Cochrane Library

Cochrane Database of Systematic Reviews

Anticoagulants for people hospitalised with COVID-19 (Review)

Flumignan RLG, Civile VT, Tinôco JDDS, Pascoal PIF, Areias LL, Matar CF, Tendal B, Trevisani VFM, Atallah ÁN, Nakano LCU

Flumignan RLG, Civile VT, Tinôco JD, Pascoal PIF, Areias LL, Matar CF, Tendal B, Trevisani VFM, Atallah ÁN, Nakano LCU.
Anticoagulants for people hospitalised with COVID-19.
Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD013739.
DOI: 10.1002/14651858.CD013739.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Rapid Review]

Anticoagulants for people hospitalised with COVID-19

Ronald LG Flumignan[1,2], Vinicius T Civile[2,3], Jéssica Dantas de Sá Tinôco[4], Patricia IF Pascoal[1], Libnah L Areias[1], Charbel F Matar[5], Britta Tendal[6], Virginia FM Trevisani[2,7], Álvaro N Atallah[2], Luis CU Nakano[1,2]

[1]Department of Surgery, Division of Vascular and Endovascular Surgery, Universidade Federal de São Paulo, São Paulo, Brazil. [2]Cochrane Brazil, Universidade Federal de São Paulo, São Paulo, Brazil. [3]Department of Physiotherapy, Universidade Paulista, São Paulo, Brazil. [4]Department of Nursing, State University of Rio Grande do Norte, Natal, Brazil. [5]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [6]Living Guidelines Program, Cochrane Australia, Melbourne, Australia. [7]Medicina de Urgência, Universidade Federal de São Paulo, São Paulo, Brazil

Contact: Ronald LG Flumignan, flumignan@gmail.com.

Editorial group: Cochrane Emergency and Critical Care Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 3, 2022.

Citation: Flumignan RLG, Civile VT, Tinôco JD, Pascoal PIF, Areias LL, Matar CF, Tendal B, Trevisani VFM, Atallah ÁN, Nakano LCU.Anticoagulants for people hospitalised with COVID-19. *Cochrane Database of Systematic Reviews* 2022, Issue 3. Art. No.: CD013739. DOI: 10.1002/14651858.CD013739.pub2.

ABSTRACT

Background

The primary manifestation of coronavirus disease 2019 (COVID-19) is respiratory insufficiency that can also be related to diffuse pulmonary microthrombosis and thromboembolic events, such as pulmonary embolism, deep vein thrombosis, or arterial thrombosis. People with COVID-19 who develop thromboembolism have a worse prognosis.

Anticoagulants such as heparinoids (heparins or pentasaccharides), vitamin K antagonists and direct anticoagulants are used for the prevention and treatment of venous or arterial thromboembolism. Besides their anticoagulant properties, heparinoids have an additional anti-inflammatory potential. However, the benefit of anticoagulants for people with COVID-19 is still under debate.

Objectives

To assess the benefits and harms of anticoagulants versus active comparator, placebo or no intervention in people hospitalised with COVID-19.

Search methods

We searched the CENTRAL, MEDLINE, Embase, LILACS and IBECS databases, the Cochrane COVID-19 Study Register and medRxiv preprint database from their inception to 14 April 2021. We also checked the reference lists of any relevant systematic reviews identified, and contacted specialists in the field for additional references to trials.

Selection criteria

Eligible studies were randomised controlled trials (RCTs), quasi-RCTs, cluster-RCTs and cohort studies that compared prophylactic anticoagulants versus active comparator, placebo or no intervention for the management of people hospitalised with COVID-19. We excluded studies without a comparator group and with a retrospective design (all previously included studies) as we were able to include better study designs. Primary outcomes were all-cause mortality and necessity for additional respiratory support. Secondary outcomes were mortality related to COVID-19, deep vein thrombosis, pulmonary embolism, major bleeding, adverse events, length of hospital stay and quality of life.

Data collection and analysis

We used standard Cochrane methodological procedures. We used Cochrane RoB 1 to assess the risk of bias for RCTs, ROBINS-I to assess risk of bias for non-randomised studies (NRS) and GRADE to assess the certainty of evidence. We meta-analysed data when appropriate.

Main results

We included seven studies (16,185 participants) with participants hospitalised with COVID-19, in either intensive care units, hospital wards or emergency departments. Studies were from Brazil (2), Iran (1), Italy (1), and the USA (1), and two involved more than country. The mean age of participants was 55 to 68 years and the follow-up period ranged from 15 to 90 days. The studies assessed the effects of heparinoids, direct anticoagulants or vitamin K antagonists, and reported sparse data or did not report some of our outcomes of interest: necessity for additional respiratory support, mortality related to COVID-19, and quality of life.

Higher-dose versus lower-dose anticoagulants (4 RCTs, 4647 participants)

Higher-dose anticoagulants result in little or no difference in all-cause mortality (risk ratio (RR) 1.03, 95% CI 0.92 to 1.16, 4489 participants; 4 RCTs) and increase minor bleeding (RR 3.28, 95% CI 1.75 to 6.14, 1196 participants; 3 RCTs) compared to lower-dose anticoagulants up to 30 days (high-certainty evidence). Higher-dose anticoagulants probably reduce pulmonary embolism (RR 0.46, 95% CI 0.31 to 0.70, 4360 participants; 4 RCTs), and slightly increase major bleeding (RR 1.78, 95% CI 1.13 to 2.80, 4400 participants; 4 RCTs) compared to lower-dose anticoagulants up to 30 days (moderate-certainty evidence). Higher-dose anticoagulants may result in little or no difference in deep vein thrombosis (RR 1.08, 95% CI 0.57 to 2.03, 3422 participants; 4 RCTs), stroke (RR 0.91, 95% CI 0.40 to 2.03, 4349 participants; 3 RCTs), major adverse limb events (RR 0.33, 95% CI 0.01 to 7.99, 1176 participants; 2 RCTs), myocardial infarction (RR 0.86, 95% CI 0.48 to 1.55, 4349 participants; 3 RCTs), atrial fibrillation (RR 0.35, 95% CI 0.07 to 1.70, 562 participants; 1 study), or thrombocytopenia (RR 0.94, 95% CI 0.71 to 1.24, 2789 participants; 2 RCTs) compared to lower-dose anticoagulants up to 30 days (low-certainty evidence). It is unclear whether higher-dose anticoagulants have any effect on necessity for additional respiratory support, mortality related to COVID-19, and quality of life (very low-certainty evidence or no data).

Anticoagulants versus no treatment (3 prospective NRS, 11,538 participants)

Anticoagulants may reduce all-cause mortality but the evidence is very uncertain due to two study results being at critical and serious risk of bias (RR 0.64, 95% CI 0.55 to 0.74, 8395 participants; 3 NRS; very low-certainty evidence). It is uncertain if anticoagulants have any effect on necessity for additional respiratory support, mortality related to COVID-19, deep vein thrombosis, pulmonary embolism, major bleeding, stroke, myocardial infarction and quality of life (very low-certainty evidence or no data).

Ongoing studies

We found 62 ongoing studies in hospital settings (60 RCTs, 35,470 participants; 2 prospective NRS, 120 participants) in 20 different countries. Thirty-five ongoing studies plan to report mortality and 26 plan to report necessity for additional respiratory support. We expect 58 studies to be completed in December 2021, and four in July 2022. From 60 RCTs, 28 are comparing different doses of anticoagulants, 24 are comparing anticoagulants versus no anticoagulants, seven are comparing different types of anticoagulants, and one did not report detail of the comparator group.

Authors' conclusions

When compared to a lower-dose regimen, higher-dose anticoagulants result in little to no difference in all-cause mortality and increase minor bleeding in people hospitalised with COVID-19 up to 30 days. Higher-dose anticoagulants possibly reduce pulmonary embolism, slightly increase major bleeding, may result in little to no difference in hospitalisation time, and may result in little to no difference in deep vein thrombosis, stroke, major adverse limb events, myocardial infarction, atrial fibrillation, or thrombocytopenia.

Compared with no treatment, anticoagulants may reduce all-cause mortality but the evidence comes from non-randomised studies and is very uncertain. It is unclear whether anticoagulants have any effect on the remaining outcomes compared to no anticoagulants (very low-certainty evidence or no data).

Although we are very confident that new RCTs will not change the effects of different doses of anticoagulants on mortality and minor bleeding, high-quality RCTs are still needed, mainly for the other primary outcome (necessity for additional respiratory support), the comparison with no anticoagulation, when comparing the types of anticoagulants and giving anticoagulants for a prolonged period of time.

PLAIN LANGUAGE SUMMARY

Do blood thinners prevent people who are hospitalised with COVID-19 from developing blood clots?

Key messages

- High-dose blood thinners result in little or no difference in death rate and increase minor bleeding compared to low-dose blood thinners for people hospitalised with COVID-19. Giving blood thinners compared to not giving blood thinners might reduce the death rate.

- It is very likely that new studies will not change the evidence about the effects of different doses of blood thinners on death rate and minor bleeding. High-quality studies are still needed to analyse the need for additional respiratory support, giving blood thinners compared to no blood thinners, comparing different blood thinners, and giving blood thinners for extended periods.

What is COVID-19?

COVID-19 typically affects the lungs and airways; however, in addition to respiratory problems, about 16% of people hospitalised with COVID-19 experience problems with their blood vessels, leading to blood clots forming in the arteries, veins and lungs. Nearly half of all people with severe COVID-19 in intensive care units develop clots in their veins or arteries.

What are blood thinners?

Blood thinners are medicines that prevent harmful blood clots from forming (deep vein thrombosis). However, they can cause unwanted effects such as bleeding. Some guidelines recommend giving blood thinners when people are first admitted to hospital with COVID-19 to prevent blood clots from developing, rather than waiting to see whether blood clots develop and then treating them with blood thinners.

What did we want to find out?

We wanted to know whether giving blood thinners to people hospitalised with COVID-19 as a preventive measure reduced the number of deaths compared to people who received no treatment or those who received a placebo treatment (an identical-seeming treatment but with no active ingredient). We also wanted to determine whether these individuals needed less support with breathing, whether they still developed harmful blood clots, whether they experienced bleeding and whether they experienced any other unwanted events.

What did we do?

We searched for studies that assessed blood thinners given to people hospitalised with COVID-19 to prevent blood clots. Studies could be of any design as long as they compared a blood thinner with another blood thinner, no treatment or a placebo. Studies could take place anywhere in the world and participants could be any age as long as they were in hospital with confirmed COVID-19 disease. We pooled the results when appropriate.

What did we find?

We included seven studies with 16,185 people hospitalised with COVID-19 in either intensive care units, hospital wards or emergency departments. Studies were from Brazil (2), Iran (1), Italy (1), and the USA (1), and two involved more than country. People in the studies were aged from 55 to 68 years on average. Studies lasted from 15 to 90 days and provided evidence on deaths, bleeding, blood clotting, length of hospital stay and unwanted effects. There was little or no evidence on need for respiratory support (help with breathing), deaths related to COVID-19, and quality of life.

Higher-dose of blood thinners compared with lower-dose (4 studies, 4647 people)
In people who received higher compared to lower doses of blood thinners there was little to no difference in death rate. However, people on higher doses were more likely to experience minor bleeding compared to in those on lower doses. People who received higher doses of blood thinners likely had reduced pulmonary embolism (blood clot in the lung or blood vessel leading to the lung), slightly increased major (more severe) bleeding, and probably had little to no difference in time spent in hospital compared to those who received the lower doses of blood thinners. In people who received higher doses of blood thinners, there was little to no difference in the rate of deep vein thrombosis, and other unwanted events compared to those who received the lower dose of blood thinners.

Blood thinners compared with no treatment (3 studies, 11,538 people)
People who received blood thinners had a reduced death rate compared to those who did not receive blood thinners, but the evidence is very uncertain.

What are the limitations of the evidence?

We are very confident that higher doses of blood thinners do not change the risk of death but do increase the risk of bleeding in people hospitalised with COVID-19.

Although our confidence in the evidence is very limited, people who receive blood thinners may have a lower death rate compared to those who did not receive any blood thinners.

What happens next?

Our searches found 62 ongoing studies with 35,470 people. We plan to add the results of these studies to our review when they are published.

How up to date is this evidence?

The evidence is up to date to 14 April 2021.

Summary of findings 1. Higher-dose anticoagulants compared to lower-dose anticoagulants for people hospitalised with COVID-19

Higher-dose anticoagulants compared to lower-dose anticoagulants for people hospitalised with COVID-19

Patient or population: people hospitalised with COVID-19
Setting: hospital
Intervention: higher-dose anticoagulants (LMWH, UFH or rivaroxaban)
Comparison: lower-dose anticoagulants (LMWH or UFH)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower-dose anticoagulants (short-term outcomes)	Risk with higher-dose anticoagulants				
All-cause mortality Follow-up: from 28-30 days	Study population 191 per 1000	196 per 1000 (175 to 221)	RR 1.03 (0.92 to 1.16)	4489 (4 RCTs)	⊕⊕⊕⊕ High[a]	Higher-dose anticoagulants results in little to no difference in all-cause mortality
Necessity for additional respiratory support Follow-up: from 28-30 days	Study population 117 per 1000	63 per 1000 (14 to 289)	RR 0.54 (0.12 to 2.47)	3407 (3 RCTs)	⊕⊝⊝⊝ Very low[b,c,d]	The evidence is very uncertain about the effect of higher-dose anticoagulants on necessity for additional respiratory support.
Mortality related to COVID-19	No studies measured this outcome					
Deep vein thrombosis Follow-up: from 28-30 days	Study population 11 per 1000	12 per 1000 (6 to 22)	RR 1.08 (0.57 to 2.03)	3422 (4 RCTs)	⊕⊕⊝⊝ Low[d]	Higher-dose anticoagulants may result in little to no difference in DVT
Pulmonary embolism Follow-up: from 28-30 days	Study population 33 per 1000	15 per 1000 (10 to 23)	RR 0.46 (0.31 to 0.70)	4360 (4 RCTs)	⊕⊕⊕⊝ Moderate[b]	Higher-dose anticoagulants likely reduce PE

Major bleeding Follow-up: from 28-30 days	Study population 14 per 1000	24 per 1000 (15 to 38)	RR 1.78 (1.13 to 2.80)	4400 (4 RCTs)	⊕⊕⊕⊖ Moderate[b]	Higher-dose anticoagulants likely increase major bleeding slightly
Adverse events (minor bleeding) Follow-up: from 28-30 days	Study population 20 per 1000	47 per 1000 (18 to 121)	RR 3.28 (1.75 to 6.14)	1196 (3 RCTs)	⊕⊕⊕⊕ High	Higher-dose anticoagulants increase adverse events (minor bleeding)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **COVID-19:** coronavirus disease 2019; **DVT:** deep vein thrombosis; **LMWH**: low-molecular-weight heparin; **PE:** pulmonary embolism; **RCT:** randomised controlled trial; **RR:** risk ratio; **UFH:** unfractionated heparin

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The largest study in the analysis was at high risk of bias in almost all domains; however, we did not downgrade for study limitations as removing this study in the sensitivity analysis did not change the pooled estimate.
[b]Downgraded one level due to study limitations. One randomised controlled trial provided high risk of bias in almost all domains leading to a different pooled estimate after sensitivity analysis.
[c]Downgraded one level due to inconsistency. We identified substantial unexplained heterogeneity (I^2 = 60%).
[d]Downgraded two levels due to imprecision. Confidence interval of the absolute difference comprises both important clinical benefit and important clinical harm.

Summary of findings 2. Anticoagulants compared to no treatment for people hospitalised with COVID-19

Anticoagulants compared to no treatment for people hospitalised with COVID-19

Patient or population: people hospitalised with COVID-19
Setting: hospital
Intervention: anticoagulants (LMWH, UFH, fondaparinux, DOACs or VKA)
Comparison: no treatment (no anticoagulants)

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with no treatment	Risk with anti-coagulants				
All-cause mortality Follow-up: from 15-30 days	Study population 307 per 1000	196 per 1000 (169 to 227)	RR 0.64 (0.55 to 0.74)	8395 (3 observational studies)	⊕⊖⊖⊖ Very low[a,b]	Anticoagulants may reduce all-cause mortality but the evidence is very uncertain due to two study results being at critical and serious risk of bias. The numerical results are very unreliable for outcomes where critical risk of bias is an issue
Necessity for additional respiratory support	No studies measured this outcome					
Mortality related to COVID-19	No studies measured this outcome					
Deep vein thrombosis Follow-up: up to 15 days	Study population 3 per 1000	19 per 1000 (4 to 82)	RR 5.67 (1.30 to 24.70)	1403 (1 observational study)	⊕⊖⊖⊖ Very low[c,d]	It is uncertain if anticoagulants have any effect on DVT. The numerical results are very unreliable for outcomes where critical risk of bias is an issue.
Pulmonary embolism Follow-up: up to 15 days	Study population 2 per 1000	40 per 1000 (5 to 292)	RR 24.19 (3.31 to 176.53)	1403 (1 observational study)	⊕⊖⊖⊖ Very low[c,d]	It is uncertain if anticoagulants have any effect on PE. The numerical results are very unreliable for outcomes where critical risk of bias is an issue.
Major bleeding Follow-up: from 15-26 days	Study population 19 per 1000	23 per 1000 (13 to 41)	RR 1.19 (0.66 to 2.12)	7218 (2 observational studies)	⊕⊖⊖⊖ Very low[b,c,e]	It is uncertain if anticoagulants have any effect on major bleeding. The numerical results are very unreliable for outcomes where critical risk of bias is an issue.
Adverse events (minor bleeding)	No studies measured this outcome					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **COVID-19:** coronavirus disease 2019; **DOACs:** direct oral anticoagulants; **DVT:** deep vein thrombosis; **LMWH**: low-molecular-weight heparin; **PE:** pulmonary embolism; **RR:** risk ratio; **UFH:** unfractionated heparin; **VKA**: vitamin K antagonist

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

---

[a]Downgraded two levels due to study limitations. Overall critical/serious risk of bias in two studies, especially related to confounding.
[b]Downgraded one level due to inconsistency. We found moderate unexplained heterogeneity (I^2 = 30% to 60%).
[c]Downgraded one level due to study limitations. Overall critical risk of bias, especially related to confounding.
[d]Downgraded two levels due to imprecision. Fewer than 300 events were included in the analysis and very large confidence interval.
[e]Downgraded one level due to imprecision. Confidence interval of the absolute difference comprises both unimportant clinical harm and important clinical harm.

BACKGROUND

See Table 1 for a glossary of terms.

Description of the condition

The novel coronavirus disease strain, coronavirus disease 2019 (COVID-19), is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 emerged in Wuhan, China and rapidly spread worldwide (Lai 2020). SARS-CoV-2 is a highly transmissible virus, and up to 16% of people hospitalised may develop a severe form of the disease (Giannis 2020). Pulmonary effects are typical, but due to high inflammation, hypoxia, immobilisation and diffuse intravascular coagulation, COVID-19 may predispose patients to both arterial and venous thromboembolism (Ackermann 2020; COVIDSurg 2021; Dolhnikoff 2020; Fox 2020; Long 2020). Venous and arterial thromboembolic complications affect 16% of people hospitalised with COVID-19 and 31% to 49% of people with COVID-19 in intensive care units (ICUs), with 90% of such cases being venous thromboembolism (Bilaloglu 2020; Klok 2020a; Klok 2020b). Viral infections induce an imbalance between anticoagulant and procoagulant mechanisms and raise the systemic inflammatory response. Indeed, people with COVID-19 commonly present with both elevated D-dimer (fibrin degradation product) and reductions of factors related to clot formation (Giannis 2020). Excessive activation of the coagulation cascade and platelets could explain these haematological findings (Giannis 2020). Coagulopathy and vascular endothelial dysfunction have been proposed as complications of COVID-19. Emerging data support the hypothesis that asymptomatic individuals with COVID-19 are at risk of developing pathological thrombosis. The association between large-vessel stroke and COVID-19 in young asymptomatic individuals requires further investigation (Oxley 2020); however, Li 2020 found the incidence of stroke among people hospitalised with COVID-19 to be approximately 5% in a retrospective cohort. Activation of the coagulation system seems to be important in the development of acute respiratory distress syndrome, one of the most typical complications of COVID-19 infection and it could be related to pulmonary microthrombosis (Ackermann 2020; Dolhnikoff 2020; Fox 2020; Marini 2020).

Description of the intervention

Anticoagulants are pharmacological interventions used in reducing hypercoagulability (Amaral 2020; Dias 2021). The decision to use thromboprophylaxis or not depends on the risk stratification of each patient (NHS 2020).

Anticoagulants are medications used in the prevention and treatment of venous or arterial thromboembolic events (Amaral 2020; Biagioni 2020; Clezar 2020; Dias 2021). When used for a prophylactic purpose, the dose of anticoagulants is usually half or significantly lower than that given for therapeutic purposes (Alquwaizani 2013). Even so, adverse events such as bleeding may occur and can have a significant impact on patient care (Amaral 2020; AVF 2020; Biagioni 2020; Clezar 2020).

How the intervention might work

D-dimers are a reflection of the pathophysiology in COVID-19, which is highly associated with increased mortality in people with COVID-19 infection (Becker 2020). The elevated D-dimer levels seen are most likely a reflection of the overall clot burden and critically ill people with COVID-19 have lower levels of fibrinolytic system activation than the reference population (Panigada 2020). Tang 2020 reported decreased mortality after the use of heparin in people with COVID-19 (40.0% versus 64.2%, P = 0.029). Long 2020 reported that anticoagulation (mainly low-molecular-weight heparin), may reduce mortality in people with severe COVID-19 infection or those with higher levels of D-dimer (e.g. greater than six times the upper limit).

Some authors had also correlated this effect with the anti-inflammatory effect of heparinoids, for instance, binding and neutralising a wide variety of mediators released from inflammatory cells, reducing IL-6 and as potent inhibitors of the complement system, which may have effects on the clinical evolution of people with COVID-19 (Liu 2019; Shi 2020; Tang 2020; Young 2008). It can attenuate ongoing tissue damage (Liu 2019; Young 2008). Practical guidelines and specialist consensus are addressing the management of thromboprophylaxis and anticoagulation in people with COVID-19 infection (Bikdeli 2020; NHS 2020; Obe 2020; Ramacciotti 2020). However, the effects of anticoagulants on people with COVID-19 is still under debate (Sobreira 2020).

OBJECTIVES

To assess the benefits and harms of anticoagulants versus active comparator, placebo or no intervention in people hospitalised with COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

The protocol for this review was prospectively registered with the Open Science Framework on 7 August 2020 (Flumignan 2020a), and a previous version of this review was published on 02 October 2020 (Flumignan 2020b), and disseminated, including a short version published in another international journal (Flumignan 2021).

We considered parallel or cluster-randomised controlled trials (RCTs), quasi-RCTs, and cohort studies. Non-randomised studies (NRS), such as cohort studies, may be useful for rare adverse events and clinical decisions if there is a lack of controlled studies. Related NRS can be developed faster than RCTs and may represent the only available evidence to guide decision making in this setting. To ensure that we captured all relevant study types, we considered a broad range of empirical studies of any size that provided a quantitative measure of impact (Reeves 2021). We did not consider studies without a comparator group or any retrospective NRS because we identified prospective NRS (better study design). We performed meta-analyses for all of the included studies (RCTs or NRS) with available data to follow Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021). When at least 400 participants were included from RCTs, we no longer considered NRS for inclusion. We considered all other types of studies irrelevant for this review. Please find further explanations in Appendix 1.

In order to minimise selection bias for NRS, we planned to include only studies that used statistical adjustment for baseline factors using multivariate analyses for at least these confounding factors: participants already using anticoagulants (e.g. atrial fibrillation), participants who underwent surgery during the hospitalisation,

active cancer treatment, concomitant antiplatelet use and history of venous thromboembolism. We only considered studies with a minimum duration of two weeks.

Types of participants

We included all participants eligible for anticoagulation, both male and female of all ages, hospitalised with the diagnosis of COVID-19. Any hospitalised participants with confirmed COVID-19 infection were eligible, independent of the disease severity (e.g. patients hospitalised in ICUs or wards). We also considered participants with a previous history of venous thromboembolism for inclusion in this review. However, participants with COVID-19 treated outside of hospital, that is, those who were not hospitalised, were not eligible for our review.

In future updates of this review, if we find studies with mixed populations, that is, hospitalised and non-hospitalised participants, and only a subset of the participants meet our inclusion criteria, we will attempt to obtain data for the subgroup of interest from the study authors in order to include the study. For studies with mixed populations for which we cannot get data for the subgroup of interest but at least 50% of the study population are of interest, we will include all participants in our analysis. Moreover, we will explore the effect of this decision in a sensitivity analysis. We will exclude studies in which less than 50% of the population are of interest and the subgroup of interest data are not available.

Types of interventions

We considered the following pharmacological interventions.

- Heparinoids, that is, both unfractionated heparin and low-molecular-weight heparin, and pentasaccharides (synthetic and selective anticoagulant drugs similar to low-molecular-weight heparin)
- Vitamin K antagonists
- Direct anticoagulants, both factor Xa inhibitors and direct thrombin inhibitors, that is, direct oral anticoagulants and non-oral direct anticoagulants (e.g. bivalirudin)

We considered studies that compared different formulations, doses, and schedules of the same intervention (e.g. heparinoids).

Some commonly applicable prophylactic doses of the interventions of interest are low-molecular-weight heparin 30 mg twice a day or 40 mg daily, and unfractionated heparin 5000 IU three times a day. However, we considered all doses of anticoagulants when used for primary or secondary prophylaxis of thromboembolism as eligible for our review.

Types of comparisons

We included studies that compared one pharmacological intervention (agent or drug) versus another active comparator, or placebo or no treatment with any combination of interventions, provided that co-treatments were balanced between the treatment and control arms. We allowed other potential interventions (e.g. antiplatelet agents, elastic stockings, intermittent pneumatic compression) as comparators or additional interventions. We also included studies that compared different doses of drugs. We pooled the studies that addressed the same comparisons.

- Anticoagulant versus placebo or no treatment (we planned to pool all anticoagulants together – heparinoids, vitamin K antagonists, direct anticoagulants, etc. – if possible)
- Anticoagulant versus a different anticoagulant
- Anticoagulant versus a different dose, formulation, or schedule of the same anticoagulant
- Anticoagulant versus other pharmacological interventions such as antiplatelet agents
- Anticoagulant versus non-pharmacological interventions

Types of outcome measures

We evaluated core outcomes as pre-defined by the Core Outcome Measures in Effectiveness Trials Initiative for people with COVID-19 (COMET 2020). We also considered the outcomes after hospital discharge. We intended to present the outcomes at two different time points following the start of the intervention if data were available: short-term outcomes (at hospital discharge or before); and long-term outcomes (after hospital discharge).

Our time point of primary interest is short-term; we, therefore, intended to produce related summary of findings tables only for this time point, and also planned to report the long-term outcomes at the longest possible time of follow-up.

Primary

- All-cause mortality
- Necessity for additional respiratory support: oxygen by non-invasive ventilators or high-flow intubation and mechanical ventilation or extracorporeal membrane oxygenation.

Secondary

- Mortality related to COVID-19
- Deep vein thrombosis, symptomatic or asymptomatic, first episode or recurrent confirmed by ultrasonography or angiography (e.g. by computed tomography (CT), magnetic resonance imaging (MRI) or by digital subtraction) from any site (e.g. lower limbs, upper limbs, abdominal)
- Pulmonary embolism (symptomatic or asymptomatic, first episode or recurrent, fatal or non-fatal): a diagnosis had to be confirmed by angiography (e.g. by CT, MRI or digital subtraction) and ventilation-perfusion scan, or both. We also considered post mortem examination as an objective confirmation of deep vein thrombosis and pulmonary embolism.
- Major bleeding: defined by a haemoglobin concentration decrease of 2 g/dL or more, a retroperitoneal or intracranial bleed, a transfusion of two or more units of blood, or fatal haemorrhagic events, as defined by International Society on Thrombosis and Haemostasis (Schulman 2010)
- Adverse events. We will consider all possible adverse events separately, as individual outcomes, such as minor bleeding, gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, abdominal pain), allergic reactions, renal failure and amputations.
- Hospitalisation time in days
- Quality of life: participant's subjective perception of improvement (yes or no) as reported by the study authors or using any validated scoring system such as the Short Form-36 Health Survey (SF-36) (Ware 1992)

We planned to include studies in the review irrespective of whether measured outcome data were reported in a 'usable' way.

Search methods for identification of studies

An information specialist (LLA) designed and conducted all searches on 20 June 2020, which were informed and verified by a content expert (RLGF) and independently peer reviewed. The search was updated on 14 April 2021.

Electronic searches

We identified eligible study references through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 6) in the Cochrane Library (searched 20 June 2020)
- MEDLINE PubMed (1946 to 20 June 2020)
- Embase.com Elsevier (1974 to 20 June 2020)
- LILACS Virtual Health Library (Latin American and Caribbean Health Sciences Literature database; 1982 to 20 June 2020)
- IBECS Virtual Health Library (Indice Bibliográfico Español de Ciencias de la Salud; 2015 to 20 June 2020)

We adapted the preliminary search strategy for MEDLINE PubMed for use in the other databases. We did not apply any RCT filters for any databases; we selected the study design manually because we also considered NRS for inclusion in this review. See Flumignan 2020b for search strategies conducted in June 2020.

For this update, we subsequently conducted systematic update searches of the following databases for relevant trials without language, publication year or publication status restrictions on 14 April 2021:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 3) in the Cochrane Library (searched from 20 June 2020 to 14 April 2021; Appendix 2)
- MEDLINE PubMed (searched from 20 June 2020 to 14 April 2021; Appendix 3)
- Embase.com Elsevier (searched from 1 January 2020 to 14 April 2021; Appendix 4)
- LILACS Virtual Health Library (searched from 1 January 2020 to 14 April 2021; Appendix 5)
- IBECS Virtual Health Library (searched from 1 January 2020 to 14 April 2021; Appendix 5)

We searched all databases from their inception to the present, and we did not restrict the language of publication or publication status. We considered the adverse effects described in the included studies only. All relevant MeSH and Emtree index terms for COVID-19 and SARS-CoV-2 will be integrated into electronic search strategies in future updates.

Searching other resources

We also conducted a search of the Cochrane COVID-19 Study Register (Appendix 6), a specialised register containing both trial registry records, journal articles and preprints, and medRxiv (Appendix 7), a preprint server, for ongoing or unpublished studies (both searched 20 June 2020). The Cochrane COVID-19 Study Register is a specialised register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- daily searches of ClinicalTrials.gov
- weekly searches of PubMed
- weekly searches of Embase.com
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP)
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

Complete data sources and search methods for the register are available at community.cochrane.org/about-covid-19-study-register.

For this update, we subsequently performed update searches of the following on 14 April 2021:

- Cochrane COVID-19 Study Register (Appendix 6);
- medRxiv (Appendix 7).

We checked the reference lists of all included studies and any relevant systematic reviews identified for additional references to studies. We examined any relevant retraction statements and errata for included studies. We contacted the authors of the included studies for any possible unpublished data. Furthermore, we contacted field specialists to enquire about relevant ongoing or unpublished studies.

Data collection and analysis

Inclusion of non-English language studies

We considered abstracts and full texts in all languages for inclusion. All potentially eligible non-English language abstracts progressed to full-text review, with methods translated for eligibility, and full text translated for data extraction.

Selection of studies

Two review authors (JDST, LCUN) independently screened titles and abstracts of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve', using the Covidence tool. If there were any disagreements, we asked a third review author to arbitrate (RLGF). We retrieved the full-text study reports/publications, and two review authors (JDST, LCUN) independently screened the full text and identified studies for inclusion, while identifying and recording reasons for the exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third person (RLGF). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021), and Characteristics of excluded studies table. We considered studies reported as full text, those published as abstract only, and unpublished data. We considered abstracts and conference proceedings if they were eligible and had usable data.

Data extraction and management

We managed and synthesised the available data using Review Manager 5 (Review Manager 2020). If there was a conflict between

data reported across multiple sources for a single study (e.g. between a published article and a trial registry record), we planned to use the article published for numerical analysis, and we planned to report the differences and consider it on the certainty of evidence (GRADE approach; Schünemann 2013).

We used a data collection form, which we piloted on at least one study in the review, for study characteristics and outcome data. One review author (RLGF) extracted study characteristics from the included studies. We planned to extract the following study characteristics.

- Methods: study design, total duration of the study, number of study centres and location, study setting, and date of the study
- Participants: comorbidities, ventilation support, pregnancy, number randomised, number lost to follow-up/withdrawn, number analysed, number of interest, mean age, age range, gender, the severity of the condition, inclusion criteria, and exclusion criteria
- Interventions: intervention and comparison characteristics (e.g. manufacture, dosage, additional procedures, method of administration), concomitant medications, and excluded medications
- Outcomes: primary and secondary outcomes specified and collected (e.g. how outcomes are measured), and time points reported. For NRS: confounding factors controlled for each relevant analysis presented
- Notes: funding for the trial, and notable conflicts of interest of study authors

One review author (RLGF) extracted outcome data from included studies independently, which were verified by the other two review authors (CM, BT). We planned to resolve disagreements by discussion. One review author (RLGF) transferred data into Review Manager 5 (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the data extraction form. Two review authors (CM, BT) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

For data from RCTs we used RoB 1 to analyse the risk of bias in the underlying study results (Higgins 2017). For data from prospective NRS, we used the Risk Of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool, version of 2016 (Sterne 2016). We also planned to use ROBINS-I to assess the risk of bias in quasi-RCTs or retrospective NRS.

Randomised controlled trials

We planned for one review author (RLGF) to assess the risk of bias for each study, and another review author (LCUN) to check all judgements, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* for RCTs (RoB 1) (Higgins 2017). We planned to resolve any disagreements by consensus or by involving other review authors (CM, BT). For RCTs, we planned to assess the risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

In cluster-randomised trials, we planned to consider particular biases as recommended by section 8.15.1.1 of the *Cochrane Handbook for Systematic Reviews of Interventions*:

- recruitment bias;
- baseline imbalance;
- loss of clusters;
- incorrect analysis; and
- comparability with individually randomised trials (Higgins 2017).

We planned to grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the risk of bias table. We planned to summarise the risk of bias judgements across different studies for each of the domains listed. Where information on the risk of bias relates to unpublished data or correspondence with a study author, we planned to note this in the risk of bias table.

When considering treatment effects, we planned to take into account the risk of bias for the studies that contributed to that outcome.

We planned to base the overall bias judgement of included RCTs on the following three domains of RoB 1:

- adequate sequence generation;
- blinding of outcome assessors; and
- selective outcome reporting.

An RCT at low risk on all of these domains we planned to label as a low-risk study. An RCT at high risk on one of these domains we planned to label as a high-risk study. If there was no clear information on the risk of bias for one or more key domains, but the RCT was not at high risk for any domain, we planned to indicate that the risk of bias in the study was unclear.

Non-randomised studies

Using the ROBINS-I tool, version of 2016, we planned to assess the risk of bias of quasi-RCTs and NRS based on the following seven domains (Sterne 2016).

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from the intended intervention
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

We planned to use our risk of bias judgements for quasi-RCTs and NRS to label all outcomes at all time points, for each comparison, on these domains as 'critical risk', 'serious risk', 'moderate risk', 'low risk', or 'no information'. We planned to judge the overall risk of bias (across domains) as the worst judgment across all the domains. We were interested in the effect of assignment (intention to treat (ITT)) and ROBINS-I was used to assess all outcomes at all time points.

We considered the following confounders for the assessment of ROBINS-I domain on 'confounding' and used the Robvis tool to create the risk of bias graphs for NRS (McGuinness 2020).

- Participants already using anticoagulants (e.g. atrial fibrillation)
- Participants who underwent surgery during hospitalisation
- Active cancer treatment
- Concomitant antiplatelet use
- History of venous thromboembolism

Measures of treatment effect

Please refer to Appendix 1 for information regarding how we had planned to measure the treatment effects of RCTs, quasi-RCTs and NRS.

Unit of analysis issues

We included RCTs (for one comparison) and NRS (for another comparison) and performed meta-analysis when appropriate.

Please refer to Appendix 1 for information regarding how we had planned to combine studies with multiple treatment groups.

Dealing with missing data

We planned to contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where possible, we planned to use the Review Manager 5 calculator to calculate missing standard deviations using other data from the study, such as confidence intervals. Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. For all outcomes, we planned to follow ITT principles to the highest degree possible: that is, we planned to analyse participants in their randomised group regardless of what intervention they received. We planned to use available case data for the denominator if ITT data were not available. We estimated the mean difference (MD) using the method reported by Wan 2014 to convert median and interquartile range (IQR) into MD and confidence intervals (CI). When it was not possible, we narratively described skewed data reported as medians and IQRs.

Dealing with sparse data

We planned to adjust comparisons (e.g. grouping broader categories of participants (all ages), grouping broader variations of intervention (all types of anticoagulants) accordingly, regardless of sparse data.

Assessment of heterogeneity

We included RCTs (for one comparison) and NRS (for another comparison) and performed meta-analysis when appropriate.

Please refer to Appendix 1 for information regarding how we had planned to assess heterogeneity.

Assessment of reporting biases

If we were able to pool more than 10 studies, we planned to create and examine a funnel plot to explore possible small-study biases for the primary outcomes.

Data synthesis

We planned to use a fixed-effect model for meta-analysis when included studies were homogeneous (considering population, interventions, comparators and outcomes characteristics). We planned to use a random-effects model if we identified at least substantial heterogeneity, or if significant clinical differences regarding participants and interventions existed among included studies.

Please refer to Appendix 1 for information regarding how we had planned to synthesise data from RCTs, quasi-RCTs and NRS. We meta-analysed data from RCTs (one comparison) and from NRS (another comparison) when appropriate. We also reported the outcome data of each included study narratively and using tables.

Synthesis without meta-analysis

We planned to synthesise the data using Review Manager 5 (Review Manager 2020). We planned to report data narratively if it was not appropriate to combine it in a meta-analysis, and planned to undertake meta-analyses only where this was meaningful, that is, if the treatments, participants and underlying clinical question were similar enough for pooling to make sense.

We aimed to analyse data from NRS separately in a spreadsheet with the exposure of the sample number and the quantitative and qualitative variables relevant to the review, and we also meta-analysed data from NRS.

We intended to describe skewed data reported as medians and IQRs narratively.

If a meta-analysis was not possible, we planned to explore the possibilities above to show data of all relevant outcomes considered in this review. Where there was substantial clinical, methodological, or statistical heterogeneity across studies that prevented the pooling of data, we aimed to use a narrative approach to data synthesis. We planned to describe skewed data reported as medians and IQRs narratively.

Subgroup analysis and investigation of heterogeneity

We planned to explore the following subgroups related to participants or interventions if heterogeneity was substantial.

- Different doses of drugs
- Duration of prophylaxis (e.g. until 30 days after the start of intervention or more)
- Age (e.g. children (up to 18 years), adults (18 years to 64 years) and seniors (65 years and over))
- Gender
- Comorbidities
- Illness severity
- Type of ventilator support:
  - oxygen by non-invasive ventilators or high flow
  - intubation and mechanical ventilation
  - extracorporeal membrane oxygenation

Sensitivity analysis

We planned to carry out the following sensitivity analyses to test whether critical methodological factors or decisions have affected

the main result. We planned to group according to study design (RCTs or cluster-RCTs, quasi-RCTs, NRS).

- Only including studies with a low risk of bias, as previously specified ('Assessment of risk of bias in included studies').
- We planned to examine both the fixed-effect model and random-effects model meta-analyses, and we planned to explore the differences between the two estimates.
- We planned to explore the decision to include all participants when at least 50% were of interest in a study with a mixed population.
- We planned to explore the impact of missing data. If we identified studies with missing data that were unobtainable, we planned to repeat analyses excluding these studies to determine their impact on the primary analyses.

We also planned to carry out sensitivity analyses considering cluster-RCTs and investigate the effect of variation in the intracluster correlation coefficient (ICC), as well as planning to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of this randomisation unit. We aimed to present these results and compare them with the overall findings. We planned to justify any post hoc sensitivity analyses that arose during the review process in the final report.

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table for both short-term and long-term time points using the following outcomes.

- All-cause mortality
- Necessity for additional respiratory support
- Mortality related to COVID-19
- Deep vein thrombosis
- Pulmonary embolism
- Major bleeding
- Minor bleeding

We used the five GRADE considerations (study limitations; consistency of effect; imprecision; indirectness; and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contributed data to the analyses for the prespecified outcomes. We used methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021), using GRADEpro GDT software. We made a separate summary of findings table for each of the following comparisons with available data.

- Anticoagulants (higher dose) versus anticoagulants (lower dose)
- Anticoagulant (all types) versus no treatment

We justified all decisions to downgrade the certainty of evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

Two review authors (RLGF, VTC) made judgements about the certainty of the evidence, with disagreements resolved by discussion or by involving a third review author (LCUN). We justified, documented and incorporated judgements into reporting of results for each outcome. We extracted study data, formatted our comparisons in data tables and prepared a summary of findings table with meta-analysis before writing the results and conclusions of our review.

Figure 1. Study flow diagram

RESULTS

Results of the search

For this update, we identified 7322 new records in addition to the 1148 potentially relevant records from the first version (altogether 8470 records). After removing duplicates, we screened 7329 records based on their titles and abstracts, and excluded 7072 records that did not meet the prespecified inclusion criteria. We selected 257 records for full-text reading. We excluded 129 studies after a full-text analysis as we considered them not relevant and we excluded 59 studies for at least one reason (see Characteristics of excluded studies). Sixty-two studies are ongoing (see Characteristics of ongoing studies).

For this review, we found seven studies with available data for inclusion; four RCTs (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021), and three NRS (Albani 2020; Rentsch 2020; Santoro 2020). See Figure 1 for the study flow diagram (Page 2021). As there is now evidence available from RCTs, and prospective NRS, we excluded the studies analysed in the previous version of this review because they were all retrospective NRS (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020; Trinh 2020) (Flumignan 2020b).

RCT: randomised controlled trial; NRS: non-randomised study

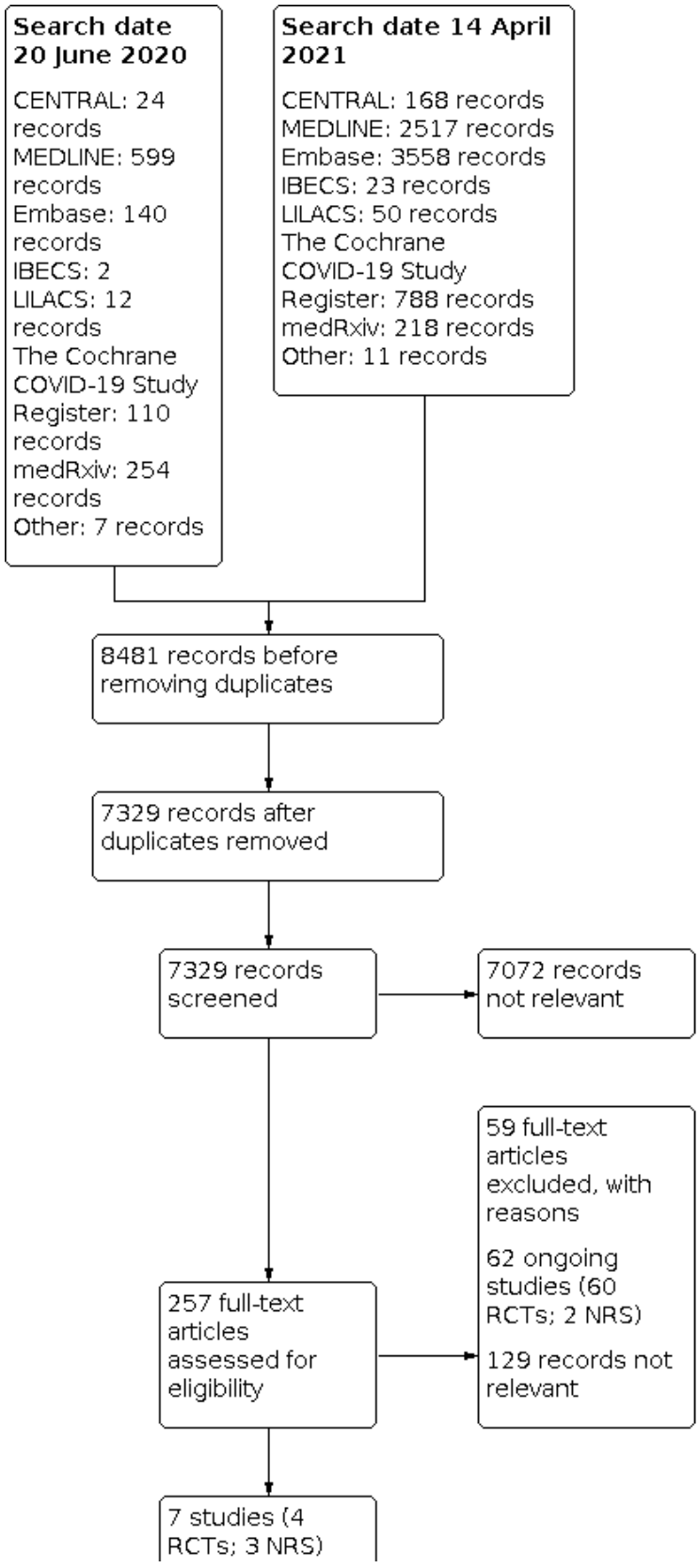
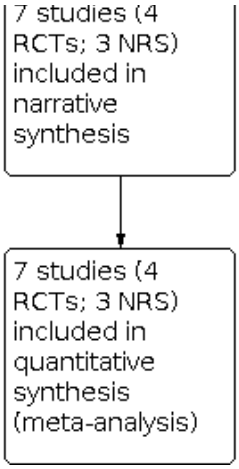


Figure 1. (Continued)



Included studies

See Table 2 for the summarised characteristics of included studies.

We included seven studies describing 16,185 participants in this review, of whom at least 9403 received anticoagulants (Albani 2020; Lemos 2020; Lopes 2021; Rentsch 2020; Sadeghipour 2021; Santoro 2020; Zarychanski 2021). From the seven included studies, four were RCTs (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021) and the other three NRS of interventions (Albani 2020; Rentsch 2020; Santoro 2020), with a comparator group. Of the seven included studies, two originated from Brazil (Lemos 2020; Lopes 2021), one from Iran (Sadeghipour 2021), one from Italy (Albani 2020), and one from the USA (Rentsch 2020), while two involved several countries (Santoro 2020; Zarychanski 2021).

All included RCTs compared different doses of anticoagulant (lower versus higher) (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021), and all included NRS compared anticoagulation versus no anticoagulation (Albani 2020; Rentsch 2020; Santoro 2020). All included studies reported a follow-up period that varied from 15 to 90 days. All included studies considered participants from all settings (ICU, hospital wards and emergency departments), but only Zarychanski 2021 reported data separately by disease severity (critically ill and moderate severity). All included studies reported data regarding the age of participants; the mean age varied from 55 to 68.66 years. All studies reported data on mortality, and four reported data for the necessity for additional respiratory support (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021).

All studies described the type and dose of anticoagulation. Four studies used only heparin in the intervention group (Albani 2020; Lemos 2020; Sadeghipour 2021; Zarychanski 2021), and the other three analysed data from heparin, vitamin K antagonist or direct anticoagulants. Only Sadeghipour 2021 compared higher-dose anticoagulation (enoxaparin 1 mg/kg once daily, modified according to body weight and creatinine clearance) versus lower-dose anticoagulation (enoxaparin 40 mg once daily, modified according to body weight and creatinine clearance) without a therapeutic dose. The other three RCTs compared therapeutic (higher) dose anticoagulation versus prophylactic (lower) dose anticoagulation.

Please refer to the Characteristics of included studies for detailed information.

Excluded studies

We excluded 59 studies for at least one reason (Characteristics of excluded studies). Four studies had ineligible interventions because they evaluated aspirin (NCT04365309), anticoagulants for arterial line heparinisation (Maurer 2020), or anti-inflammatory drugs (EUCTR2020-001748-24-SE; Mareev 2020), and there was no difference between the intervention groups regarding anticoagulants. Ten studies evaluated ineligible participants (CTRI/2021/01/030373; Kukin 2020; NCT04483830; NCT04492254; NCT04504032; NCT04516941; NCT04662684; NCT04673214; NCT04715295; NCT04757857), and all other excluded studies had an ineligible study design for one of the following reasons:

- retrospective cases series without a consistent comparator group;
- prospective cohort study without a comparator group (single-arm study);
- prospective cohort study without an intervention purpose;
- prospective before-after cohort study without a parallel comparator group;
- editorial articles;
- retrospective NRS (new registers and previously included studies from the first version of this review (Flumignan 2020b));
- prospective cohort study without a parallel comparator group of intervention.

Ongoing studies

Sixty-two ongoing studies met our inclusion criteria. They plan to evaluate 35,470 participants (120 participants from two NRS and 35,350 participants from 60 RCTs). From 60 RCTs, 28 are comparing different doses of anticoagulants, 24 are comparing anticoagulants versus no anticoagulants, seven are comparing different types of anticoagulants, and one did not report detail of the comparator group (Wilkinson 2020). We tried to contact the study authors and also searched by study registration number and title of the study on all databases of interest for this review. However, there are no additional data for all these ongoing studies. See the Characteristics of ongoing studies table for further details.

Six of the ongoing studies plan to include 1000 participants or more in RCTs (CTRI/2020/11/029345; EUCTR2020-001708-41-IT; NCT04333407; NCT04366960; NCT04512079; Wilkinson 2020).

- CTRI/2020/11/029345 plans to compare prophylactic enoxaparin, full-dose enoxaparin and apixaban versus no anticoagulant in 3600 participants to assess the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism or ischaemic stroke.
- EUCTR2020-001708-41-IT plans to compare 40 mg enoxaparin once daily versus twice daily in 2000 participants to assess the incidence of venous thromboembolism.
- NCT04333407 plans to compare aspirin, clopidogrel, rivaroxaban, atorvastatin, and omeprazole with no treatment in 3170 participants to assess mortality at 30 days.
- NCT04366960 plans to compare 40 mg subcutaneous enoxaparin twice daily versus 40 mg subcutaneous enoxaparin once daily to assess venous thromboembolism in 2712 participants. NCT04512079 plans to compare apixaban versus prophylactic enoxaparin and full-dose enoxaparin in 3600 participants to assess overt bleeding plus haemoglobin drop, cardiac tamponade, bleeding requiring surgical intervention for control, bleeding requiring vasoactive agents, or intracranial haemorrhage (time to event).
- Wilkinson 2020 plans to compare several possible interventions (without details about type or dose of anticoagulants) in 1800 participants to assess time to clinical improvement.

See Table 3 for a summary of the characteristics of ongoing studies.

Risk of bias in included studies

Risk of bias in randomised controlled trials

Overall judgement

We assessed the risk of bias at the study level using RoB 1 for RCTs (Higgins 2017). The specific judgements ('high risk', 'low risk' or 'unclear risk') by available studies are presented in Figure 2 and Figure 3, and the support for judgement is explained in the related risk of bias tables (Characteristics of included studies). Lopes 2021 and Sadeghipour 2021 had a low overall risk of bias. We judged the other two RCTs at a high overall risk of bias because of 'blinding of outcomes assessment' domain issues (Lemos 2020; Zarychanski 2021), and 'selective reporting' domain issues (Zarychanski 2021).

Figure 2. RoB 1.0 assessments for randomised controlled trials

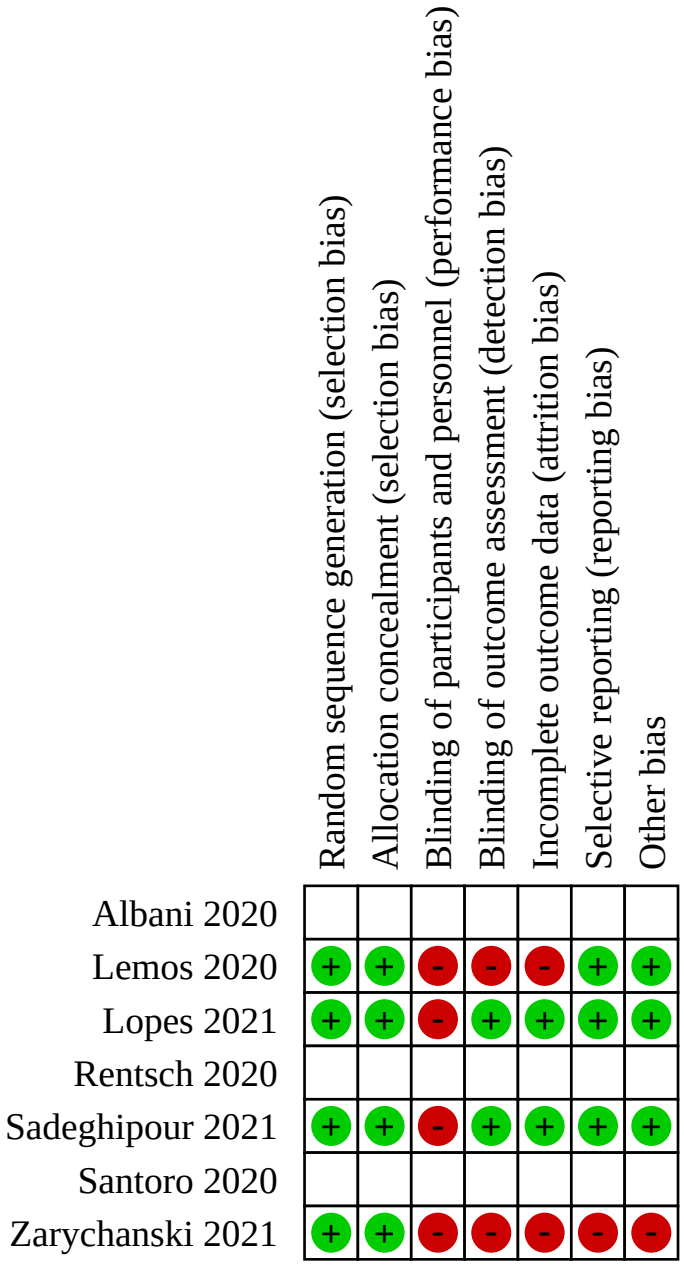
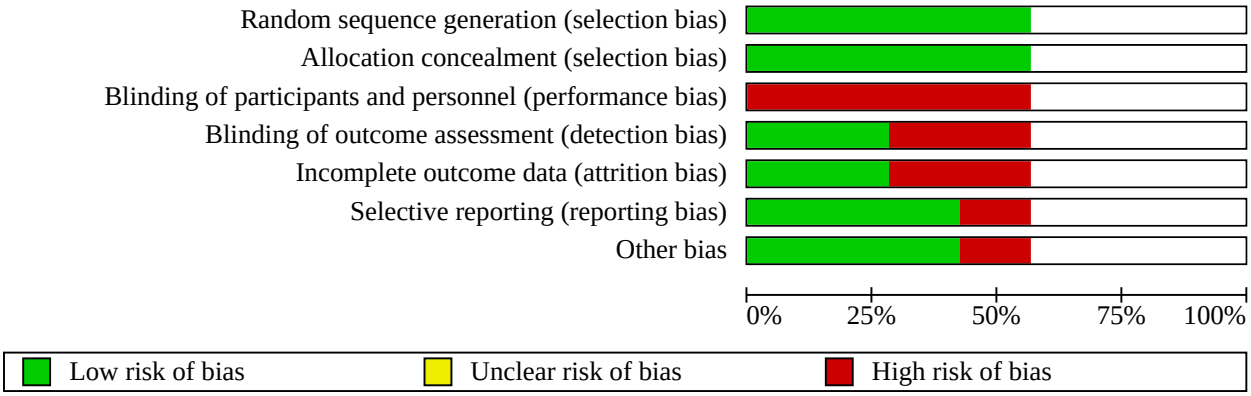


Figure 3. RoB 1.0 graph: assessments for randomised controlled trials presented as percentages across studies.



