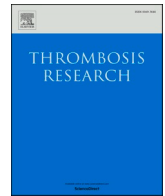




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# Anticoagulation in COVID-19 patients – An updated systematic review and meta-analysis

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## ABSTRACT

**Background:** Thromboembolic events are common complications of COVID-19. Clinical study results on safety and efficacy of anticoagulation in COVID-19 are controversial.

**Material and methods:** This report updates our systematic review and random-effects meta-analysis on randomized controlled trials (RCTs) comparing standard prophylactic anticoagulation and intermediate or therapeutic anticoagulation in COVID-19 patients. We searched eligible studies for the update up to 4 February 2022 by weekly monitoring of RCTs in the Cochrane COVID-19 Study Register. Certainty of evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

**Results:** For this update we included five new trials; a total of 13 RCTs with 7364 patients. Certainty of evidence was very low to low. We are uncertain whether low-dose prophylactic anticoagulation is favoured over placebo or no anticoagulation in the outpatient- or post-discharge-setting. In hospitalized patients with moderate and severe COVID-19, intermediate-dose anticoagulation may have little or no effect on thrombotic events or death (RR 1.03, 95 % CI 0.86–1.24), but may increase severe bleeding non-significantly (RR 1.48, 95 % CI 0.53–4.15). Therapeutic-dose anticoagulation may decrease thrombotic events or deaths in hospitalized patients with moderate COVID-19 (RR 0.64, 95 % CI 0.38–1.07; fixed-effect model RR 0.72, 95 % CI 0.57–0.91), but may have little or no effect in patients with severe disease (RR 0.98, 95 % CI 0.86–1.12). With therapeutic-dose anticoagulation, the risk of major bleeding may increase regardless of COVID-19 severity (RR 1.78, 95 % CI 1.15–2.74).

**Conclusions:** Hospitalized, moderately ill COVID-19 patients may benefit from therapeutic-dose anticoagulation, while critically ill patients may not. Risk of major bleeding must be considered.

## 1. Introduction

In its severe form, COVID-19, the clinical manifestation of SARS-CoV-2 infection, is characterized by lung failure and high rates of thromboembolic complications [1]. Given the procoagulant status and increased thrombotic risk of COVID-19 patients, modified empirical dosage regimens have been used in many places to treat COVID-19 patients and the different modes of anticoagulation were consecutively subject of several clinical trials. However, the question whether early prophylactic anticoagulation in outpatient settings or intensified prophylactic intermediate-dose or therapeutic anticoagulation in inpatient settings can reduce the risk of disease progression without increasing the

risk of adverse events remains unanswered [2]. At the same time, it is still unclear to what extent there is an increased risk of thromboembolism even after hospital discharge, and whether this can be prevented with appropriate anticoagulation [3,4]. We therefore conducted a systematic review with meta-analysis of the available randomized controlled trials (RCTs) to determine the safety and efficacy of anticoagulation at any dosage with standard low-dose prophylactic anticoagulation or no prophylaxis in COVID-19 patients regardless of disease severity and treatment setting. The present meta-analyses informed the German AWMF-S2e guideline for outpatient COVID-19 patients and the AWMF-S3 guideline for the inpatient therapy of COVID-19 patients [5,6].

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## 2. Materials and methods

This report is an update of a systematic review published in December 2021 [7]. The systematic review protocol was registered with PROSPERO on January 21, 2021 (CRD42021229228). The question is continuously updated in the sense of a ‘living systematic review’. A detailed German version of the updated systematic review is accepted for publication at a German journal. This English version addresses the worldwide community of critical care specialists, primary care specialists and other healthcare personnel dealing with COVID-19 patients.

### 2.1. Inclusion criteria for studies in this systematic review

We included RCTs that compared prophylactic anticoagulation at any dosage with anticoagulation at a different dosage or with no anticoagulation in outpatients, hospitalized, or post-discharge patients with confirmed SARS-CoV-2 infection. All studies were considered for inclusion in the analysis, regardless of the severity of the disease, age, gender, and ethnicity of the study participants. COVID-19 severity of study participants was, if possible, classified according to the definition of the WHO ‘clinical progression scale’ (WHO 0 to 10): outpatient, mildly ill COVID-19 patients (WHO 1–3); inpatient, moderately ill COVID-19 patients (WHO 4–5) and intensive care, seriously ill COVID-19 patients (WHO 6–9) [8]. Separate meta-analyses were performed and reported for patients in outpatient, inpatient and post-discharge settings as well as according to the included severity of COVID-19 disease. There were no restrictions on the type of pharmacological anticoagulation used. All heparinoids, vitamin K antagonists and direct anticoagulants (factor Xa inhibitors and direct thrombin inhibitors) were considered regardless of dosage and administration regimen. Dosage regimens of anticoagulants have been divided into low-dose, intermediate-dose or therapeutic anticoagulation according to the definition of the studies and the general drug recommendations summarized in Table S1 [9]. Standard anticoagulation in the control arm in COVID-19 inpatients included both low-dose anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH), as well as intermediate-dose anticoagulation regimens. The latter were amended in the course of the pandemic by adjustments to national therapy guidelines (i.e. in the United Kingdom) and formed part of the standard treatment [10]. We therefore expanded our definition of standard prophylactic anticoagulation to include low-dose and intermediate-dose anticoagulation regimens and created the following comparisons for meta-analyses:

- Therapeutic anticoagulation versus standard prophylactic anticoagulation (low-dose or intermediate-dose anticoagulation)
- Intermediate-dose anticoagulation versus standard prophylactic anticoagulation (low-dose anticoagulation)
- Standard prophylactic anticoagulation (low-dose) versus no prophylaxis or placebo

The evaluation of the efficacy of anticoagulation in hospitalized COVID-19 patients was carried out by recording mortality, worsening or improvement in clinical status, thrombotic events with and without death and quality of life (day 28 or longest follow-up). In COVID-19 outpatients, the combined outcome of hospitalization or death was supplemented. For this review update, no new data for the outcomes on clinical worsening or improvement of COVID-19 inpatients were available. The outcomes were therefore not included in this update. The safety of interventions was assessed by recording serious adverse events (SAEs), adverse events (AEs) and severe bleeding (according to ISTH criteria [11]) during the study period. In post-discharge patients, safety-relevant outcomes were supplemented by clinically relevant but non-severe bleedings and other bleeding according to the ISTH criteria [11].

### 2.2. Search methods

A systematic search of the Cochrane COVID-19 Study Register (consisting of MEDLINE, Embase, [ClinicalTrials.gov](https://www.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), the COVID-19 Global literature on coronavirus disease Database of the WHO and ResearchSquare, took place up to and including 24 September 2021. The subsequent period up to and including 4 February 2022 was covered by weekly RCT monitoring in the Cochrane COVID-19 Study Registry. The search strategies are reported in the supplement.

Two review authors independently examined titles and abstracts of all entries and the full texts of potentially relevant studies for their inclusion in this review. The study selection process is reported in a flowchart and follows PRISMA guidelines [12].

### 2.3. Data collection and analysis

Two review authors extracted data independently using a custom data extraction sheet according to Cochrane guidelines [13].

The Risk of Bias 2 (RoB 2) tool was used to assess the bias risk of study results that contributed information to the specified outcomes [14]. The RoB 2 ratings per study outcome were independently evaluated by two review authors according to Cochrane’s recommendations and for the following domains [15]: selection bias, performance bias, detection bias, attrition bias, and selective reporting bias. For each domain and all domains together (overall bias risk), the bias risk of a study result was classified as low, some concerns or high.

For dichotomous outcomes, the number of events and the total number of participants in both the intervention and control groups were recorded. The relative risk (RR) with 95 % confidence interval (CI) was used as an effect measure.

Meta-analyses were carried out using the Mantel Haenszel method under a random effects model [16]. Random effects meta-analyses were performed with RevMan Web 3.11.1 and R (package ‘meta’, version 5.2–0) [17,18]. Fixed-effects meta-analyses and exclusion of studies with high risk of bias were carried out as sensitivity analyses. For hospitalized individuals with moderate or severe COVID-19, subgroup analyses were performed according to the disease severity at baseline (moderate (WHO 4 to 5) versus severe COVID-19 disease (WHO 6 to 9) as defined by the WHO clinical progression scale [8]). Studies that only provided data for a mixed population of moderately and severely ill participants were included in the subgroup ‘‘moderate to severe COVID-19 (WHO 4 to 9)’. Statistical heterogeneity was defined as  $P < 0.1$  for the Chi<sup>2</sup> test for heterogeneity or an I<sup>2</sup> statistic  $\geq 50$  %.

Quality of the evidence was assessed according to the GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluations) [19]. GRADE assesses the trustworthiness (certainty) of the evidence in four levels: very low, low, moderate, and high. Certainty of evidence was downgraded by one or two levels for risk of bias, imprecision, inconsistency (heterogeneity), indirectness (indirect study results) and publication bias.

## 3. Results

The search strategy identified a total of 1153 entries in registers and databases, two more entries were identified from other sources. After removal of duplicates, 1076 titles and abstracts were viewed, of which 942 were deemed irrelevant. The screening of 134 full texts resulted in 20 studies with a total of 32 entries that were excluded and 59 included studies with 102 entries. Of these, 50 studies (66 entries) had not yet been completed at the time of the search. Nine studies (36 entries) were included in this systematic review from the search. Monitoring of the RCT database from 25 September 2021 onwards provided a further 14 entries up to and including 4 February 2022, four of which belonged to

studies not yet completed or published in full text (Letter). Four studies (10 entries) were included. The search is summarized in a PRISMA flowchart (Fig. S1).

### 3.1. Characteristics of included studies

Thirteen RCTs with a total of 7364 randomized patients, investigating anticoagulation in COVID-19 patients were included in this review (Fig. 1, Table 1). ACTIV-4B and Ananworanich-2021 studied outpatients with symptomatic COVID-19 disease (WHO 2–3) [20,21]. The ATTACC, ACTIV-4a, REMAP-CAP platform study (Lawler-2021) and the RAPID study predominantly examined moderately ill COVID-19 patients (WHO 4–5) [22,23]. Three studies, the HESA-COVID study [24], the platform study ATTACC, ACTIV-4a, REMAP-CAP (Golligher-2021) [25] and Oliynyk-2021 [26] recruited patients with severe COVID-19 disease (WHO ≥6) [24–26]. A total of five studies examined a mixed study population (WHO 4–9) [27–32]. For three of them, HEP-COVID, INSPIRATION and X-COVID, data could be evaluated separately according to disease severity; for Perepu-2021 and ACTION splitting into moderate and severe COVID-19 at baseline was not possible. MICHELLE reported data for post-discharge patients who had been hospitalized due to COVID-19 infection [33].

