by a positive polymerase chain reaction test and radiographic imaging ▪ Blood oxygen saturation <94% on ambient air **Time since symptom onset (median, range):** ▪ NR **<u>Characteristics</u>** **Age (mean, IQR)** ▪ Exp: 56.0 ▪ Ctrl: 55.6 ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: NR	**Experimental:** ▪ Tocilizumab ▪ Dose: 8mg/kg up to 800 mg max infusion ▪ N = 259 **Control:** ▪ Placebo ▪ N = 129 **Cointervention:** ▪ Steroids at baseline or any time during the study: Tocilizumab: 200 (77%) Placebo: 112 (87%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.22 (0.62 to 2.38) Tocilizumab: 26/249 SoC: 11/128
			All-cause mortality (day 60)	RR: 0.98 (0.55 to 1.76) Tocilizumab: 29/250 SoC: 15/127
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.62 (0.38 to 1.02) Tocilizumab: 29/249 SoC: 24/128
			Admission to ICU or death	Not reported
			Serious adverse events (day 60)	RR: 0.77 (0.49 to 1.22) Tocilizumab: 38/250 SoC: 25/127
			Adverse events, any grade (day 60)	RR: 0.96 (0.78 to 1.18) Tocilizumab: 127/250 SoC: 67/127
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: mean BMI 32.0 ▪ Ctrl: mean BMI 33.1 **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Salvarani, 2021 RCT-TCZ RCT, NCT04346355; EudraCT: 2020-001386-37	**Sample size:** N = 126 pts. randomized (pts. Planned: not reported) **Enrolment period:** 31.03.2020 to 11.06.2020 Italy **Inclusion criteria:** ▪ Patients 18 years and older ▪ instrumental diagnosis of COVID-19 pneumonia confirmed by a positive reverse-transcriptase polymerase chain reaction assay for SARS-CoV-2 in a respiratory tract specimen ▪ presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) ratio between 200 and 300 mm/Hg ▪ inflammatory phenotype defined by a temperature greater than 38 ‘C during the last 2 days, and/or serum CRP levels of 10mg/dL or greater and/or CRP	**Experimental:** ▪ Tocilizumab ▪ Dose: 8 mg/kg; on day 1 up to a maximum of 800 mg, followed by a second dose after 12 hours ▪ N = 60 **Control:** ▪ standard of care ▪ N = 66 **Cointervention:** ▪ Steroids at baseline or any time during the study: Tocilizumab: 6 (10%), Standard care: 7 (11%) ▪ Heparin and LMWH 81 Tocilizumab 41 (68.3) , SC 40 (60.6) ▪ Antiretrovirals Tocilizumab 21 (35.0) , SC 31 (47.0) ▪ Azithromycin Tocilizumab 10 (16.7), SC 16 (24.2) ▪ Hydroxychloroquine Tocilizumab 53 (88.3), SC 62 (93.9) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 2.10 (0.20 to 22.56) Tocilizumab: 2/60 SoC: 1/63
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 0.53 (0.05 to 5.64) Tocilizumab: 1/60 SoC: 2/63
			Adverse events, any grade (day 30)	RR: 2.10 (0.91 to 4.84) Tocilizumab: 14/60 SoC: 7/63
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	level increased to at least twice the admission measurement **Time since symptom onset (mean, range):** ▪ Exp: 7.0 days (4.0-11.0) ▪ Ctrl: 8.0 days (6.0-11.0) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 61.5 (51.5-73.5) ▪ Ctrl: 60.0 (54.0-69.0) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 10/60 (16.7%) ▪ Ctrl: 9/66 (13.6%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 16/60 (28.1%) ▪ Ctrl: 22/66 (36.1%) **Hypertension** ▪ Exp: 27/60 (45.0%) ▪ Ctrl: 29/66 (43.9%) **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases (COPD)** ▪ Exp: 2/60 (3.3%) ▪ Ctrl: 2/66 (3.0%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR			

	▪ Ctrl: NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Soin, 2021 COVINTOC RCT, CTRI/2020/05/025369	**Sample size:** N = 180 pts. (pts. Planned: not reported) **Enrolment period:** 30.03.2020 to 31.08.2020 India **Inclusion criteria:** ▪ Patients aged 18 years or older ▪ admitted to hospital with SARS-CoV-2 infection confirmed by WHO criteria (positive PCR test on any specimen) and moderate to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-19 (moderate defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO2] 90–94%; and severe defined as respiratory rate ≥30 per min or SpO2 <90% in ambient air, or ARDS or septic shock.	**Experimental:** ▪ Tocilizumab ▪ Dose: single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. An additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days after administration of the first dose. ▪ N = 91 **Control:** ▪ Cointerventions balanced (91 vs 91% Corticoids, 43 vs 41 % Remdesivir) ▪ N = 88 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.71 (0.34 to 1.46) Tocilizumab: 11/91 SoC: 15/88
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 0.97 (0.50 to 1.86) Tocilizumab: 15/91 SoC: 15/88
			Adverse events, any grade (day 30)	RR: 1.33 (0.84 to 2.13) Tocilizumab: 30/91 SoC: 22/89
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	Time since symptom onset (median, range): ▪ NR **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 56 (47-63) ▪ Ctrl: 54 (43-63) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 31/91 (34%) ▪ Ctrl: 43/88 (49%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: 36/91 (40%) ▪ Ctrl: 34/88 (39%) **Cardiovascular disease** ▪ Exp: 15/91 (16%) ▪ Ctrl: 12/88 (14%) **Lung diseases (COPD)** ▪ Exp: 1/91 (1%) ▪ Ctrl:3/88 (3%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease (renal and urinary disorders)** ▪ Exp: 4/91 (4%) ▪ Ctrl: 4/88 (5%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Stone, 2020 BACC-Bay RCT, NCT04320615	**Sample size:** N = 243 pts. randomized (pts. Planned: not reported) **Enrolment period:** 20.04.2020 to 15.06.2020 US **Inclusion criteria:** ▪ 19 to 85 years of age ▪ SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay ▪ at least two of the following signs: fever (body temperature >38°C) within 72 h before enrollment, pulmonary infiltrates, or a need for supplemental oxygen to maintain an oxygen saturation >92% ▪ At least one of the following laboratory criteria: C-reactive protein level >50 mg/l, ferritin level >500 ng/ml, d-dimer	**Experimental:** ▪ Tocilizumab ▪ Dose: 8mg/kg infusion up to 800 mg max) single dose ▪ N = 161 **Control:** ▪ placebo ▪ N = 82 **Cointervention**: ▪ Steroids at baseline or any time during the study Tocilizumab: 18 (11%) Placebo: 5 (6%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.15 (0.36 to 3.61) Tocilizumab: 9/161 SoC: 4/82
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 1.19 (0.64 to 2.21) Tocilizumab: 28/161 SoC: 12/82
			Adverse events, any grade (day 30)	RR: 0.63 (0.32 to 1.24) Tocilizumab: 16/161 SoC: 13/82
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	level >1000 ng/ml, or lactate dehydrogenase level >250 U/l ▪ Exclusion if >10l/min of Oxygen, hence no HFNC, no NIV, no IMV at inclusion **Time since symptom onset (median, range):** ▪ Exp: 9.0 (6.0-13.0) ▪ Ctrl: 10.0 (7.0-13.0) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 61.6 (46.4-69.7) ▪ Ctrl: 56.5 (44.7-67.8) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 45/161 (28%) ▪ Ctrl: 30/82 (37%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 80/161 (50%) ▪ Ctrl: 42/82 (51%) **Hypertension** ▪ Exp: 80/161 (50%) ▪ Ctrl: 38/82 (46%) **Cardiovascular disease** Heart failure ▪ Exp: 17/161 (11%) ▪ Ctrl: 7/82 (9%) History of myocardial infarction ▪ Exp: 15/161 (9%) ▪ Ctrl: 6/161 (7%) **Lung diseases** COPD			

	▪ Exp: 15/161 (9%) ▪ Ctrl: 7/82 (9%) Asthma ▪ Exp: 15/161 (9%) ▪ Ctrl: 7/82 (9%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** history of cancer ▪ Exp: 22/161 (14%) ▪ Ctrl: 8/82 (19%) **Kidney disease** ▪ Exp: 29/161 (18%) ▪ Ctrl: 13/82 (16%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Veiga, 2021 TOCIBRAS RCT, NCT04403685	**Sample size:** N = 129 pts. Randomized (pts. Planned: not reported) **Enrolment period:** 08.05.2020 to 17.06.2020 Brazil **Inclusion criteria:** ▪ Confirmed diagnosis of SARS-CoV-2 infection ▪ Computed tomography (or chest X-ray) of the chest consistent with COVID-19 ▪ More than three days of symptoms related to COVID-19 ▪ 18 years or older; ▪ Need for oxygen supplementation to maintain SpO2 > 93% OR need for mechanical ventilation less than 24 hours before the randomization ▪ Two or more of the following inflammatory tests: i. D-dimer > 1,000 ng/mL; ii. C reactive protein > 5 mg/dL; iii. Ferritin > 300 mg/dL; iv. Lactate dehydrogenase >	**Experimental:** ▪ Tocilizumab ▪ Dose: 8 mg/kg, IV) on day 1 up to a max of 800 mg ▪ N = 65 **Control:** ▪ standard of care ▪ N = 64 **Cointervention:** ▪ Steroids at baseline or any time during the study Tocilizumab: 56 (86%) Standard care: 55 (86%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 2.30 (0.94 to 5.61) Tocilizumab: 14/65 SoC: 6/64
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: 1.45 (0.60 to 3.51) Tocilizumab: 11/67 SoC: 7/62
			Adverse events, any grade (day 30)	RR: 1.28 (0.82 to 1.99) Tocilizumab: 29/67 SoC: 21/62
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	upper limit of normal **Time since symptom onset (mean, SD):** ▪ Exp: 10.0 (3.1) ▪ Ctrl: 9.5 (3.0) **<u>Characteristics</u>** **Age (mean, SD)** ▪ Exp: 57.4 ▪ Ctrl: 57.5 (13.5) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 22/65 (34%) ▪ Ctrl: 20/64 (31%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 15/65 (23%) ▪ Ctrl: 16/64 (25%) **Hypertension** ▪ Exp: 30/65 (64%) ▪ Ctrl: 34/64 (53%) **Cardiovascular disease** Heart failure ▪ Exp: 4/65 (6%) ▪ Ctrl: 3/64 (5%) Myocardial infarction ▪ Exp: 4/65 (6%) ▪ Ctrl: 3/64 (5%) **Lung diseases** COPD ▪ Exp: 2/65 (3%) ▪ Ctrl: 2/64 (3%) Asthma ▪ Exp: 4/65 (6%) ▪ Ctrl: 1/64 (2%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** Solid malignancy			

	▪ Exp: 4/65 (6%) ▪ Ctrl: 5/64 (8%) Heamatological malignancy ▪ Exp: 1/65 (1%) ▪ Ctrl: 0/64 (0%) **Kidney disease** ▪ Exp: 5/65 (8%) ▪ Ctrl: 1/64 (2%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Wang, 2020 RCT	**Sample size:** N = 65 pts. Randomized (pts. Planned: not reported) **Enrolment period:** 13.02.2020 to 13.03.2020 China **Inclusion criteria:** ▪ 18 to 85 years old ▪ Plasma IL-6 levels elevated ▪ Moderate (with bilateral pulmonary lesions) or severe in disease degree **Time since symptom onset (median, IQR):** ▪ Exp: 20 (9-29) ▪ Ctrl: 24 (19-33) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 63.5 (58-71) ▪ Ctrl: 63 (54-69) ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: 4/34 (11.76%) ▪ Ctrl: 6/31 (19.35%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension**	**Experimental:** ▪ Tocilizumab ▪ Dose: 400 mg infusion; Patients received a 2nd dose only if their condition did not improve or worsened. The number of patients received 2nd dose is not reported. ▪ N = 33 **Control:** ▪ standard of care ▪ N = 32 **Cointerventions** ▪ Steroid use at baseline or any time during the study: Tocilizumab: 15%, Standard care: &5 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	Not reported
			All-cause mortality (day 60)	Not reported
			All-cause mortality (day 180)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 30)	RR: Not estimable Tocilizumab: 0/34 SoC: 0/31
			Adverse events, any grade (day 30)	RR: 3.65 (1.56 to 8.54) Tocilizumab: 20/34 SoC: 5/31
			Hospital-acquired infections	Not reported
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	▪ Exp: 10/34 (29.41%) ▪ Ctrl: 10/31 (32.26%) **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

5.8 Schlüsselfrage 4b: hohe Dosis Tocilizumab (8 mg/kg) vs. niedrige Dosis Tocilizumab (4 mg/kg)

Autor*innen: Caroline Hirsch

Es gab 1 RCT mit 100 Teilnehmenden.

5.8.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: High-dose tocilizumab (8 mg/kg)

Vergleichsintervention: Low-dose tocilizumab (4 mg/kg)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Low-dose tocilizumab	 High-dose tocilizumab	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality up to 30 days	Relatives Risiko: 0.73 (CI 95% 0.25 - 2.14) Basierend auf Daten von 97 patienter und 1 Studien[1] Beobachtungszeit up to 30 days	**143** pro 1000	**104** pro 1000 Differenz: **39 weniger pro 1000** (CI 95% 107 weniger - 163 mehr)	**Niedrig** Due to very serious imprecision[2]	High-dose tocilizumab may decrease all-cause mortality up to 30 days compared to low-dose tocilizumab
All-cause mortality up to 60 days	Relatives Risiko: 0.77 (CI 95% 0.29 - 2.04) Basierend auf Daten von 97 patienter und 1 Studien[3] Beobachtungszeit up to 60 days	**163** pro 1000	**126** pro 1000 Differenz: **37 weniger pro 1000** (CI 95% 116 weniger - 170 mehr)	**Niedrig** Due to very serious imprecision[4]	High-dose tocilizumab may decrease all-cause mortality up to 60 days compared to low-dose tocilizumab

All-cause mortality up to longest follow-up	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at all-cause mortality up to longest follow-up
Clinical improvement: discharged alive up to 30 days	Relatives Risiko: 0.99 (CI 95% 0.81 - 1.22) Basierend auf Daten von 97 patienter und 1 Studien[5] Beobachtungszeit up to 30 days	**796** **788** pro 1000 pro 1000 Differenz: **8 weniger pro 1000** (CI 95% 151 weniger - 175 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to serious risk of bias[6]	We are uncertain whether high-dose tocilizumab increases or decreases the number of participants discharged alive up to 30 days compared to low-dose tocilizumab
Clinical worsening: new need for IMV or death up to 30 days	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at new need for IMV or death up to 30 days
Admission to ICU or death up to 30 days	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at admission to ICU or death up to 30 days
Serious adverse events up to 60 days	Relatives Risiko: 0.82 (CI 95% 0.43 - 1.56) Basierend auf Daten von 97 patienter und 1 Studien[7] Beobachtungszeit up to 60 days	**306** **251** pro 1000 pro 1000 Differenz: **55 weniger pro 1000** (CI 95% 174 weniger - 171 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to serious risk of bias[8]	We are uncertain whether high-dose tocilizumab increases or decreases the number of participants with serious adverse events up to 60 days compared to low-dose tocilizumab
Adverse events up to 60 days	Relatives Risiko: 0.8 (CI 95% 0.54 - 1.19) Basierend auf Daten von 97 patienter und 1 Studien[9] Beobachtungszeit up to 60 days	**571** **457** pro 1000 pro 1000 Differenz: **114 weniger pro 1000** (CI 95% 263 weniger - 108 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to serious risk of bias[10]	We are uncertain whether high-dose tocilizumab increases or decreases the number of participants with adverse events up to 60 days compared to low-dose tocilizumab
Hospital-acquired infections up to 60 days	Relatives Risiko: 1.02 (CI 95% 0.27 - 3.85) Basierend auf Daten von 97 patienter und 1 Studien[11] Beobachtungszeit up to 60 days	**82** **84** pro 1000 pro 1000 Differenz: **2 mehr pro 1000** (CI 95% 60 weniger - 234 mehr)	**Niedrig** Due to very serious imprecision[12]	High-dose tocilizumab may have little or no difference on hospital-acquired infections up to 60 days compared to low-dose tocilizumab
Post COVID-19 condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post COVID-19 condition
Quality of life	Gemessen mit: Skala: -	Mittelwert Mittelwert		

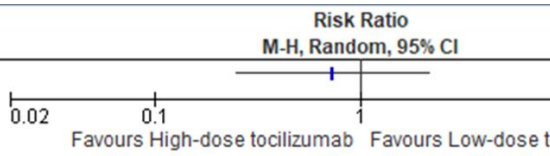
		Differenz: **MD null kleiner**		No studies were found that looked at quality of life

1. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [26].
2. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients, Only data from one study;
3. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [26].
4. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients, Only data from one study;
5. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [26].
6. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients, Only data from one study;
7. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [26].
8. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients, Only data from one study;
9. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [26].
10. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients, Only data from one study;
11. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm . Referenzen [26].
12. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients, Only data from one study;

5.8.2 Analysen / Forest Plots

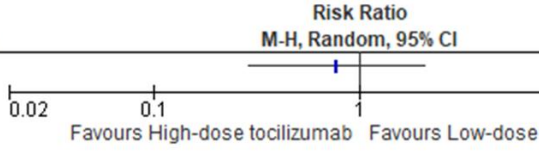
Mortality, day 30

Study or Subgroup	High-dose tocilizumab Events	Total	Low-dose tocilizumab Events	Total	Risk Ratio M-H, Random, 95% CI
Kumar 2022	5	48	7	49	0.73 [0.25, 2.14]



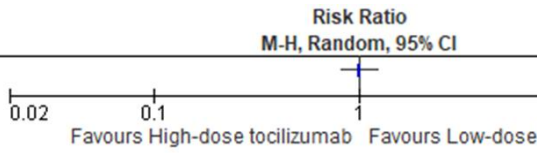
Mortality, day 60

Study or Subgroup	High-dose tocilizumab Events	Total	Low-dose tocilizumab Events	Total	Risk Ratio M-H, Random, 95% CI
Kumar 2022	6	48	8	49	0.77 [0.29, 2.04]



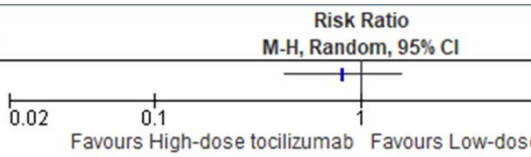
Clinical improvement: discharged alive, day 30

Study or Subgroup	Low-dose tocilizumab Events	Total	High-dose tocilizumab Events	Total	Risk Ratio M-H, Random, 95% CI
Kumar 2022	38	48	39	49	0.99 [0.81, 1.22]



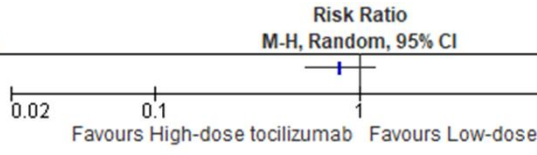
Serious adverse events, day 60

Study or Subgroup	High-dose tocilizumab Events	Total	Low-dose tocilizumab Events	Total	Risk Ratio M-H, Random, 95% CI
Kumar 2022	12	48	15	49	0.82 [0.43, 1.56]



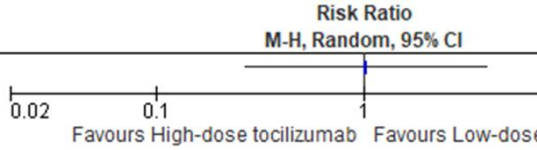
Adverse events, day 60

Study or Subgroup	High-dose tocilizumab Events	Total	Low-dose tocilizumab Events	Total	Risk Ratio M-H, Random, 95% CI
Kumar 2022	22	48	28	49	0.80 [0.54, 1.19]



Hospital-acquired infections, day 60

Study or Subgroup	High-dose tocilizumab Events	Total	Low-dose tocilizumab Events	Total	Risk Ratio M-H, Random, 95% CI
Kumar 2022	4	48	4	49	1.02 [0.27, 3.85]



5.8.3 Referenzen der eingeschlossenen Studien

- Kumar P, Hernandez-Sanchez J, Nagel S, Feng Y, Cai F, Rabin J, et al. Safety and Efficacy of Tocilizumab 4 or 8 mg/kg in Hospitalized Patients with Moderate to Severe Coronavirus Disease 2019 Pneumonia: a Randomized Clinical Trial. Open forum infectious diseases, 2022. 9(1):ofab608. doi: 10.1093/ofid/ofab608.

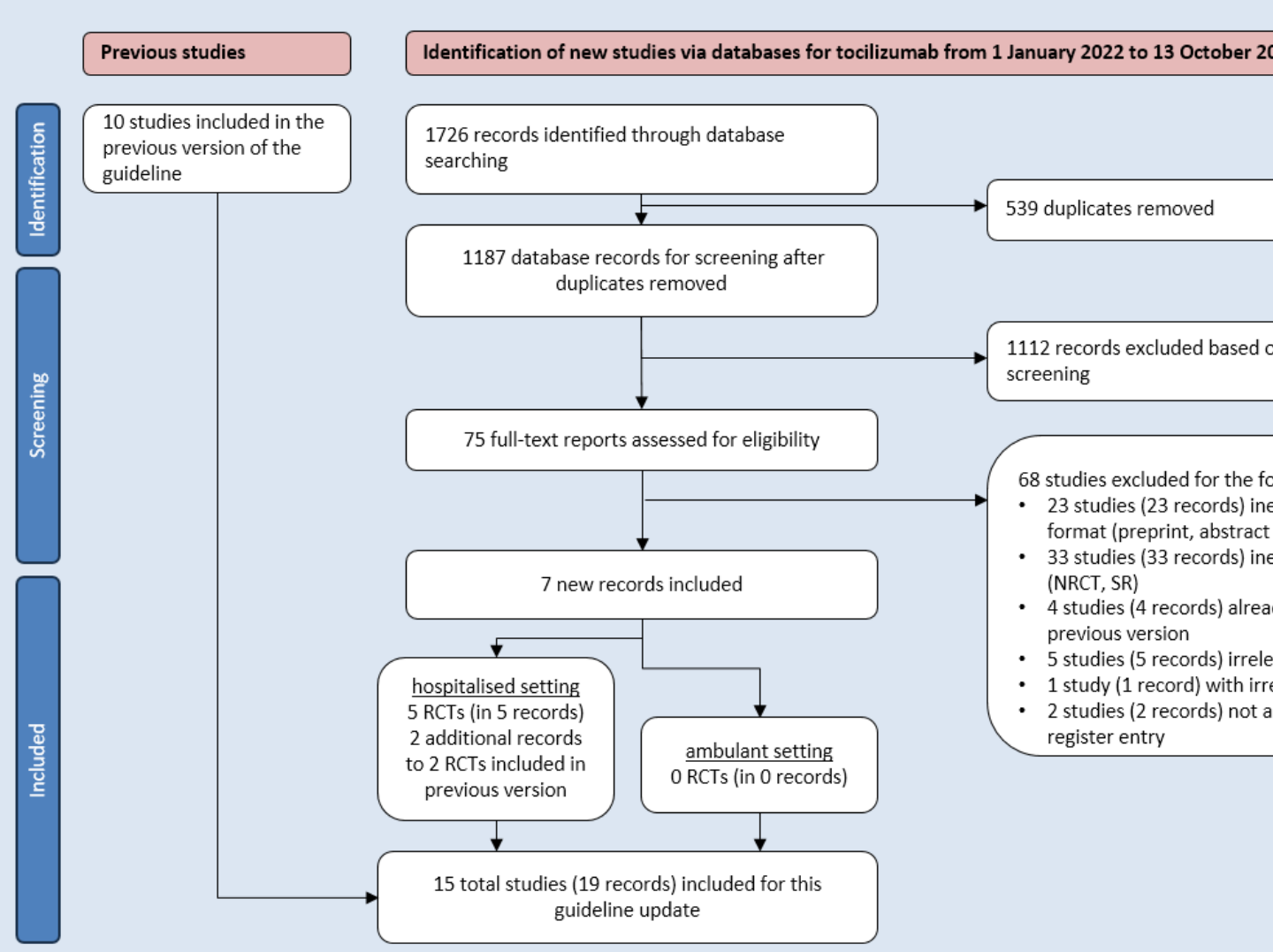
5.8.4 Charakteristika der eingeschlossenen Studien

5.8.4.1 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Kumar, 2022 Open-label RCT, NCT04363736	**Sample size:** N = 97 pts. (100 pts. planned) **Enrolment period:** 05.05.2020 to 12.08.2020 USA **Inclusion criteria:** ▪ patients ≥18 years ▪ hospitalized for moderate to severe COVID-19 pneumonia detected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive reverse-transcription polymerase chain reaction (RT-PCR) (within 7 days before randomization) ▪ confirmed by chest radiography or computed tomography scan ▪ severe COVID-19 pneumonia was defined as patients having blood oxygen saturation of ≤93% or partial pressure of oxygen to fraction of inspired oxygen ratio of <300 mm Hg	**Experimental:** ▪ Intravenous tocilizumab ▪ Dose: 8 mg/kg (max. 800 mg) ▪ N = 48 **Control:** ▪ Intravenous tocilizumab ▪ Dose: 4 mg/kg ▪ N = 49 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.73 (0.25 to 2.14) High-dose tocilizumab: 5/48 Low-dose tocilizumab: 7/49
			All-cause mortality (day 60)	RR: 0.77 (0.29 to 2.04) High-dose tocilizumab: 6/48 Low-dose tocilizumab: 8/49
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	RR: 0.99 (0.81 to 1.22) High-dose tocilizumab: 38/48 Low-dose tocilizumab: 39/49
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events (day 60)	RR: 0.82 (0.43 to 1.56) High-dose tocilizumab: 12/48 Low-dose tocilizumab: 15/49
			Adverse events, any grade (day 60)	RR: 0.80 (0.54 to 1.19) High-dose tocilizumab: 22/48 Low-dose tocilizumab: 28/49
			Hospital-acquired infections (day 60)	RR: 1.02 (0.27 to 3.85) High-dose tocilizumab: 4/48 Low-dose tocilizumab: 4/49
			Quality of life	Not reported
			Post COVID-19 condition	Not reported

	Time since symptom onset (median, range): ▪ **<u>Characteristics</u>** **Age (mean, SD)** ▪ Exp: 59.8 (14.6) ▪ Ctrl: 56.8 (14.3) ***<u>Comorbidities</u>*** **Any** ▪ Exp: 59.8 ▪ Ctrl: 56.8 **Diabetes:** ▪ Exp: NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

5.8.5 Studienselektion: Flow Chart 6a & 6b



5.8.6 Literaturrecherche 6a & 6b

LL COVID **Tocilizumab**

Suchzeitraum ab 01.01.2022

Studiendesign: RCTs

Date of search for all databases: search 13.10.2023			
Database/Register	Search	Update Search	Update Search
CCSR	550 references, 190 studies		
Scopus	965		
WHO COVID-19 DB*	211		
Total	1726		

Total (after deduplication and RCT classified Scopus refernces)	1188		

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Search string:

Tocilizumab* OR TCZ* OR atlizumab* OR actemra* OR roactemra* OR lusinex* OR r 1569 OR r1569 OR IL 6 OR interleukin 6 OR anti-interleukine 6 OR anti-interleukin drugs OR receptor OR inter leukin drugs OR IL-6 OR IL-6 blockade OR IL 6 receptor OR IL 6 inhibition OR IL 6

Suchstrategien

Cochrane COVID-19 Study Register

Search string:

tocilizumab* or TCZ* or atlizumab* or actemra* or roactemra* or lusinex* or "r 1569" or r1569 or "IL 6" or "interleukin 6" or "interleukine 6" or "anti-interleukin drugs"

Results available: report results

Study characteristics:

1) "Intervention assignment": "Randomised"; "Quasi-Randomised" OR "Unclear"
2) "Study design": "Parallel/Crossover" OR "Unclear"

Zeitraum: 01.0.2022 – 13.10.2023

Scopus (via Elsevier)

TITLE-ABS (tocilizumab* or TCZ* or atlizumab* or actemra* or roactemra* or lusinex* or "r 1569" or r1569 or "IL 6" or "interleukin 6" or "interleukine 6" or "anti-interleukin drugs")

AND TITLE-ABS(covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") AND AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023)) AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(tocilizumab* or TCZ* or atlizumab* or actemra* or roactemra* or lusinex* or "r 1569" or r1569 or "IL 6" or "interleukin 6" or "interleukine 6" or "anti-interleukin drugs")
AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")
Limit 2022, 2023

5.9 Schlüsselfrage 5a: Tixagevimab/Cilgavimab und SoC vs. SoC alone

Autor*innen: Nina Kreuzberger

5.9.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.9.1.1 *Evidenzprofil 1: Outpatients*

Population: Outpatients with confirmed COVID-19 diagnosis

Intervention: Evushield plus standard of care

Vergleichsintervention: Placebo plus standard of care

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo + SOC	Evushield + SOC	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
ICU admission or death day 29	Relatives Risiko: 0.28 (CI 95% 0.08 - 0.99) Basierend auf Daten von 833 patienter und 1 Studien	**26** pro 1000	**7** pro 1000 Differenz: **19 weniger pro 1000** (CI 95% 24 weniger - 0 weniger)	**Sehr niedrig** Due to very serious risk of bias, Due to very serious indirectness[1]	We are uncertain whether evushield plus standard of care increases or decreases the incidence of ICU admission.
Mortality, day 28	(CI 95% -) Basierend auf Daten von 337 patienter und 2 Studien	pro 1000	**0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)		There were no events in two comparisons on 337 participants.
Mortality, day 90	Relatives Risiko: 1.0 (CI 95% 0.32 - 3.07) Basierend auf Daten von 903 patienter und 1 Studien[2]	**13** pro 1000	**13** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 9 weniger - 27 mehr)	**Moderat** Due to serious imprecision[3]	Evushield plus standard of care probably has little or no difference on mortality through day 90.
Hospital admission or death	Relatives Risiko: 0.44 (CI 95% 0.27 - 0.73) Basierend auf Daten von 1171 patienter und 3 Studien[4]	**86** pro 1000	**38** pro 1000 Differenz: **48 weniger pro 1000** (CI 95% 63 weniger - 23 weniger)	**Sehr niedrig** Due to serious risk of bias, Due to very serious indirectness[5]	We are uncertain whether evushield plus standard of care improves or worsen hospital admission or death.
Symptom resolution by day 28	Relatives Risiko: 0.95 (CI 95% 0.82 - 1.2) Basierend auf Daten von 337 patienter und 2 Studien	**694** pro 1000	**659** pro 1000 Differenz: **35 weniger pro 1000** (CI 95% 125 weniger - 139 mehr)	**Moderat** Due to serious imprecision[6]	Evushield plus standard of care probably has little or no difference on symptom resolution by day 28.
Infusion-related reactions	Relatives Risiko: 1.01 (CI 95% 0.52 - 1.95) Basierend auf Daten von 1240 patienter und 3 Studien	**27** pro 1000	**27** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 13 weniger - 26 mehr)	**Moderat** Due to serious imprecision[7]	Evushield plus standard of care has probably little or no effect on infusion-related reactions.

Adverse events, grade 3-4	Relatives Risiko: 0.83 (CI 95% 0.25 - 2.76) Basierend auf Daten von 337 patienter und 1 Studien	**80** pro 1000 **66** pro 1000 Differenz: **14 weniger pro 1000** (CI 95% 60 weniger - 141 mehr)	**Sehr niedrig** Due to very serious indirectness, Due to serious imprecision[8]	We are uncertain whether evushield plus standard of care increases or decreases grade 3-4 adverse events.
Serious adverse events	Relatives Risiko: 0.59 (CI 95% 0.4 - 0.87) Basierend auf Daten von 1240 patienter und 3 Studien	**104** pro 1000 **61** pro 1000 Differenz: **43 weniger pro 1000** (CI 95% 62 weniger - 14 weniger)	**Niedrig** Due to very serious indirectness[9]	Evushield plus standard of care may decrease the incidence of serious adverse events.
Post Covid19-Condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post covid19-condition.
Adverse events, any grade	Relatives Risiko: 0.81 (CI 95% 0.67 - 0.98) Basierend auf Daten von 903 patienter und 1 Studien	**361** pro 1000 **292** pro 1000 Differenz: **69 weniger pro 1000** (CI 95% 119 weniger - 7 weniger)	**Niedrig** Due to very serious indirectness[10]	Evushield plus standard of care may decrease the number of participants with any grade adverse events.
Quality of life	Gemessen mit: Skala: - Höher ist besser	Mittelwert Mittelwert Differenz: **MD null kleiner**		No studies were found that looked at quality of life.

1. Risiko für Bias: sehr schwerwiegend. Competing events not accounted for.; Indirektheit: sehr schwerwiegend.
2. Primary study [33] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
3. Unzureichende Präzision: schwerwiegend. Wide confidence intervals, Low number of events;
4. Systematic review . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm [33], [34]
5. Risiko für Bias: schwerwiegend. For TACKLE, the larhest contributing study, competing events "deaths" were not taken into account.; Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC. Participants were not yet immunised.;
6. Unzureichende Präzision: schwerwiegend. Wide confidence intervals, Low number of patients;
7. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
8. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
9. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC. Participants were not yet immunised.;
10. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC. Participants were not yet immunised.

5.9.1.2 *Evidenzprofil 2: Inpatients*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Evushield plus standard of care

Vergleichsintervention: Placebo plus standard of care

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo + SOC Evushield + SOC	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality, day 28 28 days	Hazard ratio: 0.62 (CI 95% 0.42 - 0.92) Basierend auf Daten von 1417 patienter und 1 Studien[1]	**92** pro 1000 **58** pro 1000 Differenz: **34 weniger pro 1000** (CI 95% 52 weniger - 7 weniger)	**Sehr niedrig** Due to serious imprecision, Due to very serious indirectness[2]	We are uncertain whether Evushield plus standard of care improves or worsens mortality by day 28, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Mortality, day 90 90 days	Hazard ratio: 0.7 (CI 95% 0.5 - 0.97) Basierend auf Daten von 1417 patienter und 1 Studien[3]	**122** pro 1000 **74** pro 1000 Differenz: **1 mehr pro 1000** (CI 95% 37 weniger - 79 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to very serious indirectness[4]	We are uncertain whether Evushield plus standard of care improves or worsens mortality by day 90, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Time to sustained recovery through day 90 90 days	Hazard ratio: 1.08 (CI 95% 0.97 - 1.2) Basierend auf Daten von 1417 patienter und 1 Studien[5]	**842** pro 1000 **864** pro 1000 Differenz: **22 mehr pro 1000** (CI 95% 9 weniger - 49 mehr)	**Sehr niedrig** Due to serious imprecision, Due to very serious indirectness[6]	We are uncertain whether Evushield plus standard of care shortens or increases time to sustained recovery, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Time to hospital discharge absolute effect calculated for day 10	Hazard ratio (CI 95% -)	**0** pro 1000 pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)		No studies were found that looked at time to hospital discharge.
Adverse events, grade 3-4	Relatives Risiko: 0.95 (CI 95% 0.8 - 1.14) Basierend auf Daten von 1417 patienter und 1 Studien	**260** pro 1000 **247** pro 1000 Differenz: **13 weniger pro 1000** (CI 95% 52 weniger - 36 mehr)	**Moderat** Due to serious imprecision[7]	Evushield plus standard of care probably has little or no difference on grade 3-4 adverse events.
Need for IMV or death, day 28 28 days	Relatives Risiko: 0.8 (CI 95% 0.6 - 1.06) Basierend auf Daten von 1384 patienter und 1 Studien	**137** pro 1000 **110** pro 1000 Differenz: **27 weniger pro 1000** (CI 95% 55 weniger - 8 mehr)	**Sehr niedrig** Due to serious imprecision, Due to very serious indirectness[8]	We are uncertain whether Evushield plus standard of care improves or worsens IMV or death by day 28, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.

Adverse events, any grade 28 days	Relatives Risiko: 1.09 (CI 95% 0.9 - 1.32) Basierend auf Daten von 1417 patienter und 1 Studien	**222** pro 1000 **242** pro 1000 Differenz: **20 mehr pro 1000** (CI 95% 22 weniger - 71 mehr)	**Moderat** Due to serious imprecision[9]	Evushield plus standard of care probably has little or no difference on any adverse events.
Serious adverse events or death 90 days	Relatives Risiko: 0.76 (CI 95% 0.58 - 0.98) Basierend auf Daten von 1417 patienter und 1 Studien	**158** pro 1000 **120** pro 1000 Differenz: **38 weniger pro 1000** (CI 95% 66 weniger - 3 weniger)	**Niedrig** Due to very serious indirectness[10]	Evushield plus standard of care may decrease serious adverse events or death by day 90.
Post-Covid19 condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post-covid19 condition.
Quality of life	Gemessen mit: Skala: - Höher ist besser	Mittelwert Mittelwert Differenz: **MD null kleiner**		No studies were found that looked at quality of life.