Allocation (selection bias)

All four studies had a low risk of bias for random sequence generation and for allocation concealment (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021).

Blinding (performance bias and detection bias)

Although anticoagulation is a pharmacological intervention that allows the blinding of participants and personnel, all included studies had a high risk of bias (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021).

We assessed two studies to be at low risk of bias for blinding of outcome assessment (Lopes 2021; Sadeghipour 2021), and two at high risk of bias for this domain (Lemos 2020; Zarychanski 2021).

Incomplete outcome data (attrition bias)

Two studies had a high risk of bias for incomplete outcome reporting (Lemos 2020; Zarychanski 2021). Conversely, Lopes 2021 and Sadeghipour 2021 had a low risk of bias.

Selective reporting (reporting bias)

Zarychanski 2021 was at high risk of bias for selective reporting and none was at unclear risk of bias for this domain. All other included studies (3/4) had a low risk of bias for this domain (Lemos 2020; Lopes 2021; Sadeghipour 2021).

Other potential sources of bias

Zarychanski 2021 was at high risk of bias for other potential sources of bias and all other studies were at low risk of bias for this domain (Lemos 2020; Lopes 2021; Sadeghipour 2021).

Although the study authors declare that they harmonised their protocols into a "prospectively multiplatform uniformisation", Zarychanski 2021 combined the results from three different trials registries, with different 'centres' of randomisation and documentation. There is a possibility of additional heterogeneity in overall results when combining these three trials as a unique trial:

- There was an imbalance of losses to follow-up (moderate-severity: experimental = 19 losses (1.5%), comparator = 7 losses (0.6%)).
- There was a factorial randomisation for antiplatelet agent intervention in one of the considered trials (REMAP-CAP).
- There was a change in the primary outcome specified in the registered protocols compared to the unique reported primary outcome.

We contacted the study authors requesting the data separately, without success. Therefore, we considered Zarychanski 2021 data as a unique study.

Risk of bias in non-randomised controlled trials

Overall judgement

We assessed the risk of bias at the results level using ROBINS-I tool for all NRS (Sterne 2016). The specific judgements ('critical risk', 'serious risk', 'moderate risk', 'low risk', or 'no information') by available outcomes are presented in Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9 and Figure 10. The support for ROBINS-I judgement is explained in the related risk of bias tables (Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10). We will provide detailed risk of bias assessment data on request. The overall risk of bias for all-cause mortality, deep vein thrombosis, pulmonary embolism, major bleeding, adverse events (stroke and myocardial infarction) in the comparison 'anticoagulants (all types) versus no treatment' was critical. The overall risk of bias for hospitalisation was serious for the same comparison.

Figure 4. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (all-cause mortality)

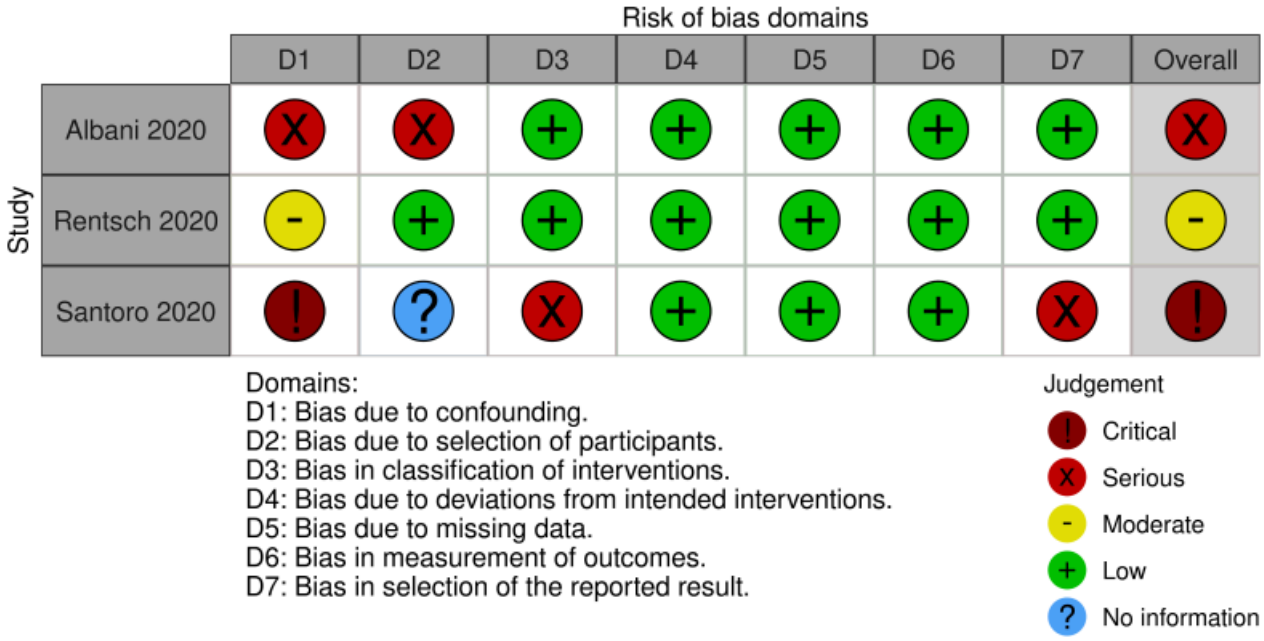


Figure 5. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (deep vein thrombosis)

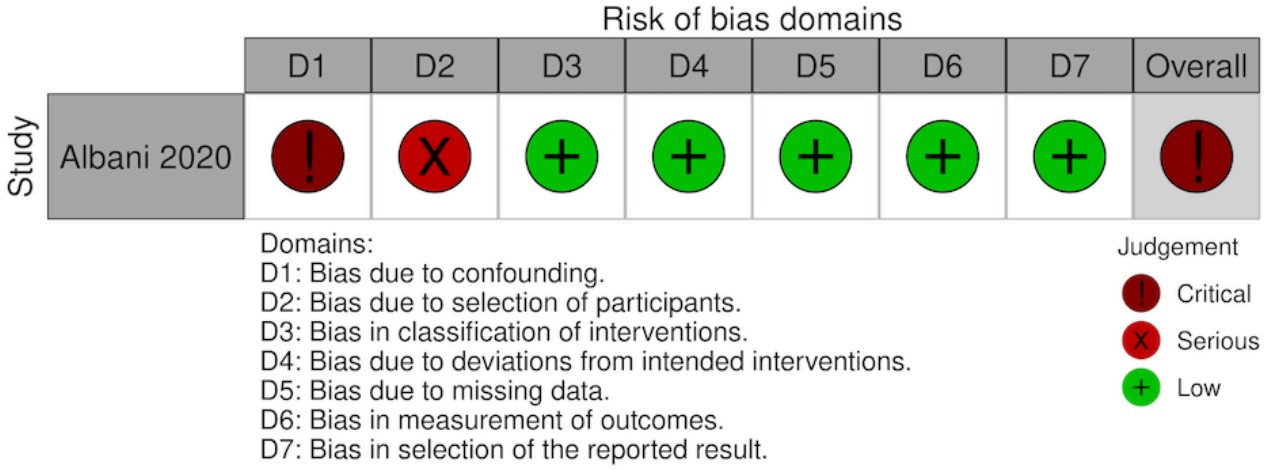


Figure 6. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (pulmonary embolism)

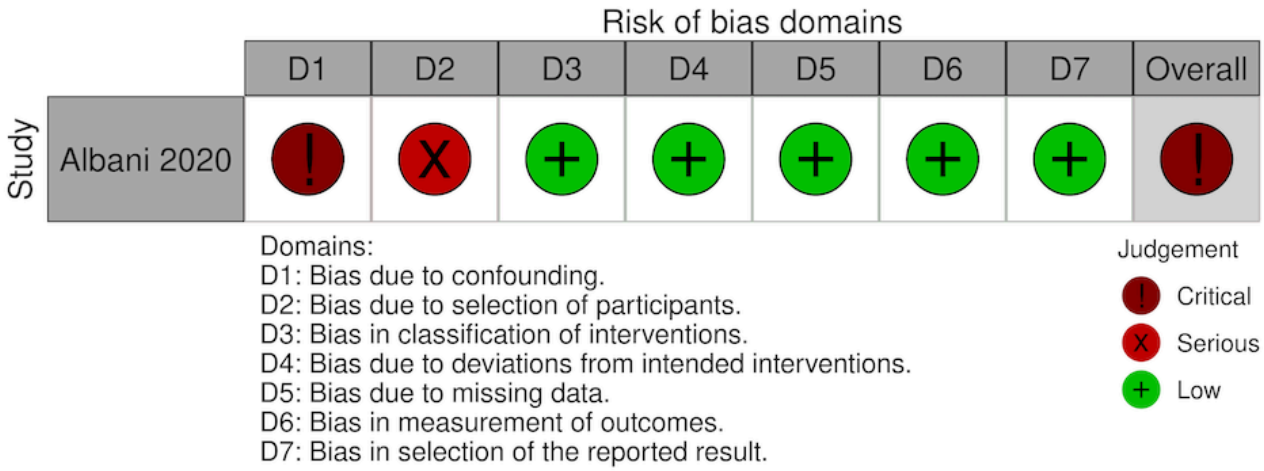


Figure 7. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (major bleeding)

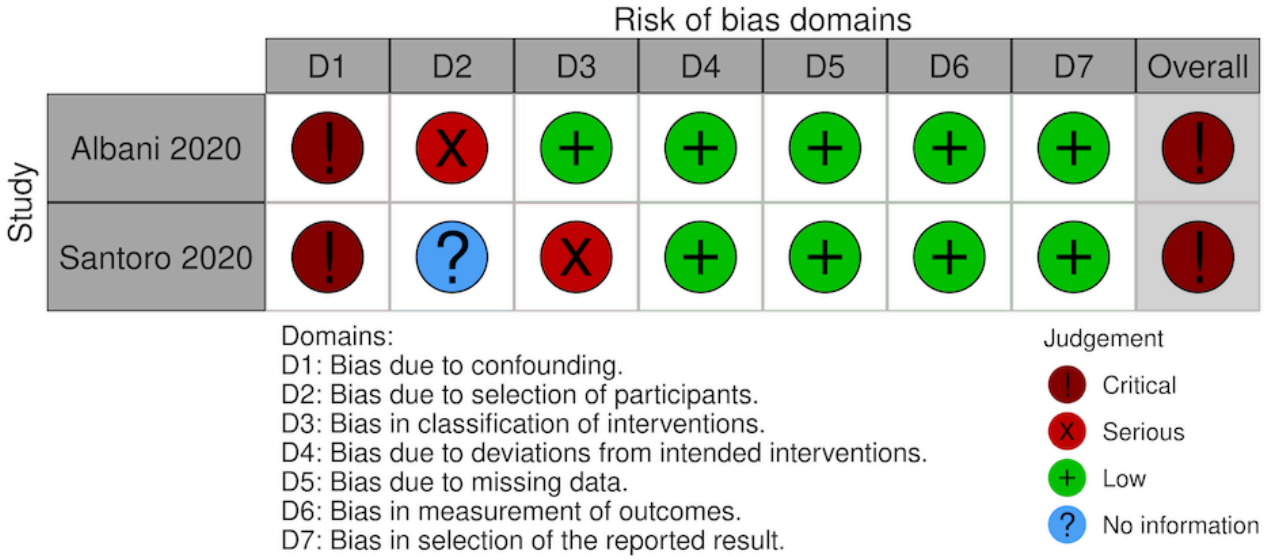


Figure 8. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (adverse events: stroke)

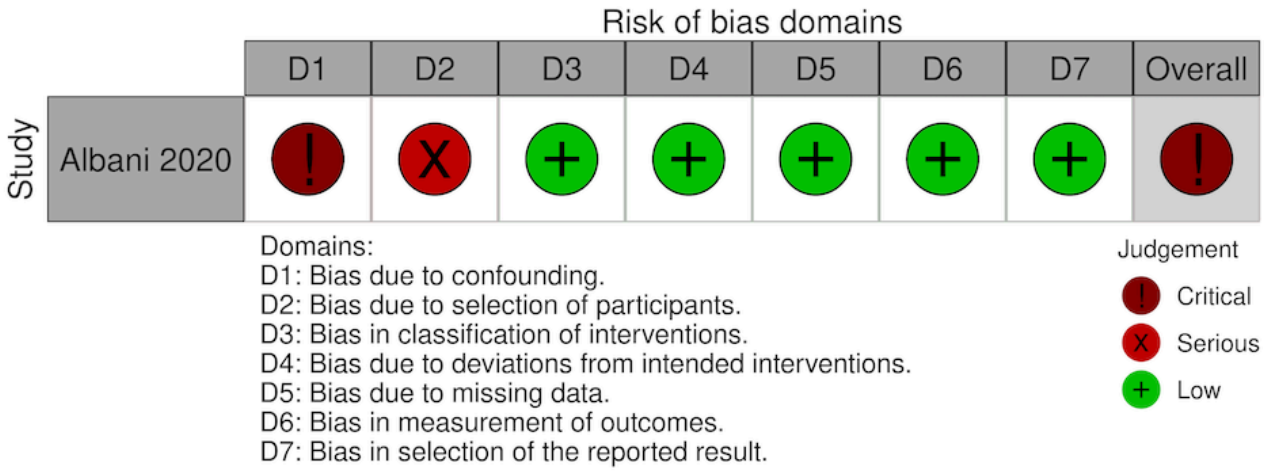


Figure 9. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (adverse events: myocardial infarction)

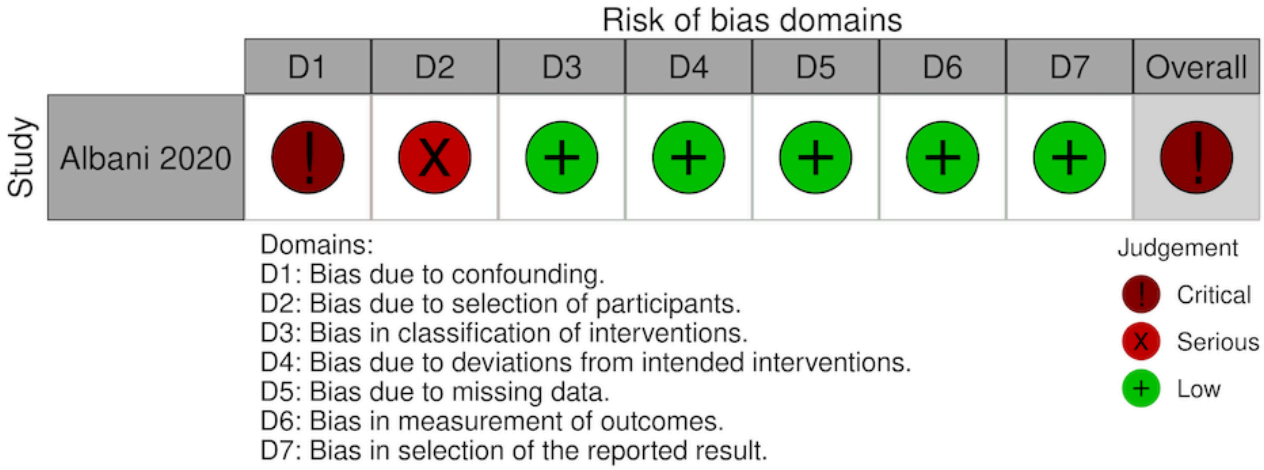
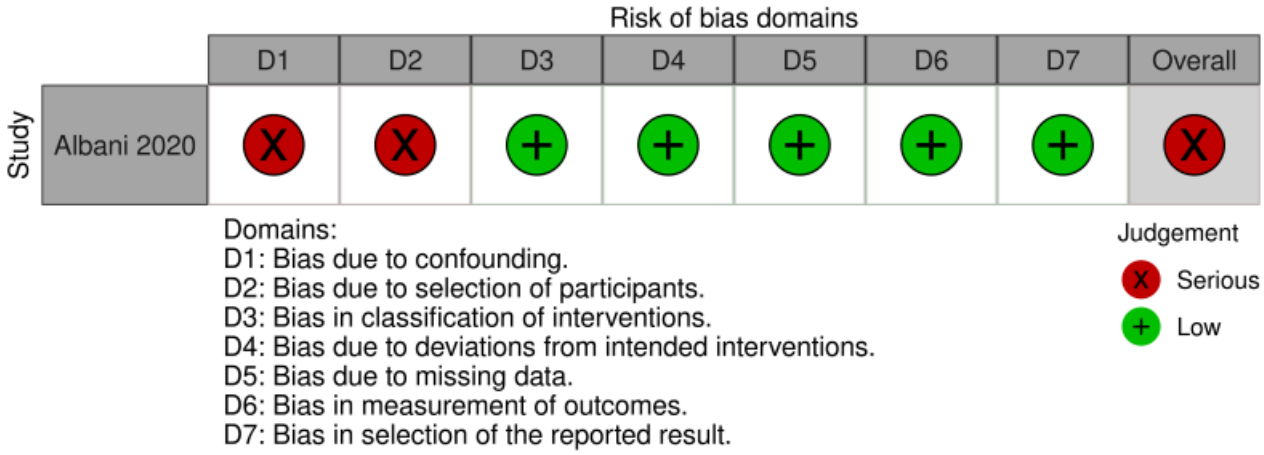


Figure 10. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (hospitalisation)



All-cause mortality

'Three studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment'. We rated Albani 2020 as serious risk due to confounding and selection of participants. We rated Albani 2020 as low risk for all other domains. We rated Rentsch 2020 as moderate risk for confounding and low risk for all other domains. We rated Santoro 2020 as a critical risk due to confounding, serious risk due to problems with the 'classification of interventions' and 'selection of reported results' items. There was no information about bias due to the selection of participants in Santoro 2020, and all other domains were at low risk. See Figure 4 and Table 4.

Deep vein thrombosis

Albani 2020 reported deep vein thrombosis for the comparison 'anticoagulants (all types) versus no treatment'. We rated Albani 2020 as a critical risk for confounding, serious risk for the selection of participants and low risk for all other domains. See Figure 5 and Table 5.

Pulmonary embolism

Albani 2020 reported pulmonary embolism for the comparison 'anticoagulants (all types) versus no treatment'. We rated Albani 2020 as a critical risk for confounding, serious risk for the selection of participants and low risk for all other domains. See Figure 6 and Table 6.

Major bleeding

Albani 2020 and Santoro 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated both studies as a critical risk of confounding, Albani 2020 as serious risk for the selection of participants and Santoro 2020 as a serious risk for the classification of interventions. Albani 2020 did not report information on the selection of participants and we rated all other domains as low risk for both studies. See Figure 7 and Table 7.

Adverse events (stroke)

Albani 2020 reported stroke for the comparison 'anticoagulants (all types) versus no treatment'. We rated Albani 2020 as a critical risk to confounding, serious risk to the selection of participants and low risk to all other domains. See Figure 8 and Table 8.

Adverse events (myocardial infarction)

Albani 2020 reported myocardial infarction for the comparison 'anticoagulants (all types) versus no treatment'. We rated Albani 2020 as a critical risk for confounding, serious risk for the selection of participants and low risk for all other domains. See Figure 9 and Table 9.

Hospitalisation

Albani 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated Albani 2020 as serious risk for confounding and for the selection of participants, and as low risk for all other domains. See Figure 10 and Table 10.

Effects of interventions

We included three NRS of interventions for the comparison 'anticoagulants (all types) versus no treatment' (short-term time point) and four RCTs for the comparison 'higher-dose anticoagulants versus lower-dose anticoagulants' (short-term and long-term time points) and performed quantitative data analysis (meta-analysis) when appropriate. We did not perform any funnel plot analysis because there is no comparison with 10 or more studies in this review.

1. Higher-dose anticoagulants versus lower-dose anticoagulants (short term)

Four RCTs (Lemos 2020; Lopes 2021; Sadeghipour 2021; Zarychanski 2021), compared heparins (unfractionated heparin) or low-molecular-weight heparin) or direct oral anticoagulants (rivaroxaban) in higher doses (2376 participants) versus heparins

(unfractionated heparin or low-molecular-weight heparin) or direct oral anticoagulants (rivaroxaban) in lower doses (2271 participants). Only Zarychanski 2021 reported outcomes data separately by moderate-severity and critically ill disease, and we, therefore, included this study in both subgroups. More than 82% of participants in Lopes 2021 had moderate-severity disease; therefore, we included them in the moderate-severity subgroup. Lemos 2020 and Sadeghipour 2021 included only participants under invasive ventilatory support or in ICU; therefore, we analysed their data in the critically ill subgroup. See Summary of findings 1.

Primary outcomes

All-cause mortality

All studies reported all-cause mortality with a follow-up of up to 30 days. Higher-dose anticoagulants result in little to no difference in all-cause mortality compared to lower-dose anticoagulants for up to 30 days (RR 1.03, 95% CI 0.92 to 1.16; I^2 = 5%; 4 studies, 4489 participants; high-certainty evidence; Analysis 1.1). The test for subgroup differences suggested that the severity of the condition has no modifying effect on the all-cause mortality (Chi^2 = 0.07, df = 1 (P = 0.80), I^2 = 0%; Analysis 1.1).

The sensitivity analysis including only trials at low risk of bias (RR 1.16, 95% CI 0.86 to 1.57; Analysis 1.2) did not substantially change the effect estimate.

Necessity for additional respiratory support

Three studies reported the necessity for additional respiratory support with a follow-up for up to 30 days (Lopes 2021; Sadeghipour 2021; Zarychanski 2021). Lemos 2020 did not report the necessity for additional respiratory support and Zarychanski 2021 reported this outcome only for moderate-severity participants. Lopes 2021 and Sadeghipour 2021 reported these outcomes for all participants. The evidence is very uncertain about the effect of higher-dose anticoagulants on necessity for additional respiratory support compared to lower-dose anticoagulants up to 30 days (RR 0.54, 95% CI 0.12 to 2.47; I^2 = 60%; 3 studies, 3407 participants; very low-certainty evidence; Analysis 1.3). The test for subgroup differences was not applicable because the effect in Sadeghipour 2021 was not estimable (no events).

The sensitivity analysis including only trials at low risk of bias (RR 0.16, 95% CI 0.02 to 1.35; Analysis 1.4) substantially changed the effect estimate.

Secondary outcomes

Mortality related to COVID-19

There were no available data for this outcome.

Deep vein thrombosis

Although Zarychanski 2021 reported this outcome only for moderate severity participants, all studies reported deep vein thrombosis with a follow-up of up to 30 days. Higher-dose anticoagulants may result in little to no difference in deep vein thrombosis compared to lower-dose anticoagulants up to 30 days (RR 1.08, 95% CI 0.57 to 2.03; I^2 = 0%; 4 studies, 3422 participants; low-certainty evidence; Analysis 1.5). The test for subgroup differences suggested that the severity of the condition has no modifying effect on deep vein thrombosis (Chi^2 = 0.82, df = 1 (P = 0.36), I^2 = 0%; Analysis 1.5).

The sensitivity analysis including only trials at low risk of bias (RR 1.21, 95% CI 0.53 to 2.79; Analysis 1.6) did not change the effect estimate substantially.

Pulmonary embolism

All studies reported pulmonary embolism with a follow-up of up to 30 days. Higher-dose anticoagulants may reduce pulmonary embolism compared to lower-dose anticoagulants for up to 30 days (RR 0.46, 95% CI 0.31 to 0.70; I^2 = 0%; 4 studies, 4360 participants; moderate-certainty evidence; Analysis 1.7). The test for subgroup differences suggested that the severity of the condition has no modifying effect on pulmonary embolism (Chi^2 = 0.08, df = 1 (P = 0.78), I^2 = 0%; Analysis 1.7).

The sensitivity analysis including only trials at low risk of bias (RR 0.50, 95% CI 0.23 to 1.10; Analysis 1.8) changed the effect estimate substantially.

Major bleeding

All studies reported major bleeding with a follow-up of up to 30 days. Higher-dose anticoagulants likely increase major bleeding slightly compared to lower-dose anticoagulants up to 30 days (RR 1.78, 95% CI 1.13 to 2.80; I^2 = 0%; 4 studies, 4400 participants; moderate-certainty evidence; Analysis 1.9). The test for subgroup differences suggested that the severity of the condition has no modifying effect on major bleeding (Chi^2 = 1.03, df = 1 (P = 0.31), I^2 = 2.8%; Analysis 1.9).

The sensitivity analysis including only trials at low risk of bias (RR 2.13, 95% CI 0.92 to 4.90; Analysis 1.10) substantially changed the effect estimate.

Adverse events (minor bleeding, gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, abdominal pain), allergic reactions, renal failure and amputations)

Minor bleeding

Three studies reported minor bleeding with a follow-up of up to 30 days (Lemos 2020; Lopes 2021; Sadeghipour 2021). Higher-dose anticoagulants increase adverse events (minor bleeding) compared to lower-dose anticoagulants up to 30 days (RR 3.28, 95% CI 1.75 to 6.14; I^2 = 0%; 3 studies, 1196 participants; high-certainty evidence; Analysis 1.11). The test for subgroup differences suggested that the severity of the condition has no modifying effect on minor bleeding (Chi^2 = 1.50, df = 1 (P = 0.22), I^2 = 33.5%; Analysis 1.11).

The sensitivity analysis including only trials at low risk of bias (RR 3.67, 95% CI 1.82 to 7.40; Analysis 1.12) did not change the effect estimate substantially.

Stroke

Three studies reported stroke with a follow-up of up to 30 days (Lopes 2021; Sadeghipour 2021; Zarychanski 2021). Higher-dose anticoagulants may result in little to no difference in adverse events (stroke) compared to lower-dose anticoagulants for up to 30 days (RR 0.91, 95% CI 0.40 to 2.03; I^2 = 0%; 3 studies, 4349 participants; low-certainty evidence; Analysis 1.13). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm). The test for

subgroup differences suggested that the severity of the condition has no modifying effect on stroke (Chi^2 = 0.00, df = 1 (P = 0.97), I^2 = 0%; Analysis 1.13).

The sensitivity analysis including only trials at low risk of bias (RR 1.62, 95% CI 0.20 to 13.13; Analysis 1.14) did not substantially change the effect estimate.

Major adverse limb events

Two studies reported major adverse limb events with a follow-up of up to 30 days (Lopes 2021; Sadeghipour 2021). Higher-dose anticoagulants may result in little to no difference in major adverse limb events compared to lower-dose anticoagulants for up to 30 days (RR 0.33, 95% CI 0.01 to 7.99; I^2 not applicable; 2 studies, 1176 participants; low-certainty evidence; Analysis 1.15). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm). The test for subgroup differences was not applicable because Sadeghipour 2021 reported no events in both groups.

We judged both studies as low risk of bias and, therefore, no sensitivity analysis was applicable.

Myocardial infarction

Three studies reported myocardial infarction with a follow-up of up to 30 days (Lopes 2021; Sadeghipour 2021; Zarychanski 2021). Higher-dose anticoagulants may result in little to no difference in myocardial infarction compared to lower-dose anticoagulants for up to 30 days (RR 0.86, 95% CI 0.48 to 1.55; I^2 = 0%; 3 studies, 4349 participants; low-certainty evidence; Analysis 1.16). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm). The test for subgroup differences suggested that the severity of the condition has no modifying effect on stroke (Chi^2 = 0.08, df = 1 (P = 0.78), I^2 = 0%; Analysis 1.16).

The sensitivity analysis including only trials at low risk of bias (RR 0.91, 95% CI 0.44 to 1.91; Analysis 1.17) did not substantially change the effect estimate.

Atrial fibrillation

Sadeghipour 2021 reported atrial fibrillation with a follow-up of up to 30 days. Higher-dose anticoagulants may result in little to no difference in atrial fibrillation compared to lower-dose anticoagulants for up to 30 days (RR 0.35, 95% CI 0.07 to 1.70, I^2 not applicable; 1 study, 562 participants; low-certainty evidence; Analysis 1.18). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm).

Thrombocytopenia

Two studies reported thrombocytopenia with a follow-up of up to 30 days (Sadeghipour 2021; Zarychanski 2021). Higher-dose anticoagulants may result in little to no difference in thrombocytopenia compared to lower-dose anticoagulants for up to 30 days (RR 0.94, 95% CI 0.71 to 1.24; I^2 not applicable; 2 studies, 2789 participants; low-certainty evidence; Analysis 1.19). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm). The test for subgroup differences and the sensitivity analysis were not applicable because Zarychanski 2021 reported no events in both groups.

Hospitalisation time in days

Two studies reported the hospitalisation time in days with a follow-up of up to 30 days for moderate-severity (Lopes 2021), and critically ill (Lemos 2020), participants. Higher-dose anticoagulants probably result in little to no difference in hospitalisation time compared to lower-dose anticoagulants up to 30 days (MD 0.28 days, 95% CI −0.87 to 1.44; I^2 = 0%; 2 studies, 634 participants; moderate-certainty evidence; Analysis 1.20). The test for subgroup differences (Chi^2 = 0.06, df = 1 (P = 0.81), I^2 = 0%; Analysis 1.20) did not change the effect estimate.

The sensitivity analysis including only trials at low risk of bias (MD 0.30, −0.86 to 1.46; Analysis 1.21) did not change the effect estimate substantially.

Quality of life

There were no available data for this outcome.

2. Higher-dose anticoagulants versus lower-dose anticoagulants (long term)

Sadeghipour 2021 compared enoxaparin (low-molecular-weight heparin) in higher doses (299 participants) versus enoxaparin in lower doses (299 participants) for participants in ICU and reported data at the follow-up of up to 90 days (long term).

Primary outcomes

All-cause mortality

Sadeghipour 2021 reported all-cause mortality with a follow-up of up to 90 days. Higher-dose anticoagulants may result in little to no difference in all-cause mortality compared to lower-dose anticoagulants up to 90 days (RR 1.07, 95% CI 0.89 to 1.28; I^2 not applicable; 1 study, 590 participants; moderate-certainty evidence; Analysis 2.1). We downgraded the evidence one level due to imprecision (fewer than 300 events were included in the analysis).

Necessity for additional respiratory support

Sadeghipour 2021 reported the necessity for additional respiratory support with a follow-up of up to 90 days. The evidence is not estimable about the effect of higher-dose anticoagulants on necessity for additional respiratory support compared to lower-dose anticoagulants up to 90 days (no events in both groups; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.2). We downgraded the evidence two levels due to imprecision (no events).

Secondary outcomes

Mortality related to COVID-19

There were no available data for this outcome.

Deep vein thrombosis

Sadeghipour 2021 reported deep vein thrombosis with a follow-up of up to 90 days. Higher-dose anticoagulants may result in little to no difference in deep vein thrombosis compared to lower-dose anticoagulants up to 90 days (RR 1.39, 95% CI 0.45 to 4.33; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.3). We downgraded the evidence two levels due to imprecision (CI of the absolute difference comprises both

important clinical benefit and harm, and fewer than 300 events were included in the analysis).

Pulmonary embolism

Sadeghipour 2021 reported pulmonary embolism with a follow-up of up to 90 days. Higher-dose anticoagulants may reduce pulmonary embolism compared to lower-dose anticoagulants up to 90 days (RR 0.40, 95% CI 0.08 to 2.03; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.4). We downgraded the evidence two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and harm, and fewer than 300 events were included in the analysis).

Major bleeding

Sadeghipour 2021 reported major bleeding with a follow-up of up to 90 days. Higher-dose anticoagulants may result in little to no difference in major bleeding compared to lower-dose anticoagulants up to 90 days (RR 1.74, 95% CI 0.51 to 5.87; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.5). We downgraded the evidence two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and harm, and fewer than 300 events were included in the analysis).

Adverse events (minor bleeding, gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, abdominal pain), allergic reactions, renal failure and amputations)

Minor bleeding

Sadeghipour 2021 reported minor bleeding with a follow-up of up to 90 days. Higher-dose anticoagulants may increase minor bleeding compared to lower-dose anticoagulants up to 90 days (RR 2.32, 95% CI 0.90 to 5.95; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.6). We downgraded the evidence two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and harm, and fewer than 300 events were included in the analysis).

Stroke

Sadeghipour 2021 reported stroke with a follow-up of up to 90 days. Higher-dose anticoagulants may result in no difference in stroke compared to lower-dose anticoagulants up to 90 days (RR 0.99, 95% CI 0.06 to 15.80; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.7). We downgraded the evidence two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and harm, and fewer than 300 events were included in the analysis).

Acute peripheral arterial thrombosis

Sadeghipour 2021 reported acute peripheral arterial thrombosis with a follow-up of up to 90 days. The evidence is not estimable about the effect of higher-dose anticoagulants on acute peripheral arterial thrombosis compared to lower-dose anticoagulants up to 90 days (no events in both groups; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.8). We downgraded the evidence two levels due to imprecision (no events).

Myocardial infarction

Sadeghipour 2021 reported myocardial infarction with a follow-up of up to 90 days. The evidence is not estimable about the effect of higher-dose anticoagulants on myocardial infarction compared to lower-dose anticoagulants up to 90 days (no events in both groups; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.9). We downgraded the evidence two levels due to imprecision (no events).

Atrial fibrillation

Sadeghipour 2021 reported atrial fibrillation with a follow-up of up to 90 days. Higher-dose anticoagulants may result in little to no difference in atrial fibrillation compared to lower-dose anticoagulants up to 90 days (RR 0.50, 95% CI 0.13 to 1.97; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.10). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm).

Thrombocytopenia

Sadeghipour 2021 reported thrombocytopenia with a follow-up of up to 90 days. Higher-dose anticoagulants may result in little to no difference in adverse events (thrombocytopenia) compared to lower-dose anticoagulants up to 90 days (RR12.91, 95% CI 0.73 to 228.18; I^2 not applicable; 1 study, 590 participants; low-certainty evidence; Analysis 2.11). We downgraded two levels due to imprecision (CI of the absolute difference comprises both important clinical benefit and important clinical harm).

Hospitalisation time in days

There were no available data for this outcome.

Quality of life

There were no available data for this outcome.

3. Anticoagulants (all types) versus no treatment

Three studies compared enoxaparin (low-molecular-weight heparin) (Albani 2020), heparinoids (unfractionated heparin, low-molecular-weight heparin or fondaparinux), direct anticoagulants or vitamin K antagonists (Rentsch 2020; Santoro 2020) (7027 participants) to no treatment (4511 participants). Albani 2020 and Rentsch 2020 compared "prophylactic anticoagulation" (including oral, subcutaneous, or intravenous forms) to no treatment. Santoro 2020 compared "prophylactic anticoagulation" in 83% of cases, while 15% received a full dose of low-molecular-weight heparin, 1% oral anticoagulation with AVK, and 1% direct anticoagulants (including oral, subcutaneous, or intravenous forms) no treatment. See Summary of findings 2.

The *Cochrane Handbook for Systematic Reviews of Interventions* states that studies judged to be at critical risk of bias should be excluded from the meta-analysis (Reeves 2021). However, given the small number of studies, there is a balance between loss of information and excluding unreliable information. Therefore, we retained all studies in the analyses, but we also stated the critical risk with the related evidence.

Primary outcomes

All-cause mortality

Albani 2020 reported all-cause mortality (follow-up of up to 15 days) as the proportion of participants and as odds ratio (OR) after adjusting for some covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). They found 200 (25%)

deaths in the intervention group and 154 (25.5%) deaths in the comparator group (adjusted OR 0.53, 95% CI 0.40 to 0.70; 1403 participants), in favour of the intervention group after all adjustments (serious risk of bias).

Rentsch 2020 reported all-cause mortality (follow-up of up to 30 days) as the proportion of participants and as hazard ratio (HR) after adjusting for some covariates (inverse probability of treatment weighting). They found 418 (11.5%) deaths in the intervention group and 92 (13.7%) deaths in the comparator group (adjusted HR 0.69, 95% CI 0.61 to 0.77; 4297 participants), in favour of the intervention group after all adjustments (moderate risk of bias).

Santoro 2020 reported all-cause mortality (follow-up of up to 26 days) as the proportion of participants and as RR after the Cox's multivariable regression analysis only for participants with respiratory failure (2859 participants, 49%). They found 467 (32%) deaths in the intervention group and 588 (42%) deaths in the comparator group (adjusted RR 0.58, 95% CI 0.49 to 0.67; 2859 participants), in favour of the intervention group after all adjustments (critical risk of bias).

We combined these results in a meta-analysis of adjusted values (Analysis 3.1). Anticoagulants may reduce all-cause mortality but the evidence is very uncertain due to two study results being at critical and serious risk of bias (RR 0.64, 95% CI 0.55 to 0.74; I^2 = 53%; 3 NRS, 8395 participants; very low-certainty evidence; Analysis 3.1). It was not possible to test for subgroup differences and carry out sensitivity analysis.

Necessity for additional respiratory support

There were no available data for this outcome.

Secondary outcomes

Mortality related to COVID-19

There were no available data for this outcome.

Deep vein thrombosis

Albani 2020 reported deep vein thrombosis (follow-up of up to 15 days) as the proportion of participants but without any adjustment for covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). They found 15 (1.87%) deep vein thromboses in the intervention group and 2 (0.33%) in the comparator group (critical risk of bias). The evidence on DVTs is uncertain (RR 5.67, 95% CI 1.30 to 24.70; I^2 not applicable; 1 NRS, 1403 participants, very low-certainty evidence; Analysis 3.2).

Pulmonary embolism

Albani 2020 reported pulmonary embolism (follow-up of up to 15 days) as the proportion of participants but without any adjustment for covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). They found 32 (4%) pulmonary embolism in the intervention group and 1 (0.1%) pulmonary embolism in the comparator group (critical risk of bias). The evidence on pulmonary embolism is uncertain (RR 24.19, 95% CI 3.31 to 176.53; I^2 not applicable; 1 NRS, 1403 participants; very low-certainty evidence; Analysis 3.3).

Major bleeding

Albani 2020 reported major bleeding (follow-up of up to 15 days) as the proportion of participants but without any adjustment for covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). They found 16 (2%) major bleeding in the intervention group and 15 (2.4%) major bleeding in the comparator group (critical risk of bias).

Santoro 2020 reported major bleeding (follow-up of up to 26 days) as the proportion of participants but without any adjustment for covariates. The Cox's multivariable regression analysis was performed to define independent risk factors only for the mortality outcome. They found 70 (2.7%) major bleeding in the intervention group and 58 (1.8%) major bleeding in the comparator group (critical risk of bias).

The evidence on major bleeding is uncertain (RR 1.19, 95% CI 0.66 to 2.12; I^2 = 58%; 2 NRS, 7218 participants; very low-certainty evidence; Analysis 3.4). It was not possible to test for subgroup differences and carry out sensitivity analysis.

Adverse events (minor bleeding, gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, abdominal pain), allergic reactions, renal failure and amputations)

Stroke

Albani 2020 reported stroke (follow-up of up to 15 days) as the proportion of participants but without any adjustment for covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). They found 6 (0.7%) stroke events in the intervention group and 4 (0.6%) in the comparator group (critical risk of bias). The evidence on stroke is uncertain (RR 1.13, 95% CI 0.32 to 4.0; I^2 not applicable; 1 NRS, 1403 participants; very low-certainty evidence; Analysis 3.5). We downgraded one level due to study limitations (overall critical risk of bias, especially related to confounding) and two levels due to imprecision (fewer than 300 events were included in the analysis and very large CI).

Myocardial infarction

Albani 2020 reported myocardial infarction (follow-up of up to 15 days) as the proportion of participants but without any adjustment for covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). They found 10 (1.2%) myocardial infarction events in the intervention group and no events in the comparator group (critical risk of bias). The evidence on myocardial infarction is uncertain (RR 15.88, 95% CI 0.93 to 270.48; I^2 not applicable; 1 NRS, 1403 participants; very low-certainty evidence; Analysis 3.6). We downgraded one level due to study limitations (overall critical risk of bias, especially related to confounding) and two levels due to imprecision (fewer than 300 events were included in the analysis and very large CI).

Hospitalisation time in days

Albani 2020 reported hospitalisation time in days (follow-up of up to 15 days) but without any adjustment for covariates (e.g. age, sex, disease severity, admission to ICU and COVID-19 treatment). Anticoagulants may increase hospitalisation time compared to no anticoagulation (MD 5.00, 95% CI 4.47 to 5.53; I^2 not applicable; 1 NRS, 1376 participants; moderate-certainty evidence; Analysis 3.7). We downgraded one level due to study limitations (overall serious risk of bias, especially related to confounding).

Quality of life

There were no available data for this outcome.

DISCUSSION

This review aimed to assess the effects of anticoagulants versus active comparator, placebo or no intervention on mortality and need for additional respiratory support for people hospitalised with COVID-19.

Summary of main results

We found no quasi-RCTs with available data assessing the effects of anticoagulants compared to active comparator, placebo or no intervention on mortality and the need for additional respiratory support for people hospitalised with COVID-19. Since we found better study designs for the comparisons of interest, we excluded all retrospective studies from this review.

We found four RCTs that compared higher versus lower doses of anticoagulants (unfractionated heparin, low-molecular-weight heparin, or direct anticoagulants (rivaroxaban)) in 4647 participants hospitalised with COVID-19 (Table 2). Higher-dose anticoagulants result in little to no difference in all-cause mortality and increase minor bleeding compared to lower-dose anticoagulants for up to 30 days. Higher-dose anticoagulants probably reduce pulmonary embolism, slightly increase major bleeding, and result in little to no difference in hospitalisation time. They may result in little to no difference in deep vein thrombosis and in adverse events (stroke, major adverse limb event, myocardial infarction, atrial fibrillation, or thrombocytopenia). We are uncertain about the effects on necessity for additional respiratory support because the certainty of evidence is very low. There were no data regarding mortality related to COVID-19, and quality of life. See Summary of findings 1.

One included RCT, which compared higher versus lower doses of anticoagulants (low-molecular-weight heparin) in 590 participants hospitalised with COVID-19 also provided data for the long-term time point (after hospital discharge) of up to 90 days after intervention (Table 2). Higher-dose anticoagulants probably result in little to no difference in all-cause mortality, deep vein thrombosis, and major bleeding, and may reduce pulmonary embolism, increase adverse events (minor bleeding), and result in little to no difference in adverse events (stroke, atrial fibrillation, and thrombocytopenia) compared to lower-dose anticoagulants for up to 90 days. The evidence is not estimable about the effect of higher-dose anticoagulants on necessity for additional respiratory support, adverse events (acute peripheral arterial thrombosis, and myocardial infarction) compared to lower-dose anticoagulants up to 90 days because there were no events. There were no data regarding mortality related to COVID-19 and quality of life.

We also found three prospective NRS, which compared anticoagulants (heparinoids (unfractionated heparin, low-molecular-weight heparin or fondaparinux), direct anticoagulants or vitamin K antagonists) versus no anticoagulants in 11,538 participants hospitalised with COVID-19 (Table 2). Anticoagulants may reduce all-cause mortality but the evidence is very uncertain due to two study results being at critical and serious risk of bias. Anticoagulants may increase hospitalisation time compared to no anticoagulants for up to 30 days. We are uncertain about the effects on deep vein thrombosis, pulmonary embolism, major bleeding, adverse events (stroke, and myocardial infarction) because the certainty of evidence is very low. There were no data regarding need for additional respiratory support, mortality related to COVID-19 or quality of life. See Summary of findings 2.

We found 62 ongoing studies (from Argentina: 2, Australia: 1, Austria: 1, Belgium: 1, Brazil: 6, Canada: 1, China: 3, Egypt: 2, France: 3, Germany: 3, India: 4, Iran: 1, Ireland: 2, Italy: 6, Mexico: 1, Qatar: 1, Spain: 6, Switzerland: 2, the UK: 3, and the USA: 13) that plan to evaluate 35,470 participants in this setting, of whom 35,350 individuals are from 60 RCTs, and 120 are from two prospective NRS. Thirty-five ongoing studies plan to report data for mortality. Twenty-six ongoing studies plan to report data on the need for additional respiratory support. Fifty-eight ongoing studies are expected to be completed in December 2021, and four in July 2022. Six of these ongoing studies plan to include 1000 participants or more. See Table 3.

One of the studies plans to compare prophylactic enoxaparin, full-dose enoxaparin and apixaban versus no anticoagulant in 3600 participants to assess the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism or ischaemic stroke. One study plans to compare higher-dose enoxaparin versus lower-dose enoxaparin in 2000 participants to assess the incidence of venous thromboembolism, while another plans to compare aspirin, clopidogrel, rivaroxaban, atorvastatin, and omeprazole with no treatment in 3170 participants to assess mortality at 30 days. One study plans to compare higher-dose enoxaparin versus lower-dose enoxaparin to assess venous thromboembolism in 2712 participants, another plans to compare apixaban versus prophylactic enoxaparin and full-dose enoxaparin in 3600 participants to assess overt bleeding plus haemoglobin drop, cardiac tamponade, bleeding requiring surgical intervention for control, bleeding requiring vasoactive agents, or intracranial haemorrhage, and another study plans to compare several possible interventions (without details about type or dose of anticoagulants) in 1800 participants to assess time to clinical improvement.

Overall completeness and applicability of the evidence

While all of the studies reported our primary outcome of all-cause mortality, we found sparse data relating to the need for additional respiratory support and hospitalisation time. It is also noteworthy that none of the studies measured our secondary outcomes such as mortality related to COVID-19 and quality of life. Furthermore, there are neither data comparing different types of anticoagulants or anticoagulants versus non-pharmacological interventions, nor data from more than 30 days after the intervention.

There was moderate heterogeneity in the methods of the included studies and many did not provide complete and clear information about their data. This hindered the qualitative analyses and the assessment of the risk of bias of many outcomes in some studies.

The number of studies for each of the possible comparisons was small, ranging from three to four studies. However, the included studies had relatively large primary sample sizes (six studies with 562 or more participants), except for only one study that evaluated 20 participants. The largest study involved 5838 participants, 2601 of whom were treated with anticoagulation in a non-randomised design but did not provide data regarding one of our primary outcomes (necessity for additional respiratory support).

There was considerable variation in the use of the same intervention (e.g. dosages, type, method of application). The variation in assessment for the confounding factor in NRS also impaired the results.

It is noteworthy that the studies included in this review were conducted in 21 different countries, most of which (52%) were high-income countries. Social and cultural aspects of the evaluated interventions can also interfere with their acceptability and effectiveness for the treatment of people hospitalised with COVID-19. Therefore, the external validity of the overall evidence presented in this review should be considered with caution.

We acknowledge that designing and conducting an appropriate study with available data for this topic is difficult. The new approach regarding prophylactic anticoagulants for people hospitalised with COVID-19 has been used to provide high levels of anticoagulants for these people, although there is now available evidence based on RCTs against their use. This reinforces the importance of this review and serves as an incentive for further investigation.

Certainty of the evidence

We found four RCTs with data for one comparison ('higher-dose anticoagulants versus lower-dose anticoagulants') at two different time points and three prospective NRS with data for another comparison ('anticoagulants versus no treatment') at a short-term time point for this review; we also excluded all retrospective studies.

The overall risk of bias was low for two and high for two RCTs included in the comparison 'higher-dose anticoagulants versus lower-dose anticoagulants'. We judged the bias domains due to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases from low to high. Although it did not change the effect estimate of all-cause mortality when excluded in a sensibility analysis, there was a high risk of bias for one large RCT (the only study reporting some of the outcomes of interest). Despite the increasing number of studies on prophylactic anticoagulants for people hospitalised with COVID-19 in the past months, the overall risk of bias for all-cause mortality, deep vein thrombosis, pulmonary embolism, major bleeding and adverse events (stroke and myocardial infarction) in the comparison 'anticoagulants versus no treatment' was critical and for hospitalisation was serious in the same comparison. We judged the bias domains due to confounding, selection of participants into the study, classification of interventions, deviations from the intended intervention, measurement of outcomes, and selection of the reported results from low to critical risk of bias.

The certainty of evidence is high to very low. We downgraded the certainty of evidence due to the risk of bias, particularly with regard to detection, performance and attrition in two RCTs and also to selection and other bias in one of them. Although three RCTs (3407 participants) assessed the necessity for additional respiratory support, there is considerable uncertainty about this primary outcome (very low-certainty evidence). In the NRS, we downgraded the certainty of evidence due to the risk of bias, particularly with regard to the overall critical/serious risk of bias across studies, especially related to confounding or selection bias. We downgraded the certainty of evidence due to study limitations (risk of bias), inconsistency (unexplained heterogeneity) and imprecision (few events and large CI). We decided to pool data, even in NRS, due to the clinically relevant question related to mortality, but the judgements of critical risk of bias mean that these data are particularly unreliable.

Potential biases in the review process

We performed a comprehensive search of the literature and performed study selection according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021). We believe that we identified all of the relevant studies that met our inclusion criteria. However, the possibility remains that we may have missed some studies, particularly in the grey literature. Although we considered 'COVID-19' and 'SARS-CoV-2' as 'Supplementary Concept' or 'free terms' in our search strategies, they were included as 'index terms' in 2021 for databases such as MEDLINE. Therefore, in the future versions of this review, we plan to include these relevant terms also as 'index terms' in our search strategies. We adhered to the inclusion and exclusion criteria prespecified in the protocol in order to limit subjectivity (Flumignan 2020a). We made efforts to obtain additional relevant data from study authors but were unable to do so for all of the included studies. If we can source supplementary data, we will consider them in future updates. Two review authors selected studies in duplicate, independently, to reduce the potential bias of the review process. One review author extracted data and assessed the risk of bias of the included studies while another checked the data extraction and 'Risk of bias' judgements, to accelerate the process and also to reduce the potential bias of the review process. Additional analysis (subgroups and sensitivity analysis) was performed as planned in our protocol, but the conclusions were based on the primary analysis (Flumignan 2020a). We assumed the pragmatic decision to include NRS at critical and serious risk of bias in meta-analysis due to the relevance of the clinical question. It is perhaps reasonable to have included these in analyses given the small number of studies, but we note that this was a decision taken in the review process. We ensure that any such syntheses were presented throughout the review with unequivocal warnings about the risk of bias and note that the findings cannot rely upon this very low-certainty evidence.

The synthesis of evidence is a field in constant transformation. Therefore, the Cochrane Reviews are periodically updated, mainly the rapid reviews. During the final process of this review, we identified at least three other trials (898 participants together) that seem to reach our inclusion criteria (Perepu 2021; Sholzberg 2021b; Spyropoulos 2021). We will consider these trials in the next update of this review, but we did not assess them for this rapid review updating.

Agreements and disagreements with other studies or reviews

Since the publication of the latest version of this review (Flumignan 2020b), a number of systematic reviews have addressed the role of anticoagulants in people with COVID-19.

- Abdel-Maboud 2021 searched MEDLINE, Scopus, Cochrane Library, Science direct, OVID, medRxiv, bioRxiv, and Web of Science without language limits on 2 July 2020. They did not specify the inclusion criteria for study design and limited their search to eight keywords related to intervention and

population for all databases and only for registers from December 2019. Abdel-Maboud 2021 included only NRS, most retrospective cohorts or consecutive series, did not assess the risk of bias or the certainty of evidence and concluded that "current evidence is not sufficient to support the role of prophylactic heparin in reducing mortality among COVID-19 patients."

- Hasan 2020 searched PubMed, Google Scholar, medRxiv and SSRN (preprint server) up to 25 June 2020. They did not specify the inclusion criteria for study design and limited their search to some keywords related to heparin (without other anticoagulant terms) and population and only for data from 2020. Hasan 2020 combined 12 prospective and retrospective cohorts with cross-sectional studies but did not assess the risk of bias or the certainty of evidence and concluded that prophylactic anticoagulants in higher doses may fail less than those in lower doses for people with COVID-19 admitted to ICU."
- Kamel 2021 searched Google Scholar, PubMed, Scopus, the Cochrane Library and Clinical Trials.gov up to 5 July 2020. They included case-control and cohort studies and limited their search to English-language studies. Kamel 2021 used an obsolete risk of bias tool (The Modified Newcastle–Ottawa Scoring System), did not assess the certainty of evidence and concluded that anticoagulants may reduce mortality in people with COVID-19 and that higher-dose anticoagulants might offer an advantage over lower-dose anticoagulants in this setting.
- Lazaridis 2021 searched PubMed, Ovid, Google Scholar, MEDLINE and Embase databases from December 2019 to 30 May 2020 with limited terms. They considered only randomised clinical trials, quasi-experimental studies, case reports and case series for inclusion. Lazaridis 2021 combined four retrospective NRS without an assessment with a validated risk of bias and certainty of evidence tool and concluded that anticoagulants may reduce the mortality in severely ill people with COVID-19.
- Matli 2021 searched Ovid MEDLINE, Web of Science, PubMed and Google Scholar from March 2020 to January 2021 with limited terms related to anticoagulants and antiplatelet agents. They included only English-language published studies and combined 12 NRS without any risk of bias or certainty of evidence assessment. Matli 2021 concluded that anticoagulants reduced mortality and reduced thromboembolic events in people hospitalised with COVID-19, but there is a paucity of data on antiplatelet use in combination with anticoagulants in this setting.
- McBane 2020 searched MEDLINE and Embase from November 2019 to May 2020. They did not specify the inclusion criteria for study design and the limits regarding study language but limited their search to studies with 100 participants or more. McBane 2020 used an obsolete risk of bias tool (The Modified Newcastle–Ottawa Scoring System), did not assess the certainty of evidence and combined 27 NRS in meta-analyses to include in their recommendations: 1) lower-dose anticoagulants for all people hospitalised with COVID-19, 2) a baseline screening venous ultrasound of lower limbs upon admission in ICU, and 3) extending anticoagulation prophylaxis to 35–45 days post-hospital discharge to reduce venous thromboembolism while it can increase bleeding, even under low-quality available evidence.
- Moonla 2021 searched PubMed, Embase, and the Cochrane Library from the inception of COVID-19 (specific date not provided) to 22 October 2020. They included only studies reporting mortality and anticoagulant use in people hospitalised with COVID-19 without limit regarding the study design, but they limited their inclusion to studies of 10 participants or more. Moonla 2021 reported only one of our included studies' results (Lemos 2020), used an obsolete risk of bias tool (The Modified Newcastle–Ottawa Scoring System) for NRS, and did not assess the certainty of evidence. They combined 17 studies into meta-analyses and concluded that lower-dose anticoagulants were associated with lower in-hospital mortality without excess bleeding compared to no anticoagulation and that the higher-dose anticoagulation revealed no survival benefit but a three-fold increase in major bleeding.
- Parisi 2021 searched MEDLINE, Embase, PubMed, Web of Science, CENTRAL, medRxiv, and Preprints.org on 8 January 2021. They reported following the *Cochrane Handbook for Systematic Reviews of Interventions* but did not provide a full search strategy and did not describe the date and language limits. Parisi 2021 considered two of our included studies (Albani 2020; Rentsch 2020), used an obsolete risk of bias tool (The Modified Newcastle–Ottawa Scoring System) for NRS, and did not assess the certainty of evidence. They combined 29 NRS in meta-analyses, including one study with a mixed population (hospitalised and non-hospitalised people), and concluded that both higher- and lower-dose anticoagulant regimens are associated with better survival in people with COVID-19, particularly the severely ill. However, Parisi 2021 added that in non-critically ill individuals with COVID-19, the lower-dose anticoagulant is probably preferred due to the higher risk of bleeding at higher doses.
- Patell 2021 searched MEDLINE, Embase, and Cochrane CENTRAL from inception to 29 August 2020. They considered RCTs, retrospective and prospective NRS, or case series of adults hospitalised with COVID-19 for inclusion and limited their search to studies in English and with 10 or more participants. Patell 2021 used the validated methodological index for non-randomised studies (MINORS) to assess the risk of bias in the included studies and did not assess the certainty of evidence. They combined 35 NRS of hospitalised people with COVID-19 in meta-analyses and concluded that hospitalised patients with COVID-19 treated with lower-dose anticoagulants have a decreased rate of thrombosis compared with those receiving no anticoagulant, while higher-dose anticoagulant regimens were not associated with decreased in-hospital thrombotic events compared with lower-dose anticoagulants.
- Talasaz 2021 systematically searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing RCTs regarding antithrombotic drugs for people hospitalised and non-hospitalised with COVID-19 and reported the results in a narrative review. They reported the results of only one of our included studies (Lemos 2020), and concluded that the "optimal thromboprophylaxis has not been established for patients with this disease".