Seven studies used markers of hypercoagulability and coagulopathy as inclusion criteria [23,24,26,29,31–33]. Three studies reported on thrombosis risk factors of the enrolled patients in the tables describing the study collective [22,25,28], three studies did not provide information [20,21,30].

MICHELLE, Ananworanich-2021 and ACTIV-4B investigated low-dose oral anticoagulation (rivaroxaban 10 mg once daily and apixaban 2.5 mg twice daily) compared to no anticoagulation [33] and placebo [20,21] respectively. ACTIV-4B also investigated a therapeutic dosage, which was not included in our meta-analysis [21]. Three studies, INSPIRATION, Perepu-2021 and X-COVID, examined intermediate-dose anticoagulation (enoxaparin 1 mg/kg OD or 40 mg BID) compared to standard prophylactic anticoagulation [27,28,30,32]. All other studies looked at therapeutic anticoagulation versus standard prophylactic anticoagulation [22–26,29,31]. Five studies defined standard prophylactic anticoagulation as low-dose anticoagulation [2,23,24,26,29,31] while new national treatment guidelines in the UK resulted in 26.5 % and 51.7 % of participants in the control groups of the large platform studies ATTAC, ACTIV-4a and REMAP-CAP receiving intermediate-dose anticoagulation [2,22,25]. The type and dosage of intervention and control treatment of the respective studies are listed in Table 1.

All studies reported relevant outcomes for this systematic review. The time period for outcomes collection was 28–30 days in the majority of studies. MICHELLE examined a period of 35 days [33] ACTIV-4B 45 days [21] and INSPIRATION reported on the 90-day mortality [27]. No study reported data on quality of life.

### 3.2. Risk of bias

In total, the thirteen studies contributed 48 study results to 23

outcomes reported here, seven outcomes for the comparison “COVID-19 outpatients: standard prophylactic anticoagulation versus placebo”, five for the comparison “COVID-19 inpatients: intermediate-dose anticoagulation versus standard prophylactic anticoagulation”, five for the comparison “COVID-19 inpatients: therapeutic anticoagulation versus standard prophylactic anticoagulation” and six for the comparison “post-discharge COVID-19 patients: standard prophylactic anticoagulation versus no prophylaxis.” One third of the 48 study results (33.3 %) were rated as “overall low risk of bias”, 54.2 % as “some concerns about the overall bias risk” and 12.5 % as “overall high risk of bias”.

COVID-19 outpatients: standard prophylactic anticoagulation versus placebo

Ananworanich-2021 [20] and ACTIV-4B [21] were included in the comparison of standard prophylactic anticoagulation with low-dose anticoagulation versus placebo in the outpatient setting (meta-analyses in Table S2). We are uncertain whether standard prophylactic anticoagulation compared to placebo treatment increases or decreases all-cause mortality (RR 0.33, 95 % CI 0.01–8.07, 778 patients, 2 studies), hospitalization rate or death (RR 0.43, 95 % CI 0.11–1.64, 444 patients, 1 study), hospitalization rate due to cardiopulmonary events or death (RR 0.62, 95 % CI 0.21–1.86, 329 patients, 1 study), any thrombotic events (RR 0.33, 95 % CI 0.01–8.07, 329 patients, 1 study) or serious adverse events (RR 0.30, 95 % CI 0.06–1.43, 449 patients, 1 study). Standard prophylactic anticoagulation may increase improvement of clinical status assessed as the rate of asymptomatic participants slightly compared to placebo (RR 1.16, 95 % CI 0.97–1.38, 444 participants, 1 study). Standard prophylactic anticoagulation may have little or no difference on the risk of adverse events compared to placebo (RR 1.02, 95 % CI 0.67–1.56, 449 patients, 1 study). Evidence certainty for adverse events and clinical improvement was considered low. For all other outcomes, evidence certainty was rated as very low (Table S2).

### 3.3. COVID-19 inpatients: intermediate-dose anticoagulation versus standard prophylactic anticoagulation (low-dose anticoagulation)

Intermediate-dose anticoagulation may have little or no effect on mortality after 30 days (RR 1.02, 95 % CI 0.75–1.40, 913 participants, 3 studies, moderate-certainty evidence, Table 2 and fig. S2) and after 90 days (RR 1.07, 95 % CI 0.89–1.28, 590 participants, 1 study, low-certainty evidence, Table 2), and the occurrence of venous thrombotic events or deaths (RR 1.02, 95 % CI 0.85–1.23, 764 participants, 2 studies, low-certainty evidence, Table 2 and Fig. S2). Intermediate-dose anticoagulation resulted in a non-significant increase in the risk of major bleeding compared to standard prophylactic anticoagulation (RR 1.43, 95 % CI 0.54–3.74, 913 participants, 3 studies, low-certainty evidence, Table 2). Certainty of evidence was downgraded once for the outcome 30-day mortality due to imprecision, and twice for all other outcomes due to risk of bias and imprecision.