1. Primary study [27] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
2. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals, Low number of events.;
3. Primary study [27] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
4. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients and events.;
5. Primary study [27] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
6. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
7. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
8. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
9. Indirektheit: keine. Differences between the population of interest and those studied; Unzureichende Präzision: schwerwiegend. Wie confidence intervals including the line of no effect.;
10. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied;

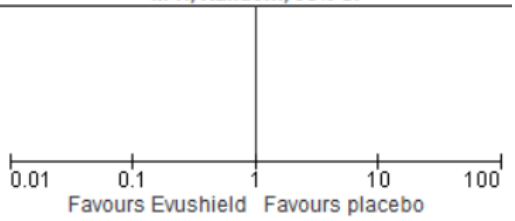
5.9.2 Analysen / Forest Plots der RCTs

5.9.2.1 *Outpatients*

Mortality, day 28

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIV-2, IM	0	106	0	117		Not estimable
ACTIV-2, IV	0	58	0	56		Not estimable
Total (95% CI)		**164**		**173**		**Not estimable**
Total events	0		0			

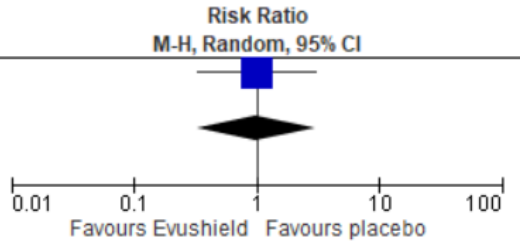
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Mortality, day 84

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TACKLE	6	452	6	451	100.0%	1.00 [0.32, 3.07]
Total (95% CI)		**452**		**451**	**100.0%**	**1.00 [0.32, 3.07]**
Total events	6		6			

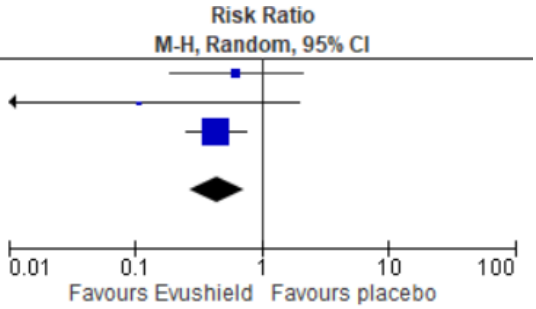
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Hospital admission or death

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIV-2, IM	4	106	7	117	16.9%	0.63 [0.19, 2.09]
ACTIV-2, IV	0	58	4	56	2.9%	0.11 [0.01, 1.95]
TACKLE	17	413	40	421	80.2%	0.43 [0.25, 0.75]
Total (95% CI)		**577**		**594**	**100.0%**	**0.44 [0.27, 0.73]**
Total events	21		51			

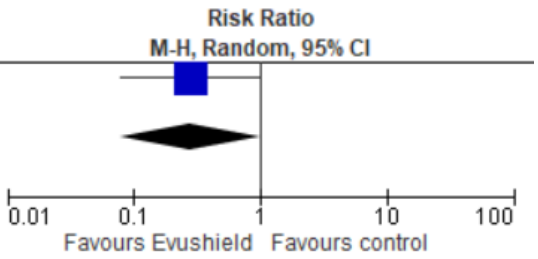
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.23 (P = 0.001)



Admission to ICU, day 29

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TACKLE	3	413	11	421	100.0%	0.28 [0.08, 0.99]
Total (95% CI)		**413**		**421**	**100.0%**	**0.28 [0.08, 0.99]**
Total events	3		11			

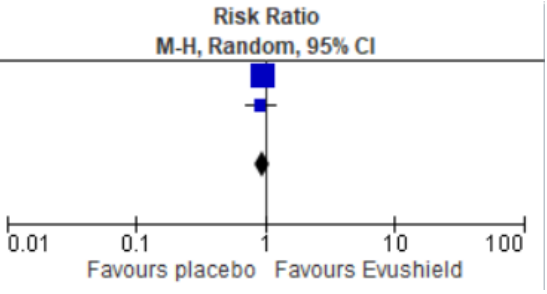
Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)



Symptom resolution by day 28

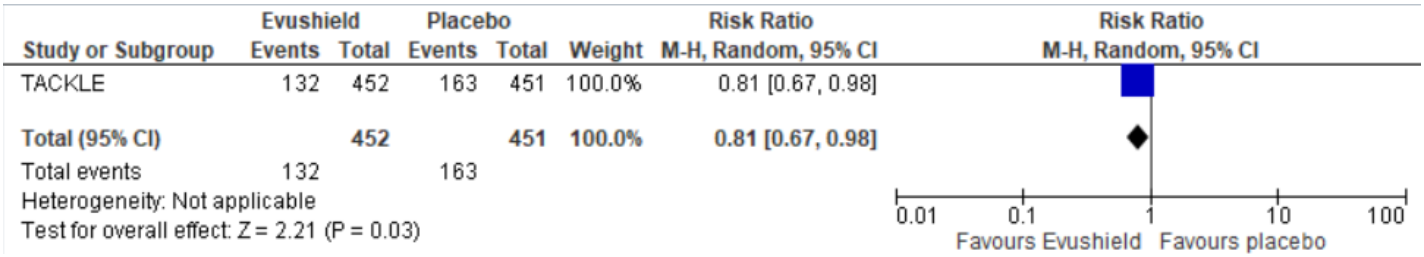
Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIV-2, IM	72	106	82	117	70.1%	0.97 [0.81, 1.16]
ACTIV-2, IV	36	58	38	56	29.9%	0.91 [0.70, 1.20]
Total (95% CI)		**164**		**173**	**100.0%**	**0.95 [0.82, 1.10]**
Total events	108		120			

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

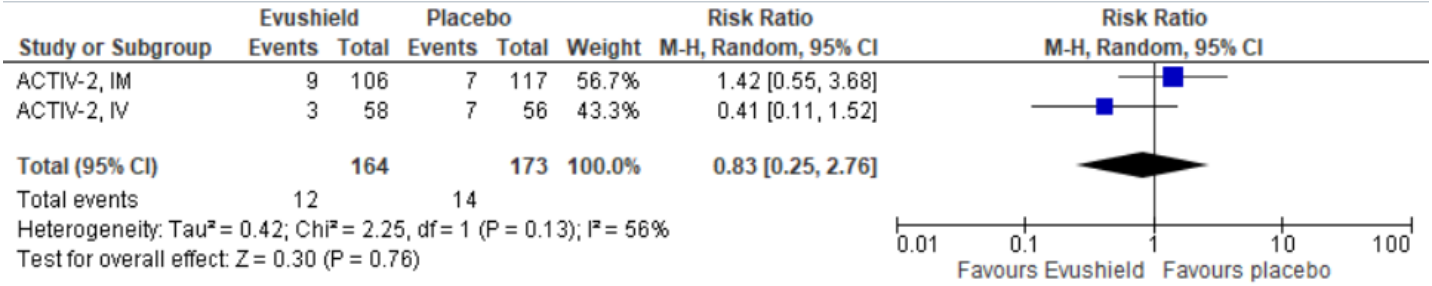


* symptom resolution by day 29 was reported for TACKLE in Hobbs 2023, however, incomplete reporting, data could not be used (unclear unit).

Adverse events, any grade

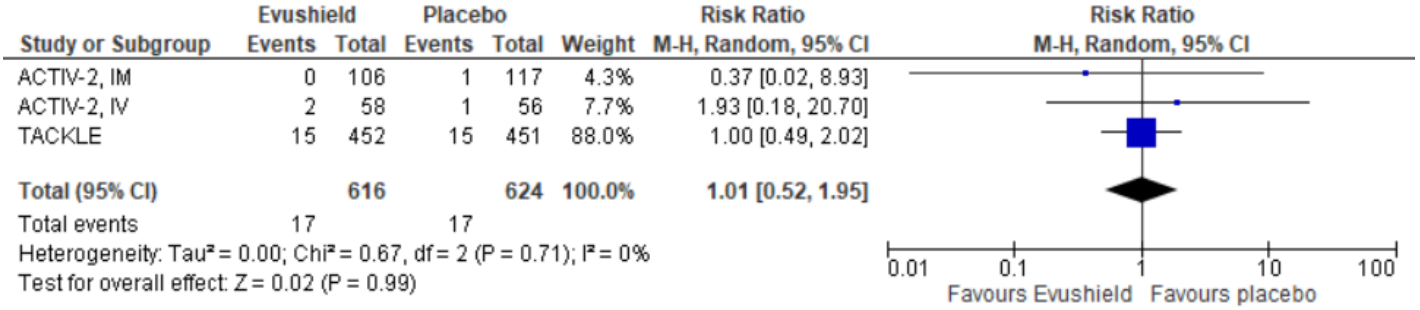


Adverse events, grade 3-4

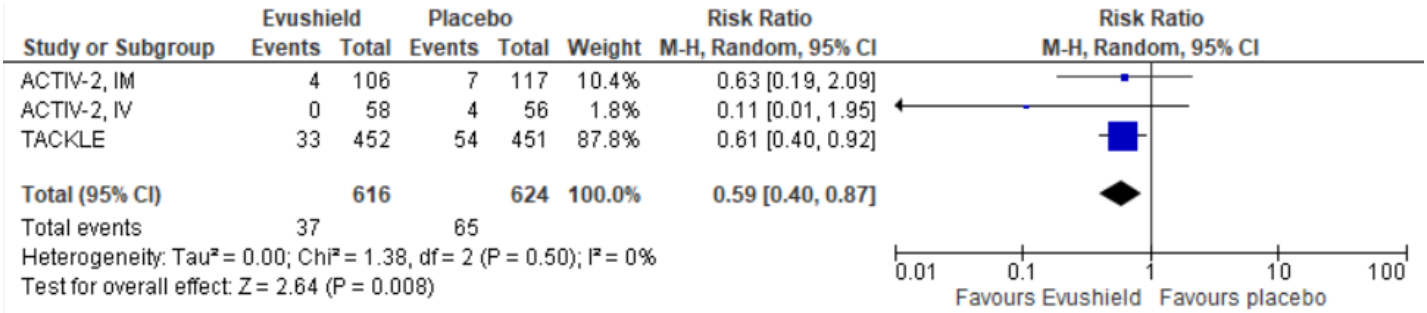


* Adverse events were reported in TACKLE as mild, moderate, severe; for short term and 170 day follow-up.

Infusion-related events



Serious adverse events / death by day 28/29

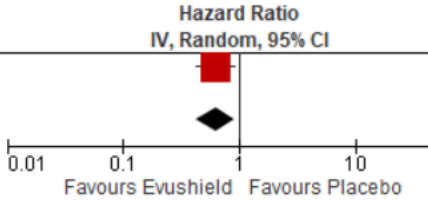


5.9.2.2 *Inpatients*

Mortality day 28

Study or Subgroup	log[Hazard Ratio]	SE	Evushield Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
ACTIV-3/TICO - Evushield	-0.478	0.1987	710	707	100.0%	0.62 [0.42, 0.92]
Total (95% CI)			**710**	**707**	**100.0%**	**0.62 [0.42, 0.92]**

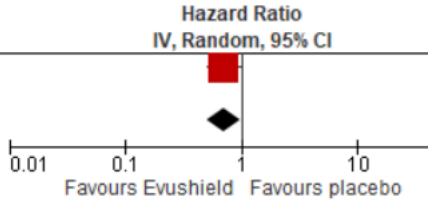
Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)



Mortality, day 90

Study or Subgroup	log[Hazard Ratio]	SE	Evushield Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
ACTIV-3/TICO - Evushield	-0.3567	0.1717	710	707	100.0%	0.70 [0.50, 0.98]
Total (95% CI)			**710**	**707**	**100.0%**	**0.70 [0.50, 0.98]**

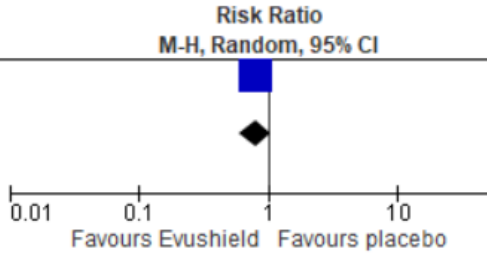
Heterogeneity: Not applicable
Test for overall effect: Z = 2.08 (P = 0.04)



IMV or death by day 28

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIV-3/TICO - Evushield	76	693	95	691	100.0%	0.80 [0.60, 1.06]
Total (95% CI)		**693**		**691**	**100.0%**	**0.80 [0.60, 1.06]**
Total events	76		95			

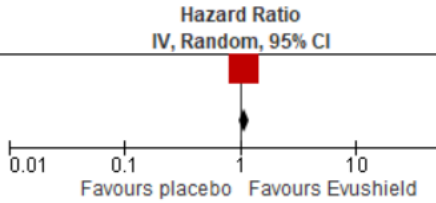
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)



Time to sustained recovery

Study or Subgroup	log[Hazard Ratio]	SE	Evushield Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
ACTIV-3/TICO - Evushield	0.077	0.0548	710	707	100.0%	1.08 [0.97, 1.20]
Total (95% CI)			**710**	**707**	**100.0%**	**1.08 [0.97, 1.20]**

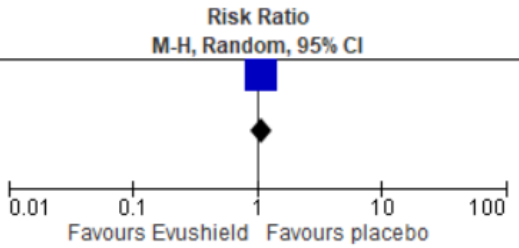
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)



Adverse events, any grade

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIV-3/TICO - Evushield	172	710	157	707	100.0%	1.09 [0.90, 1.32]
Total (95% CI)		**710**		**707**	**100.0%**	**1.09 [0.90, 1.32]**
Total events	172		157			

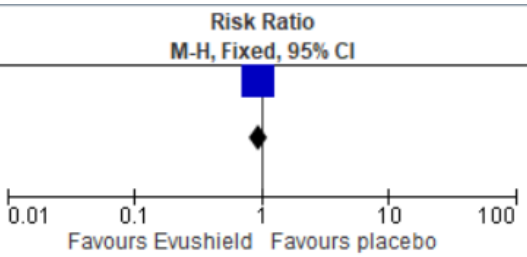
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



Adverse events, grade 3 to 4

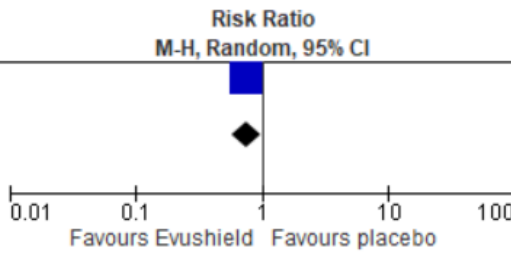
Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIV-3/TICO - Evushield	176	710	184	707	100.0%	0.95 [0.80, 1.14]
Total (95% CI)		**710**		**707**	**100.0%**	**0.95 [0.80, 1.14]**
Total events	176		184			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)



Serious adverse events by day 90

Study or Subgroup	Evushield Events	Evushield Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIV-3/TICO - Evushield	85	710	112	707	100.0%	0.76 [0.58, 0.98]
Total (95% CI)		**710**		**707**	**100.0%**	**0.76 [0.58, 0.98]**
Total events	85		112			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						



5.9.3 Referenzen der eingeschlossenen Studien

5.9.3.1 *RCT-Recherche*

- Bender Ignacio RA, Chew KW, Moser C, Currier JS, Eron JJ, Javan AC, et al. Safety and efficacy of combined tixagevimab and cilgavimab administered intramuscularly or intravenously in nonhospitalized patients with COVID-19: 2 randomized clinical trials. JAMA network open. 2023;6(4):e2310039. doi: 10.1001/jamanetworkopen.2023.10039. PubMed PMID: 23119500.
- Hobbs FDR, Montgomery H, Padilla F, Simon-Campos JA, Kim K, Arbetter D, et al. Outpatient treatment with AZD7442 (Tixagevimab/Cilgavimab) prevented COVID-19 hospitalizations over 6 months and reduced symptom progression in the TACKLE randomized trial. Infectious diseases and therapy. 2023. doi: 10.1007/s40121-023-00861-7. PubMed PMID: 23989748.
- Holland TL, Ginde AA, Paredes R, Murray TA, Engen N, Grandits G, et al. Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. The Lancet Respiratory Medicine. 2022;10(10):972-84. doi: 10.1016/S2213-2600(22)00215-6.
- Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Respiratory Medicine. 2022;10(10):985-96. doi: 10.1016/S2213-2600(22)00180-1.

5.9.3.2 *Kohorten-Recherche*

Keine Studien zur Behandlung identifiziert (Prophylaxe mit Evushield war nicht Teil dieser PICO).

5.9.4 Charakteristika der eingeschlossenen Studien

5.9.4.1 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Hobbs 2023; Montgomery, 2022 (TACKLE) outpatients RCT	**Sample size:** N = 903 pts. (1:1) randomized to tixagevimab-cilgavimab or placebo **Enrolment period:** 28.01.2021 to 22.07.2021 USA, Latin America, Europe, and Japan **Inclusion criteria:** ▪ Aged ≥18 years ▪ laboratory-confirmed SARS-CoV-2 infection ▪ World Health Organisation (WHO) Clinical Progression Scale score >1 and 0 and 1 ▪ Dosed within ≤7 days from self-reported onset of COVID-19–related symptoms (mild to moderate COVID) or measured fever ▪ ≥1 of the following present within 24 h prior to day 1: cough, sore throat, shortness of breath or difficulties breathing at rest/with activity, myalgia, fatigue, headache, chills, nasal obstruction/congestion/discharge,	**Experimental:** ▪ tixagevimab–cilgavimab ▪ Dose: 600mg (two consecutive 3ml intramuscular injections, one each of 300mg tixagevimab and 300mg cilgavimab) ▪ N = 452 **Control:** ▪ Placebo (0.9% NaCl, two consecutive 3ml intramuscular injections) ▪ N = 451 N = mind. eine Dosis und ausgewertet	Mortality at longest FU (84 days)	RR 1.00 (95% CI 0.32nto 3.07 Exp: 6/452 Ctrl: 6/451
			Admission to hospital or death (29 days)	RR 0.44 (95% CI 0.27 to 0.73 Exp: 17/413 Ctrl: 40/421
			IMV or death	Not reported
			Admission to ICU or death	RR 0.28 (95% CI 0.08, 0.99) Exp: 3/413 Ctrl: 11/421
			Adverse events, any grade	RR 0.81 (95% CI 0.67 to 0.98 Exp: 132/452 Ctrl: 163/451
			Infusion-related Adverse events	RR 1.0 (95% CI 0.52 to 1.95) Exp: 15/452 Ctrl: 15/451
			Serious adverse events	RR 0.61 (95% CI 0.40 to 0.92 Exp: 33/452 Ctrl: 54/451
			QoL	Not reported
			Incidence of Post-COVID19 condition	Not reported

	diarrhea, nw loss of taste/smell ▪ Oxygen saturation of ≥ 92% ▪ All participants were unvaccinated. **Time since symptom onset (mean, range):** ▪ Exp: 4.9 (SD 1.6) ▪ Ctrl: 5.0 (SD 1.6) **<u>Characteristics</u>** **Age (mean, sd)** ▪ Evushield: 52.9% ▪ Placebo: 47.9% **Serum for SARS-CoV-2 serology negative, n (%)** ▪ Exp: 84.7% ▪ Ctr: 83.4% ***<u>Comorbidities</u>*** **Any** ▪ Exp: 88.7% ▪ Ctrl: 88.7% **Diabetes:** ▪ Exp: 11.7% ▪ Ctrl: 12.4% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 43.1% ▪ Ctrl: 42.8% **Hypertension** ▪ Exp: 30.3% ▪ Ctrl: 26.8% **Cardiovascular disease** ▪ Exp: 9.3% ▪ Ctrl: 8.4% **Lung diseases** ▪ Exp: 12.8% ▪ Ctrl: 11.1% **Immunosuppressed** ▪ Exp: 4.9% ▪ Ctrl: 5.3%			

	Malignancy ▪ Exp: 4.2% ▪ Ctrl: 3.3% **Kidney disease** ▪ Exp: 2.2% ▪ Ctrl: 2.0%			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ignacio, 2023 (ACTIV-2) outpatient RCT	**Sample size:** N = 229 pts. Randomized (XX pts. planned) **Enrolment period:** 01.02.2021 to 31.03.2021 USA **Inclusion criteria:** ▪ Individuals ≥18 years of age ▪ laboratory-confirmed SARS-CoV-2 infection as determined by any respiratory tract specimen collected ≤240 hours prior to study entry ▪ begin study treatment no more than 8 days from selfreported onset of COVID-19 related symptoms ▪ One or more of the following signs/symptoms present within 24 hours prior to study entry: subjective fever, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle	**Experimental:** ▪ Intravenous Tixagevimab-cilgavimab ▪ Dose: 300mg (150mg of each component admixed) infused over approximately 15 minutes ▪ N = 58 **Control:** ▪ Placebo infused over approximately 15 minutes ▪ N = 56 N = (mind. eine Dosis und ausgewertet)	Mortality/death from any cause (28 days)	Exp: 0/58 Ctrl: 0/56
			Mortality at longest FU	Not reported
			IMV or death	Not reported
			Admission to hospital or death (28 days)	Exp:0/58 Ctrl: 4/56
			Admission to ICU or death	Not reported
			Discharged alive	Not reported
			Symptom resolution (at least 2 days)	Exp: 36/58 Ctrl: 38/56
			Adverse events Grade 3 or higher (28 days)	Exp: 3/58 Ctrl: 7/56
			Infusion-related AE	Exp: 0/106 Ctrl: 1/117
			Serious adverse events (28 days)	Exp: 0/58 Ctrl: 4/56
			QoL	Not reported
			Incidence of Post-COVID19 condition	Not reported

	pain/aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, nausea or vomiting, diarrhea, documented temperature >38°C ▪ Oxygenation saturation of ≥92% **Time since symptom onset (median, IQR):** ▪ Exp: 6 (4-7) ▪ Ctrl: 6 (4-7) ≤ 5 days ▪ Exp: 44.3% ▪ Ctrl: 45.3% **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 43 (33 – 51) ▪ Ctrl: 46 (35 – 58) **Serum for SARS-CoV-2 serology negative, n (%)** ▪ Exp: NR ▪ Ctrl: NR ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: median BMI 34 (26 – 37) ▪ Ctrl: median BMI 31 (27 – 36) **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease**			

	▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR ▪			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ignacio, 2023 (ACTIV-2) Outpatient RCT	**Sample size:** N = 229 pts. Randomized (XX pts. planned) **Enrolment period:** 01.02.2021 to 31.03.2021 USA **Inclusion criteria:** ▪ Individuals ≥18 years of age ▪ laboratory-confirmed SARS-CoV-2 infection as determined by any respiratory tract specimen collected ≤240 hours prior to study entry ▪ begin study treatment no more than 8 days from selfreported onset of COVID-19 related symptoms ▪ One or more of the following signs/symptoms present within 24 hours prior to study entry: subjective fever, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle	**Experimental:** ▪ intramuscular Tixagevimab-cilgavimab ▪ Dose: 600mg (300mg in 3 mL of each component, 1 component delivered to each lateral thigh) minutes ▪ N = 106 **Control:** ▪ IM saline Placebo ▪ N = 117 N = (mind. eine Dosis und ausgewertet)	Mortality/death from any cause (28 days)	Exp: 0/106 Ctrl: 0/117
			Mortality at longest FU	Not reported
			IMV or death	Not reported
			Admission to hospital or death (28 days)	Exp:4/106 Ctrl: 7/117
			Admission to ICU or death	Not reported
			Discharged alive	Not reported
			Symptom resolution (at least 2 days)	Exp: 72/106 Ctrl: 82/117
			Adverse events Grade 3 or higher (28 days)	Exp: 9/106 Ctrl: 7/117
			Infusion-related AE	Exp: 2/58 Ctrl: 1/56
			Serious adverse events (28 days)	Exp: 4/106 Ctrl: 7/117
			QoL	Not reported
			Incidence of Post-COVID19 condition	Not reported

	pain/aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, nausea or vomiting, diarrhea, documented temperature >38°C ▪ Oxygenation saturation of ≥92% **Time since symptom onset (median, range):** ▪ Exp: 6 (4-7) ▪ Ctrl: 6 (4-7) ≤ 5 days ▪ Exp: 44.3% ▪ Ctrl: 45.3% **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 40 (32 – 48) ▪ Ctrl: 38 (29 – 48) **Serum for SARS-CoV-2 serology negative, n (%)** ▪ Exp: NR ▪ Ctrl: NR ***<u>Comorbidities</u>*** **Any** ▪ Exp: NR ▪ Ctrl: NR **Diabetes:** ▪ Exp: NR ▪ Ctrl: NR **Obesity (BMI ≥30 kg/m²)** ▪ Exp: median BMI under 30 ▪ Ctrl:median BMI under 30 **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease**			

	▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

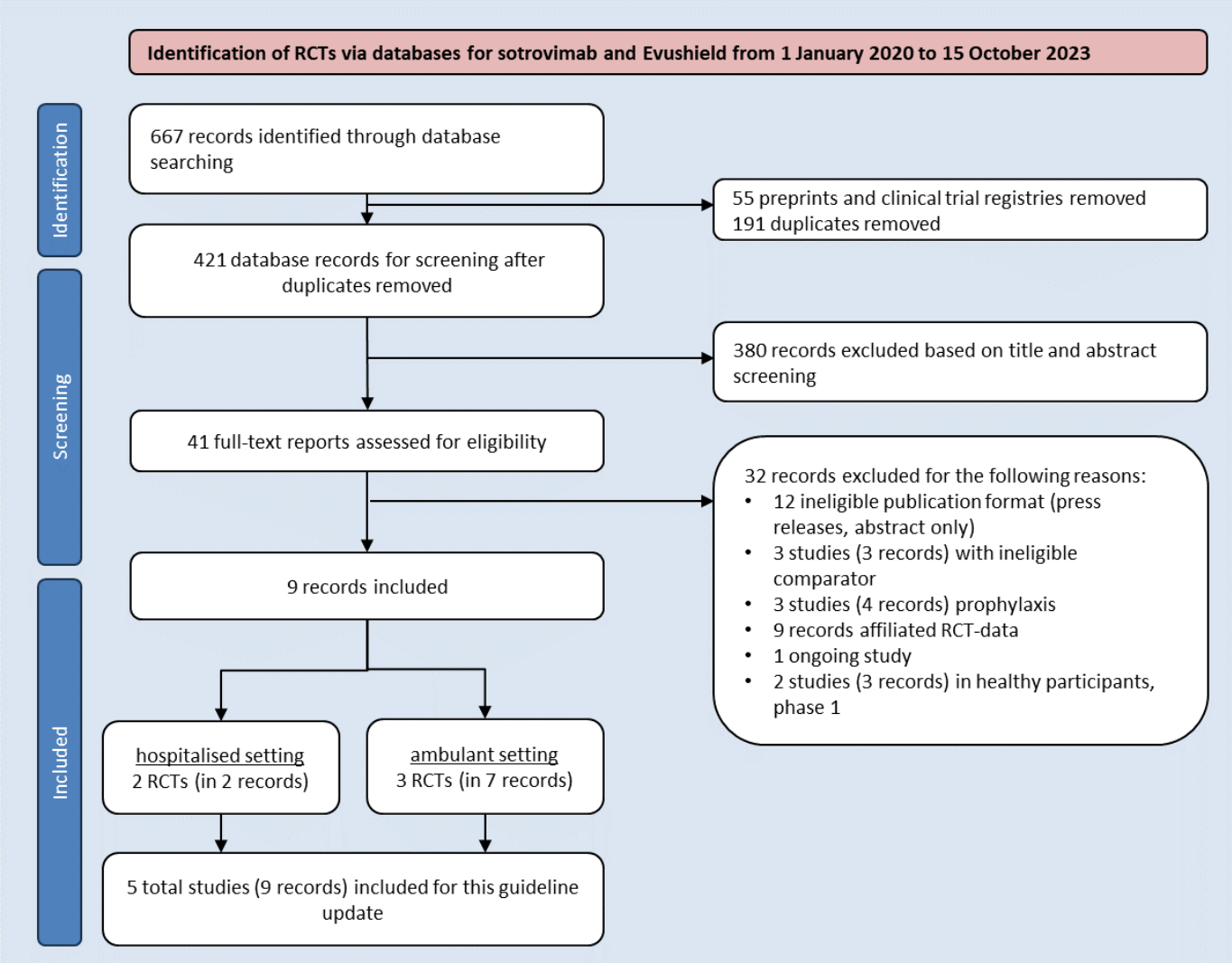
Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group, 2022 RCT	**Sample size:** N = 1455 pts. (1:1) randomized to Tixagevimab–cilgavimab or placebo (XX pts. planned) **Enrolment period:** 10.02.2021 to 30.09.2021 USA, Europe, Uganda, Singapore **Inclusion criteria:** ▪ Age ≥ 18 years ▪ SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator ▪ Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator	**Experimental:** ▪ Intravenous tixagevimab–cilgavimab ▪ Dose: 600mg (300mg of each component) administered as a single intravenous infusion over a 30-min period ▪ N = 710 **Control:** ▪ Placebo ▪ N = 707 N = (mind. eine Dosis und ausgewertet)	Mortality	HR 0.62 (0.42 – 0.92) Exp: 41/710 Ctrl: 65/707
			Mortality at longest FU (90 days)	HR 0.70 (0.50 – 0.97) Exp: 61/710 Ctrl: 86/707
			IM V or death	Exp: 76.23/693 Ctrl: 94.667/691
			Admission to hospital or death	Not applicable
			Admission to ICU or death	Not reported
			Symptom resolution (90 days)	RR 1.08 (0.97 – 1.2) Exp: 617/710 Ctrl: 595/707
			Adverse events (any grade) (28 days)	Exp: 172/710 Ctrl: 157/707
			Adverse events (grade 3-4) (28 days)	Exp: 176/710 Ctrl:184/707
			Serious adverse events (90 days)	Exp: 85/710 Ctrl: 112/707
			QoL	Not reported
			Incidence of Post-COVID19 condition	Not reported

	Time since symptom onset (median, range): ▪ Exp: 8 (6 – 10) ▪ Ctrl: 8 (6 – 10) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 55 (44 – 66) ▪ Ctrl: 55 (44 – 66) **Serum for SARS-CoV-2 serology negative, n (%)** ▪ Exp: 525/710 (74%) ▪ Ctrl: 516/707 (73%) ***<u>Comorbidities</u>*** **Any** ▪ Exp: 415/710 (40%) ▪ Ctrl: 445/707 (63%) **Diabetes:** ▪ Exp: 183/710 (26%) ▪ Ctrl: 187/707 (26%) **Obesity (BMI ≥30 kg/m²)** BMI 30 – 39.9 ▪ Exp: 281/710 (40%) ▪ Ctrl: 268/707 (38%) BMI ≥ 40 ▪ Exp: 102/710 (14%) ▪ Ctrl: 106/707 (15%) **Hypertension** ▪ Exp: 292/710 (41%) ▪ Ctrl: 300/707 (42%) **Cardiovascular disease** ▪ Exp: NR			

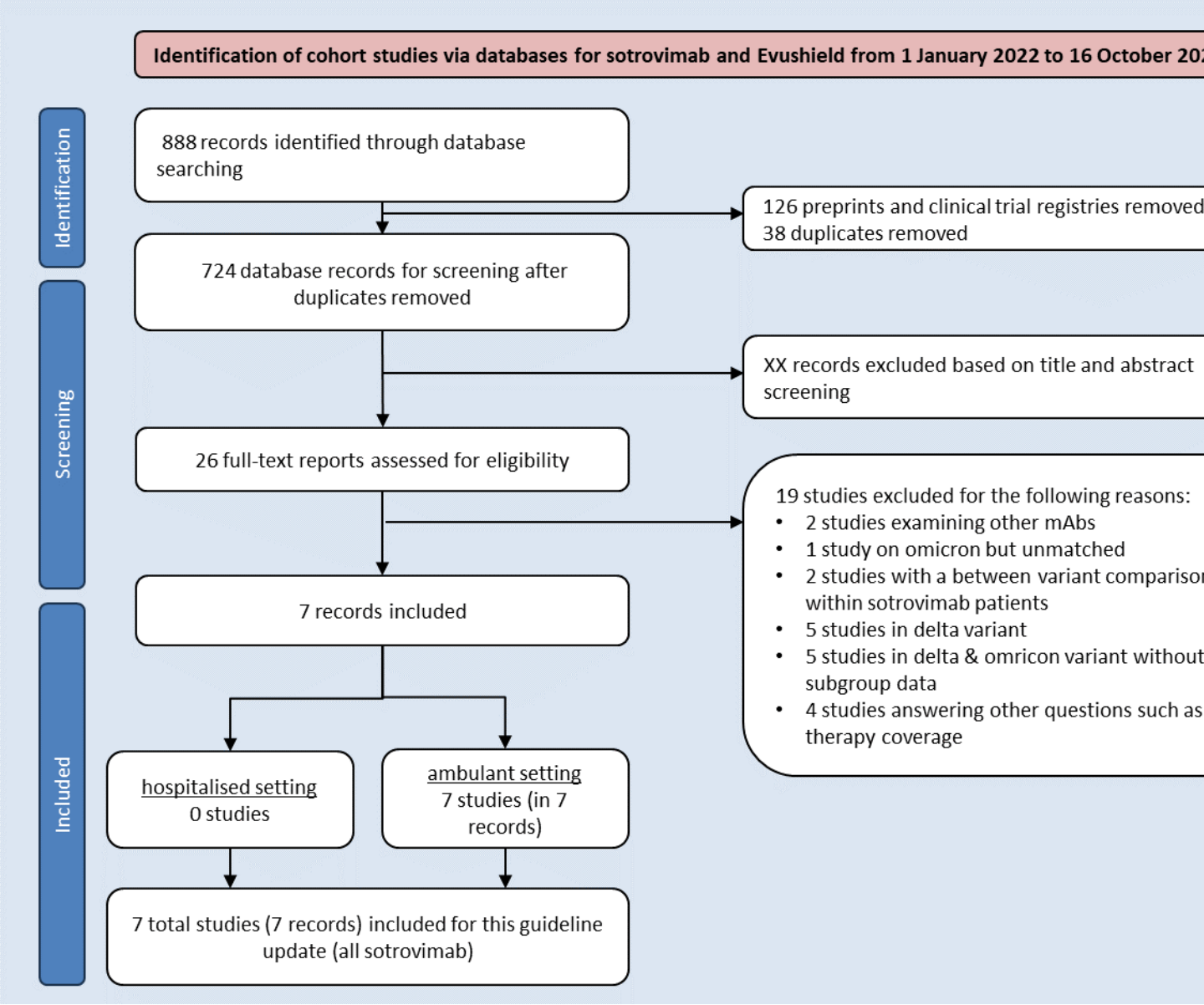
	▪ Ctrl: NR **Lung diseases** Asthma ▪ Exp: 68/710 (10%) ▪ Ctrl: 70/707 (10%) COPD ▪ Exp: 44/710 (6%) ▪ Ctrl: 42/707 (6%) **Immunosuppressed** ▪ Exp: 57/710 (8%) ▪ Ctrl: 71/707 (10%) **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease (renal impairement)** ▪ Exp: 63/710 (9%9 ▪ Ctrl: 70/707 (10%)			

5.9.5 Studienselektion: Flow Chart 7a & b

5.9.5.1 *Flow chart für die RCT-Recherche*



5.9.5.2 *Flow Chart für die Kohorten-Recherche*



5.9.6 Literaturrecherche 7a & b

5.9.6.1 *Literaturrecherche für RCTs*

Date of search for all databases: 15.10.2023			
Database/Register	**Search**	**Update Search**	**Update Search**
CCSR	281 references, 49 studies		
Scopus	268		
WHO COVID-19 DB*	118		
Total	667		
Total (after deduplication)	616		

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Cochrane COVID-19 Study Register

Search string:

VIR7831* or "VIR-7831" or GSK4182136* or "GSK-4182136" or sotrovimab* or xevudy* or AZD7442* or "AZD-7442" or AZD8895* or "AZD-8895" or tixagevimab* or "COV2-2196" or COV22196* or AZD1061* or "AZD-1061" or cilgavimab* or "COV2-2130" or COV22130* or evusheld* or "antibody combination" or "antibodies combination" or "mab combination" or "mabs combination" or "antibody combinations" or "mab combinations" or "antibody cocktail" or "antibody cocktails" or "covid-19 cocktail" or "covid-19 cocktails" or "mab treatment" or "mab treatments" or "antibody treatment" or "antibody treatments" or "antibodies treatment" or "mab therapy" or "mab therapies" or "mabs therapy" or "mabs therapies" or "antibody therapy" or "antibodies therapy" or "antibody therapies" or "antibodies therapies" or "antibody administration" or "antibodies administration" or "mab administration" or "mabs administration" or "antibody regimen" or "antibody regimens" or "mab regimen" or "mab regimens" or "antibodies target" OR "two mab" or "two mabs"

Results available: report results

Study characteristics:

1) "Intervention assignment": "Randomised"; "Quasi-Randomised" OR "Unclear"

2) "Study design": "Parallel/Crossover" OR "Unclear"

Scopus (via Elsevier)

TITLE-ABS (vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "antibodies combination" OR "mab combination" OR "mabs combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "antibody cocktails" OR "covid-19 cocktail" OR "covid-19 cocktails" OR "mab treatment" OR "mab treatments" OR "antibody treatment" OR "antibody treatments" OR "antibodies treatment" OR "mab therapy" OR "mab therapies" OR "mabs therapy" OR "mabs therapies" OR "antibody therapy" OR "antibodies therapy" OR "antibody therapies" OR "antibodies therapies" OR "antibody administration" OR "antibodies administration" OR "mab administration" OR "mabs administration" OR "antibody regimen" OR "antibody regimens" OR "mab regimen" OR "mab regimens" OR "antibodies target" OR "two mab" OR "two mabs")

AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

AND LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023)

AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "antibodies combination" OR "mab combination" OR "mabs combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "antibody cocktails" OR "covid-19 cocktail" OR "covid-19 cocktails" OR "mab treatment" OR "mab treatments" OR "antibody treatment" OR "antibody treatments" OR "antibodies treatment" OR "mab therapy" OR "mab therapies" OR "mabs therapy" OR "mabs therapies" OR "antibody therapy" OR "antibodies therapy" OR "antibody therapies" OR "antibodies therapies" OR "antibody administration" OR "antibodies administration" OR "mab administration" OR "mabs administration" OR "antibody regimen" OR "antibody regimens" OR "mab regimen" OR "mab regimens" OR "antibodies target" OR "two mab" OR "two mabs")

AND (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

5.9.6.2 *Literaturrecherche für Kohortenstudien*

Date of search for all databases: from 01.01.2022 to 16.10.2023				
Database/Register	**Search**	**Update Search**	**Update Search**	**Update Search**
CCSR	545 references, 477 studies			
Scopus	184			
WHO COVID-19 DB*	159			
Total	888			
Total (after deduplication)	724 (includes 126 CT.gov und preprints)			

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Cochrane COVID-19 Study Register

Search string:

VIR7831* or "VIR-7831" or GSK4182136* or "GSK-4182136" or sotrovimab* or xevudy* or AZD7442* or "AZD-7442" or AZD8895* or "AZD-8895" or tixagevimab* or "COV2-2196" or COV22196* or AZD1061* or "AZD-1061" or cilgavimab* or "COV2-2130" or COV22130* or evusheld* or "antibody combination" or "antibodies combination" or "mab combination" or "mabs combination" or "antibody combinations" or "mab combinations" or "antibody cocktail" or "antibody cocktails" or "covid-19 cocktail" or "covid-19 cocktails" or "mab treatment" or "mab treatments" or "antibody treatment" or "antibody treatments" or "antibodies treatment" or "mab therapy" or "mab therapies" or "mabs therapy" or "mabs therapies" or "antibody therapy" or "antibodies therapy" or "antibody therapies" or "antibodies therapies" or "antibody administration" or "antibodies administration" or "mab administration" or "mabs administration" or "antibody regimen" or "antibody regimens" or "mab regimen" or "mab regimens" or "antibodies target" OR "two mab" or "two mabs"

Results available: report results

Study characteristics:

1) "Study design": case series/case control/cohort

Scopus (via Elsevier)

TITLE-ABS (vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "mab combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "covid-19 cocktail" OR "mab treatment" OR "monoclonal antibody treatment" OR "mab therapy" OR "monoclonal antibody therapy" OR "monoclonal antibody administration" OR "mab administration" OR "monoclonal antibody regimens" OR "mab regimens" OR "two mabs")

AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS ((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*) AND LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023) AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "mab combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "covid-19 cocktail" OR "mab treatment" OR "monoclonal antibody treatment" OR "mab therapy" OR "monoclonal antibody therapy" OR "monoclonal antibody administration" OR "mab administration" OR "monoclonal antibody regimens" OR "mab regimens" OR "two mabs") AND (control AND study) OR group OR groups; limit to year 2022 and 2023

(vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "mab combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "covid-19 cocktail" OR "mab treatment" OR "monoclonal antibody treatment" OR "mab therapy" OR "monoclonal antibody therapy" OR "monoclonal antibody administration" OR "mab administration" OR "monoclonal antibody regimens" OR "mab regimens" OR "two mabs") AND ((time AND factors) OR program OR survey* OR cohort OR comparative stud* OR evaluation studies OR follow-up*); limit to year 2022 and 2023

5.10 Schlüsselfrage 5b: Sotrovimab und SoC vs. SoC alone

Autor*innen: Caroline Hirsch, Nina Kreuzberger

5.10.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Outpatients with confirmed SARS-CoV-2 infection (and at least one risk factor for severe disease)

Intervention: Sotrovimab plus standard of care

Vergleichsintervention: Placebo plus standard of care

5.10.1.1 *Evidenzprofil 1: Outpatients*

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo + SOC	Sotrovimab + SOC	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality, day 28 day 28	Relatives Risiko: 0.2 (CI 95% 0.01 - 4.16) Basierend auf Daten von 1057 patienter und 1 Studien[1]	**4** pro 1000	**1** pro 1000 Differenz: **3 weniger pro 1000** (CI 95% 4 weniger - 13 mehr)	**Sehr niedrig** Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether sotrovimab plus standard of care improves or worsen mortality by day 28 during the omicron VOC.
Mortality, day 60	Relatives Risiko (CI 95% -)	pro 1000	**0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)		
IMV or death, day 60	Relatives Risiko: 0.08 (CI 95% 0.0 - 1.36) Basierend auf Daten von 1057 patienter und 1 Studien[3]	**11** pro 1000	**1** pro 1000 Differenz: **10 weniger pro 1000** (CI 95% 11 weniger - 4 mehr)	**Sehr niedrig** Due to serious imprecision, Due to very serious indirectness[4]	We are uncertain whether sotrovimab plus standard of care improves or worsens the incidence of IMV or death by day 60 during the omicron VOC.
Admission to ICU or death, day 60	Relatives Risiko: 0.05 (CI 95% 0.0 - 0.81) Basierend auf Daten von 1057 patienter und 1 Studien[5]	**19** pro 1000	**1** pro 1000 Differenz: **18 weniger pro 1000** (CI 95% 19 weniger - 4 weniger)	**Sehr niedrig** Due to serious indirectness, Due to serious imprecision[6]	We are uncertain whether sotrovimab plus standard of care improves or worsens the incidence of admission to hospital or death by day 60 during the omicron VOC.
Hospital admission (> 24h) or death, day 29	Relatives Risiko: 0.2 (CI 95% 0.08 - 0.48) Basierend auf Daten von 1057 patienter und 1 Studien[7]	**57** pro 1000	**11** pro 1000 Differenz: **46 weniger pro 1000** (CI 95% 52 weniger - 30 weniger)	**Niedrig** Due to very serious indirectness[8]	Sotrovimab plus standard of care may decrease hospital admission or death by day 29.
Adverse events, any grade	Relatives Risiko: 0.93 (CI 95% 0.74 - 1.17) Basierend auf Daten von 1057 patienter und 1 Studien[9]	**234** pro 1000	**218** pro 1000 Differenz: **16 weniger pro 1000** (CI 95% 61 weniger - 40 mehr)	**Niedrig** Due to very serious indirectness[10]	Sotrovimab plus standard of care may decrease the incidence of any grade adverse events.
	Relatives Risiko: 1.58 (CI 95% 1.27 - 1.96)	**197** pro 1000	**311** pro 1000	**Niedrig** Due to very serious indirectness[12]	Sotrovimab plus standard of care may increase

Symptom resolution by day 14	Basierend auf Daten von 1057 patienter und 1 Studien[11]	Differenz: **114 mehr pro 1000** (CI 95% 53 mehr - 189 mehr)		symptom resolution by day 14.
Adverse events, grade 3-4	Relatives Risiko: 0.42 (CI 95% 0.23 - 0.76) Basierend auf Daten von 1057 patienter und 1 Studien[13]	**68** pro 1000	**29** pro 1000 Differenz: **39 weniger pro 1000** (CI 95% 52 weniger - 16 weniger)	**Niedrig** Due to very serious indirectness[14]	Sotrovimab plus standard of care may decrease the incidence of grade 3 to 4 adverse events.
Infusion-related reactions	Relatives Risiko: 1.01 (CI 95% 0.33 - 3.1) Basierend auf Daten von 1057 patienter und 1 Studien[15]	**11** pro 1000	**11** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 7 weniger - 23 mehr)	**Niedrig** Due to very serious indirectness[16]	Sotrovimab plus standard of care may have little or no difference on infusion-related reactions.
Serious adverse events	Relatives Risiko: 0.35 (CI 95% 0.18 - 0.68) Basierend auf Daten von 1057 patienter und 1 Studien[17]	**61** pro 1000	**21** pro 1000 Differenz: **40 weniger pro 1000** (CI 95% 50 weniger - 20 weniger)	**Niedrig** Due to very serious indirectness[18]	Sotrovimab plus standard of care may decrease the incidence of serious adverse events.
Incidence of Post COVID19 Condition	Relatives Risiko (CI 95% -)	pro 1000	pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at incidence of post covid19 condition.
Quality of life	Gemessen mit: Skala: - Höher ist besser	Mittelwert	Mittelwert Differenz: **MD null kleiner**		No studies were found that looked at quality of life.