In order to prevent thrombosis, some clinicians use higher-dose anticoagulants rather than standard prophylactic (lower) dosing for inpatients with COVID-19 (AVF 2020; Bikdeli 2020; Obe 2020). However, this practice is not supported by robust evidence. Although some practical guidelines address the management of prophylactic anticoagulation in people with COVID-19, some of these recommendations are based on non-

COVID-19 populations or low-quality COVID-19-related evidence (AVF 2020; Bikdeli 2020; NHS 2020; Obe 2020; Ramacciotti 2020). Cuker 2021 searched Cochrane COVID-19 study register, Embase, Epistemonikos COVID-19 Evidence, MEDLINE, and WHO Global Research Database in August 2020 without time or language limitations to perform a living guideline under a GRADE approach. Cuker 2021 found very low-certainty evidence, based mainly on an RCT that we also included in this review (Zarychanski 2021), and made two conditional recommendations in favour of lower-dose anticoagulation over higher-dose (intermediate or therapeutic-intensity) anticoagulation for critical or acute illness patients with COVID-19 who do not have confirmed or suspected venous thromboembolism.

Our review seems to be more comprehensive than the previous reviews identified here, which used limited search strategies, imposed language or date limits, searched overlapping databases (e.g. SCOPUS, Pubmed, MEDLINE and Web of Science in the same review) or searched a limited number of databases (e.g. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform only). None of the identified systematic reviews used the GRADE approach (excepting a guideline under GRADE approach (Cuker 2021)) to assess the certainty of evidence. Although some previous reviews identified the potential of anticoagulants in lower doses and no difference with higher doses, the evidence found is conflicting. Since we identified high-certainty evidence, our conclusions are more decisive for clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

Higher-dose anticoagulants result in little to no difference in all-cause mortality and increase minor bleeding compared to lower-dose anticoagulants for people hospitalised with COVID-19 for up to 30 days. Higher-dose anticoagulants are likely to reduce pulmonary embolism, slightly increase major bleeding, probably result in little to no difference in hospitalisation time, may result in little to no difference in deep vein thrombosis and in stroke, major adverse limb events, myocardial infarction, atrial fibrillation, or thrombocytopenia. We are uncertain about the effects on necessity for additional respiratory support, mortality related to COVID-19, and quality of life because the certainty of evidence is very low or there were no data.

Higher-dose anticoagulants may result in little to no difference in all-cause mortality, deep vein thrombosis and major bleeding, may reduce pulmonary embolism and increase minor bleeding, and may result in little to no difference in stroke, atrial fibrillation, and thrombocytopenia compared to lower-dose anticoagulants for up to 90 days. There is a lack of evidence about the effect of higher-dose anticoagulants on the need for additional respiratory support, mortality related to COVID-19, acute peripheral arterial thrombosis, myocardial infarction and quality of life compared to lower-dose anticoagulants for up to 90 days.

Anticoagulants may reduce all-cause mortality compared to no anticoagulants, but the evidence is very uncertain. We are uncertain about the effects on the need for additional respiratory support, mortality related to COVID-19, deep vein thrombosis, pulmonary embolism, major bleeding, stroke, myocardial infarction, and quality of life because the certainty of evidence is very low or there were no data.

Implications for research

Although we are very confident that new RCTs will not change the conclusion when comparing anticoagulant doses, high-quality RCTs that compare anticoagulants for people hospitalised with COVID-19 are still needed, mainly for the other primary outcome (necessity for additional respiratory support), and the comparison with no anticoagulation. There is further lack of evidence when comparing the types of anticoagulants and the effects of giving anticoagulants for a prolonged period of time (e.g. after hospital discharge).

Since there are 62 ongoing studies (60 RCTs) that plan to evaluate 35,470 participants in this setting, robust evidence may be available soon. Fifty-eight ongoing studies are expected to be completed in December 2021, and four in July 2022. Six of these plan to include 1000 participants or more, with two studies aiming for 3600 and 3170 participants, respectively, which should be compared to different anticoagulant regimens or to no anticoagulation. There is still a need for RCTs with high methodological quality, that is, adequate reporting of randomisation, allocation concealment and blinding, to assess the effects on this population prospectively in an unconfounded randomised study of anticoagulants for people hospitalised with COVID-19.

The most notable outcomes to be measured are death and the need for additional respiratory support. Other important issues to be considered are deep vein thrombosis, pulmonary embolism, major bleeding, adverse events, hospitalisation time, and quality of life.

ACKNOWLEDGEMENTS

This review was published in collaboration with the Cochrane Editorial and Methods Department. We particularly thank Sarah Hodgkinson and Liz Bickerdike (Associate Editors), Clare Dooley (Managing Editor), Denise Mitchell (Copy Editor), Theresa Moore (Cochrane Methods Support Unit), Robin Featherstone (Information Specialist) and Leticia Rodrigues (Cochrane Editorial and Methods Department) for their methodological and editorial support. Many thanks to Teo Aminah Wasteneys Quay (Managing Editor, Cochrane Emergency and Critical Care), Harald Harkner (Co-ordinating Editor, Cochrane Emergency and Critical Care) and Mike Brown (Network Senior Editor, Cochrane Acute and Emergency Care) for their support and contributions at various stages of the editorial process. Thanks to Analysis of Review Group Output (ARGO) for their comments on the Abstract and Plain language summary.

Thanks to Marcelly S Cossi (State University of Rio Grande do Norte, Natal, Brazil), Larissa Souza (Hospital Central Coronel Pedro Germano, Natal, Brazil), Maria ICD Fernandes and Isabelle KF Costa (Federal University of Rio Grande do Norte, Natal, Brazil) for their contributions to the first version of this review.

Thanks to the Division of Vascular and Endovascular Surgery, Federal University of Sao Paulo, Brazil, and Cochrane Brazil for their continuous support of this review.

The following people conducted the editorial process for this review update.

- Sign-off Editor (final editorial decision): Harald Harkner (Co-ordinating Editor, Cochrane Emergency and Critical Care)

- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Anne-Marie Stephani, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy-editing and production): Denise Mitchell, Senior Copy Editor, Cochrane Central Executive
- Peer-reviewers (provided comments and recommended an editorial decision): Vicky Mai (University of British Columbia, Canada), Roberto Pola (Tufts University School of Medicine, USA) (clinical/content review), Stella Maria O'Brien (consumer review), Liz Bickerdike and Rachel Richardson, Cochrane Editorial and Methods Department (methods review), Robin Featherstone, Cochrane Editorial and Methods Department (search review)

REFERENCES

References to studies included in this review

Albani 2020 *{published data only}*

Albani F, Sepe L, Fusina F, Prezioso C, Baronio M, Caminiti F, et al.Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study. *EClinicalMedicine* 2020;**27**:100562. [DOI: 10.1016/j.eclinm.2020.100562]

Lemos 2020 *{published data only (unpublished sought but not used)}*

Bikdeli B.Anticoagulation in COVID-19: randomized trials should set the balance between excitement and evidence. *Thrombosis research* 2020;**196**:638-40. [DOI: 10.1016/j.thromres.2020.09.033]

* Lemos AC, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, et al.Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID). *Thrombosis Research* 2020;**196**:359-66. [DOI: 10.1016/j.thromres.2020.09.026]

RBR-949z6v.Full versus prophylactic heparinization for the treatment of severe forms of SARS-COVID-19: clinical, randomized, open and controlled study - HeSAcovid trial. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=RBR-949z6v (first received 23 February 2021).

RBR-949z6v.RBR-949z6v Full versus prophylactic anticoagulation for the treatment of severe forms of COVID-19. ensaiosclinicos.gov.br/rg/RBR-949z6v/ (first received 6 April 2020).

Lopes 2021 *{published data only}*

Bavry AA, Bhatt DL.AnticoagulatIon coronavirus - ACTION. acc.org/Latest-in-Cardiology/Clinical-Trials/2021/05/14/03/11/ACTION#.YKGzh1LrUW8.linkedin (assessed 16 May 2021).

Lopes RD, Silva PG, Furtado RH, Macedo AVS, Ramacciotti E, Damini LP, et al.Randomized clinical trial to evaluate a routine full anticoagulation strategy in patients with coronavirus Infection (SARS-CoV2) admitted to hospital: rationale and design of the ACTION (AntiCoagulaTIon cOroNavirus)-Coalition IV trial. *American Heart Journal* 2021;**238**:1-11. [DOI: 10.1016/j.ahj.2021.04.005]

* Lopes RD, Silva PG, Furtado RH, Macedo AV, Bronhara B, Damiani LP, et al.Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet* 2021;**397**(10291):2253-63. [DOI: 10.1016/S0140-6736(21)01203-4]

Lopes RD.ACC.21 Presentation Slides | ACTION. acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=DC46FDC6BBA84D9B85FC064F0D73DAF2 (assessed 16 May 2021).

Lopes RD.Details about your trial data [ACTION trial] [personal communication]. Email to: RL Flumignan 22 May 2021.

NCT04394377.Randomized clinical trial to evaluate a routine full anticoagulation strategy in patients with coronavirus (COVID-19) - COALIZAO ACTION Trial. clinicaltrials.gov/ct2/show/NCT04394377 (first received 8 May 2020).

Rentsch 2020 *{published data only}*

Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, et al.Early initiation of prophylactic anticoagulation for prevention of COVID-19 mortality: a nationwide cohort study of hospitalized patients in the United States. *medRxiv [Preprint]*. [DOI: 10.1101/2020.12.09.20246579]

Sadeghipour 2021 *{published data only (unpublished sought but not used)}*

Al-Samkari H.Finding the optimal thromboprophylaxis dose in patients with COVID-19. *JAMA* 2021;**325**(16):1613-15. [DOI: 10.1001/jama.2021.4295]

Bikdeli B, Talasaz AH, Rashidi F, Bakhshandeh H, Rafiee F, Matin S, et al.Intermediate vs standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to ICU: ninety-day results from the INSPIRATION Trial. *Thrombosis and Haemostasis* 2022;**122**(1):131-41. [DOI: 10.1055/a-1485-2372]

Bikdeli B, Talasaz AH, Rashidi F, Sharif-Kashani B, Farrokhpour M, Bakhshandeh H, et al.Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: rationale and design of the INSPIRATION/INSPIRATION-S studies. *Thrombosis Research* 2020;**196**:382-94. [DOI: 10.1016/j.thromres.2020.09.027]

Bikdeli B.Details about your trial data [INSPIRATION trial] [personal communication]. Email to: RLG Flumignan 4 June 2021.

NCT04486508.Intermediate-dose vs standard prophylactic anticoagulation and statin vs placebo in ICU patients with COVID-19. clinicaltrials.gov/ct2/show/NCT04486508 (first received 22 July 2020).

NCT04486508.Intermediate-dose vs standard prophylactic anticoagulation and statin vs placebo in ICU patients with COVID-19 INSPIRATION. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=NCT04486508 (first received 22 July 2020).

* Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al.Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA* 2021;**325**(16):1620-30. [DOI: 10.1001/jama.2021.4152]

Santoro 2020 *{published data only (unpublished sought but not used)}*

Núñez-Gil IJ, Estrada V, Fernández-Pérez C, Feltes G, Vedia O, Vergara-Uzcategui CE.Health outcome predictive evaluation for COVID 19 international registry (HOPE COVID-19), rationale

and design. *Contemporary Clinical Trials Communication* 2020;**20**:100654. [DOI: 10.1016/j.conctc.2020.100654]

NCT04334291.International COVID19 clinical evaluation registry, (HOPE COVID 19). clinicaltrials.gov/ct2/show/NCT04334291 (first received 1 April 2020).

NCT04334291.International COVID-19 clinical evaluation registry 2: HOPE 2. hopeprojectmd.com/en/ (first received 1 April 2020).

Rivera-Caravaca JM, Núñez-Gil IJ, Vivas D, Viana-Llamas MC, Uribarri A, Becerra-Muñoz VM, et al.Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19. *European Journal of Clinical Investigation* 2021;**51**(1):e13436. [DOI: 10.1111/eci.13436]

Santoro F, Nunez I, Pepe M, Estrada V, Brunetti ND.A289: Anticoagulation therapy in patients with COVID-19. Results from a multi-center international prospective registry (HOPE-COVID19). *Giornale Italiano di Cardiologia* 2020;**21**(12 Suppl 2):e90.

* Santoro F, Nunez I, Pepe M, Estrada V, Brunetti ND.Anticoagulation therapy in patients with COVID-19. Results from a multi-center international prospective registry (HOPE-COVID19). *Critical Care Medicine* 2021;**49**(6):e624-e633. [DOI: 10.1097/CCM.0000000000005010]

Zarychanski 2021 *{published data only (unpublished sought but not used)}*

EUCTR2015-002340-14-NL.Randomized, embedded, multifactorial, adaptive platform trial for community-acquired pneumonia (REMAP-CAP). (COVID-19) - REMAP-CAP. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2015-002340-14-NL (first received 16 September 2015).

EUCTR2020-004285-19.A multicenter, adaptive, randomized controlled platform trial of the safety and efficacy of antithrombotic strategies in hospitalized adults with COVID-19. clinicaltrialsregister.eu/ctr-search/trial/2020-004285-19/IT (first received 23 November 2020).

Houston BL, Lawler PR, Goligher EC, Farkouh ME, Bradbury C, Carrier M, et al.Anti-thrombotic therapy to ameliorate complications of COVID-19 (ATTACC): study design and methodology for an international, adaptive Bayesian randomized controlled trial. *Clinical Trials* 2020;**17**(5):491-500. [DOI: 10.1177/1740774520943846]

Hunt BJ, De Paula EV, McLintock C, Dumantepe M.Prophylactic anticoagulation for patients in hospital with COVID-19. *BMJ* 2021;**372**:n487. [DOI: 10.1136/bmj.n487]

Lawler P, Goligher E, Berger J, Neal M, McVerry B, Nicolau J, et al.Therapeutic anticoagulation in non-critically Ill patients with COVID-19. *medRxiv [Preprint]*. [DOI: 10.1101/2021.05.13.21256846]

NCT02735707.Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP). clinicaltrials.gov/ct2/show/NCT02735707 (first received 13 April 2016).

NCT04359277.A randomized trial of anticoagulation strategies in COVID-19. clinicaltrials.gov/ct2/show/NCT04359277 (first received 20 April 2020).

NCT04372589.Antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC), in collaboration with accelerating COVID-19 therapeutic interventions and vaccines (ACTIV-4). clinicaltrials.gov/ct2/show/NCT04372589 (first received 24 April 2020).

NCT04505774.Anti-thrombotics for adults hospitalized with COVID-19 (ACTIV-4). clinicaltrials.gov/ct2/show/NCT04505774 (first received 6 August 2020).

No authors listed.Erratum for [Prophylactic anticoagulation for patients in hospital with COVID-19]. *BMJ* 2021;**372**:n538. [PMID: 10.1136/bmj.n538]

Ridker PM, Ortel TL, Hochman JS.Equipoise, trust, and the need for cardiologists to randomly assign patients Into anticoagulation trials in the time of COVID. *Circulation* 2020;**142**(24):2296-8. [DOI: 10.1161/CIRCULATIONAHA.120.052069]

* Zarychanski R, Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, et al.Therapeutic anticoagulation in critically ill patients with COVID-19 – preliminary report. *medRxiv [Preprint]*. [DOI: 10.1101/2021.03.10.21252749]

Zarychanski R.Details about your trial data [Zarychanski R, Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, et al. Therapeutic anticoagulation in critically ill patients with COVID-19 – Preliminary Report. medRxiv [Preprint]. DOI: 10.1101/2021.03.10.21252749]. Email to: RLG Flumignan 23 April 2021.

References to studies excluded from this review

Al-Samkari 2020 *{published data only}*

Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, et al.COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020;**136**(4):489-500. [PMID: 32492712]

Artifoni 2020 *{published data only}*

Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, et al.Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *Journal of Thrombosis and Thrombolysis* 2020;**50**(1):211-6. [PMID: 32451823]

Ayerbe 2020 *{published data only}*

* Ayerbe L, Risco C, Ayis S.The association between treatment with heparin and survival in patients with COVID-19. *Journal of Thrombosis and Thrombolysis* 2020;**50**(2):298-301. [DOI: 10.1007/s11239-020-02162-z]

Ayerbe L, Risco C, Ayis S.The association between treatment with heparin and survival in patients with COVID-19. medRxiv [Preprint]. [DOI: 10.1101/2020.05.27.20114694]

ChiCTR2000034796 *{published data only}*

ChiCTR2000034796.The efficacy and safety of heparin in the treatment of novel coronavirus pneumonia (COVID-19): a retrospective single center clinical trial. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=ChiCTR2000034796 (first received 18 January 2020).

CTRI/2021/01/030373 *{published data only}*

CTRI/2021/01/030373.ETHIC trial: early LMWH in symptomatic COVID-19 positive patients. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=CTRI/2021/01/030373 (first received 11 January 2021).

D'Ardes 2021 *{published data only}***10.1007/s10072-020-04887-4**

D'Ardes D, Carrarini C, Russo M, Dono F, Speranza R, Digiovanni A, et al.Low molecular weight heparin in COVID-19 patients prevents delirium and shortens hospitalization. *Neurological Sciences* 2021;**42**(4):1527-30. [DOI: 10.1007/s10072-020-04887-4]

DCTC 2021 *{published data only}*

Dutch COVID & Thrombosis Coalition.Early effects of unfractionated heparin on clinical and radiological signs and D-dimer levels in patients with COVID-19 associated pulmonary embolism: an observational cohort study. *Thrombosis Research* 2021;**200**:130-2. [DOI: 10.1016/j.thromres.2021.01.023]

Di Castelnuovo 2021 *{published data only}*

Di Castelnuovo A, Costanzo S, Antinori A, Berselli N, Blandi L, Bonaccio M, et al.Heparin in COVID-19 patients is associated with reduced in-hospital mortality: the multicenter Italian CORIST study. *Thrombosis and Haemostasis* 2021;**121**(8):1054-65. [DOI: 10.1055/a-1347-6070]

EUCTR2020-001748-24-SE *{published data only}*

EUCTR2020-001748-24-SE.A multi-center, randomized, open-label study in patients with COVID-19 and respiratory distress not requiring mechanical ventilation, to compare standard-of-care with anakinra and tocilizumab treatment. The immunomodulation-CoV assessment (ImmCoVA) study. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-001748-24-SE (first received 20 April 2020).

EudraCT2020-001823-15 *{published data only}*

EudraCT2020-001823-15.Evaluation of the concentration-effect relationship of enoxaparin for thromboembolic prevention in COVID-19 resuscitation patients. COV-ENOX study. clinicaltrialsregister.eu/ctr-search/trial/2020-001823-15/FR (first received 15 April 2020).

Falcone 2020 *{published data only}*

Falcone M, Tiseo G, Barbieri G, Galfo V, Russo A, Virdis A, et al.Role of low-molecular-weight heparin in hospitalized patients with severe acute respiratory syndrome coronavirus 2 pneumonia: a prospective observational study. *Open Forum Infectious Diseases* 2020;**7**(12):ofaa563. [DOI: 10.1093/ofid/ofaa563]

Frohlich 2021 *{published data only}*

Frohlich GM, Jeschke E, Eichler U, Thiele H, Alhariri L, Reinthaler M, et al.Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. *Clinical Research in Cardiology* 2021;**110**(7):1041-50. [PMID: 10.1007/s00392-020-01783-x]

Helms 2020 *{published data only}*

Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al.High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Medicine* 2020;**46**(6):1089-98. [DOI: 10.1007/s00134-020-06062-x]

Helms 2021 *{published data only}*

Helms J, Severac F, Merdji H, Schenck M, Clere-Jehl R, Baldacini M, et al.Higher anticoagulation targets and risk of thrombotic events in severe COVID-19 patients: bi-center cohort study. *Annals of Intensive Care* 2021;**11**(1):14. [DOI: 10.1186/s13613-021-00809-5]

Ho 2021 *{published data only}*

Ho G, Dusendang JR, Schmittdiel J, Kavecansky J, Tavakoli J, Pai A.Association of chronic anticoagulant and antiplatelet use on disease severity in SARS-CoV-2 infected patients. *Journal of Thrombosis and Thrombolysis* 2021;**52**(2):476-81. [DOI: 10.1007/s11239-021-02383-w]

Huang 2020 *{published data only}*

Huang CT, Hsu SY, Chang KW, Huang CG, Yang CT, Cheng MH.Heparin-induced thrombocytopenia and thrombosis in a patient with COVID-19. *Thrombosis Research* 2020;**196**:11-4. [DOI: 10.1016/j.thromres.2020.07.056]

Ionescu 2020 *{published data only}*

Ionescu F, Grasso-Knight G, Castillo E, Naeem E, Petrescu I, Imam Z, et al.Therapeutic anticoagulation delays death in COVID-19 patients: cross-sectional analysis of a prospective cohort. *TH open* 2020;**4**(3):e263-70. [PMID: 10.1055/s-0040-1716721]

Jiménez-Soto 2021 *{published data only}*

Jiménez-Soto R, Aguilar-Soto M, Rodríguez-Toledo CA, Camiro-Zúñiga A, Demichelis R.The impact of different prophylactic anticoagulation doses on the outcomes of patients with COVID-19. *Thrombosis Research* 2021;**202**:14-6. [DOI: 10.1016/j.thromres.2021.02.031]

Jonmarker 2020 *{published data only}*

Jonmarker S, Hollenberg J, Dahlberg M, Stackelberg O, Litorell J, Everhov ÅH, et al.Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients. *Intensive Care Medicine Experimental* 2020;**8 Suppl 2**:73. [DOI: 10.1186/s40635-020-00354-8]

Khider 2020 *{published data only}*

Khider L, Gendron N, Goudot G, Chocron R, Hauw-Berlemont C, Cheng C, et al.Curative anticoagulation prevents endothelial lesion in COVID-19 patients. *Journal of Thrombosis and Haemostasis* 2020;**18**(9):2391-9. [DOI: 10.1111/jth.14968]

Kodama 2020 *{published data only}*

Kodama R, Kalsi A, Singh A, Vishnuvardhan N, Nimkar N, Paul S, et al.Outcomes in COVID-19 patients on treatment dose anti-coagulation compared to prophylactic dose anti-coagulation. *Blood* 2020;**136 Suppl 1**:40-1. [DOI: 10.1182/blood-2020-142552]

Kow 2020 *{published data only}*

Kow CS, Hasan SS.Use of low-molecular-weight heparin in COVID-19 patients. *Journal of Vascular Surgery* 2020;**8**(5):900-1. [DOI: 10.1016/j.jvsv.2020.06.006]

Kukin 2020 *{published data only}*

Kukin A, Gale SE, Reed BN, Devabhakthuni S, Watson K, Noel Z.Effect of video-assisted counseling versus traditional counseling on patient comprehension of prescribed direct oral anticoagulants. *Journal of the American College of Clinical Pharmacy* 2020;**3**(8):1538-9. [DOI: 10.1002/jac5.1351]

Liu 2020 *{published data only}*

Liu X, Zhang X, Xiao Y, Gao T, Wang G, Wang Z, et al.Heparin-induced thrombocytopenia is associated with a high risk of mortality in critical COVID-19 patients receiving heparin-involved treatment. *medRxiv [Preprint]*. [DOI: 10.1101/2020.04.23.20076851]

Mareev 2020 *{published data only}*

* Mareev VY, Orlova YA, Pavlikova EP, Akopyan ZA, Matskeplishvili ST, Plisyk AG, et al.Proactive anti-inflammatory and anticoagulant therapy in the treatment of advanced stages of novel coronavirus infection (COVID-19). Case series and study design: coLchicine versus ruxolitinib and secukinumab in open prospective randomIzed trial (COLORIT). *Kardiologiia* 2020;**60**(9):4-21. [DOI: 10.18087/cardio.2020.9.n1338]

NCT04403243.Colchicine versus ruxolitinib and secukinumab in open prospective randomized trial (COLORIT). clinicaltrials.gov/ct2/show/NCT04403243 (first received 20 May 2020).

Martinelli 2020 *{published data only}*

Martinelli I, Ciavarella A, Abbattista M, Aliberti S, De Zan V, Folli C, et al.Increased doses of low-molecular-weight heparin in hospitalized patients with COVID-19. *Research and Practice in Thrombosis and Haemostasis* 2020;**4 Suppl 2**:15-6. [DOI: 10.1002/rth2.12413]

Maurer 2020 *{published data only}*

Maurer L, Luckhurst C, Hamidi A, Newman K, Barra M, El Hechi M, et al.A low dose heparin protocol is associated with improved duration of arterial line patency in critically ill COVID-19 patients. *Research and Practice in Thrombosis and Haemostasis* 2020;**4 Suppl 2**:8-9. [DOI: 10.1002/rth2.12413]

* Maurer LR, Luckhurst CM, Hamidi A, Newman KA, Barra ME, El Hechi M, et al.A low dose heparinized saline protocol is associated with improved duration of arterial line patency in critically ill COVID-19 patients. *Journal of Critical Care* 2020;**60**:253-9. [DOI: 10.1016/j.jcrc.2020.08.025]

NCT04354155 *{published data only}*

NCT04354155.COVID-19 anticoagulation in children - thromboprophlaxis (COVAC-TP) trial. clinicaltrials.gov/ct2/show/NCT04354155 (first received 21 April 2020).

NCT04359212 *{published data only}*

NCT04359212.Increased risk of venous thromboembolism and higher hypercoagulable state in patients recovered in intensive care unit and in medical ward for coronavirus disease 2019 (COVID-19). clinicaltrials.gov/ct2/show/NCT04359212 (first received 21 April 2020).

NCT04365309 *{published data only}*

NCT04365309.Protective effect of aspirin on COVID-19 patients (PEAC). clinicaltrials.gov/ct2/show/NCT04365309 (first received 28 April 2020).

NCT04368377 *{published data only}*

NCT04368377.Platelet inhibition with GP IIb/IIIa inhibitor in critically ill patients with coronavirus disease 2019 (COVID-19). A compassionate use protocol. clinicaltrials.gov/ct2/show/NCT04368377 (first received 29 April 2020).

NCT04393805 *{published data only}*

NCT04393805.Heparins for thromboprophylaxis in COVID-19 patients: HETHICO study in Veneto. clinicaltrials.gov/ct2/show/NCT04393805 (first received 16 May 2020).

NCT04427098 *{published data only}*

2020-001308-40.Intermediate dose enoxaparin in hospitalized patients with moderate-severe COVID-19: a pilot phase II single-arm study, INHIXACOVID19. clinicaltrialsregister.eu/ctr-search/trial/2020-001308-40/IT (first received 24 June 2020).

* NCT04427098.Intermediate dose enoxaparin in hospitalized patients with moderate-severe COVID19: a pilot phase II single-arm study, INHIXACOVID19. clinicaltrials.gov/ct2/show/study/NCT04427098 (first received 11 June 2020).

NCT04483830 *{published data only}*

NCT04483830.Suloexide in the treatment of early stages of COVID-19 (SulES-COVID). clinicaltrials.gov/ct2/show/NCT04483830 (first received 22 July 2020) (first received 22 July 2020).

NCT04492254 *{published data only}*

NCT04492254.Early prophylactic low-molecular-weight heparin (LMWH) in symptomatic COVID-19 positive patients (ETHIC). clinicaltrials.gov/ct2/show/NCT04492254 (first received 22 July 2020).

NCT04504032 *{published data only}*

EUCTR2020-005395-35.A randomized, controlled, Phase 2b study to evaluate safety and efficacy of rivaroxaban (Xarelto®) for high risk people with mild COVID-19. clinicaltrialsregister.eu/ctr-search/trial/2020-005395-35/GB (first received 26 November 2020).

* NCT04504032.A trial to evaluate safety and efficacy of rivaroxaban (COVID-19). clinicaltrials.gov/ct2/show/NCT04504032 (first received 5 August 2020).

NCT04516941 *{published data only}*

NCT04516941.Corona virus edoxaban colchicine (CONVINCE) COVID-19 (CONVINCE). clinicaltrials.gov/ct2/show/NCT04516941 (first received 5 August 2020).

NCT04662684 *{published data only}*

NCT04662684.Medically Ill hospitalized patients for COVID-19 thrombosis extended prophylaxis with rivaroxaban therapy: the MICHELLE Trial. clinicaltrials.gov/ct2/show/NCT04662684 (first received 8 December 2020).

NCT04673214 *{published data only}*

NCT04673214.Evaluation of prognostic modification in COVID-19 patients in early intervention treatment. clinicaltrials.gov/ct2/show/NCT04673214 (first received 16 December 2020).

NCT04715295 *{published data only}*

NCT04715295.Safety and efficacy of doxycycline and rivaroxaban in COVID-19 (DOXYCOV). clinicaltrials.gov/ct2/show/NCT04715295 (first received 2 October 2020).

NCT04736901 *{published data only}*

NCT04736901.Effect of prophylactic and therapeutic anticoagulants in Egyptian patients with COVID-19. clinicaltrials.gov/ct2/show/results/NCT04736901?view=results (first received 3 February 2021).

NCT04757857 *{published data only}*

NCT04757857.COVID-19 antithrombotic rivaroxaban evaluation (CARE). clinicaltrials.gov/ct2/show/NCT04757857 (first received 8 February 2021).

NCT04828772 *{published data only}*

NCT04828772.A study of anticoagulation treatment patterns and outcomes of participants hospitalized with coronavirus disease 2019 (COVID-19) in Japan. clinicaltrials.gov/ct2/show/NCT04828772 (first received 25 March 2021).

Paranjpe 2020 *{published data only}*

Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al.Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. Journal of the American College of Cardiology 2020;**76**(1):122-4. [PMID: 32387623]

Piagnerelli 2020 *{published data only}*

Piagnerelli M, Cauchie P, Wautrecht JC.Optimizing the risk-benefit balance of thromboprophylaxis in critically ill patients with coronavirus disease 2019. *Critical Care Medicine* 2020;**48**(10):e988-9. [DOI: 10.1097/CCM.0000000000004509]

Poulakou 2021 *{published data only}*

Poulakou G, Dimakakos E, Kollias A, Kyriakoulis KG, Rapti V, Trontzas I, et al.Beneficial effects of intermediate dosage of anticoagulation treatment on the prognosis of hospitalized COVID-19 patients: the ETHRA Study. *In Vivo (Athens, Greece)* 2021;**35**(1):653-61. [DOI: 10.21873/invivo.12305]

Qin 2021 *{published data only}*

Qin W, Dong F, Zhang Z, Hu B, Chen S, Zhu Z, et al.Low molecular weight heparin and 28-day mortality among patients with coronavirus disease 2019: a cohort study in the early epidemic era. *Thrombosis Research* 2021;**198**:19-22. [DOI: 10.1016/j.thromres.2020.11.020]

Rosovsky 2020 *{published data only}*

Rosovsky RP, Sanfilippo KM, Wang TF, Rajan SK, Shah S, Martin KA, et al.Anticoagulation practice patterns in COVID-19: a global survey. *Research and Practice in Thrombosis and Haemostasis* 2020;**4**(6):969-83. [DOI: 10.1002/rth2.12414]

Russo 2020 *{published data only}*

Russo V, Di Maio M, Attena E, Silverio A, Scudiero F, Celentani D, et al.Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. *Pharmacological Research* 2020;**159**:104965. [DOI: 10.1016/j.phrs.2020.104965]

Secco 2020 *{published data only}*

Secco E, Pasqualetto MC, Bombardini T, Picano E, Rigo F.A possible benefit from therapeutic anticoagulation in patients with coronavirus disease 2019: the Dolo hospital experience in Veneto, Italy. *Kardiologia Polka* 2020;**78**(9):919-21. [DOI: 10.33963/KP.15489]

Shi 2020 *{published data only}*

Shi C, Wang C, Wang H, Yang C, Cai F, Zeng F, et al.The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective clinical study. *medRxiv [Preprint]*. [DOI: 10.1101/2020.03.28.20046144]

Sivaloganathan 2020 *{published data only}*

Sivaloganathan H, Ladikou EE, Chevassut T.COVID-19 mortality in patients on anticoagulants and antiplatelet agents. *British Journal of Haematology* 2020;**190**(4):e192-e195. [DOI: 10.1111/bjh.16968]

Smith 2020 *{published data only}*

Smith SR, Waite A, Johnston BW, Welters ID.P520 Survey of current practice in management of anticoagulation in adult critically ill patients with COVID-19 in the northwest of England. *Critical Care* 2020;**24 Suppl 2**:P520. [PMID: 10.1186/s13054-020-03187-9]

Stessel 2020 *{published data only}*

NCT04394000.Impact of implementation of an intensified thromboprofylaxis protocol in critically ill ICU patients with COVID-19: a longitudinal controlled before-after study. clinicaltrials.gov/ct2/show/record/NCT04394000 (first received 19 May 2020).

* Stessel B, Vanvuchelen C, Bruckers L, Geebelen L, Callebaut I, Vandenbrande J, et al.Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: a longitudinal controlled before-after study. *Thrombosis Research* 2020;**194**:209-15. [DOI: 10.1016/j.thromres.2020.07.038]

Tacquard 2021 *{published data only}*

NCT04405869.Thromboembolic events in severe COVID-19 patients (COVICLOT). clinicaltrials.gov/ct2/show/NCT04405869 (first received 25 May 2020).

* Tacquard C, Mansour A, Godon A, Godet J, Poissy J, Garrigue D, et al.Impact of high-dose prophylactic anticoagulation in critically ill patients with coronavirus disease 2019 pneumonia. *Chest* 2021;**S0012-3692**(21):00047-7. [DOI: 10.1016/j.chest.2021.01.017]

Tamargo 2021 *{published data only}*

Tamargo J.Does anticoagulation reduce mortality in patients with atrial fibrillation who later developed a COVID-19 infection? *International Journal of Cardiology* 2021;**331**:340-1. [DOI: 10.1016/j.ijcard.2021.01.019]

Tang 2020 *{published data only}*

Tang N, Bai H, Chen X, Gong J, Li D, Sun Z.Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis : JTH* 2020;**18**(5):1094-9. [PMID: 32220112]

Trinh 2020 *{published data only}*

Trinh M, Chang DR, Govindarajulu US, Kane E, Fuster V, Kohli-Seth R, et al.Therapeutic anticoagulation is associated with decreased mortality in mechanically ventilated COVID-19 patients. *medRxiv [Preprint]*. [DOI: 10.1101/2020.05.30.20117929]

Zhang 2020 *{published data only}*

Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, et al.Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. *Zhonghua Xue Ye Xue za Zhi* 2020;**41**(0):E006. [PMID: 32220276]

References to ongoing studies

ACTRN12620000517976 *{published data only}*

* ACTRN12620000517976.A randomised controlled trial of nebulised heparin in critically ill mechanically ventilated patients with COVID-19 to assess the effect on the duration of mechanical ventilation. anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000517976 (first received 27 April 2020).

ACTRN12620000517976.Can nebulised heparin reduce time to extubation in SARS CoV 2. The CHARTER study protocol. apps.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12620000517976 (first received 27 April 2020).

Dixon B, Smith RJ, Artigas A, Laffey J, McNicholas B, Schmidt E, et al.Can nebulised heparin reduce time to extubation in SARS CoV 2. The CHARTER study protocol. *medRxiv [Preprint]*. [DOI: 10.1101/2020.04.28.20082552]

Busani 2020 *{published data only}*

* Busani S, Tosi M, Mighali P, Vandelli P, D'Amico R, Marietta M, et al.Multi-centre, three arm, randomized controlled trial on the use of methylprednisolone and unfractionated heparin in critically ill ventilated patients with pneumonia from SARS-CoV-2 infection: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;**21**:724. [DOI: 10.1186/s13063-020-04645-z]

EUCTR2020-001921-30.Steroids and unfractionated heparin in critically-ill patients with pneumonia from COVID-19 infection. A multicenter, interventional, randomized, three arms study design. clinicaltrialsregister.eu/ctr-search/trial/2020-001921-30/IT (first received 26 June 2020).

NCT04528888.Steroids and unfractionated heparin in critically-ill patients with pneumonia from COVID-19 infection. A multicenter, interventional, randomized, three arms study design. clinicaltrials.gov/ct2/show/NCT04528888 (first received 21 August 2020).

Chambers 2020 *{published data only}*

* Chambers I, Dayal S, Eyck PT, Eustes A, Sutamtewagul G, Rosenstein L, et al.COVID-19-associated coagulopathy: safety and efficacy of prophylactic anticoagulation therapy in hospitalized adults with COVID-19. *Blood* 2020;**136 Suppl 1**:11. [10.1182/blood-2020-141951]

NCT04360824.COVID-19-associated coagulopathy: safety and efficacy of prophylactic anticoagulation therapy in hospitalized adults with COVID-19. clinicaltrials.gov/ct2/show/NCT04360824 (first received 24 April 2020).

ChiCTR2000030700 *{published data only}*

ChiCTR2000030700.Study for the efficacy and safety of prolongin (enoxaparin sodium injection) in treatment of novel coronavirus pneumonia (COVID-19) adult common patients. apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000030700 (first received 10 March 2020).

* ChiCTR2000030700.Study for the efficacy and safety of prolongin (enoxaparin sodium injection) in treatment of novel coronavirus pneumonia (COVID-19) adult common patients. www.chictr.org.cn/showprojen.aspx?proj=50786 (first received 10 March 2020).

ChiCTR2000030701 *{published data only}*

ChiCTR2000030701.A randomized, parallel controlled open-label trial for the efficacy and safety of prolongin (enoxaparin sodium injection) in the treatment of adult patients with novel coronavirus pneumonia (COVID-19). chictr.org.cn/showprojen.aspx?proj=50795 (first received 10 March 2020).

ChiCTR2000030701.A randomized, parallel controlled open-label trial to evaluate the efficacy and safety of Prolongin (enoxaparin sodium injection) in adult hospitalized patients with novel coronavirus pneumonia (COVID-19). ictrptest.azurewebsites.net/Trial2.aspx?TrialID=ChiCTR2000030701 (first received 10 March 2020).

ChiCTR2000030946 *{published data only}*

ChiCTR2000030946.Effects of different VTE prevention methods on the prognosis of hospitalized patients with novel coronavirus pneumonia (COVID-19). chictr.org.cn/showprojen.aspx?proj=51265 (first received 19 March 2020).

CTRI/2020/06/026220 *{published data only}*

CTRI/2020/06/026220.An open label, randomized, multicenter, controlled clinical study to evaluate the efficacy and safety of nafamostat mesilate in the treatment of moderate COVID-19 disease. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=CTRI/2020/06/026220 (first received 17 July 2020).

CTRI/2020/08/027033 *{published data only}*

CTRI/2020/08/027033.SARS-COV-2 and COVID-19 - a randomized controlled trail (unblinded). ictrptest.azurewebsites.net/Trial2.aspx?TrialID=CTRI/2020/08/027033 (first received 07 August 2020).

CTRI/2020/11/029175 *{published data only}*

CTRI/2020/11/029175.Role of heparin inhalation in reducing the duration the patient is breathing with the help of a ventilator. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=CTRI/2020/11/029175 (first received 17 November 2020).

CTRI/2020/11/029345 *{published data only}*

CTRI/2020/11/029345.To determine efficacy, safety and optimal dosing of anticoagulant strategies to prevent adverse outcomes in hospitalized COVID-19 patients. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=CTRI/2020/11/029345 (first received 25 November 2020).

EUCTR2020-001302-30-AT *{published data only}*

EUCTR2020-001302-30-AT.A multicenter, randomized, active controlled, open label, platform trial on the efficacy and safety of experimental therapeutics for patients with a lung disease caused by coronavirus infection ACOVACT (Austrian CoronaVirus Adaptive Clinical Trial). ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-001302-30-AT (first received 09 April 2020).

EUCTR2020-001708-41-IT *{published data only}*

EUCTR2020-001708-41-IT.Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: comparison of 40 mg o.d. versus 40 mg b.i.d. A randomized clinical trial. clinicaltrialsregister.eu/ctr-search/trial/2020-001708-41/IT (first received 24 June 2020).

EUCTR2020-001709-21-FR *{published data only}*

EUCTR2020-001709-21-FR.Effectiveness of low molecular weight heparin at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of venous thromboembolism in coronavirus disease 2019 (COVID-19) hospitalized patients: the randomized multicentric controlled open-label trial COVI-DOSE. clinicaltrialsregister.eu/ctr-search/trial/2020-001709-21/FR (first received 24 March 2020).

EUCTR2020-001709-21-FR.Low-molecular-weight heparin to prevent venous thromboembolism in COVID-19 patients: a randomized controlled trial of different doses. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-001709-21-FR (first received 29 April 2020).

EUCTR2020-001891-14-ES *{published data only}*

EUCTR2020-001891-14-ES.Impact of the use of low molecular weight heparins (LMWH), at prophylactic versus intermediate doses, on SARS-CoV2 infection (COVID-19). ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-001891-14-ES (first received 05 May 2020).

EUCTR2020-002234-32-IT *{published data only}*

EUCTR2020-002234-32-IT.Efficacy and safety of edoxaban and or colchicine for patients with SARS-CoV-2 infection managed in the out of hospital setting (COVID 19) - CorONa Virus edoxabaN ColchicinE (CONVINCE). ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-002234-32-IT (first received 4 January 2021).

EUCTR2020-002504-39-DE *{published data only}*

EUCTR2020-002504-39-DE.Hamburg edoxaban for anticoagulation in COVID-19 study - HERO-19. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-002504-39-DE (first received 14 August 2020).

EUCTR2020-003349-12-IE *{published data only}*

EUCTR2020-003349-12-IE.This is a proof of principle / feasibility study aiming to evaluate the effect of nebulised unfractionated heparin on procoagulant markers related to acute respiratory distress syndrome in patients invasively ventilated for COVID 19 lung disease - Charter Trial. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-003349-12-IE (first received 14 August 2020).

Goldin 2020 *{published data only}*

* Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Sharifova G, et al.Treatment-dose LMWH versus prophylactic/intermediate dose heparins in high risk COVID-19 inpatients: rationale and design of the HEP-COVID Trial. *Thrombosis and Haemostasis* 2021;**121**(12):1684-95. [DOI: 10.1055/a-1475-2351]

NCT04401293.Systemic anticoagulation with full dose low molecular weight heparin (LMWH) vs. prophylactic or intermediate dose LMWH in high risk COVID-19 patients (HEP-COVID Trial). clinicaltrials.gov/ct2/show/NCT04401293 (first received 26 May 2020).

IRCT20200515047456N1 *{published data only}*

IRCT20200515047456N1.The role of anticoagulant and thrombolitic in treatment of COVID patients. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=IRCT20200515047456N1 (first received 28 June 2020).

ISRCTN14212905 *{published data only}*

ISRCTN14212905.Understanding how COVID-19 leads to respiratory failure in COVID-19 positive patients. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=ISRCTN14212905 (first received 03 July 2020).

Kharma 2020 *{published data only}*

* Kharma N, Roehrig S, Shible AA, Elshafei MS, Osman D, Elsaid IM, et al.Anticoagulation in critically ill patients on mechanical ventilation suffering from COVID-19 disease, The ANTI-CO trial: a structured summary of a study protocol for a randomised controlled trial. Trials 2020;**21**(1):769. [PMID: 32895056]

NCT04445935.Anticoagulation in patients suffering from COVID-19 disease the ANTI-CO Trial. clinicaltrials.gov/ct2/show/NCT04445935 (first received 23 June 2020).

Lasky 2021 *{published data only}*

* Lasky JA, Fuloria J, Morrison ME, Lanier R, Naderer O, Brundage T, et al.Design and rationale of a randomized, double-blind, placebo-controlled, phase 2/3 study evaluating dociparstat in acute lung injury associated with severe COVID-19. *Advances in Therapy* 2021;**38**(1):782-91. [DOI: 10.1007/s12325-020-01539-z]

NCT04389840.Dociparstat for the treatment of severe COVID-19 in adults at high risk of respiratory failure. clinicaltrials.gov/ct2/show/NCT04389840 (first received 13 May 2020).

Lins 2020 *{published data only}*

* Lins PR, de Albuquerque CC, Assis CF, Rodrigues BC, e Siqueira Campos BP, de Oliveira Valle E, et al.CoV-Hep study: heparin in standard anticoagulation based on citrate for continuous veno-venous hemodialysis in patients with COVID-19: a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020;**21**(1):920. [DOI: 10.1186/s13063-020-04814-0]

NCT04487990.CoV-Hep study: comparative study between different anti-coagulation strategies in continuous hemodialysis in COVID-19 patients. clinicaltrials.gov/ct2/show/NCT04487990 (first received 23 July 2020).

Marietta 2020 *{published data only}*

EUCTR2020-001972-13-IT.High versus low LMWH dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy COVID-19 HD. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=NCT04408235 (first received 26 May 2020).

Marietta M, Vandelli P, Mighali P, Vicini R, Coluccio V, D'Amico R.Randomised controlled trial comparing efficacy and safety of high versus low low-molecular weight heparin dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation (COVID-19 HD). *Blood Transfusion* 2020;**18 Suppl 4**:S490. [DOI: 10.2450/2020.S4]

* Marietta M, Vandelli P, Mighali P, Vicini R, Coluccio V, D'Amico R.Randomised controlled trial comparing efficacy and safety of high versus low molecular weight heparin dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation (COVID-19 HD): a structured summary of a study protocol. *Trials* 2020;**21**(1):574. [PMID: 32586394]

NCT04408235.High versus low LMWH dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy (COVID-19 HD). clinicaltrials.gov/ct2/show/NCT04408235 (first received 29 May 2020).

NCT04333407 *{published data only}***NCT04333407**

NCT04333407.Preventing cardiac complication of COVID-19 disease with early acute coronary syndrome therapy: a randomised controlled trial. clinicaltrials.gov/ct2/show/NCT04333407 (first received 3 April 2020).

NCT04344756 *{published data only}*

NCT04344756.Trial evaluating efficacy and safety of anticoagulation in patients with COVID-19 infection, nested in the Corimmuno-19 cohort (CORIMMUNO-COAG). clinicaltrials.gov/ct2/show/study/NCT04344756 (first received 14 April 2020).

NCT04345848 *{published data only}*

NCT04345848.Preventing COVID-19-associated thrombosis, coagulopathy and mortality with low- and high-dose anticoagulation: a randomized, open-label clinical trial. clinicaltrials.gov/ct2/show/NCT04345848 (first received 15 April 2020).

NCT04352400 *{published data only}*

NCT04352400.Efficacy of nafamostat in COVID-19 patients (RACONA Study) (RACONA). clinicaltrials.gov/ct2/show/NCT04352400 (first posted 20 April 2020).

NCT04366960 *{published data only}*

NCT04366960.Comparison of two doses of enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients. clinicaltrials.gov/ct2/show/NCT04366960 (first received 29 April 2020).

NCT04367831 *{published data only}*

NCT04367831.Intermediate or prophylactic-dose anticoagulation for venous or arterial thromboembolism in severe COVID-19: a cluster based randomized selection trial (IMPROVE-COVID). clinicaltrials.gov/ct2/show/NCT04367831 (first received 27 April 2020).

NCT04373707 *{published data only}*

NCT04373707.Effectiveness of weight-adjusted prophylactic low molecular weight heparin doses compared with lower fixed prophylactic doses to prevent venous thromboembolism in COVID-2019. The multicenter randomized controlled open-label trial COVI-DOSE. clinicaltrials.gov/ct2/show/record/NCT04373707 (first received 4 May 2020).

NCT04377997 *{published data only}*

NCT04377997.A randomized, open-label trial of therapeutic anticoagulation in COVID-19 patients with an elevated D-dimer. clinicaltrials.gov/ct2/show/NCT04377997 (first received 7 May 2020).

NCT04397510 *{published data only}*

NCT04397510.Nebulized heparin vs. placebo for the treatment of COVID-19 induced lung injury. clinicaltrials.gov/ct2/show/NCT04397510 (first received 21 May 2020).

NCT04406389 *{published data only}*

NCT04406389.Anticoagulation in critically ill patients with COVID-19 (The IMPACT Trial). www.clinicaltrials.gov/ct2/show/NCT04406389 (first received 26 May 2020).

NCT04409834 *{published data only}*

NCT04409834.Prevention of arteriovenous thrombotic events in critically-ill COVID-19 patients trial (COVID-PACT). clinicaltrials.gov/ct2/show/NCT04409834 (first received 28 May 2020).

NCT04416048 *{published data only}*

EUCTR2020-002282-33-DE.Effect of anticoagulation therapy on clinical outcomes in COVID-19 COVID-PREVENT. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=NCT04416048 (first received 30 November 2020).

* NCT04416048.Effect of anticoagulation therapy on clinical outcomes in moderate to severe coronavirus disease 2019 (COVID-19). clinicaltrials.gov/ct2/show/NCT04416048 (first received 4 June 2020).

NCT04420299 *{published data only}*

NCT04420299.Clinical trial on the efficacy and safety of bemiparin in patients hospitalized because of COVID-19. clinicaltrials.gov/ct2/show/NCT04420299 (first received 5 June 2020).

NCT04444700 *{published data only}*

NCT04444700.A pragmatic randomized controlled trial of therapeutic anticoagulation versus standard care as a rapid response to (SARS-CoV-2) COVID-19 pandemic (RAPID-BRAZIL). clinicaltrials.gov/ct2/show/NCT04444700 (first received 22 June 2020).

NCT04485429 *{published data only}*

NCT04485429.Efficacy assessment of methylprednisolone and heparin in patients with COVID-19 Pneumonia. clinicaltrials.gov/ct2/show/NCT04485429 (first received 20 July 2020).

NCT04508439 *{published data only}*

NCT04508439.Effect of the use of anticoagulant therapy during hospitalization and discharge in patients with COVID-19 infection. clinicaltrials.gov/ct2/show/NCT04508439 (first received 5 August 2020).

NCT04511923 *{published data only}*

NCT04511923.Nebulised heparin to reduce COVID-19 induced acute lung injury (CHARTER-Irl). clinicaltrials.gov/ct2/show/NCT04511923 (first received 10 August 2020).

NCT04512079 *{published data only}*

NCT04512079.Freedom COVID-19 anticoagulation strategy (FREEDOM COVID). clinicaltrials.gov/ct2/show/NCT04512079 (first received 11 August 2020).

NCT04530578 *{published data only}*

NCT04530578.Nebulized heparin in severe scute respiratory syndrome COVID-19 (NEBUHEPA). clinicaltrials.gov/ct2/show/NCT04530578 (first received 17 August 2020).

NCT04542408 *{published data only}*

NCT04542408.Hamburg edoxaban for anticoagulation in COVID-19 study. clinicaltrials.gov/ct2/show/NCT04542408 (first received 6 September 2020).

NCT04545541 *{published data only}*

NCT04545541.Nebulised heparin in patients with severe COVID-19 (CHARTER-MT). clinicaltrials.gov/ct2/show/NCT04545541 (first received 5 September 2020).

NCT04584580 *{published data only}*

NCT04584580.D-dimer adjusted versus therapeutic dose low-molecular-weight heparin in patients with COVID-19 pneumonia. clinicaltrials.gov/ct2/show/NCT04584580 (first received 6 October 2020).

NCT04600141 *{published data only}*

NCT04600141.Clinical efficacy of heparin and tocilizumab in patients with severe COVID-19 infection: a randomized clinical trial. clinicaltrials.gov/ct2/show/NCT04600141 (first received 22 October 2020).

NCT04604327 *{published data only}*

NCT04604327.Comparison of two different doses of bemiparin in COVID-19 (BEMICOP). clinicaltrials.gov/ct2/show/NCT04604327 (first received 23 October 2020).

NCT04623177 *{published data only}*

NCT04623177.Thromboprophylaxis for patients in ICU with COVID-19. clinicaltrials.gov/ct2/show/NCT04623177 (first received 02 November 2020).

NCT04640181 *{published data only}*

NCT04640181.Factor Xa inhibitor versus standard of care heparin in hospitalized patients with COVID-19 (XACT). clinicaltrials.gov/ct2/show/NCT04640181 (first received 19 November 2020).

NCT04646655 *{published data only}*

NCT04646655.Enoxaparin at prophylactic or therapeutic doses in COVID-19 (EMOS-COVID). clinicaltrials.gov/ct2/show/NCT04646655?term=NCT04646655&draw=2&rank=1 (first received 30 November 2020).

NCT04655586 *{published data only}*

NCT04655586.Assessing safety, hospitalization and efficacy of rNAPc2 in COVID-19 (ASPEN). clinicaltrials.gov/ct2/show/NCT04655586?term=Assessing+Safety%2C+Hospitalization+and+Efficacy+of+rNAPc2+in+COVID-19&draw=2&rank=1 (first received 7 December 2020).

NCT04723563 *{published data only}*

NCT04723563.Nebulized heparin for the treatment of COVID-19 (INHALE-HEP). clinicaltrials.gov/ct2/show/NCT04723563 (first received 22 January 2021).

NCT04730856 *{published data only}*

NCT04730856.Standard vs high prophylactic doses or anticoagulation in patients with high risk of thrombosis admitted with COVID-19 pneumonia (PROTHROMCOVID). clinicaltrials.gov/ct2/show/NCT04730856 (first received 14 January 2021).

NCT04743011 *{published data only}*

NCT04743011.Enriched heparin anti COVID-19 trial (EnHanCed). clinicaltrials.gov/ct2/show/NCT04743011 (first received 3 February 2021).

NCT04745442 *{published data only}*

NCT04745442.Pilot study of antithrombin as prophylaxis of acute respiratory distress syndrome in patients with COVID-19.

clinicaltrials.gov/ct2/show/NCT04745442 (first received 8 February 2021).

PACTR202007606032743 *{published data only}*

PACTR202007606032743.Nebulized heparin in patients with mainly moderate coronavirus disease 2019: randomized controlled trial. COVID-19. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=PACTR202007606032743 (first received 15 June 2020).

RBR-7y8j2bs *{published data only}*

RBR-7y8j2bs.Inhalational high molecular weight heparin for the treatment of SARS-Cov-2. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=RBR-7y8j2bs (first received 23 February 2021).

Sholzberg 2021a *{published data only}*

NCT04362085.Coagulopathy of COVID-19: a pragmatic randomized controlled trial of therapeutic anticoagulation versus standard care as a rapid response to the COVID-19 pandemic (RAPID COVID COAG). clinicaltrials.gov/ct2/show/NCT04362085 (first received 24 April 2020).