Mildly ill Outpatients WHO 1-3	Moderately ill Inpatients WHO 4-5	Severely ill Intensive Care WHO 6-9	Recovered Post-discharge
Ananworanich-2021 ACTIV-4B	INSPIRATION X-COVID HEP-COVID ATTACC, ACTIV-4a, REMAP-CAP (Lawler-2021) RAPID	INSPIRATION X-COVID HEP-COVID ATTACC, ACTIV-4a, REMAP-CAP (Golligher-2021) Oliynyk-2021 HESA-COVID	MICHELLE
	Perepu-2021 ACTION		

Fig. 1. Classification of included studies according to COVID-19 severity of participants at randomization (WHO clinical progression scale, WHO 0 to 10).

**Table 1**  
Characteristics of included studies.

Study reference	Study design	Randomized patients (n)	Patient status	Intervention	Comparator	Outcomes
Ananworanich-2021 [20]	RCT, double-blind, 14 centers in the U.S. Recruitment: 08/2020–02/2021 Up to 10 days after positive SARS-CoV-2 test	497	Outpatient WHO 2–3 At least 1 risk factor for severe course Thrombosis risk factors <sup>A</sup> : NA COVID-19 risk factors <sup>B</sup> : 3	Low dose <sup>C</sup> : Rivaroxaban 10 mg OD for 21 days	Placebo	35-Day mortality, hospitalization within 28 days, severe adverse events within 35 days, adverse events within 35 days, severe bleeding within 35 days
ACTIV 4B, Connors-2021 [21]	RCT, double-blind, 4 study arms, 52 centers in the U.S. Recruitment: 09/2020–06/2021 Start of therapy: NA	657	Outpatient WHO 2–3 Thrombosis risk factors <sup>A</sup> : NA COVID-19 risk factors <sup>B</sup> : 3	Low dose <sup>C</sup> : Apixaban 2.5 mg BID for 45 days	Placebo	45-Day mortality, hospitalization due to cardiovascular events or death within 45 days, thrombotic events within 45 days, severe bleeding within 45 days
INSPIRATION, Sadeghipour-2021 [27,28]	RCT, open-label, 10 Centers in Iran Recruitment: 07/2020–11/2020 Start of therapy: NA	600	Hospitalized + Intensive Care Unit WHO 5–9, with 45 % WHO 5 Stratified results according to WHO 4–5 and WHO 6–9 Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 3	Intermediate dose <sup>C</sup> : Enoxaparin 1 mg/kg OD weight and CrCl adjusted, for 30 days	Low dose <sup>C</sup> : enoxaparin 40 mg OD; Weight and CrCl adjusted	30-Day mortality, 90-day mortality, venous thrombotic events, venous thrombotic events or death, major bleeding
Perepu-2021 [32]	RCT open-label, multicentric: 3 centers in the USA Recruitment: 04/2020–01/2021 Start of therapy: NA	173	Hospitalized + Intensive Care Unit and/or mod. ISTH Overt DIC Score $\geq$ 3, WHO 5–9 * no information on respiratory status reported  Thrombosis risk factors <sup>A</sup> : 2 COVID-19 risk factors <sup>B</sup> : 4	Intermediate dose <sup>C</sup> : Enoxaparin 1 mg/kg OD weight and CrCl adjusted until discharge from hospital	Low dose <sup>C</sup> : Enoxaparin 40 mg OD weight and CrCl adjusted, until discharge	30-Day mortality, venous thrombotic events, major bleeding
X-COVID, Morici-2021 [30]	RCT open-label, multicentric: 9 centers in Italy Recruitment: 04/2020–04/2021 Start of therapy: within 6–7 days after admission	186	Hospitalized + Intensive Care Unit WHO 4–7 with 61 % WHO 4–5 Stratified results according to WHO 4–5 and WHO 6–7 Thrombosis risk factors <sup>A</sup> : NA COVID-19 risk factors <sup>B</sup> : 2	Intermediate dose <sup>C</sup> : Enoxaparin 40 mg BID until discharge from the hospital	Low dose <sup>C</sup> : Enoxaparin 40 mg OD until discharge	30-Day mortality, venous thrombotic events, venous thrombotic events or deaths, major bleeding
HESACOVID, Lemos-2020 [24]	RCT open-label, uniconic: Brazil Recruitment: 05/2020–05/2021 Start of therapy: NA	20	Hospitalized + Intensive Care Unit + $\uparrow$ D-Dimer WHO $\geq$ 7 Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 4	Therapeutic dose <sup>C</sup> : Enoxaparin 1 mg/kg BID for at least 96 h and up to 14 days	Low dose <sup>C</sup> : Enoxaparin 40 mg OD, weight and CrCl adjusted	28-Day mortality, hospital mortality, thrombotic events
ACTION, Lopes-2021 [31]	RCT open-label, multicentric: 31 centers in Brazil Recruitment: 06/2020–02/2021 Start of therapy: Up to 14 days after symptom onset	614	Hospitalized + intensive care unit + $\uparrow$ D-dimer, WHO 4–9, with 85 % WHO 4–5 Thrombosis risk factors <sup>A</sup> :1 COVID-19 risk factors <sup>B</sup> : 4	Therapeutic dose <sup>C</sup> : Rivaroxaban 20 mg OD (280 patients, 90 %) for 30 days	Low dose <sup>C</sup> : Enoxaparin 40 mg OD, weight and CrCl adjusted, continued until discharge	30-Day mortality, survival until discharge from hospital (30 days), thrombotic events, thrombotic events or deaths, major bleeding
ATTACC, ACTIV-4a, REMAP-CAP, Lawler-2021 [22]	RCT open-label, Platform study: 121 centers in 9 countries Recruitment: 04/2020–01/2022 Start of therapy:	2244	Hospitalized WHO 4–5, of which 5 % WHO 6–7 Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 3	Therapeutic dose <sup>C</sup> : Enoxaparin 1 mg/kg sc minus 10 % BID, weight and CrCl adjusted (79.6 %)	Low/intermediate dose <sup>C</sup> : 78.7 %: enoxaparin, 9.6 %: dalteparin; Low dose: 71.7 %, Intermediate dose: 26.5 %	Mortality in hospital, clinical improvement: discharge without organ support, thrombotic event, thrombotic event or death, major bleeding