1. Primary study [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
2. Risiko für Bias: keine. No concerns regarding risk of bias.; Inkonsistenz: keine. No concerns regarding inconsistency.; Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals due to very low number of events.;
3. Systematic review mit eingeschlossenen Studien: [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
4. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals, Low number of events;
5. Primary study [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
6. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals, Low number of events;
7. Primary study [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
8. Indirektheit: sehr schwerwiegend.

9. Primary study [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
10. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
11. Primary study . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm [24]
12. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
13. Primary study [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
14. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
15. Primary study [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
16. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
17. Systematic review mit eingeschlossenen Studien: [24] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
18. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;

5.10.1.2 *Evidenzprofil 2: Inpatients*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Sotrovimab, 500 mg plus standard of care

Vergleichsintervention: Placebo plus standard of care

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo + SOC	Sotrovimab + SOC	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
28-day mortality 28 days	Hazard ratio: 0.97 (CI 95% 0.39 - 2.41) Basierend auf Daten von 360 patienter und 1 Studien[1]	**51** pro 1000	**50** pro 1000 Differenz: **1 weniger pro 1000** (CI 95% 31 weniger - 68 mehr)	**Niedrig** Due to very serious imprecision[2]	Sotrovimab may have little or no effect on 28-day mortality.
Time to hospital discharge absolute effect calculated for day 10	Hazard ratio: 1.13 (CI 95% 0.93 - 1.37) Basierend auf Daten von 360 patienter und 1 Studien	**145** pro 1000	**162** pro 1000 Differenz: **17 mehr pro 1000** (CI 95% 9 weniger - 48 mehr)	**Moderat** Due to serious imprecision[3]	Sotrovimab probably has little or no effect on time to hospital discharge.
Need for IMV or death 5 days	Relatives Risiko: 0.49 (CI 95% 0.09 - 2.65) Basierend auf Daten von 359 patienter und 1 Studien	**23** pro 1000	**11** pro 1000 Differenz: **12 weniger pro 1000** (CI 95% 21 weniger - 38 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to serious indirectness[4]	There were too few who experienced an event to determine whether sotrovimab has an effect on clinical status assessed by need for intubatioin or death by day 5.

90-day mortality 90 days	Hazard ratio: 1.02 (CI 95% 0.48 - 2.17) Basierend auf Daten von 360 patienter und 1 Studien[5]	**73** pro 1000 **74** pro 1000 Differenz: **1 mehr pro 1000** (CI 95% 37 weniger - 79 mehr)	**Niedrig** Due to very serious imprecision[6]	Sotrovimab may have little or no effect on 90-day mortality.
Adverse events, any grade 28 days	Relatives Risiko: 1.05 (CI 95% 0.77 - 1.45) Basierend auf Daten von 360 patienter und 1 Studien	**287** pro 1000 **301** pro 1000 Differenz: **14 mehr pro 1000** (CI 95% 66 weniger - 129 mehr)	**Niedrig** Due to very serious imprecision[7]	Sotrovimab may have little or no effect on adverse events, any grade by day 28.
Serious adverse events or death 28 days	Relatives Risiko: 0.86 (CI 95% 0.44 - 1.67) Basierend auf Daten von 360 patienter und 1 Studien	**96** pro 1000 **83** pro 1000 Differenz: **13 weniger pro 1000** (CI 95% 54 weniger - 64 mehr)	**Niedrig** Due to very serious imprecision[8]	Sotrovimab may have little or no effect on serious adverse events or death by day 28.
Time to sustained recovery through day 90 day 90	Hazard ratio: 1.12 (CI 95% 0.91 - 1.37) Basierend auf Daten von 360 patienter und 1 Studien[9]	**848** pro 1000 **879** pro 1000 Differenz: **31 mehr pro 1000** (CI 95% 28 weniger - 76 mehr)	**Sehr niedrig** Due to serious imprecision, Due to very serious indirectness[10]	We are uncertain whether sotrovimab plus soc improves or worsen time to sustained recovery through day 90.
Serious adverse events or death 90 days	Relatives Risiko: 0.9 (CI 95% 0.53 - 1.52) Basierend auf Daten von 360 patienter und 1 Studien	**140** pro 1000 **126** pro 1000 Differenz: **14 weniger pro 1000** (CI 95% 66 weniger - 73 mehr)	**Niedrig** Due to very serious imprecision[11]	Sotrovimab may have little or no effect on serious adverse events or death by day 90.
Infusion-related reactions day 1	Relatives Risiko: 1.26 (CI 95% 0.65 - 2.45) Basierend auf Daten von 360 patienter und 1 Studien	**79** pro 1000 **100** pro 1000 Differenz: **21 mehr pro 1000** (CI 95% 28 weniger - 115 mehr)	**Niedrig** Due to very serious imprecision[12]	Sotrovimab may increase the occurence of infusion-related reactions.
Post-Covid19 condition	Relatives Risiko (CI 95% -)	pro 1000 pro 1000 Differenz: **weniger pro 1000**		No studies were found that looked at post-covid19 condition.
Quality of life	Gemessen mit: Skala: - Höher ist besser	Mittelwert Mittelwert		No studies were found that looked at quality of life.

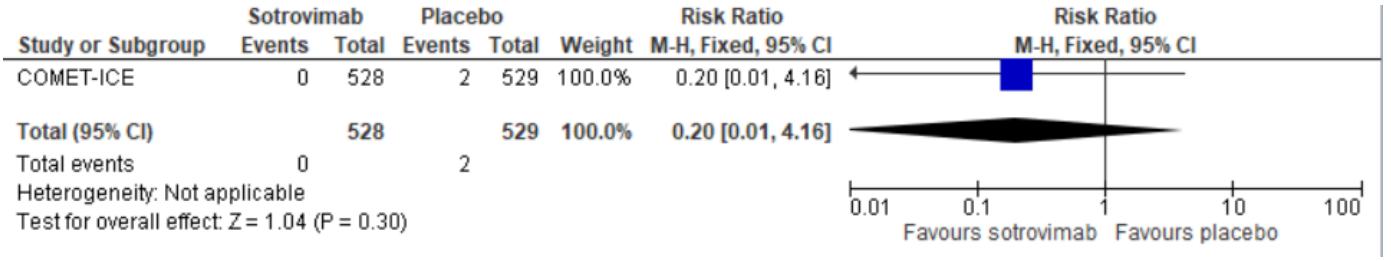
1. Primary study [25] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
2. Indirektheit: keine. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients and events.;

3. Indirektheit: keine. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: schwerwiegend. Low number of patients;
4. Indirektheit: schwerwiegend. The outcome time frame in studies were insufficient, only 5-day follow-up ; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients and events.;
5. Primary study [25] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
6. Indirektheit: keine. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients and events.;
7. Unzureichende Präzision: sehr schwerwiegend. Low number of patients, Optimal information size (OIS) criterion not met;
8. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients;
9. Primary study [25] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
10. Indirektheit: sehr schwerwiegend. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
11. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients;
12. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients;

5.10.2 Analysen / Forest Plots

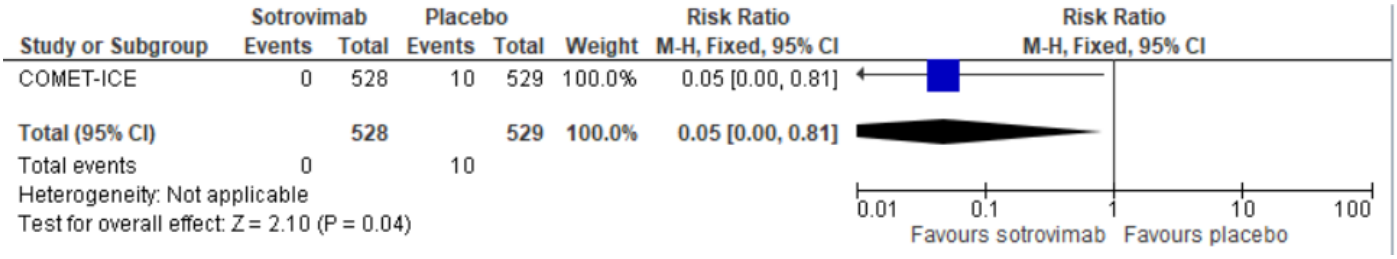
5.10.2.1 *Outpatients*

Mortality, day 28



IMV or death, day 60

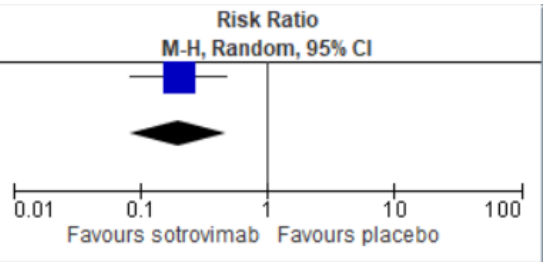
ICU admission or death, day 60



ICU admission (>= 24 h) or death

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
COMET-ICE	6	528	30	529	100.0%	0.20 [0.08, 0.48]
Total (95% CI)		**528**		**529**	**100.0%**	**0.20 [0.08, 0.48]**
Total events	6		30			

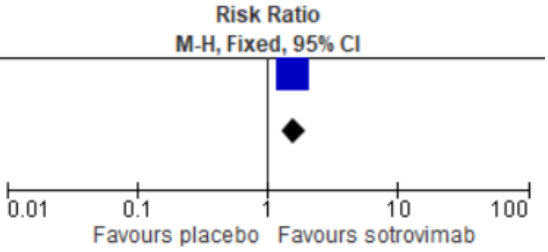
Heterogeneity: Not applicable
Test for overall effect: Z = 3.63 (P = 0.0003)



Symptom resolution by day 14

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMET-ICE	164	528	104	529	100.0%	1.58 [1.28, 1.96]
Total (95% CI)		**528**		**529**	**100.0%**	**1.58 [1.28, 1.96]**
Total events	164		104			

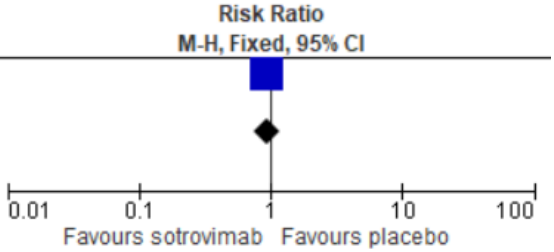
Heterogeneity: Not applicable
Test for overall effect: Z = 4.19 (P < 0.0001)



Adverse events, any grade

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMET-ICE	114	523	123	526	100.0%	0.93 [0.74, 1.17]
Total (95% CI)		**523**		**526**	**100.0%**	**0.93 [0.74, 1.17]**
Total events	114		123			

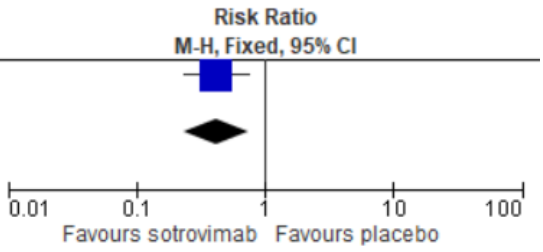
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)



Adverse events, grade 3-4

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMET-ICE	15	523	36	526	100.0%	0.42 [0.23, 0.76]
Total (95% CI)		**523**		**526**	**100.0%**	**0.42 [0.23, 0.76]**
Total events	15		36			

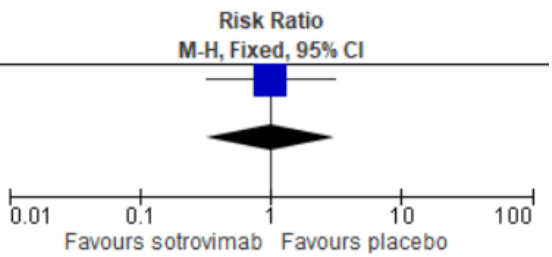
Heterogeneity: Not applicable
Test for overall effect: Z = 2.89 (P = 0.004)



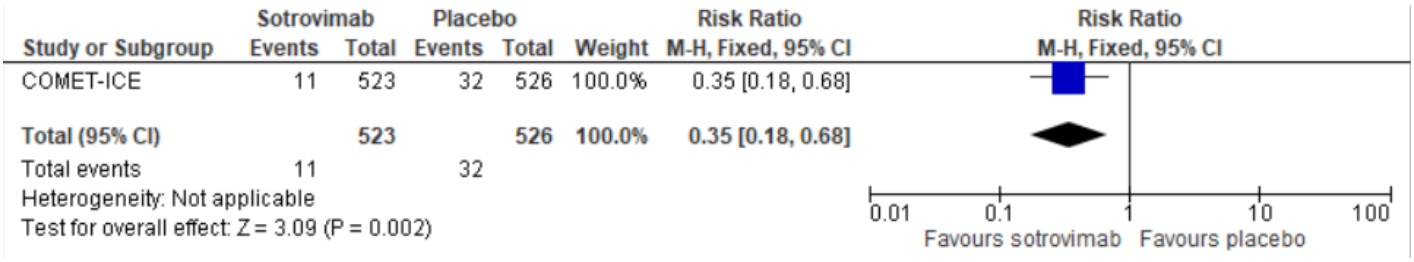
Infusion-related events

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMET-ICE	6	523	6	526	100.0%	1.01 [0.33, 3.10]
Total (95% CI)		**523**		**526**	**100.0%**	**1.01 [0.33, 3.10]**
Total events	6		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)

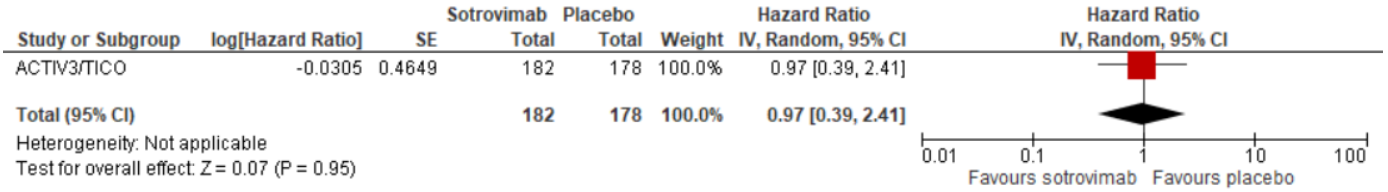


Serious adverse events

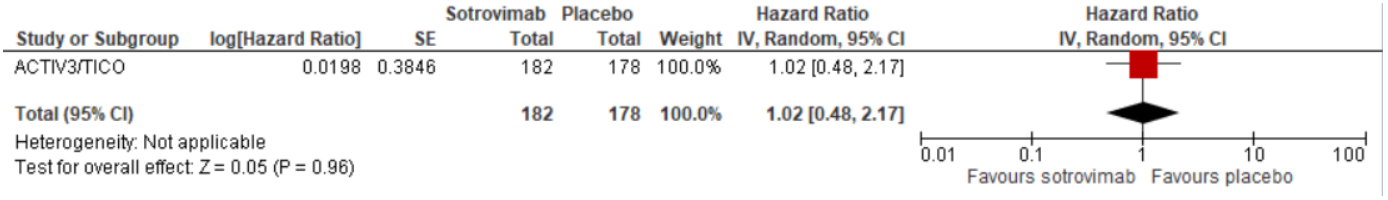


5.10.2.2 *Inpatients*

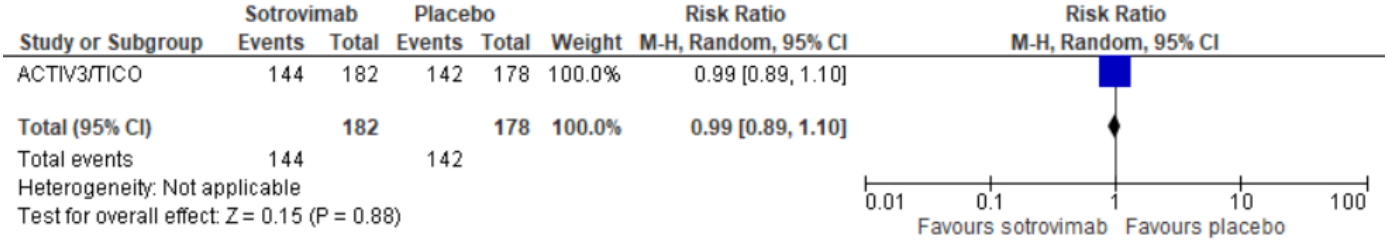
Mortality, day 28



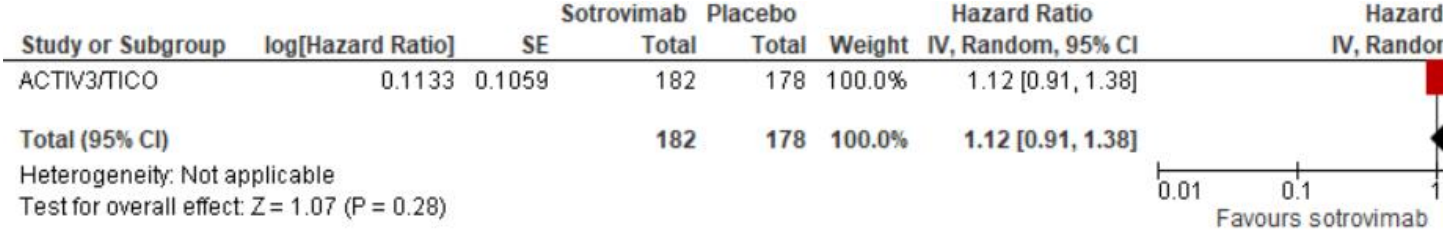
Mortality, day 90



Discharged alive, day 14



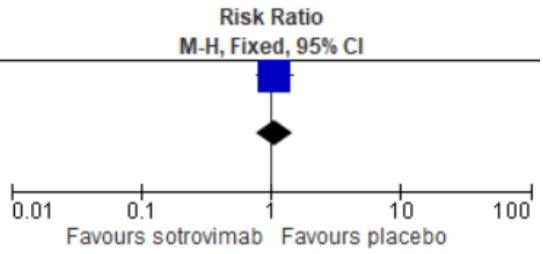
Symptom resolution, here defined as sustained recovery through day 90



Adverse events, any grade

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIV3/TICO	55	182	51	178	100.0%	1.05 [0.77, 1.45]
Total (95% CI)		**182**		**178**	**100.0%**	**1.05 [0.77, 1.45]**
Total events	55		51			

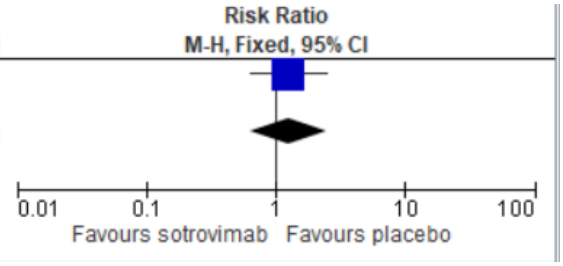
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)



Infusion-related events

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIV3/TICO	18	182	14	178	100.0%	1.26 [0.65, 2.45]
Total (95% CI)		**182**		**178**	**100.0%**	**1.26 [0.65, 2.45]**
Total events	18		14			

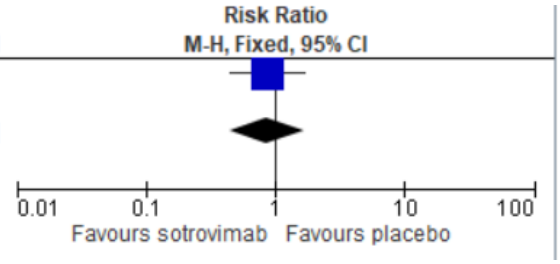
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



Serious adverse events

Study or Subgroup	Sotrovimab Events	Sotrovimab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIV3/TICO	15	182	17	178	100.0%	0.86 [0.44, 1.67]
Total (95% CI)		**182**		**178**	**100.0%**	**0.86 [0.44, 1.67]**
Total events	15		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)



5.10.3 Referenzen der eingeschlossenen Studien

5.10.3.1 *RCT-Recherche*

- ACTIV-3/Therapeutics for Inpatients with COVID-19 Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. The lancet Infectious diseases. 2022;22(5):622-35. doi: 10.1016/S1473-3099(21)00751-9. PubMed PMID: 19576625.
- Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. New Engl J Med. 2021;385(21):1941-50. doi: 10.1056/NEJMoa2107934. PubMed PMID: 19158404.
- Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Rodrigues Falci D, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2022;327(13):1236-46. doi: 10.1001/jama.2022.2832. PubMed PMID: 20415675.
- Lokhandwala T, Acharya M, Farrelly E, Coutinho AD, Bell CF, Svedsater H. Within-trial economic analysis of resource use from COMET-ICE: a phase 3 clinical trial evaluating sotrovimab for the treatment of patients with COVID-19 at high risk of progression. Journal of managed care & specialty pharmacy. 2022;28(11):1261-71. doi: 10.18553/jmcp.2022.28.11.1261. PubMed PMID: 21970543.
- Satram S, Ghafoori P, Reyes CM, Keeley TJH, Birch HJ, Brintziki D, et al. Assessment of symptoms in COMET-ICE, a phase 2/3 study of sotrovimab for early treatment of non-hospitalized patients with COVID-19. Journal of patient-reported outcomes. 2023;7(1):92. doi: 10.1186/s41687-023-00621-8. PubMed PMID: 23941529.

5.10.3.2 *Kohorten-Recherche*

- Aggarwal NR, Beaty LE, Bennett TD, Carlson NE, Mayer DA, Molina KC, et al. Change in effectiveness of sotrovimab for preventing hospitalization and mortality for at-risk COVID-19 outpatients during an Omicron BA.1 and BA.1.1-predominant phase. International Journal of Infectious Diseases. 2023;128:310-7. Epub 2022/10/14. doi: 10.1016/j.ijid.2022.10.002. PubMed PMID: 36229005; PubMed Central PMCID: PMCPMC9549713.
- Ambrose N, Amin A, Anderson B, Barrera-Oro J, Bertagnolli M, Campion F, et al. Neutralizing monoclonal antibody use and COVID-19 infection outcomes. JAMA Network Open. 2023;6(4):e239694. doi: 10.1001/jamanetworkopen.2023.9694. PubMed PMID: 23098879.
- Cheng MM, Reyes C, Satram S, Birch H, Gibbons DC, Drysdale M, et al. Real-world effectiveness of sotrovimab for the early treatment of COVID-19 during SARS-CoV-2 delta and omicron waves in the USA. Infectious Diseases and Therapy. 2023;12(2):1-15. doi: 10.1007/s40121-022-00755-0. PubMed PMID: 22411921.
- Evans A, Qi C, Adebayo JO, Underwood J, Coulson J, Bailey R, et al. Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study. Journal of Infection. 2023. doi: 10.1016/j.jinf.2023.02.012. PubMed PMID: 22626237.
- Kikuchi K, Nangaku M, Ryuzaki M, Yamakawa T, Ota Y, Hanafusa N, et al. Efficacy of molnupiravir and sotrovimab in Japanese dialysis patients with COVID-19 in clinical practice during the Omicron (BA.1 and BA.2) pandemic. Therapeutic Apheresis and Dialysis. 2023. doi: 10.1111/1744-9987.14033.
- Miyashita N, Nakamori Y, Ogata M, Fukuda N, Yamura A, Ishiura Y, et al. Clinical efficacy of the neutralizing antibody therapy sotrovimab in patients with SARS-CoV-2 Omicron BA.1 and BA.2 subvariant infections. Viruses. 2023;15(6). doi: 10.3390/v15061300.
- Zheng B, Green ACA, Tazare J, Curtis HJ, Fisher L, Nab L, et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ (Clinical research ed). 2022;379:e071932. doi: 10.1136/bmj-2022-071932. PubMed PMID: 22119283.

5.10.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
ACTIV-3 2021 Inpatients RCT	**Sample size:** N = 546 (2:1:2:1) randomised to sotrovimab, placebo, BRII-196/BRII-198, placebo ▪ Sotrovimab: N = 184 ▪ Placebo: N = 183; placebo groups pooled for analysis **Enrolment period:** 16.12.2020 to 01.03.2021 USA, Denmark, Switzerland, and Poland **Most important inclusion criteria:** ▪ ≤12 days since SO ▪ SARS-CoV-2 infection, documented by NAT or equivalent testing within 3 days prior to randomization OR more than 3 days AND progressive disease suggestive of ongoing infection ▪ Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19 **Time since symptom onset (median, range):** ▪ 8 days **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 61 (50 to 74) ▪ Ctrl: 60 (49 to 70) ***<u>Comorbidities</u>*** **Any** ▪ Exp: 74% ▪ Ctrl: 76% **Diabetes:** ▪ Exp: 39% ▪ Ctrl: 35% **Obesity (BMI ≥30 kg/m²)**	**Experimental:** ▪ intravenous sotrovimab plus standard of care (SOC) ▪ Dose: 500 mg ▪ N = 182 **Control:** ▪ Placebo (saline) plus standard of care (SOC) ▪ N = 178	Mortality (day 28)	RR: 0.98 (0.40 to 2.41) Sotrovimab: 9/182 Placebo: 9/178
			Mortality (day 60)	Not reported
			Mortality (day 90)	RR: 1.05 (0.51 to 2.18) Sotrovimab: 14/182 Placebo: 13/178
			Time to hospital discharge	HR: 1.13 (0.93 to 1.37)
			IMV requirement or death (day 5); no other timings reported	RR: 0.49 (0.09 to 2.65) Sotrovimab: 2/181 Placebo: 4/178
			Adverse events, any grade (day 28)	RR: 1.05 (0.77 to 1.45) Sotrovimab: 55/182 Placebo: 51/178
			Serious adverse events or death	RR: 0.90 (0.53 to 1.52) Sotrovimab: 23/182 Placebo: 25/178
			Infusion reactions	RR: 1.26 (0.65 to 2.45) Sotrovimab: 18/182 Placebo: 14/178
			QoL	Not reported
			Post Covid19 condition	Not reported

	▪ Exp: 56% ▪ Ctrl: 56% **Hypertension** ▪ Exp: 57% ▪ Ctrl: 58% **Heart failure** ▪ Exp: 7% ▪ Ctrl: 4% **Lung diseases (Asthma)** ▪ Exp: 10.4% ▪ Ctrl: 9.6% **Lung diseases (COPD)** ▪ Exp: 7.1% ▪ Ctrl: 7.3% **Immunosuppressed** ▪ Exp: 5.5% ▪ Ctrl: 6.2% **Malignancy** ▪ Exp: 3.8% ▪ Ctrl: 3.9% **Renal impairment** ▪ Exp: 15% ▪ Ctrl: 11%			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
COMET-ICE Gupta 2022, final analysis Outpatients RCT	**Sample size:** N = 1057 ▪ Sotrovimab: N = 528 ▪ Placebo: N = 529 **Enrolment period:** 27.08.2020 to 11.03.2021 Brazil, Canada, Peru, Spain, USA **Most important inclusion criteria:** ▪ ≤5 days since SO ▪ Antigen or PCR test ▪ At least 1 symptom ▪ ≥1 Risk factor **Time since symptom onset (median, range):** ▪ Sotrovimab: 59% ≤3 days, 40% 4-5 days ▪ Placebo: 59% ≤ 3 days, 41% 4-5 days **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 53 (41.5-62) ▪ Ctrl: 53 (43-63) ***<u>Comorbidities</u>*** **Any risk factor for progression** ▪ Exp: 99% ▪ Ctrl: 99% **Diabetes (req. medication)** ▪ Exp: 23% ▪ Ctrl: 21% **Obesity (BMI ≥30 kg/m²)** ▪ Exp: 63% ▪ Ctrl: 64% **Hypertension: NR** **Heart failure**	**Experimental:** ▪ intravenous sotrovimab plus standard of care (SOC) ▪ Dose: 500 mg ▪ N = 528 ▪ median duration of follow-up: 103 days (IQR, 79-128 days) **Control:** ▪ placebo plus standard of care (SOC) ▪ N = 529 ▪ Median duration of follow-up: 102 days (IQR, 77-128 days)	Mortality (day 29)	RR: 0.20 (0.01 to 4.17) Sotrovimab: 0/528 Placebo: 2/529
			Mortality (day 60)	Not reported
			Mortality (day 90)	Not reported
			Hospitalisation or death	RR: 0.20 (0.08 to 0.48) Sotrovimab: 6/528 Placebo: 30/529
			Admission to ICU or death, day 60	RR: 0.05 (0.00 to 0.81) Sotrovimab: 0/528 Placebo: 10/529
			IMV requirement or death	RR: 0.08 (0.00 to 1.36) Sotrovimab: 0/528 Placebo: 6/529
			Sustained symptom alleviation day 14 (also reported for d7 and 21)	RR 1.84 (1.39 to 2.44) Sotrovimab: 164/528 Placebo: 104/529 *in Satram 2023
			Adverse events, any grade (day 28)	RR: 0.93 (0.74 to 1.17) Sotrovimab: 114/528 Placebo: 123/526 *as treated data set
			Adverse events, grade 3-4	RR 0.42 (0.23 to 0.76) Sptrovimab: 15/528 Placebo: 36/529 *as treated data set
			Serious adverse events	RR: 0.90 (0.53 to 1.52) Sotrovimab: 11/523 Placebo: 32/526 *as treated data set
			Systemic Infusion reactions	RR: 1.01 (0.33 to 3.10) Sotrovimab: 6/523 Placebo: 6/526 *as treated data set
			QoL	Not reported
			Incidence of Post-COVID19 condition	Not reported

	▪ Exp: <1% ▪ Ctrl: <1% **Lung diseases (Asthma): NR** **Lung diseases (COPD)** ▪ Exp: 6% ▪ Ctrl: 5% **Immunosuppressed: NR** **Malignancy: NR** **Kidney disease** ▪ Exp: <1% ▪ Ctrl: <1%			

5.10.4.1 *Cohort studie overview (finally not used, as the current omicron variant is not comparable to the variant circulation at the*

Study	Study/ database	design	setting	enrolment dates	country	vaccination status	interve
Aggarwal 2022	Colorado state-wide data (CDPHE)	propensity-matched ("nearest-neighbor propensity matching with logistic regression to match patients with treatment status as the outcome. The propensity model included age, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of other comorbid conditions, number of vaccinations, and week in the study (categorical)"	outpatient	26.12.2021 to 10.03.2022	USA	>=2 vaccines Sotrovimab: 73.8% Untreated: 70.5%	sotrov (within days a positiv
Ambrose 2023	California, Minnesota, texas and Utah	propensity-matched	outpatient, at least 1 risk factor for severe disease (extraction for omicron BA.1 epoch 2022.01)	9.11.2020 to 31.01.2022; omicron analysed separately; January 2022	USA	Fully vaccinated or boosted:* treated: 37.8% untreated: 33.9%	sotrov
Cheng 2023	FAIR Health National Private Insurance Claims database	Multivariable and propensity score-matched Poisson and logistic regression	outpatients at higher risk of hospitalization and death	01.09.2021 to 30.04.2022; January	USA	Documented COVID-19 vaccine, no. (%) sotrovimab: 20.32% no mAb: 15.17%	sotrov
Evans 2023	SAIL Databank	adjusted: "Participants' baseline covariates included age, sex, number of comorbidities, Charlson comorbidity index (CCI) score, clinical subgroup (categorized as	outpatients at higher risk of hospitalization and death	16.12.2021 to 22.04.2022	UK, Wales	1 or more vaccinations (inkl. 4 and more) sotrovimab:	sotrov

		immunosuppressed conditions including hematological cancers, non-hematological cancers, other high-risk conditions, or unknown), Welsh Index of Multiple Deprivation (WIMD) version 2019 as quintiles mapped from LSOAs, COVID-19 vaccination status (unvaccinated, one to three vaccinations, or four or more vaccinations), and type of treatment received (molnupiravir, nirmatrelvir-ritonavir, or sotrovimab)"				98.5% untreated: 95.6%	
Kikuchi 2022	Registry of COVID-19 in Japan	adjusted	both, dialysis patients	01.01.2022 to 26.05.2022	Japan	2 or more vaccinations sotrovimab: 413/453 combination: 216/231 control: 174/193	Sotrov (+- Molnu
Miyashita 2023	Japan	propensity score matched	outpatients, within 5 days of symptom onset and at least one risk factor for severe disease	12.2021 to 07.2022, BA.1	Japan	2 or more vaccinations sotrivimab: 83.1% control: 81.3%	sotrov
Miyashita 2023	Japan	propensity score matched	outpatients, within 5 days of symptom onset and at least one risk factor for severe disease	12.2021 to 07.2022, BA.2	Japan	2 or more vaccinations sotrivimab: 64.4% control: 61.4%	sotrov
Zheng 2022	OpenSavely Platform		outpatients, within 5 days of symptom onset and at least one risk factor for severe disease	16.12.2021 to 10.02.2022	UK, England	2 or more vaccinations sotrovimab: 96.4% molnupiravir: 95.5%	sotrov

	Mortality				**Hospitalisation**		
Study	Definition	Exp. deaths	Ctrl. Deaths	adjusted effect estimate	Definition	exp. hospitalisations	ctrl hospitalisatio
Aggarwal 2022	all-cause mortality day 28	1/1542 (0.1%)	7/3663 (0.2%)	adjusted OR: 0.62 (0.07 to 2.78)	All-cause hospitalisation within 28 days of test	39/1542 (2.5%)	116/3663 (3.2%)

Ambrose 2023	death by day 30	0.00%	0.20%	OR 0.10 (0.01 to 1.68)	All cause hospitalisation or death	5.10%	2.60%
Cheng 2023	February 2022				30-day all-cause hospitalisation or facility-reported mortality (by diagnosis month)	4859 (1.85%)	19192 (3.37%
Cheng 2023	March 2022				30-day all-cause hospitalisation or facility-reported mortality (by diagnosis month)	2329 (3.26%)	9548 (6.9%)
Cheng 2023	April 2022				30-day all-cause hospitalisation or facility-reported mortality (by diagnosis month)	1046 (2.01%)	1046 (4.37)
Evans 2023					all-cause hospitalisation or death by day 30	53/1079 (4.9%)	544/4973 (10.9%)
Kikuchi 2022	all-cause mortality, day 15			HR 0.446 (0.223 to 0.895)			
Kikuchi 2022, + molnupiravi	all-cause mortality, day 15			HR 0.208 (0.060 to 0.723)			
Miyashita 2023, BA.1	all-cause mortality	0/642	0/642	NR	No. (%) of patients who required oxygen therapy	26/642	56/642
Miyashita 2023, BA.2	all-cause mortality	0/202	0/202	NR	No. (%) of patients who required oxygen therapy	8/202	20/202
Zheng 2022					hospital admission or death by day 28	127/3331	123/2689

5.11 Schlüsselfrage 6: Anakinra und SoC vs. SoC alone

Autor*innen: Nora Cryns

Es wurden insgesamt 8 RCTs und 1957 Teilnehmende eingeschlossen.