* Sholzberg M, Tang GH, Negri E, Rahhal H, Kreuziger LB, Pompilio CE, et al.Coagulopathy of hospitalised COVID-19: a pragmatic randomised controlled trial of therapeutic anticoagulation versus standard care as a rapid response to the COVID-19 pandemic (RAPID COVID COAG - RAPID Trial): a structured summary of a study protocol for a randomised controlled trial. *Trials* 2021;**22**(1):202. [DOI: 10.1186/s13063-021-05076-0]

Vanassche 2020 *{published data only}*

EUCTR2020-001739-28-BE.A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=EUCTR2020-001739-28-BE (first received 10 April 2020).

* Vanassche T, Engelen MM, Van Thillo Q, Wauters J, Gunst J, Wouters C, et al.A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19: the DAWn-Antico study. *Trials* 2020;**21**:1005. [DOI: 10.1186/s13063-020-04878-y]

Vanassche T, Engelen MM, Van Thillo Q, Wauters J, Gunst J, Wouters C, et al.Correction to: A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19: the DAWn-Antico study. *Trials* 2020;**21**:1033. [DOI: 10.1186/s13063-020-04991-y]

Van Haren 2020 *{published data only}*

NCT04635241.Inhaled heparin for hospitalised COVID-19 patients (INHALE-HEP). clinicaltrials.gov/ct2/show/NCT04635241 (first received 19 November 2020).

* Van Haren FMP, Richardson A, Yoon H-J, Artigas A, Laffey JG, Dixon B, et al.Inhaled nebulised unfractionated heparin for the treatment of hospitalised patients with COVID-19 (INHALE-HEP): protocol and statistical analysis plan for an investigator-initiated international metatrial of randomised studies. *British Journal of Clinical Pharmacology* 2020;**88**(8):3075-91. [DOI: 10.1111/bcp.14714]

Wilkinson 2020 *{published data only}*

EudraCT2020-001736-95.ACCORD 2: a multicentre, seamless, phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID 19 in hospitalised patients. clinicaltrialsregister.eu/ctr-search/trial/2020-001736-95/GB (first received 23 April 2020).

ISRCTN57085639.A platform to investigate the safety and effectiveness of several new medicines for the treatment of COVID-19 in hospitalised patients. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=ISRCTN57085639 (first received 24 September 2020).

* Wilkinson T, Dixon R, Page C, Carroll M, Griffiths G, Ho L-P, et al.ACCORD: a multicentre, seamless, phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID-19 in hospitalised patients: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;**21**(1):691. [DOI: 10.1186/s13063-020-04584-9]

Additional references

Abdel-Maboud 2021

Abdel-Maboud M, Menshawy A, Elgebaly A, Bahbah EI, El Ashal G, Negida A.Should we consider heparin prophylaxis in COVID-19 patients? a systematic review and meta-analysis. Journal of Thrombosis and Thrombolysis 2021;**51**(3):830-2. [PMID: 32816197]

Ackermann 2020

Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al.Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *New England Journal of Medicine* 2020;**383**(2):120-8. [PMID: 32437596]

Alquwaizani 2013

Alquwaizani M, Buckley L, Adams C, Fanikos J.Anticoagulants: a review of the pharmacology, dosing, and complications. *Current Emergency and Hospital Medicine Reports* 2013;**1**(2):83-97. [PMID: 23687625]

Amaral 2020

Amaral FC, Baptista-Silva JC, Nakano LC, Flumignan RL.Pharmacological interventions for preventing venous thromboembolism in patients undergoing bariatric surgery. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No: CD013683. [DOI: 10.1002/14651858.CD013683]

AVF 2020

American Venous Forum.Considerations in prophylaxis and treatment of VTE in COVID-19 patients. www.veinforum.org/wp-content/uploads/2020/04/COVID-19-White-Paper-04-17-2020-FINAL-1.pdf (accessed 3 July 2020).

Becker 2020

Becker RC.COVID-19 update: COVID-19-associated coagulopathy. *Journal of Thrombosis and Thrombolysis* 2020;**50**(1):54-67. [PMID: 32415579]

Biagioni 2020

Biagioni RB, Lopes RD, Agati LB, Sacilotto R, Wolosker N, Sobreira ML, et al.Rationale and design for the study apixaban versus clopidogrel on a background of aspirin in patients undergoing infrapopliteal angioplasty for critical limb ischemia: AGRIPPA trial. *American Heart Journal* 2020;**227**:100-6. [DOI: 10.1016/j.ahj.2020.06.010]

Bikdeli 2020

Bikdeli B, Madhavan M, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al.COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state of the art review. *Journal of American College of Cardiology* 2020;**75**(23):2950-73. [DOI: 10.1016/j.jacc.2020.04.031]

Bilaloglu 2020

Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS.Thrombosis in hospitalized patients with COVID-19 in a New York City health system. *JAMA* 2020;**324**(8):799-801. [PMID: 32702090]

Clezar 2020

Clezar CN, Cassola N, Flumignan CD, Nakano LC, Trevisani VF, Flumignan RL.Pharmacological interventions for asymptomatic carotid stenosis. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No: CD013573. [DOI: 10.1002/14651858.CD013573]

COMET 2020

Core outcome set developers' response to COVID-19. comet-initiative.org/Studies/Details/1538 (accessed 04 August 2020).

Covidence [Computer program]

Covidence.Version accessed 1 August 2020. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

COVIDSurg 2021

COVIDSurg Collaborative, GlobalSurg Collaborative.SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. Anaesthesia 2021 Aug 24 [Epub ahead of print]. [DOI: 10.1111/anae.15563]

Cuker 2021

Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, et al.American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Advances* 2021;**5**(3):872-88. [PMID: 10.1182/bloodadvances.2020003763]

Deeks 2021

Deeks JJ, Higgins JP, Altman DG, editor(s).Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Dias 2021

Dias SV, Flumignan RL, Iared W.Evidence from Cochrane systematic reviews for effects of antithrombotic drugs for lower-limb revascularization. A narrative review. Sao Paulo Medical Journal 2021 Aug 13 [Epub ahead of print]. [DOI: 10.1590/1516-3180.2020.0640.110321]

Dolhnikoff 2020

Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, da Silva LF, de Oliveira EP, Saldiva PH, et al.Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. Journal of Thrombosis and Haemostasis : JTH 2020;**18**(6):1517-9. [PMID: 32294295]

Fox 2020

Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy-Brown J, Vander-Heide RS.Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respiratory Medicine* 2020;**8**(7):681-6. [PMID: 32473124]

Giannis 2020

Giannis D, Ziogas IA, Gianni P.Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *Journal of Clinical Virology* 2020;**127**:104362. [PMID: 32305883]

GRADEpro GDT [Computer program]

GRADEpro GDT.Version accessed 1 August 2020. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Hasan 2020

Hasan SS, Radford S, Kow CS, Zaidi ST.Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis. *Journal of Thrombosis and Thrombolysis* 2020;**50**(4):814-21. [PMID: 32748122]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG.Measuring inconsistency in meta-analyses. *BMJ* 2003;**326**:557-60.

Higgins 2017

Higgins JP, Altman DG, Sterne JA, editor(s).Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Higgins 2020a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors).Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Higgins 2020b

Higgins JP, Eldridge S, Li T, editor(s).Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al editor(s). Cochrane

Handbook for Systematic Reviews of Interventions *V*ersion 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Kamel 2021

Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S.Anticoagulation outcomes in hospitalized COVID-19 patients: a systematic review and meta-analysis of case-control and cohort studies. *Reviews in Medical Virology* 2021;**31**(3):e2180. [PMID: 33022834]

Klok 2020a

Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, et al.Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research* 2020;**191**:145-7. [PMID: 32291094]

Klok 2020b

Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers D, Kant KM, et al.Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thrombosis Research* 2020;**191**:148-50. [PMID: 32381264]

Lai 2020

Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR.Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *International Journal of Antimicrobial Agents* 2020;**55**(4):105946. [PMID: 32199877]

Lazaridis 2021

Lazaridis D, Leung S, Kohler L, Smith CH, Kearson ML, Eraikhuemen N.The impact of anticoagulation on COVID-19 (SARS CoV-2) patient outcomes: a systematic review. Journal of Pharmacy Practice 2021 May 7 [Epub ahead of print]. [DOI: 10.1177/08971900211015055]

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al.Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Li 2020

Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al.Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke and Vascular Neurology* 2020;**5**(3):279-84. [DOI: 10.1136/svn-2020-000431]

Liu 2019

Liu Y, Mu S, Li X, Liang Y, Wang L, Ma X.Unfractionated heparin alleviates sepsis-induced acute lung injury by protecting tight junctions. *Journal of Surgical Research* 2019;**238**:175-85. [PMID: 30771687]

Long 2020

Long B, Brady WJ, Koyfman A, Gottlieb M.Cardiovascular complications in COVID-19. *American Journal of Emergency Medicine* 2020;**38**(7):1504-7. [PMID: 32317203]

Marini 2020

Marini JJ, Gattinoni L.Management of COVID-19 respiratory distress. *JAMA* 2020;**323**(22):2329-30. [DOI: 10.1001/jama.2020.6825] [PMID: 32329799]

Matli 2021

Matli K, Farah R, Maalouf M, Chamoun N, Costanian C, Ghanem G.Role of combining anticoagulant and antiplatelet agents in COVID-19 treatment: a rapid review. *Open Heart* 2021;**8**(1):e001628. [PMID: 34099529]

McBane 2020

McBane RD 2nd, Torres Roldan VD, Niven AS, Pruthi RK, Franco PM, Linderbaum JA, et al.Anticoagulation in COVID-19: a systematic review, meta-analysis, and rapid guidance from Mayo Clinic. *Mayo Clinic Proceedings* 2020;**95**(11):2467-86. [PMID: 33153635]

McGuinness 2020

McGuinness LA, Higgins JP.Risk-of-bias visualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020;**12**(1):55-61. [DOI: 10.1002/jrsm.1411]

Moonla 2021

Moonla C, Sosothikul D, Chiasakul T, Rojnuckarin P, Uaprasert N.Anticoagulation and in-hospital mortality from coronavirus disease 2019: a systematic review and meta-analysis. *Clinical and Applied Thrombosis/hemostasis* 2021;**27**:10760296211008999. [PMID: 33874753]

NHS 2020

NHS England and NHS Improvement.Clinical guide for the management of anticoagulant services during the coronavirus pandemic. www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf (accessed 3 July 2020).

Obe 2020

Obe BH, Retter A, McClintock C.Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. thrombosisuk.org/downloads/T&H%20and%20COVID.pdf (accessed 3 July 2020).

Oxley 2020

Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al.Large-vessel stroke as a presenting feature of COVID-19 in the young. *New England Journal of Medicine* 2020;**382**(20):e60. [DOI: 10.1056/NEJMc2009787]

Page 2021

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]

Panigada 2020

Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al.Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *Journal of Thrombosis and Haemostasis* 2020;**18**(7):1738-42. [PMID: 32302438]

Parisi 2021

Parisi R, Costanzo S, Di Castelnuovo A, de Gaetano G, Donati MB, Iacoviello L.Different anticoagulant regimens, mortality, and bleeding in hospitalized patients with COVID-19: a systematic review and an updated meta-analysis. *Seminars in Thrombosis and Hemostasis* 2021;**47**(4):372-91. [PMID: 33851386]

Patell 2021

Patell R, Chiasakul T, Bauer E, Zwicker JI.Pharmacologic thromboprophylaxis and thrombosis in hospitalized patients with COVID-19: a pooled analysis. *Thrombosis and Haemostasis* 2021;**121**(1):76-85. [PMID: 33378787]

Perepu 2021

Perepu US, Chambers I, Wahab A, Eyck PT, Wu C, Dayal S, et al.Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomized controlled trial. *Journal of Thrombosis and Haemostasis* 2021;**19**(9):2225-34. [DOI: 10.1111/jth.15450]

Ramacciotti 2020

Ramacciotti E, Macedo AS, Biagioni RB, Caffaro RA, Lopes RD, Guerra JC, et al.Evidence-based practical guidance for the antithrombotic management in patients with coronavirus disease (COVID-19) in 2020. *Clinical and Applied Thrombosis/hemostasis* 2020;**26**:1076029620936350. [PMID: 32649232]

Reeves 2021

Reeves BC, Deeks JJ, Higgins JP, Shea B, Tugwell P, Wells GA.Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Review Manager 2020 [Computer program]

Review Manager 5 (RevMan 5).Version 5.4. Copenhagen: The Cochrane Collaboration, 2020.

Robvis [Computer program]

Robvis (visualization tool).Version accessed 20 August 2020. Bristol, UK: Luke McGuinness. Available at mcguinlu.shinyapps.io/robvis/.

Schulman 2010

Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W.Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *Journal of Thrombosis and Haemostasis : JTH* 2010;**8**(1):202-4. [PMID: 19878532]

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s).Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.gradepro.org/app/handbook/handbook.html.

Schünemann 2021

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al.Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Sholzberg 2021b

Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Ní Áinle F, et al.Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial. *BMJ* 2021;**375**:n2400. [DOI: 10.1136/bmj.n2400]

Sobreira 2020

Sobreira ML, Marques MA.Anticoagulants as panacea in COVID-19 infection. *Jornal Vascular Brasileiro* 2020;**19**:e20200063. [DOI: 10.1590/1677-5449.200063]

Spyropoulos 2021

Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al.Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Internal Medicine 2021 October 7 [Epub ahead of print]. [DOI: 10.1001/jamainternmed.2021.6203]

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al.ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical Research Ed.)* 2016;**355**:i4919. [PMID: 27733354]

Talasaz 2021

Talasaz AH, Sadeghipour P, Kakavand H, Aghakouchakzadeh M, Kordzadeh-Kermani E, Van Tassell BW, et al.Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. *Journal of the American College of Cardiology* 2021;**77**(15):1903-21. [PMID: 33741176]

Wan 2014

Wan X, Wang W, Liu J, Tong T.Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014;**14**:135. [PMID: 25524443]

Ware 1992

Ware JE Jr, Sherbourne CD.The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992;**30**(6):473-83. [PMID: 1593914]

Young 2008

Young E.The anti-inflammatory effects of heparin and related compounds. *Thrombosis Research* 2008;**122**(6):743-52. [PMID: 17727922]

References to other published versions of this review

Flumignan 2020a

Flumignan RL, Tinôco JD, Pascoal PI, Areias LL, Cossi MS, Fernandes MI, et al.Prophylactic anticoagulants for patients hospitalised with COVID-19 (Protocol). available from doi.org/10.17605/OSF.IO/8PRXW (registered 7 August 2020).

Flumignan 2020b

Flumignan RL, Tinôco JD, Pascoal PI, Areias LL, Cossi MS, Fernandes MI, et al.Prophylactic anticoagulants for people hospitalised with COVID-19. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No: CD013739. [DOI: 10.1002/14651858.CD013739]

Flumignan 2021

Flumignan RL, Tinôco JD, Pascoal PI, Areias LL, Cossi MS, Fernandes MI, et al.Prophylactic anticoagulants for people hospitalized with COVID-19: systematic review. British Journal of Surgery 2021 Jun 10 [Epub ahead of print]. [DOI: 10.1093/bjs/znab197]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Albani 2020

Study characteristics	
Methods	• Study design: prospective cohort NRS • Type of publication: peer-reviewed journal publication • Setting and dates: hospital, 20 February 2020-10 March 2020 • Country: Italy • Language: English • Number of centres: 1 • Trial registration number: NR
Participants	• Number of participants: 1403 allocated (experimental = 799; comparator = 604), 27 excluded (1 < 18 years, 26 were still admitted to the hospital and, because of this, the discharge status was not available at time of analysis), 1376 analysed (experimental = 780; comparator = 596) • Age, years (mean ± SD): 68.66 ± 12.62 (experimental), 70.6 ± 15.01 (comparator) • Gender (male/female): 545/254 (experimental), 379/225 (comparator) • Comorbidities (experimental/comparator): hypertension 35.9%/35.1%, diabetes 21.8%/19% • Confounding factors: prior anticoagulation (experimental = 53, comparator = 13), surgery (NR), cancer (NR), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: NR Inclusion criteria • Admitted to the hospital • Real time-PCR from a nasopharyngeal swab or bronchoalveolar lavage resulted positive for SARS-CoV-2 Exclusion criteria • Age < 18 years • Being still admitted to hospital so that a definitive outcome was not available at the time of analysis
Interventions	• Experimental: anticoagulation with enoxaparin 40-80 mg/day, duration 3-9 days • Comparator: without anticoagulation • Concomitant therapy: NR • Duration of follow-up: until death or hospital discharge

Albani 2020 *(Continued)*

Outcomes	Primary outcomes • Mortality Secondary outcomes • Admission to ICU • Hospital length of stay • PE • VTE • Acute myocardial infarction • Cerebral infarction • Haemorrhagic events
Notes	• Sponsor/funding: quote "The authors received no specific funding for this work." • COIs: quote "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." • Protocol not available

Lemos 2020

Study characteristics	
Methods	• Study design: single-centre, open-label, 2-armed, parallel-assignment RCT • Type of publication: peer-reviewed journal publication • Setting and dates: hospital, April 2020-July 2020 • Country: Brazil • Language: English • Number of centres: 1
Participants	• 20 participants randomised (experimental (therapeutic anticoagulation) = 10; comparator (prophylactic anticoagulation) = 10), 20 participants analysed • Mean age (years) ± SD: 55 ± 10 (experimental), 58 ± 16 (comparator) • Gender (male/female): 9/11 (experimental), 7/13 (comparator) • Severity of condition: all under mechanical ventilation • Comorbidities (experimental/comparator): diabetes (4/3), hypertension (4/3), cardiovascular disease (1/1), immunocompromise (1/0) • Confounding factors: prior anticoagulation (NR), surgery (NR), cancer (NR), antiplatelet use (NR), history of VTE (NR) • BMI (kg/m^2), mean ± SD: 33 ± 8 (experimental), 34 ± 8 (comparator) • Anticoagulation before randomisation (experimental/comparator): prophylactic anticoagulation 4/7, therapeutic anticoagulation 0/0 • Baseline medication (experimental/comparator): norepinephrine 6/6, neuromuscular blocking agent 10/10, corticosteroids 7/7, hydroxychloroquine 4/1, macrolide antibiotic 9/9, antiplatelet agents 0/0, remdesivir 0/0, interleukin-6 inhibitors 0/0 Inclusion criteria • Age > 18 years-old • SARS-CoV-2 infection confirmed by RT-PCR • Presence of ARDS according to the Berlin definition • Severe clinical presentation with respiratory failure requiring mechanical ventilation • D-dimer levels > 1000 µg/L • Prothrombin time/INR < 1.5

Lemos 2020 *(Continued)*

- aPTT ratio < 1.5
- Platelet count > 100,000/mm^3

Exclusion criteria

- Age > 85 years-old
- CrCl < 10 ml/min
- Severe circulatory shock with a dose of norepinephrine > 1.0 µg/kg/min
- Chronic renal failure in renal replacement therapy
- Child B and C chronic liver disease
- Advanced diseases, such as active cancer, heart failure with functional class III and IV (New York Heart Failure Association), COPD using home oxygen, advanced dementia, significant disability from stroke or severe head injury, cardiorespiratory arrest
- Pregnant women
- Recent major surgery or severe trauma in the last 3 weeks
- Recent stroke in the last 3 months
- Active bleeding
- Blood dyscrasia such as haemophilia, Von Willebrand factor deficiency
- Participation in another clinical investigation
- Indication for therapeutic anticoagulation due to PE, and ACS

Interventions	• Experimental: therapeutic anticoagulation with heparin (subcutaneous enoxaparin with the dose according to age and adjusted daily by the CrCl estimated by the CKD Epidemiology Collaboration equation). The maximum dose of enoxaparin allowed was 140 mg twice daily. • Comparator: subcutaneous UFH at a dose of 5000 IU three times/day (if weight < 120 kg) and 7500 IU three times/day (if weight > 120 kg) or enoxaparin at a dose of 40 mg once daily (if weight < 120 kg) and 40 mg twice daily (if weight > 120 kg) according to the doctor's judgment. • Concomitant therapy: NR
Outcomes	Primary (specified) • PaO_2 / FIO_2 ratio • Days without mechanical ventilation (within 28 days of follow-up) Primary (collected) • PaO2/FiO2 ratio • Ventilator-free days Secondary (specified) • Plasma D-dimer levels (D0, D4) • Biomarkers of endothelial glycocalyx lesion levels (syndecan-1; hyalurane; thrombomodulin; CD44s) between D0/D4 • Endothelial glycocalyx thickness assessment assessed by sublingual microscopy using the Glycocheck equipment between D0/D4/D7/D14 • Assessment of organ dysfunction assessed using the SOFA score between D0/D4 • Overall 28-day mortality Secondary (collected) • Number of prone positioning sessions • All-cause 28-day mortality • In-hospital mortality • ICU-free days • Length of hospital stay • Thrombotic events

Lemos 2020 *(Continued)*

	• Adverse events • Major bleeding • Minor bleeding • Bleeding requiring medical attention • Drop in haemoglobin levels • Drop in haemoglobin levels > 5.0 g/dL Time points reported: at 0, 4, 7, 14 and 28 days after the start of the intervention
Notes	• Sponsor/funding: quote "This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors."; quote "Supporting source: Conselho Nacional de Pesquisa e Desenvolvimento tecnológico CNPq" (protocol) • COIs: quote "all authors declare no conflicts of interest" • Trial registration number: REBEC RBR-949z6v

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Quote "We used blocked randomisation, and the participants were randomised in a 1:1 ratio within two blocks of ten patients each."
Allocation concealment (selection bias)	Yes	Quote " The patients were assigned to each treatment by drawing the sequential numbering of opaque envelopes containing the treatment allocation."
Blinding of participants and personnel (performance bias)	No	Quote "In this randomised, controlled, open-label..."
Blinding of outcome assessment (detection bias)	No	Quote "In this randomised, controlled, open-label..."
Incomplete outcome data (attrition bias)	No	Quote "The third arm of this study with therapeutic intravenous unfractionated heparin (UFH) was abandoned due to difficulties in adjusting the activated partial thromboplastin time (aPTT) during the pandemic."
Selective reporting (reporting bias)	Yes	All prespecified outcomes were reported
Other bias	Yes	We do not suspect any other bias related to this study.

Lopes 2021

Study characteristics	
Methods	• Study design: multicentre, open-label with blinded outcomes adjudication, investigator-sponsored, 2-armed, phase IV, parallel-assignment RCT • Type of publication: abstract of event • Setting and dates: hospital, 21 June 2020-28 February 2021 • Country: Brazil • Language: English • Number of centres: 8

Lopes 2021 *(Continued)*

Participants	• 3331 participants were assessed for eligibility, 615 participants randomised, 614 analysed (experimental (therapeutic anticoagulation) = 310, comparator (prophylactic anticoagulation) = 304, 1 participant withdrew consent), ≥ 18 years • Mean age (years) ± SD: 56.7 ± 14.1 (experimental), 56.5 ± 14.5 (comparator) • Gender (male/female): 192/119 (experimental), 176/128 (comparator) • Severity of condition: need for oxygen in 76% (catheter or mask 60%, high-flow nasal cannula 8%, tracheal intubation 7%); unstable clinical condition 23 (7.4%) experimental, 16 (5.3%) comparator, stable clinical condition 288 (92.6%) experimental, 288 (94.7%) comparator; disease state at baseline (experimental/comparator): mild 30 (9.6%) / 39 (12.8%), moderate 257 (82.6%) / 249 (81.9%), severe 24 (7.7%) / 16 (5.3%) • Comorbidities (experimental/comparator): chronic lung disease 7 (2.3%) / 12 (3.9%), diabetes 83 (26.7%) / 67 (22.0%), current smoker/former smoker 56 (18.0%)/63 (20.7%), hypertension 151 (48.6%)/151 (49.7%), heart failure 8 (2.6%)/5 (1.6%), coronary disease 12 (3.9%)/16 (5.3%) • BMI (kg/m^2), mean ± SD: 30.3 ± 6.0 (experimental), 30.3 ± 6.1 (comparator) • Anticoagulation before randomisation (experimental/comparator): 285 (91.7%) / 275 (90.5%) • Baseline medication (experimental/comparator): antiplatelet 22 (7.1%) / 26 (8.6%), vasopressor 16 (5.1%) / 8 (2.6%), systemic corticosteroids 257 (82.6%)/253 (83.2%) • D-dimer ≥ 3 x ULN (experimental/comparator): 84 (27.0%) / 83 (27.3%) Inclusion • Patients with confirmed diagnosis of COVID-19 admitted to hospital • Onset of symptoms leading to hospitalisation < 14 days • Patients ≥ 18 years • D-dimer ≥ 3 x the ULN • Agreement to participate by providing the informed consent form Exclusion • Patients with indication for full anticoagulation during inclusion (for example, diagnosis of VTE, atrial fibrillation, mechanical valve prosthesis) • Platelets < 50,000/m^3 • Need for ASA therapy > 100 mg • Need for P2Y12 inhibitor therapy (clopidogrel, ticagrelor or prasugrel) • Chronic use of non-hormonal anti-inflammatory drugs • Sustained uncontrolled systolic BP of ≥ 180 mmHg or diastolic BP of ≥ 100 mmHg • INR > 1.5 • Patients contraindicated to full anticoagulation (active bleeding, liver failure, blood dyscrasia or prohibitive haemorrhage risk as evaluated by the investigator) • Criteria for DIC • A history of haemorrhagic stroke or any intracranial bleeding at any time in the past or current intracranial neoplasm (benign or malignant), cerebral metastases, arteriovenous (AV) malformation, or aneurysm; • Active cancer (excluding non-melanoma skin cancer) defined as cancer not in remission or requiring active chemotherapy or adjunctive therapies such as immunotherapy or radiotherapy • Hypersensitivity to rivaroxaban • Use of strong inhibitors of cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) (e.g. protease inhibitors, ketoconazole, Itraconazole) and/or use of P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) • Known HIV infection • CrCl < 30 mL/min according to the Cockcroft-Gault Formula • Pregnancy or breastfeeding

Lopes 2021 *(Continued)*

Interventions	• Experimental: routine full anticoagulation strategy. Stable patients received rivaroxaban 20 mg daily. Unstable patients received enoxaparin 1 mg/kg twice daily. Followed by rivaroxaban for 30 days, irrespective of the duration of hospitalisation • Comparator: usual standard care and currently have no indication of full anticoagulation. Control group with enoxaparin 40 mg/d
Outcomes	Primary (specified) • Hierarchical composite endpoint composed of mortality, number of days alive, number of days in the hospital and number of days with oxygen therapy at the end of 30 days (time frame: in 30 days) The primary objective will be analysed using the win ratio approach comparing every participant of treatment group to every participant of control group to determine a winner. Primary (collected) • Hierarchical analysis of mortality, duration of hospitalisation, and duration of oxygen use through 30 days • Major or clinically relevant non-major bleeding according to ISTH criteria Secondary (specified) • Incidence of VTE (time frame: 30 days) • Incidence of acute myocardial infarction (time frame: 30 days) • Incidence of stroke (time frame: 30 days) • Number of days using oxygen therapy (time frame: 30 days) • Peak of troponin (time frame: 30 days) • Peak of D-dimer (time frame: 30 days) • Incidence of major bleeding and clinically relevant non-major bleeding by the ISTH criteria (time frame: 30 days). It will be considered the main safety endpoint Secondary (collected) • Death • Myocardial infarction • VTE • Stroke • Major adverse limb event • Hospitalisation time • Any bleeding • Need for respiratory support Time points reported: at 30 days after the start of the intervention
Notes	• Protocol available (NCT04394377) • Sponsor/funding: quote "Unrestricted research grant from Bayer S.A., which was not involved in design, conduct or interpretation of the study" • COIs: all listed study authors declared some financial support from the industry

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Quote "Concealed randomisation will be performed using a central, automated, electronic web-based system."
Allocation concealment (selection bias)	Yes	Quote "Concealed randomisation will be performed using a central, automated, electronic web-based system."

Lopes 2021 *(Continued)*

Blinding of participants and personnel (performance bias)	No	Quote "The study is open-label with blinded outcomes adjudication"
Blinding of outcome assessment (detection bias)	Yes	Quote "The study is open-label with blinded outcomes adjudication"
Incomplete outcome data (attrition bias)	Yes	There was one loss in the experimental group (1/311, 0.3%): one participant withdrew consent and declined to contribute data.
Selective reporting (reporting bias)	Yes	All prespecified outcomes were reported.
Other bias	Yes	We do not suspect any other bias related to this study.

Rentsch 2020

Study characteristics	
Methods	• Study design: prospective cohort • Type of publication: preprint available, accepted for publication in *BMJ* • Setting and dates: hospital, 1 March 2020-31 July 2020 • Country: USA • Language: English • Number of centres: 1200 points of care nationwide • Trial registration number: NR
Participants	• Number of participants: 4297 allocated (intervention = 3627; comparator = 670) • Age, years (mean ± SD): 67.03 ± 12.31 (experimental), 67.83 ± 13.74 (comparator) • Gender (male/female): 3395/232 (experimental), 620/50 (comparator) • Comorbidities (experimental/comparator): acute myocardial infarction 1.8%/1.6%, asthma 4.9%/4.9%, cancer 13.6%/14.5%, cerebrovascular disease 10.2%/12.7%, CKD 19.1%/20.3%, COPD 15%/15.7%, coronary artery disease 2.5%/3.7%, dementia 10.4%/15.5%, diabetes 43.4%/40.1%, heart failure 10.3%/11.5%, hypertension 68.1%/66.6%, liver disease 8.9%/10.6%, peripheral arterial disease 10.7%/10.4% • Confounding factors (experimental/comparator): prior anticoagulation (NR, but therapeutic anticoagulation was excluded), surgery (NR), cancer 13.6%/14.5% (adjusted), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: NR Inclusion criteria • All patients hospitalised between 1 March 2020-31 July 2020 who had a laboratory-confirmed positive SARS-CoV-2 test result on or within 14 days prior to hospital admission Exclusion criteria • Patients who had no history of care (defined as at least one outpatient or inpatient encounter in the two years prior to 1 March 2020 • Received therapeutic anticoagulation in the 30 days prior to hospital admission • Received a red blood cell transfusion with 24 h of admission • Experienced any of the primary outcomes (i.e. died or initiated therapeutic anticoagulation) within 24 h of admission and therefore did not have equal chance to be classified as exposed in this study

Rentsch 2020 *(Continued)*

Interventions	• Experimental: prophylactic doses of subcutaneous UFH (5000 IU twice or three times/day (1094 participants = 30.2%), LMWH (enoxaparin 40 mg once or twice daily (2506 participants = 69.1%), fondaparinux 2.5 mg once daily (4 participants = 0.1%), dalteparin 2500-5000 IU once daily, all subcutaneously) or DOACs (apixaban 2.5 mg bid (21 participants = 0.6%), rivaroxaban 10 mg once daily or 2.5 mg twice daily (2 participants = 0.1%), dabigatran 220 mg once daily, all orally) • Comparator: without anticoagulation • Concomitant therapy (experimental/comparator): dexamethasone 16.2%/11.0%, remdesivir 12.0%/5.2% • Duration of follow-up: up to 30 days after hospitalisation
Outcomes	Primary outcomes • 30-day mortality (in hospital or after discharge) Secondary outcomes • Inpatient mortality • Initiating therapeutic anticoagulation
Notes	• Sponsor/funding: quote "This work was supported by the National Institute on Alcohol Abuse and Alcoholism (U01-AA026224, U24-AA020794, U01-AA020790, U10-AA013566), and by the Department of Veterans Affairs Health Services Research & Development (C19 20-405) and Office of Research and Development (MVP000). Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The views and opinions expressed in this manuscript are those of the authors and do not necessarily represent those of the Department of Veterans Affairs or the United States Government. • COIs: quote "JAB reports consulting with Amgen, Bayer, JanOne, and Janssen. He serves on the Data Safety Monitoring Committee for Novartis. PMH is supported by grants from National Heart, Lung, and Blood Institute, VA Health Services Research & Development, and University of Colorado School of Medicine. He has a research agreement with Bristol-Myers Squibb through the University of Colorado. He serves as the Deputy Editor for Circulation: Cardiovascular Quality and Outcomes. IJD reports grants from UK National Health Service National Institute for Health Research, and has received unrestricted research grants and holds shares in GlaxoSmithKline, outside of the submitted work. All other authors declare no conflicts of interests." • Protocol not available

Sadeghipour 2021

Study characteristics	
Methods	• Study design: multicentre, open-label with blinded outcomes adjudication, investigator-sponsored, 2-armed, 2 × 2 factorial design, phase IV, parallel-assignment RCT • Type of publication: peer-reviewed publication • Setting and dates: hospital, 29 July 2020-19 November 2020 • Country: Iran • Language: English • Number of centres: 10
Participants	• 600 participants randomised (experimental (higher dose anticoagulation) = 299; comparator (prophylactic anticoagulation) = 299), 562 participants analysed (experimental = 276; comparator = 286), 38 participants were lost to follow-up (experimental/comparator): withdrew consent and declined to contribute data (15/13), duplicate entry (1/1), did not meet eligibility criteria (1/0), did not receive at least 1 dose of the assigned treatment (4/0) • Mean age (years) ± SD: 61.23 ± 14.68 (experimental); 59.66 ± 17.88 (comparator) • Gender (male/female): 162/114 (experimental), 163/123 (comparator)

Sadeghipour 2021 *(Continued)*

- Severity of condition (experimental/comparator): systolic blood pressure < 100 mmHg at the time of randomisation 25/33, vasopressor agent support within 72 h of enrolment 63/64, FiO_2 > 50% at the time of randomisation 112/122, acute physiology and chronic health evaluation II score at the time of randomisation 8/8
- Acute respiratory support (experimental/comparator): nasal cannula 10/14, face mask 33/27, reservoir mask 76/96, high-flow nasal cannula 9/6, non-invasive positive pressure ventilation 93/85, invasive positive-pressure ventilation (endotracheal intubation) 55/58
- Comorbidities (experimental/comparator): hypertension 131/118, diabetes 82/73, hyperlipidaemia 75/68, coronary artery disease 45/33, obstructive airway disease 23/16, heart failure 7/6, ischaemic cerebrovascular accidents 6/11, hemorrhagic stroke 0/0, VTE 0/0
- Confounding factors: surgery (NR), cancer (NR)
- BMI (kg/m^2), mean ± SD: 26.73 ± 3.50 (experimental), 26.86 ± 3.57 (comparator)
- Anticoagulation before randomisation (experimental/comparator): prophylactic anticoagulation NR, therapeutic anticoagulation 0/0
- Baseline medication (experimental/comparator): aspirin 91/81, platelet ADP P2Y12 receptor inhibitors 7/6

Inclusion criteria for anticoagulation hypothesis

- Adult patients (≥ 18 years), with PCR-confirmed COVID-19 admitted to ICU within 7 days of initial hospitalisation, who do not have another firm indication for anticoagulation (such as mechanical valve, high-risk atrial fibrillation, VTE, or left ventricle thrombus, who are not enrolled in another blinded randomised trial, and are willing to participate in the study and provide informed consent
- Estimated survival of at least 24 h at the discretion of enrolling physician

Exclusion criteria for anticoagulation hypothesis

- Weight < 40 kg
- Overt bleeding at the day of enrolment
- Known major bleeding within 30 days (according to the Bleeding Academic Research Consortium (BARC) definition)
- Platelet count < 50,000/µL
- Pregnancy (as confirmed by Beta HCG testing among female patients < 50 years)
- Patients on ECMO
- History of heparin-induced thrombocytopenia or immune thrombocytopenia
- Ischemic stroke within the past 2 weeks
- Craniotomy/major neurosurgery within the past 3 months
- Major head or spinal trauma in the past 30 days
- Known brain metastases or vascular malformations (aneurysm)
- Presence of an epidural, spinal or pericardial catheter
- Major surgery other than neurosurgery within 14 days prior to enrolment
- Coexistence of severe obesity (weight > 120 kg or BMI > 35 kg/m^2 along with severe renal insufficiency defined as CrCl < 30 mL/s)
- Allergic reaction to study medications
- Lack or withdrawal of informed consent

Interventions	• Experimental: intermediate-dose anticoagulation (enoxaparin, 1 mg/kg daily), with modification according to body weight and CrCl • Comparator: standard prophylactic anticoagulation (enoxaparin, 40 mg daily), with modification according to body weight and CrCl • Concomitant therapy (experimental/comparator): antiviral therapy 226/217, remdesivir 168/170, favipiravir 52/43, lopinavir/ritonavir 3/3, atazanavir/ritonavir 27/19, corticosteroid use 262/262, renin-angiotensin-aldosterone system inhibitors 78/74, tocilizumab 34/40
Outcomes	Primary (specified) • Composite of adjudicated acute VTE, arterial thrombosis, treatment with ECMO, or all-cause mortality

Sadeghipour 2021 *(Continued)*

Primary (collected)

- Composite of adjudicated acute VTE, arterial thrombosis, treatment with ECMO, or all-cause mortality

Secondary (specified)

- Rate of all-cause mortality
- Rate of objectively-confirmed VTE
- Ventilator-free days
- Rate of major bleeding
- Rate of clinically-relevant non-major bleeding
- Rate of severe thrombocytopenia
- Rate of rise in liver enzymes
- Clinically-diagnosed myopathy
- Objectively-confirmed arterial thrombosis. Imaging-confirmed acute arterial thrombosis (by ultrasonography, CT, MRI, or invasive angiography)

Secondary (collected)

- All-cause mortality
- Adjudicated VTE
- Ventilator-free days
- Objectively clinically diagnosed type I acute myocardial infarction
- Objectively clinically diagnosed stroke
- Objectively clinically diagnosed acute peripheral arterial thrombosis
- ICU length of stay
- Patients discharged from the ICU
- Incident atrial fibrillation
- New in-hospital kidney replacement therapy
- Major bleeding
- Clinically relevant non-major bleeding
- Composite of major and non-major bleeding
- Thrombocytopenia

Time points reported: at 30 and 90 days after the start of the intervention

Notes

- Sponsor/funding: quote "The study was funded by the Rajaie Cardiovascular Medical and Research Center. Some study authors, including the lead author, are affiliated with the Rajaie Cardiovascular Medical and Research Center. Enoxaparin was provided through Alborz Darou, Pooyesh Darou, and Caspian Pharmaceuticals companies, and atorvastatin and matching placebo was provided by Sobhan Darou. None of these companies were study sponsors. Neither the founder, nor the companies who donated the study drugs (Alborz Darou, Pooyesh Darou and Caspian Pharmaceuticals) had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication."
- COIs: the major study authors declared financial relationship with the industry.
- Trial registration number: NCT04486508

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Quote "Randomization was done using an electronic web-based system with permuted blocks of 4 and allocation sequence concealment."

Sadeghipour 2021 *(Continued)*

Allocation concealment (selection bias)	Yes	Quote "For the first hypothesis, allocation sequence concealment and blinded endpoint adjudication."
Blinding of participants and personnel (performance bias)	No	Quote "an open-label randomised clinical trial with blinded outcome adjudication."
Blinding of outcome assessment (detection bias)	Yes	Quote "an open-label randomised clinical trial with blinded outcome adjudication."
Incomplete outcome data (attrition bias)	Yes	The losses were balanced between the groups (experimental = 24 (8%); comparator = 14 (4%))
Selective reporting (reporting bias)	Yes	All prespecified outcomes were reported.
Other bias	Yes	We do not suspect any other bias related to this study.

Santoro 2020

Study characteristics	
Methods	• Study design: prospective cohort • Type of publication: peer reviewed published article • Setting and dates: hospital, 23 March 2020-5 May 2020 • Country: Spain, Italy, Ecuador, Cuba, Germany, China, Canada, Serbia, USA, Chile, and Colombia • Language: English • Number of centres: 65 listed hospitals • Trial registration number: NCT04334291
Participants	• Number of participants: 5838 allocated (experimental = 2601; comparator = 3214; 23 excluded from analysis); study authors reported 31 exclusion from analysis due to no available information about anticoagulation • Age, years (mean ± SD): 66 ± 15 (experimental), 63 ± 27 (comparator) • Gender (male/female): 1561/1040 (experimental), 1864/1350 (comparator) • Comorbidities (experimental/comparator): history of cancer 14%/14%, CKD 7%/6%, history of lung disease 21%/17%, history of heart disease 26%/21%, diabetes 21%/17%, hypertension 53%/46%, obesity 24%/21% • Confounding factors (experimental/comparator): prior anticoagulation (327 (12%) of included participants had history of anticoagulation treatment), surgery (NR), cancer 14%/14%, antiplatelet use (NR), history of VTE (97 of included participants were taking anticoagulants for previous DVT and PE) • Type of ventilator support: during hospitalisation, 13% of participants required non-invasive ventilation and 7% invasive ventilation Inclusion criteria • Patients discharged (deceased or alive) from any hospital centre with a confirmed diagnosis or a COVID-19 high suspicion Exclusion criteria • There are no exclusion criteria, except for the patient's explicit refusal to participate
Interventions	• Experimental: treated during hospitalisations with systemic or prophylactic anticoagulation, including oral, subcutaneous, or IV forms. Of the 2601 participants in this group, 327 (12%) had a history of

Santoro 2020 *(Continued)*

	anticoagulation treatment. Anticoagulation therapy in participants not anticoagulated before admission was given for prophylaxis (lower dose) in 83% of cases, while 15% received a full dose of LMWH, 1% oral anticoagulation with VKA, and 1% DOACs • Comparator: without anticoagulation • Concomitant therapy (experimental/comparator): NR • Duration of follow-up: mean 15 ± 11 (SD) days
Outcomes	Primary (specified) • All-cause death (Time Frame: through study completion, an average of 1 month) Primary (collected) • All-cause mortality during hospitalisation Secondary (specified) • In hospital stay (days) (time frame: through study completion, an average of 1 month) • Heart failure (time frame: through study completion, an average of 1 month) • Renal failure (time frame: through study completion, an average of 1 month) • Respiratory insufficiency. (time frame: through study completion, an average of 1 month) • Upper respiratory tract involvement (time frame: through study completion, an average of 1 month) • Pneumonia (time frame: through study completion, an average of 1 month) • Sepsis (time frame: through study completion, an average of 1 month) • Systemic inflammatory response syndrome (time frame: through study completion, an average of 1 month) • Clinically relevant bleeding (time frame: through study completion, an average of 1 month) • Other complications (time frame: through study completion, an average of 1 month) Secondary (collected) • Respiratory insufficiency • Haemoptysis • Embolic events (retrospectively) Time point reported: during hospitalisation or up to 30 days
Notes	• Sponsor/funding: quote "Non conditioned grant (Fundación Interhospitalaria para la Investigación cardiovascular, FIC. Madrid, Spain). This nonprofit institution had no role in the study design; collection, analysis, interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication." • COIs: quote " Drs. Romero and García Aguado received support for article research from the National Institutes of Health. Dr. Moreno Munguia received support for article research from Instituto de Investigación Sanitaria del Hospital Clínico San Carlos. The remaining authors have disclosed that they do not have any potential conflicts of interest." • Protocol available (NCT04334291)

Zarychanski 2021

Study characteristics	
Methods	• Study design: international multiplatform, adaptive, open-label, 2-armed, phase IV, parallel-assignment RCT • Type of publication: 2 preliminary reports by COVID-19 severity, preprint and 2 published articles • Setting and dates: hospital, 21 April 2020-19 December 2020 (critically ill participants) and 22 January 2021 (moderate-severity participants)

Zarychanski 2021 *(Continued)*

- Country: UK, USA, Canada, Brazil, Ireland, Netherlands, Australia, Nepal, Saudi Arabia, and Mexico
- Language: English
- Number of centres: 129 listed

Participants

- 13,377 participants were assessed for eligibility (3450 randomised)
  - critically ill: 1205 randomised (1074 analysed, 10.8% lost), experimental (therapeutic anticoagulation = 590 (529 analysed, 10 withdrew consent, 4 outcome not available, 47 SARS-CoV-2 not confirmed (10.3% lost)), comparator (prophylactic anticoagulation) = 615 (545 analysed, 15 withdrew consent, 11 outcome not available, 44 SARS-CoV-2 not confirmed (11.3% lost))
  - moderate-severity: 2245 randomised (2219 analysed, 1.1% lost), experimental (therapeutic anticoagulation = 1190 (1171 analysed, 9 withdrew consent, 1 outcome not available, 9 SARS-CoV-2 not confirmed (1.5% lost)), comparator (prophylactic anticoagulation) = 1055 (1048 analysed, 2 withdrew consent, 2 outcome not available, 3 SARS-CoV-2 not confirmed (0.6% lost))
- Mean age (years) ± SD:
  - critically ill: 60.2 ± 13.1 (experimental), 61.6 ± 12.5 (comparator)
  - moderate-severity: 59.0 ± 14.1 (experimental), 58.8 ± 13.9 (comparator)
- Gender (male/female):
  - critically ill: 383/149 (experimental), 379/178 (comparator)
  - moderate-severity: 713/468 (experimental), 597/453 (comparator)
- Severity of condition (experimental/comparator):
  - critically ill: no oxygen/supplemental oxygen (1.5%/1.3%), high-flow nasal oxygen (32.3%/33.8%), non-invasive ventilation (40.2%/35.9%), invasive mechanical ventilation (25.9%/29.1%), vasopressors/inotropes (16.7%/18.2%)
  - moderate-severity: no oxygen/supplemental oxygen (13.2%/11.7%), low-flow nasal cannula/face mask (66.8%/66.3), high-flow nasal cannula (2.1%/2.7), non-invasive mechanical ventilation (1.8%/2.3%), unspecified (16.1%/17.1%)
- Comorbidities (experimental/comparator):
  - critically ill: diabetes mellitus (type 1 or 2) 168 (32.1%)/182(33.3%), severe cardiovascular disease 36 (7.3%)/34 (6.6%), chronic kidney disease 56 (11.2%)/40 (8%), chronic respiratory diseased 121(24.1%)/125 (24.2%), chronic liver disease 6(1.2%)/2 (0.4%)
  - moderate-severity: hypertension 546 (53.4%)/447 (50.1%), diabetes mellitus 352 (29.8%)/311(29.6%), severe cardiovascular disease 123(10.6%)/123 (10.6%), chronic kidney disease 83 (7.1%)/69 (6.7%), chronic respiratory disease 249(22%)/212(21.5%), immunosuppressive disease 105 (9.2%)/103 (10.2%)
- BMI (kg/m^2), mean ± SD:
  - critically ill: 31.06 ± 6.69 (experimental), 30.4 ± 6.09 (comparator)
  - moderate-severity: 30.26 ± 6.23 (experimental), 30.63 ± 6.08 (comparator)
- Anticoagulation before randomisation (experimental/comparator): not described
- Baseline medication (experimental/comparator):
  - critically ill: antiplatelet agent 36 (7.4%)/42 (8.1%), remdesivir 149 (30.5%)/161 (31.1%), corticosteroids 387 (79.3%)/410 (79.3%), tocilizumab 9 (1.8%)/9 (1.7%)
  - moderate-severity: antiplatelet agent 148 (13.0%)/111 (11.0%), remdesivir 428 (36.3%)/383 (36.5%), corticosteroids 479 (60.6%)/415 (63.3%), tocilizumab 6 (0.5%)/7 (0.7%)
- D-dimer (experimental/comparator):
  - critically ill: D-dimer ≥ 2 times site ULN (n/N) 88/185 (47.6%)/ 87/187 (46.5%)
  - moderate-severity: D-dimer relative to site ULN (mean ± SD) 1.7 ± 1.27/1.73 ± 1.26

Inclusion criteria

- Adults
- Expected hospital length of stay > 48 h (REMAP-CAP) or 72 h (ACTIV-4a, ATTACC)
- Confirmed or suspected with intent to test for COVID-19. Only participants with confirmed infection were included in the mpRCT primary analysis

Exclusion criteria

- Admitted to the ICU with COVID-19 for > 48 h (REMAP-CAP) or to hospital for > 72 h (ACTIV-4a, ATTACC) prior to randomisation

Zarychanski 2021 *(Continued)*

- At imminent risk of death without an ongoing commitment to full organ support
- At high risk of bleeding
- Receiving dual antiplatelet therapy
- Separate clinical indication for therapeutic anticoagulation
- History of heparin sensitivity including heparin-induced thrombocytopenia

Interventions	Experimental: therapeutic-dose LMWH or UFH was administered according to local protocols used for the treatment of acute VTE for up to 14 days or until recovery (defined as hospital discharge, or liberation from supplemental oxygen for ≥ 24 h) • REMAP-CAP: for UFH, suggested target for aPTT of 1.5-2.5 times the ULN or therapeutic anti-Xa levels; LMWH dosed according to patient weight • ACTIV-4a: for UFH, suggested target of anti-Xa of 0.3-0.7 IU/mL or aPTT 1.5-2.5 times the ULN; LMWH dosed according to patient weight and CrCl • ATTACC: for UFH, suggested target of aPTT 1.5-2.5 times the ULN or therapeutic anti-Xa levels; LMWH dosed according to patient weight and CrCl according to local practice and policy Comparator: pharmacological thromboprophylaxis was administered according to local practice or with guidance from the trial protocol on maximum dosing, which included either standard low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis • REMAP-CAP: dose of chosen agent should not be sufficient to result in therapeutic anticoagulation • ACTIV-4a: dose of agent specified to be consistent with guidelines for low-dose thromboprophylaxis • ATTACC: dose of chosen agent should not be more than half of the approved therapeutic dose for the treatment of VTE Concomitant therapy: NR

Outcomes	Primary (specified)
	• REMAP-CAP: all-cause mortality (day 90); and days alive and not receiving organ support in ICU (day 21)
	• ACTIV-4a: days alive and not receiving organ support in ICU (day 21)
	• ATTACC: mortality and days alive and not receiving organ support in ICU (day 21) as a unique outcome
	Primary (collected)
	• Organ support-free days; was an ordinal scale composed of survival to hospital discharge and, in survivors, the number of days free of organ support to day 21
	Secondary (specified)
	• REMAP-CAP
	  ○ ICU mortality (time frame: day 90)
	  ○ ICU length of stay (time frame: day 90)
	  ○ Hospital length of stay (time frame: day 90)
	  ○ Ventilator-free days (time frame: day 28)
	  ○ Organ failure-free days (time frame: day 28)
	  ○ All-cause mortality (time frame: 6 months)
	  ○ Health-related quality of life assessment (time frame: 6 months)
	  ○ Proportion of intubated patients who receive a tracheostomy (time frame: day 28)
	  ○ Destination at time of hospital discharge (time frame: free text day 90). Characterised as home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospital
	  ○ Readmission to the index ICU during the index hospitalisation (time frame: day 90)
	  ○ WHO 8-point ordinal scale outcome (time frame: hospital discharge
	• ACTIV-4a

Zarychanski 2021 *(Continued)*

- Key platform secondary thrombotic endpoint (time frame: 28 days from study enrolment). Composite endpoint of death, PE, systemic arterial thromboembolism, myocardial infarction, or ischaemic stroke at hospital discharge or 28 days, whichever occurs first
- Other platform secondary endpoints of morbidity and hospitalisation (time frame: 28 days from study enrolment). Acute kidney injury defined by KDIGO criteria, individual endpoints comprising the key secondary endpoint, death during hospitalisation, 28-day ventilator-free days, 28-day vasopressor-free days, 28-day renal replacement-free days, WHO clinical scale, 28-day hospital -free days, 28-day organ support-free days
- All cause mortality (time frame: 90 days from enrolment). Any mortality of patients enrolled within 90 days
- Primary safety endpoint of major bleeding (time frame: 28 days from study enrolment). Major bleeding (as defined by the ISTH)
- Secondary safety endpoint of HIT (time frame: 28 days from study enrolment). Confirmed HIT

- ATTACC
  - Arterial and venous thrombotic conditions (time frame: 28 days and 90 days). A composite endpoint of death, DVT, PE, systemic arterial thromboembolism, myocardial infarction, or ischaemic stroke collected during hospitalisation or at 28 days and 90 days after enrolment (whichever is earlier)
  - Intubation and mortality (time frame: 30 days). Ordered categorical endpoint with 3 possible outcomes based on the worst status of each patient through day 30 following randomisation: no invasive mechanical ventilation, invasive mechanical ventilation, or death
  - All-cause mortality (time frame: 28 days and 90 days)
  - Intubation (time frame: 30 days). Invasive mechanical ventilation
  - Hospital-free days (time frame: 28 days). Days alive outside of the hospital through 28 days following randomisation
  - Ventilator-free days (time frame: 28 days). Days alive not on a ventilator assessed at 28 days following randomisation
  - Myocardial infarction (time frame: 28 days and 90 days)
  - Ischaemic stroke (time frame: 28 days and 90 days)
  - VTE (time frame: 28 days and 90 days). Symptomatic proximal VTE (DVT or PE)
  - Vasopressor-free days (time frame: 28 days). Days alive not on a vasopressor assessed at 28 days following randomisation
  - Renal replacement-free days (time frame: 28 days). Days alive not on renal replacement assessed at 28 days following randomisation
  - Hospital re-admission (time frame: 28 days). Hospital re-admission within 28 days
  - Acute kidney injury (time frame: duration of study). As defined by KDIGO criteria
  - Systemic arterial thrombosis or embolism (time frame: 28 days and 90 days)
  - ECMO support (time frame: duration of study). Use of ECMO support
  - Mechanical circuit thrombosis (time frame: duration of study). Dialysis or ECMO
  - WHO ordinal scale (time frame: 28 days). Peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrolment, at 28 days
  - Major bleeding (time frame: intervention period (maximum 14 days)). As defined by ISTH
  - HIT (time frame: intervention period (maximum 14 days)). Laboratory-confirmed

Secondary (collected)

- Survival to hospital discharge
- Survival without organ support through 28 days
- Survival without intubation through 28 days
- Survival to hospital discharge without major thrombosis
- Freedom from major bleeding
- Major thrombotic event or death in hospital
- Composite secondary thrombosis
- Major bleeding
- PE

Zarychanski 2021 *(Continued)*

- Myocardial infarction
- Ischemic cerebrovascular event
- Systemic arterial thromboembolism

Time points reported: at 21, 28, or 90 (days after the start of the intervention

Notes

- Protocol available: 3 international adaptive platform trials harmonised their protocols ('randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia' (REMAP-CAP, NCT02735707), 'accelerating COVID-19 therapeutic interventions and vaccines-4 antithrombotics inpatient platform trial' (ACTIV-4a, NCT04505774 and PROTECT, NCT04359277), and 'antithrombotic therapy to ameliorate complications of COVID-19' (ATTACC; NCT04372589). The PROTECT (NCT04359277) study was terminated (the PROTECT study was transitioned to ACTIV4 ACUTE anticoagulation inpatient study)
- Sponsor/funding
  - REMAP-CAP: supported by the European Union — through FP7-HEALTH-2013-INNOVATION: the Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) consortium (602525), and Horizon 2020 research and innovation program: the Rapid European Covid-19 Emergency Research response (RECOVER) consortium (101003589) — and by the Australian National Health and Medical Research Council (APP1101719), the Health Research Council of New Zealand (16/631), a Canadian Institutes of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant (158584), the U.K. NIHR and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (CTN 2014-012), the UPMC Learning While Doing Program, the Breast Cancer Research Foundation, the French Ministry of Health (PHRC-20-0147), the Minderoo Foundation, Amgen, Eisai, the Global Coalition for Adaptive Research, and the Wellcome Trust Innovations Project (215522). Dr. Gordon is funded by an NIHR Research Professorship (RP-2015-06-18), and Dr. Shankar-Hari by an NIHR Clinician Scientist Fellowship (CS-2016-16-011).
  - ATTACC: The ATTACC platform was supported by grants from the Canadian Institutes of Health Research, LifeArc Foundation, Thistledown Foundation, Research Manitoba, Ontario Ministry of Health, and the Peter Munk Cardiac Centre.
  - ACTIV-4a: The ACTIV-4a platform was sponsored by the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD and administered through OTA-20-011.
- COIs: the major study authors declared a financial relationship with the industry. Quote "An Adjudicator is free of conflict of interest. One of adjudicators will also be the CEC Chairperson."