(continued on next page)

Table 1 (continued)

Study reference	Study design	Randomized patients (n)	Patient status	Intervention	Comparator	Outcomes
ATTAC, ACTIV-4a, REMAP-CAP, Goligher-2021 [25]	within 72 h after admission RCT open-label, Platform study: 121 centers in 9 countries Recruitment: 04/2020–01/2022 Start of therapy: Randomization within 72 h after hospital admission	1207	Intensive care unit WHO 6–9, 1.5 % WHO 4–5 Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 3	Therapeutic dose <sup>C</sup> : Enoxaparin 1 mg/kg minus 10 % BID, weight and CrCl adjusted (77.6 %)	Low/intermediate dose <sup>C</sup> : 52.1 %: enoxaparin, 32.8 %: dalteparin; Low dose: 40.4 %, Intermediate dose: 51.7 %	Mortality in hospital, thrombotic events, thrombotic events or deaths, major bleeding
RAPID, Sholzberg-2021 [23]	RCT open-label, multicentric: 28 centers in 6 countries Recruitment: 05/2020–04/2021 Start of therapy 24 h/48 h after randomization	465	Hospitalized + ↑ D-Dimer, WHO 4–5, with 6 % WHO 6 Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 3	Therapeutic dose <sup>C</sup> : Enoxaparin 1 mg/kg BID; Weight and CrCl adjusted	Low dose <sup>C</sup> : Enoxaparin 40 mg OD, weight and CrCl adjusted	28-day mortality, thrombotic events, major bleeding
HEP-COVID, Spyropoulos-2021 [29]	RCT open-label, multicentric: 12 centers in the USA Recruitment: 05/2020–05/2021 Start of therapy: Screening within 72 h from hospital admission	257	Hospitalized + ↑ D-Dimer or ISTH SIC Score ≥ 4, WHO 5–7, with 77 % WHO 5 Stratified results according to WHO 5 and WHO 6–7 Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 4	Therapeutic dose <sup>C</sup> : Enoxaparin 1 mg/kg BID or 40 mg OD/BID weight and CrCl adjusted, until discharge	Low dose <sup>C</sup> : Enoxaparin 40 mg OD/BID weight and CrCl adjusted until discharge	30-day mortality, thrombotic events, thrombotic events or deaths, major bleeding
Oliynyk-2021 [26]	RCT double-blind, unicentric: Ukraine Recruitment: 07/2020–03/2021 Start of treatment: NO	126	Intensive care unit + CAC, not intubated WHO 6 Thrombosis risk factors <sup>A</sup> : 3 COVID-19 risk factors <sup>B</sup> : 2	Therapeutic dose <sup>C</sup> : Enoxaparin: 100 Anti-Xa IU/kg BID or UFH: Initial: 80 U/kg/h i.v.; danac 18 U/kg/h until normalization of D-dimer	Low dose <sup>C</sup> : Enoxaparin 50 Anti-Xa IU/kg QD for 28 days	28-day mortality
MICHELLE, Ramacciotti-2022 [33]	RCT open-label, multi-centric: 14 centers in Brazil Recruitment: 10/2020–06/2021 Start of therapy: 24 h after hospital discharge	318	Post discharge + IMPROVE-Score ≥ 4 or 2–3 + ↑ D-Dimer Thrombosis risk factors <sup>A</sup> : 1 COVID-19 risk factors <sup>B</sup> : 3	Low dose <sup>C</sup> : Rivaroxaban 10 mg OD for 35 days	No anticoagulation	Any thrombotic event and cardiovascular death, any symptomatic venous thrombotic event or all causes, major bleeding, clinically relevant non-severe bleeding, other bleeding

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

<sup>A</sup> Thrombosis risk factors: D-dimer elevation, genetic predisposition, clinical signs of DVT/LAE, LAE/DVT more likely than other diagnoses, tachycardia (heart rate > 100/min), surgery/immobilization (at least 3 days) within the last month, Previous LAE or DVT, Hemoptysis, Malignancy (under therapy, palliative therapy or diagnosis younger than 6 months), Wells Score.