5.11.1 Evidenzprofile / Summary of Findings (MAGICapp)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** standard care with or without placebo or no treatment	 Anakinra	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Discharged alive (by day 28-30)	Relatives Risiko: 1.99 (CI 95% 1.21 - 3.29) Basierend auf Daten von 71 patienter und 1 Studien	**353** pro 1000	**702** pro 1000 Differenz: **349 mehr pro 1000** (CI 95% 74 mehr - 808 mehr)	**Niedrig** Due to very serious imprecision[1]	Anakinra may improve discharged alive (by day 28-30)

28-day mortality	Relatives Risiko: 1.01 (CI 95% 0.71 - 1.44) Basierend auf Daten von 1905 patienter und 7 Studien[2]	**201** pro 1000 **203** pro 1000 Differenz: **2 mehr pro 1000** (CI 95% 58 weniger - 88 mehr)	**Sehr niedrig** Due to serious imprecision, Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[3]	We are uncertain whether anakinra improves or worsen 28-day mortality
Admission to ICU	Relatives Risiko: 0.78 (CI 95% 0.48 - 1.29) Basierend auf Daten von 236 patienter und 2 Studien	**226** pro 1000 **176** pro 1000 Differenz: **50 weniger pro 1000** (CI 95% 118 weniger - 66 mehr)	**Niedrig** Due to serious inconsistency, Due to serious indirectness, Due to very serious risk of bias[4]	Anakinra may improve admission to ICU
Need for invasive mechanical ventilation or death	Relatives Risiko: 0.69 (CI 95% 0.31 - 1.56) Basierend auf Daten von 709 patienter und 2 Studien[5]	**138** pro 1000 **95** pro 1000 Differenz: **43 weniger pro 1000** (CI 95% 95 weniger - 77 mehr)	**Niedrig** Due to serious inconsistency, Due to serious indirectness, Due to very serious inconsistency[6]	Anakinra may improve need for invasive mechanical ventilation or death
60-day mortality	Relatives Risiko: 1.86 (CI 95% 0.82 - 4.21) Basierend auf Daten von 115 patienter und 1 Studien	**125** pro 1000 **233** pro 1000 Differenz: **108 mehr pro 1000** (CI 95% 22 weniger - 401 mehr)	**Sehr niedrig** Due to serious imprecision, Due to very serious imprecision, Due to serious indirectness[7]	We are uncertain whether anakinra improves or worsen 60-day mortality
Serious adverse events	Relatives Risiko: 0.93 (CI 95% 0.75 - 1.14) Basierend auf Daten von 1150 patienter und 6 Studien	**258** pro 1000 **240** pro 1000 Differenz: **18 weniger pro 1000** (CI 95% 64 weniger - 36 mehr)	**Niedrig** Due to serious inconsistency, Due to serious risk of bias, Due to serious indirectness[8]	Anakinra may have little or no difference on serious adverse events
Adverse events (any grade)	Relatives Risiko: 1.17 (CI 95% 0.82 - 1.68) Basierend auf Daten von 556 patienter und 5 Studien	**538** pro 1000 **629** pro 1000 Differenz: **91 mehr pro 1000** (CI 95% 97 weniger - 366 mehr)	**Niedrig** Due to very serious imprecision, Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness[9]	Anakinra may have little or no difference on adverse events (any grade)

1. Unzureichende Präzision: sehr schwerwiegend. Low number of patients, Only data from one study;
2. Systematic review mit eingeschlossenen Studien: [46], [44], [45] Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
3. Risiko für Bias: schwerwiegend. Incomplete data and/or large loss to follow up, baseline differences; Inkonsistenz: schwerwiegend. Point estimates vary widely, The direction of the effect is not consistent between the included studies; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
4. Risiko für Bias: sehr schwerwiegend. Incomplete data and/or large loss to follow up + baseline differences;
5. Systematic review [43] . Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm .
6. Inkonsistenz: sehr schwerwiegend. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2:... %.; Indirektheit: keine. Differences between the population of interest and those studied, -> nearly all participants recruited in 2020, Can conclusions be drawn about current Covid variants?;
7. Inkonsistenz: keine. Point estimates vary widely; Indirektheit: keine. Differences between the population of interest and those studied, -> nearly all participants recruited in 2020, Can conclusions be drawn about current Covid

variants?; Unzureichende Präzision: sehr schwerwiegend. Low number of patients, Only data from one study, Wide confidence intervals, Wide confidence intervals;

8. Risiko für Bias: schwerwiegend. Incomplete data and/or large loss to follow up, baseline differences; Inkonsistenz: schwerwiegend. The direction of the effect is not consistent between the included studies; Indirektheit: keine. Differences between the population of interest and those studied, -> nearly all participants recruited in 2020, Can conclusions be drawn about current Covid variants?;

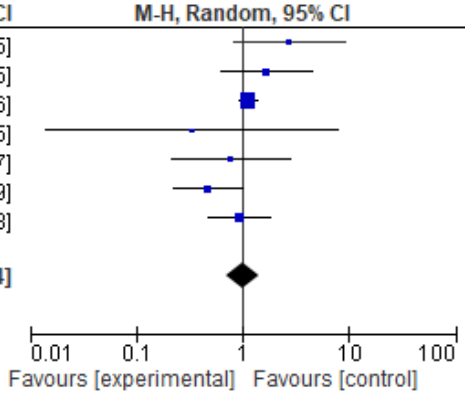
9. Risiko für Bias: schwerwiegend. Inkonsistenz: schwerwiegend. The magnitude of statistical heterogeneity was high, with I^2:... %.; Indirektheit: keine. Differences between the population of interest and those studied; Unzureichende Präzision: keine. Wide confidence intervals, Low number of patients, Only data from one study;

5.11.2 Analysen / Forest Plots

Mortality, day 28

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Audemard-Verger 2022	9	35	3	32	7.2%	2.74 [0.81, 9.25]	
Declercq 2021	7	43	7	72	10.3%	1.67 [0.63, 4.45]	
Derde 2021	135	365	134	405	41.9%	1.12 [0.92, 1.36]	
Elmekaty 2023	0	40	1	40	1.2%	0.33 [0.01, 7.95]	
Fanlo 2023	4	84	5	81	6.6%	0.77 [0.21, 2.77]	
Kyriazopoulou 2021	13	405	13	189	15.2%	0.47 [0.22, 0.99]	
Tharaux 2021	13	59	13	55	17.5%	0.93 [0.47, 1.83]	
Total (95% CI)		**1031**		**874**	**100.0%**	**1.01 [0.71, 1.44]**	
Total events	181		176				

Heterogeneity: Tau² = 0.07; Chi² = 8.96, df = 6 (P = 0.18); I² = 33%
Test for overall effect: Z = 0.08 (P = 0.94)

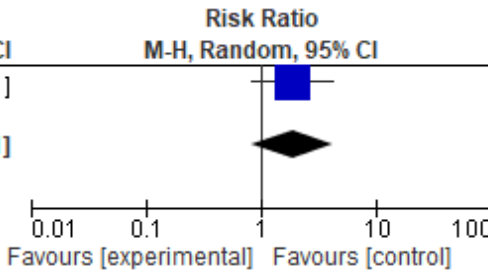


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Mortality, day 60

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Declercq 2021	10	43	9	72	100.0%	1.86 [0.82, 4.21]
Total (95% CI)		**43**		**72**	**100.0%**	**1.86 [0.82, 4.21]**
Total events	10		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)

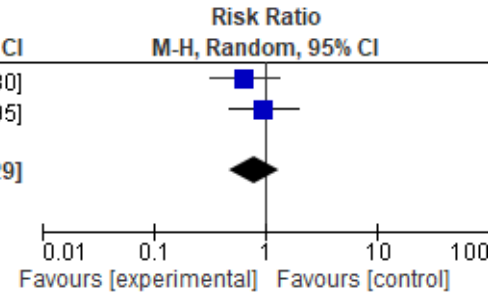


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Admission to ICU

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Audemard-Verger 2022	9	37	13	34	49.6%	0.64 [0.31, 1.30]
Fanlo 2023	13	84	13	81	50.4%	0.96 [0.48, 1.95]
Total (95% CI)		**121**		**115**	**100.0%**	**0.78 [0.48, 1.29]**
Total events	22		26			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0\%$
Test for overall effect: Z = 0.95 (P = 0.34)

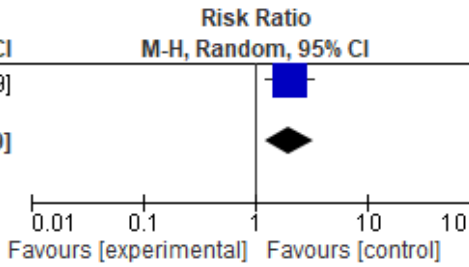


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Discharged alive (by day 28)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Audemard-Verger 2022	26	37	12	34	100.0%	1.99 [1.21, 3.29]
Total (95% CI)		**37**		**34**	**100.0%**	**1.99 [1.21, 3.29]**
Total events	26		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)

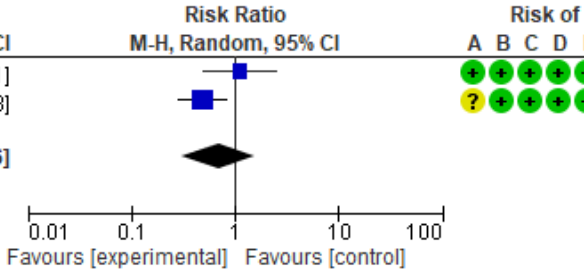


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Need for IMV or death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Declercq 2021	8	43	12	72	43.0%	1.12 [0.50, 2.51]
Kyriazopoulou 2021	25	405	24	189	57.0%	0.49 [0.29, 0.83]
Total (95% CI)		**448**		**261**	**100.0%**	**0.69 [0.31, 1.56]**
Total events	33		36			

Heterogeneity: Tau² = 0.22; Chi² = 2.82, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 0.88 (P = 0.38)

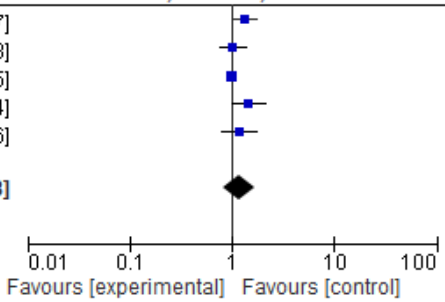


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Any adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Audemard-Verger 2022	32	37	22	34	20.5%	1.34 [1.01, 1.77]
Declercq 2021	26	43	43	72	19.9%	1.01 [0.74, 1.38]
Elmekaty 2023	40	40	40	40	23.2%	1.00 [0.95, 1.05]
Fanlo 2023	40	89	27	87	18.4%	1.45 [0.98, 2.14]
Tharaux 2021	29	59	23	55	18.0%	1.18 [0.78, 1.76]
Total (95% CI)		**268**		**288**	**100.0%**	**1.17 [0.82, 1.68]**
Total events	167		155			

Heterogeneity: Tau² = 0.15; Chi² = 42.62, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.86 (P = 0.39)

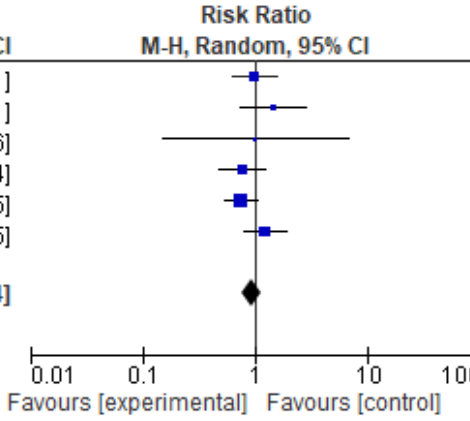


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Serious adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Audemard-Verger 2022	19	37	18	34	20.2%	0.97 [0.62, 1.51]
Declercq 2021	12	43	14	72	9.2%	1.44 [0.73, 2.81]
Elmekaty 2023	2	40	2	40	1.2%	1.00 [0.15, 6.76]
Fanlo 2023	21	89	27	87	17.0%	0.76 [0.47, 1.24]
Kyriazopoulou 2021	65	405	41	189	31.4%	0.74 [0.52, 1.05]
Tharaux 2021	27	59	21	55	21.0%	1.20 [0.77, 1.85]
Total (95% CI)		**673**		**477**	**100.0%**	**0.93 [0.75, 1.14]**
Total events	146		123			

Heterogeneity: Tau² = 0.00; Chi² = 5.26, df = 5 (P = 0.39); I² = 5%
Test for overall effect: Z = 0.72 (P = 0.47)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

5.11.3 Referenzen der eingeschlossenen Studien

- Audemard-Verger, A., Le Gouge, A., Pestre, V., Courjon, J., Langlois, V., Vareil, M. O., ... & Caille, A. (2022). Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial. PLoS One, 17(8), e0269065.
- Dahms, K., Mikolajewska, A., Ansems, K., Metzendorf, M. I., Benstoem, C., & Stegemann, M. (2023). Anakinra for the treatment of COVID-19 patients: a systematic review and meta-analysis. European Journal of Medical Research, 28(1), 1-12.
- Elmekaty, E. Z. I., Maklad, A., Abouelhassan, R., Munir, W., Ibrahim, M. I. M., Nair, A., ... & Al Maslamani, M. (2023). Evaluation of anakinra in the management of patients with COVID-19 infection: A randomized clinical trial. Frontiers in Microbiology, 14, 1098703.
- Fanlo, P., del Carmelo Gracia-Tello, B., Aizpuru, E. F., Álvarez-Troncoso, J., Gonzalez, A., Prieto-González, S., ... & Pardos-Gea, J. (2023). Efficacy and safety of anakinra plus standard of care for patients with severe COVID-19: a randomized phase 2/3 clinical trial. JAMA Network Open, 6(4), e237243-e237243.

5.11.4 Charakteristika der eingeschlossenen Studien

5.11.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodis
Dahms, 2023 Systematic review with MA	**Study design** RCTs **Search time frame** Inception of each database to 13.12.2021 **Sources:** Cochrane COVID-19 Study Register (MEDLINE, Embase, ▪ ClinicalTrials.go, ▪ WHO International Clinical Trials Registry Platform, medRxiv, ▪ Cochrane Central Register of	**Intervention A** ▪ Anakinra **Intervention B** ▪ Placebo ▪ Standard care alone (SCO)	5 studies on 1627 patients included in meta-analysis **Descriptive statistics (meta-analysis):** ▪ Age: 59.63 ▪ 64% male ▪ comorbidities not reported ▪ vaccination status not reported	**Comparison X:** Number of studies: 5 Number of participants: 1627 **Critical outcomes:** ▪ All-cause mortality (at up to day 28): Anakinra makes little or no difference to all-cause mortality; RR 0.96, 95% CI 0.64–1.45; RD 9 fewer per 1000; 95% CI 84 fewer to 104 more (4 studies, n = 1593) ▪ All-cause mortality (at up tp day 60): Anakinra 233 per 1000 vs. placebo/SCO 125 per 1000; RD 108 more per 1000; RR 1.22 (0.77 – 1.92) (2 studies, n = 115) ▪ In-hospital mortality at up to longest follow-up: Anakinra 404 per 1000 vs. placebo/SCO 331 per 1000; RD 73 more per 1000; RR 1.22 (0.77 – 1.92) (2 studies, n = 889) ▪ Clinical worsening: new need for IMV or death within 28 days: Anakinra 95 per 1000 vs. placebo/SCO 127 per 1000; RD 43 fewer per 1000; RR 0.69 (0.31 – 1.56) (4 studies, n = 1593)	**Methodologica** **included studi** **using GRADE t** **Evidence synth** ▪ Random-e **GRADE** ▪ All-cause due to ser inconsiste imprecisio ▪ In-hospita moderate imprecisio ▪ Clinical wo due to ser inconsiste impreciso ▪ Clinical im due to ser inconsiste imprecisio ▪ Serious ad low due to inconsiste imprecisio

	Controlled Trials) ▪ WHO COVID-19 Global literature on coronavirus disease database **Eligibility criteria** **Study type:** ▪ randomized controlled trials reported as full texts, abstract only and unpublished data ▪ Studies comparing treatment with Anakinra to placebo or standard care alone in adult hospitalized patients with SARS-CoV-2 infection			▪ Clinical improvement participants discharges alive at up to day 28: Anakinra 766 per 1000 vs. placebo/SCO 744 per 1000; RD 22 more per 1000; RR 1.03 (0.88 – 1.21) (3 studies, n = 823) ▪ Serious adverse events at up to day 28: Anakinra 246 per 1000 vs. placebo/SCO 241 per 1000; RD 5 more per 1000; RR 1.02 (0.68 – 1.53) (3 studies, n = 823) ▪ Adverse events (any grade) at up to day 28: Anakinra 556 per 1000 vs. Placebo/SCO 520 per 1000; RD 36 more per 1000; RR 1.07 (0.84 – 1.37) (2 studies, n = 229) **Additional outcomes:**	▪ Adverse e grade): lo inconsiste imprecisio

5.11.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Audemard-Verger, 2022 RCT	**Sample size:** N = 71 pts. (1:1) randomised to anakrina or optimized standard of care alone (240 pts. planned) **Enrolment period:** 27.04.2020 to 6.10.2020 **Inclusion criteria:** ▪ confirmed SARS-CoV-2 infection: ▪ - positive rRT-PCR and/or typical chest or computed tomographic scan of COVID 19 ▪ - pneumonia and required oxygen therapy: O2 4L/min to maintain Sp02> 92% and respiratory rate ≥ 24/min or O2 ≥n1L/min and increase in oxygen therapy ≥ 2L/min to maintain Sp02> 92% ▪ inflammatory component (reactive C-protein ≥ 50mg/L ▪ treated with antibiotics **Time since symptom onset (median, range):** ▪ Exp: 9 [IQR: 7; 11] ▪ Ctrl: 9 [IQR: 7; 11] **Characteristics** **Age (median, IQR)** ▪ Exp: 71 (15%) ▪ Ctrl: 70 (14%) **Vaccination status** ▪ NR **Country** ▪ France ***Comorbidities*** **Any** ▪ NR	**Experimental:** ▪ intravenous anakinra plus optimized standard of care (oSOC) ▪ Dose: 400mg/day (100mg every 6 hours) for 3 days; then 200mg/day (100mg every 12 hours) for 7 days ▪ N = 37 **Control:** ▪ optimized standard of care (oSOC) alone ▪ N = 34	All-cause mortality (day 30)	RR 2.74 (0.81 to 9.25) Anakinra: 9/35 SoC: 3/32
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	1.99 (1.21 to 3.29) Anakinra: 26/37 SoC: 12/34
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	RR 0.64 (0.31 to 1.30) Anakinra: 9/27 SoC: 13/34
			Serious adverse events	RR 0.97 (0.62 to 1.51) Anakinra: 19/37 SoC: 18/34
			Adverse events, any grade	RR 1.34 (1.01 to 1.77) Anakinra: 32/37 SoC: 22/34
			Hospital-acquired infections	Not reported
			Quality of life	Not reported

	Diabetes: ▪ Exp: 9 (24%) ▪ Ctrl: 6 (18%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: median BMI under obesity ▪ Ctrl: median BMI under obesity **Hypertension** ▪ Exp: 20 (54%) ▪ Ctrl: 15 (44%) **Cardiovascular disease** ▪ Exp: 2 (5%) ▪ Ctrl: 7 (21%) **Lung diseases** COPD ▪ Exp: 1 (3%) ▪ Ctrl: 6 (18%) Asthma ▪ Exp: 2 (5%) ▪ Ctrl: 1 (3%) **Immunosuppressed** ▪ Exp: 0 (0%) ▪ Ctrl: 1 (3%) **Malignancy** ▪ Exp: 1 (3%) ▪ Ctrl: 1 (3%) **Kidney disease (chronic)** ▪ Exp: 5 (13%) ▪ Ctrl: 2 (6%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Fanlo, 2023 RCT	**Sample size:** N = 179 pts. (1:1) randomised to anakinra or optimized standard of care alone (pts. Planned: NR) **Enrolment period:** 08.05.2020 to 01.03.2021 **Inclusion criteria:** ▪ Age 18-80 years ▪ Nasopharyngeal smear with RCP positive for SARS-CoV-2 ▪ X-Rays (or other technique) pulmonary infiltrates compatible with pneumonia. ▪ 1 or more of the following criteria: ▪ - Ambient air oxygen saturation ≤ 94% ▪ - Pa:FiO2 ≤ 300 ▪ - Sa:FiO2 ≤ 350 ▪ High suspicion of CSS that could resemble MAS-like: IL-6 values > 40 pg/mL and/or ferritin >500 ug/L and/or PCR > 30 mg/L and/or LDH >300 UI/L **Time since symptom onset (median, range):** ▪ NR **Characteristics** **Age (mean, IQR)** ▪ Exp: 61.1 (11.7) ▪ Ctrl: 59.8 (SD: 11.3) **Vaccination status** ▪ NR	**Experimental:** ▪ intravenous anakinra plus optimized standard of care (oSOC) ▪ Dose: 400mg/day (100mg 4 times a day) for a maximum of 15 days ▪ N = 92 **Control:** ▪ optimized standard of care (oSOC) alone ▪ N = 87	All-cause mortality (day 30)	RR 0.77 (0.21 to 2.77) Anakinra: 4/84 SoC: 5/81
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	RR 0.96 (0.48 to 1.95) Anakinra: 13/84 SoC: 13/81
			Serious adverse events	RR 0.76 (0.47 to 1.24) Anakinra: 21/89 SoC: 27/87
			Adverse events, any grade	RR 1.45 (0.98 to 2.14) Anakinra: 40/89 SoC: 27/87
			Hospital-acquired infections	Not reported
			Quality of life	Not reported

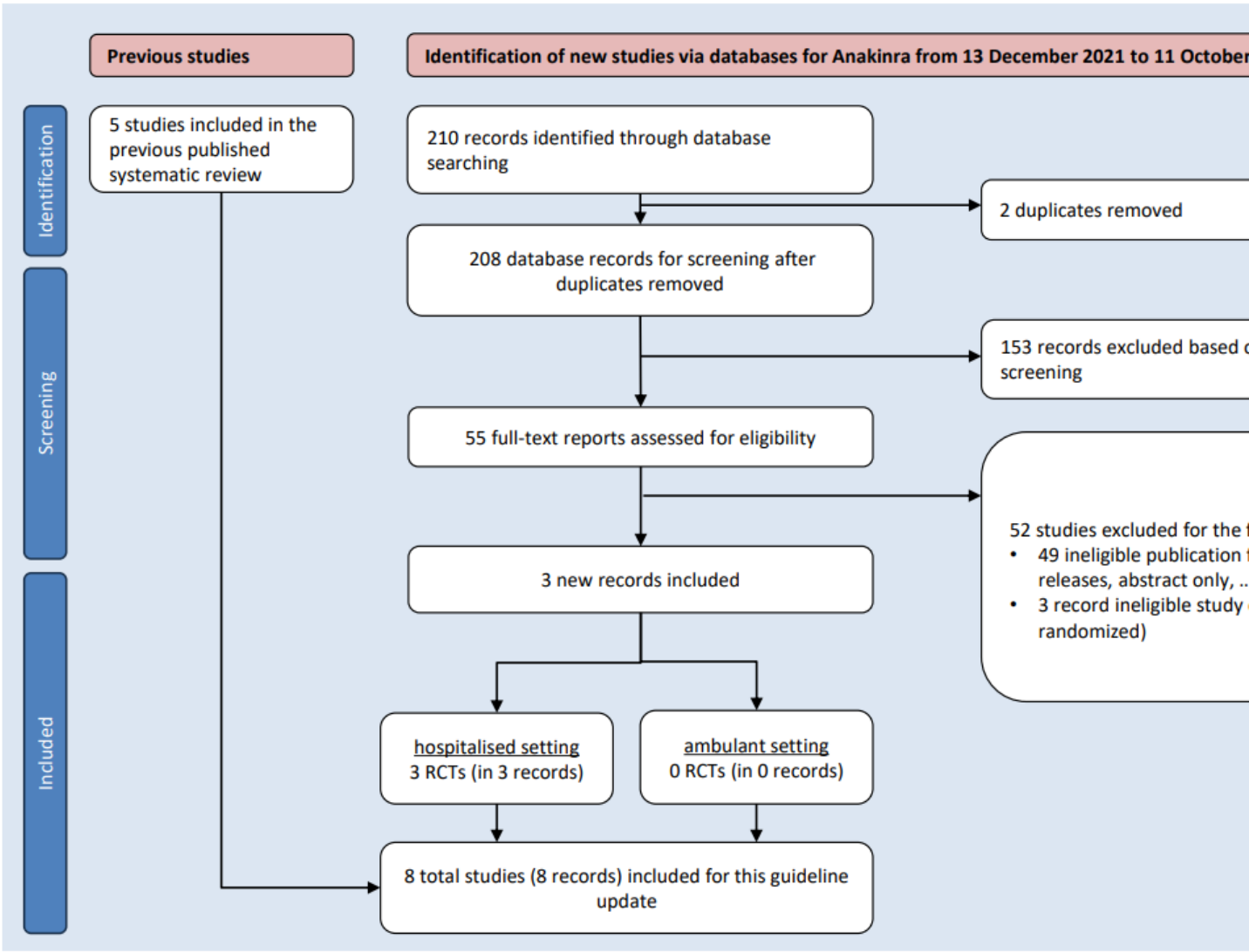
	Country ▪ Spain ***<u>Comorbidities</u>*** **Any** ▪ NR **Diabetes:** ▪ Exp: 10/89 (11.2%) ▪ Ctrl: 15/87 (17.2%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: 34/89 (38.2%) ▪ Ctrl: 36/ 87(41.4%) **Cardiovascular disease (Chronic heart failure)** ▪ Exp: 13/89 (14.6%) ▪ Ctrl: 17/87 (19.5%) **Lung diseases** <u>Chronic pulmonary disease</u> ▪ Exp: 6/89 (6.7%) ▪ Ctrl: 8/87 (9.2%) <u>Asthma</u> ▪ Exp: 9/89 (10.1%) ▪ Ctrl: 9/87 (10.3%) **Immunosuppressed** ▪ Exp: NR ▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: 4/89 (4.5%) ▪ Ctrl: 7/87 (8.0%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Elmekaty, 2023 RCT	**Sample size:** N = 80 pts. (1:1) randomised to anakinra or standard of care alone (327 pts. assessed) **Enrolment period:** 30.10.2020 to 28.02.2021 **Inclusion criteria:** ▪ Confirmed COVID-19 diagnosis ▪ associated presence of respiratory distress: PaO2/FiO2 ≤ 300 mm Hg or respiratory Rate (RR) ≥24 breaths/min or SpO2 ≤ 94% at room air ▪ radiological evidence of pneumonia based on chest X-ray and/or CT ▪ signs of cytokine release syndrome: Ferritin >600 mcg/L at presentation or > 300 mcg/L with doubling within 24h, LDH >250 IU/l, D-dimer >1 mg/L, CRP > 70 mg/L and rising since last 24 h with the absence of bacterial infection,	**Experimental:** ▪ subcutaneous anakinra plus standard of care (SOC) ▪ Dose: 200mg/day (100 mg every 12 h) for 3 days; then 100 mg/day for 4 days ▪ N = 40 **Control:** ▪ standard of care (SOC) alone ▪ N = 40	All-cause mortality (day 30)	RR 0.33 (0.01 to 7.95) Anakinra: 0/40 SoC: 1/40
			All-cause mortality (day 60)	Not reported
			All-cause mortality (longest follow-up)	Not reported
			Clinical improvement: discharged alive (day 30)	Not reported
			Clinical worsening: new need for IMV or death (day 30)	Not reported
			Admission to ICU or death	Not reported
			Serious adverse events	RR 1.00 (0.15 to 6.76) Anakinra: 2/40 SoC: 2/40
			Adverse events, any grade	RR 1.00 (0.95 to 1.05) Anakinra: 40/40 SoC: 40/40
			Hospital-acquired infections	Not reported
			Quality of life	Not reported

	Interleukin-6 level > 10 × UNL (reference range ≤ 7 pg/mL)] **Time since symptom onset (median, range):** ▪ NR **Characteristics** **Age (mean, IQR)** ▪ Exp: 49.5 (SD: 12.2) ▪ Ctrl: 50.3 (SD: 11.4) **Vaccination status** ▪ NR **Country** ▪ Quatar ***<u>Comorbidities</u>*** **Any** ▪ Exp: 17 (42.5%) ▪ Ctrl: 20 (50.0%) **Diabetes:** ▪ Exp: 17/40 (42.5%) ▪ Ctrl: 18/40 (45.0%) **Obesity (BMI ≥30 kg/m²)** ▪ Exp: median BMI 30.9 (IQR:7.0) ▪ Ctrl: median BMI under 30 **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease (Myocardial infarction)** ▪ Exp: 2/40 (5.0%) ▪ Ctrl: 5/40 (12.5%) **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR **Immunosuppressed** ▪ Exp: NR			

	▪ Ctrl: NR **Malignancy** ▪ Exp: NR ▪ Ctrl: NR **Kidney disease** ▪ Exp: NR ▪ Ctrl: NR			

5.11.5 Studienselektion: Flow Chart



5.11.6 Literaturrecherche

Date of search for all databases: 13.12.2021; Update für LL 11.10.2023		
Database/Register	Search	Update Search

CCSR	92 references (nicht berichten: 70 bisherige, 22 neue)	196 references, 52 studies
Scopus (neue Aufnahme 11.10.2023)		134
WHO COVID-19 DB*	147	32*
Total	239	364
Total (after deduplication)	Total: 204	210

The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.

Search strategies

Cochrane COVID-19 Study Register

Search string:

Anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR Antril OR Kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor"

Study characteristics:

1) "Intervention assignment": “Randomised” OR “unclear” OR
2) "Study design": "Parallel/Crossover" OR “unclear”

Scopus (neue Datenbank seit 11.10.2023)

TITLE-ABS (anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR antril OR kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor") AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") AND PUBYEAR > 2019 AND PUBYEAR < 2024 AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") AND PUBYEAR > 2019 AND PUBYEAR < 2024 AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

Title, abstract, subject:
(Anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR Antril OR Kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor") AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

5.12 Schlüsselfrage 7: Antikoagulation

Autor*innen: Stephanie Weibel, Stefanie Reis, Amon Faske

5.12.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.12.1.1 *Evidenzprofil 1*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Standard thromboprophylaxis (low dose)

Vergleichsintervention: No anticoagulation (placebo/SoC)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** No anticoagulation	 Low dose	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality 28 days	Relatives Risiko: 0.7 (CI 95% 0.29 - 1.67) Basierend auf Daten von 3305 patienter und 6 Studien	**7** pro 1000	**5** pro 1000 Differenz: **2 weniger pro 1000** (CI 95% 5 weniger - 5 mehr)	**Niedrig** Due to very serious imprecision[1]	Low dose may have little or no difference on all-cause mortality
All-cause mortality 90 days	Relatives Risiko: 3.25 (CI 95% 0.13 - 79.03) Basierend auf Daten von 219 patienter und 1 Studien	**0** pro 1000	**0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	**Sehr niedrig** Due to extremely serious imprecision[2]	There were too few who experienced the all-cause mortality, to determine whether low dose made a difference
Any thrombotic event or death up to 28 days	Relatives Risiko: 0.29 (CI 95% 0.06 - 1.37) Basierend auf Daten von 1284 patienter und 1 Studien	**11** pro 1000	**3** pro 1000 Differenz: **8 weniger pro 1000** (CI 95% 10 weniger - 4 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether low dose increases or decreases any thrombotic event or death
Any thrombotic event up to 28 days	Relatives Risiko: 0.44 (CI 95% 0.17 - 1.16) Basierend auf Daten von 2637 patienter und 4 Studien	**11** pro 1000	**5** pro 1000 Differenz: **6 weniger pro 1000** (CI 95% 9 weniger - 2 mehr)	**Moderat** Due to serious imprecision[4]	Low dose probably has little or no difference on any thrombotic event
Any thrombotic event up to 90 days	Relatives Risiko: 0.51 (CI 95% 0.09 - 2.75) Basierend auf Daten von 470 patienter und 1 Studien	**17** pro 1000	**9** pro 1000 Differenz: **8 weniger pro 1000** (CI 95% 15 weniger - 30 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether low dose increases or decreases any thrombotic event
Clinical worsening: Admission to hospital or death up to 28 days	Relatives Risiko: 0.91 (CI 95% 0.57 - 1.44) Basierend auf Daten von 2748 patienter und 5 Studien	**28** pro 1000	**25** pro 1000 Differenz: **3 weniger pro 1000** (CI 95% 12 weniger - 12 mehr)	**Moderat** Due to serious imprecision[6]	Low dose probably has little or no difference on clinical worsening: admission to hospital or death
	Relatives Risiko: 1.02 (CI 95% 0.45 - 2.3)	**46** pro 1000	**47** pro 1000	**Niedrig** Due to very serious imprecision[7]	Low dose may have little or no difference on clinical worsening:

Clinical worsening: Admission to hospital or death up to 90 days	Basierend auf Daten von 472 patienter und 1 Studien	Differenz: **1 mehr pro 1000** (CI 95% 25 weniger - 60 mehr)		admission to hospital or death
Clinical improvement: all initial symptoms resolved at 28 days	Relatives Risiko: 1.16 (CI 95% 0.97 - 1.38) Basierend auf Daten von 444 patienter und 1 Studien	**486** pro 1000 **564** pro 1000 Differenz: **78 mehr pro 1000** (CI 95% 15 weniger - 185 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[8]	Thromboprophylaxis may increase improvement of clinical status (asymptomatic according to Gates MRI scale 1) slightly
Major bleeding up to 28 days	Relatives Risiko: 1.49 (CI 95% 0.24 - 9.44) Basierend auf Daten von 3214 patienter und 6 Studien	**1** pro 1000 **1** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 1 weniger - 8 mehr)	**Sehr niedrig** Due to extremely serious imprecision[9]	There were too few who experienced the major bleeding, to determine whether low dose made a difference
Clinically relevant non-major bleeding up to 28 days	(CI 95% -)	Differenz: **weniger**		No study was found that looked at clinically relevant non-major bleeding
Serious adverse events up to 28 days	Relatives Risiko: 0.3 (CI 95% 0.06 - 1.43) Basierend auf Daten von 449 patienter und 1 Studien	**30** pro 1000 **9** pro 1000 Differenz: **21 weniger pro 1000** (CI 95% 28 weniger - 13 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether thromboprophylaxis increases or decreases serious adverse events
Any grade adverse event up to 28 days	Relatives Risiko: 1.16 (CI 95% 0.83 - 1.64) Basierend auf Daten von 668 patienter und 2 Studien	**154** pro 1000 **179** pro 1000 Differenz: **25 mehr pro 1000** (CI 95% 26 weniger - 99 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[11]	Low dose may have little or no difference on any grade adverse event
Any grade adverse event up to 90 days	Relatives Risiko: 1.37 (CI 95% 0.8 - 2.35) Basierend auf Daten von 219 patienter und 1 Studien	**167** pro 1000 **229** pro 1000 Differenz: **62 mehr pro 1000** (CI 95% 33 weniger - 225 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether low dose increases or decreases any grade adverse event
Quality of life	Gemessen mit: Skala: -	Differenz: **null kleiner**		No study was found that looked at quality of life

1. Unzureichende Präzision: sehr schwerwiegend. Low number of events, Wide confidence intervals;
2. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Low number of events.;
3. Risiko für Bias: schwerwiegend. One study with overall some concern of bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of events;
4. Unzureichende Präzision: schwerwiegend. Low number of patients;
5. Risiko für Bias: schwerwiegend. one study with overall some concern of bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of events.;

6. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
7. Unzureichende Präzision: sehr schwerwiegend. Only data from one study, Wide confidence intervals;
8. Risiko für Bias: schwerwiegend. one study with overall some concern of bias; Unzureichende Präzision: schwerwiegend. Only data from one study;
9. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Low number of events.;
10. Risiko für Bias: schwerwiegend. one study with overall some concern of bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients and few events;
11. Risiko für Bias: schwerwiegend. two studies with overall some concern of bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
12. Risiko für Bias: schwerwiegend. one study with overall some concern of bias; Unzureichende Präzision: sehr schwerwiegend. Only data from one study, Wide confidence intervals;

5.12.1.2 *Evidenzprofil 2*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Therapeutic dose anticoagulation

Vergleichsintervention: No anticoagulation (placebo/SoC)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** No anticoagulation	**Absolute Effektschätzer** Therapeutic dose	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality 28 days	Relatives Risiko: 1.0 (CI 95% 0.06 - 15.85) Basierend auf Daten von 328 patienter und 1 Studien	**6** pro 1000	**6** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 6 weniger - 89 mehr)	**Sehr niedrig** Due to extremely serious imprecision[1]	There were too few who experienced the all-cause mortality, to determine whether therapeutic dose made a difference
Any thrombotic event or death up to 28 days	(CI 95% -)		Differenz: **weniger**		No study was found that looked at any thrombotic event or death
Any thrombotic event up to 28 days	Relatives Risiko: 1.0 (CI 95% 0.06 - 15.85) Basierend auf Daten von 328 patienter und 1 Studien	**6** pro 1000	**6** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 6 weniger - 89 mehr)	**Sehr niedrig** Due to extremely serious imprecision[2]	There were too few who experienced the any thrombotic event, to determine whether therapeutic dose made a difference
Clinical worsening: Admission to hospital or death up to 28 days	Relatives Risiko: 0.63 (CI 95% 0.21 - 1.87) Basierend auf Daten von 328 patienter und 1 Studien	**49** pro 1000	**31** pro 1000 Differenz: **18 weniger pro 1000** (CI 95% 39 weniger - 43 mehr)	**Sehr niedrig** Due to extremely serious imprecision[3]	We are uncertain whether therapeutic dose increases or decreases clinical worsening: admission to hospital or death due to an effect of important benefit, with possibility of important harm
Clinical improvement: all	(CI 95% -)				No study was found that looked at clinical

initial symptoms resolved[5] at 28 days		Differenz: **weniger**		improvement (all initial symptoms resolved)
Clinically relevant non-major bleeding up to 28 days	(CI 95% -) Basierend auf Daten von 328 patienter und 1 Studien	Differenz: **weniger**		No study was found that looked at clinically relevant non-major bleeding
Serious adverse events up to 28 days	(CI 95% -)	Differenz: **weniger**		No study was found that looked at serious adverse events
Any grade adverse event up to 28 days	(CI 95% -)	Differenz: **mehr**		No study was found that looked at any grade adverse events
Quality of life	Gemessen mit: Skala: -	Differenz: **null kleiner**		No study was found that looked at quality of life
Major bleeding up to 28 days	Basierend auf Daten von 328 patienter und 1 Studien			There were too few (zero events) who experienced major bleeding, to determine whether therapeutic dose made a difference

1. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study;
2. Unzureichende Präzision: extrem ernst. Low number of patients, Wide confidence intervals, Only data from one study;
3. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study;

5.12.1.3 *Evidenzprofil 3*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Therapeutic dose anticoagulation

Vergleichsintervention: Standard thromboprophylaxis (low dose)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer**		**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
		Low dose	Therapeutic dose		
All-cause mortality	Relatives Risiko: 3.02 (CI 95% 0.12 - 73.55)	**0** pro 1000	**0** pro 1000	**Sehr niedrig**	There were too few who experienced the all-cause mortality, to