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Quote: "Randomization was performed using central web-based systems." Quote: "ACTIV-4a randomised all participants in a 1:1 ratio. The other two platforms specified response-adaptive randomisation; randomisation probabilities were updated in the severe patient group within REMAP-CAP and ATTACC during the interim period between the mpRCT interim data cut and the halt of enrolment"
Allocation concealment (selection bias)	Yes	Quote: "Randomization was performed using central web-based systems." Quote "The ATTACC and REMAP-CAP designs specified the possibility for response-adaptive randomisation, whereby blinded randomisation allocation ratios could be modified during the trial based on adaptive analyses to favor allocation of participants to the treatment arm demonstrating greater benefit."
Blinding of participants and personnel (performance bias)	No	Quote "One limitation of our trial is the open-label design"

Zarychanski 2021 *(Continued)*

Blinding of outcome assessment (detection bias)	No	Not all outcomes were assessed in a blinding approach Quote "The open label strategy may also introduce systematic bias in the ascertainment of thrombotic events." Quote "All reported bleeding and thrombotic events were adjudicated in a blinded fashion by clinical endpoints committees using consensus definitions"
Incomplete outcome data (attrition bias)	No	There was an acceptable loss rate (critically ill: 1205 randomised, 1074 analysed, 10.8% lost; moderate-severity: 2245 randomised, 2219 analysed, 1.1% lost). However, there was a high and imbalanced cross-over rate (experimental/comparator): critically ill 92 (22.3%)/23 (5.3%), moderate-severity 213 (20.4%)/8 (0.9%). Supplemental data
Selective reporting (reporting bias)	No	The trial protocol also planned to assess other outcomes of interest for this review. However, the available manuscript did not report 'quality of life' and reported 'hospitalisation time', 'necessity of additional respiratory support', 'thrombocytopenia', and 'DVT' only for moderate-severity participants. The study authors planned to report data at 90 days of follow-up but there are no available data at this time point.
Other bias	No	Although study authors declare that they harmonised their protocols into a "prospectively multiplatform uniformisation", they combined results from 3 different trials registries, with different centres of randomisation and documentation. It was reflected in an imbalance of losses to follow-up (moderate-severity: experimental = 19 losses (1.5%), comparator = 7 losses (0.6%)) Quote "may be imbalanced due to response adaptive randomisation" There was a factorial randomisation for antiplatelet agent intervention in one of the considered trials (REMAP-CAP). Quote "A subset of participants enrolled in REMAP-CAP were also randomised in the antiplatelet agent domain and in other domains of that trial." There is a possibility of additional heterogeneity in overall results when combining these 3 trials as a unique trial Although the trial authors merged their platforms, there was a change in the primary outcome specified in the registered protocols compared to the unique reported primary outcome.

ACS: acute coronary syndrome; **ACTIV-4a:** accelerating COVID-19 therapeutic interventions and vaccines-4 antithrombotics inpatient platform trial; **ARDS:** acute respiratory distress syndrome; **aPTT:** activated partial thromboplastin time; **ASA:** acetylsalicylic acid (aspirin); **ATTACC:** antithrombotic therapy to ameliorate complications of COVID-19; **BMI:** body mass index; **BP:** blood pressure; **CEC:** clinical events committee; **CKD:** chronic kidney disease; **COPD:** chronic obstructive pulmonary disease; **COI:** conflict of interest; **CPR:** cardiopulmonary resuscitation; **CrCl:** creatinine clearance; **CT:** computed tomography; **DIC:** disseminated intravascular coagulation; **DOACs:** direct oral anticoagulants; **DVT:** deep vein thrombosis; **ECMO:** extracorporeal membrane oxygenation; **FiO2:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HIT:** heparin-induced thrombocytopenia; **ICU:** intensive care unit; **INR:** international normalised ratio; **IQR:** interquartile range; **ISTH:** International Society on Thrombosis and Haemostasis; **INR:** international normalised ratio; **IU:** international unit; **IV:** intravenously; **LMWH:** low-molecular-weight heparin; **µL:** microlitre; **MRI:** magnetic resonance imaging; **NR:** not reported; **NRS:** non-randomised study; **PaO2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **PE:** pulmonary embolism; **RCT:** randomised controlled trial; **REMAP-CAP:** Randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia; **RT-PCR:** reverse transcription polymerase chain reaction; **SC:** subcutaneous(ly); **SD:** standard deviation; **SOFA:** sequential organ failure assessment score; **UFH:** unfractionated heparin; **ULN:** upper limit of normal; **VKA:** vitamin K antagonists; **VTE:** venous thromboembolism; **WHO:** World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Samkari 2020	Ineligible study design. Retrospective cohort study without a parallel comparator group of intervention
Artifoni 2020	Ineligible study design. Retrospective cohort study without a comparator group (single-arm study)
Ayerbe 2020	Ineligible study design. Retrospective cohort study
ChiCTR2000034796	Ineligible study design. Retrospective cohort study comparing people hospitalised with COVID-19 receiving LMWH versus those not receiving LMWH
CTRI/2021/01/030373	Ineligible participants. RCT of non-hospitalised people with COVID-19
D'Ardes 2021	Ineligible study design. Retrospective cohort study without a prospective parallel comparator group of intervention
DCTC 2021	Ineligible study design. Prospective cohort study without a comparator group (single-arm study)
Di Castelnuovo 2021	Ineligible study design. Retrospective cohort study comparing people hospitalised with COVID-19 receiving anticoagulation versus those not receiving anticoagulation
EUCTR2020-001748-24-SE	Ineligible participants. The RCT did not assess the effects of any anticoagulant
EudraCT2020-001823-15	Ineligible study design. Prospective cohort study without a comparator group (single-arm study)
Falcone 2020	Ineligible study design. Prospective cohort study without a comparator group (single-arm study)
Frohlich 2021	Ineligible study design. Retrospective cohort study without a comparator group (single-arm study)
Helms 2020	Ineligible study design. Prospective cohort study without an intervention purpose
Helms 2021	Ineligible study design. Prospective cohort study comparing prophylactic and therapeutic anticoagulant
Ho 2021	Ineligible study design. Retrospective cohort study comparing people hospitalised with COVID-19 receiving anticoagulants versus people not receiving anticoagulants in USA
Huang 2020	Ineligible study design. Case report
Ionescu 2020	Ineligible study design. Prospective cohort study comparing people hospitalised with COVID-19 receiving anticoagulants (higher dose) versus anticoagulants (lower dose) in USA
Jiménez-Soto 2021	Ineligible study design. Prospective cohort study comparing people hospitalised with COVID-19 receiving anticoagulants (higher dose) versus anticoagulants (lower dose) in Mexico
Jonmarker 2020	Ineligible study design. Prospective cohort study comparing people hospitalised with COVID-19 receiving three different doses of anticoagulants in Sweden
Khider 2020	Ineligible study design. Prospective cohort study without a parallel comparator group of intervention
Kodama 2020	Ineligible study design. Retrospective cohort study comparing people hospitalised with COVID-19 receiving 2 different doses of anticoagulants in USA
Kow 2020	Ineligible study design. Letter to editor

Study	Reason for exclusion
Kukin 2020	Ineligible participant. RCT comparing non-pharmacological intervention for people without COVID-19
Liu 2020	Ineligible study design. Retrospective cohort study
Mareev 2020	Ineligible intervention. RCT comparing anti-inflammatory pharmacological interventions. There is no comparison with anticoagulants
Martinelli 2020	Ineligible study design. Prospective cohort study comparing people hospitalised with COVID-19 receiving two different doses of anticoagulants
Maurer 2020	Ineligible intervention. RCT comparing arterial line heparinisation versus no-heparinisation in people hospitalised with COVID-19
NCT04354155	Ineligible study design. Prospective cohort study without a parallel comparator group of intervention
NCT04359212	Ineligible study design. Prospective cohort study without a parallel comparator group of intervention
NCT04365309	Ineligible intervention. RCT of aspirin for COVID-19. There is no difference between the intervention groups regarding anticoagulants.
NCT04368377	Ineligible study design. Prospective cohort study without a comparator group (single-arm study)
NCT04393805	Ineligible study design. Retrospective cohort study
NCT04427098	Ineligible study design. Prospective cohort study without a comparator group (single-arm study)
NCT04483830	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04492254	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04504032	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04516941	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04662684	Ineligible participants. RCT where the participants received the intervention after hospital discharge (non-hospitalised people with COVID-19)
NCT04673214	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04715295	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04736901	Ineligible study design. Prospective cohort study comparing five different anticoagulant regimens
NCT04757857	Ineligible participants. RCT of non-hospitalised people with COVID-19
NCT04828772	Ineligible study design. Retrospective cohort study comparing people hospitalised with COVID-19 receiving anticoagulants versus people not receiving anticoagulants in Japan
Paranjpe 2020	Ineligible study design. Retrospective cohort study
Piagnerelli 2020	Ineligible study design. Letter to editor

Study	Reason for exclusion
Poulakou 2021	Ineligible study design. Retrospective cohort study comparing different doses of anticoagulants in people hospitalised with COVID-19
Qin 2021	Ineligible study design. Retrospective cohort study comparing different doses of anticoagulants in people hospitalised with COVID-19
Rosovsky 2020	Ineligible study design. Prospective survey about physician practice. There was no participant with COVID-19.
Russo 2020	Ineligible study design. Retrospective cohort study
Secco 2020	Ineligible study design. Retrospective cohort study comparing different doses of anticoagulants in people hospitalised with COVID-19
Shi 2020	Ineligible study design. Retrospective cohort study
Sivaloganathan 2020	Ineligible study design. Case-control study comparing mortality in people hospitalised with COVID-19 who previously used anticoagulants and antiplatelet agents versus those who did not
Smith 2020	Ineligible study design. Prospective survey about physician practice. There was no participant with COVID-19.
Stessel 2020	Ineligible study design. Prospective before-after cohort study without a parallel comparator group
Tacquard 2021	Ineligible study design. Prospective cohort study comparing different doses of anticoagulants in people hospitalised with COVID-19
Tamargo 2021	Ineligible study design. Editorial
Tang 2020	Ineligible study design. Retrospective cohort study
Trinh 2020	Ineligible study design. Retrospective cohort study
Zhang 2020	Ineligible study design. Retrospective cases series. Description of 7 participants without a consistent comparator group

LMWH: low molecular weight heparin, **RCT:** randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12620000517976

Study name	A randomised controlled trial of nebulised heparin in critically ill mechanically ventilated patients with COVID-19 to assess the effect on the duration of mechanical ventilation
Starting date	21 May 2020
Contact information	Barry Dixon St Vincent's Hospital, Melbourne, Australia +613439618815 | barry.dixon@svha.org.au
Methods	Prospective, multicentre, 2-armed, parallel-assignment RCT
Participants	172 participants, ≥ 18 years, female and male

ACTRN12620000517976 *(Continued)*

	Inclusion criteria • Confirmed or suspected COVID-19 infection • Age ≥ 18 years • Endotracheal tube in place • Intubated yesterday or today • PaO2 to FIO2 ratio ≤ 300 while intubated • Acute opacities on chest imaging affecting at least 1 lung quadrant Exclusion criteria • Enrolled in another clinical study that is unapproved for co-enrolment • Heparin allergy or heparin-induced thrombocytopaenia • aPTT > 120 s and this is not due to anticoagulant therapy • Platelet count < 20 x 109/L • Pulmonary bleeding • Uncontrolled bleeding • Obvious or suspected pregnancy • Receiving or about to commence ECMO or HFOV • Myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome • Usually receives home oxygen • Dependent on others for personal care due to physical or cognitive decline • Death is imminent or inevitable within 24 h • The clinical team would not be able to set up the study nebuliser and ventilator circuit as required including with active humidification • Clinician objection
Interventions	Experimental: nebulised (vibrating mesh nebuliser) heparin sodium 25,000 IU in 5 mL 6-hourly/day 10 while invasively ventilated in addition to standard care. The medication will be prescribed and administration documented in the medical record. Comparator: standard care represents the treatments routinely provided by the medical team managing the patient. Standard care will be at the discretion of the medical team.
Outcomes	Primary • Time to separation from invasive ventilation, censored at day 28, with non-survivors treated as though never separated from the ventilator. This will be assessed from review of the medical records. Secondary • Time to separation from invasive ventilation, censored at day 28, among survivors. This will be assessed from review of the medical records. • Time to separation from ICU, censored at day 28, with non-survivors treated as though not separated from the ICU. This will be assessed from review of the medical records. • Time to separation from ICU, censored at day 28, among survivors. This will be assessed from review of the medical record. • Tracheotomy. This will be assessed from review of the medical records. • Readmission to ICU. This will be assessed from review of the medical records. • Survival to hospital discharge. This will be assessed from review of the medical records. • Survival. This will be assessed from review of the medical records. • Place of residence. This will be assessed from review of the medical records and contact with the participant.
Notes	ACTRN12620000517976p | No data provided

Busani 2020

Study name	Steroids and unfractionated heparin in critically ill patients with pneumonia from COVID-19 infection
Starting date	25 November 2020
Contact information	Massimo Girardis, PD ICU- University Hospital Modena, Modena, Italy, 41124 0594225878 ext 0039 | massimo.girardis@unimore.it
Methods	Multicentre RCT with 3 parallel arms, 1:1:1
Participants	210 participants; ≥ 18 years, female and male Inclusion criteria: • Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) • Positive pressure ventilation (either non-invasive or invasive) from > 24 h • Invasive mechanical ventilation from < 96 h • PaO2/FiO2 ratio < 150 • D-dimer level > 6 x upper limit of local reference range • PCR > 6 fold upper limit of local reference range Exclusion criteria: • Age < 18 years • On-going treatment with anticoagulant drugs • Platelet count < 100.000/mmc • History of heparin-induced thrombocytopenia • Allergy to sodium enoxaparin or other LMWH, unfractionated heparin or methylprednisolone • Active bleeding or on-going clinical condition deemed at high risk of bleeding contraindicating anticoagulant treatment • Recent (in the last 1 month prior to randomisation) brain, spinal or ophthalmic surgery • Chronic assumption or oral corticosteroids • Pregnancy or breastfeeding or positive pregnancy test. In childbearing age women, before inclusion, a pregnancy test will be performed if not available • Clinical decision to withhold life-sustaining treatment or "too sick to benefit" • Presence of other severe diseases impairing life expectancy (e.g. patients are not expected to survive 28 days given their pre-existing medical condition) • Lack or withdrawal of informed consent
Interventions	Drug: enoxaparin • Enoxaparin will be administered SC at standard prophylactic dose (i.e. 4000 UI once/d, increased to 6000 UI once/d for patients weighting > 90 kg). The treatment will be administered daily up to ICU discharge. After ICU discharge it may be continued or interrupted in the destination ward up to clinical judgement of the attending physician. • Other name: Inhixa Drug: methylprednisolone • Methylprednisolone will be administered IV with an initial bolus of 0.5 mg/kg followed by administration of 0.5 mg/kg 4 times daily for 7 days, 0.5 mg/kg 3 times daily from day 8 to day 10, 0.5 mg/kg 2 times daily at days 11 and 12 and 0.5 mg/kg once daily at days 13 and 14 • Other Name: Solu-medrol

Busani 2020 *(Continued)*

Drug: unfractionated heparin

- Patients in this group will receive unfractionated heparin and methylprednisolone. Unfractionated heparin will be administered IV at therapeutic doses. The infusion will be started at an infusion rate of 18 IU/kg/h and then modified to attain aPTT ratio in the range 1.5-2.0. aPTT will be periodically checked at intervals no longer than 12 hours. The treatment with unfractionated heparin will be administered up to ICU discharge. After ICU discharge anticoagulant therapy may be interrupted or switched to prophylaxis with LMWH in the destination ward up to clinical judgement of the attending physician.
- Other Name: Veracer

Outcomes

Primary

- All-cause mortality at day 28, defined as the comparison of proportions of patients' deaths for any cause at day 28 from randomisation

Secondary

- All-cause mortality at ICU discharge (time frame: from randomisation to ICU discharge, censored at day 30)
- All-cause mortality at hospital discharge (time frame: from randomisation to ICU discharge, censored at day 90)
- Need of rescue administration of high-dose steroids or immune-modulatory drugs (time frame: from randomisation to ICU discharge, censored at day 28)
- New organ dysfunction during ICU stay (time frame: from randomisation to ICU discharge, censored at day 28)
- Grade of organ dysfunction during ICU stay (time frame: from randomisation to ICU discharge, censored at day 28)
- ICU-free days at day 28 (time frame: from randomisation to day 28)
- Occurrence of new infections (time frame: from randomisation to day 28)
  - Occurrence of new infections including bacterial infections, fungal infections by Candida, Aspergillus, and viral reactivations including Adenovirus, Herpes virus and Cytomegalovirus
- Ventilation-free days at day 28 (time frame: from randomisation to day 28, censored at hospital discharge)
- Vasopressors free-days at day 28 (time frame: from randomisation to day 28, censored at hospital discharge)
- Switch from non-invasive to invasive mechanical ventilation (time frame: from randomisation to ICU discharge, censored at day 28)
- Delay from start of non-invasive ventilation to switch to invasive ventilation (time frame: from randomisation to ICU discharge, censored at day 28)
- Occurrence of protocol-related AEs (time frame: from randomisation to day 28). AEs occurred from randomisation to day 28
- Occurrence of VTE, stroke or myocardial infarction (time frame: from randomisation to ICU discharge, censored at day 28)
- Occurrence of major bleeding (safety end point) (time frame: from randomisation to ICU discharge, censored at day 28)
- Occurrence of clinically relevant non-major bleeding (safety end point) (time frame: from randomisation to ICU discharge, censored at day 28)

Other outcomes

- Mean arterial pressure (time frame: daily from inclusion until ICU discharge, censored day 28)
- Heart rate (time frame: daily from inclusion until ICU discharge, censored day 28)
- Respiratory rate (time frame: daily from inclusion until ICU discharge, censored day 28)
- Eiuresis (time frame: daily from inclusion until ICU discharge, censored day 28)
- Systemic body temperature (time frame: daily from inclusion until ICU discharge, censored day 28)
- Fluid balance (time frame: daily from inclusion until ICU discharge, censored day 28)

Busani 2020 *(Continued)*

- Haemoglobin concentration (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Platelets count (time frame: daily from inclusion to ICU discharge (censored at day 28)
- White blood cells count (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Troponin (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Coagulative function (time frame: daily from inclusion to ICU discharge (censored at day 28)
- D-dimer (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Anti-thrombin (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Liver function (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Bilirubin (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Creatinine (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Blood cells count (time frame: daily from inclusion to ICU discharge (censored at day 28)
- C-reactive protein (CRP) (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Procalcitonin (PCT) (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Interleukin 6 (IL-6) (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Ventilation mode (time frame: daily from inclusion to ICU discharge (censored at day 28)
- FiO2 (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Gas exchanges (time frame: daily from inclusion to ICU discharge (censored at day 28)
- Lactates (time frame: daily from inclusion to ICU discharge (censored at day 28)
- pH (time frame: daily from inclusion to ICU discharge (censored at day 28)
- SpO2 (time frame: daily from inclusion to ICU discharge (censored at day 28)
- New infections (time frame: from randomisation to day 28)
- Viral reactivation (time frame: from randomisation to day 28)
- Need of new renal replacement therapy (time frame: from randomisation to day 28)
- Adjunctive treatments (time frame: from randomisation to ICU discharge (censored at day 28)

Notes	NCT04528888 | No data provided

Chambers 2020

Study name	COVID-19-associated coagulopathy: safety and efficacy of prophylactic anticoagulation therapy in hospitalized adults with COVID-19
Starting date	6 May 2020
Contact information	Usha Perepu, MBBS Gundersen Health System La Crosse, Wisconsin, United States, 54601 319-356-2195 | usha-perepu@uiowa.edu
Methods	Multicentre, open-label, 2-armed, parallel-assignment RCT
Participants	170 participants, ≥ 18 years, female and male Inclusion criteria • Laboratory-confirmed SARS-CoV-2 infection • Age: ≥ 18 years • Requires hospital admission for further clinical management • Modified ISTH overt DIC score ≥ 3

Chambers 2020 *(Continued)*

	Exclusion criteria • Indication for full therapeutic-dose anticoagulation • Acute VTE (DVT or PE) within prior 3 months • Acute cardiovascular event within prior 3 months • Acute stroke (ischaemic or haemorrhagic) within prior 3 months • Active major bleeding • Severe thrombocytopenia (< 25,000/mm^3) • Increased risk of bleeding, as assessed by the investigator • Acute or chronic renal insufficiency with CrCl < 30 mL/min calculated by the modified Cockcroft and Gault formula • Weight < 40 kg • Known allergies to ingredients contained in enoxaparin, allergy to heparin products or history of HIT
Interventions	Interventional: intermediate-dose enoxaparin (1 mg/kg SC daily if BMI < 30 kg/m^2 or 0.5 mg/kg SC twice daily if BMI ≥ 30 kg/m^2) Comparator: standard care. Standard prophylactic dose enoxaparin (40 mg SC daily if BMI < 30 kg/m^2 and 30 mg SC twice daily or 40 mg SC twice daily if BMI ≥ 30 kg/m^2)
Outcomes	Primary • Risk of all-cause mortality (time frame: 30 days post-intervention) Secondary • Risk of ISTH-defined major bleeding (time frame: 30 days post-intervention) • Arterial thrombosis (time frame: 30 days post-intervention). Risk of ischaemic stroke, myocardial infarction and/or limb ischaemia • VTE (time frame: 30 days post-intervention). Risk of symptomatic VTE • ICU admission, intubation/ventilation (time frame: 30 days post-intervention). Duration of intensive care measures • PRBC transfusions (time frame: 30 days post-intervention). The number of units of PRBCs transfused • Platelet transfusions (time frame: 30 days post-intervention). The number of units of platelets transfused • Fresh frozen plasma transfusions (time frame: 30 days post-intervention). The number of units of fresh frozen plasma transfused • Cryoprecipitate transfusions (time frame: 30 days post-intervention). The number of units of cryoprecipitate transfused • Prothrombin complex concentrate transfusions (time frame: 30 days post-intervention). The number of units of prothrombin complex concentrate transfused Other outcomes • The endogenous thrombin potential will be determined within 24 h of randomisation and weekly for 30 days or until hospital discharge (time frame: 30 days post-intervention). Will be performed in stored plasma using calibrated automated thrombogram. The endogenous thrombin potential will be calculated in units of nM.Min • Plasma levels of cell-free DNA will be determined within 24 h of randomisation and weekly for 30 days or until hospital discharge (time frame: 30 days post-intervention). These assays will be performed in stored plasma. Quantification of cfDNA will be performed using Qubit dsDNA HS Assay kit. Histones H4, citrullinated-histone and DNA-myeloperoxidase will be measured using commercially available ELISA kit • PAI-1 (time frame: 30 days post-intervention) will be measured in stored plasma using a commercially available ELISA kit

Chambers 2020 *(Continued)*

Notes	NCT04360824 | No data provided

ChiCTR2000030700

Study name	An evaluative clinical study: efficacy and safety of Prolongin (enoxaparin sodium injection) in treatment of hospitalized adult patients with common novel coronavirus pneumonia (COVID-19)
Starting date	09 March 2020
Contact information	Zhang Yu Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China +86 13901849660 | whxhzy@163.com
Methods	Prospective, open-label, 2-armed, 1:1; parallel-assignment RCT
Participants	60 participants, ≥ 18 years, female and male Inclusion criteria • Those who agree to take part in the test and sign the informed consent form voluntarily • Adults aged ≥ 18 years, male or female • Inpatients with mild or common type of COVID-19 confirmed according to the diagnostic criteria "COVID-19 diagnosis and treatment plan - Sixth trial edition" issued by the National Health Commission • Respiratory specimens (including but not limited to sputum, nasopharyngeal swab and secretion of lower respiratory tracts) are positive for 2019-nCoV nucleic acid by real-time fluorescent RT-PCR; or respiratory specimens are genetically sequenced and highly homologous to known 2019-nCoV. Exclusion criteria • Participation in the study is not in accordance with the rights and interests of the patient based on Principal Investigator's judgement, or any other circumstances that investigators consider inappropriate for participation • With bleeding or bleeding associated with severe coagulation disorders (except for disseminated intravascular coagulation unrelated to heparin therapy), with a history of severe type II HIT, whether or not caused by UFH or LMWH (significantly reduced by platelet count previously), active peptic ulcer or organ damage with bleeding tendency, clinically significant active bleeding, cerebral haemorrhage • Have any situation that treatment with LMWH is required • Women who are pregnant or likely to be pregnant, or who are lactating and unable to stop breastfeeding, or who have positive pregnancy tests during screening • Men or women who have a birth plan or are unwilling to take reliable contraceptive measures for contraception within 90 d from signing the informed consent to the last dose • With severe liver disease: patient with basic diseases of liver cirrhosis, or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased > 5 times of the ULN • Patients known to have severe renal impairment (CrCl < 30 mL/min), or to receive continuous renal replacement therapy, haemodialysis or peritoneal dialysis • At rest without oxygen inhalation, SPO2 ≤ 93%, or PaO2/FiO2 ≤ 300 mmHg • Patients allergic to enoxaparin, heparin or its derivatives, including other LMWHs
Interventions	Experimental: based on the standard treatment recommended in the guidelines, a combination of Prolongin (enoxaparin sodium injection) was used

ChiCTR2000030700 *(Continued)*

	Comparator: follow the guidelines for standard treatment
Outcomes	Primary • Time to virus eradication Secondary • The incidence of mild or common novel coronavirus pneumonia progressing to severe • Time for the main clinical manifestations to subside (fever, cough, respiratory rate, SPO2)
Notes	ChiCTR2000030700 | No data provided

ChiCTR2000030701

Study name	A randomized, parallel controlled open-label trial to evaluate the efficacy and safety of Prolongin (enoxaparin sodium injection) in adult hospitalized patients with novel coronavirus pneumonia (COVID-19)
Starting date	10 March 2020
Contact information	Cai Qingxian The Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China +86 13901849660 | 41180423@qq.com
Methods	Single-centre, open-label, 2-armed, parallel assignment RCT
Participants	60 participants, ≥ 18 years, female and male Inclusion criteria • Those who agree to take part in the test and sign the informed consent form voluntarily • Adult aged ≥ 18 years old, male or female • Inpatients with mild or common type of COVID-19 confirmed according to the diagnostic criteria "COVID-19 diagnosis and treatment plan - Sixth trial edition" issued by the National Health Commission • Respiratory specimens (including but not limited to sputum, nasopharyngeal swab and secretion of lower respiratory tracts) were positive for 2019-nCoV nucleic acid by real-time fluorescent RT-PCR; or respiratory specimens were genetically sequenced and highly homologous to known 2019-nCoV Exclusion criteria • Participation in the study is not in accordance with the rights and interests of the patient based on Principal Investigator's judgement, or any other circumstances that investigators consider inappropriate for participation • Low body-weight patients (female < 45 kg, male < 57 kg) • With bleeding or bleeding associated with severe coagulation disorders (except for disseminated intravascular coagulation unrelated to heparin therapy), with a history of severe type II HIT, whether or not caused by UFH or LMWH (significantly reduced by platelet count previously), active peptic ulcer or organ damage with bleeding tendency, clinically significant active bleeding, cerebral haemorrhage • Have any situation that treatment with LMWH is required • Women who are pregnant or likely to be pregnant, or who are lactating and unable to stop breastfeeding, or who have positive pregnancy tests during screening

ChiCTR2000030701 *(Continued)*

	• Men or women who have a birth plan or are unwilling to take reliable contraceptive measures for contraception within 90 days from signing the informed consent to the last dose • With severe liver disease: patient with basic diseases of liver cirrhosis, or ALT)/AST increased > 5 times of the ULN • Patients known to have severe renal impairment CrCl < 30 mL/min), or to receive continuous renal replacement therapy, haemodialysis or peritoneal dialysis • At rest without oxygen inhalation, SPO2 ≤ 93%, or PaO2/ FiO2 ≤ 300 mmHg • Patients allergic to enoxaparin, heparin or its derivatives, including other LMWHs
Interventions	Experimental: based on the standard treatment recommended in the guidelines, a combination of Prolongin (enoxaparin sodium injection) was used Comparison: follow the guidelines for standard treatment
Outcomes	Primary • Time to virus eradication Secondary • The incidence of mild or common novel coronavirus pneumonia progressing to severe • Time for the main clinical manifestations to subside (fever, cough, respiratory rate, SPO2)
Notes	ChiCTR2000030701 | No data provided

ChiCTR2000030946

Study name	Effects of different VTE prevention methods on the prognosis of hospitalized patients with novel coronavirus pneumonia (COVID-19)
Starting date	10 February 2020
Contact information	Chunli Liu The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China +86 13560158649 | chunli@gird.cn
Methods	Prospective cohort, non-randomised, open-label, 2 parallel and comparative arms
Participants	120 participants, 18-80 years, female and male Inclusion criteria • Patients diagnosed with new coronavirus pneumonia and in need of hospitalisation: they meet the diagnostic criteria of the diagnosis and treatment programme for new coronavirus pneumonia (trial 5th edition) issued by the National Health Commission • Pneumonia with novel coronavirus confirmed by aetiological nucleic acid test • Aged 18-80 years • Signed informed consent • VTE score was ≥ 4, and there were no higher blood risk factors Exclusion criteria • Pregnant women or lactating women • Severe liver function damage (Child-Pugh grade C) • Severe renal impairment (CrCl ≤ 15mL/min)

ChiCTR2000030946 *(Continued)*

	• Have any co-existing medical conditions or diseases that the investigator determines may impair the conduct of the study • Social and mental disability, no legal capacity/restricted capacity • Refuse to sign the informed consent • VTE score < 4 • Higher blood risk factors
Interventions	Experimental: 7/5000 LMWH therapy Comparison: mechanical prevention
Outcomes	Primary: biochemical indicators Secondary: not described
Notes	ChiCTR2000030946 | No data provided

CTRI/2020/06/026220

Study name	A study to evaluate the efficacy and safety of nafamostat mesilate in treatment of coronavirus infection
Starting date	17 July 2020
Contact information	Guruprasad Palekar Sun Pharma Laboratories Limited Sun House, 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063 390020 Mumbai, MAHARASHTRA India 02656612829 maulik.doshi@sunpharma.com
Methods	Multicentre, open-label RCT with 3 parallel arms

Participants	40 participants; ≥ 18 years and ≥ 65 years, female and male
	Inclusion criteria:
	• Male or non-pregnant, non-lactating female patient aged ≥ 18 and ≤ 65 years
	• Patient presenting with symptoms of fever (axillary ≥ 98.6 °F or oral ≥ 99.5 °F) with cough/shortness of breath
	• Patient with moderate COVID -19 infection meeting the clinical criteria of (note) -
	  ○ pneumonia (confirmed on chest imaging) and
	  ○ respiratory rate 15-30 breaths/min (both inclusive) and
	  ○ oxygen saturation- SpO2 90%-94% (both inclusive) on room air or PaO2/FiO2: 200-300 mmHg (both inclusive)
	• Patient with RT-PCR-confirmed diagnosis of COVID-19
	• Patient randomised within 72 h of diagnosis of pneumonia
	• Patient who provides written informed consent and agrees to comply with study procedures
	• Women of childbearing potential must have a negative urine pregnancy test prior to study entry as per MOHFW guideline
	Exclusion criteria:
	• Patient requiring ECMO or invasive ventilation
	• Patient with multiple organ failure requiring ICU monitoring and the treatment

CTRI/2020/06/026220 *(Continued)*

- Patient with rapidly deteriorating clinical condition or low likelihood to complete the study according to the investigator
- Patient with eGFR < 30 mL/min/m^2 assessed with CKI EPI formula
- Patient with pre-existing renal failure on haemodialysis or peritoneal dialysis requiring renal replacement therapy
- Patient with current or chronic history of liver disease (Child Pugh score > 10), or known hepatic or biliary abnormalities
- Patient with known active hepatitis, TB and definite bacterial or fungal infections
- Patient with history of chronic interstitial lung disease on imaging
- Patient with history of hospitalisation for respiratory failure within the past 6 months
- Patient with history of chronic vascular disease resulting in severe exercise restriction (i.e. unable to perform household duties)
- Patient with history of secondary polycythaemia, severe pulmonary hypertension, or ventilator dependency
- Patient with history of vasculitis with diffuse alveolar haemorrhage
- Patient with severe active bleeding at screening or with bleeding tendency (platelet count < 50,000/µL, INR > 3, aPTT > 65 seconds)
- Patient with diabetes
- Patient with any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g. heart failure (NYHA III/IV), COPD, hypertension (> 160/100 mm Hg), chronic respiratory failure, anaemia (< 8 g/dL) etc.) that, in the opinion of the Investigator precludes the patient's participation in the study or interferes with the interpretation of the study results
- Patient with history of serology tests positive for hepatitis B or hepatitis C or HIV
- Patient with altered mental state
- Patient with history of retinopathy or macular degeneration
- Patient with history of glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Patient with prolonged QTc-interval at baseline ECG (> 450 ms in men or > 470 ms in women)
- Patient taking concomitant medication associated with QTc-interval prolongation, which cannot be withdrawn prior to study drug administration
- Patient requiring high doses of loop diuretics (i.e. > 240 mg furosemide daily) with significant intravascular volume depletion, as assessed clinically
- Patient taking immunosuppressive treatment
- Patient having history of sensitivity to heparin or heparin-induced thrombocytopenia
- Patient with history of hypersensitivity towards any drug of standard of care or nafamostat including their excipients
- Patient who participated in a clinical trial with an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)
- Patient participated in trials for COVID-19 within 30 days before screening
- Patient with hyperkalaemia, i.e. serum K+ levels > 5.0 mEq/L

Interventions	Experimental: nafamostat mesilate injection 50 mg/100 mg vial: dissolve a daily dose of nafamostat mesilate in 1000 mL of 5% dextrose and to be infused at dose of 0.1 mg/kg/h for 24 h by continuous infusion for 10 days Comparator: standard care as per institutional practice Patients may be given prophylactic LMWH (e.g. enoxaparin 1mg/kg per day SC) as per investigator discretion. Before starting LMWH, investigator should check for bleeding tendency risk and presence of any contraindications. When nafamostat and LMWH are given concomitantly daily PT/INR and aPTT should be monitored
Outcomes	Primary • Proportion of patients showing clinical improvement. Time point: by day 14 Secondary

CTRI/2020/06/026220 *(Continued)*

- Duration (days) of supplemental oxygen therapy. Time point: up to day 28
- Number of deaths (all-cause mortality). Time point: up to day 28
- Percent change in 24 h PaO2/FiO2 ratio on days 7, 14, day of discharge compared to baseline. Time point: day 7, day 14 and day of discharge
- Proportion of patients showing clinical improvement. Time point: by day 7 and day 28
- Proportion of patients showing deterioration of clinical condition as assessed by at least 1 point worsening on 7 point ordinal scale (non-invasive ventilation, mechanical ventilation, ECMO or death). Time point: day 14, day 28
- Safety evaluation, as measured by treatment emergent adverse events, adverse reactions, serious adverse reactions. Time point: up to day 28
- Time to clinical improvement. Time point: up to day 28
- Time to first negative SARS-CoV-2 RT-PCR in upper or lower respiratory tract specimen. Time point: up to day 28
- Time to improvement of lung imaging. Time point: up to Day 28
- Time to normalisation of fever without use of antipyretics in last 24 hours. Time point: up to day 28

Notes	CTRI/2020/06/026220 | No data provided | Source(s) of monetary support: Sun Pharmaceutical Industries Limited Sun House, 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063

CTRI/2020/08/027033

Study name	SARS-COV-2 and COVID-19 - a randomized controlled trail
Starting date	07 August 2020
Contact information	Dr N Anbu Department of General Medicine, Government Siddha Medical College, Arumbakkam Chennai 106 600106 Chennai, TAMIL NADU India 9443279412 | nanbu.sumi@gmail.com
Methods	Interventional, RCT, multiple arm trial, 1:1; open label
Participants	100 participants, ≥ 18 years, female and male Inclusion criteria: • RT-PCR-positive patients • Asymptomatic patients • Fever • Dry cough • Sore throat • Difficulty in breathing Exclusion criteria: • Bronchogeniccarcinoma • Pulmonary TB • Pregnancy and lactating mothers • Status asthmatic
Interventions	Experimental: • Kabasura kudineer: tab azithromycin 500 mg twice daily oral administration • Tab hydroxychloroquine 200 mg oral administration

CTRI/2020/08/027033 *(Continued)*

- Tab paracetamol 650 mg twice daily oral administration
- Inj methylprednisolone IV
- Inj enoxaparin IV
- Tab vitamin C oral administration
- Tab zinc oral administration
- Tab multivitamin oral administration
- Kabasura kudineer 60 mL oral administration

Comparator:

- Nilavembu kudineer 60 mL twice daily oral administration for 14 days
- Kabasura kudineer 60 mL twice daily oral administration for 14 days
- Thippili rasayanam 5 g twice daily oral administration for 14 days
- Aadathodai manapagu 5 mL twice daily hot water oral administration for 14 days
- Swasakudori maathirai 2 twice-daily hot-water oral administration for 14 days
- Thoothuvalai legiyam 5 g twice daily with milk oral administration for 14 days
- Amukara chooranam 2 g twice daily oral administration for 14 days
- Seenthil chooranam 2 g twice daily oral administration for 14 days
- Pavala parpam 100 mg twice daily oral administration for 14 days
- Silasathu parpam 100 mg oral administration twice daily for 14 days
- Sivanar amirtham 60 g twice daily oral administration for 14 days
- Muthu parpam 100 mg twice daily oral administration for 14 days
- Gargle- with turmeric, thripala, alum, glycyrrhiza glabra, salt

Outcomes	Primary • Outcomes mainly assessed by reduction in clinical symptoms and RT-PCR test negative. Time point: 3 months Secondary • Outcomes mainly assessed by reduction in clinical symptoms and RT-PCR test negative • The outcome is assessed by patients' recovery progress with faster reductions in clinical symptoms and RT-PCR test negative, also to avoid the mortality rate by administering allopathy and Siddha medicines for the easy recovery and safety measures in the treatment for SARS-CoV-2 and COVID-19. Time point: 3 months
Notes	CTRI/2020/08/027033 | No data provided | Source(s) of monetary support: Govt Kilpauk Medical College Hospital Chennai 600010

CTRI/2020/11/029175

Study name	Role of heparin inhalation in reducing the duration the patient is breathing with the help of a ventilator
Starting date	17 November 2020
Contact information	Shagufta Naaz Associate professor, department of Anaesthesiology, AIIMS Patna, Phulwarisharif Patna 801507 801507 Kancheepuram, BIHAR India 07765937919 | drshaguftanaaz@gmail.com
Methods	Interventional, RCT, 1:1, active controlled trial, participant blinded

CTRI/2020/11/029175 *(Continued)*

Participants	58 participants, ≥ 18 years, female and male Inclusion criteria: • Confirmed COVID-19 • Endotracheal tube in place • Intubated the day before or same day • PaO2 to FIO2 ratio ≤ 300 while intubated • Acute opacities not fully explained by effusions, lobar/lung collapse and nodules, affecting at least one lung quadrant on chest X-ray or CT • Currently in the ICU or scheduled for transfer to the ICU Exclusion criteria: • Enrolled in another clinical trial that is unapproved for co-enrolment • Heparin allergy or HIT • aPTT > 120 s and this is not due to anticoagulant therapy • Platelet count < 20 x 109/L • Pulmonary bleeding, which is frank bleeding in the trachea, bronchi or lungs with repeated haemoptysis or requiring repeated suctioning • Uncontrolled bleeding • Pregnant or might be pregnant • Myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome • Usually receives home oxygen • Death is imminent or inevitable within 24 h
Interventions	Experimental: • Heparin nebulization plus standard care: each participant will be assigned to nebulised heparin sodium 25,000 Units in 5 mL or an equivalent unfractionated heparin, the frequency being 6-hourly till extubation or up to 10 days whichever is earlier Comparator: • Standard care: each participant will be assigned to standard care. They will not be nebulized with heparin
Outcomes	Primary • The primary outcome is the time to separation from mechanical ventilation (duration of mechanical ventilation) up to day 28. Time point: up to day 28 Secondary • Change in oxygenation index, driving pressure and ventilatory ratio at day 2 • Change in white cell count, platelet count, C-reactive protein, D-dimer and INR to day 10 • Number tracheotomised to day 28 • Time to separation from the ICU to day 28, among survivors • Survival to day 28; survival to day 60; and survival to hospital discharge, censored at day 60 • Number residing at home or in a community setting at day 60, among survivors • Time point: the time to separation from mechanical ventilation (duration of mechanical ventilation) up to day 10 or 28 or 60 days as applicable
Notes	CTRI/2020/11/029175 | No data provided | Source(s) of monetary support: AIIMS Patna

CTRI/2020/11/029345

Study name	To determine efficacy, safety and optimal dosing of anticoagulant strategies to prevent adverse outcomes in hospitalized COVID-19 patients
Starting date	25 November 2020
Contact information	Dr Viral Shah 401, 4th Floor Kshamalaya Building, 37 New Marine Lines. Mumbai MAHARASHTRA 400020 India 400020 Mumbai, MAHARASHTRA India 02240645101 | vshah@spectrumcr.com
Methods	Interventional, RCT, 1:1, open label

Participants	3600 participants; ≥ 18 years, female and male
	Inclusion criteria:
	• Hospitalisation within the prior 24 h for either confirmed (based on PCR or antigen-positive test for SARS-CoV-2) or suspected COVID-19 based on 3 criteria (all 3 must be present for suspected cases):
	  ○ Fever > 38 ° C
	  ○ O2 saturation ≤ 94
	  ○ Abnormal laboratory marker (at least 1)
	  ■ D-dimer ≥ 1.0 µg /mL
	  ■ CPR > 2 mg/L
	  ■ Ferritin > 300 µg /L
	  ■ Lymphopenia < 1500 cells /m^3
	• Patient or legal guardian provides written informed consent
	Exclusion criteria:
	• Age < 18 years
	• Mechanical ventilation on admission or high likelihood for the need for invasive mechanical ventilation within 24 h of admission
	• Anticipated duration of hospital stay < 72 h
	• Treatment with therapeutic dose UFH or LMWH, vitamin K antagonists, or NOACS within 7 days
	• Active bleeding
	• Risk factors for bleeding
	  ○ intracranial surgery or stroke within 3 months
	  ○ history of intracerebral arteriovenous malformation
	  ○ cerebral aneurysm or mass lesions of the central nervous system
	  ○ intracranial malignancy
	  ○ history of intracranial bleeding
	  ○ history of bleeding diatheses (e.g. haemophilia)
	  ○ history of gastrointestinal bleeding within previous 3 months
	  ○ thrombolysis within the previous 7 days
	  ○ presence of an epidural or spinal catheter
	  ○ recent major surgery < 14 days
	  ○ uncontrolled hypertension (SBP > 200 mmHg or DBP > 120 mmHg)
	  ○ other physician-perceived contraindications to anticoagulation
	  ○ platelet count < 50 x 109/L, INR > 2.0, or baseline aPTT > 50 seconds
	  ○ haemoglobin < 80 g/L (to minimise the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)
	  ○ current treatment with antithrombotics or antiplatelet agents

CTRI/2020/11/029345 *(Continued)*

- Acute or subacute bacterial endocarditis
- History of HIT or other heparin allergy including hypersensitivity
- Patients with non-COVID-19-related clinical condition for which life expectancy is < 6 months
- Pregnancy (women of childbearing potential are required to have a negative pregnancy test prior to enrolment)
- Active enrolment in other trials related to anticoagulation
- Patient has ESKD on chronic dialysis
- Patient is a member of a vulnerable population: in the judgment of the investigator the patient is unable to give informed consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: individuals with mental disability, people in nursing homes, children, impoverished people, people in emergency situations, homeless people, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and people kept in detention.

Interventions	Experimental: nil Comparator: • Prophylactic enoxaparin: 40 mg SC once daily; 30 mg SC once daily for CrCl 30 mL/min • Full-dose enoxaparin: 1 mg/kg SC every 12 h; 1 mg/kg SC once daily for CrCl 30 mL/min • Apixaban: 5 mg every 12 h; 2.5 mg every 12 h for patients with at least 2 of 3 of age ≤ 80 years, weight ≥ 60 kg or s. creatinine ≤ 1.5 mg/dL

Outcomes	Primary
	• Effectiveness
	  ◦ The primary effectiveness outcome endpoint is the time to first event rate within 30 days of randomisation of the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism (including pulmonary emboli) confirmed by imaging or requiring surgical intervention OR ischaemic stroke confirmed by imaging
	• Safety
	  ◦ The primary safety outcome endpoint is the in-hospital rate of BARC 3 or 5 bleeding (binary)
	• Time point: within 30 days of randomisation
	Secondary
	• Myocardial infarction
	• DVT
	• Intubation and mechanical ventilation
	• All-cause death
	• Cause-specific death
	• Stroke
	• Pulmonary emboli
	• Systemic thromboembolism surgical intervention
	• Organ support-free days
	• Total ICU days
	• Need for non-invasive mechanical ventilation/high flow nasal cannula
	• Ventilator-free days
	• Total hospital days
	• Hospital-free days
	• BARC 2, 3 or 5 bleeding
	• Laboratory-confirmed HIT
	• Time point: each assessed at 30 days and 90 days after randomisation

CTRI/2020/11/029345 *(Continued)*

Notes	CTRI/2020/11/029345 | No data provided | Source(s) of monetary support: Icahn School of Medicine at Mount Sinai One Gustave L. Levy Place, Box 1030 New York, NY 10029

EUCTR2020-001302-30-AT

Study name	A multicenter, randomized, active controlled, open label, platform trial on the efficacy and safety of experimental therapeutics for patients with a lung disease caused by coronavirus infection ACOVACT (Austrian CoronaVirus Adaptive Clinical Trial)
Starting date	09 April 2020
Contact information	Medical University of Vienna Währinger Gürtel 18-20 1090 Vienna Austria klin-pharmakologie@meduniwien.ac.at
Methods	Interventional, multicentre, open-label RCT with 4 parallel arms
Participants	500 participants; ≥ 18 years, female and male Inclusion criteria: • Laboratory-confirmed (i.e. PCR-based assay) infection with SARS-CoV-2 (ideally but not necessarily 72 h before randomisation for "antiviral" treatments) OR radiological signs of COVID-19 in chest X-ray or CT • Hospitalisation due to SARS-CoV-2 infection (for anti-viral treatment arms) • Requirement of oxygen support (due to oxygen saturation < 94% on ambient air or > 3% drop in case of COPD) • Informed consent obtained, the patient understands and agrees to comply with the planned study procedures, except for sub-study C: obtaining informed consent may be impossible due to the severe condition of the patient and may be waived • 18 years of age • For female patients with childbearing potential: willingness to perform effective measures of contraception during the study • For treatment arm 4 (convalescent plasma) only immunocompromised patients (e.g. after having received chemotherapy, with inherited or acquired immunodeficiency syndromes) are eligible • Sub-study A: eGFR of > 20 mL/min • Sub-study B: outpatients with COVID-19 may be included • Sub-study B: blood pressure =130/85 mmHg in 2 consecutive measurements or patients with established and treated hypertension • Sub-study B: control group 1: patients with suspected but negative tests for COVID-19. This group may consist of hospitalised and non-hospitalised patients • Sub-study B: control group 2: healthy volunteers • Sub-study C: signs of respiratory deterioration and progressing inflammation: need for oxygen supplementation, non-invasive ventilation, high-flow oxygen devices or mechanical ventilation and CRP levels > 5 mg/dL (for pentaglobin only), and admission to an ICU (for pentaglobin only) • If for any given reason a patient does not qualify to participate in the main study, this will not preclude participation in sub-study C • In case of negative PCR but clear radiological signs of COVID-19 patients have to be retested with serial nasopharyngeal swabs and PCR and, if possible antibody-based assays. In any case, a laboratory-based proof of COVID-19 is required or else the patient may be excluded from the per protocol analysis. Exclusion criteria:

EUCTR2020-001302-30-AT *(Continued)*

- Moribund or estimated life expectancy < 1 month (e.g. terminal cancer, etc.)
- Patient does not qualify for intensive care, based on local triage criteria
- Pregnancy or breastfeeding
- Severe liver dysfunction (e.g. ALT/AST > 5 times upper limit of normal)
- Stage 4 CKD or requiring dialysis for direct anticoagulant treatment
- Allergy or intolerances to any of the experimental substances -> exclusion for the respective treatment arm; for asunercept known hereditary fructose intolerance
- Anticipated discharge of hospital within 48 h (for anti-viral treatment arms)
- Contraindications treatment arm 2 (lopinavir/ritonavir): severe hepatic impairment, CYP3A4/5 metabolised drugs as deemed relevant by treating physicians, HIV positive
- Contraindication treatment arm 3 (remdesivir): bodyweight < 40 kg
- Contraindications treatment arm 5 (convalescent plasma): IgA deficiency
- Sub-study A contraindications: active bleeding or bleeding diathesis, lesion or condition considered as major risk factor for bleeding, recent brain or spinal injury, recent brain or spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, major intraspinal or intracerebral vascular abnormalities
- Sub-study A: ongoing therapeutic anticoagulation, which will continue, according to clinical practice
- Sub-study B contraindications chronic heart failure, allergies, hypersensitivities and intolerances, severe hepatic impairment and/or cholestasis, concomitant therapy with aliskiren-containing medications (for patients with diabetes mellitus or a GFR < 60 mL/min/1.73 m^2), known significant bilateral renal artery stenosis or renal artery stenosis of a solitary kidney
- Sub-study B: control group 1: with or without RAS blockers, control group 2: healthy volunteers: concomitant medication with RAS-blockers
- Sub-study C: known active HIV or viral hepatitis
- Asunercept: women of childbearing potential
- Sub-Study C: known active TB

Interventions	Kaletra: • Lopinavir - concentration unit: mg milligram(s); concentration number: 200 • Ritonavir - concentration unit: mg milligram(s); concentration number: 50 Xarelto • Rivaroxaban - concentration unit: mg milligram(s); concentration number: 10 • Candesartan - concentration unit: mg milligram(s); concentration number: 4 Asunercept • Asunercept - concentration unit: mg/mL milligram(s)/millilitre; concentration number: 20 Veklury • Remdesivir - concentration unit: mg/mL milligram(s)/millilitre; concentration number: 5 Pentaglobin • Pentaglobin - concentration unit: mg/mL milligram(s)/millilitre; concentration number: 50
Outcomes	Primary • Main objective: to investigate the efficacy of various experimental therapeutics for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); for efficacy assessment an ordinal scale for clinical severity assessment as proposed by the WHO will be used ○ Time to sustained improvement of 1 category from admission • Primary end point(s): time to sustained improvement of 1 category from admission in the 7-point clinical performance scale

EUCTR2020-001302-30-AT *(Continued)*

- Secondary objective:
  - Time to discharge or to a NEWS of 2 and maintained for 24 h, whichever occurs first
  - Change from baseline
  - Oxygenation-free days until day 29
  - Incidence and duration of new oxygen use during trial
  - Ventilator-free days until day 29
  - Incidence and duration of new mechanical ventilation use
  - Viral load/viral clearance change at baseline and 3 times/week
  - Duration of hospitalisation, ICU treatments and admissions
  - 15-, 29- & 60-day mortality
  - RAS-fingerprint at baseline and at least once weekly (on days 7 ± 1, 14 ± 1, 21 ± 1, 28 ± 1, through recovery
  - Within all participants, the impact of obesity and associated diseases on mortality will be investigated
  - Cumulative incidence of SAEs
  - Discontinuation or temporary suspension of therapy
  - Changes in WBC, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST
  - Time point(s) of evaluation of this end point: measured daily until day 29

Secondary

- Secondary end point(s): clinical status of participants according to the above-mentioned WHO scale:
  - Time to improvement of 1 category from admission
  - Clinical status daily
  - Mean change in the ranking on an ordinal scale from baseline
- NEWS:
  - Time to discharge or to a NEWS of 2 and maintained for 24 h, whichever occurs first
  - Change from baseline
- Oxygenation
  - Oxygenation-free days until day 29
  - Incidence and duration of new oxygen use during the trial (e.g. oxygen insufflation, high-flow oxygen, non-invasive ventilation, mechanical ventilation, etc.)
- Mechanical ventilation
  - Ventilator-free days until day 29
  - Incidence and duration of new mechanical ventilation use during the trial
- Viral load/viral clearance
  - Baseline, and 3 times/week until infection has resolved
- Hospitalisation
  - Duration of hospitalisation
- Mortality
  - 15-day, 29-day, 60-day mortality
- Sub-study A: number of thromboembolic events
- Within all participants, the impact of obesity and associated diseases on mortality will be investigated (e.g. mortality, inflammatory response, duration of hospitalisation, ICU admission, new oxygen use, duration of oxygen)
  - Exploratory assessment of transaminases (including alkaline phosphatase, GGT, AST), ALT) and liver function parameters (including bilirubin, prothrombin time, INR, albumin, fibrinogen) and their course during the disease and treatment
  - An exploratory endpoint will encompass a comprehensive assessment of inflammatory parameters and their changes during treatment and wash-out time, as well as exploratory genotype and RNA analysis with a focus on inflammation, coagulation, and the specific pathophysiology of the disease (if possible for centre)
  - Sub-study C: modified SOFA score, paO2/FiO2 ratio, or SpO2/FiO2 ratio

EUCTR2020-001302-30-AT *(Continued)*

- Sub-study B: to investigate the RAS fingerprint of patients with SARS-CoV-2 infection, with and without RAS-blocking treatment, as specified above; to investigate blood pressure, dyspnoea, body temperature, fear/anxiety

- Time point(s) of evaluation of this end point:
  - NEWS: daily
  - NEWS change from baseline (daily) up to day 29
  - Oxygenation-free days until day 29
  - Incidence and duration of new oxygen use during trial
  - Ventilator-free days until day 29
  - Incidence and duration of new mechanical ventilation use
  - Viral load/viral clearance change from baseline and 3 times/week
  - Duration of hospitalisation
  - 15-day, 29-day mortality
  - RAS-fingerprint at baseline and at least once weekly (on days 7 ± 1, 14 ± 1, 21 ± 1, 28 ± 1, through recovery
  - All included scores in sub-study B: approximately once weekly
  - Cumulative incidence of SAEs
  - Discontinuation or temporary suspension of therapy
  - Changes in WBC, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST until day 29

Notes	EUCTR2020-001302-30-AT | No data provided | Source(s) of monetary support: Medical University of Vienna

EUCTR2020-001708-41-IT

Study name	Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: comparison of 40 mg o.d. versus 40 mg b.i.d. A randomized clinical trial
Starting date	24 June 2020
Contact information	Azienda Ospedaliera Ao Ospedale Niguarda Ca' Granda ASST Grande Ospedale Metropolitano Niguarda Segreteria Unità Intensive Cure Ca Piazza Ospedale Maggiore 3 Milano 0264442576 | ucict@ospedaleniguarda.it
Methods	Prospective, multicentre, open-label, parallel-assignment RCT
Participants	2000 participants, ≥ 18 years and ≤ 64 years, 700 participants, ≥ 65 years, female and male Inclusion criteria • All-comers patients aged ≥ 18 years and admitted to hospital with laboratory-confirmed SARS-CoV-2 infection Exclusion criteria • Patients admitted directly to an ICU • Estimated CrCl < 15 mL/min/1.73 m^2