<sup>B</sup> COVID-19 risk factors [34]: Age > 50, Male, Smoker, BMI > 30, Pregnancy, Trisomy 21, Cardiovascular Disease (High Blood Pressure, Coronary Heart Disease), Chronic Lung Disease (COPD, Asthma), Chronic Kidney or Liver Disease, Neurological or Psychiatric Diseases, Diabetes Mellitus, Immunodeficiency, Cancer.

<sup>C</sup> According to study definition.

### 3.4. COVID-19 inpatients: therapeutic dose anticoagulation versus standard prophylactic anticoagulation (low-dose or intermediate-dose anticoagulation)

Seven studies [22–26,29,31] involving 4933 hospitalized patients with moderate to severe COVID-19 were included in the comparison of therapeutic-dose anticoagulation versus standard prophylactic anticoagulation with low-dose or intermediate-dose anticoagulation (Table 3). In the pooled meta-analysis with moderately and severely ill COVID-19 patients, therapeutic-dose anticoagulation may have little or no effect on reduction of all-cause mortality after 28 days (RR 0.69, 95 % CI 0.42–1.14, 1478 participants, 5 studies, low-certainty evidence,

Table 3 and fig. S3), with high heterogeneity regarding individual study results ( $P = 0.02$ ;  $I^2 = 63$  %). Subgroup analysis by COVID-19 severity showed a significant subgroup difference ( $P = 0.02$ ). In moderately ill COVID-19 patients, therapeutic-dose anticoagulation may reduce mortality (RR 0.39, 95 % CI 0.16–0.96, 635 participants, 2 studies, low-certainty evidence, Table 3 and Fig. S3). The meta-analysis of in-hospital mortality showed no difference in therapeutic-dose anticoagulation compared to standard prophylactic anticoagulation (RR 0.97, 95 % CI 0.79–1.19, 3344 participants, 3 studies, low-certainty evidence, Table 3 and Fig. S3) with low heterogeneity regarding study results with moderate and severe COVID-19 participants ( $P = 0.25$ ;  $I^2 = 28$  %). In the pooled meta-analysis, therapeutic-dose anticoagulation

**Table 2**

Meta-analysis for intermediate-dose anticoagulation versus standard prophylactic anticoagulation in COVID-19 inpatients including absolute effect estimates, risk of bias assessment, and certainty of evidence.

Outcome	Study population*	Relative effect (RR, M-H, Random, 95 % CI)	Relative effect (RR, M-H, Fixed, 95 % CI)	Absolute effect per 1000 (95 % CI)	Heterogeneity	Risk of bias** (overall)	Certainty of evidence	
				Standard prophylactic anticoagulation	Intermediate anticoagulation			
30-Day mortality	Pooled effect, mixed study population (WHO 4–9), 913 participants, 3 studies (27,28,30,32)	1.02 [0.75–1.40]	1.00 [0.84–1.20]	296 per 1000	302 per 1000	Chi <sup>2</sup> = 6.20, df = 4 (P = 0.18); I <sup>2</sup> = 35 %	Some concerns	Moderate due to imprecision (–1)
90-Day mortality	Mixed study population (WHO 4–9), 590 participants, 1 study (27,28)	1.07 [0.89–1.28]	1.07 [0.89–1.28]	418 per 1000	447 per 1000	NA	Some concerns	Low due to risk of bias (–1) and imprecision (1–)
Venous thrombotic events or death (30 days)	Pooled effect, mixed study population (WHO 4–9), 764 participants, 2 studies (27,28,30)	1.02 [0.85–1.23]	1.02 [0.85–1.22]	346 per 1000	353 per 1000	Chi <sup>2</sup> = 0.26, df = 2 (P = 0.88); I <sup>2</sup> = 0 %	High	Low due to risk of bias (–1) and imprecision (–1)
Major bleeding (30 days)	Pooled effect, mixed study population (WHO 4–9), 913 participants, 3 studies (27,28,30,32)	1.43 [0.54–3.74]	1.44 [0.55–3.73]	15 per 1000	21 per 1000	Chi <sup>2</sup> = 0.32, df = 3 (P = 0.96); I <sup>2</sup> = 0 %	Some concerns	Low due to risk of bias (–1) and imprecision (–1)

RR, relative risk; M-H, Mantel-Haenszel; CI, confidence interval.

\* Patient status according to WHO clinical progression scale.