28 days	Basierend auf Daten von 329 patienter und 1 Studien	Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	Due to extremely serious imprecision[1]	determine whether therapeutic dose made a difference
Any thrombotic event or death up to 28 days	(CI 95% -)	Differenz: **weniger**		No study was found that looked at any thrombotic event or death
Any thrombotic event up to 28 days	Relatives Risiko: 3.02 (CI 95% 0.12 - 73.55) Basierend auf Daten von 329 patienter und 1 Studien	**0** pro 1000 **0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	**Sehr niedrig** Due to extremely serious imprecision[2]	There were too few who experienced the any thrombotic event, to determine whether therapeutic dose made a difference
Clinical worsening: Admission to hospital or death up to 28 days	Relatives Risiko: 1.01 (CI 95% 0.3 - 3.41) Basierend auf Daten von 329 patienter und 1 Studien	**30** pro 1000 **30** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 21 weniger - 72 mehr)	**Sehr niedrig** Due to extremely serious imprecision[3]	We are uncertain whether therapeutic dose increases or decreases clinical worsening: admission to hospital or death
Clinical improvement: all initial symptoms resolved[5] at 28 days	(CI 95% -)	Differenz: **weniger**		No study was found that looked at clinical improvement (all initial symptoms resolved)
Clinically relevant non-major bleeding up to 28 days	(CI 95% -)	Differenz: **weniger**		No study was found that looked at Clinically relevant non-major bleeding
Serious adverse events up to 28 days	(CI 95% -)	Differenz: **weniger**		No study was found that looked at serious adverse events
Any grade adverse event up to 28 days	(CI 95% -)	Differenz: **mehr**		No study was found that looked at any grade adverse event
Quality of life	Gemessen mit: Skala: -	Differenz: **null kleiner**		No study was found that looked at quality of life

Major bleeding up to 28 days	Basierend auf Daten von 329 patienter und 1 Studien			There were too few (zero events) who experienced major bleeding, to determine whether therapeutic dose made a difference

1. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study, Low number of patients;
2. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study;
3 Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study

5.12.1.4 *Evidenzprofil 4*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection and with moderate to severe disease, according to the WHO clinical progression scale (WHO 4 to 9)

Intervention: Therapeutic dose anticoagulation

Vergleichsintervention: Standard thromboprophylaxis (low dose/intermediate dose))

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Low dose/intermediate dose	 Therapeutic dose	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality (WHO 4 to 9) 28 days	Relatives Risiko: 0.8 (CI 95% 0.65 - 0.98) Basierend auf Daten von 5935 patienter und 12 Studien	**108** pro 1000	**86** pro 1000 Differenz: **22 weniger pro 1000** (CI 95% 38 weniger - 2 weniger)	**Moderat** Due to serious risk of bias[1]	Therapeutic dose probably decreases all-cause mortality (WHO 4 to 9)
All-cause mortality (subgroup WHO 4 to 5) 28 days	Relatives Risiko: 0.65 (CI 95% 0.48 - 0.88) Basierend auf Daten von 4209 patienter und 6 Studien	**73** pro 1000	**47** pro 1000 Differenz: **26 weniger pro 1000** (CI 95% 38 weniger - 9 weniger)	**Moderat** Due to serious risk of bias[2]	Therapeutic dose probably decreases all-cause mortality (subgroup WHO 4 to 5)
All-cause mortality (subgroup WHO 6 to 9) 28 days	Relatives Risiko: 0.82 (CI 95% 0.64 - 1.04) Basierend auf Daten von 619 patienter und 4 Studien	**332** pro 1000	**272** pro 1000 Differenz: **60 weniger pro 1000** (CI 95% 120 weniger - 13 mehr)	**Niedrig** Due to very serious risk of bias[3]	Therapeutic dose may decrease all-cause mortality (subgroup WHO 6 to 9)
All-cause mortality (WHO 4 to 9) 90 days	Relatives Risiko: 0.83 (CI 95% 0.51 - 1.33) Basierend auf Daten von 634 patienter und 2 Studien	**116** pro 1000	**96** pro 1000 Differenz: **20 weniger pro 1000** (CI 95% 57 weniger - 38 mehr)	**Niedrig** Due to very serious imprecision[4]	Therapeutic dose may have little or no difference on all-cause mortality (WHO 4-9)
All-cause mortality (WHO 4 to 9)	Relatives Risiko: 0.97 (CI 95% 0.79 - 1.19)	**180** pro 1000	**175** pro 1000	**Niedrig**	Therapeutic dose may have little or no difference

in hospital	Basierend auf Daten von 3344 patienter und 3 Studien	Differenz: **5 weniger pro 1000** (CI 95% 38 weniger - 34 mehr)	Due to serious risk of bias, Due to serious imprecision[5]	on all-cause mortality (WHO 4 to 9)
Any thrombotic event or death (WHO 4 to 9) up to 28 days	Relatives Risiko: 0.84 (CI 95% 0.73 - 0.97) Basierend auf Daten von 8075 patienter und 8 Studien	**162** pro 1000 **136** pro 1000 Differenz: **26 weniger pro 1000** (CI 95% 44 weniger - 5 weniger)		Significant subgroup difference (p=0.007) between WHO 4-5 and WHO 6-9. Pooled estimate not considered.
Any thrombotic event or death (subgroup WHO 4 to 5) up to 28 days	Relatives Risiko: 0.72 (CI 95% 0.6 - 0.86) Basierend auf Daten von 5865 patienter und 5 Studien	**94** pro 1000 **68** pro 1000 Differenz: **26 weniger pro 1000** (CI 95% 38 weniger - 13 weniger)	**Hoch**	Therapeutic dose decreases any thrombotic event or death (subgroup WHO 4 to 5)
Any thrombotic event or death (subgroup WHO 6 to 9) up to 28 days	Relatives Risiko: 0.98 (CI 95% 0.86 - 1.12) Basierend auf Daten von 1262 patienter und 3 Studien	**400** pro 1000 **392** pro 1000 Differenz: **8 weniger pro 1000** (CI 95% 56 weniger - 48 mehr)	**Moderat** Due to serious imprecision[6]	Therapeutic dose probably has little or no difference on any thrombotic event or death (subgroup WHO 6 to 9)
Any thrombotic event (WHO 4 to 9)[13] up to 28 days	Relatives Risiko: 0.6 (CI 95% 0.49 - 0.74) Basierend auf Daten von 5458 patienter und 9 Studien	**83** pro 1000 **50** pro 1000 Differenz: **33 weniger pro 1000** (CI 95% 42 weniger - 22 weniger)	**Hoch**	Therapeutic dose decreases any thrombotic event (WHO 4 to 9)
Any thrombotic event (WHO 4 to 9) up to 90 days	Relatives Risiko: 0.64 (CI 95% 0.13 - 3.1) Basierend auf Daten von 300 patienter und 1 Studien	**30** pro 1000 **19** pro 1000 Differenz: **11 weniger pro 1000** (CI 95% 26 weniger - 63 mehr)	**Sehr niedrig** Due to extremely serious imprecision[7]	We are uncertain whether therapeutic dose increases or decreases any thrombotic event (WHO 4 to 9) due to an effect of important benefit, with possibility of important harm
Worsening of clinical status: Progression to intubation or death (WHO 4 to 5) 28 days	Relatives Risiko: 0.9 (CI 95% 0.72 - 1.14) Basierend auf Daten von 2231 patienter und 1 Studien	**121** pro 1000 **109** pro 1000 Differenz: **12 weniger pro 1000** (CI 95% 34 weniger - 17 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[8]	Therapeutic dose may have little or no difference on worsening of clinical status: progression to intubation or death (WHO 4 to 5)
Worsening of clinical status: Admission to ICU or death (WHO 4 to 5) up to 28 days	Relatives Risiko: 0.75 (CI 95% 0.51 - 1.1) Basierend auf Daten von 465 patienter und 1 Studien	**211** pro 1000 **158** pro 1000 Differenz: **53 weniger pro 1000** (CI 95% 103 weniger - 21 mehr)	**Sehr niedrig** Due to extremely serious imprecision[9]	We are uncertain whether therapeutic dose increases or decreases worsening of clinical status: admission to ICU or death (WHO 4 to 5) due to an effect of important benefit, with possibility of important harm

Improvement of clinical status: participants discharged alive (WHO 4 to 9) 28 days	Relatives Risiko: 0.96 (CI 95% 0.9 - 1.02) Basierend auf Daten von 614 patienter und 1 Studien	**882** pro 1000 **847** pro 1000 Differenz: **35 weniger pro 1000** (CI 95% 88 weniger - 18 mehr)	**Moderat** Due to serious imprecision[10]	Therapeutic anticoagulant probably has little or no difference on improvement of clinical status (participants discharged alive) at day 28 (WHO 4 to 9)
Improvement of clinical status: survival until hospital discharge without receiving organ support (WHO 4 to 5) hospital discharge	Relatives Risiko: 1.05 (CI 95% 1.0 - 1.1) Basierend auf Daten von 2219 patienter und 1 Studien	**764** pro 1000 **802** pro 1000 Differenz: **38 mehr pro 1000** (CI 95% 0 weniger - 76 mehr)	**Moderat** Due to serious risk of bias[11]	Therapeutic dose probably increases improvement of clinical status: survival until hospital discharge without receiving organ support (WHO 4 to 5)
Major bleeding (WHO 4 to 9)[21] up to 28 days	Relatives Risiko: 1.79 (CI 95% 1.25 - 2.56) Basierend auf Daten von 9107 patienter und 12 Studien	**12** pro 1000 **21** pro 1000 Differenz: **9 mehr pro 1000** (CI 95% 3 mehr - 19 mehr)	**Moderat** Due to serious risk of bias[12]	Therapeutic dose probably increases major bleeding (WHO 4 to 9)
Major bleeding (subgroup WHO 4 to 5)[23] up to 28 days	Relatives Risiko: 1.74 (CI 95% 0.95 - 3.19) Basierend auf Daten von 6507 patienter und 8 Studien	**6** pro 1000 **10** pro 1000 Differenz: **4 mehr pro 1000** (CI 95% 0 weniger - 13 mehr)	**Niedrig** Due to very serious risk of bias[13]	Therapeutic dose may increase major bleeding (WHO 4 to 5)
Major bleeding (subgroup WHO 6 to 9) up to 28 days	Relatives Risiko: 1.85 (CI 95% 1.09 - 3.14) Basierend auf Daten von 1652 patienter und 4 Studien	**25** pro 1000 **46** pro 1000 Differenz: **21 mehr pro 1000** (CI 95% 2 mehr - 54 mehr)	**Moderat** Due to serious risk of bias[14]	Therapeutic dose probably increases major bleeding (WHO 6 to 9)
Adverse events (any grade) during the study period	(CI 95% -)	Differenz: **weniger**		No study reported any adverse events
Quality of life at longest follow-up available	Basierend auf Daten von 240 patienter und 1 Studien			One study reported EQ-5D-5L score. No difference between groups (reported as median with IQR).
Serious adverse events during the study period	Basierend auf Daten von 65 patienter und 1 Studien			There were too few (zero events) who experienced serious adverse events, to determine whether therapeutic dose made a difference

1. Risiko für Bias: schwerwiegend. Five studies with overall some concerns of bias and two studies with overall high risk of bias. Six studies with low risk of bias (effect estimate excluding biased studies RR 0.83 (0.52; 1.34)).;

2. Risiko für Bias: schwerwiegend. Three studies with overall some concern of bias. Three studies with overall no concern of bias. (effect estimate excluding biased studies RR 0.48 (0.19; 1.18)).;
3. Risiko für Bias: sehr schwerwiegend. Two studies with overall high risk of bias and one study with overall some concern of bias. One study with overall no concern of bias. (effect estimate excluding biased studies RR 0.90 (0.52; 1.57)).;
4. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals;
5. Risiko für Bias: schwerwiegend. three studies with overall some concern of bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
6. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
7. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study;
8. Risiko für Bias: schwerwiegend. one study with overall some concern of bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
9. Unzureichende Präzision: extrem ernst. Only data from one study, Wide confidence intervals (effect of important benefit, with possibility of important harm);
10. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
11. Risiko für Bias: schwerwiegend. one study with overall some concern of bias;
12. ISTH criteria
13. Risiko für Bias: schwerwiegend. One study with overall high risk of bias and eight studies with overall some concern of bias. Five studies with overall no concern of bias. (effect estimate excluding biased studies RR 1.45 (0.73; 2.84)).;
14. ISTH criteria
15. Risiko für Bias: sehr schwerwiegend. Six sudies with overall some concern of bias. Two studies with overall no concern of bias. (effect estimate excluding biased studies RR 0.70 (0.20; 2.49)).;
16. ISTH criteria
17. Risiko für Bias: schwerwiegend. One study with overall high risk of bias, two studies with overall some concern of bias. One study with overall no concern of bias. (effect estimate excluding biased studies RR 7.63 (0.42; 137.36)).;

5.12.1.5 *Evidenzprofil 5*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection and with moderate to severe disease, according to the WHO clinical progression scale (WHO 4 to 9)

Intervention: Intermediate dose anticoagulation

Vergleichsintervention: Standard thromboprophylaxis (low dose)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Low dose	 Intermediate dose	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality (WHO 4-9) 28 days	Relatives Risiko: 1.02 (CI 95% 0.85 - 1.22) Basierend auf Daten von 1137 patienter und 4 Studien	**265** pro 1000	**270** pro 1000 Differenz: **5 mehr pro 1000** (CI 95% 40 weniger - 58 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[1]	Intermediate dose may have little or no difference on all-cause mortality (WHO 4-9)
All-cause mortality (subgroup WHO 4-5) 28 days	Relatives Risiko: 5.87 (CI 95% 0.29 - 119.44) Basierend auf Daten von 111 patienter und 1 Studien	**0** pro 1000	**0** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	**Sehr niedrig** Due to extremely serious imprecision[2]	There were too few who experienced the all-cause mortality (subgroup WHO 4-5), to determine whether intermediate dose made a difference

All-cause mortality (subgroup WHO 6-9) 28 days	Relatives Risiko: 1.06 (CI 95% 0.88 - 1.29) Basierend auf Daten von 629 patienter und 2 Studien	**377** pro 1000 **400** pro 1000 Differenz: **23 mehr pro 1000** (CI 95% 45 weniger - 109 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[3]	Intermediate dose may have little or no difference on all-cause mortality (subgroup WHO 6-9)
All-cause mortality (WHO 4-9) 90 days	Relatives Risiko: 1.07 (CI 95% 0.9 - 1.27) Basierend auf Daten von 1011 patienter und 3 Studien	**286** pro 1000 **306** pro 1000 Differenz: **20 mehr pro 1000** (CI 95% 29 weniger - 77 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[4]	Intermediate dose may have little or no difference on all-cause mortality (WHO 4-9)
All-cause mortality (WHO 4-9) in hospital	Relatives Risiko: 1.17 (CI 95% 0.43 - 3.18) Basierend auf Daten von 124 patienter und 1 Studien	**103** pro 1000 **121** pro 1000 Differenz: **18 mehr pro 1000** (CI 95% 59 weniger - 225 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether intermediate dose increases or decreases all-cause mortality in hospital (WHO 4-9)
Any thrombotic event or death (WHO 4-9) up to 28 days	Relatives Risiko: 0.73 (CI 95% 0.33 - 1.59) Basierend auf Daten von 814 patienter und 2 Studien	**385** pro 1000 **281** pro 1000 Differenz: **104 weniger pro 1000** (CI 95% 258 weniger - 227 mehr)	**Niedrig** Due to serious risk of bias, Due to serious inconsistency[6]	Intermediate dose may decrease any thrombotic event or death (WHO 4-9)
Any thrombotic event or death (subgroup WHO 4-5) up to 28 days	(CI 95% -)	Differenz: **weniger**		No studies were found that looked at any thrombotic event or death (subgroup WHO 4-5)
Any thrombotic event or death (subgroup WHO 6-9) up to 28 days	Relatives Risiko: 1.03 (CI 95% 0.86 - 1.24) Basierend auf Daten von 590 patienter und 1 Studien	**429** pro 1000 **442** pro 1000 Differenz: **13 mehr pro 1000** (CI 95% 60 weniger - 103 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[7]	Intermediate dose may have little or no difference on any thrombotic event or death (subgroup WHO 6-9)
Any thrombotic event (WHO 4-9) up to 28 days	Relatives Risiko: 0.53 (CI 95% 0.14 - 1.94) Basierend auf Daten von 790 patienter und 2 Studien	**83** pro 1000 **44** pro 1000 Differenz: **39 weniger pro 1000** (CI 95% 71 weniger - 78 mehr)	**Niedrig** Due to serious risk of bias, Due to serious inconsistency[8]	Intermediate dose may decrease any thrombotic event (WHO 4-9)
Any thrombotic event (subgroup WHO 4-5) up to 28 days	(CI 95% -)	Differenz: **weniger**		No studies were found that looked at any thrombotic event (subgroup WHO 4-5)
	Relatives Risiko: 1.02 (CI 95% 0.43 - 2.42)	**35** pro 1000 **36** pro 1000	**Niedrig**	Intermediate dose may have little or no difference

Any thrombotic event (subgroup WHO 6-9) up to 28 days	Basierend auf Daten von 566 patienter und 1 Studien	Differenz: **1 mehr pro 1000** (CI 95% 20 weniger - 50 mehr)	Due to serious risk of bias, Due to serious imprecision[9]	on any thrombotic event (subgroup WHO 6-9)
Any thrombotic event (WHO 4-9) up to 90 days	Relatives Risiko: 1.08 (CI 95% 0.2 - 5.77) Basierend auf Daten von 287 patienter und 1 Studien	**20** pro 1000 **22** pro 1000 Differenz: **2 mehr pro 1000** (CI 95% 16 weniger - 95 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[10]	Intermediate dose may have little or no difference on any thrombotic event (WHO 4-9)
Worsening of clinical status: Progression to intubation or death (WHO 4 to 5) up to 28 days	(CI 95% -)	Differenz: **weniger**		No study reported worsening of clinical status (progression to intubation or death)
Worsening of clinical status: Admission to ICU or death[17] up to 28 days	(CI 95% -)	Differenz: **weniger**		No study reported worsening of clinical status (admission to ICU or death)
Improvement of clinical status: participants discharged alive without clinical deterioration or death up to 28 days	(CI 95% -)	Differenz: **weniger**		No study reported improvement of clinical status (participants dicharged alive without clincial deterioration or death)
Improvement of clinical status: Survival until hospital discharge without receiving organ support up to 28 days	(CI 95% -)	Differenz: **weniger**		No study reported improvement of clinical status (survival until hospital discharge without receiving organ support)
Major bleeding (WHO 4-9) up to 28 days	Relatives Risiko: 1.48 (CI 95% 0.66 - 3.33) Basierend auf Daten von 1137 patienter und 4 Studien	**17** pro 1000 **25** pro 1000 Differenz: **8 mehr pro 1000** (CI 95% 6 weniger - 40 mehr)	**Niedrig** Due to very serious imprecision[11]	Intermediate dose may increase major bleeding (WHO 4-9)
Serious adverse events during the study period	(CI 95% -)	Differenz: **weniger**		No study reported serious adverse events

Adverse events (any grade) during the study period	(CI 95% -)	Differenz: **weniger**		No studies were found that looked at adverse events (any grade)
Quality of life at longest follow-up available	Basierend auf Daten von 334 patienter und 1 Studien			One study reported EQ-5D-5L score. No difference between groups (reported as median with IQR).

1. Risiko für Bias: schwerwiegend. One study with overall some concern of bias. Three studies with overall no concern of bias (effect estimate excluding biased studies RR 0.85 (0.54; 1.33)).; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
2. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study, Low number of events;
3. Risiko für Bias: schwerwiegend. One study with overall some concern of bias. One study with overall no concern of bias. (effect estimate excluding biased studies RR 2.25 (0.25; 20.46)).; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
4. Risiko für Bias: schwerwiegend. Two studies with overall some concern of bias. One study with overall no concern of bias. Effect estimate excluding biased studies (RR 1.75 (0.30; 10.23)); Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
5. Risiko für Bias: schwerwiegend. One study with overall some concern of bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Only data from one study, Low number of events;
6. Risiko für Bias: schwerwiegend. One study with overall somce concern of bias. One study with overall no concern of bias. Effect estimate excluding biased studies RR 0.47 (0.26; 0.83).; Inkonsistenz: schwerwiegend. I^2=85%, The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.;
7. Risiko für Bias: schwerwiegend. One study with some concern of bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
8. Risiko für Bias: schwerwiegend. One study with overall some concern of bias. One study with overall low risk of bias. Effect estimate excluding biased study RR (0.27 (0.11; 0.64).; Inkonsistenz: schwerwiegend. The magnitude of statistical heterogeneity was high, with I^2=78%;
9. Risiko für Bias: schwerwiegend. One study with some concern of bias; Unzureichende Präzision: schwerwiegend. Wide confidence intervals, Only data from one study;
10. Risiko für Bias: schwerwiegend. One study with overall somoe concern of bias; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Only data from one study, Low number of events;
11. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of events;

5.12.1.6 *Evidenzprofil 6*

Population: Post-discharge COVID-19 patients

Intervention: Standard thromboprophylaxis (low dose)

Vergleichsintervention: No anticoagulation (placebo/SoC)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** No anticoagulation	Low dose	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality 28 days	Relatives Risiko: 0.7 (CI 95% 0.26 - 1.85)	**17** pro 1000	**12** pro 1000	**Sehr niedrig**	We are uncertain whether low dose increases or decreases all-cause

	Basierend auf Daten von 1535 patienter und 2 Studien	Differenz: **5 weniger pro 1000** (CI 95% 13 weniger - 14 mehr)	Due to extremely serious imprecision[1]	mortality due to an effect of important benefit, with possibility of important harm
Any thrombotic event or death up to 28 days	Relatives Risiko: 0.64 (CI 95% 0.28 - 1.44) Basierend auf Daten von 1535 patienter und 2 Studien	**38** pro 1000 **24** pro 1000 Differenz: **14 weniger pro 1000** (CI 95% 27 weniger - 17 mehr)	**Sehr niedrig** Due to extremely serious imprecision[2]	We are uncertain whether low dose increases or decreases any thrombotic event or death due to an effect of important benefit, with possibility of important harm
Any thrombotic event or death up to 90 days	Relatives Risiko: 1.11 (CI 95% 0.58 - 2.12) Basierend auf Daten von 1217 patienter und 1 Studien	**28** pro 1000 **31** pro 1000 Differenz: **3 mehr pro 1000** (CI 95% 12 weniger - 31 mehr)	**Sehr niedrig** Due to extremely serious imprecision[3]	We are uncertain whether low dose increases or decreases any thrombotic event or death due to an effect of important benefit, with possibility of important harm
Any thrombotic event up to 28 days	Relatives Risiko: 0.36 (CI 95% 0.13 - 0.97) Basierend auf Daten von 318 patienter und 1 Studien	**88** pro 1000 **32** pro 1000 Differenz: **56 weniger pro 1000** (CI 95% 77 weniger - 3 weniger)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[4]	Low dose may decrease any thrombotic event
Clinical worsening: Admission to hospital or death up to 28 days	(CI 95% -)	Differenz: **weniger**		No study reported worsening of clinical status (admission to hospital or death)
Major bleeding up to 28 days	Relatives Risiko: 1.99 (CI 95% 0.18 - 21.89) Basierend auf Daten von 1535 patienter und 2 Studien	**1** pro 1000 **2** pro 1000 Differenz: **1 mehr pro 1000** (CI 95% 1 weniger - 21 mehr)	**Sehr niedrig** Due to extremely serious imprecision[5]	We are uncertain whether low dose increases or decreases major bleeding due to an effect of important harm, with possibility of important benefit
Clinically relevant non-major bleedings up to 28 days	Relatives Risiko: 0.63 (CI 95% 0.2 - 1.94) Basierend auf Daten von 1535 patienter und 2 Studien	**10** pro 1000 **6** pro 1000 Differenz: **4 weniger pro 1000** (CI 95% 8 weniger - 9 mehr)	**Niedrig** Due to very serious imprecision[6]	Low dose may have little or no difference on clinically relevant non-major bleedings
Other bleedings up to 28 days	Relatives Risiko: 2.0 (CI 95% 0.18 - 21.84) Basierend auf Daten von 318 patienter und 1 Studien	**6** pro 1000 **12** pro 1000 Differenz: **6 mehr pro 1000** (CI 95% 5 weniger - 125 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[7]	We are uncertain whether low dose increases or decreases other bleedings
Serious adverse events during the study period	Relatives Risiko: 1.05 (CI 95% 0.73 - 1.52) Basierend auf Daten von 1217 patienter und 1 Studien	**84** pro 1000 **88** pro 1000 Differenz: **4 mehr pro 1000** (CI 95% 23 weniger - 44 mehr)	**Moderat** Due to serious imprecision[8]	Low dose probably has little or no difference on serious adverse events

Any grade adverse events during the study period	(CI 95% -)	Differenz: **mehr**		No study reported any grade adverse events
Quality of life at longest follow-up available	Gemessen mit: Skala: -	Differenz: **null Größer**		No studies were found that looked at quality of life

1. Unzureichende Präzision: extrem ernst. Wide confidence intervals;
2. Unzureichende Präzision: extrem ernst. Wide confidence intervals;
3. Unzureichende Präzision: extrem ernst. Wide confidence intervals, Only data from one study;
4. Risiko für Bias: schwerwiegend. Unzureichende Präzision: schwerwiegend. Only data from one study;
5. Unzureichende Präzision: extrem ernst. Wide confidence intervals;
6. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals;
7. Risiko für Bias: schwerwiegend. Unzureichende Präzision: sehr schwerwiegend.
8. Unzureichende Präzision: schwerwiegend. Wide confidence intervals;

5.12.2 Analysen / Forest Plots

5.12.2.1 *Outpatients: Standard thromboprophylaxis (low dose) versus no anticoagulation (SoC/placebo)*

Mortality, day 28

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV–4B, Connors–2021 (vs placebo)	0	165	1	164	11.7%	7.5%	0.33 [0.01; 8.07]
Ananworanich–2021	0	219	0	230	0.0%	0.0%	
CARE–COALITION VIII, Avezum–2023	5	272	9	280	69.0%	65.2%	0.57 [0.19; 1.68]
ETHIC, Cools–2022	1	105	0	114	3.7%	7.5%	3.26 [0.13; 79.05]
OVID, Barco–2022	0	234	0	238	0.0%	0.0%	
PREVENT HD, Piazza–2023	2	641	2	643	15.5%	19.9%	1.00 [0.14; 7.10]
Total (fixed effect, 95% CI)		**1636**		**1669**	**100.0%**	**--**	**0.71 [0.31; 1.65]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.70 [0.29; 1.67]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.37$, df = 3 (P = 0.71); $I^2 = 0\%$

Admission to hospital or death

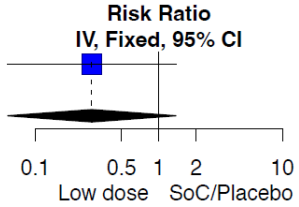
Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV–4B, Connors–2021 (vs placebo)	5	165	8	164	21.4%	17.7%	0.62 [0.21; 1.86]
Ananworanich–2021	3	222	7	222	18.7%	11.8%	0.43 [0.11; 1.64]
ETHIC, Cools–2022	12	105	12	114	30.7%	37.2%	1.09 [0.51; 2.31]
OVID, Barco–2022	8	234	8	238	21.2%	22.9%	1.02 [0.39; 2.66]
PREVENT HD, Piazza–2023	5	641	3	643	8.0%	10.4%	1.67 [0.40; 6.97]
Total (fixed effect, 95% CI)		**1367**		**1381**	**100.0%**	**--**	**0.90 [0.57; 1.41]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.91 [0.57; 1.44]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.64$, df = 4 (P = 0.62); $I^2 = 0\%$

Any thrombotoc event or death

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
PREVENT HD, Piazza–2023	2	641	7	643	100.0%	0.29 [0.06; 1.37]
Total (95% CI)		**641**		**643**	**100.0%**	**0.29 [0.06; 1.37]**

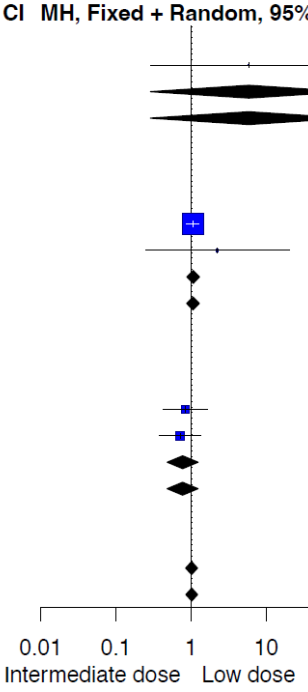
Heterogeneity: $Tau^2 = NA$; $Chi^2 = 0.00$, df = 0 (P = NA); $I^2 = NA\%$



5.12.2.2 *Inpatients: intermediate dose anticoagulation versus standard thromboprophylaxis (low dose)*

Mortality, day 28

Study or Subgroup	Intermediate Events	Intermediate Total	Low Events	Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Moderate disease (WHO 4 to 5)							
X–COVID, Morici–2021	2	51	0	60	0.3%	0.3%	5.87 [0.29; 119.59]
Total (fixed effect, 95% CI)		51		60	0.3%	—	5.87 [0.29; 119.59]
Total (random effects, 95% CI)					—	0.3%	5.87 [0.29; 119.59]
Heterogeneity: not applicable							
subgroup = Severe disease (WHO 6–9)							
INSPIRATION, Sadeghipour 2021	121	280	117	286	76.6%	84.7%	1.06 [0.87; 1.28]
X–COVID, Morici–2021	3	36	1	27	0.8%	0.7%	2.25 [0.25; 20.46]
Total (fixed effect, 95% CI)		316		313	77.3%	—	1.07 [0.88; 1.30]
Total (random effects, 95% CI)					—	85.3%	1.06 [0.88; 1.29]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.45$, df = 1 (P = 0.50); $I^2 = 0\%$							
subgroup = Mixed moderate to severe disease (WHO 4–9)							
ANTICOVID, Labbé–2023	13	110	16	114	10.4%	6.8%	0.84 [0.43; 1.67]
Perepu–2021	13	87	18	86	12.0%	7.5%	0.71 [0.37; 1.37]
Total (fixed effect, 95% CI)		197		200	22.4%	—	0.77 [0.48; 1.24]
Total (random effects, 95% CI)					—	14.3%	0.77 [0.48; 1.24]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$							
Total (fixed effect, 95% CI)		**564**		**573**	**100.0%**	—	**1.02 [0.85; 1.22]**
Total (random effects, 95% CI)					—	**100.0%**	**1.02 [0.85; 1.22]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.38$, df = 4 (P = 0.50); $I^2 = 0\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 0.57$, df = 2 (P = 0.75); $I^2 = 0\%$							



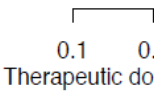
Any thrombotic event or death, 28 days

Study or Subgroup	Intermediate Events	Intermediate Total	Low Events	Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Severe disease (WHO 6–7)							
INSPIRATION, Sadeghipour 2021	131	296	126	294	80.6%	56.0%	1.03 [0.86; 1.24]
Total (fixed effect, 95% CI)		296		294	80.6%	—	1.03 [0.86; 1.24]
Total (random effects, 95% CI)					—	56.0%	1.03 [0.86; 1.24]
Heterogeneity: not applicable							
subgroup = Mixed moderate to severe disease (WHO 4–9)							
ANTICOVID, Labbé–2023	14	110	31	114	19.4%	44.0%	0.47 [0.26; 0.83]
Total (fixed effect, 95% CI)		110		114	19.4%	—	0.47 [0.26; 0.83]
Total (random effects, 95% CI)					—	44.0%	0.47 [0.26; 0.83]
Heterogeneity: not applicable							
Total (fixed effect, 95% CI)		**406**		**408**	**100.0%**	—	**0.92 [0.77; 1.10]**
Total (random effects, 95% CI)					—	**100.0%**	**0.73 [0.33; 1.59]**
Heterogeneity: $Tau^2 = 0.2747$; $Chi^2 = 6.81$, df = 1 (P < 0.01); $I^2 = 85\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 0.00$, df = 0 (P = NA); I^2 = NA%							

5.12.2.3 *Inpatients: therapeutic dose anticoagulation versus standard thromboprophylaxis (low and intermediate dose)*

Mortality, day 28

Study or Subgroup	Therapeutic Events	Therapeutic Total	Interm./Low Events	Interm./Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Moderate disease (WHO 4 to 5)							
BEMICOP, Marcos–Jubilar–2022 (bemiparin)	2	32	1	33	0.3%	0.8%	2.06 [0.20; 21.64]
COVID–PREVENT, Rauch–Kröhnert–2023	2	55	1	56	0.3%	0.7%	2.04 [0.19; 21.82]
FREEDOM–COVID, Stone–2023 (apixaban)	54	1121	39	571	18.1%	14.7%	0.71 [0.47; 1.05]
FREEDOM–COVID, Stone–2023 (enoxaparin)	54	1136	39	570	18.2%	14.7%	0.69 [0.47; 1.04]
HEP–COVID, Spyropoulos 2021	9	84	16	86	5.5%	6.0%	0.58 [0.27; 1.23]
RAPID, Sholzberg–2021	4	228	18	237	6.2%	3.4%	0.23 [0.08; 0.67]
Total (fixed effect, 95% CI)		**2656**		**1553**	**48.8%**	—	**0.65 [0.50; 0.83]**
Total (random effects, 95% CI)					—	**40.2%**	**0.65 [0.48; 0.88]**
Heterogeneity: $Tau^2 = 0.0205$; $Chi^2 = 5.8$, df = 5 (P = 0.33); $I^2 = 14\%$							
subgroup = Severe disease (WHO 6 to 9)							
COVID–PACT, Bohula–2022	55	197	62	193	22.0%	19.1%	0.87 [0.64; 1.18]
HEP–COVID, Spyropoulos 2021	16	45	15	38	5.7%	9.7%	0.90 [0.52; 1.57]
HESACOVID, Lemos–2020	1	10	3	10	1.1%	1.0%	0.33 [0.04; 2.69]
Oliynyk–2021	17	84	14	42	6.6%	8.6%	0.61 [0.33; 1.11]
Total (fixed effect, 95% CI)		**336**		**283**	**35.3%**	—	**0.81 [0.64; 1.03]**
Total (random effects, 95% CI)					—	**38.3%**	**0.82 [0.64; 1.04]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.92$, df = 3 (P = 0.59); $I^2 = 0\%$							
subgroup = Mixed moderate to severe disease (WHO 4 to 9)							
ACTION, Lopes–2021	35	310	23	304	8.2%	11.1%	1.49 [0.90; 2.46]
ANTICOVID, Labbé–2023	14	110	29	224	6.7%	8.8%	0.98 [0.54; 1.78]
COVID–HEP, Blondon–2022	3	79	3	80	1.0%	1.6%	1.01 [0.21; 4.87]
Total (fixed effect, 95% CI)		**499**		**608**	**15.9%**	—	**1.25 [0.86; 1.81]**
Total (random effects, 95% CI)					—	**21.5%**	**1.24 [0.85; 1.80]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.17$, df = 2 (P = 0.56); $I^2 = 0\%$							
Total (fixed effect, 95% CI)		**3491**		**2444**	**100.0%**	—	**0.80 [0.68; 0.94]**
Total (random effects, 95% CI)					—	**100.0%**	**0.80 [0.65; 0.98]**
Heterogeneity: $Tau^2 = 0.0342$; $Chi^2 = 16.42$, df = 12 (P = 0.17); $I^2 = 27\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 8.89$, df = 10 (P = 0.54); $I^2 = 0\%$							



Any thrombotic event or death, day 28

Study or Subgroup	Intermediate Events	Intermediate Total	Low Events	Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Severe disease (WHO 6–7)							
INSPIRATION, Sadeghipour 2021	131	296	126	294	80.6%	56.0%	1.03 [0.86; 1.24]
Total (fixed effect, 95% CI)		296		294	80.6%	—	1.03 [0.86; 1.24]
Total (random effects, 95% CI)					—	56.0%	1.03 [0.86; 1.24]
Heterogeneity: not applicable							
subgroup = Mixed moderate to severe disease (WHO 4–9)							
ANTICOVID, Labbé–2023	14	110	31	114	19.4%	44.0%	0.47 [0.26; 0.83]
Total (fixed effect, 95% CI)		110		114	19.4%	—	0.47 [0.26; 0.83]
Total (random effects, 95% CI)					—	44.0%	0.47 [0.26; 0.83]
Heterogeneity: not applicable							
Total (fixed effect, 95% CI)		**406**		**408**	**100.0%**	—	**0.92 [0.77; 1.10]**
Total (random effects, 95% CI)					—	**100.0%**	**0.73 [0.33; 1.59]**

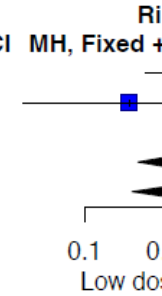
Heterogeneity: $Tau^2 = 0.2747$; $Chi^2 = 6.81$, df = 1 ($P < 0.01$); $I^2 = 85\%$
Residual heterogeneity: $Tau^2 = NA$; $Chi^2 = 0.00$, df = 0 ($P = NA$); $I^2 = NA\%$

5.12.2.4 *Post-discharge COVID-19 patients: Standard thromboprophylaxis versus standard of care*

Mortality, day 28

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV 4C, Wang–2023	8	610	9	607	69.3%	81.1%	0.88 [0.34; 2.28]
MICHELLE, Ramacciotti–2022	1	159	4	159	30.7%	18.9%	0.25 [0.03; 2.21]
Total (fixed effect, 95% CI)		**769**		**766**	**100.0%**	—	**0.69 [0.30; 1.60]**
Total (random effects, 95% CI)					—	**100.0%**	**0.70 [0.26; 1.85]**

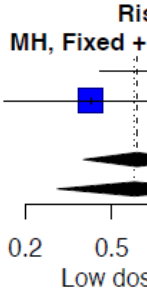
Heterogeneity: $Tau^2 = 0.0721$; $Chi^2 = 1.10$, df = 1 ($P = 0.29$); $I^2 = 9\%$



Any thrombotic event or death, day 28

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV 4C, Wang–2023	13	610	14	607	48.3%	55.4%	0.92 [0.44; 1.95]
MICHELLE, Ramacciotti–2022	6	159	15	159	51.7%	44.6%	0.40 [0.16; 1.00]
Total (fixed effect, 95% CI)		**769**		**766**	**100.0%**	—	**0.65 [0.37; 1.15]**
Total (random effects, 95% CI)					—	**100.0%**	**0.64 [0.28; 1.44]**

Heterogeneity: $Tau^2 = 0.1680$; $Chi^2 = 1.92$, df = 1 ($P = 0.17$); $I^2 = 48\%$



5.12.3 Referenzen der eingeschlossenen Studien

5.12.3.1 *Evidenzprofil 1*

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5.12.3.2 *Evidenzprofil 2*

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5.12.3.3 *Evidenzprofil 3*

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5.12.3.4 *Evidenzprofil 4:*

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5.12.3.5 *Evidenzprofil 5*

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5.12.3.6 *Evidenzprofil 6*

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5.12.4 Charakteristika der eingeschlossenen Studien