EUCTR2020-001708-41-IT *(Continued)*

- Patients needing anticoagulant for prior indication
- Patients treated with heparin at any increased dose compared to prophylactic regimen before enrolment
- Patients at high bleeding risk or experiencing clinically significant bleeding
- Patients involved in competitive clinical trials exploring antithrombotic treatments
- Any other significant disease or disorder which, in the opinion of the investigator, may either put the patients at risk because of participation in the trial, or may influence the result of the trial, or the patient's ability to participate in the trial

Interventions	Main objective of the trial • To compare the effects of 40 mg SC enoxaparin once daily versus 40 mg enoxaparin twice daily on the incidence of VTE (a composite of incident asymptomatic and symptomatic proximal DVT diagnosed by serial CUS, and symptomatic PE diagnosed by CT scan), in patients with SARS-CoV-2 infection Secondary objectives of the trial • To compare the effects of 40 mg SC enoxaparin once daily versus 40 mg enoxaparin twice daily on the incidence of in-hospital major complications, defined as the composite of death, VTE, use of mechanical ventilation, stroke, acute myocardial infarction and admission to ICU in patients with SARS-CoV-2 ◦ To compare each single component of the primary endpoint between the 2 groups ◦ To compare maximum SOFA score between the 2 groups ◦ To compare C-reactive protein, D-dimer, IL-6 and hs-troponin levels (as % above the upper reference limit (URL)) among the 2 groups ◦ To compare the incidence of SARS-CoV-2-related ARDS between the 2 groups ◦ To compare length of hospital stay between the 2 groups ◦ To compare measures of right ventricular function at trans-thoracic echocardiography or CT between admission and follow-up, whenever available
Outcomes	Primary • To compare the effects of 40 mg SC enoxaparin once daily versus 40 mg enoxaparin twice daily on the incidence of VTE (a composite of incident asymptomatic and symptomatic proximal deep vein thrombosis (DVT) diagnosed by serial compression ultrasonography (CUS), and symptomatic pulmonary embolism (PE) diagnosed by CT scan), in patients with SARS-CoV-2 infection. • Time point(s) of evaluation of this end point: 30 days Secondary • To compare the effects of 40 mg SC enoxaparin once daily versus 40 mg enoxaparin twice daily on the incidence of in-hospital major complications, defined as the composite of death, VTE, use of mechanical ventilation, stroke, acute myocardial infarction and admission to ICU in patients with SARS-CoV-2 • To compare each single component of the primary endpoint between the 2 groups • To compare maximum SOFA score between the 2 groups • To compare C-reactive protein, D-dimer, IL-6 and hs-troponin levels (as % above the upper reference limit (URL)) among the 2 groups • To compare the incidence of SARS-CoV-2-related ARDS between the 2 groups • To compare length of hospital stay between the 2 groups • To compare measures of right ventricular function at trans-thoracic echocardiography or CT between admission and follow-up, whenever available • Time point(s) of evaluation of this end point: 30 days
Notes	EUCTR2020-001708-41-IT | No data provided

EUCTR2020-001709-21-FR

Study name	Low-molecular-weight heparin to prevent venous thromboembolism in COVID-19 patients: a randomized controlled trial of different doses
Starting date	29 April 2020
Contact information	Direction de la Recherche Clinique Bâtiment Recherche - rue du Morvan 54511 Vandoeuvre lès Nancy France 33383 155285 | dripromoteur@chru-nancy.fr
Methods	Open-label, 2-armed, parallel assignment RCT

Participants	230 participants of 18-64 years and 320 participants ≥ 65 years, female and male
	Inclusion criteria:
	• Adult
	• Having been given an informed consent to participate or consent from relatives in case of vital emergency (patients not able to give a consent)
	• Hospitalisation for a acute respiratory COVID-19 infection probable or confirmed
	• SARS-Cov-2 infection diagnosed by biology (positive PCR for COVID-19 on a nasopharyngeal swab or any other sample and/or serological method) or by a composite criterion associating lung injury on imaging and clinical/biological symptoms suggestive of COVID-19 (e.g. dyspnoea, cough, fever, biological inflammatory syndrome, lymphopenia, elevated liver enzymes)
	• Health insurance coverage
	Exclusion criteria:
	• ESKD (glomerular filtration rate < 15 mL/min/1.73m^2)
	• Acute kidney failure KDIGO 3
	• Having received at least 3 doses prophylaxis of low-molecular-weight heparin before the inclusion
	• Therapeutic-dose of anticoagulant treatment for > 24 h, whatever the route or the drug prescribed for an other indication such as atrial fibrillation, thromboembolic venous disease needing an prolonged treatment, prosthetic heart valves
	• Iterative catheter-related thrombosis or thrombosis of an ECMO
	• ECMO to be implemented within 24 h
	• All contraindication to treatment with LMWH
	• High haemorrhagic risk: resistant systolic (> 180 mmHg) or diastolic (> 110 mmHg) hypertension for > 12 h or needing an IV treatment, recent (< 7j) major bleeding or non-resolved bleeding, coagulopathy (INR > 2 or activated clotting time > 2), thrombocytopenia < 75 G/L, HIT, contraindication to blood-derived products
	• Lower limb venous Doppler ultrasound not feasible (bilateral transfemoral amputation, or severe burns)
	• Death expected within 48 h
	• Peoople referred to in articles L.1121-5 to L.1121-8 and L.1122-2 of the Public Health Code:
	  ◦ pregnant, parturient or breastfeeding woman
	  ◦ person deprived of liberty for judicial or administrative decision
	  ◦ person under psychiatric care
	  ◦ minor (non-emancipated)
	  ◦ adult under legal protection (any form of public guardianship)

Interventions	Enoxaparin (Lovenox or other specialties) • Enoxaparin - concentration unit: IU international unit(s); concentration number: 14,000 Tinzaparine (Innohep)

EUCTR2020-001709-21-FR *(Continued)*

- Tinzaparin sodium - concentration unit: IU international unit(s); concentration number: 14,000

Dalteparin (Fragmine=E)

- Dalteparin sodium - concentration unit: IU international unit(s); concentration number: 12,500

Nadroparin (Fraxiparine)

- Nadroparin calcium - concentration unit: IU international unit(s); concentration number: 114,000

Enoxaparin (Lovenox or other specialities)

- Enoxaparin sodium - concentration unit: IU international unit(s); concentration number: 8000

Tinzaparin (Innohep)

- Tinzaparin sodium - concentration unit: IU international unit(s)

Outcomes

Primary

- Main objective: to evaluate the effectiveness, during the hospitalisation, of LMWH at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of VTE, causing death or not, in COVID-19 patients hospitalised in medical care units or ICUs
- Primary end point(s): the primary endpoint is the onset of a symptomatic VTE event, during the hospitalisation stay (and limited to D28 of hospitalisation), as defined by a:
  - symptomatic DVT, whatever the site and confirmed by a CUS or an abnormal CT angiogram with venous opacification or symptomatic PE, confirmed by:
    - a CT angiogram
    - or a ventilation perfusion scan
    - or the presence, in a patient with a recent worsening dyspnoea, of a DVT and/or a right ventricular dysfunction diagnosed by a transthoracic echocardiography in unstable patients unable to benefit from a CT angiogram (2019 European Society of Cardiology Guidelines)
    - unexplained death when a PE cannot be excluded.
- The primary endpoint is a composite measure of clinical events and/or survival, as recommended by the WHO guidelines on COVID-19 Therapeutic Trial Synopsis (February 2020)
- For each included participant, the onset of each event considered in the composite primary endpoint will be evaluated by a blinded independent endpoint adjudication committee.
- Secondary objective: to evaluate the effectiveness of a weight-adjusted increased prophylactic dose of LMWH, compared with a lower prophylactic dose, on:
  - major bleeding
  - major and clinical relevant non-major bleeding
  - net clinical benefit corresponding to the association of VTE and major bleeding
  - venous thrombosis at other sites than the primary outcome
  - symptomatic arterial thrombosis
  - all-cause mortality
  - primary outcome in predefined sub-groups (e.g. renal function)
  - to identify variables associated with the risk of VTE
  - time point(s) of evaluation of this end point: between the trial inclusion and the hospitalisation discharge (with a limitation of 28 days of hospitalisation)

Secondary

- Secondary end point(s):
- The onset of major bleeding as defined by ISTH
  - bleeding causing a fall in haemoglobin level = 2 g/dL or needing a transfusion (whole blood or red cells) = 2 units, and/or
  - bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
  - fatal bleeding

EUCTR2020-001709-21-FR *(Continued)*

- The onset of clinically-relevant non major bleeding as defined by ISTH as any sign or symptom of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
  - requiring medical intervention by a healthcare professional, and/or
  - needing a temporary cessation of the study treatment, and/or
  - causing discomfort for the patient such as pain
- The clinically-relevant non major bleeding may be: macroscopic haematuria, gastrointestinal bleeding, haemoptysis, muscle hematoma, spontaneous SC hematoma > 25 cm^2 or provoked SC hematoma > 100 cm^2, multiple source bleeding, haematoma/bleeding from other site
- The net clinical benefit defined as composite criterion associating VTE and major bleeding
- The onset of venous thrombosis at other sites than the primary outcome:
  - superficial venous thrombosis, and/or
  - venous central catheter-related thrombosis/PiCC-line/midline, and/or
  - thrombosis of an extracorporeal dialysis circuit (diagnosed by a dysfunction of the circuit), and/or
  - thrombosis of an ECMO (diagnosed by a dysfunction of the circuit)
  - DVT in other sites (e.g. upper limb, splanchnic vein thrombosis, cerebral thrombophlebitis)
- These thromboses must be confirmed by a reference gold standard test according to most recent guidelines
- The onset of symptomatic arterial thrombosis, whatever the arterial site:
  - stroke, and/or
  - acute coronary syndrome, and/or
  - acute mesenteric ischaemia, and/or
  - other arterial thrombosis on other sites (e.g. splanchnic arterial or peripheral arteries
- All-cause mortality
- Same outcome as the primary outcome
- Variables associated with the occurrence of VTE that will be recorded are: age, gender, cardiovascular risk factors, past medical history, treatments, clinical characteristics, laboratory parameters recorded during patient management
- The occurrence (or not) of the secondary outcomes in each included patient will be reviewed blindly of the randomisation arm by an independent adjudication committee
- Time point(s) of evaluation of this end point: between the trial inclusion and the hospitalisation discharge (with a limitation of 28 days of hospitalisation)

Notes	EUCTR2020-001709-21-FR | No data provided | Source(s) of monetary support: DGOS (being obtained), Région Grand Est (being obtained)

EUCTR2020-001891-14-ES

Study name	Impact of the use of low molecular weight heparins (LMWH), at prophylactic versus intermediate doses, on SARS-CoV2 infection (COVID-19)
Starting date	04 May 2020
Contact information	Alejandro Calle Editor José Manuel Lara, 28, 1B 41013 Sevilla Spain +34630157890 | secretaria@delosclinical.com
Methods	Open-label, 2-armed, parallel-assignment RCT
Participants	140 participants, ≥ 18 years, female and male

EUCTR2020-001891-14-ES *(Continued)*

	Inclusion criteria: • Patients > 18 years old • Signature of informed consent • Diagnosis by positive PCR for SARS-CoV2 infection • They require hospital admission due to fever and other of the established CoV2 admission criteria • Patients with a weight ≥ 60 kg Exclusion criteria: • Allergy to LMWH • Contraindication for anticoagulation (platelets < 25 x 10e9/L or severe active bleeding, major or clinically relevant bleeding) • Pregnancy • Patients with extreme weights. BMI > 40 • Need for chronic anticoagulant treatment • Need for treatment with high-flow oxygen therapy or mechanical ventilation at the time of study recruitment (within the first 24 h after admission) • Participation in another disease treatment trial • Venous thromboembolic
Interventions	Enoxaparin sodium • Concentration unit: mg/kg • Concentration number: 1
Outcomes	Primary • Main objective: to assess the impact of treatment with LMWH, using prophylactic versus intermediate doses, in terms of escalation in oxygen therapy or the need for invasive mechanical ventilation or mortality in patients admitted with SARS-CoV2 infection • Primary end point(s): need for oxygen therapy escalation due to oxygen saturation (Sat O2) = 92% with FiO2 = 0.5 and respiratory rate (FR) = 30 (IROX index = SatO2/FiO2/FR < 5.5) or invasive mechanical ventilation or mortality during admission • Secondary objective: know the safety of LMWH guideline used in terms of bleeding events, days in hospital and to establish the most favourable patient profile for LMWH treatment • Time point(s) of evaluation of this end point: 30 days Secondary • Secondary end point(s): need for rescue medication (e.g. parenteral corticosteroids, tocilizumab) and days of hospital stay in surviving participants • Time point(s) of evaluation of this end point: 30 days
Notes	EUCTR2020-001891-14-ES | No data provided | Source(s) of monetary support: Fundación Neumosur

EUCTR2020-002234-32-IT

Study name	Efficacy and safety of edoxaban and or colchicine for patients with SARS-CoV-2 infection managed in the out of hospital setting (COVID 19)
Starting date	28 December 2020
Contact information	Cardiologia

EUCTR2020-002234-32-IT *(Continued)*

	Freiburgstrasse, 8 3010 Bern Switzerland +41316325492 | marco.valgimigli@insel.ch
Methods	Prospective, multicentre, open-label, 4-armed RCT
Participants	420 participants, ≥ 18 years, female and male Inclusion criteria: • Patients ≥ 18 years old with symptoms compatible with active coronavirus infection and laboratory-confirmed SARS-CoV-2 infection (under RT PCR) who are managed at home or in another out-of-hospital setting Exclusion criteria: • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh C cirrhosis with portal hypertension • Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities • Uncontrolled severe hypertension • Ongoing or planned treatment with parenteral or oral anticoagulants • Unilateral or bilateral above-knee, lower-extremity amputation • Inability to take oral medication or otherwise unable or unwilling to undergo/perform study-specified procedures • Have received or will receive an experimental drug or used an experimental medical device within 30 days before the planned start of treatment • Pregnancy or breastfeeding or any plan to become pregnant during the study. Women (and men, for colchicine group only) with child-bearing potential not using adequate birth control method (note: as adequate method of birth control oral contraception is recommended. If oral contraception is not feasible, both partners should use adequate barrier birth control) • Need for dual anti-platelet therapy consisting of aspirin and an oral P2Y12 inhibitor • Inflammatory bowel disease or chronic diarrhoea or neuromuscular disease • CrCl < 15 mL/min • Anticipated use of hydroxychloroquine • Participation in any other clinical trial • Inability to understand the requirements of the study and to provide informed consent
Interventions	Lixiana 30 mg • Edoxaban - concentration unit: mg milligram(s); concentration number: 30 Colchicine • Colchicine - concentration unit: µg microgram(s); concentration number: 500 Lixiana 60 mg • Edoxaban - concentration unit: mg milligram(s); concentration number: 60
Outcomes	Primary • Main objective: the aim of the CONVINCE study is therefore to assess the safety and efficacy of edoxaban and/or colchicine administration in SARS-CoV-2-infected patients who are managed outside the hospital with respect to the occurrence of fatalities, hospitalisation, major vascular thrombotic events or the SARS-CoV-2 clearance rate under RT-PCR • Primary end point(s): this study has 2 co-primary endpoints, one each randomisation as follows:

EUCTR2020-002234-32-IT *(Continued)*

- Edoxaban vs. no active treatment
- Major vascular thrombotic events (MVTE) at 25 (+/-3) days defined as a composite of:
  - Asymptomatic proximal DVT
  - Symptomatic proximal or distal DVT
  - Symptomatic PE or pulmonary thrombosis
  - Myocardial infarction
  - Ischemic stroke
  - Non-CNS systemic embolism
  - Death
- Colchicine vs no active treatment
- The SARS-CoV-2 detection rates at day 14 (+/-3) under RT-PCR or freedom from death or hospitalisation
- Secondary objective: not applicable
- Time point(s) of evaluation of this end point: 14 (+/-3) and 25 (+/-3) days

Secondary

- Secondary end point(s): the secondary endpoints of the study are the following:
  - Each component of the co-primary endpoints
  - Need for non-invasive or invasive ventilation
  - Need for oxygen therapy
  - Body temperature kinetics
  - Need for analgesics including NSAIDs and/or paracetamol
  - Need for hospitalisation and total days in the hospital
  - Any combination of the above endpoints
  - Each component of the primary endpoint as well as pre-specified composite endpoints at the time all SARS have come to a resolution
  - Impact of either intervention on coagulation and inflammatory biomarkers including IL-6, CRP, D-dimers, sCD40L, Fibrinogen, Factor X activity and Factor XIa
  - ECG analyses for QT segment measures and for detection of EKC changes associated to myopericarditis
  - HsTroponin levels
  - Bleeding endpoints according to BARC 2, 3 or 5 and ISTH major and clinically relevant non-major bleeding

Notes	EUCTR2020-002234-32-IT | No data provided | Source(s) of monetary support: Daiichi Sankyo Europe GmbH

EUCTR2020-002504-39-DE

Study name	Hamburg edoxaban for anticoagulation in COVID-19 study
Starting date	10 November 2020
Contact information	Lilli Gerstenmaier Martinistrasse 64 20251 Hamburg Germany +49040524719216 | regulatory@ctc-north.com
Methods	Prospective, single-blind, 2-armed, parallel-assignment RCT
Participants	172 participants, ≥ 18 years, female and male Inclusion criteria:

EUCTR2020-002504-39-DE *(Continued)*

- Diagnosis of COVID-19 and hospitalisation on ICU, or
- Diagnosis of COVID-19 and hospitalisation on normal ward, or
- Diagnosis of COVID-19 and troponin = ULN and/or D-dimer = 0.5 mg/L
- Legally effective declaration of informed consent

Exclusion criteria:

- Age < 18
- Life expectancy < 3 months before COVID-19
- Resuscitation > 30 min
- Contraindications against the use of each of the standard LMWH/fondaparinux according to the respective summary of product characteristics
- Hypersensitivity to the active substance, to edoxaban or any of its excipients
- Significantly increased bleeding risk
- Other indication for anticoagulation beyond COVID-19
- GFR < 15 mL/min
- Planned transfer of the patient to another clinic within the next 42 days

Interventions

Experimental:

- Lixiana
  - Edoxaban - concentration unit: mg milligram(s); concentration number: 60 and 30
- Arixtra
  - Fondaparinux sodium - concentration unit: mg milligram(s); concentration number: 7.5

Comparator:

- Film-coated tablet; route of administration of the placebo: oral use

Outcomes

Primary

- Main objective: (i) to evaluate if an intensive anticoagulation strategy using edoxaban on top of standard care of COVID-19 therapy is superior to standard care (in-hospital moderate anticoagulation strategy = low-dose LMWH, ambulatory no anticoagulation, i.e. placebo within this trial) in reduction of morbidity and mortality endpoints in patients with COVID-19
- To assess safety and tolerability of edoxaban and high-dose LMWH on top of standard care in patients with COVID-19
- Primary end point(s): efficacy
- Combined endpoint: all-cause mortality and/or VTE and/or arterial thromboembolism within 42 days
- Safety endpoints:
  - Rate of SAEs/AEs/suspected unexpected serious adverse reactions in both arms within 42 days
  - Major and clinically relevant non-major bleeding according ISTH
  - Interruption of therapy due to intolerability to edoxaban
  - New treatment-emergent AEs (and changes in severity and frequency in these) related to edoxaban
- Secondary objective: furthermore, secondary objectives intend to evaluate the effect of both treatment regimes with respect to all-cause mortality, mortality related to VTE and arterial thromboembolism, rate of arterial embolism/VTE, rate and length of mechanical ventilation, length of initial stay at ICU, rehospitalisation, rate and length of renal replacement therapy, cardiac arrest and CPR
- Time point(s) of evaluation of this end point: 42 days

Secondary

- Secondary end point(s): the secondary efficacy objectives are to compare the active treatment and placebo groups with respect to:
  - All-cause mortality within 42 days

EUCTR2020-002504-39-DE *(Continued)*

- Mortality related to VTE
- Mortality related to arterial thromboembolism
- Rate of VTE and/or arterial thromboembolism
- Rate and length of mechanical ventilation until day 42
- Length of initial stay at ICU after application of investigational medicinal product up to a total of 42 days
- Rehospitalisation within 42 days
- Rate and length of renal replacement therapy until day 42
- Cardiac arrest/CPR until day 42

- Further assessment of safety:
  - An expanded safety composite event including death, myocardial infarction, stroke, recurrent hospitalisation, bleeding, acute kidney injury, and gastrointestinal disorders will be collected, analysed and reported. Upon medical need and/or regulatory requirements additional visits may be scheduled.
  - Time point(s) of evaluation of this end point: 42 days

Notes	EUCTR2020-002504-39-DE | No data provided | Source(s) of monetary support: Daiichi Sankyo Europe GmbH; University Medical Center Hamburg-Eppendorf

EUCTR2020-003349-12-IE

Study name	This is a proof of principle/feasibility study aiming to evaluate the effect of nebulised unfractionated heparin on procoagulant markers related to acute respiratory distress syndrome in patients invasively ventilated for COVID-19 lung disease
Starting date	09 October 2020
Contact information	Prof John Laffey University Road H91 TK33 Galway Ireland 35391524411 | john.laffey@nuigalway.ie
Methods	Prospective, open-label, 1-armed, parallel-assignment RCT

Participants	40 participants, ≥ 18 years, female and male
	Inclusion criteria:
	• To be eligible, a patient must satisfy all these inclusion criteria:
	  ○ confirmed or suspected COVID-19,
	  ○ if 'suspected', results must be pending or testing intended
	  ○ age ≥ 18 years
	  ○ endotracheal tube in place
	  ○ intubated current or previous day
	  ○ PaO2 to FIO2 ratio ≤ 300 while intubated
	  ○ acute opacities on chest imaging affecting at least one lung quadrant ('acute opacities' do not include effusions, lobar/lung collapse or nodules)
	  ○ Currently in the ICU or scheduled for transfer to the ICU (the 'ICU' is an area designated for inpatient care of the critically ill where therapies including invasive mechanical ventilation can be provided)
	Exclusion criteria:
	• To be eligible, a patient must have none of these exclusion criteria:
	  ○ enrolled in another clinical trial that is unapproved for co-enrolment

EUCTR2020-003349-12-IE *(Continued)*

- heparin allergy or HIT
- aPTT > 120 seconds and this is not due to anticoagulant therapy
- platelet count < 20 x 109 per L
- pulmonary bleeding, which is frank bleeding in the trachea, bronchi or lungs with repeated haemoptysis or requiring repeated suctioning
- uncontrolled bleeding
- pregnant or suspected pregnancy (urine or serum HCG will be recorded)
- receiving or about to commence ECMO or HFOV
- myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome
- usually receives home oxygen
- dependent on others for personal care due to physical or cognitive decline
- death is imminent or inevitable within 24 h
- the clinical team would not be able to set up the study nebuliser and ventilator circuit as required including with active humidification
- clinician objection
- the use or anticipated use of nebulised tobramycin during this clinical episode

Interventions	Experimental: • Heparin Sodium: concentration unit: IU/mL international unit(s)/millilitre; concentration number: 5000 Comparator: nil

Outcomes	Primary
	• Main objective: effect of nebulised heparin on D-dimer profile, assessed via D-dimer AUC and via a mixed-effects model, with data collected on days 1, 3, 5 and 10
	• Safety of nebulised heparin delivered by aerogen solo nebuliser in patients with COVID-19-induced severe respiratory failure, as measured by the incidence of SAEs
	• Primary end point(s): nebulised heparin is administered 6-hourly from enrolment to day 10 post-enrolment, provided the patient is receiving invasive mechanical ventilation. Data collection will be completed at day 60
	• Secondary objective: to determine the impact nebulised heparin on oxygenation index (OI)
	  ○ To determine the effect of nebulised heparin on pulmonary compliance measured on days 1, 3, 5 and 10
	  ○ Effect of nebulised heparin on other inflammatory and coagulation indices will be assessed to assess for any potential markers of COVID 19 ARDS
	  ○ Time to separation from invasive ventilation to day 28, where non-survivors to day 28 are treated as though not separated from invasive ventilation
	  ○ In this study, ‘day 0’ describes the period from randomisation to midnight on the day of enrolment, ‘day 1’ the first calendar day after the day of enrolment, ‘day 2’ the second calendar day after the day of enrolment, and so forth
	  ○ Number tracheotomised to day 28
	  ○ Time to separation from the ICU to day 28, where non-survivors to day 28 are treated as though not separated from intensive care
	  ○ Survival to day 28; survival to day 60; and survival to hospital discharge, censored at day 60
	• Time point(s) of evaluation of this end point: nebulised heparin is administered 6-hourly from enrolment to day 10 post enrolment, provided the patient is receiving invasive mechanical ventilation. Data collection will be completed at day 60
	Secondary
	• Secondary end point(s): not applicable
	• Time point(s) of evaluation of this end point: data collection will be completed at day 60

EUCTR2020-003349-12-IE *(Continued)*

Notes	EUCTR2020-003349-12-IE | No data provided | Source(s) of monetary support: Aerogen; CURAM/SFI

Goldin 2020

Study name	Systemic anticoagulation with full dose low molecular weight heparin (LMWH) vs. prophylactic or intermediate dose LMWH in high risk COVID-19 patients (HEP-COVID Trial)
Starting date	26 April 2020
Contact information	Damian N Inlall Northwell Health, USA (516) 600-1482 | dinlall@northwell.edu
Methods	Prospective, multicentre, triple-blinded, 2-armed, parallel-assignment RCT

Participants	308 participants, ≥ 18 years, female and male
	Inclusion criteria
	• Participant (or legally authorised representative) provides written informed consent prior to initiation of any study procedures
	• Understands and agrees to comply with planned study procedures
	• Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
	• Participant consents to randomisation within 72 h of hospital admission or transfer from another facility within 72 h of index presentation
	• Participants with a positive COVID-19 diagnosis by nasal swab or serologic testing
	• Hospitalised with a requirement for supplemental oxygen
	• Have: either a D-dimer > 4.0 x ULN, OR SIC score of ≥ 4
	Exclusion criteria
	• Indications for therapeutic anticoagulation
	• Absolute contraindication to anticoagulation including:
	  ○ active bleeding
	  ○ recent (within 1 month) history of bleed
	  ○ dual (but not single) antiplatelet therapy
	  ○ active gastrointestinal and intracranial cancer
	  ○ a history of bronchiectasis or pulmonary cavitation
	  ○ hepatic failure with a baseline INR > 1.5
	  ○ CrCl < 15 mL/min
	  ○ a platelet count < 25,000
	  ○ a history of HIT within the past 100 days or in the presence of circulating antibodies
	  ○ contraindications to enoxaparin including a hypersensitivity to enoxaparin sodium, hypersensitivity to heparin or pork products, hypersensitivity to benzyl alcohol
	  ○ pregnant female
	  ○ inability to give or designate to give informed consent
	  ○ participation in another blinded trial of investigational drug therapy for COVID-19

Interventions	Experimental: full-dose LMWH anticoagulation therapy Participants in this study arm will be treated with therapeutic doses of SC LMWH (enoxaparin). Enoxaparin 1 mg/kg SC twice a day for CrCl ≥ 30 mL/min (or enoxaparin 0.5 mg/kg SC twice a day for CrCl ≥ 15 mL/min and < 30 mL/min) during the course of their hospitalisation

Goldin 2020 *(Continued)*

	Comparator: prophylactic/intermediate-dose LMWH or UFH therapy Participants in this study arm will be treated with local institutional standard care for prophylactic-dose or intermediate-dose UFH or LMWH. Regimens allowed are UFH up to 22,500 IU daily in twice daily or three times daily doses (i.e. UFH 5000 IU SC twice a day/three times a day or 7500 IU twice a day/three times a day), enoxaparin 30 mg and 40 mg SC daily or twice daily (the use of weight-based enoxaparin i.e. 0.5 mg/kg SC twice a day for this arm is acceptable but strongly discouraged), dalteparin 2500 IU or 5000 IU a day
Outcomes	Primary • Composite outcome of arterial thromboembolic events, VTE events and all-cause mortality at day 30 ± 2 days (time frame: day 30 ± 2 days). Risk of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), VTE (including symptomatic DVT of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal PE), and all-cause mortality at day 30 ± 2 days Secondary • Major bleeding (time frame: day 30 ± 2 days). Risk of major bleeding defined using the ISTH criteria • Composite outcome of arterial thromboembolic events, VTE events and all-cause mortality at hospital day 10 + 4 (time frame: day 10 + 4). The composite of arterial VTE (including myocardial infarction, stroke, systemic embolism), VTE (including symptomatic DVT) of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal PE), and all-cause mortality at hospital day 10 + 4 • SIC score (time frame: day 30 ± 2 days). SIC score based on ISTH guidelines. Platelets, K/µL (thousands per microlitre) (0-2) INR (0-2), D-dimer levels, ng/mL (0-3), fibrinogen, mg/dL (0-1), calculated (SIC) scores ≥ 4 predicted higher mortality rates within 30 days and greater risk of PE • Progression to ARDS (time frame: day 30 ± 2 days) based on monitoring of participant conditions • Need for intubation (time frame: day 30 ± 2 days) based on monitoring of participant conditions • Re-hospitalisation (time frame: day 30 ± 2 days) based on monitoring of participant conditions
Notes	NCT04401293 | No data provided

IRCT20200515047456N1

Study name	The role of anticoagulant and thrombolitic in treatment of COVID patients
Starting date	17 June 2020
Contact information	Farid Rashidi Daneshgah 5166614756 Iran (Islamic Republic of) +98 41 3336 4901 | fr2652@yahoo.com
Methods	Single-blinded, 2-armed, parallel-assignment RCT
Participants	15 participants, ≥ 18 years, female and male Inclusion criteria: • COVID patients with P/F ratio < 100 • D-dimer > 3000 without response to other medications Exclusion criteria: • Active bleeding

IRCT20200515047456N1 *(Continued)*

	• Platelet < 30,000 • Without any contraindication for thrombolytic therapy
Interventions	Experimental: • First intervention group, anticoagulant • Participants will be started on UFH • Blood sample to keep PTT > 50 • Second intervention group, thrombolytic (tPA) • They will be started 25 mg over 2 h and 25 mg for next 22 h Comparator: without placebo
Outcomes	Primary • Decrease D-dimer level. Time point: from first to 6th day of study. Method of measurement: blood sample • Improve compliance. Time point: from first to 6th day of study. Method of measurement: ventilator parameter • Improve of oxygenation. Time point: from first to 6th day of study. Method of measurement: arterial blood gas • Improve SOFA score. Time point: from first to 6th day of study. Method of measurement: questionnaire
Notes	IRCT20200515047456N1 | No data provided | Source(s) of monetary support: Tabriz University of Medical Sciences

ISRCTN14212905

Study name	Understanding how COVID-19 leads to respiratory failure in COVID-19 positive patients
Starting date	03 July 2020
Contact information	Annya Bruce Queen's Medical Research Institute Little France Crescent EH16 4TJ Edinburgh United Kingdom +44 (0)131 2429180 | Annya.Bruce@ed.ac.uk
Methods	Single-centre RCT
Participants	100 participants, ≥ 18 years, female and male Inclusion criteria: • Provision of informed consent from the patient or representative • Aged at least 16 years • If the patient is of childbearing potential, the patient, and their partner(s), agree to use medically-accepted double-barrier methods of contraception (e.g. barrier methods, including male condom, female condom or diaphragm with spermicidal gel) during the study and for at least 90 days after the termination of study therapy. A vasectomised partner would be considered an appropriate birth control method provided that the partner is the sole male sexual partner and the absence of sperm has been confirmed. • COVID-19 positive Exclusion criteria:

ISRCTN14212905 *(Continued)*

	• Current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled cardiac disease (NYHA class IV), uncontrolled renal disease (eGFR < 30 mL/min/1.73 m^2), severe liver dysfunction (ALT/AST > 5 x ULN) or bone marrow failure (Hb < 8 g/dL and absolute neutrophil count < 0.5 mm^3 and platelet count <50,000 µL) • Women who are pregnant or breastfeeding • Participation in another clinical trial of an investigational medicinal product • Known hypersensitivity to the investigational medicinal product or excipients • Pre-existing or concomitant use of off-label treatments for COVID-19
Interventions	Patients will be divided into cohorts • community • hospitalised requiring supplemental oxygen and • hospitalised requiring assisted ventilation 2 treatments will be compared to standard care. Nafamostat (anti-viral and anti-coagulant) and TD139 (galectin 3 inhibitor). For nafamostat, it is intended that the licensed dose (0.2 mg/kg/h) in Japan will be used. Patients randomised to nafamostat will receive a continuous IV infusion at 0.2 mg/kg/h for 7 days. If a participant is discharged from hospital or can no longer receive this treatment, the treatment will be stopped. For TD139, patients will inhale 5 mg x 2 (10 mg) twice daily for the first 48 h and then subsequently 5 mg x 2 (10 mg) once daily for the remaining 12 days. Unless a participant is discharged from hospital or can no longer use an inhaler – in which case treatment will be stopped at such time. Follow-up will be at 30, 60 and 90 days post-treatment

Outcomes	Primary
	• Safety of candidate agents as add-on therapy to standard care in patients with COVID-19 measured at 30, 60 and 90 days post-treatment using:
	• Haematological and biochemical safety laboratory investigations:
	  ◦ Haematology: full blood count and differential white cell count
	  ◦ Coagulation: D-dimer, fibrinogen, aPTT, prothrombin time, INR, Cd39, ecto-ADPase, nitrous oxide, PGI2, antithrombin, thrombomodulin, protein c, electronic patient care reporting, kallikrein
	  ◦ Biochemistry: random glucose, urea and electrolytes (urea, sodium, potassium, chloride, magnesium, bicarbonate, creatinine); liver function tests (total protein, albumin, globulin, total bilirubin, AST, ALT, GGT, LDH, alkaline phosphatase); C-reactive protein (CRP); ferritin; triglycerides; troponin; creatine kinase (MB fraction)
	• Physical examination performed at screening, including assessment of presenting symptoms. At subsequent assessments, a symptom-directed (targeted) physical examination will be performed as required by the condition of the patient and the presenting complaint
	• Vital signs (blood pressure/heart rate/temperature and respiratory rate)
	• Daily ECG readings
	• AEs that are not related to the patient's underlying condition or clinical interventions will be recorded following consent. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment
	Secondary
	• Pharmacokinetic (PK)/pharmacodynamic (PD) information measured using daily blood samples
	• Response of key exploratory biomarkers during treatment period, namely IL-1ß, IL-6, IL-8 and TNF-a, CXCL-10 and IL-1ra. Due to the nature of this research additional analytical tests may be developed or required in order to profile COVID-19 and develop therapies
	• Improvement or deterioration of patients measured using WHO ordinal scale and NEWS2 at 30, 60 and 90 days post treatment
	• Number of oxygen-free days measured at 30, 60 and 90 days post-treatment
	• Ventilator-free days and incidence and duration of any form of new ventilation use measured at 30, 60 and 90 days post-treatment

ISRCTN14212905 *(Continued)*

	• SpO2/FiO2, measured daily from randomisation to day 15, hospital discharge, or death • SARS-CoV-2 viral load measured using qualitative and quantitative PCR determination of SARS-CoV-2 in oropharyngeal/nasal/saliva swab while hospitalised on days 1, 3, 5, 8, 11, 15 • Time to discharge (days) • The use of renal dialysis or haemofiltration (not used/used and duration of use) at 30, 60 and 90 days post-treatment
Notes	ISRCTN14212905 | No data provided | Source(s) of monetary support: Life Arc

Kharma 2020

Study name	Anticoagulation in patients suffering from COVID-19 disease-The Anti-Co Trial
Starting date	28 June 2020
Contact information	Marcus Lance, MD, PhD Hamad Medical Corporation Doha, Qatar 00974 ext 33530292 | mlance@hamad.qa
Methods	Triple-blind, 2-armed, parallel-assignment RCT
Participants	100 participants, ≥ 18 years, female and male Inclusion criteria: • Adult patient (≥ 18 years of age) • Positive COVID-test • Under mechanical ventilation • D-dimers > 1.2 mg/L Exclusion criteria: • Pregnancy • Allergy to the drug (bivalirudin) • Inherited coagulation abnormalities • No informed consent

Interventions	Experimental:
	• Drug: bivalirudin injection
	  ○ This group will receive standard anticoagulation with LMWH/UFH
	• Drug: standard treatment
	  ○ The participants will receive IV bivalirudin according to the institutional HIT protocol
	Comparator:
	• Standard treatment
	• In this arm the participants will be treated according to our standard anticoagulation protocol
	• The participants will not be treated with bivalirudin (the investigational drug)

Outcomes	Primary • P/F ratio (time frame: 3 days of intervention)

Kharma 2020 *(Continued)*

	• the P/F ratio is a surrogate parameter for oxygenation in ARDS Secondary • Kidney function (time frame: 3 days of intervention) • The kidney function frequently is deteriorated in COVID-19 patients
Notes	NCT04445935 | No data provided

Lasky 2021

Study name	A phase 2/3 study to evaluate the safety and eficacy of dociparstat sodium for the treatment of severe COVID-19 in adults at high risk of respiratory failure
Starting date	3 June 2020
Contact information	Marion Morrison, MD University of Alabama at Birmingham Birmingham, Alabama, USA, 35294 919-313-2977 | mmorrison@chimerix.com
Methods	Double-blind, 2-armed, 2:1 parallel-assignment RCT
Participants	525 participants, ≥ 18 years, female and male Inclusion criteria: • Hospitalised for laboratory-documented COVID-19 disease (e.g. positive for SARS-CoV-2 via nasopharyngeal swab RT-PCR (or other commercial or public health assay)) • Age ≥ 18 years and ≤ 85 years • Resting SaO2 of < 94% while breathing ambient air • Score of 3 or 4 on the NIAID ordinal scale (requires supplemental oxygen or noninvasive ventilation) • Provide informed consent to participate in the study (by participant or legally-acceptable representative) Exclusion criteria: • Currently receiving invasive mechanical ventilation (e.g. via an endotracheal tube) (score of 2 on NIAID ordinal scale) • Active or uncontrolled bleeding at the time of randomisation; a bleeding disorder, either inherited or caused by disease; history of known arterial-venous malformation, intracranial haemorrhage, or suspected or known cerebral aneurysm; or clinically significant (in the judgment of the investigator) gastrointestinal bleeding within the 3 weeks prior to randomisation • Receiving any other investigational (non-approved) therapy for the treatment of COVID-19 or participating in the treatment period of any other therapeutic invention clinical study • Receiving systemic corticosteroids for a chronic condition • Receiving chronic anticoagulation with warfarin or DOACs (e.g. rivaroxaban, dabigatran, apixaban, edoxaban) • Receiving or anticipated to require other systemic anticoagulation dosing at a therapeutic intensity. Prophylaxis of VTE using SC UFH or enoxaparin is permitted with appropriate monitoring of coagulation status and within guidelines provided in the protocol • Receiving antiplatelet therapy, alone or in combination, including aspirin and other antiplatelet agents (e.g. clopidogrel, ticagrelor, and prasugrel), unless able to discontinue these agents at the

Lasky 2021 *(Continued)*

	time of randomisation and to remain off these agents throughout the duration of the study intervention infusion period • Treatment with systemic (nonsteroid) immunomodulators or immunosuppressant medications, including but not limited to TNF inhibitors, anti-interleukin-1 agents, and Janus kinase (JAK) inhibitors within 5 half-lives or 30 days (whichever is longer) prior to randomisation • Severe chronic liver disease • Severe renal impairment • QTc > 500 msec (or > 530-550 msec in patients with QRS > 120 msec) • ALT or AST > 5 x ULN • aPTT > 42 s • Thrombocytopenia with a platelet count < 80,000/mm^3 • Evidence of clinical improvement in COVID-19 status including, but not limited to, a sustained reduction in oxygen requirements over the previous 48 h, or extubated and/or no longer requiring mechanical ventilation following intubation for COVID-19 • Any other condition, including abnormal laboratory values, that, in the judgment of the investigator, could put the participant at increased risk, or would interfere with the conduct or planned analysis of the study
Interventions	Experimental: dociparstat sodium (DSTAT) • Dociparstat 4 mg/kg IV bolus on day 1, followed by dociparstat by continuous IV infusion for 24 h daily for 7 days (starting on day 1 and ending on day 8 (168 h)) • Dociparstat is a glycosaminoglycan derived from porcine heparin Comparator: placebo • Placebo IV bolus on day 1, followed by placebo by continuous IV infusion for 24 h daily for 7 days (starting on day 1 and ending on day 8 (168 h)) • 0.9% normal saline

Outcomes	Primary
	• Proportion of participants who are alive and free of invasive mechanical ventilation (time frame: through day 28)
	  ◦ Alive and free of invasive mechanical ventilation
	Secondary
	• All-cause mortality (time frame: through day 28)
	  ◦ Time to all-cause mortality

Notes	NCT04389840 | No data provided

Lins 2020

Study name	CoV-Hep Study: randomized and paired clinical trial comparing regional anticoagulation modalities in continuous venous venous hemodialysis in patients with COVID-19
Starting date	29 June 2020
Contact information	Paulo Lins, MD University of São Paulo General Hospital São Paulo, SP, Brazil, 05403-010 +55.11.98279-2696 | paulo.lins@hc.fm.usp.br

Lins 2020 *(Continued)*

Methods	Open-label, 2-armed, parallel RCT
Participants	90 participants, ≥ 18 years, female and male Inclusion criteria: • Confirmed or probable SARS-CoV-2 infection • Presence of acute kidney injury with indication and agreement between ICU and nephrology teams for the introduction of renal CVVHD Exclusion criteria: • Hypersensitivity to any of the substances used in the study (citric acid dextrosol 2.2% and UFH) • Previous diagnosis of coagulopathy or thrombophilia • Contraindication to the use of UFH by the assistant team • Risk of citrate poisoning - (lactate > 30 mg/dL, INR > 2.5, total bilirubin > 15mg/dL) • Pregnancy
Interventions	Experimental: • Participants on continuous haemodialysis (blood flow 150 mL/min, dose of 30 mL/kg/h) receiving anticoagulation with sodium citrate at 4 mmol/L associated with UFH at 10 U/kg/h • Addition of UFH to CVVHD system already running under citrate regional anticoagulation Comparator • Participants on continuous haemodialysis (blood flow 150 mL/min, dose of 30 mL/kg/h) receiving anticoagulation with sodium citrate at 4 mmol/L

Outcomes	Primary
	
	• Clotted dialyzers (time frame: Day 3 of dialysis)
	  ◦ The percentage of clotted dialyzers within 72 h in each of the studied groups.
	
	Secondary
	
	• Time-free of clotting (time frame: day 3 of dialysis)
	  ◦ Number of h until a dialyser clots in the first 72 h of dialysis
	• Number of dialysers used (time frame: day 3 of dialysis)
	  ◦ The amount of dialysers used in the first 72 h of haemodialysis
	• Pressure variation (time frame: day 3 of dialysis)
	  ◦ Variation in dialysis system and vascular access pressures in the first 72 h of dialysis
	• Urea sieving (time frame: day 3 of dialysis)
	  ◦ Variation in urea sieving between the first, second and third days of dialysis
	• Downtime of dialysis (time frame: day 3 of dialysis)
	  ◦ Time of dialysis stop due to clotting in the first 72 h

Notes	NCT04487990 | No data provided |

Marietta 2020

Study name	Randomised controlled trial comparing high versus low LMWH dosages in hospitalised patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation
Starting date	1 June 2020
Contact information	Marco Marietta, MD

Marietta 2020 *(Continued)*

	Azienda Ospedaliero-Universitaria di Modena, Italy 0594224640 ext +39 | marco.marietta@unimore.it
Methods	Multicentre, open-label, investigator-sponsored, 2-arm, parallel-assignment RCT

Participants	300 participants, 18-80 years, female and male
	Inclusion criteria (all required)
	• Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material)
	• Severe pneumonia defined by the presence of at least one of the following criteria:
	  ○ respiratory rate ≥ 25 breaths/min
	  ○ arterial oxygen saturation ≤ 93% at rest on ambient air
	  ○ PaO2/FiO2 ≤ 300 mmHg
	• Coagulopathy, defined by the presence of at least one of the following criteria:
	  ○ D-dimer > 4 times the ULN reference range
	  ○ sepsis-induced coagulopathy score > 4
	• No need for invasive mechanical ventilation
	Exclusion criteria
	• Invasive mechanical ventilation
	• Thrombocytopenia (platelet count < 80.000 mm^3)
	• Coagulopathy: INR > 1.5, aPTT ratio > 1.4
	• Impaired renal function (eGFR calculated by CKD-EPI creatinine equation < 30 mL/min)
	• Known hypersensitivity to enoxaparin
	• History of HIT
	• Presence of active bleeding or a pathology susceptible of bleeding in presence of anticoagulation (e.g. recent haemorrhagic stroke, peptic ulcer, malignant cancer at high risk of haemorrhage, recent neurosurgery or ophthalmic surgery, vascular aneurysms, arteriovenous malformations)
	• Concomitant anticoagulant treatment for other indications (e.g. atrial fibrillation, VTE, prosthetic heart valves)
	• Concomitant double antiplatelet therapy
	• Administration of therapeutic doses of LMWH, fondaparinux, or UFH for > 72 h before randomisation; prophylactic doses are allowed
	• Pregnancy or breastfeeding or positive pregnancy test
	• Presence of other severe diseases impairing life expectancy (e.g. patients are not expected to survive 28 days given their pre-existing medical condition)
	• Lack or withdrawal of informed consent

Interventions	Experimental: high-dose LMWH: 70 IU/kg twice daily, other name: Inhixa Comparator: low-dose LMWH: enoxaparin 4000 IU daily

Outcomes	Primary
	• Clinical worsening, defined as the occurrence of at least 1 of the following events, whichever comes first: (time frame: through study completion, up to 30 days)
	  • Death
	  • Acute myocardial infarction
	  • Objectively confirmed, symptomatic arterial or VTE
	  • Need for either non-invasive - CPAP or NIV - or invasive mechanical ventilation for participants, who are in standard oxygen therapy by delivery interfaces at randomisation
	  • Need for invasive mechanical ventilation for participants, who are in non-invasive mechanical ventilation at randomisation
	Secondary

Marietta 2020 *(Continued)*

- Any of the following events occurring within the hospital stay (time frame: through study completion, up to 30 days)
  - Death
  - Acute myocardial infarction
  - Objectively confirmed, symptomatic arterial or VTE
  - Need for either non-invasive - CPAP or NIV - or invasive mechanical ventilation for participants, who are in standard oxygen therapy by delivery interfaces at randomisation
  - Need for invasive mechanical ventilation for participants, who are in non-invasive mechanical ventilation at randomisation
  - Improvement of laboratory parameters of disease severity, including: D-dimer level, plasma fibrinogen levels, mean platelet volume, lymphocyte/neutrophil ratio, IL-6 plasma levels
- Mortality at 30 days (time frame: 30 days). Information about participants' status will be sought in those who are discharged before 30 days on day 30 from randomisation

Notes	NCT04408235 | EudraCT 2020-001972-13 | No data provided

NCT04333407

Study name	Preventing cardiac complication of COVID-19 disease with early acute coronary syndrome therapy: a randomised controlled trial
Starting date	3 April 2020
Contact information	Alena Marynina Charing Cross Hospital, London, UK 07776 224520 | alena.marynina@nhs.net
Methods	Multicentre, open-label RCT with 2 parallel arms, 1:1
Participants	3170 participants, ≥ 18 years, female and male Inclusion criteria • Confirmed COVID-19 infection • Age ≥ 40 years, or diabetes, or known coronary disease, or hypertension • Requires hospital admission for further clinical management Exclusion criteria • Clear evidence of cardiac pathology needing ACS treatment • Myocarditis with serum troponin > 5000 • Bleeding risk suspected e.g. recent surgery, history of GI bleed, other abnormal blood results (Hb < 10 g/dL, platelets < 100, any evidence of DIC) • Study treatment may negatively impact standard best care (physician discretion) • Unrelated co-morbidity with life expectancy < 3 months • Pregnancy • Age: < 18 years or > 85 years
Interventions	Experimental: active arm • Drug: aspirin 75 mg. If participant not on aspirin, add aspirin 75 mg once daily unless contraindicated • Drug: clopidogrel 75 mg. If participant not on clopidogrel or equivalent, add clopidogrel 75 mg once daily unless contraindicated

NCT04333407 *(Continued)*

	• Drug: rivaroxaban 2.5 mg. If participant not on an anticoagulation, add rivaroxaban 2.5 mg twice a day unless contraindicated. If participant on DOAC then change to rivaroxaban 2.5 mg unless contraindicated • Drug: atorvastatin 40 mg. If participant not on a statin, add atorvastatin 40 mg once daily unless contraindicated • Drug: omeprazole 20 mg. If participant not on a proton pump inhibitor, add omeprazole 20 mg once daily Comparator: no intervention
Outcomes	Primary • All-cause mortality at 30 days after admission (time frame: at 30 days after admission) Secondary • Absolute change in serum troponin from admission to peak value (time frame: within 7 days and within 30 days of admission). Absolute change in serum troponin from admission (or from suspicion/diagnosis of COVID-19 if already an inpatient) measurement to peak value (measured using high-sensitivity troponin assay). (Phase I interim analysis) • Discharge rate (time frame: at 7 days and 30 days after admission). Discharge rate: proportion of participants discharged (or documented as medically fit for discharge) • Intubation rate (time frame: at 7 days and at 30 days after admission). Intubation rate: proportion of participants who have been intubated for mechanical ventilation
Notes	NCT04333407 | No data provided

NCT04344756

Study name	Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients CORIMUNO-COAG trial
Starting date	20 April 2020
Contact information	Tristan Mirault Assistance Publique - Hôpitaux de Paris, France 1 56 09 50 41 ext 33 | tristan.mirault@aphp.fr
Methods	Randomised clinical trial with 2 parallel arms, 1:1, stratified on disease severity (ventilation or not)

Participants	808 participants, ≥ 18 years, female and male
	
	Inclusion criteria
	
	• Group 1: participants not requiring ICU at admission with mild disease to severe pneumopathy according to the WHO criteria of severity of COVID-19 pneumopathy, and with symptom onset before 14 days, with need for oxygen but no NIV or high flow
	• Group 2 :
	  ◦ respiratory failure AND requiring mechanical ventilation
	  ◦ WHO progression scale ≥ 6
	  ◦ no do-not-resuscitate order
	
	Exclusion criteria
	
	• Participants with contraindications to anticoagulation
	  ◦ Congenital haemorrhagic disorders

NCT04344756 *(Continued)*

- Hypersensitivity to tinzaparin or UHF or to any of the excipients
- Current or history of immune-mediated HIT
- Active major haemorrhage or conditions predisposing to major haemorrhage. Major haemorrhage is defined as fulfilling any one of these 3 criteria:
  - occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine or intramuscular with compartment syndrome)
  - causes a fall in haemoglobin level of ≥ 20 g/L (1.24 mmol/L)
  - leads to transfusion of ≥ 2 units of whole blood or red blood cells
- Septic endocarditis

- Participants with need for anticoagulant therapy, e.g. atrial fibrillation, VTE, mechanical valve, etc

Interventions	Experimental: tinzaparin or UFH • Tinzaparin Innohep 175 IU/kg/24 h for 14 days if CrCl Cockcroft ≥ 20 mL/min, otherwise UFH (Calciparine, Héparine Sodique Choay) SC or IV with an anti-Xa target between 0.5 and 0.7 IU/mL for 14 days Comparator: standard care • Control participants will receive the best standard care and a SC preventive anticoagulation for at least 14 days with enoxaparin 4000 IU/24 h, tinzaparin 3500 IU/24 h or dalteparin 5000 IU/24 h if CrCl (Cockcroft) ≥ 30 mL/min or UFH 5000 IU/12 h if CrCl < 30 mL/min
Outcomes	Primary • Survival without ventilation (NIV or mechanical ventilation) (time frame: day 14) group 1 • ventilator-free survival (time frame: day 28) group 2 Secondary • WHO progression scale ≤ 5 (time frame: day 4) range from 0 (healthy) to 10 (death) values ≤ 5 correspond to the absence of any oxygen supply beside nasal or facial mask • WHO progression scale (time frame: day 4, 7 and 14) range from 0 (healthy) to 10 (death) • Overall survival (time frame: day 14, 28 and 90) • Length of hospital stay (time frame: day 28) • Length of ICU stay (time frame: day 28) • Time to oxygenation supply independency (time frame: day 28) • Time to ventilator (non-invasive or invasive) (time frame: day 28) • Rate of AKI (time frame: day 28) according to AKI classification system • Time to renal replacement therapy initiation (time frame: day 28) • Rate of clinically overt PE or proximal DVT (time frame: day 14 and day 90) confirmed by objective testing • Rate of clinically overt arterial thrombosis (time frame: day 14 and day 90) confirmed by objective testing • Rate of unscheduled central venous catheter replacement for catheter dysfunction (time frame: day 28) • Rate of central venous catheter-related DVT (time frame: day 28) as a thrombus extending from the catheter into the lumen of the deep vein where the catheter is inserted diagnosed with radiologic imaging in case of a clinical suspicion of upper/lower limb DVT or PE or compulsory catheter removal • Rate of unscheduled indwelling arterial catheter replacement for catheter dysfunction (time frame: day 28) • Rate of acute clotting leading to the replacement the renal replacement therapy circuit stratified by regional citrate anticoagulation or not (time frame: day 28) • Time to acute clot formation within the oxygenator (acute oxygenator thrombosis) leading to the exchange of an ECMO system (time frame: day 28)

NCT04344756 *(Continued)*

	• Time to acute clot formation within the pump head (pump head thrombosis) leading to the exchange of an ECMO system (time frame: day 28) • Incidence of AEs (time frame: day 28)
Notes	NCT04344756 | APHP200389-6 | No data provided

NCT04345848

Study name	Preventing COVID-19-associated thrombosis, coagulopathy and mortality with low- and high-dose anticoagulation: a randomized, open-label clinical trial
Starting date	28 April 2020
Contact information	Marc Blondon University Hospital, Geneva, Switzerland +41.22.372.92.92 | marc.blondon@hcuge.ch
Methods	Prospective, multicentre, single-blind (outcomes assessor), 2-armed, parallel-assignment RCT
Participants	200 participants, ≥ 18 years, female and male Inclusion criteria Adult patient with COVID-19 infections, admitted to: • an acute non-critical medical ward with admission D-dimer levels > 1000 ng/mL, or • an acute critical ward (ICU, intermediate care unit) Exclusion criteria • Ongoing or planned therapeutic anticoagulation for any other indication • Contra-indication to therapeutic anticoagulation • Hypersensitivity to heparin • Personal history of HIT • Suspected or confirmed bacterial endocarditis • Bleeding events or tendency due to a suspected or confirmed haemostatic bleeding disorder • Organic lesion prone to bleeding • Platelet count < 50 G/L, Hb level < 80 g/L • Ongoing or recent (< 30 days) major bleeding, ischaemic stroke, trauma, surgery • Use of dual antiplatelet therapy • Pregnancy • Bodyweight < 40 kg or > 150 kg • End-of-life care setting • Unwillingness to consent • Ongoing participation in a COVID-19 randomised clinical trial testing another therapeutic intervention
Interventions	Experimental: therapeutic anticoagulation Participants will be treated with therapeutic doses of SC LMWH (enoxaparin) or IV UFH, from admission until the end of hospital stay or clinical recovery Comparator: prophylactic anticoagulation