\*\* Overall bias risk of studies with events in at least one study arm.

may have little or no effect on the occurrence of thrombotic events or deaths within 28 days (RR 0.86, 95 % CI 0.71–1.06, 4184 participants, 4 studies, low-certainty evidence, Table 3 and Fig. S3) with high heterogeneity between the individual study results ( $P = 0.07$ ;  $I^2 = 54$  %). Subgroup analysis by COVID-19 severity showed no significant subgroup difference ( $P = 0.27$ ). However, in patients with moderate COVID-19, therapeutic-dose anticoagulation may decrease the risk of thrombotic events or death compared to standard prophylactic anticoagulation when using the fixed-effect model in a sensitivity analysis (RR 0.72, 95 % CI 0.57–0.91, 2396 participants, 2 studies, low-certainty evidence, Table 3 and Fig. S3). In participants with severe COVID-19, therapeutic-dose anticoagulation may have little or no effect on this outcome compared to standard thromboprophylaxis (RR 0.98, 95 % CI 0.86–1.12, 1174 participants, 2 studies, low-certainty evidence, Table 3 and Fig. S3). Therapeutic-dose anticoagulation may increase the risk of major bleeding compared to standard prophylactic anticoagulation, regardless of disease severity (RR 1.78, 95 % CI 1.15–2.74, 4650 participants, 5 studies, low-certainty evidence, Table 3). Certainty of evidence was assessed as low for all outcomes and downgraded due to risk of bias, indirectness, imprecision, or inconsistency (Table 3). The indirectness was assumed based on two studies with major weight in the analyses that used a mixture of low- and intermediate-dose anticoagulation in the control arm [22,25].

### 3.5. Post-discharge COVID-19 patients: standard prophylactic anticoagulation versus no prophylaxis

Only data from one study on post-discharge anticoagulation were available (Table S3) [33]. We are uncertain whether post-discharge low-dose anticoagulation increases or decreases mortality after 35 days (RR 0.25, 95 % CI 0.03–2.21, 318 patients, 1 study), symptomatic venous thrombotic events or death (RR 0.44, 95 % CI 0.14–1.41, 318 patients, 1 study), serious bleeding (318 patients, 1 study, no events), clinically relevant non-serious bleeding (RR 1.00, 95 % CI 0.14–7.01, 318 patients, 1 study) and other bleedings (RR 2.00, 95 % CI 0.18–21.84, 318 patients, 1 study) compared to no prophylaxis. Anticoagulation reduced the occurrence of venous thrombotic events or cardiovascular deaths compared to control intervention (RR 0.33, 95 % CI 0.12–0.90, 318 patients, 1 study). Because this single significant outcome was not prospectively defined in the study protocol, this effect estimate is subject to a high risk of bias due to the suspicion of selective outcome reporting. Evidence certainty was rated as very low for all outcomes (Table S3).

## 4. Discussion

In this updated systematic review, the high heterogeneity regarding the anticoagulation schemes continues to make the interpretation of the meta-analyses difficult and reduces the certainty of evidence. The

**Table 3**

Meta-analyses of therapeutic-dose anticoagulation versus standard prophylactic anticoagulation in COVID-19 inpatients including absolute effect estimates, risk of bias assessment, and certainty of evidence.

Outcome	Study population*	Relative effect (RR, M-H, Random, 95 % CI)	Relative effect (RR, M-H, Fixed, 95 % CI)	Absolute effect estimation per 1000 (95 % CI)		Heterogeneity	Risk of bias** (overall)	Certainty of evidence
				Standard prophylactic anticoagulation	Therapeutic anticoagulation			
28-Day mortality	Moderately ill population (WHO 4–5), 635 participants, 2 studies (23,29)	0.39 [0.16–0.96]	0.39 [0.21–0.73]	105 per 1000 Difference 64 fewer 95 % CI 88 less–4 less	41 per 1000	Chi <sup>2</sup> = 1.92, df = 1 (P = 0.17); I <sup>2</sup> = 48 %	Low	Low due to imprecision (–1) and inconsistency (–1)
	Severely ill population (WHO 6–9), 229 participants, 3 studies (24,26,29)	0.73 [0.49–1.09]	0.71 [0.48–1.06]	356 per 1000 Difference 96 fewer 96 % CI 182 less–32 more	260 per 1000	Chi <sup>2</sup> = 1.46, df = 2 (P = 0.48); I <sup>2</sup> = 0 %	Some concerns	Low due to risk of bias (–1) and imprecision (–1)
	Mixed population (WHO 4–9), 614 participants, 1 study (31)	1.49 [0.90–2.46]	1.49 [0.90–2.46]	76 per 1000 Difference 37 more 96 % CI 8 less–35 more	113 per 1000	NA	Low	Low due to imprecision (–2)
	Pooled effect, mixed population (WHO 4–9), 1478 participants, 5 studies (23,24,26,29,31)	0.69 [0.42–1.14]	0.79 [0.60–1.04]	124 per 1000 Difference 38 fewer 95 % CI 72 less–17 more	86 per 1000	Chi <sup>2</sup> = 13.53, df = 5 (P = 0.02); I <sup>2</sup> = 63 %	Some concerns	Low due to imprecision (–1) and inconsistency (–1)
All-cause mortality in hospital	Pooled effect, mixed population (WHO 4–9), 3344 participants, 3 studies (22,24,25)	0.97 [0.79–1.19]	0.99 [0.86–1.13]	180 per 1000 Difference 5 fewer 95 % CI 38 less – 34 more	175 per 1000	Chi <sup>2</sup> = 2.78, df = 2 (P = 0.25); I <sup>2</sup> = 28 %	Some concerns	Low due to bias risk (–1) and indirectness (–1)
Thrombotic events or death (28 days)	Moderately diseased population (WHO 4–5), 2396 participants, 2 studies (22,29)	0.64 [0.38–1.07]	0.72 [0.57–0.91]	123 per 1000 Difference 44 fewer 95 % CI 76 less – 9 more	77 per 1000	Chi <sup>2</sup> = 2.90, df = 1 (P = 0.09); I <sup>2</sup> = 66 %	Some concerns	Low due to bias risk (–1) and indirectness (–1)
	Severely ill population (WHO 6–9), 1174 participants, 2 studies (25,29)	0.98 [0.86–1.12]	0.98 [0.86–1.12]	423 per 1000 Difference 8 fewer 95 % CI 59 less–51 more	415 per 1000	Chi <sup>2</sup> = 0.09, df = 1 (P = 0.77); I <sup>2</sup> = 0 %	Some concerns	Low due to bias risk (–1) and indirectness (–1)
	Mixed population WHO 4–9), 614 participants, 1 study (31)	1.03 [0.70–1.50]	1.03 [0.70–1.50]	145 per 1000 Difference 4 more 96 % CI 43 less–73 more	149 per 1000	NA	Some concerns	Low due to risk of bias (–1) and imprecision (–1)
	Pooled effect, mixed population (WHO 4–9), 4184 participants, 4 studies (22,25,29,31)	0.86 [0.71–1.06]	0.90 [0.8–1.01]	214 per 1000 Difference 30 fewer 95 % CI 62 less–13 more	184 per 1000	Chi <sup>2</sup> = 8.61, df = 4 (P = 0.07); I <sup>2</sup> = 54 %	Some concerns	Low due to risk of bias (–1) and indirectness/inconsistency (–1)
Major bleeding (28 days)	Pooled effect, mixed population (WHO 4–9), 4650 participants, 5 studies (22,23,25,29,31)	1.78 [1.15–2.74]	1.82 [1.19–2.78]	14 per 1000 Difference 11 more 95 % CI 2 more–24 more	25 per 1000	Chi <sup>2</sup> = 3.95, df = 5 (P = 0.56); I <sup>2</sup> = 0 %	Some concerns	Low due to bias risk (–1) and indirectness (–1)