Study Reference	Study design	Enrollment / Pandemic phase[B]	Randomized patients (n)	Patient status	Intervention	Comparator	Outcomes (Time points as reported)
			Inpatient trials				
ACTION, Lopes-2021	RCT, open-label, national, multicenter (Brasil; 31)	Recruitment: 06/2020 - 02/2021 Before Omicron	614	Hospitalized + intensive care unit + ↑ D-dimer; Classified as WHO 4-9, with 85% WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Rivaroxaban 20 mg OD (280 patients, 90%) or enoxaparin 1mg/kg BID for 30 days	Low dose: Enoxaparin 40mg OD, weight and CrCl adjusted, continued until discharge	All-cause mortality (30d), Clinical improvement, any thrombotic event, any thrombotic event or death, major bleeding
ANTICOVID, Labbé-2023	RCT, open-label, national, multicenter (France; 23)	Recruitment: 04/2021 - 12/2021 Before Omicron	339	Hospitalized, WHO ≥5 with hypoxemic COVID-19; Classified as WHO 4-9 Vaccination status n (%): NA	Therapeutic dose: Tinzaparin 175IU/kg OD for 14 days/until discharge, Intermediate dose: Tinzaparin 7000IU OD for 14 days/until discharge	Intermediate dose: Tinzaparin 7000IU OD for 14 days/until discharge Low-dose: Tinzaparin 3500IU OD for 14 days/until discharge	All-cause mortality (28; 90d), any thrombotic event, any thrombotic event or death, major bleeding, QoL
BEMICOP, Marcos-Jubilar-2022	RCT, open-label national, multicenter (Spain; 5)	Recruitment: 10/2020 - 05/2021 Before Omicron	70	Hospitalized, WHO 3-4 +↑ D-Dimer + CURB65 ≤ 2; Classified as WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Bemiparin sc 115IU/kg OD for 10 days (weight adjusted: 50-70 kg: 7,500IU; 70–100 kg: 10,000IU; >100 kg: 12,500IU) 63.6% continued low-dose for a	Low dose: Bemiparin 3500IU OD for 10 days 63.6% continued low-dose for a median of 10 additional days	All-cause mortality (30d), any thrombotic event, major bleeding (10d), serious adverse events (10d)

					median of 10 additional days		
COVID-HEP, Blondon-2022	RCT, open-label, national, multicenter (Switzerland; 4)	Recruitment: 04/2020 - 06/2021 Before Omicron	160	Hospitalized, intermediate care unit (IMCU), or intensive care unit +↑ D-Dimer Classified as WHO 4-9, with max. WHO 7, stratified results according to WHO 4-5 and WHO 6-9 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1mg/kg BID until discharge/clinical improvement/for 30 days	Low or intermediate dose: Enoxaparin, weight adjusted: 40–49.9 kg: 20mg, 50–99.9 kg: 40mg, ≥100 kg: 60mg, Critically ill participants: intermediate dose enoxaparin weight adjusted: 40-99.9 kg: 40mg BID, ≥100 kg: 60mg BID for 30 days	Any thrombotc event or death (30d; WHO 4-5); Any thrombotic event or death (30d; WHO 6-9); 30 day Mortality; Major bleeding (30d; WHO 4-5); Major bleeding (30d; WHO 6-9)
COVID-PACT, Bohula-2022	RCT, open-label, national, multicenter (USA;34)	Recruitment: 08/2020 - 03/2022 Including Omicron	672 (382)	Intensive Care Unit Classified as WHO 6-9 with 79% and 88% WHO6 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1mg/kg BID for 28 days (median duration 9.9 days)	Low dose: Enoxaparin 40mg OD for 28 days (median duration 6.6 days) High crossover rate to therapeutic dose: 34%	All-cause mortality (30d), any thrombotic event, major bleeding
COVID-PREVENT, Rauch-Kröhnert-2023	RCT, open-label, national, multicenter (Germany; 14)	Recruitment: 11/2020 - 05/2021 Before Omicron	111	Ambulatory, Hospitalized +↑ D-Dimer/troponin T + known coronary artery disease/diabetes mellitus/active smoking Classified as WHO 4-5 with 2.7% WHO 6 and 1% WHO 3 Vaccination status n (%): NA	Therapeutic dose: Rivaroxaban 20mg OD for 7 days/until discharge followed by rivaroxaban 10mg OD for 4 weeks	Low dose: Prophylactic dose UFH/LMWH for 7 days/until discharge, no details stated	All-cause mortality (35d), major bleeding
FREEDOM COVID, Stone-2023	RCT, open-label, internation	Recruitment:	3398	Hospitalized	Therapeutic dose:	Low dose:	All-cause mortality (30d), any

	al, multicentr, in 77 centers in North America (29), South America (26), Asia (13), Europe (8)	08/2020 - 09/2022 Including Omicron		Classified as WHO 4-5 Vaccination status n (%): NA	Enoxaparin sc 1mg/kg BID or Apixaban 5mg BID Until discharge	Enoxaparin 40mg OD until discharge	thrombotic event or death, major bleeding
HEP-COVID, Spyropoulos-2021	RCT , open-label, national, multicenter (USA; 12)	Recruitment: 05/2020 - 05/2021 Before Omicron	257	Hospitalized + supplemental oxygen + ↑ D-Dimer or ISTH SIC Score ≥ 4, Classified as WHO 4-9, with 77% ≤WHO 5 Stratified results according to WHO 4-5 and WHO 6-9 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg BID, until discharge	Low/Intermediate dose: Enoxaparin 30-40mg OD/BID until discharge	All-cause mortality, any thrombotic event, any thrombotic event or death, major bleeding
HESACOVID, Lemos-2020	RCT, open-label, national, unicenter (Brasil)	Recruitment: 05/2020 - 05/2021 Before Omicron	20	Intensive Care Unit + ARDS requiring mechanical ventilation + ↑ D-Dimer Classified as WHO 6-9 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg BID for at least 96h and up to 14 days	Low dose: Enoxaparin 40 mg OD for at least 96h and up to 14 days	All-cause mortality (28d), any thrombotic event
INSPIRATION,Sadeghipour-2021	RCT, open-label, national, multicenter (Iran; 10)	Recruitment: 07/2020 - 11/2020 Before Omicron	600	Intensive Care Unit classified as WHO 6-9[A] Vaccination status n (%): NA	Intermediate dose: Enoxaparin 1mg/kg OD for 30 days	Low dose: Enoxaparin 40mg OD	All-cause mortality (30d; 90d), any thrombotic event, any thrombotic event or death, major bleeding

Mohamed-2022	RCT, open-label, national, unicenter (Egypt)	Recruitment: 08/2021 - 10/2021 Before Omicron	124	Intermediate Care Unit (IMCU), pneumonia without hypoxia (SpO2>92%) Classified as WHO 4-5 Vaccination status n (%): NA	Intermediate dose: Enoxaparin 0.5mg/kg BID, duration unclear	Low dose: Rivaroxaban 10mg OD, Duration unclear	All-cause mortality
Oliynyk-2021 (26)	RCT, double-blind, national, unicenter (Ukraine)	Recruitment: 07/2020 - 03/2021 Before Omicron	126	Intensive Care Unit + CAC + ↑ D-Dimer + respiratory failure Classified as WHO 6-9, with 100% WHO 6 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin: 100 Anti-Xa IU/kg BID or UFH: Initial: 80 U/kg/h i.v.; followed by 18 U/kg/h until normalization of D-dimer	Low dose: Enoxaparin 50 Anti-Xa IU/kg QD for 28 days	All-cause mortality (28d)
Perepu-2021	RCT, open-label, national, multicenter (USA; 3)	Recruitment: 04/2020 - 01/2021 Before Omicron	173	Hospitalized + Intensive Care Unit and/or mod. ISTH Overt DIC Score ≥3, Classified as WHO 5-9, no information on respiratory status reported Vaccination status n (%): NA	Intermediate dose: Enoxaparin 1mg/kg OD until discharge from hospital	Low dose: Enoxaparin 40mg OD, until discharge	All-cause mortality (30d), major bleeding
PROTHROMCOVID, Munos-Rivas-2022	RCT, open-label, national, multicenter (Spain; 18)	Recruitment: 02/2021 - 09/2021 Before Omicron	311	Hospitalized + either ↑ D-Dimer, ↑ CRP, ↑ IL6 or SpO_2<94%, Classified as WHO 4-5 Vaccination status n(%): 78 (26) 1-2 doses	Therapeutic dose: Tinzaparin 175IU/kg OD Intermediate dose: Tinzaparin 100 IU/kg OD Until discharge, followed by tinzaparin	Low dose: Tinzaparin 4500IU OD Intermediate dose Tinzaparin 100 IU/kg OD Until discharge	All-cause mortality (30; 90d), any thrombotic event,

					4500 IU OD for seven days		
RAPID, Sholzberg-2021	RCT, open-label, international, multicenter (28)	Recruitment: 05/2020 - 04/2021 Before Omicron	465	Hospitalized + ↑ D-Dimer, Classified as WHO 4-5, with 6% WHO 6 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg BID For 28 days/until discharge	Low dose: Enoxaparin 40 mg OD, For 28 days/until discharge	All-cause Mortality (28d), any thrombotic event, major bleeding, clinical worsening
REMAP-CAP, ATTAC, ACTIV-4a, Goligher-2021	RCT , open-label, international, multicenter (121)	Recruitment: 04/2020-12/2020 Before Omicron	1207	Intensive care unit Classified as WHO 6-9, with 1.5% WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg minus 10% BID (received by 77.6%)	Low/Intermediate dose: enoxaparin low dose 40.4%: 40mg OD intermediate dose 51.7%: 0.5mg/kg BID or 40mg BID	All-cause mortality, any thrombotic event, any thrombotic event or death, major bleeding
REMAP-CAP, ATTACC, ACTIV-4a, Lawler-2021	RCT , open-label, international, multicenter (121)	Recruitment: 04/2020 - 01/2021 Before Omicron	2244	Hospitalized classified as WHO 4-5, with 5% WHO 6-7 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg minus 10% BID (received by 79.6%)	Low/intermediate dose: enoxaparin low dose 71.7%: 40mg OD intermediate dose 26.5%: 0.5mg/kg BID or 40mg BID	All-cause mortality, any thrombotic event, any thrombotic event or death, major bleeding, clinical worsening, clinical improvement
X-COVID-19, Morici-2021	RCT, open-label, national, multicenter (Italy; 9)	Recruitment: 04/2020 - 04/2021 Before Omicron	186	Hospitalized + Intensive Care Unit Classified as WHO 4-9 with 61% WHO 4-5 and no patients >WHO 7 stratified results according to WHO 4-5 and WHO 6-9 Vaccination status n (%): NA	Intermediate dose: Enoxaparin 40mg BID until discharge	Low dose: Enoxaparin 40mg OD until discharge	All-cause mortality (30d), major bleeding

Post-discharge trials							
ACTIV 4C, Wang-2023	RCT, double-blinded, national, multicenter (USA; 127)	Recruitment: 02/2021 - 06/2022 Including Omicron	1217	Post-discharge Vaccination status n (%): NA	Low dose: Apixaban 2.5mg BID for 30 days	Placebo	All-cause mortality (30d), any thrombotic event or death, major bleeding, non-major clinical relevant bleeding, serious adverse events, QoL
MICHELLE, Ramacciotti-2022 (33)	RCT, open-label, national multicenter (Brasi; 14)	Recruitment: 10/2020 - 06/2021 Before Omicron	318	Post discharge + IMPROVE-Score ≥ 4 or 2-3 + ↑ D-Dimer Vaccination status n (%): NA	Low dose: Rivaroxaban 10mg OD for 35 days	No anticoagulation	All-cause mortality (35d), any thrombotic event, any thrombotic event or death, major bleeding, non-major clinical relevant bleeding, other bleedings
				Outpatient trials			
ACTIV 4B, Connors-2021	RCT, double-blind, national, multicenter (USA; 52)	Recruitment: 09/2020 - 06/2021 Before Omicron	657	Symptomatic outpatients Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Apixaban 2.5mg BID for 45 days	Placebo	All-cause Mortality (45d), hospitalization due to cardiovascular events or death within 45 days, thrombotic events within 45 days, severe bleeding within 45 days
Ananworanich-2021	RCT, double-blind, national, multicenter (USA 14)	Recruitment: 08/2020 - 02/2021 Before Omicron	497	Symptomatic outpatients + at least 1 risk factor for severe COVID-19 Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Rivaroxaban 10mg OD for 21 days	Placebo	All-cause mortality (35d), major bleeding, clinical worsening, clinical improvement, serious adverse events

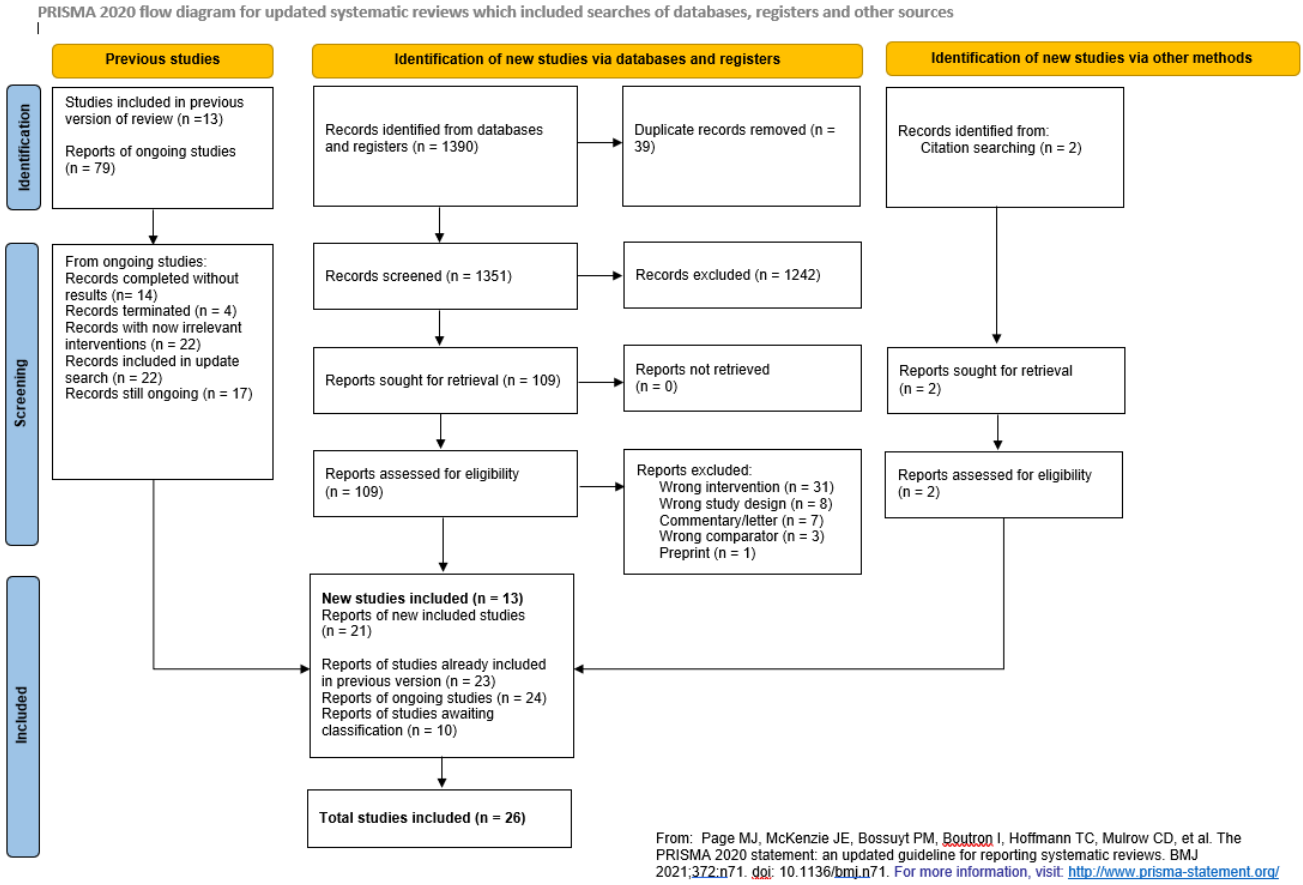
CARE-COALITION VIII, Avezum-2023	RCT, open-label, national, multicenter (Brasil; 33)	Recruitment: 09/2020 - 05/2022 Including Omicron	660	Symptomatic outpatients + at least 2 risk factors for severe COVID-19, Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Rivaroxaban 10mg OD for 14 days	No anticoagulation	All-cause mortality (30d), any thrombotic event, major bleeding
ETHIC, Cools-2022	RCT, open-label, international, multicenter (6; 15)	Recruitment: 10/2020 - 11/2021 Before Omicron	219	Symptomatic outpatients + at least 1 risk factor for severe COVID-19 Classified as WHO 2-3 Vaccination status n (%): 0 vaccinated (exclusion criteria)	Low dose: Enoxaparin 40mg OD (BID if >100kg) for 21 days	No anticoagulation	All-cause mortality (21; 50; 90d), major bleeding, clinical worsening, serious adverse events
OVID, Barco-2022	RCT, open-label, international; multicenter (2; 9)	Recruitment: 08/2020 - 01/2022 Including Omicron	475	Symptomatic outpatients, Age >50, Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Enoxaparin 40mg OD for 14 days	No anticoagulation	All-cause mortality (90d), any thrombotic event, major bleeding, clinical worsening Any thrombotic Events (90d) Voci-2023
PREVENT-HD, Piazza-2023	RCT, double-blinded, national, , multicenter (USA; 14)	Recruitment: 08/2020 - 04/2022 Including Omicron	1284	Symptomatic outpatients + at least one risk factor for thrombosis/severe COVID-19 Classified as WHO 2-3 Vaccination status n (%): 27 (2.1) vaccinated	Low dose: Rivaroxaban 10mg OD for 35 days	Placebo	All-cause mortality (35d), 35 day hospitalization, thrombotic events or pulmonary embolism, major bleeding events,

RCT, randomized controlled trial; ↑ D-Dimer, D-Dimer elevation; OD, once daily; BID, twice daily; UFH, unfractionated heparin; CrCl, creatinine clearance, CAC, COVID-19-19 associated coagulopathy,;

[A] Formerly classified as WHO 5-9 with stratified data, now re-classified as WHO 6-9 due to high mortality rate

[B]COVID-19 Pandemic Phases according to the German Robert Koch Institute for public health: Epidemiologisches Bulletin RKI Stand 22.09.2022 (dritte Aktualisierung)

5.12.5 Studienselektion: Flow Chart



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

5.12.6 Literaturrecherche

5.12.6.1 *Literaturrecherche für CEOsys:*

Search string:

anticoagula* OR antithromb* OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor" OR "Xa inhibitors" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin

OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR Sulodexid* OR aterina OR "glucuronyl glucosamine glycan sulfate" OR Dociparastat

Study characteristics: "Intervention assignment": Randomised/quasi-randomised/unclear

Date of search: 14.01.2021

Total: 142 Studien; 181 Referenzen

Date of search Update: 09.06.2021

Total Update: 332 references (197 Studien); new: 151 references

5.12.6.2 *Literaturrecherche für Systematic Review:*

Date of search for all databases: 24.09.2021; update 25.07.2023		
Database/Register	Search	Update Search
CCSR	431 references (245 studies)	786 references (387 stuudies)
WOS (SCI+ECI)	471	1080
WHO COVID-19 DB	250	291*
ResearchSquare	1	-
Total	1153	2157
Total (after deduplication)	1074 (nur Update: 742)	*2184 (nur update 25.07.23:: 1110)*

**Die WHO COVID-19-Forschungsdatenbank ist eine Ressource, die als Reaktion auf die Public Health Emergency of International Concern (PHEIC) geschaffen wurde. Ihr Inhalt ist weiterhin durchsuchbar und deckt den Zeitraum von März 2020 bis Juni 2023 ab. Ab dem 23. Juni 2023 wurden die manuellen Aktualisierungen pausiert, da wir die Notwendigkeit der Fortführung der Datenbank überprüfen.*

Abstract

Search methods:

We searched the Cochrane COVID-19 Study Register (comprising MEDLINE, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, medRxiv, and the Cochrane Central Register of Controlled Trials), Web of Science (Emerging Citation Index and Science Citation Index), WHO COVID-19 Global literature on coronavirus disease, and ResearchSquare to identify completed and ongoing studies to 24 September 2021.

Electronic searches

Our Information Specialist (MIM) conducted systematic searches of the following sources from the inception of each database to 24 September 2021 (date of last search for all databases) and did not place restrictions on the language of publication:

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
  - MEDLINE (PubMed), daily upadates;
  - Embase, weekly updates;
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  - World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates;
  - medRxiv (www.medrxiv.org), weekly updates;
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates.
- Web of Science Core Collection:
  - Science Citation Index Expanded (1945-present);
  - Emerging Sources Citation Index (2015-present).
- WHO COVID-19 Global literature on coronavirus disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).
- ResearchSquare (https://www.researchsquare.com/browse)

For detailed search strategies, see Appendix 1.

Searching other sources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews and meta-analyses. In addition, we contacted the investigators of included studies to obtain additional information on the retrieved studies.

We compared our identified studies with results from projects that aim to track COVID-19 intervention research, i.e. www.covid-trials.org, covid-nma.com/dataviz.

Cochrane COVID-19 Study Register

Search string:

anticoagula* OR antithromb* OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor" OR "Xa inhibitors" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat

Study characteristics:

1) "Intervention assignment": “Randomised” OR “quasi-randomised” or “unclear” OR

2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover"

3) "Study type": "Interventional" AND "Study design": "Unclear"

4) "Study type": "Adaptive/Platform"

= 245 studies (431 references)

Web of Science Core Collection (Advanced search)

#1

TI=(anticoagula* OR antithromb* OR "Thrombin Inhibitor*" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor*" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat)

OR AB=(anticoagula* OR antithromb* OR "Thrombin Inhibitor*" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor*" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat)

#2

TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3

TI=(random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

#4

#1 AND #2 AND #3

Indexes=SCI-EXPANDED, ESCI

= 471

WHO COVID-19 Global literature on coronavirus disease (heißt jetzt anders!)

Search string:

(anticoagula* OR antithromb* OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor" OR "Xa inhibitors" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

 excluding databases: MEDLINE, ICTRP, EMBASE, Scopus, PubMed, PMC, Web of Science

= 250 references

ResearchSquare (nicht mehr nötig da in WHO DB enthalten)

Article type: Research Article

Abstract:

- anticoagulant = 35
- antithrombotic = 2
- thrombin = 2

= selected on page: 1

5.13 Schlüsselfrage 8: Prone positioning vs. standard of care

Autor*innen: Nina Kreuzberger

Es wurden insgesamt 15 RCTs eingeschlossen, davon 6 RCTs mit einer Dauer der Wachbauchlagerung von mehr als 5 Stunden.

5.13.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Individuals with COVID-19 and ARDS

Intervention: Prone positioning (> 5 hours)

Vergleichsintervention: Any position

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Any position	 Prone positioning (> 5 hours)	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Intubation or death (day 30)	Relatives Risiko: 0.78 (CI 95% 0.67 - 0.92) Basierend auf Daten von 830 patienter und 2 Studien	**491** pro 1000	**383** pro 1000 Differenz: **108 weniger pro 1000** (CI 95% 162 weniger - 39 weniger)	**Moderat** Due to serious indirectness[1]	Prone positioning (> 5 hours) probably decreases the number of participants with intubation or death by day 30.
Death (day 30)	Relatives Risiko: 0.9 (CI 95% 0.47 - 1.71) Basierend auf Daten von 655 patienter und 4 Studien	**287** pro 1000	**258** pro 1000 Differenz: **29 weniger pro 1000** (CI 95% 152 weniger - 204 mehr)	**Niedrig** Due to serious inconsistency, Due to serious imprecision[2]	Prone positioning (> 5 hours) may have little or no effect on the number of deaths byday 30.
Death (day 60)	Relatives Risiko: 0.95 (CI 95% 0.66 - 1.36) Basierend auf Daten von 400 patienter und 1 Studien Beobachtzungszeit 60 days	**236** pro 1000	**224** pro 1000 Differenz: **12 weniger pro 1000** (CI 95% 80 weniger - 85 mehr)	**Niedrig** Due to very serious imprecision[3]	Prone positioning (> 5 hours) may have little or no difference on death by day 60.
Death (day 90)	Relatives Risiko: 1.17 (CI 95% 0.76 - 1.79)	**500** pro 1000	**585** pro 1000	**Sehr niedrig**	We are uncertain whether prone positioning (> 5 hours) increases or

	Basierend auf Daten von 40 patienter und 1 Studien	Differenz: **85 mehr pro 1000** (CI 95% 120 weniger - 395 mehr)	Due to serious risk of bias, Due to very serious imprecision[4]	decreases the number of people with death by day 90.
Intubation (day 30)	Relatives Risiko: 0.77 (CI 95% 0.65 - 0.91) Basierend auf Daten von 1055 patienter und 5 Studien Beobachtzungszeit 30 days	**380** pro 1000 **293** pro 1000 Differenz: **87 weniger pro 1000** (CI 95% 133 weniger - 34 weniger)	**Moderat** Due to serious risk of bias[5]	Prone positioning (> 5 hours) probably decreases the number of persons requiring intubation by day 30.
Length of hospital stay	Gemessen mit: Skala: - Höher ist schlechter Basierend auf Daten von 60 patienter und 1 Studien	**9.97** Days (Mittelwert) **11.53** Days (Mittelwert) Differenz: **MD 1.56 weniger** (CI 95% 1.65 weniger - 4.77 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to serious risk of bias[6]	We are uncertain whether prone positioning (> 5 hours) increases or decreases length of hospital stay.

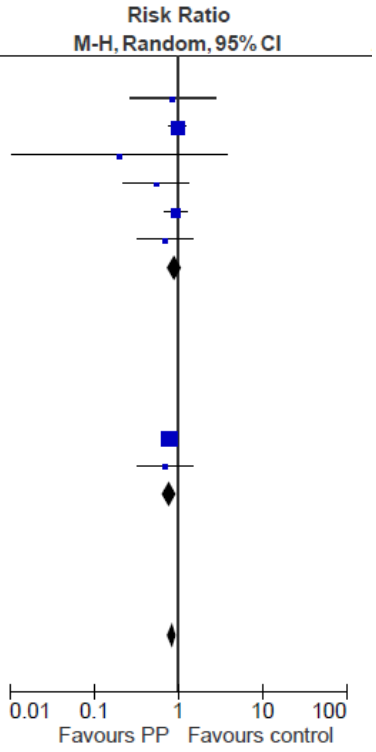
1. Risiko für Bias: keine. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirektheit: schwerwiegend. Differences between the intervention/comparator of interest and those studied: The prone positioning was shorter than wished for in COVI-prone (median 5h), no subgroups were provided.;
2. Inkonsistenz: schwerwiegend. Point estimates vary widely; Indirektheit: keine. Differences between the intervention/comparator of interest and those studied: PP duration varied between studies; e.g., in Jayakumar median around 5h, while PROFLO and PRO-CARF achieved a median around 9h.; Unzureichende Präzision: schwerwiegend. Wide confidence intervals;
3. Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients;
4. Risiko für Bias: schwerwiegend. concealment of allocation during randomization process not described, resulting in potential for selection bias. Adherence/drop-out/follow-up of participants not reported.; Unzureichende Präzision: sehr schwerwiegend. Wide confidence intervals, Low number of patients;
5. Risiko für Bias: schwerwiegend. Intubation can have death as competing event. In addition, only one included study had clear intubation criteria (PRO-CARF).;
6. Risiko für Bias: schwerwiegend. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Unzureichende Präzision: sehr schwerwiegend. Low number of patients;

5.13.2 Analysen / Forest Plots

5.13.2.1 *All studies, subgrouped by duration of prone position, cutoff 5h*

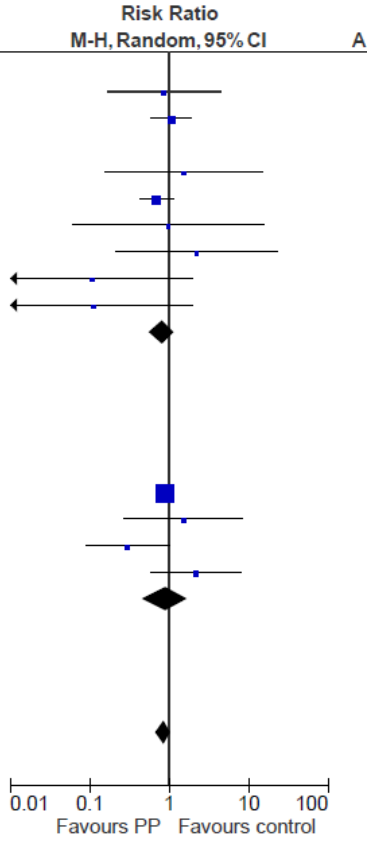
2.1 Intubation or death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 < 5h prone positioning						
1 COVAYDE	3	7	3	6	1.3%	0.86 [0.27, 2.77]
2 HIGH-PRONE-COVID-19	82	200	85	202	32.0%	0.97 [0.77, 1.23]
3 APPROVE-CARE	0	12	2	12	0.2%	0.20 [0.01, 3.77]
5 PR(AG)198/2020	5	17	7	13	2.2%	0.55 [0.22, 1.33]
6 NCT04325906	45	112	48	110	17.9%	0.92 [0.68, 1.26]
PROVID-19	10	135	14	132	2.9%	0.70 [0.32, 1.52]
Subtotal (95% CI)		**483**		**475**	**56.4%**	**0.91 [0.77, 1.09]**
Total events	145		159			
Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 5 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
2.1.2 > 5h prone positioning						
4 PRO-CARF	88	216	112	214	40.8%	0.78 [0.63, 0.96]
COVI-PRONE	10	135	14	132	2.9%	0.70 [0.32, 1.52]
Subtotal (95% CI)		**351**		**346**	**43.6%**	**0.77 [0.63, 0.94]**
Total events	98		126			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 2.54 (P = 0.01)						
Total (95% CI)		**834**		**821**	**100.0%**	**0.85 [0.74, 0.97]**
Total events	243		285			
Heterogeneity: Tau² = 0.00; Chi² = 4.68, df = 7 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
Test for subgroup differences: Chi² = 1.51, df = 1 (P = 0.22), I² = 33.9%						



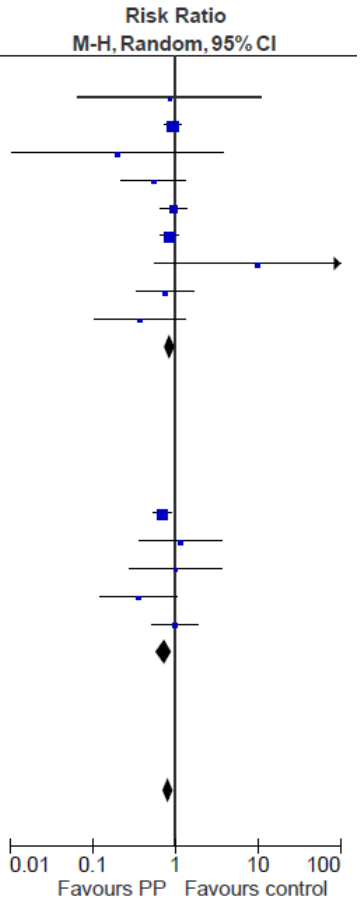
2.2 Death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 < 5h prone positioning						
1 COVAYDE	2	7	2	6	1.9%	0.86 [0.17, 4.37]
2 HIGH-PRONE-COVID-19	21	200	20	202	13.8%	1.06 [0.59, 1.89]
3 APPROVE-CARE	0	12	0	12		Not estimable
5 PR(AG)198/2020	2	17	1	13	0.9%	1.53 [0.15, 15.09]
6 NCT04325906	21	112	30	110	18.7%	0.69 [0.42, 1.12]
COVID-PRONE	1	126	1	122	0.7%	0.97 [0.06, 15.31]
EPCoT	2	29	1	32	0.9%	2.21 [0.21, 23.08]
PROVID-19	0	135	4	132	0.6%	0.11 [0.01, 2.00]
Yarahmadi 2022	0	41	4	41	0.6%	0.11 [0.01, 2.00]
Subtotal (95% CI)		**679**		**670**	**38.0%**	**0.81 [0.57, 1.15]**
Total events	49		63			
Heterogeneity: Tau² = 0.00; Chi² = 6.00, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
2.2.2 > 5h prone positioning						
4 PRO-CARF	71	216	79	214	54.2%	0.89 [0.69, 1.15]
Jayakumar 2021	3	30	2	30	1.7%	1.50 [0.27, 8.34]
Nasrallah 2023	3	45	10	45	3.3%	0.30 [0.09, 1.02]
PROFLO	6	36	3	39	2.9%	2.17 [0.58, 8.03]
Subtotal (95% CI)		**327**		**328**	**62.0%**	**0.90 [0.47, 1.71]**
Total events	83		94			
Heterogeneity: Tau² = 0.19; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**1006**		**998**	**100.0%**	**0.86 [0.69, 1.07]**
Total events	132		157			
Heterogeneity: Tau² = 0.01; Chi² = 11.36, df = 11 (P = 0.41); I² = 3%						
Test for overall effect: Z = 1.35 (P = 0.18)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



2.3 Intubation by day 30

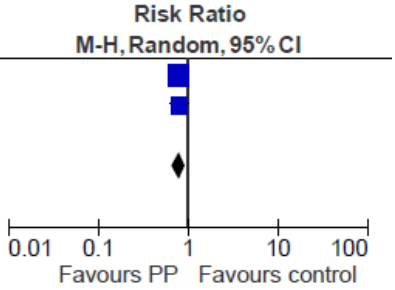
Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 < 5h prone positioning						
1 COVAYDE	1	7	1	6	0.2%	0.86 [0.07, 10.96]
2 HIGH-PRONE-COVID-19	76	200	82	202	26.5%	0.94 [0.73, 1.19]
3 APPROVE-CARE	0	12	2	12	0.2%	0.20 [0.01, 3.77]
5 PR(AG)198/2020	5	17	7	13	2.0%	0.55 [0.22, 1.33]
6 NCT04325906	38	112	39	110	12.0%	0.96 [0.67, 1.37]
COVI-PRONE	70	205	79	195	24.1%	0.84 [0.65, 1.09]
EPCoT	4	29	0	32	0.2%	9.90 [0.56, 176.29]
PROVID-19	10	135	13	132	2.5%	0.75 [0.34, 1.66]
Yarahmadi 2022	3	41	8	41	1.0%	0.38 [0.11, 1.31]
Subtotal (95% CI)		**758**		**743**	**68.7%**	**0.87 [0.75, 1.02]**
Total events	207		231			
Heterogeneity: Tau² = 0.00; Chi² = 7.28, df = 8 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)						
2.3.2 > 5h prone positioning						
4 PRO-CARF	65	216	92	214	24.1%	0.70 [0.54, 0.90]
COVID-PRONE	6	126	5	122	1.2%	1.16 [0.36, 3.71]
Jayakumar 2021	4	30	4	30	0.9%	1.00 [0.28, 3.63]
Nasrallah 2023	4	45	11	45	1.4%	0.36 [0.13, 1.06]
PROFLO	12	36	13	39	3.8%	1.00 [0.53, 1.90]
Subtotal (95% CI)		**453**		**450**	**31.3%**	**0.73 [0.59, 0.91]**
Total events	91		125			
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 4 (P = 0.48); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
Total (95% CI)		**1211**		**1193**	**100.0%**	**0.83 [0.73, 0.94]**
Total events	298		356			
Heterogeneity: Tau² = 0.00; Chi² = 12.48, df = 13 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Test for subgroup differences: Chi² = 1.69, df = 1 (P = 0.19), I² = 40.8%						



5.13.2.2 *Studies with duration of prone positioning more than 5h*

3.1 Intubation or death by day 30

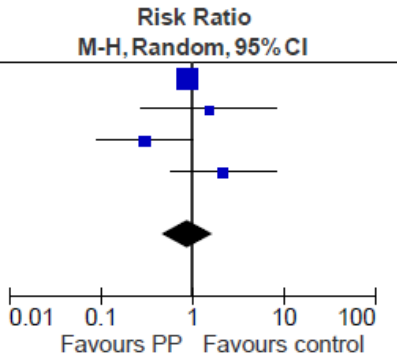
Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4 PRO-CARF	88	216	112	214	57.3%	0.78 [0.63, 0.96]
COVI-PRONE	74	205	89	195	42.7%	0.79 [0.62, 1.00]
Total (95% CI)		**421**		**409**	**100.0%**	**0.78 [0.67, 0.92]**
Total events	162		201			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 3.07 (P = 0.002)						



3.2 Death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4 PRO-CARF	71	216	79	214	52.6%	0.89 [0.69, 1.15]
Jayakumar 2021	3	30	2	30	11.4%	1.50 [0.27, 8.34]
Nasrallah 2023	3	45	10	45	18.9%	0.30 [0.09, 1.02]
PROFLO	6	36	3	39	17.1%	2.17 [0.58, 8.03]
Total (95% CI)		**327**		**328**	**100.0%**	**0.90 [0.47, 1.71]**
Total events	83		94			

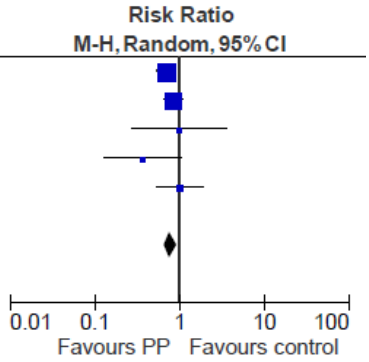
Heterogeneity: Tau² = 0.19; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 0.33 (P = 0.74)



3.3 Intubation by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4 PRO-CARF	65	216	92	214	44.3%	0.70 [0.54, 0.90]
COVI-PRONE	70	205	79	195	44.4%	0.84 [0.65, 1.09]
Jayakumar 2021	4	30	4	30	1.7%	1.00 [0.28, 3.63]
Nasrallah 2023	4	45	11	45	2.5%	0.36 [0.13, 1.06]
PROFLO	12	36	13	39	7.0%	1.00 [0.53, 1.90]
Total (95% CI)		**532**		**523**	**100.0%**	**0.77 [0.65, 0.91]**
Total events	155		199			

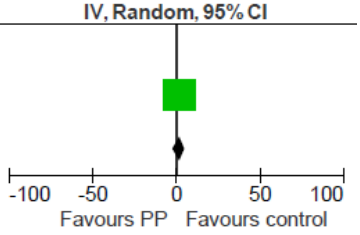
Heterogeneity: Tau² = 0.00; Chi² = 3.73, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)



3.4 Length of hospital stay

Study or Subgroup	Pronepositioning Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jayakumar 2021	0	0	0	0	0	0		Not estimable
Nasrallah 2023	0	0	0	0	0	0		Not estimable
PROFLO	11.53	6.92	30	9.97	5.69	30	100.0%	1.56 [-1.65, 4.77]
Total (95% CI)			**30**			**30**	**100.0%**	**1.56 [-1.65, 4.77]**

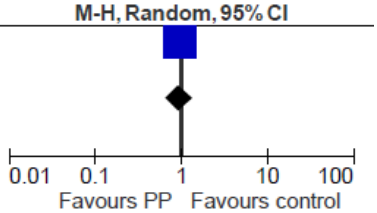
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



Study entry with 0 means study has reported results, but not as mean (i.e., as median and IQR).