NCT04345848 *(Continued)*

	Participants will be treated with prophylactic doses of SC LMWH (enoxaparin) or UFH, from admission until the end of hospital stay or clinical recovery. If hospitalised in the ICU, they will receive an augmented thromboprophylaxis regimen as standard care.
Outcomes	Primary • Composite outcome of arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality (time frame: 30 days). Risk of arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality Secondary • Arterial thrombosis (time frame: 30 days). Risk of ischaemic stroke, myocardial infarction and/or limb ischaemia • VTE (time frame: 30 days). Risk of symptomatic VTE or asymptomatic proximal leg DVT • Disseminated intravascular coagulation (time frame: 30 days). Risk of DIC • All-cause mortality (time frame: 30 days). Risk of all-cause mortality • Risk of SIC (time frame: 30 days) • Risk of ARDS (time frame: 30 days) • Durations of hospital stay, ICU stay, ventilation (time frame: 30 days). Number of days with these care processes • SOFA score (time frame: 30 days). Highest score per participant • Clinical deterioration (time frame: 30 days). Risk of clinical deterioration Other outcome • Risk of ISTH-defined major bleeding (time frame: 30 days) • Risk of ISTH-defined clinically relevant non-major bleeding (time frame: 30 days) • Risk of documented HIT (time frame: 30 days)
Notes	NCT04345848 | No data provided

NCT04352400

Study name	RAndomized clinical trial in COvid19 patients to assess the efficacy of the transmembrane protease serine 2 (TMPRSS2) inhibitor NAfamostat (RACONA Study)
Starting date	1 April 2020
Contact information	Gian Paolo Rossi University Hospital Padova, Italy 00390498217821 | gianpaolo.rossi@unipd.it
Methods	Multicentre, double-blind, 2-armed, parallel-assignment RCT

Participants	256 participants, 18-85 years, female and male
	Inclusion criteria
	• Hospitalised, COVID-19-positive, between 18 and ≤ 85 years of age
	• Signed informed consent form
	• Body temperature > 37.3 °C
	• Oxygenation criterion (any of the following):
	  ○ oxygen saturation ≤ 94% on room air
	  ○ PaO2/FiO2 ratio ≤ 300 mmHg but > 100 mmHg, if participant on supplemental oxygen

NCT04352400 *(Continued)*

- SpO2/FiO2 < 200 if no arterial blood gas available
- Respiratory rate (RR) ≥ 25 breaths/min

Exclusion criteria

- Pregnant or lactating women
- Unwillingness or inability to complete the study
- Rapidly deteriorating clinical condition or low likelihood to complete the study according to the investigator
- eGFR < 30 mL/min/m^2 assessed with CKD-EPI formula
- Current or chronic history of liver disease (Child-Pugh score ≥ 10), or known hepatic or biliary abnormalities
- Participation in a clinical trial with an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)
- participants requiring high doses of loop diuretics (i.e. > 240 mg furosemide daily) with significant intravascular volume depletion, as assessed clinically
- History of allergy
- History of sensitivity to heparin or HIT
- Unstable haemodynamics in the preceding 4 h (SBP < 90 mmHg, and/or vasoactive agents required)
- Haemoglobin < 7 at time of drug infusion. Transfusion is allowed to increase haemoglobin levels before entry into the study
- Malignancy or any other condition for which estimated 6-month mortality > 50%
- Arterial blood pH < 7.2
- Known evidence of chronic interstitial infiltration at imaging
- Known hospitalisation within the past 6 months for respiratory failure (PaCO2 > 50 mmHg or PaO2 < 55 mmHg, or oxygen saturation < 88% on FiO2 = 0.21)
- Known chronic vascular disease resulting in severe exercise restriction (i.e. unable to perform household duties)
- Known secondary polycythaemia, severe pulmonary hypertension, or ventilator dependency
- Known vasculitis with diffuse alveolar haemorrhage
- Pre-existing renal failure on haemodialysis or peritoneal dialysis requiring renal replacement therapy
- ECMO
- Immunosuppressive treatment
- Participant in studies for COVID-19 within 30 days before
- Unstable haemodynamics in the preceding 4 h (MAP ≤ 65 mmHg, or SAP < 90 mmHg, DAP < 60 mmHg, and vasoactive agents required)
- Hyperkalemia, i.e. serum K+ levels > 5.0 mEq/L
- Severe active bleeding
- Any other uncontrolled comorbidities that increase the risks associated with the study drug administration, as assessed by the medical expert team

Interventions	Experimental: nafamostat mesilate, administered IV as a continuous infusion Comparator: placebo, administered IV as a continuous infusion
Outcomes	Primary • Time-to-clinical improvement (time frame: day 1 until day 28). Time-to-clinical improvement (time from randomisation to an improvement of 2 points (from the status at randomisation) on a 7-category ordinal scale or live discharge from the hospital, whichever came first Secondary

NCT04352400 *(Continued)*

- Responders (time frame: day 1 until day 28). Rate of participants showing improvement of 2 points in 7-category ordinal scale (with 7 points the worst) (PubMed ID: 32187464)
- Critical or dead participants (time frame: day 1 until day 28). Proportion of participants who will progress to critical illness/death
- PaO2/FiO2 ratio (time frame: day 1 until day 28). Change in PaO2/FiO2 ratio over time
- SOFA score over time (time frame: day 1 until day 28). Change SOFA score over time. The score ranges from 0-24 (with 24 the worst) (PubMed ID: 11594901)
- Hospitalisation (time frame: day 1 until day 28). Duration of hospitalisation in survivors (days)
- Mechanical ventilation (time frame: day 1 until day 28). Number of participants who require ventilation
- Mechanical ventilation duration (time frame: day 1 until day 28). Duration of ventilation (days)
- Cardiovascular disease (time frame: day 1 until day 28). Proportion of participants who develop arrhythmia, or myocardial infarction, or other cardiovascular disease not present at the baseline

Notes	NCT04352400 | No data provided

NCT04366960

Study name	Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: comparison of 40 mg o.d. versus 40 mg b.i.d. a randomized clinical trial
Starting date	14 May 2020
Contact information	Nuccia Morici Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda, Milano, Italy +396444 ext 2565 | nuccia.morici@ospedaleniguarda.it
Methods	Prospective, multicentre, open-label, 1:1, 2-armed, parallel-assignment RCT
Participants	2712 participants, ≥ 18 years, female and male Inclusion criteria • All-comers patients aged ≥ 18 years and admitted to hospital with laboratory-confirmed SARS-CoV-2 infection Exclusion criteria • Patients admitted directly to an ICU • Estimated CrCl < 15 mL/min/1.73 m^2 • Patients needing anticoagulant for prior indication • Participants involved in other clinical studies • Any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
Interventions	Experimental: 40 mg SC enoxaparin twice a day Comparator: 40 mg SC enoxaparin once a day
Outcomes	Primary • Incidence of VTE detected by imaging (time frame: 30 days). DVT events diagnosed by serial compression ultrasonography and PE events diagnosed by CT scan

NCT04366960 *(Continued)*

	Secondary • In-hospital major complications (time frame: 30 days). Death, VTE, use of mechanical ventilation, stroke, acute myocardial infarction and admission to an ICU • Number of DVT events (time frame: 30 days). DVT events diagnosed by serial compression ultrasonography • Sequential organ failure assessment (time frame: 30 days). Maximum SOFA score comparison between the 2 groups. The SOFA score ranges from 0-24. Higher SOFA score is associated with a greater risk of death or prolonged ICU stay • C-reactive protein (time frame: 30 days). To compare C-reactive protein levels as % above the upper reference limit) among the 2 groups • Interleukin-6 (time frame: 30 days). To compare Interleukin-6 levels as % above the upper reference limit) among the 2 groups • D-dimer (time frame: 30 days). To compare D-dimer levels as % above the upper reference limit) among the 2 groups • hs-troponin levels (time frame: 30 days). To compare hs-troponin levels as % above the upper reference limit) among the 2 groups • ARDS (time frame: 30 days). To compare the incidence of SARS-CoV-2-related ARDS between the 2 groups • Hospital stay (time frame: 30 days). To compare length of hospital stay between the 2 groups • Right ventricular function (time frame: 30 days). To compare measures of right ventricular function at transthoracic echocardiography or CT between admission and follow-up, whenever available • Number of PE events (time frame: 30 days). PE events diagnosed by CT scan
Notes	NCT04366960 | No data provided

NCT04367831

Study name	Intermediate or prophylactic-dose anticoagulation for venous or arterial thromboembolism in severe COVID-19: a cluster based randomized selection trial (IMPROVE-COVID)
Starting date	2 May 2020
Contact information	Sahil A. Parikh Columbia University, New York, New York, USA 212-305-7060 | sap2196@cumc.columbia.edu
Methods	Prospective, single-centre, single-blinded (outcomes assessor), 2-armed, parallel-assignment, cluster-RCT
Participants	100 participants, ≥ 18 years, female and male Inclusion criteria • Confirmed diagnosis of COVID-19 by RT-PCR • New admission to eligible ICUs within 5 days. Transfer from non-participating to participating ICU is eligible if otherwise meets eligibility criteria. Patients transferred between participating ICUs will maintain initial treatment assignment. Patients not on therapeutic anticoagulation and who were already admitted to participating ICU within 5 days of trial initiation are additionally eligible. Exclusion criteria • Weight < 50 kg

NCT04367831 *(Continued)*

- Contraindication to anticoagulation in the opinion of the treating clinician including overt bleeding platelet count < 50,000; BARC major bleeding in the past 30 days; GI bleeding within 3 months; history of intracranial haemorrhage; ischemics stroke within the past 2 weeks; craniotomy/major neurosurgery within the past 30 days; cardiothoracic surgery within the past 30 days; intra-abdominal surgery within 30 days prior to enrolment; head or spinal trauma in the last months; history of uncorrected cerebral aneurysm or arteriovenous malformation (AVM); intracranial malignancy; presence of an epidural or spinal catheter; recent major surgery within the last 14 days; decrease in haemoglobin > 3 g/dL over the last 24 h; allergic reaction to anticoagulants (e.g. HIT) as documented in the electronic health records; ECMO support or other mechanical circulatory support
- Severe chronic liver dysfunction (history of portosystemic hypertension (HTN), oesophageal varices, or ≥ Child-Pugh class C or similar; Model For End-Stage Liver Disease (MELD) scores), abnormality in liver function tests (AST, ALT, bilirubin) 5 times > ULN
- A history of congenital bleeding diatheses or anatomical anomaly that predisposes to haemorrhage (e.g. haemophilia, hereditary hemorrhagic telangiectasia)
- Treating physician preference for therapeutic anticoagulation
- Enrolment in other concurrent studies related to anticoagulant or antiplatelet therapy
- Existing treatment with therapeutic anticoagulation during the previous 7 days of hospitalisation prior to ICU admission (e.g. for VTE, atrial fibrillation, mechanical valve, etc).
- Do-not-resuscitate (DNR)/do-not-intubate (DNI) or comfort measures only (CMO) orders prior to randomisation

Interventions	Experimental: intermediate-dose anticoagulation UFH infusion at 10 units/kg/h with goal anti-Xa 0.1 -0.3U/mL If estimated GFR ≥ 30 mL/min: enoxaparin 1 mg/kg SC daily Comparator: enoxaparin prophylactic dose following local guideline If estimated GFR ≥ 30 mL/min (stable kidney function): • BMI < 40 kg/m^2: enoxaparin 40 mg SC daily • BMI 40-50 kg/m^2: enoxaparin 40 mg SC every 12 h • BMI > 50 kg/m^2: enoxaparin 60 mg SC every 12 h UFH at 5000-7500 units SC every 8 h
Outcomes	Primary • Total number of participants with clinically relevant venous or arterial thrombotic events in ICU (time frame: discharge from ICU or 30 days). Composite of being alive and without clinically-relevant venous or arterial thrombotic events at discharge from ICU (without transfer to another ICU or palliative care unit/hospice) or at 30 days (if ICU duration lasted 30 days or longer) Secondary • Total number of participants with in-hospital clinically relevant venous or arterial thrombotic events (time frame: discharge from hospital or 30 days). Composite of being alive and without clinically-relevant venous or arterial thrombotic events at discharge from ICU (without transfer to another ICU or palliative care unit/hospice) or at 30 days (if ICU duration lasted 30 days or longer) • ICU length of stay (time frame: discharge from ICU or 30 days). Length of stay measured in days • Total number of participants with the need for renal replacement therapy in the ICU (time frame: discharge from hospital or 30 days). The impact of intermediate-dose anti-coagulation compared with prophylactic anti-coagulation on rates of AKI and renal recovery in the ICU will be measured with the total number of participants who need renal replacement therapy in the ICU • Total number of participants with major bleeding in the ICU (time frame: discharge from hospital or 30 days). Major bleeding will be assessed by BARC criteria, also explored by ISTH and Thrombolysis in Myocardial Infarction (TIMI) criteria

NCT04367831 *(Continued)*

	• Hospital length of stay (time frame: discharge from hospital or 30 days). Length of stay measured in days
Notes	NCT04367831 | No data provided

NCT04373707

Study name	Effectiveness of weight-adjusted prophylactic low molecular weight heparin doses compared with lower fixed prophylactic doses to prevent venous thromboembolism in COVID-2019. The multicenter randomized controlled open-label trial COVI-DOSE
Starting date	13 May 2020
Contact information	Yohann Bernard Central Hospital, Nancy, France +33.3.83.15.52.72 | y.bernard@chru-nancy.Fr
Methods	Multicentre, open-label, 2-armed, parallel-assignment RCT; stratified on disease severity (admission to ICU or not)
Participants	602 participants, ≥ 18 years, female and male Inclusion criteria • Adult patient hospitalised for a probable/confirmed COVID-19 infection (confirmed by serology/PCR or by radiologic signs of COVID-19 pneumonia in the setting of clinical and laboratory abnormalities suggestive of a SARS-CoV-2 infection) • Signed informed consent • Patient affiliated to Social Security Exclusion criteria • Renal insufficiency with a GFR < 15 mL/min/1.73 m^2 • AKI KDIGO3 • Prophylactic dose of LMWH for > 3 days • Curative dose of LMWH for > 1 day • Recurrent catheter/haemodialysis access thromboses • ECMO required in the next 24 h • Contraindication to LMWH • High bleeding risk (e.g. uncontrolled severe systemic hypertension, recent major bleeding, disseminated intravascular coagulopathy, thrombocytopenia < 75 g/L) • History of HIT • Contraindication to blood-derived products • Impossibility to perform a doppler ultrasound of the lower limbs (e.g. above-the-knee amputation, severe burn injuries) • Expected death in the next 48 h • Vulnerable patients according to articles L. 1121-5, L. 1121-7 et L1121-8 of French Public Health Code
Interventions	Experimental: weight-adjusted prophylactic dose LMWH For example (enoxaparin): • 4000 IU twice a day in participants < 50 kg

NCT04373707 *(Continued)*

	• 5000 IU twice a day in participants 50-70 kg • 6000 IU twice a day in participants 70-100 kg • 7000 IU twice a day in participants above 100 kg Other names: tinzaparin, nadroparin, dalteparin Comparator: low prophylactic dose of LMWH For example (enoxaparin): from 4000 IU once a day in participants admitted in medical ward to 4000 IU twice a day in participants admitted in the ICU. In participants with severe renal insufficiency (GFR = 15-30 mL/min/1.73 m^2), LMWH doses will be reduced by 50%. Other names: tinzaparin, nadroparin, dalteparin
Outcomes	Primary • VTE (time frame: 28 days). Risk of DVT or PE or VTE-related death Secondary • Major bleeding (time frame: 28 days). Risk of major bleeding defined by the ISTH • Major bleeding and clinically relevant non-major bleeding (time frame: 28 days). Risk of major bleeding and clinically relevant non-major bleeding defined by the ISTH • Net clinical benefit (time frame: 28 days and 2 months). Risk of VTE and major bleeding • VTE at other sites (time frame: 28 days). Risk of venous thrombosis at other sites: e.g. superficial vein, catheters, haemodialysis access, ECMO, splanchnic, encephalic, upper limb • Arterial thrombosis (time frame: 28 days). Risk of arterial thrombosis at any site • All-cause mortality (time frame: 28 days and 2 months). Risk of all-cause mortality • Factors associated with the risk of VTE (time frame: 28 days). Identification of associations between the risk of VTE and clinical (e.g. past medical history of thrombosis, cardiovascular risk factors, treatments, severity of COVID-19) and laboratory variables (e.g. D-dimers, fibrinogen, C-reactive protein) collected in the electronic Case Report Form
Notes	NCT04373707 | 2020-001709-21 | No data provided

NCT04377997

Study name	A randomized, open-label trial of therapeutic anticoagulation in COVID-19 patients with an elevated D-dimer
Starting date	15 May 2020
Contact information	Mazen Albaghdadi Massachusetts General Hospital, USA 617-726-7400 | MALBAGHDADI@mgh.harvard.edu
Methods	Open-label, 2-armed, parallel-assignment RCT
Participants	300 participants, ≥ 18 years, female and male Inclusion • COVID-19-positive on admission or during hospitalisation (having been tested within the past 5 days) with symptoms consistent with COVID-19 including fever (≥ 38 °C (100.4 F)), pneumonia, symptoms of lower respiratory illness (e.g. cough, difficulty breathing), loss of smell or taste, myalgias, pharyngitis, or diarrhoea

NCT04377997 *(Continued)*

	• Admitted to the regular medical floor or ICU without severe SARS (P/F ratio<100) • Elevated D-dimer (> 1.5 g/mL) • Age > 18 years and not older than 90 • Fibrinogen > 100 • Platelets > 50,000 • No prior intracranial haemorrhage or recent ischaemic stroke or TIA within 6 months • D-dimer > 1500 ng/mL • No other clinical indication for therapeutic anticoagulation (e.g. DVT, PE, atrial fibrillation, acute coronary syndromes, or ECMO) Exclusion • DIC according to the ISTH overt DIC definition • Haemoglobin < 8 g/dL • Hypersensitivity to heparin or heparin formulation including HIT • Thrombocytopenia: platelets < 50,000 platelets/µL • Uncontrolled or active/recent bleeding including intracranial haemorrhage, signs of active bleeding (e.g. blood transfusion within 30 days), any GI bleed within the past 6 months, or internal bleeding within the past 1 month • High bleeding risk: significant closed-head or facial trauma within 3 months, traumatic or prolonged CPR (> 10 min), or use of dual anti-platelet therapy • Known or suspected pregnancy • Recent (< 48 h) or planned spinal or epidural anaesthesia or puncture • If the patient is on other anticoagulants, antihistamines, NSAIDs (i.e. aspirin) or hydroxychloroquine • Uncontrolled hypertension
Interventions	Experimental: therapeutic anticoagulation group Higher dose (not described) of heparin (LMWH for most participants but UFH for those with morbid obesity or moderate to severe renal dysfunction) Comparator: standard care anticoagulation group There is no dose or drug description.
Outcomes	Primary • Risk of the composite efficacy endpoint of death, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, or haemodynamic shock (time frame: 12 weeks) • Risk of major bleeding event according to the ISTH definition (time frame: 12 weeks) Secondary • There is no description
Notes	NCT04377997 | No data provided

NCT04397510

Study name	Nebulized heparin vs. placebo for the treatment of COVID-19 induced lung injury
Starting date	1 June 2020
Contact information	Thomas Smoot

NCT04397510 *(Continued)*

	Frederick Health Hospital, Frederick, Maryland, USA
Methods	Multicentre, single-masking (outcomes assessor), investigator-sponsored, 2-armed, parallel-assignment RCT
Participants	50 participants, ≥ 18 years, female and male Inclusion criteria • Age ≥ 18 years • Admitted to the ICU • Positive COVID-19 PCR • Mechanical ventilation for ≤ 48 h • PaO2/FiO2 ≤ 300 Exclusion criteria • Heparin allergy • Active bleeding • Death or withdrawal of care anticipated by intensivist within 24 h • Platelets < 50,000 cells/µL • Clinically significant coagulopathy, as decided by the intensivist • O2-dependent at baseline
Interventions	Experimental: nebulised heparin 5000 units/mL IV formulation diluted with 3 mL of 0.9% sodium chloride. Dose: 10,000 units. Frequency: every 4 h. Duration: 10 days Comparator: placebo. 0.9% sodium chloride. Dose: 5 mL. Frequency: every 4 h. Duration: 10 days
Outcomes	Primary • Mean daily PaO2 to FiO2 ratio (time frame: 10 days) Secondary • Duration of mechanical ventilation (time frame: 30 days) • ICU length of stay (time frame: 30 days) • Mortality rate (time frame: 30 days) • Incidence of adverse drug events (time frame: 10 days)
Notes	NCT04397510 | FHHep518 | No data provided

NCT04406389

Study name	InterMediate ProphylACtic versus Therapeutic dose anticoagulation in critically ill patients with COVID-19: a prospective randomized study (The IMPACT Trial)
Starting date	13 October 2020
Contact information	Maria T DeSancho, MD, MSc Weill Cornell Medicine New York, New York, United States, 10065 646-962-2065 | mtd2002@med.cornell.edu

NCT04406389 *(Continued)*

Methods	Open-label, 2-armed, 1:1, parallel-assignment RCT
Participants	186 participants, ≥ 18 years, female and male Inclusion criteria: • Age >18 years old • COVID-19 positive on (RT-PCR) nasopharyngeal swab, or suspected COVID-19 infection with detectable SARS-CoV-2 IgG or IgM • ICU patient or non-ICU patient on invasive mechanical ventilation, BiPAP, 100% non-rebreather mask, or high-flow oxygen or supplemental oxygen of at least 4 L/min nasal cannula • D-dimer level > 700 ng/mL (3 times the ULN) Exclusion criteria: • Objectively documented DVT or PE • Patients in whom there is very high suspicion for PE and are on full-dose anticoagulation as per the treating physician • Platelets < 30,000 not due to DIC, based on ISTH criteria and American Society of Hematology (ASH) Frequently Asked Questions • Active bleeding that poses a contraindication to therapeutic anticoagulation in the opinion of the investigator • History of bleeding diathesis (e.g. haemophilia, severe von Willebrand disease, severe thrombocytopathy) • History of intracranial haemorrhage in the last 90 days • History of ischaemic stroke in the past 2 weeks • Major neurosurgical procedure in the past 30 days • Cardiothoracic surgery in the past 30 days • Intra-abdominal surgery in the past 30 days • Intracranial malignancy • Patients who require therapeutic anticoagulation for other reasons like atrial fibrillation, DVT, PE, or antiphospholipid syndrome

Interventions	Experimental: therapeutic-dose anticoagulation
	
	Participants will receive 1 of the following interventions, at their physician's discretion
	
	• UFH to target anti-Xa level 0.3-0.7 IU/mL or aPTT (according to institutional protocol)
	• Enoxaparin 1 mg/kg SC every 12 h
	• Argatroban (if HIT), dosed according to institutional protocol
	• Fondaparinux (if HIT and CrCl ≥ to 50 mL/min) dosed by weight:
	  ○ ≥ 100 kg: 10 mg daily
	  ○ < 100 kg but ≥50 kg: 7.5 mg daily
	  ○ < 50 kg: 5 mg daily
	
	Comparator: intermediate-dose prophylaxis
	
	Participants will receive 1 of the following interventions, at their physician's discretion
	
	• Enoxaparin 0.5 mg/kg SC every 12 h if CrCl ≥ 30 mL/min
	• Enoxaparin 0.5 mg/kg SC every 24 h if CrCl < 30 mL/min
	• If patient develops acute kidney injury: UFH 7500 units SC every 8 h
	• Fondaparinux (if history of HIT) 2.5 mg daily SC

Outcomes	Primary • 30-day mortality (time frame: 30 days)

NCT04406389 *(Continued)*

	Secondary • Length of ICU stay in days (time frame: 6 months) • Number of documented VTE, arterial thrombosis (stroke, myocardial infarction, other) and microthrombosis events (time frame: 6 months) • Number of major and clinically relevant non-major bleeding events (time frame: 6 months)
Notes	NCT04406389 | No data provided

NCT04409834

Study name	A multicenter, randomized-controlled trial to evaluate the efficacy and safety of antithrombotic therapy for prevention of arterial and venous thrombotic complications in critically-ill COVID-19 patients
Starting date	5 August 2020
Contact information	Vivian Baird-Zars Brigham and Women's Hospital Boston, Massachusetts, USA, 02459 800-385-4444 | vbaird-zars@bwh.harvard.edu
Methods	Multicentre, open-label, parallel-assignment RCT

Participants	750 participants, ≥ 18 years, female and male
	Inclusion criteria:
	• Age ≥18 years (male or female)
	• Acute infection with SARS-CoV2
	• Currently admitted to ICU
	Exclusion criteria:
	• Ongoing (> 48 h) or planned full-dose (therapeutic) anticoagulation for any indication
	• Ongoing or planned treatment with dual antiplatelet therapy
	• Contraindication to antithrombotic therapy or high risk of bleeding due to conditions including, but not limited to, any of the following:
	  ○ history of intracranial haemorrhage, known CNS tumour or CNS vascular abnormality
	  ○ active or recent major bleeding within the past 30 days with untreated source
	  ○ platelet count < 70,000 or known functional platelet disorder
	  ○ fibrinogen < 200 mg/dL
	  ○ INR > 1.9
	• History of HIT
	• Ischemic stroke within the past 2 weeks
	Patients who meet the following criterion are excluded from the second randomisation (antiplatelet therapy vs no antiplatelet therapy):
	• Ongoing or planned antiplatelet therapy, including aspirin monotherapy

Interventions	Experimental • Full-dose anticoagulation + antiplatelet therapy

NCT04409834 *(Continued)*

	◦ Full-dose anticoagulation: UFH IV continuous targeting aPTT of 1.5-2.5 times control, or enoxaparin 1 mg/kg SC every 12 h ◦ Anti-platelet therapy: clopidogrel 300 mg oral x 1, followed by clopidogrel 75 mg oral once daily • Full-dose anticoagulation + no antiplatelet therapy ◦ Full-dose anticoagulation: UFH IV continuous targeting aPTT of 1.5-2.5 times control, or enoxaparin 1 mg/kg SC every 12 h ◦ Prophylactic anticoagulation + antiplatelet therapy ◦ Standard prophylactic anticoagulation: enoxaparin 40 mg SC once daily or UFH 5000 IU SC three times/d ◦ Antiplatelet therapy: clopidogrel 300 mg oral x1, followed by clopidogrel 75 mg oral once daily Comparator • Prophylactic anticoagulation + no antiplatelet therapy • Standard prophylactic anticoagulation: enoxaparin 40 mg SC once daily or UFH 5000 IU SC three times/d
Outcomes	Primary • Primary endpoint: venous or arterial thrombotic events (time frame: 28 days or until hospital discharge, whichever earlier) Secondary • Key secondary endpoint: clinically evident venous or arterial thrombotic events (time frame: 28 days or until hospital discharge, whichever earlier)
Notes	NCT04409834 | No data provided

NCT04416048

Study name	Effect of anticoagulation therapy on clinical outcomes in moderate to severe coronavirus disease 2019 (COVID-19)
Starting date	15 June 2020
Contact information	Ulf Landmesser Charite University, Berlin, Germany +49 30 450 513 702 | ulf.landmesser@charite.de
Methods	Prospective, multicentre, event-driven, 2-armed, parallel-assignment RCT
Participants	400 participants, ≥ 18 years, female and male Inclusion criteria • Participant must be willing, understanding and able to provide written informed consent • Participant must be a man or a woman aged > 18 years at screening • Participant must have active moderate to severe COVID-19 confirmed by a positive SARS-CoV-2 PCR test in the last 14 days • At least 1 of the following features should be present: ◦ D-Dimer elevation > 1.5 ULN (age-adjusted cut-offs) ◦ cardiac injury reflected by an elevation in high-sensitive cardiac troponin > 2.0 ULN ◦ at least 1 of the following conditions: known coronary artery disease; known diabetes mellitus; active smoking

NCT04416048 *(Continued)*

- A woman of childbearing potential must have a negative serum or urine pregnancy test before randomisation occurs. Before randomisation, a woman must be either: postmenopausal, defined as > 45 years of age with amenorrhoea for at least 18 months, if menstruating: if heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g. condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel), or male partner sterilisation, consistent with local regulations regarding use of birth control methods for participants in clinical studies, for the duration of their participation in the study, or surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or not heterosexually active

Exclusion criteria:

- Participant has a very high bleeding risk: any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would have an unacceptable risk of bleeding, such as, but not limited to, the following:
  - any bleeding (defined as bleeding requiring hospitalisation, transfusion, surgical intervention, invasive procedures, occurring in a critical anatomical site, or causing disability) within 1 month prior to randomisation or occurring during index hospitalisation
  - major surgery, biopsy of a parenchymal organ, ophthalmic surgery (excluding cataract surgery), or serious trauma (including head trauma) within 4 weeks before randomisation
  - history of haemorrhagic stroke or any intracranial bleeding at any time in the past, evidence of primary intracranial haemorrhage on CT or magnetic resonance imaging scan of the brain, or clinical presentation consistent with intracranial haemorrhage. This applies as well to participants hospitalised for ischaemic stroke upon randomisation
  - participant has a history of or current intracranial neoplasm (benign or malignant), cerebral metastases, arteriovenous (AV) malformation, or aneurysm
  - active gastroduodenal ulcer, defined as diagnosed within 1 month or currently symptomatic or known AV malformations of the gastrointestinal tract
  - platelet count < 90,000/µL at screening
  - participants with the diagnosis of bronchiectasis, that due to the investigator's judgement are at an increased bleeding risk
- Participant has any of the following diseases in the medical history
  - active cancer (excluding non-melanoma skin cancer) defined as cancer not in remission or requiring active chemotherapy or adjunctive therapies such as immunotherapy or radiotherapy. Chronic hormonal therapy (e.g. tamoxifen, anastrozole, leuprolide acetate) for cancer in remission is allowed
  - any medical condition (e.g. atrial fibrillation) that requires use of any therapeutic parenteral or oral anticoagulant(s) (e.g. warfarin sodium or other VKA, Factor IIa or FXa inhibitors, fibrinolytics) concomitantly with study medication
  - participant has known allergies, hypersensitivity, or intolerance to rivaroxaban or any of its excipients
  - baseline estimated GFR < 30 mL/min/1.73 m^2 calculated using CKD-EPI formula
  - known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis), which is associated with coagulopathy or moderate or severe hepatic impairment.
  - known HIV infection
- Participant has undergone any of the following procedures or received any of the following drugs
  - received fibrinolysis during index hospitalisation
  - use of antiplatelet therapy with prasugrel or ticagrelor up to 7 days prior to randomisation. Other P2Y12 antagonists can be given. However, the use of concomitant antiplatelet therapy should be carefully considered. Acetylsalicylic acid > 100 mg/d and continuous NSAIDs should be avoided
  - use of dual antiplatelet therapy, such as aspirin plus clopidogrel during the study
- Participant is a woman who is pregnant or breastfeeding
- Known intolerance or history of hypersensitivity to the active substance or to any of the excipients of the investigational medicinal product
- Participants who are legally detained in an official institution

NCT04416048 *(Continued)*

	• Participants who may be dependent on the sponsor, the investigator or the study sites, are not eligible to enter the study
Interventions	Experimental: rivaroxaban Treatment with rivaroxaban 20 mg (15 mg for participants with an estimated GFR ≥ 30 mL/min/1.73 m^2 and < 50 mL/min/1.73 m^2) once daily for at least 7 days. In case of hospitalisation for > 7 days, the therapeutic treatment with rivaroxaban will be continued for the duration of the hospital stay until discharge. After at least 7 days of therapeutic treatment with rivaroxaban or after hospital discharge, the study dose of rivaroxaban will be adjusted as follows: • participants randomised to the rivaroxaban study arm will reduce daily dosage to 10 mg once daily, provided that they were not diagnosed with a condition requiring continued therapeutic anticoagulation • thromboprophylaxis therapy will be given for 28 days up to day 35 post-randomisation or even longer • if the participant cannot be discharged from the hospital prior to day 35 post-randomisation, the thromboprophylaxis phase will also start upon hospital discharge, but is then shorter than 28 days, because the study ends at day 60 post-randomisation. Other Name: Xarelto Comparator: standard care Participants will receive standard care treatment including prophylactic LMWH or UFH, when considered appropriate according to the judgment of the treating physician.
Outcomes	Primary • Composite endpoint of VTE (DVT and/or fatal or non-fatal PE), arterial thromboembolism, new myocardial infarction, non-hemorrhagic stroke, all-cause mortality or progression to intubation and invasive ventilation (time frame: 35 days post-randomisation) Secondary • Development of disseminated intravascular coagulation according to the ISTH criteria (time frame: 35 days post randomisation) • Number of days requiring invasive ventilation (time frame: 35 days post-randomisation) • Number of days requiring non-invasive ventilation (time frame: 35 days post-randomisation) • Improvement on a 7-category ordinal scale recommended by the WHO as clinical improvement scale for participants with respiratory infections (time frame: 35 days post-randomisation) scale range from 1-7; improvement means a reduction in the scale number of at least 1 point
Notes	NCT04416048 | 2020-002282-33 | No data provided

NCT04420299

Study name	A randomized, single-blind study with a parallel control group on the efficacy and safety of bemiparin at therapeutic dose vs. prophylactic dose in patients hospitalized for COVID-19
Starting date	4 June 2020
Contact information	Antonio Cubillo, MD Hospital Universitario HM Montepríncipe Recruiting Boadilla Del Monte, Madrid, Spain, 28660

NCT04420299 *(Continued)*

	+34 917567800 | secretaria@fundaciónhm.com
Methods	Single-blind, parallel-assignment RCT
Participants	120 participants, ≥ 18 years, female and male Inclusion criteria: • Informed consent • Aged ≥ 18 years • Patient with suspected COVID-19 and who meets hospitalisation criteria • D-dimer > 500 ng/mL • Clinical characteristics highly compatible with SARS-CoV-2 infection and confirmation by RT-qPCR at baseline or in the second sample in case of a first negative test and clinical suspicion remains • Patient admitted to hospital Exclusion criteria: • ICU admission criteria • Need for invasive or non-invasive mechanical ventilation • Pregnancy • CrCl < 30 mL/min (Cockroft-Gault) • Severe liver or pancreatic function disorder • Acute bacterial endocarditis and slow endocarditis • Patient previously anticoagulated (although it is allowed to have received heparin at a previous low dose without time limit) • Patient with high haemorrhagic risk due to previous medical-surgical history • Severe thrombocytopenia (< 80,000 platelets/mm^3) or known history of HIT • Active bleeding or increased risk of bleeding from haemostasis disorders or from organic lesions that are liable to bleed (e.g. active peptic ulcer, hemorrhagic stroke, aneurysms, or brain malignancies) • Damage or surgical interventions in the CNS, eyes and ears that have taken place in the last 2 months • Simultaneous participation in another clinical trial that could have a conflictive interaction with what it is intended to evaluate • Any situation that in the opinion of the researcher could interfere with the treatment or with the evolution of the patient
Interventions	Experimental: • Experimental - therapeutic bemiparin dose • SC dose of bemiparin at therapeutic dose for 10 days Comparator: • Control - prophylactic bemiparin dose • SC dose of bemiparin at prophylactic dose for 10 days

Outcomes	Primary
	
	• Combined worsening variable. Presence of any of the following will be considered worsening:
	  ◦ Death
	  ◦ ICU admission
	  ◦ Need for either non-invasive or invasive mechanical ventilation
	  ◦ Progression to moderate/severe respiratory distress syndrome according to objective criteria (Berlin definition)
	  ◦ VTE (DVT or PE) or arterial (acute myocardial infarction or stroke)

NCT04420299 *(Continued)*

	◦ Proportion of patients that worsen (time frame: day 10 +/- 1) Secondary • Mortality from any cause at day 28 (time frame: day 28) • Proportion of participants that requires admission to the ICU (time frame: from study start to day 28) • Proportion of participants requiring non-invasive mechanical ventilation (time frame: from study start to day 28) • Proportion of participants requiring invasive mechanical ventilation (time frame: from study start to day 28) • Proportion of participants with some organ failure (time frame: from study start to day 28) • Proportion of participants who have modified their oxygen therapy requirements between treatment assessment visit and baseline (time frame: from study start to day 28) • Proportion of participants with pathological angioTAC (time frame: at day 10 +/-1) • Proportion of participants with improvement in chest radiography (time frame: at day 10 +/-1) • Proportion and median hospital discharge between participants in both groups (time frame: from study start to day 28) • Titration score (time frame: from study start to day 28) • Ferritin score (time frame: from study start to day 28) • D-dimer modification score (time frame: from study start to day 28) • AEs (total and serious) (time frame: from study start to day 28) • Related AEs (total and serious) (time frame: from study start to day 28) • Clinically relevant major and non-major haemorrhages (time frame: from study start to day 28)
Notes	NCT04420299 | No data provided

NCT04444700

Study name	Utilização da enoxaparina em dose anticoagulante em pacientes hospitalizados com síndrome respiratória aguda grave por COVID-19
Starting date	4 July 2020
Contact information	Hassan Rahhal, MD Hospital das Clínicas da FMUSP São Paulo, SP, Brazil, 05402-000 +551126619033 | hassan.r@hc.fm.usp.br
Methods	Open-label, parallel-assignment RCT
Participants	462 participants, ≥ 18 years, female and male Inclusion criteria • laboratory-confirmed diagnosis of SARS-CoV-2 as per the WHO protocols • admitted to hospital • ≥ 18 years of age • oxygen saturation < 94% • informed consent from the patient (or legally authorised substitute decision maker) Exclusion criteria:

NCT04444700 *(Continued)*

	• pregnancy • haemoglobin < 80 g/L in the last 72 h • platelet count < 50 x 109/L in the last 72 h • known fibrinogen < 1.5 g/L (if testing deemed clinically indicated by the treating physician prior to the initiation of anticoagulation) • known INR > 1.8 (if testing deemed clinically indicated by the treating physician prior to the initiation of anticoagulation) • patient already on intermediate dosing of LMWH that cannot be changed (determination of what constitutes an intermediate dose is to be at the discretion of the treating clinician taking the local institutional thromboprophylaxis protocol for high-risk patients into consideration) • patient already on therapeutic anticoagulation at the time of screening (low- or high-dose nomogram UFH, LMWH, warfarin, DOAC (any dose of dabigatran, apixaban, rivaroxaban, edoxaban) • patient on dual antiplatelet therapy, when one of the agents cannot be stopped safely • known bleeding within the last 30 days requiring emergency room presentation or hospitalisation • known history of a bleeding disorder of an inherited or active acquired bleeding disorder • known history of HIT • known allergy to UFH or LMWH • admitted to the ICU at the time of screening • treated with non-invasive positive pressure ventilation or invasive mechanical ventilation at the time of screening

Interventions	Experimental: therapeutic anticoagulation
	• Therapeutic anticoagulation with enoxaparin 1 mg/kg twice daily will be administered until discharged from the hospital or after 7 days, whichever is longer, or death
	• If the patient is admitted to the ICU or requiring ventilatory support, we recommend the continuation of the allocated treatment as long as the treating physician is in agreement.
	Comparator: standard care
	• Standard care will be administered until discharged from the hospital or after 7 days, whichever is longer, or death
	• If BMI < 40 kg/m^2, the treating physician may select one of the following options considered appropriate and available in Brazil
	  ◦ Enoxaparin 40 mg once daily, enoxaparin 60 mg once daily, UFH 5000 twice daily, UFH 5,000 three times/d
	• If BMI ≥ 40 kg/m^2, the treating physician may select one of the following options considered appropriate and available in Brazil:
	  ◦ Enoxaparin 40 mg twice daily, UFH 7500 three times/d

Outcomes	Primary • Composite main outcome (time frame: up to 28 days) Secondary • All-cause death (time frame: 28 days) • Composite outcome of ICU admission or all-cause death (time frame: 28 days) • Major bleeding (time frame: 28 days) • Number of participants who received red blood cell transfusion (time frame: 28 days) • Number of participants with transfusion of platelets, frozen plasma, prothrombin complex concentrate, cryoprecipitate and/or fibrinogen concentrate (time frame: 28 days) • Number of hospital-free days alive up to day 28 (time frame: 28 days) • Number of ICU-free days alive up to day 28 (time frame: 28 days) • Number of ventilator-free days alive up to day 28 (time frame: 28 days) • Number of participants with VTE (time frame: 28 days) • Number of participants with arterial thromboembolism (time frame: 28 days)

NCT04444700 *(Continued)*

	• Number of participants with HIT (time frame: 28 days)
Notes	NCT04444700 | No data provided

NCT04485429

Study name	Efficacy assessment of methylprednisolone and heparin in patients with COVID-19 pneumonia: a randomized, controlled, 2x2 factorial study
Starting date	20 July 2020
Contact information	Eduardo M Rego, MD, PhD D'Or Institute for Research and Education Rio de Janeiro, Brazil 55 16 981110090 | edumrego@hotmail.com
Methods	Open-label, 2:2, parallel-assignment RCT

Participants	268 participants, ≥ 18 years, female and male
	Inclusion criteria:
	• Confirmed diagnosis of COVID-19 by RT-PCR or serology with presence of IgM-positive antibodies
	• Lung image (X-ray or chest CT) with involvement of at least 25% of the parenchyma
	• O2 saturation in ambient air ≤ 93%
	• Alteration of inflammatory tests
	  ◦ D-Dimer above the reference value and
	  ◦ elevation of C-reactive protein, ferritin or lactic dehydrogenase
	• Sign the consent form
	Exclusion criteria:
	• QT interval prolongation
	• Imminence of orotracheal intubation (intubation prediction in the first 4 h after randomisation)
	• Women who are pregnant or breastfeeding
	• Corticosteroid allergy or intolerance
	• Chronic corticosteroid users (prednisone equivalent > 10 mg daily)
	• Patients diagnosed with cancer with increased bleeding potential
	• Patients in haemodialysis
	• History of peptic ulcer
	• Herpes zoster infection
	• History or active treatment of TB
	• Systemic fungal infection
	• Use of anticoagulation due to previous pathology
	• Glaucoma
	• Live virus vaccine up to 90 days before randomisation
	• Known coagulopathy or thrombocytopenia (< 40,000/mm^3) or hypofibrinogenaemia (< 50 mg/dL)
	• Recent bleeding
	• Another limiting comorbidity for administering the therapies provided for in this protocol in researcher's opinion

Interventions	Experimental:

NCT04485429 *(Continued)*

	• Methylprednisolone + standard treatment
	  ○ Participants will receive the standard treatment and methylprednisolone
	• Full-dose heparin + standard treatment
	  ○ Participants will receive the standard treatment and full-dose heparin
	• Methylprednisolone + full-dose heparin + standard treatment
	  ○ Participants will receive the standard treatment, methylprednisolone and full-dose heparin
	
	Comparator: standard treatment
	
	• Participants will receive the standard treatment

Outcomes	Primary • Rate of invasive mechanical ventilation (time frame: 28 days) Secondary • Severity assessment by ordinal severity scale (time frame: 3 days, 7 days, 14 days, 28 days after randomisation) • Severity assessment by SOFA score (time frame: 3 days, 7 days, 14 days, 28 days after randomisation) • Length of hospital stay (time frame: 28 days) • Length of stay in ICU (time frame: 28 days) • Death rate (time frame: 14 days, 28 days, 60 days, 90 days after randomisation)
Notes	NCT04485429 | No data provided

NCT04508439

Study name	Effect of the use of anticoagulant therapy during hospitalization and discharge in patients with COVID-19 infection
Starting date	20 June 2020
Contact information	Omar Ramos-Peñafiel, MD, PhD Hospital Regional de Alta Especialidad de Ixtapaluca Mexico City, Ixtapaluca, Mexico, 56530 +525523351588 | christian.ramos.penafiel@gmail.com
Methods	Double-blind, 1:1, parallel-assignment RCT
Participants	130 participants, ≥ 18 years, female and male Inclusion criteria: • Patients with a diagnosis of COVID-19 infection confirmed by RQ-PCR requiring hospital care for the administration of supplemental oxygen Exclusion criteria: • Patients with life expectancy < 48h • Patients who require ventilatory support upon admission • Age > 75 years or with a history of atrial fibrillation • History of venous or arterial thrombosis • Severe neurological impairment

NCT04508439 *(Continued)*

	• Absence of a primary caregiver to supervise the administration of medication • History of cerebral haemorrhage • History of previous use of oral anticoagulants • History of major surgery 30 days prior to admission • Uncontrolled systemic arterial hypertension • KDIGO stage III chronic kidney disease or less • Haemodialysis or peritoneal dialysis treatment • History of active or inactive cancer • Pregnant or postpartum patients
Interventions	Experimental: prophylactic enoxaparin • Enoxaparin dose of 1 mg/kg/dose twice daily Comparator: therapeutic enoxaparin • Enoxaparin dose of 1 mg/kg/dose daily
Outcomes	Primary • LMWH (enoxaparin) and ventilatory support time (time frame: 30 days) • Thrombotic complications and rivaroxaban (time frame: 30 days) • LMWH (enoxaparin) and length of hospital stay (time frame: 30 days) • LMWH (enoxaparin) and mortality rate (time frame: 30 days)
Notes	NCT04508439 | No data provided

NCT04511923

Study name	Can nebulised heparin reduce acute lung injury in patients with SARS-CoV-2 requiring respiratory support in Ireland
Starting date	23 December 2020
Contact information	John Laffey University Hospital Galway Galway, Ireland +353 91 544074 | John.laffey@nuigalway.ie
Methods	Open-label, parallel-assignment RCT
Participants	40 participants, ≥ 18 years, female and male Inclusion criteria: • Confirmed or suspected COVID-19. Note, if 'suspected', results must be pending or testing intended • Ability to obtain informed consent/assent to participate in study • Age ≥ 18 years • Requiring high-flow nasal oxygen or positive pressure ventilator support or invasive mechanical ventilation for a time period of no greater than 48 h • D-dimers > 200 ng/mL • PaO2 to FIO2 ratio ≤ 300

NCT04511923 *(Continued)*

- Acute opacities on chest imaging affecting at least one lung quadrant. Note 'Acute opacities' do not include effusions, lobar/lung collapse or nodules
- Currently in a higher level of care area designated for inpatient care of patients where therapies including non-positive pressure ventilatory support can be provided

Exclusion criteria

- Enrolled in another clinical trial that is unapproved for co-enrolment
- Heparin allergy or HIT
- aPTT > 100 seconds
- Platelet count < 50 x 109/L
- Pulmonary bleeding, which is frank bleeding in the trachea, bronchi or lungs with repeated haemoptysis or requiring repeated suctioning
- Uncontrolled bleeding
- Pregnant or suspected pregnancy (urine or serum HCG will be recorded)
- Receiving or about to commence ECMO or HFOV
- Myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome
- Usually receives home oxygen
- Dependent on others for personal care due to physical or cognitive decline (pre-morbid status)
- Death is imminent or inevitable within 24 h
- The clinical team would not be able to set up the study nebuliser and ventilator circuit as required including with active humidification
- Clinician objection
- The use or anticipated use of nebulised tobramycin during this clinical episode
- Any other specific contraindication to anticoagulation including prophylactic anticoagulation not otherwise listed here
- Relapse in clinical condition in patient that had fully weaned from advanced respiratory support
- Any systemic anticoagulation other than prophylactic anticoagulation

Interventions	Experimental: heparin • Standard care plus nebulised UFH 25,000 units every 6 h for 10 days Comparator: standard care
Outcomes	Primary • D-dimer profile (time frame: up to day 10) • Frequency of SAEs (time frame: up to day 60) Secondary • Oxygenation index (time frame: up to day 10) • Indices of inflammation (time frame: up to day 10) • Ratios of indices of inflammation (time frame: up to day 10) • Indices of coagulation (time frame: up to day 10) • Quasi-static lung compliance (time frame: up to day 10) • Time to separation from advanced respiratory support (time frame: up to day 28) • Number treated with neuromuscular blockers (time frame: up to day 10) • Number treated with prone positioning (time frame: up to day 10) • Number treated with ECMO (time frame: up to day 10) • Number requiring tracheostomy (time frame: up to day 28) • Time to separation from invasive ventilation among survivors (time frame: up to day 28) • Discharge to ward (time frame: up to day 28) • Discharge to ward in survivors (time frame: up to day 28)

NCT04511923 *(Continued)*

- Patient survival (time frame: up to day 60)
- Number of participants residing at home or in a community setting at day 60 (time frame: up to day 60)
- Number of surviving participants residing at home or in a community (time frame: up to day 60)
- Ventilatory ratio (time frame: up to day 10)
- Number treated with awake prone positioning (time frame: up to day 10)

Notes	NCT04511923 | No data provided

NCT04512079

Study name	FREEDOM COVID anticoagulation strategy randomized trial
Starting date	8 September 2020
Contact information	Debra Fitzpatrick, MS Icahn School of Medicine at Mount Sinai Gustave L. Levy Pl, New York, NY 10029, USA 212-659-9151 | debra.fitzpatrick@mssm.edu
Methods	Prospective, multicentre, open-label, 1:1:1, 3-armed, parallel-assignment RCT

Participants	3600 participants, ≥ 18 years, female and male
	Inclusion criteria:
	• Hospitalization within the prior 24 h for either confirmed (based on PCR or antigen-positive test for SARS-CoV-2) or suspected COVID-19 based on 3 criteria (all 3 must be present for suspected cases):
	  • Fever > 38 °C
	  • O2 saturation ≤ 94
	  • Abnormal laboratory marker (at least 1)
	  ○ D-dimer ≥ 1.0 µg/mL
	  ○ CRP > 2 mg/L
	  ○ Ferritin > 300 µg/L
	  ○ Lymphopenia < 1500 cells/m^3
	  • Patient or legal guardian provides written informed consent
	Exclusion criteria:
	• Age < 18 years
	• Mechanical ventilation on admission or high likelihood for the need for invasive mechanical ventilation within 24 h of admission
	• Anticipated duration of hospital stay < 72 h
	• Treatment with therapeutic dose UFH or LMWH, VKA, or NOACs within 7 days
	• Active bleeding
	• Risk factors for bleeding, including:
	  ○ intracranial surgery or stroke within 3 months
	  ○ history of intracerebral arteriovenous malformation
	  ○ cerebral aneurysm or mass lesions of the CNS
	  ○ intracranial malignancy
	  ○ history of intracranial bleeding

NCT04512079 *(Continued)*

- history of bleeding diatheses (e.g. haemophilia)
- history of GI bleeding within previous 3 months
- thrombolysis within the previous 7 days
- presence of an epidural or spinal catheter
- recent major surgery < 14 days
- uncontrolled hypertension (SBP > 200 mmHg or DBP > 120 mmHg)
- other physician-perceived contraindications to anticoagulation
- platelet count < 50 x109/L, INR > 2.0, or baseline aPTT > 50 seconds
- haemoglobin < 80 g/L (to minimise the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)
- current treatment with antithrombotics or antiplatelet agents including but not limited to ticagrelor, prasugrel, and aspirin > 100 mg, or NSAIDs (e.g. ibuprofen, naproxen, etc.) due to increased risk of bleeding, unless such agents can be permanently discontinued (aspirin ≤ 100 mg and clopidogrel ≤ 75 mg is permitted)

- Acute or subacute bacterial endocarditis
- History of HIT or other heparin allergy including hypersensitivity
- Patients with non-COVID-19-related clinical condition for which life expectancy is < 6 months
- Pregnancy (women of childbearing potential are required to have a negative pregnancy test prior to enrolment)
- Active enrolment in other trials related to anticoagulation
- Patients has ESKD on chronic dialysis
- Patient is a member of a vulnerable population: in the judgment of the investigator the patient is unable to give informed consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with mental disability, in nursing homes, children, impoverished people, people in emergency situations, homeless people, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and people kept in detention

Interventions	Experimental: • Apixaban (5 mg every 12 h; 2.5 mg every 12 h for patients with at least 2 of 3 of age ≥ 80 years, weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL) Comparator: • Prophylactic enoxaparin (40 mg SC once daily; 30 mg SC once daily for CrCl < 30 mL/min) • Full-dose enoxaparin (1 mg/kg SC every 12 h; 1 mg/kg SC once daily for CrCl < 30 mL/min)

Outcomes	Primary
	• Time to first event (time frame: 30 days)
	• Number of in-hospital rate of BARC 3 or 5 (time frame: 30 days)
	  ○ Number of in-hospital rate of BARC 3 or 5 bleeding (binary). BARC type 3:
	  ■ overt bleeding plus haemoglobin drop of 3 to < 5 g/dL (provided haemoglobin drop is related to bleed); transfusion with overt bleeding
	  ■ overt bleeding plus haemoglobin drop < 5 g/dL (provided haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents
	  ■ intracranial haemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision. BARC type 5
	Secondary
	• Number of participants with myocardial infarction (time frame: 30 days after randomisation)
	• Number of participants with myocardial infarction (time frame: 90 days after randomisation)

NCT04512079 *(Continued)*

	• Number of participants with DVT (time frame: 30 days after randomisation) • Number of participants with DVT (time frame: 90 days after randomisation) • Number of participants requiring ventilation (time frame: 30 after randomisation) • Number of participants requiring ventilation (time frame: 90 days after randomisation) • Number of all death (time frame: 30 days after randomisation) • Number of all death (time frame: 90 days after randomisation) • Cause of death (time frame: 30 days after randomisation) • Cause of death (time frame: 90 days after randomisation) • Number of participants with stroke (time frame: 30 days after randomisation) • Number of participants with stroke (time frame: 90 days after randomisation) • Number of participants with PE (time frame: 30 days after randomisation) • Number of participants with PE (time frame: 90 days after randomisation) • Number of participants with systemic thromboembolism (time frame: 30 days after randomisation) • Number of participants with systemic thromboembolism (time frame: 90 days after randomisation)
Notes	NCT04512079 | No data provided

NCT04530578

Study name	Efficacy and safety study to evaluate the use of nebulized heparin in patients with severe acute respiratory syndrome COVID-19 (SARS-CoV-2)
Starting date	1 June 2020
Contact information	ALICIA B VILASECA, DR Clinica San Camilo Ciudad Autonoma de Buenos Aire, Buenos Aires, Argentina, 1405 +5401148588144 ext 244 | avilaseca@clinicasancamilo.org.ar
Methods	Prospective, open-label RCT

Participants	200 participants, ≥ 18 years, female and male
	Inclusion criteria:
	• People > 18 years of age of any sex admitted with a diagnosis of a suspected case of COVID-19, in accordance with the definition of the Ministry of Health of the Nation (MSal) as of 20 May 2020, who present at the time of admission or in its evolution pulmonary infiltrates compatible with imaging studies (chest X-ray or chest CT) and at least one of the following biochemical parameters of systemic inflammation:
	  ○ D-dimer > 1.0 µg/dL
	  ○ Ferritin > 500 ng/mL
	  ○ Fibrinogen > 500 mg/dL
	Exclusion criteria:
	• < 18 years old
	• Pregnant women
	• Known allergy to heparin
	• Participant in another clinical trial that is not approved for joint enrolment
	• aPTT > 120 seconds, not due to anticoagulant therapy

NCT04530578 *(Continued)*

	• Platelet count < 20 x 109/L • Lung bleeding • Uncontrolled bleeding • Advanced neurological impairment • Advanced oncological disease
Interventions	Experimental: nebulised heparin • Nebulised heparin (UNF) 5000 IU in saline solution 1 mL every 8 h plus enoxaparin 40 mg/d or 60 mg/d, adjusted by BMI and calculated CrCl Comparator: enoxaparin • Enoxaparin 40 mg/d or 60 mg/d adjusted by BMI and calculated CrCl

Outcomes	Primary
	• Percentage of patients requiring mechanical ventilation (time frame: 15 days)
	  ○ Blood gas criteria: PaO2/FiO2 < 200 (or the inability to maintain an SpO2 of at least 92% with a reservoir mask)
	  ○ Acute ventilatory failure (pH < 7.35 with PaCO2 > 45 mmHg)
	Secondary
	• Percentage of patients with PaO2 to Fi02 ratio > 300 (time frame: 7 days)
	• Lengths of hospital-stay (time frame: 60 days)
	• Mortality rate (time frame: 30 days)

Notes	NCT04530578 | No data provided

NCT04542408

Study name	Hamburg edoxaban for anticoagulation in COVID-19 study
Starting date	12 November 2020
Contact information	Stefan Kluge, MD Universitätsklinikum Düsseldorf Düsseldorf, Germany +49 40 7410 ext 57010 | s.kluge@uke.de
Methods	Prospective, multicentre, double-blinded, 1:1, parallel assignment RCT
Participants	172 participants, ≥ 18 years, female and male Inclusion criteria: • Diagnosis of COVID-19 and hospitalisation on ICU, or • Diagnosis of COVID-19 and hospitalisation on normal ward, or • Diagnosis of COVID-19 (within 10 days) and troponin ≥ ULN and/or D-dimer ≥ 0.5 mg/L Exclusion criteria: • Age < 18 • Life expectancy < 3 months before COVID-19

NCT04542408 *(Continued)*

	• Resuscitation > 30 minutes • Hypersensitivity to the active substance, to edoxaban or any of its excipients • Significantly increased bleeding risk • Other indication for anticoagulation beyond COVID-19 • GFR < 15 mL/min • Planned transfer of the patient to another clinic within the next 42 days
Interventions	Experimental: intensive anticoagulation strategy • In-hospital (ICU and normal ward): weight-adapted LMWH, high dose/therapeutic dose (according to respective summary of product characteristics). After discharge and in ambulatory patients: edoxaban according to summary of product characteristics Comparator: moderate anticoagulation strategy • In-hospital (ICU and normal ward): LMWH, prophylactic dose as part of standard care. After discharge and in ambulatory patients: administration of oral placebo according to the dosing rules for edoxaban
Outcomes	Primary • Combined endpoint: all-cause mortality and/or VTE and/or arterial thromboembolism (time frame: 42 days) ◦ All-cause mortality and/or VTE and/or arterial thromboembolism during follow-up (42 days). Thromboembolisms will be detected by duplex ultrasonography of arms and legs. Secondary • All-cause mortality (time frame: 42 days) • Mortality related to VTE (time frame: 42 days) • Mortality related to arterial thromboembolism (time frame: 42 days) • Rate of venous and/or arterial thromboembolism (time frame: 42 days) • Rate and length of mechanical ventilation (time frame: 42 days) • Length of initial stay at ICU after application of investigational medicinal product (time frame: 42 days) • Rehospitalisation (time frame: 42 days) • Rate and length of renal replacement therapy (time frame: 42 days) • Cardiac arrest/CPR (time frame: 42 days)
Notes	NCT04542408 | No data provided

NCT04545541

Study name	Can nebulised heparin reduce mortality and time to extubation in patients with COVID-19 requiring mechanical ventilation meta-trial (CHARTER-MT): protocol for an investigator-initiated international meta-trial of randomised studies
Starting date	1 November 2020
Contact information	Frank MP van Haren, MD, PhD Frederick Health Hospital Frederick, Maryland, USA, 21701 +61467051809 | fvanharen@me.com

NCT04545541 *(Continued)*

Methods	Prospective, multicentre, double-blinded, 1:1, parallel-assignment RCT
Participants	300 participants, ≥ 18 years, female and male Inclusion criteria: • Age ≥ 18 years • Currently in ICU or scheduled for transfer to the ICU. During the pandemic, critically ill inpatients might be cared for outside of the walls of the usual physical environment of ICU. For this reason, ICU is defined as an area designated for inpatient care of the critically ill where therapies including invasive mechanical ventilation can be provided. • Endotracheal tube in place • Intubated previous or current day • PaO2 to FIO2 ratio ≤ 300 while intubated • Acute opacities not fully explained by effusions, lobar/lung collapse and nodules, affecting at least 1 lung quadrant on chest X-ray or CT • The acute opacities on chest X-ray or CT are most likely due to COVID-19 • There is a PCR-positive sample for SARS-CoV-2 within the past 21 days or there are results pending or further testing is planned. The sample can be a nasal or pharyngeal swab, sputum, tracheal aspirate, bronchoalveolar lavage, or another sample from the patient. Exclusion criteria: • Enrolled in another clinical trial that is unapproved for co-enrolment • Heparin allergy or HIT • aPTT > 120 seconds and this is not due to anticoagulant therapy • Platelet count < 20 x 109/L • Pulmonary bleeding, which is frank bleeding in the trachea, bronchi or lungs with repeated haemoptysis or requiring repeated suctioning • Uncontrolled bleeding • Pregnant or might be pregnant. Women aged 18-49 years are excluded unless there is documented menopause or hysterectomy or a pregnancy test was performed and is negative. • Receiving or about to commence ECMO or HFOV • Myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome • Acute brain injury that may result in long-term disability • Usually receives home oxygen • Dependent on others for personal care due to physical or cognitive decline • Death is imminent or inevitable within 24 h • The clinical team would not be able to set up the study nebuliser and ventilator circuit as required including with active humidification • Clinician objection • Refusal of participant (person responsible) consent
Interventions	Experimental: nebulised heparin • Participants assigned to "nebulised UFH" will receive nebulised UFH in addition to the standard care required as determined by the treating team. Nebulised UFH (25,000 Units in 5 mL) will be administered 6-hourly via an Aerogen Solo vibrating mesh nebuliser while patients receive invasive mechanical ventilation in ICU and for a maximum of 10 days. Comparator: • Participants assigned to standard care will receive the standard care required as determined by the treating team and will not be treated with nebulised heparin (Australia, Ireland).