RR relative risk; M-H, Mantel-Haenszel; CI, confidence interval.

\* Patient status according to WHO clinical progression scale.

\*\* Overall bias risk of studies with events in at least one study arm.

insufficient standardized definition of COVID-19 severity in individual studies however could be improved by newly identified studies and requests for additional stratified data from the study authors. So far, little is known about the extent to which individual virus variants and the vaccination status affect the risk of thrombosis. Measured by the lower rate of severe courses with the current Omicron variant [35] and an assumed increasing thrombotic risk proportional to the disease severity, one could assume that the predominant variant at the time of study has also influenced the presented findings and may explain the heterogeneous results between studies. Unfortunately, no information (e.g. genome sequencing) was available for the included patients to allow further exploration of these assumptions.

To the best of our knowledge, there is currently no comparable and more up-to-date systematic review with meta-analysis which includes more RCTs on this topic available. Despite being published recently, the latest update of the Cochrane Review entitled ‘Anticoagulants for people hospitalised with COVID-19’ from March 2022 only includes four RCTs based on a search from April 2021 and is therefore lacking important study results [36]. Given the fast pace of the pandemic, we believe it is

more than ever important to base clinical practice on up-to-date evidence.

Based on the data available so far, intermediate-dose anticoagulation cannot be expected to have an effect on all-cause mortality after 30 and 90 days or on the risk of thrombotic events or death. However, even intermediate-dose anticoagulation may increase the risk of major bleeding based on a clinically relevant, non-significant effect estimate.

Therapeutic-dose anticoagulation may have a benefit in terms of mortality after 28 days in the subgroup of patients with moderate COVID-19, based on data from the RAPID and HEP-COVID study of 635 participants. While based on the large ATTACC, ACTIV-4a, REMAP-CAP platform study with 2226 moderately ill participants, little or no effect on the risk of in-hospital mortality can be expected. The certainty of evidence for these contradictory results is low and further studies may change the interpretation. Therapeutic-dose anticoagulation may reduce the rate of thrombotic events or deaths in patients with moderate COVID-19 but has had no effect in patients with severe COVID-19. However, this effect was only statistically significant when using the fixed-effect model. Therapeutic-dose anticoagulation can increase the



rate of severe bleeding events compared to standard prophylactic anticoagulation. Thus, moderately ill COVID-19 patients without increased bleeding risks may be considered for therapeutic anticoagulation, the increased risk of bleeding should however be taken into account in decision-making and anticoagulated COVID-19 patients should be carefully monitored for bleeding events [5,6]. Severely ill COVID-19 patients may not benefit from therapeutic anticoagulation while at the same time the risk of severe bleeding can be increased. Without further specific indication, therapeutic anticoagulation can therefore not be recommended for critically ill COVID-19 patients [5,6].

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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#### CRedit authorship contribution statement

**Stefanie Reis:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Maria Popp:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Selina Schießer:** Writing – review & editing. **Maria-Inti Metzendorf:** Conceptualization, Writing – review & editing. **Peter Kranke:** Conceptualization, Resources, Writing – review & editing. **Patrick Meybohm:** Conceptualization, Resources, Writing – review & editing. **Stephanie Weibel:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2022.09.001>.

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