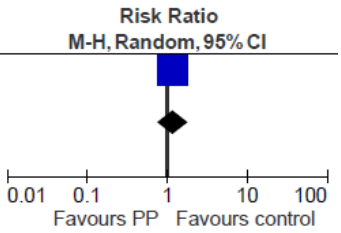
Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
COVI-PRONE	46	205	46	195	100.0%	0.95 [0.66, 1.36]
Total (95% CI)		**205**		**195**	**100.0%**	**0.95 [0.66, 1.36]**
Total events	46		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.78)



3.6 Death by day 90

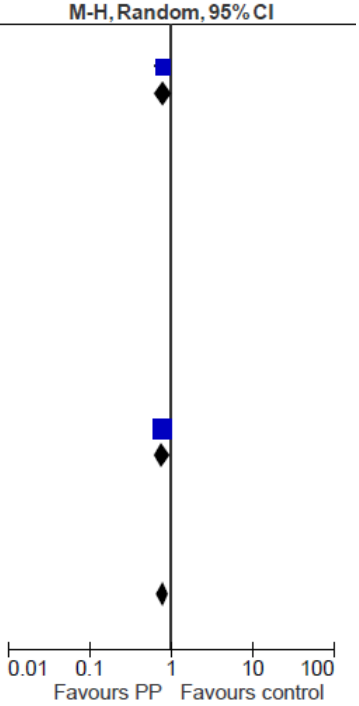
Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Javed 2023	21	36	18	36	100.0%	1.17 [0.76, 1.79]
Total (95% CI)		**36**		**36**	**100.0%**	**1.17 [0.76, 1.79]**
Total events	21		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						



5.13.2.3 *Studies with duration of prone positioning more than 5h, subgroup respiratory support*

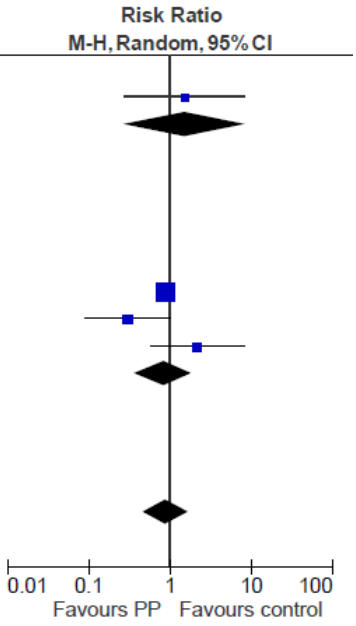
4.1 Intubation or death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 mixed respiratory support						
COVI-PRONE	74	205	89	195	42.7%	0.79 [0.62, 1.00]
Subtotal (95% CI)		**205**		**195**	**42.7%**	**0.79 [0.62, 1.00]**
Total events	74		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
4.1.2 Low flow						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.1.3 High flow						
4 PRO-CARF	88	216	112	214	57.3%	0.78 [0.63, 0.96]
Subtotal (95% CI)		**216**		**214**	**57.3%**	**0.78 [0.63, 0.96]**
Total events	88		112			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.39 (P = 0.02)						
Total (95% CI)		**421**		**409**	**100.0%**	**0.78 [0.67, 0.92]**
Total events	162		201			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



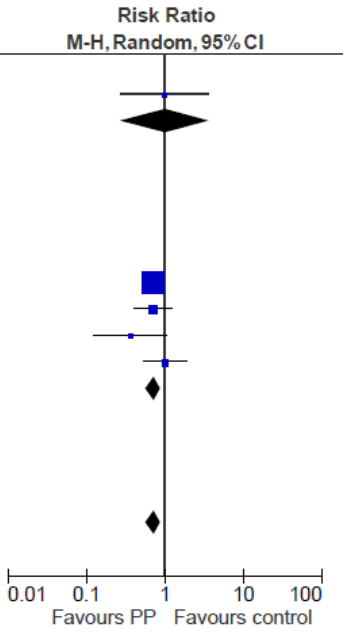
4.2 Death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Low flow						
Jayakumar 2021	3	30	2	30	11.4%	1.50 [0.27, 8.34]
Subtotal (95% CI)		**30**		**30**	**11.4%**	**1.50 [0.27, 8.34]**
Total events	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
4.2.2 High flow						
4 PRO-CARF	71	216	79	214	52.6%	0.89 [0.69, 1.15]
Nasrallah 2023	3	45	10	45	18.9%	0.30 [0.09, 1.02]
PROFLO	6	36	3	39	17.1%	2.17 [0.58, 8.03]
Subtotal (95% CI)		**297**		**298**	**88.6%**	**0.83 [0.37, 1.88]**
Total events	80		92			
Heterogeneity: Tau² = 0.31; Chi² = 4.82, df = 2 (P = 0.09); I² = 58%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**327**		**328**	**100.0%**	**0.90 [0.47, 1.71]**
Total events	83		94			
Heterogeneity: Tau² = 0.19; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						



4.3 Intubation by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Low flow						
Jayakumar 2021	4	30	4	30	2.7%	1.00 [0.28, 3.63]
Subtotal (95% CI)		**30**		**30**	**2.7%**	**1.00 [0.28, 3.63]**
Total events	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.3.2 High flow						
4 PRO-CARF	65	216	92	214	68.0%	0.70 [0.54, 0.90]
COVI-PRONE	14	45	19	43	14.7%	0.70 [0.41, 1.22]
Nasrallah 2023	4	45	11	45	3.9%	0.36 [0.13, 1.06]
PROFLO	12	36	13	39	10.8%	1.00 [0.53, 1.90]
Subtotal (95% CI)		**342**		**341**	**97.3%**	**0.71 [0.57, 0.88]**
Total events	95		135			
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.15 (P = 0.002)						
Total (95% CI)		**372**		**371**	**100.0%**	**0.72 [0.58, 0.88]**
Total events	99		139			
Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 4 (P = 0.58); I² = 0%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						



5.13.2.4 *Studies with duration of prone positioning more than 5h, subgroup PaO2/FiO2, cutoff 200 mmHg*

5.1 Intubation or death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 < 200 mmHg						
4 PRO-CARF	88	216	112	214	57.3%	0.78 [0.63, 0.96]
COVI-PRONE	74	205	89	195	42.7%	0.79 [0.62, 1.00]
Subtotal (95% CI)		**421**		**409**	**100.0%**	**0.78 [0.67, 0.92]**
Total events	162		201			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.07 (P = 0.002)

5.2 Death by day 30

Study or Subgroup	Pronepositioning Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 > 200 mmHg						
Nasrallah 2023	3	45	10	45	18.9%	0.30 [0.09, 1.02]
Subtotal (95% CI)		**45**		**45**	**18.9%**	**0.30 [0.09, 1.02]**
Total events	3		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)

5.2.2 < 200 mmHg						
4 PRO-CARF	71	216	79	214	52.6%	0.89 [0.69, 1.15]
PROFLO	6	36	3	39	17.1%	2.17 [0.58, 8.03]
Subtotal (95% CI)		**252**		**253**	**69.7%**	**1.09 [0.52, 2.29]**
Total events	77		82			

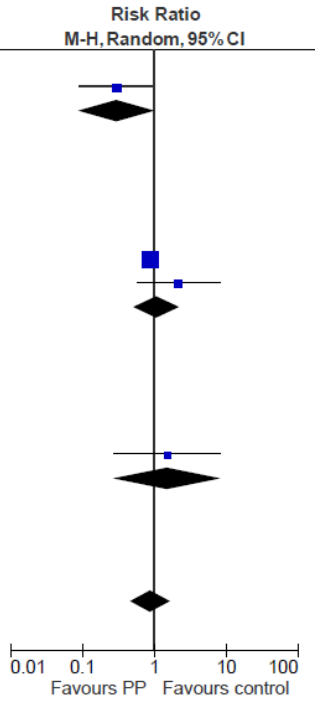
Heterogeneity: Tau² = 0.17; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 0.24 (P = 0.81)

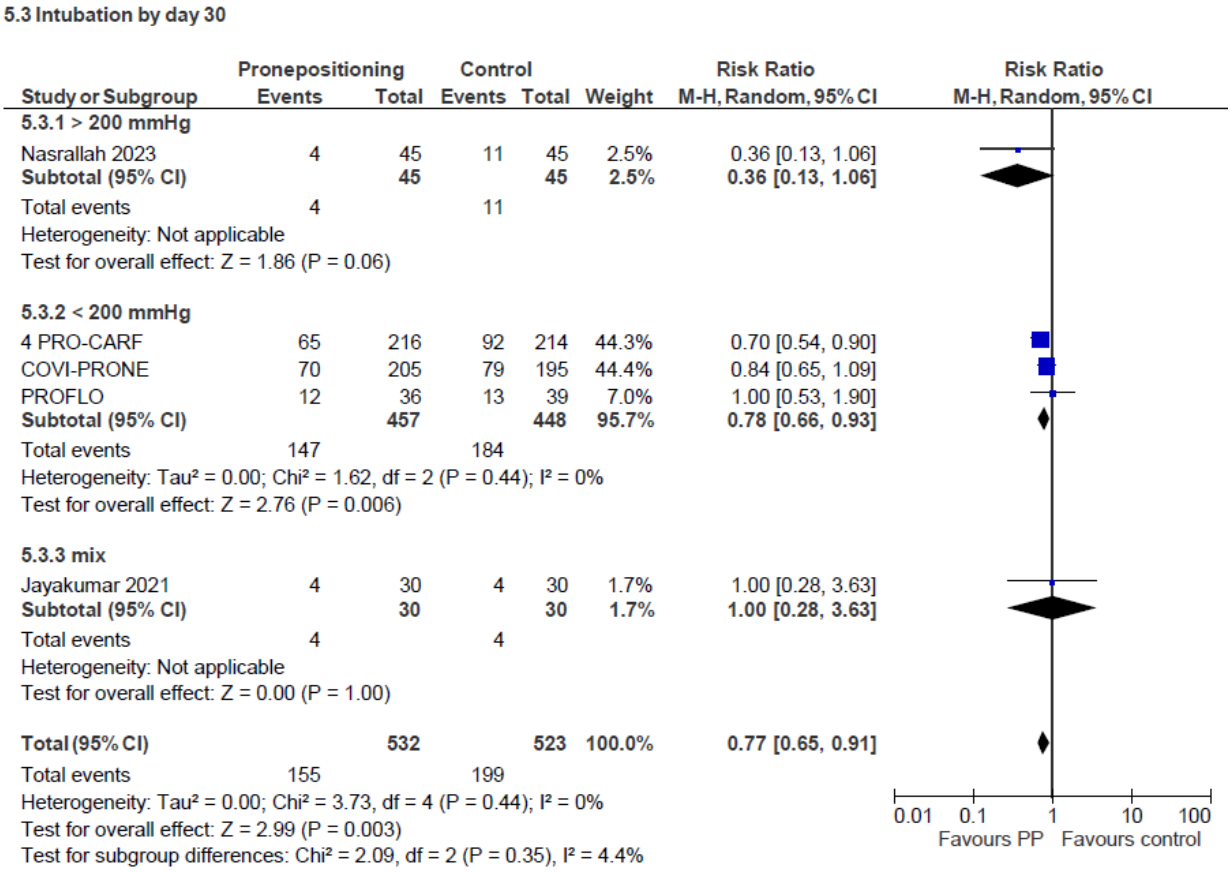
5.2.3 mix						
Jayakumar 2021	3	30	2	30	11.4%	1.50 [0.27, 8.34]
Subtotal (95% CI)		**30**		**30**	**11.4%**	**1.50 [0.27, 8.34]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)

Total (95% CI)		**327**		**328**	**100.0%**	**0.90 [0.47, 1.71]**
Total events	83		94			

Heterogeneity: Tau² = 0.19; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Chi² = 3.66, df = 2 (P = 0.16), I² = 45.3%





5.13.3 Referenzen der eingeschlossenen Studien

5.13.3.1 *>5h prone positioning*

- Ehrmann S. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet respiratory medicine. 2021;9(12):1387-95. doi: 10.1016/S2213-2600(21)00356-8. PubMed PMID: 18589421.
- Nasrallah BZN, Mahmoud MS, ElGendy HMA, Youssri Mahmoud NM, ElGendy MAEA. Patients self-proning with high-flow nasal cannula improves oxygenation in mild ARDS patients: a randomized clinical trial. Anaesthesia, Pain and Intensive Care. 2023;27(3):351-5. doi: 10.35975/apic.v27i3.2079.
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- Alhazzani W, the Saudi Critical Care Trials G. Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: a Randomized Clinical Trial. JAMA. 2022;327(21):2104-13. doi: 10.1001/jama.2022.7993. PubMed PMID: 20818322.
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5.13.3.2 *<5h prone positioning*

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- Fezzi M. Early prone positioning does not improve the outcome of patients with mild pneumonia due to SARS-CoV-2: results from an open-label randomised controlled trial - the EPCoT study. ERJ open research. 2023;9(4). doi: 10.1183/23120541.00181-2023. PubMed PMID: 23578942.
- Fralick M. Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ (Clinical research ed). 2022;376:e068585. doi: 10.1136/bmj-2021-068585. PubMed PMID: 20511973.
- Ehrmann S. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet respiratory medicine. 2021;9(12):1387-95. doi: 10.1016/S2213-2600(21)00356-8. PubMed PMID: 18589421.

5.13.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Fralick 2022 COVID-PRONE NCT04383613 *open-label RCT*	**Sample size:** N = 129 (prone positioning), 128 (control group) **Enrolment period:** May 2020 and 31 May 2021 **Countries** ▪ Canada, United States **Inclusion criteria:** ▪ laboratory confirmed or clinically highly suspected diagnosis of covid-19, ▪ needed supplemental oxygen (up to 50% fraction of inspired oxygen), ▪ were able to independently adopt a prone position with verbal instruction. **Time since symptom onset (median, range):** ▪ within 48 hours of admission to hospital, or diagnosed for nosocomial infection in the last 48 hours during their hospital stay **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 59.5 (45-68) ▪ Ctrl: 54 (44-62) ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: 44% ▪ Ctrl: 34%	**Experimental:** "were recommended to adopt a prone position four times a day (up to two hours for each session) and encouraged to sleep in prone position overnight. These practices were recommended for up to seven days in hospital, until hospital discharge, or until the patient no longer needed supplemental oxygen (whichever came first)." ▪ Prone positioing ▪ 8h/24h "The median total time spent in prone position up to the first 72 hours was 6 (1.5-12.8) hours; approximately 2.5 hours per day" ▪ N = 129 **Control:** **median 0 (0 to 2) hours** ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 128 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: median 5 (IQR 3-9) Control: median 4 (IQR 3-8)
			death (any cause)	PP: 1/126 Ctrl: 1/122
			intubation	PP: 6/126 Ctrl: 5/122

	Cardiovascular disease ▪ Exp: 3% ▪ Ctrl: 2% **Lung diseases** ▪ Exp: 10% ▪ Ctrl: 12% ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ Exp: 93% ▪ Ctrl: 98% **High Flow Oxygen** ▪ Exp: 4% ▪ Ctrl: 2% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Jayakumar 2021 CTRI/2020/12/029702 *open-label RCT*	**Sample size: 60** **Enrolment period:** Not reported **Countries** ▪ India **Inclusion criteria:** ▪ Patients ≥18 years of age ▪ requiring 4 or more LPM of supplemental oxygen to maintain SpO2 ≥ 92% or if ABG was available, PaO2/FiO2 ratio between 100 and 300 mmHg (mild to moderate ARDS) with PaCO2 less than 45 mmHg ▪ Patients with AHRF and hemodynamic shock requiring <0.1mcg/kg/min of norepinephrine **Time since symptom onset (median, range):** ▪ unclear **<u>Characteristics</u>** **Age (mean, sd)** ▪ Exp: 54.8 ± 11.1 ▪ Ctrl: 57.3 ± 12.1 ***<u>Comorbidities</u>*** **Obesity (BMI, mean, sd)** ▪ Exp: 28.2 ± 5.7 ▪ Ctrl: 25.8 ± 2.6 **Hypertension** ▪ Exp: 43% ▪ Ctrl: 30% **Cardiovascular disease** ▪ Exp: NR	**Experimental:** "patients were encouraged by bedside nurses to lie prone for a minimum of 6 hours in a day (cumulative). Additional pillows were provided for comfort to facilitate prone position." ▪ Prone positioing ▪ 6h/24h ▪ ▪ "43% 6 or more hours a day ▪ 70% 4 hours a day" ▪ N = 30 **Control:** **median 0 (0 to 2) hours** ▪ standard of care (oSOC) alone ▪ "Patients randomized to standard care were allowed to change their position as per their comfort (supine, semi sitting, sitting or lateral). If patients in the standard arm wished to lie prone for comfort, this was allowed." ▪ N = 30	length of hospital stay (ICU)	PP: mean 11.53 (sd 6.92) Control: mean 9.97 (sd 5.69)
			death (any cause)	PP: 3/30 Ctrl: 2/30
			intubation	PP: 4/30 Ctrl: 4/30

	▪ Ctrl: NR **Lung diseases** ▪ Exp: 6.7% ▪ Ctrl: 10% ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ Exp: 90% ▪ Ctrl: 100% **High Flow Oxygen** ▪ Exp: 10% ▪ Ctrl: 0% **<u>Parameters</u>** **PaO2/FiO2** ▪ 201.4 ± 118.8 ▪ 185.6 ± 126.1			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Fezzi 2023 EPCoT NCT05008380 open-label RCT	**Sample size:** N = 29 (prone positioning), 32 (control group) **Enrolment period:** 15 August 2021 and 31 May 2022 **Countries** ▪ Italy **Inclusion criteria:** ▪ 18 years and older ▪ positive PCR test for SARS-CoV-2 RNA on a respiratory sample within 7 days of enrolment ▪ at least one of the following conditions: 1) radiological evidence of pneumonia or 2) clinical evidence of respiratory disease, defined as either room air arterial oxygen tension (PaO2 oxygen saturation (SpO2) <94% or need for oxygen supplementation in order to maintain SpO2 > 93% **Time since symptom onset (median, range):** ▪ test within 7 days of enrolment **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 61.0 ▪ Ctrl: 57.5	**Experimental:** "encouraged to adopt PP for at least three consecutive hours (up to 6 h according to tolerability) twice a day" ▪ Prone positioing ▪ at least 6h/24h, up to 12h/24h ▪ Actual duration: day 1: median 3h (IQR 0-6h) day 3: median 4h (IQR 0-7h) "44.8% and 40.7% maintained pronation for <3 h·day−1 on day 1 and 3, respectively" ▪ N = 29 **Control:** "patients in the control group were free to adopt and maintain any position during the day."; 0h ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 32 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: mean 15.2 (SD 11.0) days Control: mean 12.7 (SD 7.2) da
			death (any cause)	PP: 2/29 Ctrl: 1/32
			intubation	PP: 4/29 Ctrl: 0/32

	<u>Comorbidities</u> **Obesity** ▪ Exp: 6.9% ▪ Ctrl: 6.2% **Hypertension** ▪ Exp: 41.4% ▪ Ctrl: 18.7% **Cardiovascular disease** ▪ Exp: 3.4% ▪ Ctrl: 6.2% **Lung diseases** ▪ Exp: 13.7% ▪ Ctrl: 9.3% ***<u>Respiratory support</u>*** **Low flow oxygen** 98% **High Flow Oxygen** 0% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Nay 2023 PROVID-19 NCT04363463 *open-label RCT*	**Sample size: 167** **Enrolment period:** 28 August 2020 to 5 January 2022 **Countries** ▪ France, Monaco **Inclusion criteria:** ▪ hospitalised in medical wards for < 72 h, ▪ 18–85 years old ▪ had laboratory-confirmed COVID-19 pneumonia, ▪ were breathing spontaneously with supplemental oxygen (via standard nasal prongs, mask or high-flow nasal cannula) ▪ were able to selfposition in the prone position or with the assistance of one person. **Time since symptom onset (median, range):** ▪ hospitalised in medical wards for < 72 **<u>Characteristics</u>** **Age (mean, sd)** ▪ Exp: 58.4 (12.1) ▪ Ctrl: 59.2 (11.0) ***<u>Comorbidities</u>*** **Obesity (BMI, mean, sd)** ▪ Exp: 28.6 (4.2) ▪ Ctrl: 28.6 (4.7) **Hypertension** ▪ Exp: 19.3%	**Experimental:** "patients assigned to the intervention group had to lie in a prone position for a minimum of two sessions with the goal of a cumulative time of at least 150 min in the prone position during the daytime. Patients were encouraged to lie in the prone position as much as possible. Time and duration of each mobilisation were recorded in a notebook by the patient or a staff member, except at night" ▪ Prone positioing ▪ >150 min/24h ▪ ▪ day 1: 74.8% proned; median time per day proned 138 min [IQR 90 - 176] ▪ N = 135 **Control:** **median 0 (0 to 2) hours** ▪ standard of care (oSOC) alone ▪ "Patients randomized to standard care were allowed to change their position as per their comfort (supine, semi sitting, sitting or lateral). If patients in the standard arm wished to lie prone for comfort, this was allowed."	length of hospital stay (ICU)	PP: median 7 (IQR 5 to 11) Control: median 7 (IQR 5 to 12
			Intubation or death (any cause)	PP: 10/135 Ctrl: 14/132
			death	PP: 0/135 Ctrl: 4/135
			Intubation	PP: 10/135 Ctrl: 13/132

	▪ Ctrl: 26.5% **Coronary heart disease** ▪ Exp: 6.7% ▪ Ctrl: 3.8% **Lung diseases (COPD, asthma)** ▪ Exp: 4.4%, 8.1% ▪ Ctrl: 0.8%, 6.8% ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ Exp: 96% ▪ Ctrl: 95%% **High Flow Oxygen** ▪ Exp: 4% ▪ Ctrl: 5% **<u>Parameters</u>** **PaO2/FiO2 (median, IQR, mmHg)** ▪ 178 (151–226) ▪ 173 (131–226)	▪ N = 132		

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Yarahmadi 2022 IRCT20160126026217N4 *open-label RCT*	**Sample size: 82** **Enrolment period:** August 2020 to April 2021 **Countries** ▪ Iran **Inclusion criteria:** ▪ lack of supportive ventilation ▪ age 35 to 70 ▪ no supportive ventilation ▪ no COPD or asthma ▪ no orthopedic or spine disorder ▪ no thoracic surgery last 6 months **Time since symptom onset (median, range):** ▪ Time gap between onset of symptoms and intervention (Mean (SD)) 1.61 (0.92) **<u>Characteristics</u>** **Age (>=50, %)** ▪ Exp: 61% ▪ Ctrl: 61% ***<u>Comorbidities</u>*** **Obesity (BMI, mean, sd)** ▪ Exp: 24.98 (2.45) ▪ Ctrl: 24.44 (2.50) **Hypertension** ▪ Exp: 51.2% ▪ Ctrl: 17.1% **Coronary heart disease: NR** **Lung diseases: NR** ***<u>Respiratory support</u>*** No oxygen to low flow oxygen **<u>Parameters</u>**	**Experimental:** "PP group were asked to lie comfortably in a PP for 90 min and then resume to supine"; "At the end of the 90 min, the participants in the PP group were free to resume the SP or maintain the PP. Still, they were asked to intermittently stay in a PP for a total of 8 h during the 24 h of hospitalisation" ▪ Prone positioing ▪ 8h/24h ▪ Not observed ▪ N = 41 **Control:** **median 0 (0 to 2) hours** ▪ standard of care (oSOC) alone ▪ "asked to lie comfortably in a SP at an angle of 30° for 90 min" ▪ N = 41	length of hospital stay (ICU)	PP: mean 14.970 (sd 0.854) da Control: mean 14.978 (sd 1.10
			Intubation or death (any cause)	NR
			Death (at hospital discharge; survival; at the time of patient discharge to home/ house spice, transfer to the ICU, or patient's death)	PP: 0/41 Ctrl: 4/41
			Intubation	PP: 3/41 Ctrl: 8/41

	PaO2/FiO2 (median, IQR, mmHg) ▪ NR			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Alhazzani 2022 COVI-PRONE NCT04350723 Open-label RCT	**Sample size:** N = 205 (prone positioning), 195 (control group) **Enrolment period:** 19 May 2020 to 18 May 2021 **Countries** ▪ Canada, Kuwait, Saudi Arabia, and the US **Inclusion criteria:** ▪ aged 18 years or older ▪ not intubated ▪ suspected or confirmed COVID-19 ▪ required at least 40% oxygen (via low- or high-flow oxygen devices) or noninvasive positive pressure ventilation ▪ being treated in an intensive care unit (ICU) or a monitored acute care unit. **Time since symptom onset (median, range):** ▪ time from hospital admission to	**Experimental:** "target duration of prone positioning was 8 h/d to 10 h/d with 2 to 3 breaks (1-2 hours each), if needed. Daily prone positioning sessions were protocolized to continue until 1 of the following stopping criteria was met: a relative improvement in the FIO2 requirement by 40% from the baseline value that was sustained for 24 hours; endotracheal intubation; or discharge from the ICU or acute care unit" ▪ Prone positioing ▪ at least 8h/24h, up to 10h/24h ▪ Actual duration: ▪ day 1: 5.0 hours (IQR, 2.0-8.0 hours) day 1-4: 4.8 h/d (IQR, 1.8-8.0 h/d) ▪ N = 205 **Control:** "Patients randomized to the control group, and their treating team, were informed of their group assignment. Nurses instructed patients not to position themselves in the prone position."; 0h ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 195	length of hospital stay	PP: NR Control: NR
			death (any cause)	PP: 46/205 Ctrl: 46/195
			intubation	PP: 70/205 Ctrl: 79/195
			Intubation or death	Number of particpants (PP): 7 Number of Participants (ctrl):

	randomisation was median 1.6 days IQR 0.8 to 3.7 **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 56.8 ▪ Ctrl: 58.3 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: 46% ▪ Ctrl: 49% **Cardiovascular disease** ▪ Exp: 49% ▪ Ctrl: 52% **Lung diseases** ▪ Exp: 11% ▪ Ctrl: 13% ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ Exp: 22% ▪ Ctrl: 22% **High Flow Oxygen** ▪ Exp: 72% ▪ Ctrl: 68% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg	N = (mind. eine Dosis und ausgewertet)		

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Javed 2023 NCT05405335 open-label RCT	**Sample size:** N = 36 (prone positioning), 36 (control group) **Enrolment period:** 15 October 2021 to 28 February 2022 **Countries** ▪ Pakistan **Inclusion criteria:** ▪ positive COVID-19 PCR or evidence of COVID-19 pneumonia/ARDS on HRCT chest **Time since symptom onset (median, range):** ▪ unclear **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 56.8 ▪ Ctrl: 58.3 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR	**Experimental:** "Patients who were to be subjected to prone positioning were assisted by experienced staff if the patient requested. The duration of each prone positioning cycle was set for thirty minutes to three hours (duration controlled by the patient) alternating with lying on the right side then on the left side and afterward sitting upright and so on. Total prone positioning duration lasted for eight hours per day for seven days. The duration of each cycle was recorded on the file by the staff." ▪ Prone positioing ▪ 8h/24h ▪ Actual duration: NR ▪ N = 36 **Control:** **Usual care** ▪ standard of care (oSOC) alone ▪ N = 36 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: NR Control: NR
			death (any cause) day 14	PP: 2/36 Ctrl: 10/36
			death (any cause) day 90	PP: 21/ 36 Ctrl: 18/36
			death day 30	NR
			Intubation or death	NR

	Lung diseases ▪ Exp: NR ▪ Ctrl: NR ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ Exp: NR ▪ Ctrl: NR **High Flow Oxygen** ▪ Exp: NR ▪ Ctrl: NR **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ehrmann 2021 COVAYDE NCT04395144 *open-label RCT*	**Sample size:** N = 7 (prone positioning), 6 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** ▪ Canada **Inclusion criteria:** ▪ Covid-19 pneumonia based on the center for disease control guidelines ▪ Presence of acute hypoxemic respiratory failure; ▪ Acute onset within 7 days of insult, or new (within 7 days) or worsening respiratory symptoms; ▪ Bilateral opacities on chest x-ray or computer tomographic scanner not fully explained by effusions, lobar or lung collapse, or nodules; ▪ Cardiac failure not the primary cause of acute respiratory failure	**Experimental:** "PP will be performed before or 1 hour after meal. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. PP will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. PP will be performed minimum twice a day for the first 3 days after the patient's enrolment. Patients will be informed to maintain prone position as long as they can. FIO2 will be adjusted to maintain SpO2 at 90-94%. PP is not protocolized once the patient has been weaned off HFNC. No sedation will be used during the PP. The patients will be monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP session, and at least once for each subsequent session" ▪ Prone positioing ▪ 5/24 (IQR 1.6 to 8.8h) ▪ Actual duration: ▪ median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) ▪ N = 7 **Control:** **"The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."**	length of hospital stay* for all studies included in Ehrmann	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7
			Intubation or death	PP: 3/7 Ctrl: 3/6
			death (any cause)	PP: 2/7 Ctrl: 2/6
			intubation	PP: 1/7 Ctrl: 1/6

	▪ PaO2 / FiO2 ratio <200 mmHg or SO2 / FiO2 < 240 with HFNC at 50 L/min and SpO2 maintained at 92-95% **Time since symptom onset (median, range):** ▪ Number of days from admission in hospital to enrolment in study: median, IQR: 0.2 (0 to 0.4) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 65.1 ▪ Ctrl: 68.3 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: 17% ▪ Ctrl: 50% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 43% ▪ Ctrl: 50% **Lung diseases** ▪ Exp: 29% ▪ Ctrl: 17% ***<u>Respiratory support</u>*** ▪ **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg	▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 6 N = (mind. eine Dosis und ausgewertet)		

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ehrmann 2021 HIGH-PRONE-COVID-19 France NCT04358939 *open-label RCT*	**Sample size:** N = 200 (prone positioning), 202 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** ▪ France **Inclusion criteria:** ▪ Adult patient suffering from Covid-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected. ▪ Patient treated by nasal high flow therapy ▪ Moderate or severe ARDS: bilateral radiological opacities not explained entirely by effusions, atelectasis or nodules; acute hypoxemia with worsening within the 7 previous	**Experimental:** **"depending on tolerance, the objective is to spend as much time as possible, up to 16h and beyond, in prone position per period of 24 hours. At least two sessions of at least 30 minutes each must be performed daily."** ▪ Prone positioing ▪ 5/24 (IQR 1.6 to 8.8h) ▪ Actual duration: ▪ median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) ▪ N = 200 **Control:** **"The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."** ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 202 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7
			Intubation or death	PP: 82/200 Ctrl: 85/202
			death (any cause)	PP: 21/200 Ctrl: 20/202
			intubation	PP: 76/200 Ctrl: 82/202

	days, not entirely explained by left ventricular failure; Pa O2 ratio <300 mmHg (or equivalent Sp)./ Fi FiO2 ▪ Written informed consent in France, oral consent in Spain **Time since symptom onset (median, range):** ▪ Number of days from admission in hospital to enrolment in study: median, IQR: 1.5 (1 to 3) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 64.2 ▪ Ctrl: 62.9 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: 31% ▪ Ctrl: 37% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 11% ▪ Ctrl: 5% **Lung diseases** ▪ Exp: 14% ▪ Ctrl: 14% ***<u>Respiratory support</u>*** ▪ **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ehrmann 2021 Ireland APPROVE-CARE NCT04347941 *open-label RCT*	**Sample size:** N = 12 (prone positioning), 12 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** ▪ Ireland **Inclusion criteria:** ▪ Suspected or confirmed Covid-19 infection ▪ Bilateral Infiltrates on chest X-ray ▪ SpO2 <94% on FiO2 40% by ▪ either venturi facemask or high flow nasal cannula ▪ Respiratory rate<40 breath/min ▪ Written informed consent **Time since symptom onset (median, range):** ▪ Number of days from admission in hospital to enrolment in study: median, IQR: 1 (1 to 2.5) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 62.8 ▪ Ctrl: 59.3 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: 50%	**Experimental:** "Awake prone positioning will be performed before or 1 hour after meal. Call bell will be given to the patient and an oxygen probe will be attached to the patient to monitor spO2 during the procedure. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. Awake prone positioning will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. Patients will be informed to maintain prone position as long as they can. FIO2 will be adjusted to maintain SpO2 at 92-95%. Protocol for sedation and comfort evaluation during PP: No sedation will be used during the PP on ward. The patients are monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP in each day." ▪ Prone positioing ▪ 5/24 (IQR 1.6 to 8.8h) ▪ Actual duration: ▪ median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) ▪ N = 12 **Control:**	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9
			Intubation or death	PP: 0/12 Ctrl: 2/12
			death (any cause)	PP: 0/12 Ctrl: 0/12
			intubation	PP: 0/12 Ctrl: 2/12

	▪ Ctrl: 67% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 58% ▪ Ctrl: 33% **Lung diseases** ▪ Exp: 17% ▪ Ctrl: 33% ***<u>Respiratory support</u>*** ▪ **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg	"The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation." ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 12 N = (mind. eine Dosis und ausgewertet)		

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ehrmann 2021 Mexico PRO-CARF NCT04477655 open-label RCT	**Sample size:** N = 216 (prone positioning), 214 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** ▪ Mexico **Inclusion criteria:** ▪ Adult patients (18 y) with RT-PCRconfirmed Covid-19 and respiratory distress (regardless of Berlin criteria for ARDS). ▪ Requirement of a FiO2 ≥30% through high-flow nasal cannula (HFNC) to maintain a capillary SpO2 ≥90%. ▪ Written informed consent **Time since symptom onset (median, range):** ▪ Number of days from admission in hospital to enrolment in study: median, IQR: 0.6 (0.4 to 1) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 58.6 ▪ Ctrl: 58.2	**Experimental:** "Patients of the experimental group will be also treated with oxygen therapy through high flow nasal cannula (HFNC). Patients will be asked to remain in prone position throughout the day as long as possible, with breaks according to tolerance. Pillows will be offered for maximizing comfort at chest, pelvis and knees. Monitoring of vital signs will not be suspended. Inspired fraction of oxygen will be titrated to maintain a capillary saturation of 92%-95%. Staff intensivist will monitor adherence to protocol and patient's status of both groups on a 24/7 basis." ▪ Prone positioing ▪ 5/24 (IQR 1.6 to 8.8h) ▪ Actual duration: ▪ median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) ▪ N = 216 **Control:** **"The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."** ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 214	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9
			Intubation or death	PP: 88/216 Ctrl: 112/214
			death (any cause)	PP: 71/216 Ctrl: 79/214
			intubation	PP: 65/216 Ctrl: 92/214

	Comorbidities **Obesity** ▪ Exp: 40% ▪ Ctrl: 38% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 29% ▪ Ctrl: 31% **Lung diseases** ▪ Exp: 8% ▪ Ctrl: 5% ***Respiratory support*** ▪ **HFNC** **Parameters** **PaO2/FiO2** inclusion P/F >200 mmHg	N = (mind. eine Dosis und ausgewertet)		

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ehrmann 2021 Spain PR(AG)198/2020 NCT04391140 *open-label RCT*	**Sample size:** N = 17 (prone positioning), 13 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** ▪ Spain **Inclusion criteria:** ▪ Adult patient suffering from Covid-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected. ▪ Patient treated by nasal high flow therapy ▪ Moderate or severe ARDS: bilateral radiological opacities not explained entirely by effusions, atelectasis or nodules; acute hypoxemia with worsening within the 7 previous days, not entirely explained by left ventricular failure; Pa O2 ratio <300 mmHg (or equivalent Sp). / Fi FiO2 ▪ Written informed consent in France, oral consent in Spain	**Experimental:** "Prone position: depending on tolerance, the objective is to spend as much time as possible, up to 16h and beyond, in prone position per period of 24 hours. At least two sessions of at least 30 minutes each must be performed daily." ▪ Prone positioing ▪ 5/24 (IQR 1.6 to 8.8h) ▪ Actual duration: ▪ median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) ▪ N = 17 **Control:** "The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation." ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 13 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7
			Intubation or death	PP: 5/17 Ctrl: 7/13
			death (any cause)	PP: 2/17 ctrl: 1/13
			intubation	PP: 5/17 ctrl: 7/13

	Time since symptom onset (median, range): ▪ Number of days from admission in hospital to enrolment in study: median, IQR: 1.5 (0 to 4) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 58.1 ▪ Ctrl: 52.4 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: 47% ▪ Ctrl: 39% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 6% ▪ Ctrl: 8% **Lung diseases** ▪ Exp: 12% ▪ Ctrl: 0% ***<u>Respiratory support</u>*** ▪ **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Ehrmann 2021 USA NCT04325906 *open-label RCT*	**Sample size:** N = 112 (prone positioning), 110 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** ▪ USA **Inclusion criteria:** ▪ Covid-19 pneumonia based on the center for disease control guidelines ▪ Presence of acute hypoxemic respiratory failure; ▪ Acute onset within 7 days of insult, or new (within 7 days) or worsening respiratory symptoms; ▪ Bilateral opacities on chest x-ray or computer tomographic scanner not fully explained by effusions, lobar or lung collapse, or nodules; ▪ Cardiac failure not the primary cause of acute respiratory failure ▪ PaO2 / FiO2 ratio <200 mmHg or SO2 / FiO2 < 240 with HFNC at 50 L/min and SpO2 maintained at 92-95% **Time since symptom onset (median, range):**	**Experimental:** "PP will be performed before or 1 hour after meal. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. PP will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. PP will be performed minimum twice a day for the first 3 days after the patient's enrollment. Patients will be informed to maintain prone position as long as they can. F I O will be adjusted to maintain SpO at 92-95%." ▪ Prone positioing ▪ 5/24 (IQR 1.6 to 8.8h) ▪ Actual duration: mean time, SD: 4.4 ± 4.7 ▪ N = 112 **Control:** "The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation." ▪ standard of care (oSOC) alone ▪ Instructed not to prone ▪ N = 110	length of hospital stay	PP: mean 16.4, sd 10 Control: mean 16.5,
			Intubation or death	PP: 45/112 ctrl: 48/110
			death (any cause)	PP: 21/112 ctrl: 30/110
			intubation	PP): 38/112 ctrl: 39/110

	▪ Within 7 days from insult; Number of days from admission in hospital to enrolment in study: median, IQR: 0.8 (0.3 to 1.8) **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 62.2 ▪ Ctrl: 62.5 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: 53% ▪ Ctrl: 56% **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: 22% ▪ Ctrl: 37% **Lung diseases** ▪ Exp: 10% ▪ Ctrl: 19% ***<u>Respiratory support</u>*** ▪ **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg	N = (mind. eine Dosis und ausgewertet)		

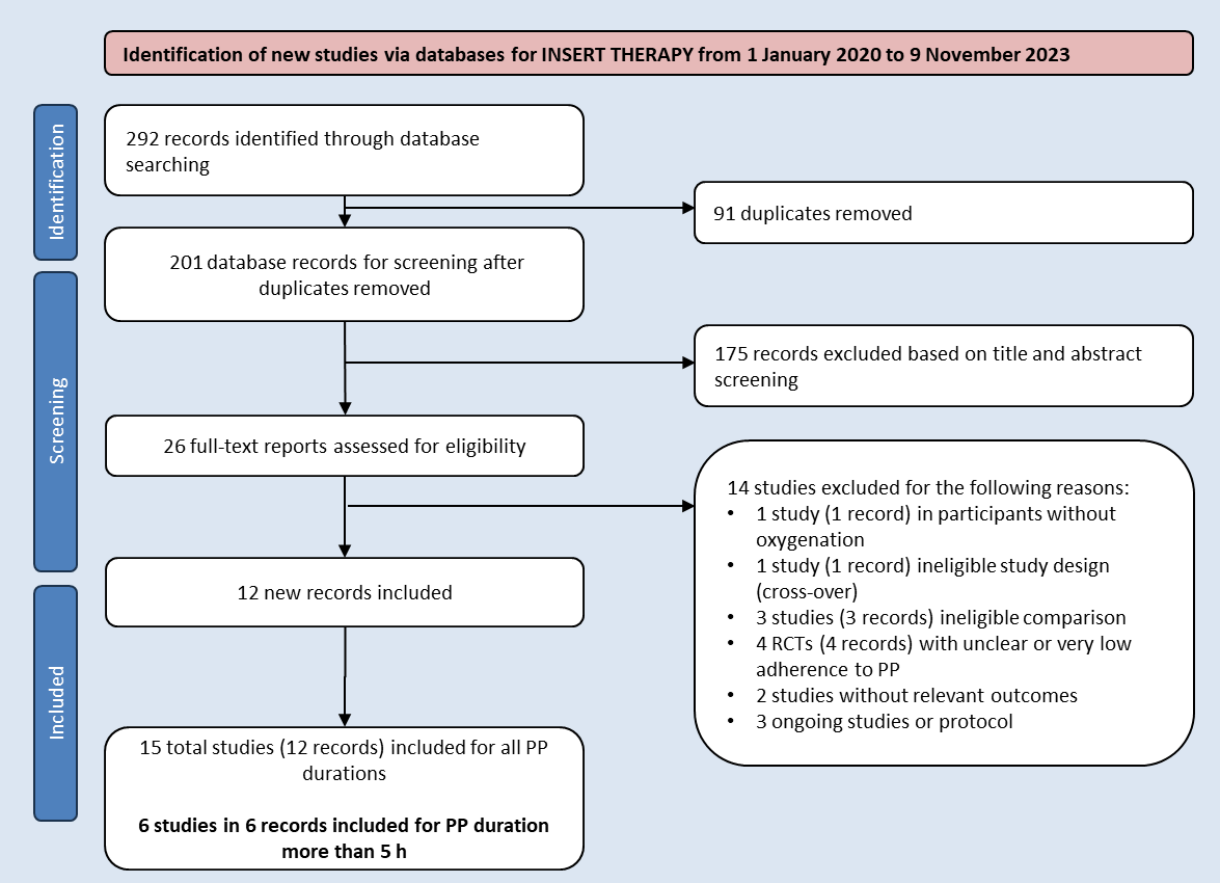
Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Rosen 2021 PROFLO ISRCTN54917435 open-label RCT	**Sample size:** N = 36 (prone positioning), 39 (control group) **Enrolment period:** 7 October 2020 to 7 February 2021 **Countries** ▪ Sweden **Inclusion criteria:** ▪ ≥ 18 years old ▪ confirmed SARS-CoV-2 ▪ HFNO or NIV for respiratory support ▪ PaO2/FiO2 ≤ 20 kPa **Time since symptom onset (median, range):** ▪ NR **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 66 ▪ Ctrl: 65 ***<u>Comorbidities</u>*** **Obesity** ▪ Exp: 23% ▪ Ctrl: 32% **Hypertension** ▪ Exp: 47% ▪ Ctrl: 55% **Cardiovascular disease** ▪ Exp: 17% ▪ Ctrl: 13% **Lung diseases** ▪ Exp: 11%	**Experimental:** "A protocol targeting at least 16 h APP per day was initiated. Prone and semi-prone positioning was allowed. Flat supine positioning was discouraged and patients were instructed to place themselves in the semirecumbent or lateral position in between proning sessions." ▪ Prone positioing ▪ 16h/24h ▪ Actual duration: median 9.0 [IQR 4.4–10.6] ▪ N = 36 **Control:** "APP was not encouraged but could be prescribed by the attending clinician at his/her discretion." ▪ standard of care (oSOC) alone ▪ N = 39 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: median 16 (IQR days Control: median 18 (30) days
			death (any cause)	PP: 6/36 ctrl: 3/39
			intubation	PP: 12/36 ctrl: 13/39

	▪ Ctrl: 26% ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ NR **High Flow Oxygen** ▪ Exp: 86% ▪ Ctrl: 74% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome
Nasrallah 2023 pactr202204746577792 *open-label RCT*	**Sample size:** N = 45 (prone positioning), 45 (control group) **Enrolment period:** NR, probably from December 2020 (registration date) **Countries** ▪ Egypt **Inclusion criteria:** ▪ ≥ 18 years old ▪ BMI ≤ 30kg/m² ▪ mild ARDS acc. to Berlin criteria ▪ bilateral opacities ▪ moderate to severe ARDS (PaO2/FiO2 ratio less than 200) were excluded! **Time since symptom onset (median, range):** ▪ occurrence within 1 week of a known clinical insult or worsening respiratory symptoms upon admission to ICU **<u>Characteristics</u>** **Age (median, IQR)** ▪ Exp: 62.24 ▪ Ctrl: 58.47 ***<u>Comorbidities</u>***	**Experimental:** "Group 2: Patients were subjected to HFNC with a target of SpO2 > 90% with FiO2 ≤ 0.6, and combined with self proning. At first self-proning was applied with HFNC for at least 30 min, if the patient tolerated it well, the position was maintained. The duration of the prone position was 8 h per day" ▪ Prone positioing ▪ 8h/24h ▪ Actual duration: NR ▪ N = 45 **Control:** "Group 1: Patients were subjected to HFNC with a target SpO2 ≥ 90% with FiO2 < 0.6." ▪ standard of care (oSOC) alone ▪ N = 45 N = (mind. eine Dosis und ausgewertet)	length of hospital stay	PP: median 12 (IQR 10 to 12) Control: median 19 (18 to 21)
			death (any cause)	PP: 3/45 ctrl: 10/45
			intubation	PP: 4/45 ctrl: 11/45

	Obesity ▪ Exp: NR ▪ Ctrl: NR **Hypertension** ▪ Exp: NR ▪ Ctrl: NR **Cardiovascular disease** ▪ Exp: NR ▪ Ctrl: NR **Lung diseases** ▪ Exp: NR ▪ Ctrl: NR ***<u>Respiratory support</u>*** **Low flow oxygen** ▪ NR **High Flow Oxygen** ▪ Exp: NR ▪ Ctrl: NR **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg			

5.13.5 Studienselektion: Flow Chart



5.13.6 Literaturrecherche

Date of search for all databases: 09.11.2023		
Database/Register	**Search**	**Update Search**
CCSR	82	
Scopus	130	
WHO COVID-19 DB*	80	
Total	292	
Total (after deduplication)	201	

The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.

5.13.6.1 *Cochrane COVID-19 Study Register*

Search string:
position*
AND
prone* or proning* or pronation*

AND
early or awake or wakefulness* or noninvasive or "non invasive" or nonintubat* or "non intubated" or "non intubation" or nonventilat* or "non ventilated" or "non ventilation" or "face down" or "nasal cannula"

Results available:
reprt results

Study characteristics:
1) "Intervention assignment": “Randomised” OR “unclear” OR
2) "Study design": "Parallel/Crossover" OR “unclear”

5.13.6.2 *Scopus (via Elsevier)*

TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS (position*)

AND TITLE-ABS (prone* OR proning* OR pronation*)

AND TITLE-ABS (early OR awake OR wakefulness* OR noninvasive OR "non invasive" OR nonintubat* OR "non intubated" OR "non intubation" OR nonventilat* OR "non ventilated" OR "non ventilation" OR "face down" OR "nasal cannula")

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

AND (LIMIT-TO (DOCTYPE , "ar"))

AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023))

5.13.6.2.1 WHO COVID-19 Global literature on coronavirus disease

Title, abstract, subject:
(position*) AND (prone* OR proning* OR pronation*) AND (early OR awake OR wakefulness* OR noninvasive OR "non invasive" OR nonintubat* OR "non intubated" OR "non intubation" OR nonventilat* OR "non ventilated" OR "non ventilation" OR "face down" OR "nasal cannula") AND (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

6 Darlegung von Interessen und Umgang mit Interessenkonflikten

Im Folgenden sind die Interessenerklärungen (Stand Januar 2024) als tabellarische Zusammenfassung dargestellt sowie die Ergebnisse der Interessenkonfliktbewertung und Maßnahmen, die nach Diskussion der Sachverhalte von der der LL-Gruppe beschlossen und im Rahmen der Konsensuskonferenz umgesetzt wurden. Folgende Kriterien wurden angewendet:

- Geringe Interessenkonflikte: Einzelne Vorträge für Firmen, zu deren Produkten ein thematischer Bezug zur Leitlinie bestehen.
    - Konsequenz: Keine alleinige Leitungsfunktion (Koordination/AG) – Peer.
- Moderate Interessenkonflikte: Advisory Board Tätigkeit für Firmen, zu deren Produkten ein thematischer Bezug zur Leitlinie bestehen oder Managementverantwortung für industriefinanziert Studie.
    - Konsequenz: Keine Teilnahme an Abstimmungen zum Thema oder Doppelabstimmung
- Hohe Interessenkonflikte: Relevanter Aktienbesitz von Firmen zu deren Produkten ein thematischer Bezug zur Leitlinie bestehen oder Anstellung bei der Industrie.
    - Konsequenz: keine Teilnahme an Diskussion und Abstimmung zum Thema.

Als Schutzfaktoren werden für diese Leitlinie die unabhängige Evidenzaufarbeitung durch ein Methodenteam und die neutrale Moderation geltend gemacht.

Leitlinienkoordination: Kluge, Stefan; Peer: Nothacker, Monika (LL-Methodik)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
Prof. Dr. Berlit, Peter	Norwegischer Wissenschaftsrat	Nein	Nordrheinische Ärzteakademie	Autor und Herausgeber von mehreren Lehrbüchern	Nein	Nein	Wissenschaftliche Tätigkeit: Vaskulitis Schlaganfall bei jungen Patienten Peripheres Nervensystem Neuroimmunologie COVID-19, Beteiligung an Fort-/Ausbildung: DGN-Zeitschriften DGN-Fortbildungen DGN-Jahreskongress DGN-Facharzttraining Neurologie	COI: keine: keine
Prof. Dr. Bracht, Hendrik	Nein	Philips Medical Advisory Board, Sedana Medical Advisory Board	Nein	Nein	Nein	Nein	Mitglied: Wissenschaftlicher Arbeitskreis Intensivmedizin DGAI Schriftführer, Mitglied: Forschungsgruppenleiter TIFOnet Immunsystem der DGAI, Mitglied: European Society of Intensive Care Medicine (ESICM) Chair Workgroup Antibiotic Use, Mitglied: European Society of Clinical Microbiology and Infectious Diseases (ESMID) Secretary Study Group Critically ill patients, Wissenschaftliche Tätigkeit: Sepsis, septischer Schock Infektionsmanagement Management von Delir und Sedierung Theraopeutisches Drugmonitoring, Klinische Tätigkeit: Intensivmedizin Klinische Akut- und Notfallmedizin, Beteiligung an Fort-/Ausbildung: keine, Persönliche Beziehung: keine	Advisory Board mit Thema Medizintechnik/inhalative Sedierung, kein Themenbezug zu COVID-19 Therapie COI: keine: keine
PD Dr. Brandt, Christian	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: Verbund für angewandte Hygiene (VAH) e.V. (Vorstandsmitglied - für DGHM), Wissenschaftliche Tätigkeit: Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM) e.V. - Sprecher der Ständigen Arbeitsgemeinschaft "Allgemeine und Krankenhaushygiene", Klinische Tätigkeit: Universitätsklinikum Frankfurt (AöR) der Goethe-Universität, Berater für Bauhygiene, Beteiligung an Fort-/Ausbildung: Landeskrankenhaus AöR, Andernach (Fachkrankenhaus für Neurologie und Psychiatrie) mit mehreren Standorten in	COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							Rheinland-Pfalz. In diesem Rahmen auch Vorträge.	
Prof. Dr. Böttiger, Bernd W.	C. R. Bard GmbH TTM in den Guidelines15, C. R. Bard GmbH TTM 2018 ? was kommt auf uns in der Praxis zu?	Nein	McMaster International Review Course in International Medicine How can we improve survival after cardiac arrest: focus on postresuscitation care, Laerdal Medical GmbH Webinar KIDS SAVE LIVES, Telefonreanimation, Cardiac-Arrest-Zentren et al., deutscher und europäischer Reanimationskongress im September 2017 in Freiburg, Forum für medizinische Fortbildung FomF GmbH Vortrag Reanimationsleitlinien, Forum für medizinische Fortbildung FomF GmbH Wissenschaftliche Leitung, Vorsitz, Moderation, Vorträge Kardiopulmonale Reanimation 2017 / KIDS SAFE LIVES /NAWIB?, Robert-Müller-Stiftung Vortrag Update Wiederbelebung, VDBW e.V. Verband Deutscher Betriebs- und Werksärzte e.V Vortrag Laienreanimation ? welchen Beitrag	Georg Thieme Verlag KG, Mitautor Kapitel Lungenembolie, Georg Thieme Verlag KG Mitautor Kapitel Reanimation, MWV Medizinisch Wissenschaftliche Verlagsgesellschaft mbH Co. KG Co-Herausgeber DIVI Jahrbuch 2019/2020, Deutscher Ärzteverlag GmbH MitherausgeberZeitschrift DIVI	Nein	Nein	Mitglied: Bernd W. Böttiger ist Schatzmeister und Immediate Past Director Science and Research des European Resuscitation Council (ERC); Vorstandsvorsitzender des Deutschen Rates für Wiederbelebung / German Resuscitation Council (GRC), Mitglied im Präsidium der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI), Gründer der Deutschen Stiftung Wiederbelebung, Bundesarzt des Deutsches Roten Kreuz (DRK), , Wissenschaftliche Tätigkeit: Herz-Kreislaufstillstand	Berater-/Gutachtertätigkeit, Vortragstätigkeit zum Thema Wiederbelebung, kein thematischer Bezug zu COVID-19 Therapie COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			Betriebsärzte leisten können , Zoll Medical Deutschland Vortrag UPDATE 2017 ERC Resuscitation Guidelines 2015 Ein starkes Statement zum Targeted Temperature Management, Baxalta Deutschland GmbH Vorsitz Gerinnungsstörungen in der Intensivmedizin: komplexe Fälle schnell diagnostiziert, Forum für medizinische Fortbildung FomF GmbH Vortrag Reanimationsleitlinien, Klinikum der Stadt Ludwigshafen Vortrag Cardiac-Arrest-Zentren Tool or Toy?, GS Elektromedizinische Geräte G. Stemple GmbH Vorsitz und Vortrag CPR per App Technologien retten Leben. Leben retten: vom Laien bis zur Intensivstation Der Erfolg ist Gemeinschaftssache, McMaster International Review Course in International Medicine Vortrag Cardiac arrest and resuscitation: 2018 update., Forum für medizinische Fortbildung				

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			FomF GmbH Wissenschaftliche Leitung, Vorsitz, Moderation, Vorträge Kardiopulmonale Reanimation / KIDS SAFE LIVES / und Postreanimationsversorgung, C. R. Bard GmbH Moderation, Vorsitz, Vorträge Klinische und ökonomische Evidenz für nicht-invasives, Bio-Feedback gesteuertes Temperaturmanagement., Zoll Medical Deutschland+ Vorsitz Temperaturmanagement ? Ja, aber TTM1, TTM2 oder TTH48?!, Novartis Pharma GmbH Vortrag Cardiac-Arrest-Zentren Tool or toy? Warum immer noch 2 Jumbojets pro Tag abstürzen., C. R. Bard GmbH Beratung, Moderation und Vorträge TTM Teaching Course From Proof to Practice, C. R. Bard GmbH Beratung und Moderation TTM 2019 the circle of survival, Forum für medizinische Fortbildung FomF GmbH Wissenschaftliche Leitung, Vorsitz, Moderation, Vorträge Kardiopulmonale Reanimation und Postreanimationsphase					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			2019 • KSL /WRAH /GRC / ERC / ILCOR et. Al., Lücke Kongress GmbH Vortrag Outcome nach Herzstillstand, Philips GmbH Market DACH Vortrag Leben retten durch Frühwarnsysteme. Wie weit sind Krankenhäuser und Technik? • Wie umgehen mit unterwünschten Ereignissen auf Normalstation: Das sagen die Leitlinien, Lücke Kongress GmbH Vortrag •KIDS SAVE LIVES• • schnell vor Ort mit Mut, Zoll Medical Deuschland Vortag Epidemiology of cardiac arrest, C. R. Bard GmbH Vortrag, TTM Symposium in Bremen, Forum für medizinische Fortbildung FomF GmbH Moderation/Vortrag Kadiopulmonale Reanimation und Porsteanimations-phese •Udate im Jahr der neuen Leitlinien 2020 , mekontor GmbH Co. KG, Akademie für Ärztliche Fortbildung – Ärzteakademie c/o Asklepios Klinik St. Georg, Bard Limited , Forum für medizinische Fortbildung – FomF GmbH, Bard Limited, Springer Medien Verlag GmbH, C.T.I					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			GmbH, Lücke Kongress GmbH, Zoll Medical Deutschland GmbH, Forum für medizinische Fortbildung – FomF GmbH, Forum für medizinische Fortbildung – FomF GmbH, Zoll Medical Deutschland GmbH, Forum für medizinische Fortbildung – FomF GmbH, Lücke Kongress GmbH, C.R. Bard GmbH, Beiersdorf AG, Barmherzige Brüder, Klinikum St. Elisabeth, Straubing, Becton Dickinson S.A.U., Ärztekammer Nordrhein, Fundacja Polski Instytut Evidence Based Medicine, Forum für medizinische Fortbildung FomF GmbH, Nein					
Cryns, Nora	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: systematische Reviews und Evidenz-basierte Leitlinienerstellung	COI: keine: keine
Faske, Amon	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: Nein, Wissenschaftliche Tätigkeit: Nein, Klinische Tätigkeit: Nein, Beteiligung an Fort-/Ausbildung: Nein, Persönliche Beziehung: Nein	COI: keine: keine
Goldkuhle, Marius	-	-	-	Keine Veröffentlichungen mit Bezug zur Leitlinie	Keine Forschungsvorhaben mit Bezug zur Leitlinie	-	Mitglied: Deutsches Netzwerk Evidenz-basierte Medizin e.V., Wissenschaftliche Tätigkeit: Methodik von Meta-Analysen, GRADE, Cochrane Reviews zu Hämato-Onkologischen Fragestellungen, Klinische Tätigkeit: -, Beteiligung an Fort-/Ausbildung: -, Persönliche Beziehung: -	COI: keine: keine
Haase, Reiner	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
Hirsch, Caroline	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Prof. Dr. Hoffmann, Florian	---	---	PAEDSIM e.V. - Simulationstraining für Kindernotfälle	Kindernotfall-ABC (Springer) Kinderchrirugie für Pädiater Springer)	Nein	Nein	Mitglied: Mitgliedschaft /Funktion in Interessenverbänden - Schriftführer der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI) und Leiter der Sektion Pädiatrische Intensiv- und Notfallmedizin - Leiter der Arbeitsgruppe Paediatric Life Support des German Resuscitation Councils (GRC) - Mitglied Paediatric science and educational committee (SEC) des European Resuscitation Councils (ERC) - Vorstandsmitglied der Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin (GNPI), Wissenschaftliche Tätigkeit: Optimierung der Versorgungsqualität kritisch kranker Kinder, pädiatrische Reanimation, Kinderintensivmedizin, Klinische Tätigkeit: Oberarzt interdisziplinäre Kinderintensivstation (100%), Beteiligung an Fort-/Ausbildung: PAEDSIM e.v. ◆Teamtraining für Kindernotfälle (pädiatrische Simulationskurse), Persönliche Beziehung: nein	COI: keine: keine
Iannizzi, Claire	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: Methodische Expertise, Meta-Analyen, systematische Übersichtsarbeiten	COI: keine: keine
Prof. Dr. Janssens, Uwe	Keine	Keine	Keine	Keine	Keine	Keine, Nein	Mitglied: Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin; Generalsekretär, Mitglied: Deutsche Gesellschaft für interdisziplinäre Intensivmedizin und Notfallmedizin (DIVI); Präsident / PAst Präsident / Generalsekretär, Mitglied: Deutsche Gesellschaft für Innere Medizin; Mitglied, Mitglied: Deutsche Gesellschaft für Kardiologie; Mitglied, Wissenschaftliche Tätigkeit: Intensivmedizin; Ethik, Klinische Tätigkeit: Kardiologie/Innere	COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							Medizin/Intensivmedizin, Beteiligung an Fort-/Ausbildung: DIVI/DGIIN/DGIM, Persönliche Beziehung: keine	
Dr. Jarczak, Dominik	nein	nein	nein	nein	nein	nein	Mitglied: Mitglied: DGIIN, DIVI, Wissenschaftliche Tätigkeit: nein, Klinische Tätigkeit: nein, Beteiligung an Fort-/Ausbildung: nein, Persönliche Beziehung: nein	COI: keine: keine
Prof. Dr. Karagiannidis, Christian	Nein	Bayer AG , Xenios	Nein	Nein	Nein	Nein	Mitglied: Präsident DGIIN	Extrakorporale CO2 Elimination, Pegyliertes Adrenomedullin bei ARDS COI: moderat: Stimmenthaltung
Dr. Kersten, Alexander	Jafron Biomedical	Gilead	Edwards, Sedana Medical, Astra-Zeneca	Nein	Jafron Biomedical	Nein	Mitglied: DGK/ESC, Mitglied: DGIIN, Mitglied: DIVI, Mitglied: ESICM, Wissenschaftliche Tätigkeit: Sepsis, ARDS, Klinische Tätigkeit: Intensivmedizin Kardiologie, Pneumologie, ECMO, Persönliche Beziehung: n/a	Advisoryboardtätigkeit Medikamentöse Therapie Remdesivir, Vortragstätigkeit für Astra Zeneca COI: moderat: COVID-19 Impfung - Einschränkung von Leitungsfunktion
Prof. Dr. med. Kluge, Stefan	Nein, Nein	Fresenius, Gilead, MSD, Pfizer, ADVITOS	Biotest, Fresenius , Gilead, MSD, Pfizer, Zoll, Daiichi Sankyo, Mitsubishi Tanabe Pharma , Shionogi	Nein	Daiichi Sankyo, Cytosorbents	Nein	Nein	Advisory-Board-Tätigkeit Medikamentöse Therapie, ggf Prophylaxe: Remdesivir, Paxlovid, Studienverantwortung für Antikoagulation Medikation/ggf. Prophylaxe COI: moderat: Stimmenthaltung
PD Dr. Krawczyk, Marcin	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: Hapatologie, Genetik, Klinische Tätigkeit: Gastroenterologie, Hepatologie	COI: keine: keine Interessenerklärung zur Nachbearbeitung COI: noch nicht bewertet: keine
Kreuzberger, Nina	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: keine, Wissenschaftliche Tätigkeit: systematische Reviews Hämatologie, Onkologie und COVID-19; Leitlinienkoordination (Hodgkin Lymphom), Klinische Tätigkeit: keine, Beteiligung an Fort-/Ausbildung: keine, Persönliche Beziehung: keine	COI: keine: keine

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Prof. Dr. Langer, Florian	LEO Pharma , Aspen	LEO Pharma, Bristol-Myers Squibb, Pfizer, Bayer, CSL Behring, SOBI, Roche, BioMarin, Chugai, Shire/Takeda, Alexion, Mitsubishi Tanabe Pharma , AstraZeneca, BioNTech	LEO Pharma, Aspen , Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Bayer, SOBI, Grifols, Shire/Takeda, Alexion, Werfen	Nein	Nein	Keine	Mitglied: Sekretär im Vorstand der Gesellschaft für Thrombose- und Hämostaseforschung (GTH) e.V. , Mitglied: Mitglied der Deutschen Gesellschaft für Hämatologie und Onkologie (DGHO) e.V. , Mitglied: Mitglied der Gesellschaft für Thrombose- und Hämostaseforschung (GTH) e.V. , Mitglied: Mitglied der International Society on Thrombosis and Haemostasis (ISTH) , Mitglied: Mitglied im Berufsverband der Deutschen Hämostaseologen (BDDH) e.V. , Mitglied: Mitglied in der Interessengemeinschaft Hämophiler (IGH) e.V. , Mitglied: Mitglied in der Deutschen Hämophiliegesellschaft (DHG) e.V. , Wissenschaftliche Tätigkeit: Grundlagenwissenschaftliche und klinische Originalpublikationen und Übersichtsarbeiten zu den Themen Thrombose, Hämostase und Vaskuläre Biologie; Co-Autor der GTH Empfehlungen zur Thromboseprophylaxe bei COVID-19 , Klinische Tätigkeit: Leiter der Gerinnungsambulanz und des Hämophiliezentrums am UKE, hämostaseologischer Konsiliardienst , Beteiligung an Fort-/Ausbildung: Ausrichter (wissenschaftliche Leitung) des jährlich stattfindenden Eppendorfer Gerinnungssymposiums, Co-Kongresspräsident der GTH-Jahrestagung in Bremen 2020 , Persönliche Beziehung: Keine	Antikoagulation mit Faktor Xa-Hemmern COI: moderat: Stimmenthaltung Prophylaktische und therapeutische orale Antikoagulation/Antikoagulation mit niedermolekularen Heparinen. COI: moderat: Stimmenthaltung
Dr. Malin, Jakob	MAPLE Health Group, MAPLE Health Group	ATRIVA Therapeutics GmbH, Gilead Sciences, Astra Zeneca, Gilead Sciences, Gilead Sciences, Astra Zeneca, Astra Zeneca, Gilead Sciences	Gilead Sciences, Janssen Cilag, Gilead Sciences, Gilead Sciences	Nein	NIAID / NIH, NIAID/NIH	keine	Mitglied: Deutsche Gesellschaft für Innere Medizin Deutsche Gesellschaft für Infektiologie, Wissenschaftliche Tätigkeit: Therapieansätze bei COVID-19 Antimikrobielle Effekte von small molecule Lipid II Binders HIV , Klinische Tätigkeit: Klinische Infektiologie , Beteiligung an Fort-/Ausbildung: nein,	Medikamentöse Therapie von COVID-19: Remdesivir, Medikamente von Janssen Cilag, Impfstoff (Astra Zeneca) COI: moderat: Stimmenthaltung

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							Persönliche Beziehung: nein	
Prof. Dr. med. Marx, Gernot	BBraun Melsungen AG, Adrenomed, 4TEEN4	Nein	Nein	Nein	Nein	Clinomic (Gründer)	Mitglied: DIVI (Präsident elct, Präsident), DGAI (Mitglied des engeren Präsidiums, DG Telemed (Vorstandsvorsitzender), Wissenschaftliche Tätigkeit: Sepsis, Volumentherapie, Telemedizin	Kein Themenbezug zur Leitlinie COI: keine: keine
Monsef, Ina	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Prof. Dr. Müller, Oliver	Europäische Kommission, Schweizer Nationalfonds (SNF), Deutsche Forschungsgemeinschaft (DFG)	Pfizer/BMS, Bayer	Pfizer/BMS, Bayer, Novartis, Daiichi-Sankyo, Berlin-Chemie	Servier	Rheacell, Anthos Therapeutics	Dinaqor AG	Mitglied: Deutsche Gesellschaft für Angiologie, Vorstandsmitglied , Mitglied: Deutsche Gesellschaft für Kardiologie, Nukleusmitglied AG2 und AG40, Mitglied: Gesellschaft für Thrombose und Hämostaseforschung, Mitglied ohne spez. Funktion, Wissenschaftliche Tätigkeit: pAVK, Wissenschaftliche Tätigkeit: Thrombose und Gerinnungsstörungen, Marfan-Syndrom, Kardiomyopathien, Herzinsuffizienz, Klinische Tätigkeit: Angiologie, Herzinsuffizienz	Vortrags- und Advisoryboard-Tätigkeit für Pharmazeutische Industrie in Bezug auf Antikoagulation: Prophylaxe/Therapie COI: moderat: Stimmenthaltung
Dr. med. Nehls, Wiebke	Nein	Nein	verschiedene Bildungsakademien im Palliativbereich	Nein	Nein	Nein	Mitglied: Deutsche Gesellschaft für Palliativmedizin - Vorstandsmitglied (Mandatsträger für diverse LL) , Wissenschaftliche Tätigkeit: verschiedene pneumologische und palliativmed. Fachzeitschriften, Klinische Tätigkeit: Palliativmedizin und Geriatrie	COI: keine: keine
Dr. Nothacker, Monika	keine bezahlten Tätigkeiten	Versorgungsforschungsprojekt INDiQ (Messung von Indikationsqualität aus Routinedaten - Vergütung wie angegeben Steuergruppe Nationaler	Berlin School of Public Health	Nein	German Cancer Aid , Network University Medicine COVID-19, BMG, Network University Medicine for Pandemic Preparedness 2.0 , G-BA Innovationfund	no	Mitglied: - German Network Evidence Based Medicine (member) - German Cancer Society (member until 12/2020) - Guidelines International Network/GRADE Working Group (member), Wissenschaftliche Tätigkeit: Guidelines and Guideline Methodology, Methodology of guidelines based performance measures/quality indicators, Klinische Tätigkeit: no clinical activity or clinical research, Beteiligung an Fort-/Ausbildung: Guideline seminars within Curriculum for guideline developers in	COI: keine: keine

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		Krebsplan keine Vergütung, IQTIG					Germany , Persönliche Beziehung: no	
Prof. Dr. Pfeifer, Michael	Charite Berlin	Boehringer Ingelheim	Boehringer Astra Glaxo Novartis	Nein	Boehringer Janssens	Nein	Mitglied: DGP DGIM DGK, BDI, BDP, ERS, ATS , Wissenschaftliche Tätigkeit: Interstitielle Lungenerrkrankungen, pulmoanle Hypertonie, COPD , Klinische Tätigkeit: Pneumologie und Intensivmedizin , Beteiligung an Fort-/Ausbildung: Pneumoupdate Jahrestagung DGP und DGIM Pneumologisches Kolloqium Regensburg , Persönliche Beziehung: nein	COI: keine: keine
Prof. Dr. Rabe, Klaus F.	Sanofi Regeneron, Boehringer Ingelheim	AstraZeneca, GSK	Novartis, Chiesi Pharmaceuticals, Roche Pharma, Orion Menarini, Berlin Chemie	Astra Zeneca	Nein, TU München	Nein	Mitglied: DGP, wiss. Beirat, Wissenschaftliche Tätigkeit: Atemwegserkrankungen, Klinische Tätigkeit: Pneumologie	Berater-/Gutachtertätigkeit für Firmen, die Covid-19 Impfstoffe herstellen. Öffentlich geförderte Forschung für die Therapie von COVID-19 ausgelösten Lungenschäden. Kein aktueller thematischer Bezug COI: keine: keine
Reis, Stefanie	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Dr. med. Schorrlepp, Marcel	coliquio GmbH, colquio GmbH	wikoneckt GmbH fresh up Hausarzt Medizin	wikoneckt GmbH fresh up Hausarzt Medizin	keine	keine	keine	Mitglied: DGIM: Sprecher AG Hausärztliche Internisten BDI: Mitglied, Klinische Tätigkeit: Hausärtlicher Internist, Beteiligung an Fort-/Ausbildung: keine, Persönliche Beziehung: keine	COI: keine: keine
Prof. Dr. Schälte, Gereon	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: DGAI BDA TREMA ESA NAEMT, Wissenschaftliche Tätigkeit: Inflammation Biomarker Airwaymanagement Empfehlungen Atemwegsmanagement bei CoViD-19 Notfallmedizin, Klinische Tätigkeit:	COI: keine: keine

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							Kardioanästhesie Kinderanästhesie ECMO Notfallmedizin	
Prof. Dr. med. Skoetz, Nicole	Cochrane, Senior Editor	Scientific Committee Cochrane (bis 03.2023), Editorial Board, GRADE Guidance Group (ab 01.2023)	AWMF	Nein	BMBF, Deutsche Krebshilfe, WHO, Cochrane, DFG, BMG, g-BA	Nein	Mitglied: EbM Netzwerk, Vorstand seit 03.2023 (vorher Mitglied) DGHO, Mitglied WHO Collaborating Center, Leitung (ab 01.2023) GRADE Guidance Group Member (seit 02.2023), vorher Mitglied, Wissenschaftliche Tätigkeit: Systematic Reviews, Cochrane Reviews, GRADE Methodik, Methodik living reviews	COI: keine: keine
Prof. Dr. med. Specker, Christof	Gemeinsamer Bundesausschuss	AbbVie, Boehringer, Novartis, Otsuka, GSK	AbbVie, Boehringer, GSK, Lilly, MSD, Novartis, Otsuka, Pfizer, Sanofi, Takeda, StreamedUP, AstraZeneca, Medac, Abbvie, Hexal, Rheumaakademie, Rheumaakademie, Lilly	KOOP. RHEUMAZ.R.-R.EV, MED UPDATE, WORTREICH Verlag	Nein	Nein	Mitglied: DGRh BDI RHZ-Rhein-Ruhr G-BA Fachgutachter, Wissenschaftliche Tätigkeit: entzündlich-rheumatische Erkrankungen, immunologische Systemerkrankungen, eHEalth, Klinische Tätigkeit: Rheumatologie klinische Immunologie, Beteiligung an Fort-/Ausbildung: DGRh, Universitäten Düsseldorf und Essen, DGIM, BDI	Vortragstätigkeiten für Firmen, die COVID-19 Medikamente herstellen. COI: gering: Limitierung von Leitungsfunktion
PD Dr. Spinner, Christoph	Nein	AstraZeneca, BBraun, Gilead Sciences, GSK, MSD, Janssen-Cilag, Eli Lilly, Molecular Partners, Pifzer, Roche, Formycon, SOBI	AstraZeneca, BBraun, Gilead Sciences, GSK, MSD, Janssen-Cilag, Eli Lilly, Molecular Partners, Pifzer, Roche, Formycon, SOBI	Gilead Sciences	AstraZeneca, BBraun, Gilead Sciences, GSK, MSD, Janssen-Cilag, Eli Lilly, Molecular Partners, Pifzer, Roche, Formycon, SOBI	Keine	Mitglied: Deutsche AIDS-Gesellschaft, Deutsche Gesellschaft für Infektiologie	Advisory Board Tätigkeit für multiple Firmen, die COVID-19 Medikamente herstellen. Studienverantwortung für industriefinanzierte Studien zu medikamentöser COVID-19 Therapie COI: moderat: Stimmenthaltung
Dr. Stegemann, Miriam	Nein	Nein	Deutsche Gesellschaft für Infektiologie, Akademie für Infektionsmedizin, Sandoz	Fachjournale, Autor von Lehrbuch	Nein	Nein	Mitglied: Mitgliedschaft in Fachgesellschaften: Deutsche Gesellschaft für Infektiologie, Deutsche Gesellschaft für Innere Medizin, Deutsche Gesellschaft für Tropenmedizin, European Society of Clinical Microbiology and Infectious Diseases,	COI: keine: keine

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							Wissenschaftliche Tätigkeit: https://www.ncbi.nlm.nih.gov/myncbi/1-eYs7zxJilQ8/bibliography/public/ Antibiotic Stewardship, Infektionsmedizin, Global Health, Klinische Tätigkeit: Antibiotic Stewardship, Infektiologie, Beteiligung an Fort-/Ausbildung: Beteiligung an Fort-/Ausbildung: DGI-Fortbildungen, DGI-Kongress, DGIM-Kongress, Internistisches Facharzttraining, Beteiligung an Erstellung von Therapiehinweisen FG COVRIIN (RKI), Beteiligung an Erstellung der „Living WHO guideline on drugs to prevent covid-19“ und „Living WHO guideline on drugs for covid-19”	
Prof. Dr. Trummer, Georg	Medela AG	Nein	Nein	Nein	Nein	Resuscitec GmbH	Mitglied: Schriftführer GRC	COI: keine: keine
PD Dr. rer. nat. Weibel, Stephanie	Nein	Nein	Universität Marburg	Nein	NUM CEOsys, GBA, Innofond, S3Cov19live	Nein	Mitglied: Cochrane Anaesthesia, Content Editor, Wissenschaftliche Tätigkeit: Systemtische Übersichtsarbeiten, Meta-Analysen, Cochrane Reviews im Bereich COVID-19, perioperative Medizin und Anästhesie, Beteiligung an Fort-/Ausbildung: Workshops zu Meta-Analysen	öffentlich geförderte Evidenzsynthesen zu COVID-19 COI: keine: keine
Prof. Dr. Weinmann-Menke, Julia	Deutsche Forschungsgesellschaft (DFG	Boehringer Ingelheim, Bayer, Novartis, Chiesi, Novartis, AstraZeneca, GSK, Osuka	Vifor, GSK, medupdate, medupdate, Chiesi, Osuka	GSK	Novartis Boerhinger-Ingelheim GSK Morphopsys Chiesi Astellas	Nein	Mitglied: Deutsche Gesellschaft für Nephrologie, Vorsitzende der Kommission Leitlinien, Pressesprecherin, Mitglied: Deutsche Gesellschaft für Innere Medizin, gewähltes Mitglied des Wissenschaftlichen Beirats, Wissenschaftliche Tätigkeit: Pathogenese der Lupusnephritis NTX-immunologische Mechanismen nach NTX Vaskulitiden (Pathogenese und Therapie), Klinische Tätigkeit: Systemischer Lupus erythematodes Nierentransplantation Glomerulonephritiden chronische Niereninsiffizienz	industriefinanzierte Studien und Advisoryboard-Tätigkeit sowie Vorträge im Bereich Nierenerkrankungen, kein unmittelbarer thematischer Bezug zu COVID-19 Therapie COI: keine: keine
Prof. Dr. Welte,	WHO Solidarity	AstraZeneca,	AstraZeneca, Bayer,	Nein	Nein	Nein	Mitglied: Past Präsident European	Advisory Board TÄtigkeit,

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Tobias	Trial Steering Committee + BMBF Förderung, Netzwerk Universitätsmedizin (NUM) BMBF Förderung + post COVID Förderung des Landes Niedersachsen, Verschiedene Spenden (Privatleute, Hannover Rück), klinische Studie zu COVID19 mit Biotest, Roche, Novartis, AstraZeneca, Immunic, Boehringer, Dompe, BMG Studie COMET (Rekonvaleszentenplasma, inhaled GI Hope	Bayer, Boehringer, GSK, Immunic, Janssens, Novartis, Pfizer, Roche	Boehringer, Chiesi, MSD, Novartis, Pfizer, Roche				Respiratory Society + Mitglied der Task Force COVID19, Mitglied: Past Präsident Forum of Internationl Respiratory Societies, Mitglied: Treasurer Biomed Alliance, Mitglied: Past Präsident Paul Ehrlich Gesellschaft, Wissenschaftliche Tätigkeit: pulmonale Infektionen, Klinische Tätigkeit: Pneumologie, Infektiologie und internisstische Intensivmedizin mit eineem SChwerpunkt für pulmonale Infektionen, Beteiligung an Fort-/Ausbildung: Stiftungsratvorsitzender CAPNETZ Kuratoriumsvorsitzender Deutsche Lungenstiftung und Deutsche Sepsisstiftung Kuratorium der Novartis Stiftung	industriefinanizierte Studien zu COVID-19 Medikation COI: moderat: Stimmenthaltung
PD Dr. Westhoff, Michael	Nein	Nein	Fa. Löwenstein Medical	Nein	Nein	Nein	Mitglied: Deutsche Gesellschaft für Pneumologie DIVI European Respiratory Society American College of Chest Physicians, Wissenschaftliche Tätigkeit: Aussatemluftforschung Beatmungsmedizin Schlafmedizin Intensivmedizin, Klinische Tätigkeit: Beatmungsmedizin Schlafmedizin Intensivmedizin, Beteiligung an Fort-/Ausbildung: Ausbildung	industriefinanzierte Vorträge über nichtinvasive Beatmung bis 2020. COI: keine: keine

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							Atmungstherapeuten Vorlesungen an Uni Witten-Herdecke Kongresse DIVI, DGSM, DGP	
Zorger, Ana-Mihaela	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: Onkologie, Infektiologie, Leitlinienerstellung und Implementierung	COI: keine: keine

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