NCT04545541 *(Continued)*

	• Participants assigned to "placebo" will receive nebulised 0.9% sodium chloride (5 mL) administered 6-hourly via an Aerogen Solo vibrating mesh nebuliser while patients receive invasive mechanical ventilation in ICU and for a maximum of 10 days (USA)
Outcomes	Primary • Alive and ventilator-free score (time frame: day 28)
Notes	NCT04545541 | No data provided

NCT04584580

Study name	D-dimer adjusted versus therapeutic dose low-molecular-weight heparin in patients with COVID-19 pneumonia
Starting date	1 August 2020
Contact information	Ashraf Madkour Faculty of Medicine Ain Shams University Research Institute- Clinical Research Center Cairo, Non-US, Egypt, 11566 +20 100 177 0703 | asfrah_madkour@yahoo.com
Methods	Single-blinded, parallel-assignment RCT
Participants	50 participants, ≥ 18 years, female and male Inclusion criteria: • All adult (> 18 years) patients from both sexes with COVID-19 pneumonia with positive nucleic acid test for SARS-CoV-2 hospitalised either in the ward or ICU Exclusion criteria: • Patients with absolute contraindication of pharmacological thromboprophylaxis and/anticoagulation • Congenital haemorrhagic disorders • Hypersensitivity to heparin • Personal history of heparin-induced thrombocytopenia • Active major bleeding or conditions predisposing to major bleeding. Major bleeding is defined as fulfilling any one of these three criteria: a) occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine or intramuscular with compartment syndrome), b) causes a fall in haemoglobin level (Hb) of ≥ 2 g/dL in a 24 h period, or c) leads to transfusion of ≥ 2 units of whole blood or red blood cells • Suspected or confirmed bacterial endocarditis • Ongoing or planned therapeutic anticoagulation for any other indication • Platelet count < 50,000/µL within the past 24 h or Hb level < 8 g/dL • Prothrombin time (PT) ≥ 2 seconds above the upper limit of age-appropriate local reference range within the past 24 h • aPTT ≥ 4 seconds above the upper limit of age-appropriate local reference range within the past 24 h • Fibrinogen < 2.0 g/L • Severe renal impairment (CrCl < 30 mL/min) or acute kidney injury • Use of dual antiplatelet therapy • Pregnancy

NCT04584580 *(Continued)*

	• Unwillingness to consent
Interventions	Experimental: • D-dimer levels and weight adjusted LMWH therapy from admission until the end of hospital stay. Patients will be stratified according to their body weight and D-dimer level and receive LMWH • D-Dimer level body weight LMWH dose < 1 mg/dL <100 kg enoxaparin 40 mg OD 100-150 kg enoxaparin 40 mg twice daily > 150 kg enoxaparin 60 mg twice daily 1-3 mg/dL < 100 kg enoxaparin 40 mg twice daily 100-150 kg enoxaparin 80 mg twice daily > 150 kg enoxaparin 120 mg twice daily > 3 mg/dL enoxaparin 80 mg twice daily Comparator: therapeutic-dose LMWH • Therapeutic-dose LMWH from admission until the end of hospital stay enoxaparin 1 mg/kg SC every 12 h
Outcomes	Primary • Mortality (time frame: until patient is discharged or up to 4 weeks whichever comes first) • Occurrence of venous and/or arterial thrombosis (time frame: until patient is discharged or up to 4 weeks whichever comes first) Secondary • Occurrence of sepsis-induced coagulopathy (time frame: until patient is discharged or up to 4 weeks whichever comes first) • Occurrence of ARDS (time frame: until patient is discharged or up to 4 weeks whichever comes first) • Occurrence of sepsis (time frame: until patient is discharged or up to 4 weeks whichever comes first) • ICU admission and need for mechanical ventilation (time frame: until patient is discharged or up to 4 weeks whichever comes first)
Notes	NCT04584580 | No data provided

NCT04600141

Study name	Clinical efficacy of heparin and tocilizumab in patients with severe COVID-19 infection: a randomized clinical trial
Starting date	10 November 2020
Contact information	Ludhmila A Hajjar, MD, PhD Fundação São Francisco Xavier Ipatinga, Minas Gerais, Brazil 551126614177 | ludhmila@terra.com.br
Methods	Open-label, parallel-assignment RCT
Participants	308 participants, ≥ 18 years, female and male Inclusion criteria: • Age ≥ 18 years • Informed consent form signed by the patient or guardian or by audio with the guardian

NCT04600141 *(Continued)*

- Positive result for COVID-19 in PCR in nasopharyngeal swab or tracheal secretion up to 10 days before the inclusion and radiological evidence of COVID-19, by chest radiography or chest CT
- Need for ≥ 4 L of supplemental oxygen to maintain peripheral oxygen saturation ≥ 93% or need for invasive mechanical ventilation

Exclusion criteria:

- Risk of bleeding:
  - clinical: active bleeding, major surgery in the last 30 days, GI bleeding within 30 days
  - laboratory: platelet count < 50,000, INR > 2 or aPTT > 50 s
- Known or suspected adverse reaction to UFH, including HIT
- Adverse reaction or allergy to tocilizumab
- Use of any of the following treatments: UFH to treat a thrombotic event within 12 h before inclusion; LMWH in therapeutic dose within 12 h before inclusion; warfarin (if used 7 days before and if INR > 2; thrombolytic therapy within 3 days before; and use of glycoprotein IIb/IIIa inhibitors within the previous 7 days
- Pregnant or lactating
- Absolute indication of anticoagulation due to atrial fibrillation or diagnosed thromboembolic event
- Refusal by family members and/or patient
- Active TB
- Bacterial infection confirmed by culture
- Neutropenia (< 1000 neutrophils/mm^3)
- Use of another immunosuppressive therapy that is not a corticosteroid
- Septic shock

Interventions	Experimental:
	• Group 1 - therapeutic anticoagulation with tocilizumab
	  ◦ IV UFH initiated at a dose of 18 IU/kg/h, adjusted according to a nomogram to achieve a aPTT of 1.5 to 2.0 times the reference value associated with 8 mg/kg/tocilizumab infusion/IV dose in a single dose, or
	  ◦ SC LMWH - enoxaparin 1 mg/kg per dose every 12 h associated with an infusion of tocilizumab 8 mg/kg/dose in a single dose
	• Group 2 - prophylactic anticoagulation with tocilizumab
	  ◦ SC UFH 5000 IU every 8 h associated with an infusion of tocilizumab 8 mg/kg/IV dose in a single dose; or
	  ◦ SC LMWH - enoxaparin 40 mg daily associated with an infusion of tocilizumab 8 mg/kg/IV dose in a single dose
	Comparator:
	• Group 1 - therapeutic anticoagulation
	  ◦ IV UFH started at a dose of 18 IU/kg/h, adjusted according to a nomogram to achieve an aPTT of 1.5-2.0 times the reference value; or
	  ◦ SC LMWH - enoxaparin 1 mg/kg per dose every 12 h
	• Group 2 - prophylactic anticoagulation
	  ◦ SC UFH 5000 IU every 8 h; or
	  ◦ SC LMWH - enoxaparin 40 mg daily

Outcomes	Primary
	• Proportion of patients with clinical improvement (time frame: 30 days)
	  ◦ Not hospitalised, with no limitations on activities
	  ◦ Not hospitalised, but limited to activities
	  ◦ Hospitalised, with no need for supplemental oxygen
	  ◦ Hospitalised, needing supplemental oxygen

NCT04600141 *(Continued)*

	○ Hospitalised, requiring high-flow oxygen therapy, non-invasive mechanical ventilation or both ○ Hospitalised, requiring ECMO, invasive mechanical ventilation or both ○ Death Secondary • Hospital and ICU length of stay (time frame: 30 days) • Duration of invasive mechanical ventilation (time frame: 30 days) • Duration of vasopressor use (time frame: 30 days) • Renal failure by AKIN criteria (time frame: 30 days) • Incidence of cardiovascular complications (time frame: 30 days) • Incidence of VTE (time frame: 30 days) • Mortality (time frame: 30, 60 and 90 days)
Notes	NCT04600141 | No data provided

NCT04604327

Study name	Ensayo clínico aleatorizado, abierto, para evaluar el efecto de dosis profilácticas o terapéuticas de bemiparina en pacientes con COVID-19
Starting date	26 October 2020
Contact information	Ramon Lecumberri, MD, PhD Hospital Rey Juan Carlos Móstoles, Madrid, Spain +34 948296397 | rlecumber@unav.es
Methods	Open-label, parallel-assignment RCT
Participants	164 participants, ≥ 18 years, female and male Inclusion criteria: • Age (≥ 18 years) • Hospitalisation at conventional wards due to COVID-19 related mild or moderate pneumonia (CURB65 < 3 points; Saturated O2 > 90%) • 3-4 points according to the WHO ordinal scale • Confirmed COVID-19 (PCR or other validated test) • D-dimer > 500 ng/mL • Signed informed consent • The patient is able, according to investigator's opinion, to deal with all the requirements of the clinical trial Exclusion criteria: nil
Interventions	Experimental: full therapeutic bemiparin (weight adjusted) • Bemiparin at full therapeutic dose, adjusted to body weight, for 10 days Comparator: prophylactic bemiparin (3500 IU/day) • Bemiparin 3500 IU daily for 10 days

NCT04604327 *(Continued)*

Outcomes	Primary • Clinical deterioration (time frame: 10 days) • Combined outcome that includes number of patients who suffer any of the following: death, ICU admission, mechanical ventilatory support, progression to moderate or severe ARDS (according to Berlin criteria) or arterial or venous thrombosis
Notes	NCT04604327 | No data provided

NCT04623177

Study name	Thromboprophylaxis for patients in ICU With COVID-19
Starting date	1 March 2020
Contact information	Raquel Ferrandis, MD Hospital Universitario La Fe, Valencia, Spain phone and email not available
Methods	Prospective cohort, non-randomised, open-label, 3 parallel and comparative arms
Participants	950 participants, ≥ 18 years, female and male Inclusion criteria • Confirmed SARS-CoV-2 infection from a respiratory tract sample using a PCR assay • Admitted to ICU Exclusion criteria • Non-confirmed SARS-CoV-2 infection • No data at first day ICU admission • Patient with do-not-resuscitate orders • A patient who did not meet the outcomes of death or ICU discharge by the time of study completion date
Interventions	Experimental: anticoagulant dose (≥ 150 IU/kg/24 h) of LMWH within the first 48 h after the ICU admission Experimental: prophylactic dose (lower than 150 IU/kg/24 h) of LMWH within the first 48 h after the ICU admission Comparator: no anticoagulant drug within the first 48 h after the ICU admission
Outcomes	Primary • ICU mortality rate (time frame: from admission to ICU discharge, an average of 1 month) Secondary • ICU incidence of thrombotic events (time frame: from admission to ICU discharge, an average of 1 month). A composite endpoint to evaluate efficacy made up of myocardial infarction, stroke, incidental PE, PE with worsening of hypoxaemia, PE with haemodynamic repercussion, other venous thromboses without PE

NCT04623177 *(Continued)*

	• ICU incidence of bleeding events (time frame: from admission to ICU discharge, an average of 1 month). Composite endpoint to evaluate safety made up of bleeding needing a transfusion, bleeding with haemodynamic repercussion, another bleeding (minor bleeding) • Length of ICU stay (time frame: from admission to ICU discharge, an average of 1 month). Days admitted in ICU • Length of invasive mechanical ventilation (time frame: from admission to ICU discharge, an average of 1 month). Days treated with invasive mechanical ventilation (controlled or assisted) • Effect of LMWH in other parameters (time frame: from admission to ICU discharge, an average of 1 month). Description of the relationship if any between the use of LMWH and thrombotic or inflammatory parameters (D-dimer levels, ferritin) or lung dead space
Notes	NCT04623177 | No data provided

NCT04640181

Study name	A phase 2-3, multi-center, randomized trial to study the potential benefit of factor Xa inhibitor (rivaroxaban) versus standard of care low molecular weight heparin (Lovenox) in hospitalized patients with COVID-19 (XACT)
Starting date	1 December 2020
Contact information	Matt Cowperthwaite, PhD St. David's Medical Center Austin, Texas, USA, 78705 512-544-2626 | info@stdavidsresearch.com
Methods	Prospective, multicentre, open-label, 1:1, parallel-assignment RCT

Participants	150 participants, ≥ 18 years, female and male
	Inclusion criteria:
	• Patients aged 18-100 admitted to hospital with laboratory-confirmed SARS-CoV-2 infection
	• Not be intubated or mechanically ventilated or imminently at risk for same or ICU admission within 24 h of enrolment
	• Not be admitted for CNS diagnosis
	• Not have a current history of a condition requiring full therapeutic anticoagulation such as VTE, atrial fibrillation.
	Exclusion criteria:
	• Medical conditions
	  ○ Life expectancy of < 6 months
	  ○ Active or recent GI bleeding in the past 6 months
	  ○ Intracranial bleeding in the past 6 months
	  ○ Major trauma or head trauma in the past 2 months
	  ○ Major surgery in the past 2 months or planned within 2 weeks after completion of the study
	  ○ Recent spinal or epidural procedures in the past 2 weeks
	  ○ Ischaemic stroke in the past 2 weeks
	  ○ History of intracranial neoplasm, arteriovenous malformation or aneurysm
	  ○ History of acquired or spontaneous impairment of haemostasis such as but not limited to haemophilia, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), von Willebrand disease

NCT04640181 *(Continued)*

- Allergy to heparin or rivaroxaban or any factor Xa inhibitors, including a history of HIT
- History of antiphospholipid syndrome
- End-stage renal failure requiring dialysis
- Valvular heart disease requiring chronic anticoagulation
- History of atrial fibrillation, atrial flutter or VTE currently requiring anticoagulation
- History of solid organ transplant requiring immunosuppressant therapy
- Cancer requiring ongoing anticoagulation
- History of cirrhosis or liver failure, hepatorenal syndrome
- History of baseline bronchiectasis
- History of systemic lupus erythematosus or other autoimmune diseases requiring immunosuppressant therapy

Vital signs

- Uncontrolled hypertension: SBP > 180 mm Hg or DBP > 105 mmHg. Participants who have a transient, higher blood pressure elevation (SBP 180-200 mmHg) may enter the study if a repeat confirmation is back in range prior to enrolment

Laboratory

- PT INR > 2.0
- Platelet < 90 10^3/µL
- Total bilirubin > 3.0 mg/dL
- Haemoglobin < 9.0 g/dL
- Urine with gross haematuria (not due to menses)
- Estimated GFR < 30 mL/min calculated with the Cockcroft-Gault formula

Medications

- Patients on dual anti-platelet therapy
- Patients taking hypoxia-inducible factor prolyl hydroxylase inhibitors (such as roxadustat)
- Erythropoiesis-stimulating agents (such as epoetin alfa, darbepoetin alfa)

Other COVID-19 drug studies or trials

- Any COVID-19 vaccination trials
- Experimental COVID drug trial except for treatment(s) that has become accepted standard care

Interventions	Experimental: adaptive dosing: rivaroxaban • Low 10 mg oral daily • Intermediate 10 mg oral daily • therapeutic 20 mg oral daily Comparator: adaptive dosing: enoxaparin • Low 40 mg SC daily, or • Intermediate 40 mg SC every 12 h, or • Therapeutic 1 mg/kg SC every 12 h
Outcomes	Primary • Death or 30-day all-cause mortality (time frame: 30 days) • Mechanical ventilation, intubation (time frame: 30 days) • Transfer to an ICU setting (time frame: 30 days) Secondary

NCT04640181 *(Continued)*

	• New requirement for haemodialysis or continuous renal replacement therapy or ECMO (time frame: 30 days) • New thrombotic events (time frame: 30 days) • Major bleeding event (time frame: 30 days) • Time to recovery (defined as no limitation or minor limitation in activity level or hospitalised but require no oxygen) (time frame: 30 days)
Notes	NCT04640181 | No data provided

NCT04646655

Study name	Enoxaparin at prophylactic or therapeutic doses with monitoring of outcomes in subjects infected with COVID-19: a pilot study on 300 cases enrolled at ASST-FBF-Sacco
Starting date	27 July 2020
Contact information	Maddalena A Wu, M.D. ASST Fatebenefratelli Sacco Milan, Italy, 20157 +390239041 | maddalena.ale.wu@gmail.com
Methods	Single-centre, open-label, 2-armed, parallel assignment RCT
Participants	300 participants, ≥ 18 years and ≤ 80 years, female and male Inclusion criteria: • COVID-19-related pneumonia with moderate-severe respiratory failure (PaO2/FiO2 < 250) and/or markedly increased D-dimer level (> 2000 ng/mL) • Signed informed consent Exclusion criteria: • Age < 18 and > 80 years • History of bleeding (peptic ulcer, oesophageal varices, cerebral aneurysm, cancer at high risk of bleeding, cirrhosis, hemorrhagic stroke < 1 year) • Thrombocytopenia (< 100 x 109/L) • Anemia (Hb < 8 g/dL) • Coagulation abnormalities (PT or aPTT > 1.5; fibrinogen < 150 mg/dL) • Consumption coagulopathy (ISTH criteria) (15, 16) • DVT or PE • Dual antiplatelet therapy • Ongoing anticoagulant therapy • Allergic reaction to LMWH • Previous HIT • Major surgery < 1 month; neurosurgery < 3 months; eye surgery < 3 months • Pregnancy • Arterial hypertension (SBP > 160 mmHg; DBP > 100 mmHg) • Renal failure (CrCl 30 mL/min) • ICU admission or endotracheal intubation
Interventions	Experimental: enoxaparin at therapeutic dose

NCT04646655 *(Continued)*

	• Enoxaparin at therapeutic dose: 70 U/kg twice daily (every 12 h)
	• In order to easily calculate the correct therapeutic dose of enoxaparin for each participant, a simplified categorisation will be applied, as follows:
	  ○ weight < 65 kg: 4000 IU twice daily (every 12 h)
	  ○ weight ≥ 65 kg: 6000 IU twice daily (every 12 h)
	  ○ weight ≥ 100 kg: 8000 IU twice daily (every 12 h).
	• The most appropriate dose will be evaluated in participants with CrCl between 30 and 50 mL/min
	
	Comparator: enoxaparin at prophylactic dose
	
	• Enoxaparin at prophylactic dose: standard 4000 IU once daily via SC injection (6000 IU if body weight > 100 kg)

Outcomes	Primary • Mortality rate (time frame: 30 days from enrolment) • Progression of respiratory failure (time frame: 30 days from enrolment) • Progression of respiratory failure (time frame: 30 days from enrolment) • Progression of respiratory failure (time frame: 30 days from enrolment) • Number of major bleeding episodes (time frame: up to 6 months from randomisation) Secondary • Respiratory function improvement (time frame: at 72 h) ○ Amelioration of the respiratory function defined as a PaO2/FiO2 increase > 300 and/or respiratory rate < 20 breaths/min • Respiratory function improvement (time frame: 1 week from randomisation) • Number of major cardiovascular events (time frame: 6 months from randomisation) • DVT (time frame: 6 months from randomisation)
Notes	NCT04646655 | No data provided

NCT04655586

Study name	Assessing safety, hospitalization and efficacy of rNAPc2 in COVID-19 (ASPEN-COVID-19)
Starting date	10 December 2020
Contact information	Jennifer Meriwether ARCA Investigational Site Fairhope, Alabama, USA, 36532 720-940-2132 | jennifer.meriwether@arcabio.com
Methods	Multicentre, double-blind, parallel-assignment RCT
Participants	100 participants, ≥ 18 years and ≤ 90 years, female and male
Interventions	Experimental: • rNAPc2 higher dose - loading dose of 7.5 µg/kg SC on day 1 followed by 5 µg/kg SC on days 3 and 5 • rNAPc2 lower dose - loading dose of 5 µg/kg SC on day 1 followed by 3 µg/kg SC on days 3 and 5 Comparator: heparin

NCT04655586 *(Continued)*

	• Heparin at either prophylactic or therapeutic doses per standard care at Institution
Outcomes	Primary • Change in D-dimer level from baseline to day 8, or day of discharge if prior to day 8 (phase 2b) (time frame: 8 days) • Number of major or non-major clinically relevant bleeding events within 8 days of randomisation (time frame: 8 days) • Time to recovery within 30 days of randomisation using the ACTT ordinal scale (phase 3) (time frame: 30 days) Secondary • Change in D-dimer level from baseline to 24 h post-dose (day 2) and day 3 (phase 2b) (time frame: 3 days) • Number of major or non-major clinically relevant bleeding events with rNAPc2 vs heparin (phase 2b and 3) (time frame: 30 days) • Number of bleeding events in participants treated with higher- vs lower-dose rNAPc2 through day 30 (phase 2b) (time frame: 30 days) • Time to first occurrence of a composite of thrombotic events and all-cause mortality within 30 days of randomisation (phase 3 only) (time frame: 30 days) • Time to first occurrence of thrombotic events within thirty (30) days of randomisation (Phase 3 only) (time frame: 30 days) • Time to all-cause mortality within 30 days of randomisation (phase 3 only) (time frame: 30 days) • Change in tissue factor laboratory values in rNAPc2-treated participants who had clinical events related to coagulation and inflammation from baseline through day 8 (phase 2b) (time frame: 8 days) • Change in interleukin-6 laboratory values in rNAPc2-treated participants who had clinical events related to coagulation and inflammation from baseline through day 8 (phase 2b) (time frame: 8 days) • Change in high-sensitivity C-reactive protein laboratory values in rNAPc2-treated participants who had clinical events related to coagulation and inflammation from baseline through day 8 (phase 2b) (time frame: 8 days)
Notes	NCT04655586 | No data provided

NCT04723563

Study name	Inhaled unfractionated heparin for the treatment of hospitalized patients with COVID-19 pneumonia
Starting date	21 February 2021
Contact information	Thomas Smoot, PharmD Frederick Health Hospital Frederick, Maryland, USA, 21701
Methods	Quadruple-blind, parallel-assignment RCT
Participants	50 participants, ≥ 18 years, female and male Inclusion criteria: • Admitted to the hospital

NCT04723563 *(Continued)*

	• There is a PCR-positive sample for SARS-CoV-2 within the past 21 days. The sample can be a nasal oropharyngeal swab, sputum, tracheal aspirate, bronchoalveolar lavage, or another sample from the patient • Modified Ordinal Clinical Scale for COVID-19 of 3-5 Exclusion criteria: • Intubated and on mechanical ventilation, or requiring immediate intubation as per the treating clinician's assessment • Heparin allergy or HIT • aPTT > 120 seconds, not due to anticoagulant therapy and does not correct with administration of fresh frozen plasma • Platelet count < 20 x 109/L • Pulmonary bleeding or uncontrolled bleeding • Pregnant or might be pregnant • Acute brain injury that may result in long-term disability • Myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome • Treatment limitations in place, i.e. not for intubation, not for ICU admission • Death is imminent or inevitable within 24 h • Clinician objection • Refusal of participant (person responsible) consent
Interventions	Experimental: nebulised heparin • Heparin 5000 units/mL. Dose: 25,000 units. Frequency: 4 times/day. Duration: until hospital discharge Comparator: placebo • 0.9% sodium chloride. Dose: 5 mL. Frequency: 4 times/day. Duration: until hospital discharge
Outcomes	Primary • Need for mechanical ventilation at day 28 (time frame: 28 days) Secondary • Hospital length of stay (time frame: 60 days) • Average daily SaO2/FiO2 (time frame: 28 days)
Notes	NCT04723563 | No data provided

NCT04730856

Study name	Standard vs high prophylactic doses or anticoagulation in patients with high risk of thrombosis admitted with COVID-19 pneumonia (PROTHROMCOVID)
Starting date	1 February 2021
Contact information	ANGEL PUEYO Hospital Universitario Infanta Leonor Gran Vía del Este, 80, 28031 Madrid, Spain +34 618 448 807 | angel.pueyo@salud.madrid.org

NCT04730856 *(Continued)*

Methods	Open-label, parallel-assignment RCT

Participants	600 participants, ≥ 18 years, female and male
	
	Inclusion criteria:
	
	• Patients admitted to hospital with COVID-19, PCR and/or antigen test + SARS-CoV-2 infection or (presence of infiltrate compatible with Chest X-ray or CT)
	• Patients with, at least, one of the following evolution disease risk criteria:
	  ○ SpO2 < 94%
	  ○ Need for oxygen therapy or PaO2/FiO2 < 300 mmHg or estimated PaO2/FiO2 based on SpO2/FiO2 < 300 mmHg
	  ○ D-dimer > 1000 µg/L
	  ○ PCR > 150 mg/L
	  ○ IL6 > 40 pg/mL
	• Age > 18 years
	• Weight 50-100 kg
	• After receiving oral and written information about the study, patient must give informed consent duly signed and dated before performing any activity related to the study
	
	Exclusion criteria:
	
	• Patients who need mechanical ventilation (invasive or non-invasive), high-flow nasal cannula or admission to ICU at the moment of randomisation
	• Current diagnosis of acute bronchial asthma attack
	• History or clinical suspicion of pulmonary fibrosis
	• Current diagnosis or suspicion of pulmonary thromboembolism or DVT
	• Patients who need anticoagulant treatment due to previous venous or arterial thrombotic disease, or due to atrial fibrillation
	• Patients with pneumonectomy or lobectomy
	• Renal failure with GFR < 30 mL/min/1.73 m^2
	• Patients with contraindication for anticoagulant treatment
	• Congenital bleeding disorders
	• Hypersensitivity to tinzaparin or UFH or some of its excipients
	• History of HIT
	• Active bleeding or situation that predispose to bleeding
	• Moderate or severe anaemia (Hb < 10 g/dL)
	• Low platelet count < 80000/µL
	• Patients with life expectancy < 3 months due to primary disease evaluated by the physician
	• Patients currently intubated or intubated between the screening and the randomisation
	• Pregnancy

Interventions	Experimental: tinzaparin 4500 UI/day
	
	• Procedure: tinzaparin 4500 UI/day SC until hospital discharge
	
	Comparator:
	
	• Tinzaparin 100 UI/kg/day
	  ○ Procedure: tinzaparin 100 UI/kg/day SC until hospital discharge
	• Tinzaparin 175 UI/kg/day
	  ○ Procedure: tinzaparin 175 UI/kg/day SC until hospital discharge

Outcomes	Primary • Reduction of suspicion of systemic thrombotic symptomatic events (time frame: 30 days) • Use of mechanical ventilation (time frame: 30 days)

NCT04730856 *(Continued)*

- Progression on the WHO Progression Scale during follow-up (time frame: 30 days)
- Overall survival at 30 days (time frame: 30 days)
- Length of hospital stay (days) (time frame: 30 days)
- Length of ICU stay (days) (time frame: 30 days)

Secondary

- Number of bleedings and AEs (time frame: 30 days): incidence of major bleeding, defined as meeting any of these criteria:
  - fatal bleeding or bleeding that occurs in a critical area or organ (for example, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome)
  - causes a drop in haemoglobin level of ≥ 20 g/L
  - requires the transfusion of ≥ 2 units of whole blood or packed red blood cells

Notes	NCT04730856 | No data provided

NCT04743011

Study name	Nebulized enriched heparin to treat no critical patients with SARS-CoV-2 - triple blind clinical trial
Starting date	1 June 2021
Contact information	Matheus Bertanha, PhD School of Medicine at Botucatu- Paulista State University- UNESP, São Paulo, Brazil Botucatu, SP, Brazil, 18607030 +55(14)3880-1444 | matheusbertanha@gmail.com
Methods	Triple-blind, parallel-assignment RCT
Participants	50 participants, ≥ 18 years, female and male Inclusion criteria: • Signature and agreement to the free consent form • Both sexes, of any ethnic origin, aged between 18 and 90 years • COVID-19-infected patients diagnosed by RT-PCR or with a strong suspicion of COVID-19 by clinical evaluation through compatible clinical and radiological findings • Time of disease evolution < 10 days • Radiological diagnosis of grade 2A pneumonia, with gas exchange ratio > 200 on blood gas analysis (paO2/pFiO2), characterising mild hypoxaemia • Indication of hospital treatment regime, provided that the period of hospitalisation before inclusion is not more than 24 h • Need for supplemental oxygen therapy (O2) < 5 L/min Exclusion criteria: • No agreement to the terms of this study • Moderate or severe respiratory failure requiring admission to the ICU and the need for invasive mechanical ventilation or non-invasive ventilation (NIV) with positive pressure • Pregnancy or puerperium • Patients with haematological diseases, coagulation disorders, use of anticoagulants, previous heparin-induced allergy or HIT, thrombocytopenia with a count of < 50,000 platelets/mm^3

NCT04743011 *(Continued)*

	• COVID-19 not confirmed by RT-PCR within 72 h of inclusion in the study
Interventions	Experimental: heparin sodium • Participants will receive inhalation with 5 mL 0.9% saline solution + 2.5 mg of high molecular weight heparin - enriched heparin, 4/4 h, during the day period (5 doses) Comparator: placebo • Participants will receive inhalation with 5 mL 0.9% saline solution (placebo), 4/4 h, during the day period (5 doses)
Outcomes	Primary • Change in aPTT > 1.5 (time frame: immediately or up to 8 days after starting treatment) • Viral load in nasal swab RT-PCR (time frame: immediately or up to 8 days after starting treatment) Secondary • Number of participants needing supplemental oxygen therapy (time frame: immediately or up to 8 days after starting treatment) • Number of participants needing mechanical pulmonary ventilation (time frame: immediately or up to 8 days after starting treatment) • Number of hospitalisation days (time frame: immediately or up to 8 days after starting treatment) • Number of participants that develop renal failure (time frame: immediately or up to 8 days after starting treatment) • Number of participants that develop major cardiovascular events (time frame: immediately or up to 8 days after starting treatment) • Number of participants transferred to the ICU (time frame: immediately or up to 8 days after starting treatment) • Number of participants presenting secondary pulmonary bacterial infections (time frame: immediately or up to 8 days after starting treatment) • Number of participants that develop DVT (time frame: immediately or up to 8 days after starting treatment) • Number of participants that develop pancreatitis (time frame: immediately or up to 8 days after starting treatment) • Number of participants that need corticosteroid therapy (time frame: immediately or up to 8 days after starting treatment) • Number of deaths among participants (time frame: immediately or up to 8 days after starting treatment) • Number of participants with increased white blood cell count (time frame: immediately or up to 8 days after starting treatment) • Number of participants with increased C reactive protein test (time frame: immediately or up to 8 days after starting treatment) • Number of participants with deterioration of arterial blood gas PaO2/pFiO2 ratio (time frame: immediately or up to 8 days after starting treatment) • Number of participants with altered sodium (time frame: immediately or up to 8 days after starting treatment) • Number of participants with altered potassium (time frame: immediately or up to 8 days after starting treatment) • Number of participants with increased pulmonary area compromised (%) (time frame: immediately or up to 8 days after starting treatment)
Notes	NCT04743011 | No data provided

NCT04745442

Study name	Pilot study of antithrombin as prophylaxis of acute respiratory distress syndrome in patients with COVID-19
Starting date	27 April 2020
Contact information	Maimónides Biomedical Research Institute of Córdoba Hospital Universitario Reina Sofía Córdoba, Spain, 14004
Methods	Single-centre, open-label, parallel-assignment RCT

Participants	48 participants, ≥ 18 to ≤ 85 years, female and male
	Inclusion criteria:
	• Age ≥ 18 and < 85 years
	• COVID-19 diagnosis confirmed
	• Radiological image compatible with COVID-19
	• Present any of the following clinical-functional criteria considered risk:
	  ○ respiratory distress: tachypnoea > 26 breaths/min
	  ○ PaO2/FiO2 oxygenation index # 300
	  ○ alteration of ≥ 1 of the following parameters:
	  ■ D-dimer > 1000 µg/L. Ferritin > 800 ng/mL. Lymphocytes < 800 cells/µL. PCR > 100 mg/L. LDH > 500 U/L. IL-6 > 15 pg/mL
	  ○ Direct or delegated verbal informed consent
	Exclusion criteria:
	• Signs of active bleeding
	• Immunosuppression by cancer or transplant
	• Intolerance or allergy to AT or its components
	• Pregnancy

Interventions	Experimental: best available treatment + antithrombin • The participant will be treated with antithrombin (50 IU/kg/12 h) for 72 h and the best available treatment for COVID-19 Active comparator: best available treatment • The participant will be treated with the best available treatment for COVID-19
Outcomes	Primary • Combined variable: mortality or worsening rate with need for non-invasive mechanical ventilation or with need for invasive mechanical ventilation (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first) Secondary • Time to clinical improvement (decreased risk of developing SARS or death) (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first) • Evaluate the improvement of the oxygenation index - PaO2/FiO2- at 24 and 48 h (time frame: at 24 and 48 h) • Improvement of the analytical parameters: time (in days) until the tendency to normalisation (decrease ≥ 20%) of D-dimer, ferritin, LDH, PCR and IL-6; the criteria reached before will be used (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)

NCT04745442 *(Continued)*

- Time (in days) until improvement in oxygenation: time until the SpO2/FiO2 ratio exceeds the worst SpO2/FiO2 prior to antithrombin treatment. (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)
- Time to radiological improvement in radiological report (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)
- Time (in days) of non-invasive mechanical ventilation (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)
- Time (in days) of invasive mechanical ventilation. (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)
- Mortality rate in hospital and 1 month after pharmacological intervention (time frame: 1 month after pharmacological intervention)
- Percentage of participants who suffer any AE related to pharmacological intervention (time frame: 1 month after pharmacological intervention)
- Incidence of AEs related to medication and its administration (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)
- Incidence in the appearance of allergic type hypersensitivity (time frame: At day 31 after randomisation or hospital discharge (whichever occurs first))
- Incidence of B19 parvovirus infection (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)
- Bleeding (time frame: at day 31 after randomisation or hospital discharge, whichever occurs first)

Notes	NCT04745442 | No data provided

PACTR202007606032743

Study name	Nebulized heparin in patients with mainly moderate coronavirus disease 2019: randomized controlled trial. COVID-19
Starting date	15 June 2020
Contact information	Tarek Ismail Al Gamaa, Al Masaken Al Iqtisadeyah, Qism Helwan Cairo Egypt 00201112277417 | tareksalem00@gmail.com
Methods	RCT
Participants	100 participants, ≥ 18 years, female and male Inclusion criteria: • Age:18-60 years old • Recently diagnosed (within 24 h) and moderate symptoms of the disease • Ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with RT-PCR • Willingness to participate • Pneumonia on chest CT will not be mandatory for inclusion Exclusion criteria: • Age < 18 years • Severe conditions including malignancies, heart, liver, or kidney disease, poorly controlled metabolic diseases, pregnancy or lactation, severe hepatic impairment (e.g. Child Pugh grade C, ALT > five times the upper limit), severe renal impairment (estimated GFR 30 mL/min/1.73 m^2), receipt of continuous renal replacement therapy, haemodialysis, peritoneal dialysis, allergy to heparin

PACTR202007606032743 *(Continued)*

	(including any history of HIT), pulmonary haemorrhage in the previous 3 months, uncontrolled bleeding or a significant bleeding disorder, an intracranial haemorrhage in the past 12 months • Patients with mild and severe COVID-19 will be excluded
Interventions	Standard care plus nebulised heparin, every 6 h started 24 h after randomisation and will continue for 1 week
Outcomes	Primary • The primary outcome will be the average daily ratio of PaO2/FiO2 while the participant is on room air for 7 days Secondary • Secondary outcomes will be levels in pulmonary lavage fluid of fibrin degradation products (FDPs) as a marker of coagulation activation, measured at baseline and on study days 3 and 7, it will be measured through mini bronchoalveolar lavage (BAL) fluid samples as patients remained non-ventilated. Daily APPT levels in seconds and platelet count (× 109/L) will be recorded to assess the systemic effects of nebulised heparin • Incidence of serious respiratory events that need further respiratory support from randomisation to 14 days
Notes	PACTR202007606032743 | No data provided

RBR-7y8j2bs

Study name	Enriched heparin anti COVID-19 trial
Starting date	03 January 2021
Contact information	Matheus Bertanha Departamento de Cirurgia Vascular do Hospital das Clínicas de Botucatu: Avenida Professor Emérito Mário Rubens Guimarães Montenegro, s/nº 18618687 Botucatu Brazil +551438801444 | matheusbertanha@gmail.com
Methods	Triple-blind RCT
Participants	≥ 18 years, female and male Inclusion criteria: • Sign and agree to the informed consent form • Both sexes, of any ethnic origin, aged between 18 and 90 years • COVID-19 patients diagnosed by RT-PCR or with a strong suspicion of COVID-19 by clinical evaluation through compatible clinical and radiological findings • Time of disease evolution < 10 days • Radiological diagnosis of pneumonia grade 2 A, with gas exchange ratio > 200 on blood gas analysis (paO2/pFiO2), characterising mild hypoxaemia • Indication of hospital treatment regime, provided that the period of hospitalisation before inclusion is not more than 24 h • Need for supplemental oxygen therapy (O2) < 5L/min Exclusion criteria: • Do not agree with the terms of the study

RBR-7y8j2bs *(Continued)*

	• Moderate or severe respiratory failure requiring admission to the ICU with the need for invasive mechanical ventilation or non-invasive ventilation with positive pressure (NIV) • Pregnancy or puerperium • People with haematological diseases, coagulation disorders, use of anticoagulants; previous heparin-induced allergy or HIT, thrombocytopenia with a count of < 50,000 platelets/mm^3 • No diagnostic confirmation of COVID-19 by RT-PCR within 72 h of inclusion in the study
Interventions	High molecular weight inhalational heparin (HMWH) (250 µg/mL 0.9% normal saline), who will receive care with the experimental treatment with inhaled HMWH applied in 4-4 h, for 7 days
Outcomes	Safety: related to the use of inhalational high molecular weight heparin in patients with SARS-COV-2 through the assessment of haemorrhagic events of any nature, alteration of the coagulogram that indicates an increase in aPTT > 1, 5 and HIT Efficacy: relative to the proposed treatment, through the analysis of the viral load of the SARS-COV-2 virus in the participants treated by the sequential evaluation of the viral load in RT-PCR of nasal swab
Notes	RBR-7y8j2bs | No data provided

Sholzberg 2021a

Study name	Coagulopathy of COVID-19: a pragmatic randomized controlled trial of therapeutic anticoagulation versus standard care as a rapid response to the COVID-19 pandemic (RAPID COVID COAG)
Starting date	11 May 2020
Contact information	Michelle Sholzberg St. Michael's Hospital, Toronto, Ontario, Canada 416-864-5389 | Michelle.Sholzberg@unityhealth.to
Methods	Multicentre, quadruple masking (participant, care provider, investigator, outcomes assessor), investigator-sponsored, 2-armed, parallel-assignment RCT
Participants	462 participants, ≥ 18 years, female and male Inclusion criteria • Laboratory-confirmed diagnosis of SARS-CoV-2 via RT-PCR as per the WHO protocol or by nucleic acid-based isothermal amplification • Admitted to hospital • 1 D-dimer value ≥ 2 times ULN (within 72 h of hospital admission) • ≥ 18 years • Informed consent from the participant (or legally authorised substitute decision maker) Exclusion criteria • Pregnancy • BMI < 18.5 kg/m^2 or ≥ 40 kg/m^2 • Haemoglobin < 80 g/L in the last 72 h • Platelet count < 50 x 109/L in the last 72 h • Known fibrinogen < 1.5 g/L (if testing deemed clinically indicated by the treating physician prior to the initiation of anticoagulation) • Known INR > 1.8 (if testing deemed clinically indicated by the treating physician prior to the initiation of anticoagulation)

Sholzberg 2021a *(Continued)*

	• Participant already on intermediate dosing of LMWH that cannot be changed (determination of what constitutes an intermediate dose is to be at the discretion of the treating clinician taking the local institutional thromboprophylaxis protocol for high-risk participants into consideration) • Participant already on therapeutic anticoagulation at the time of screening (low- or high-dose nomogram UFH, LMWH, warfarin, DOAC (any dose of dabigatran, apixaban, rivaroxaban, edoxaban) • Participant on dual antiplatelet therapy, when one of the agents cannot be stopped safely • Known bleeding within the last 30 days requiring emergency room presentation or hospitalisation • Known history of a bleeding disorder of an inherited or active acquired bleeding disorder • Known history of HIT • Known allergy to UFH or LMWH • Admitted to the ICU at the time of screening • Treated with non-invasive positive pressure ventilation or invasive mechanical ventilation at the time of screening (of note: high-flow oxygen delivery via nasal cannula is acceptable and is not an exclusion criterion)
Interventions	Experimental: therapeutic anticoagulation • Therapeutic anticoagulation with LMWH or UFH (high-dose nomogram). The choice of LMWH versus UFH will be at the clinician's discretion and dependent on local institutional supply • Therapeutic anticoagulation will be administered until discharged from hospital, 28 days or death. If the participant is admitted to the ICU or requiring ventilatory support, we recommend continuation of the allocated treatment as long as the treating physician is in agreement Comparison: standard care • In Canada and the USA, administration of LMWH, UFH or fondaparinux at thromboprophylactic doses for acutely ill hospitalised medical patients, in the absence of contraindication, is considered standard care
Outcomes	Primary • Composite outcome of ICU admission (yes/no), non-invasive positive pressure ventilation (yes/no), invasive mechanical ventilation (yes/no), or all-cause death (yes/no) up to 28 days (time frame: up to 28 days) Secondary • All-cause death (time frame: up to 28 days) • Composite outcome of ICU admission or all-cause death (time frame: up to 28 days) • Major bleeding (time frame: up to 28 days). Major bleeding as defined by the ISTH Scientific and Standardization Committee recommendation • Number of participants who received red blood cell transfusion (time frame: up to 28 days). Red blood cell transfusion (≥ 1 unit) • Number of participants with transfusion of platelets, frozen plasma, prothrombin complex concentrate, cryoprecipitate and/or fibrinogen concentrate (time frame: up to 28 days) • Number of hospital-free days alive up to day 28 (time frame: up to 28 days) • Number of ICU-free days alive up to day 28 (time frame: up to 28 days) • Number of ventilator-free days alive up to day 28 (time frame: up to 28 days) • Number of participants with VTE (time frame: up to 28 days) • Number of participants with arterial thromboembolism (time frame: up to 28 days) • Number of participants with HIT (time frame: up to 28 days) • Changes in D-dimer up to day 3 (time frame: up to day 3)
Notes	NCT04362085 | No data provided

Vanassche 2020

Study name	A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19: the DAWn-Antico study
Starting date	25/jun/2020
Contact information	Caroline Devooght Herestraat 49 3000 Leuven Belgium caroline.devooght@uzleuven.be
Methods	Multicentre, open-label, randomised clinical trial
Participants	210 participants, ≥ 18 years, female and male Male or non-pregnant female adult ≥ 18 years of age at the time of enrolment, participants eligible for inclusion are hospitalised, adult patients with confirmed and severe COVID-19
Interventions	We compare LMWHs at 50 IU anti-Xa/kg twice daily—or 75 IU anti-Xa twice daily for ICU patients—in combination with aprotinin to standard thromboprophylaxis in hospitalised COVID-19 patients
Outcomes	Primary • Time from day 0 to sustained clinical improvement or live discharge, whichever comes first, whereby a sustained clinical improvement is defined as an improvement of > 2 points vs the highest value of days 0 and 1 and sustained for at least 3 days
Notes	EUCTR2020-001739-28-BE | No data provided

Van Haren 2020

Study name	Nebulised heparin in patients with severe COVID-19 (CHARTER-MT)
Starting date	01 November 2020
Contact information	Frank MP van Haren, MD, PhD Australian National University Helwan University Clinica San Camilo, Argentina +61467051809 | frank.vanharen@anu.edu.au
Methods	Randomised clinical trial
Participants	712 participants, ≥ 18 years, female and male • Age ≥ 18 years • Currently in an ICU or scheduled for transfer to the ICU. During the pandemic, critically ill inpatients might be cared for outside of the walls of the usual physical environment of ICU. For this reason, ICU is defined as an area designated for inpatient care of the critically ill where therapies including invasive mechanical ventilation can be provided. • Endotracheal tube in place • Intubated current or previous day

Van Haren 2020 *(Continued)*

	• PaO2 to FIO2 ratio ≤ 300 while intubated • Acute opacities not fully explained by effusions, lobar/lung collapse and nodules, affecting at least 1 lung quadrant on chest X-ray or CT • The acute opacities on chest X-ray or CT are most likely due to COVID-19 • There is a PCR-positive sample for SARS-CoV-2 within the past 21 days or there are results pending or further testing is planned. The sample can be a nasal or pharyngeal swab, sputum, tracheal aspirate, bronchoalveolar lavage, or another sample from the patient
Interventions	Nebulised UFH (25,000 Units in 5 mL) will be administered 6-hourly via an Aerogen Solo vibrating mesh nebuliser while patients receive invasive mechanical ventilation in ICU and for a maximum of 10 days
Outcomes	Primary • Alive and ventilator-free score (time frame: day 28). Validated hierarchical composite endpoint, based on mortality and ventilator-free days, which is less prone to favour a treatment with discordant effects on survival and days free of ventilation
Notes	NCT04635241 | No data provided

Wilkinson 2020

Study name	A platform to investigate the safety and effectiveness of several new medicines for the treatment of COVID-19 in hospitalised patients
Starting date	08 May 2020
Contact information	Tom Wilkinson Southampton University Faculty of Medicine Mailpoint 810, Level F, South Block Southampton General Hospital SO16 6YD Southampton UK +44 (0)2381 205341 | accord@uhs.nhs.uk
Methods	Multicentre, open-label RCT
Participants	1800 participants, ≥ 18 years, female and male Inclusion criteria: • Adults (= 18 years) with SARS-CoV-2 infection confirmed by laboratory tests and/or point-of-care tests • A score of Grade 3-5 on the 9-point ordinal scale • Is a woman who is not of childbearing potential or the patient, and their partner(s), agree to use medically-accepted double-barrier methods of contraception (e.g. barrier methods, including male condom, female condom or diaphragm with spermicidal gel) during the study and for at least 6 weeks after termination of study therapy • Ability to provide informed consent signed by the study patient or legally authorised representative Exclusion criteria: • Patients who have previously had a score of 6 or 7 on the 9-point ordinal scale • Any patient whose interests are not best served by study participation, as determined by a senior attending clinician • ALT/AST > 5 × the ULN • Known active infection with HIV or hepatitis B or C

Wilkinson 2020 *(Continued)*

- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated GFR < 30 mL/min/1.73 m^2)
- History of the following cardiac conditions:
  - myocardial infarction within 3 months prior to the first dose
  - unstable angina
  - history of clinically significant dysrhythmias (long QT features on ECG, sustained bradycardia (= 55 beats/min)), left bundle branch block, cardiac pacemaker or ventricular arrhythmia) or history of familial long QT
- Screening 12-lead ECG with a measurable QTc interval according to Fridericia correction (QTcF) > 500 ms
- Anticipated transfer to another hospital that is not a study centre within 72 h
- Allergy to any study medication
- Experimental off-label usage of medicinal products as treatments for COVID-19
- Patients participating in another clinical study of an investigational medicinal product

Interventions	The study consists of 2 stages: • Stage 1 of the study (evaluation/pilot) will evaluate the candidate agents as an add-on to the standard care to assess preliminary safety and efficacy. A patient will be considered to be a responder if they show an improvement of at least 2 points (from randomisation) on a 9-point category ordinal scale, are discharged from hospital, or are considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by day 29. The time to response will be analysed on day 29 and used to evaluate if an agent should proceed to Stage 2 of the study. Stage 1 data will additionally be used to determine optimal study endpoints, and the number of patients to enrol into Stage 2 of the study. • Stage 2 of the study (confirmation) is intended to provide confirmatory data of the identified candidate agents from Stage 1, to fully evaluate disease outcomes, including severe AEs, overall AEs, sdverse event of special interest, disease-related co-infection complications (e.g. pneumonia, septic shock), and overall mortality in an expansion stage. Patients and outcomes from Stage 1 will not form part of Stage 2 • Some candidate agents will still be in Stage 1 of the study at the point where other candidate agents have progressed to Stage 2 • First dose of candidate agent must take place within 72 h of investigator receipt of laboratory or validated point-of-care test confirmation of SARS-CoV-2 infection. This may include results from a test that was performed prior to hospital admission if, in the opinion of the Investigator, it is relevant to ongoing COVID-19 infection. Any exceptions to this must be authorised by the Chief Investigator or delegate
Outcomes	Primary • Time to clinical improvement of at least 2 points (from randomisation) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by day 29 (this will also define the 'responder' for the response rate analyses) Secondary Measured from patient records unless otherwise noted: • The proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on days 2, 8, 15, 22, and 29 • Duration (days) of oxygen use and oxygen-free days • Duration (days) of ventilation and ventilation-free days • Incidence of any form of new ventilation use and duration (days) of new ventilation use • Qualitative and quantitative PCR determination of SARS CoV 2 in oropharyngeal/nasal swab while hospitalised on days 1, 3, 5, 8, 11, 15, and (optional) day 29 • Response rate (number and %) by treatment arm at days 2, 8, 15, 22, and 29 • Time to live discharge from the hospital

Wilkinson 2020 *(Continued)*

- Mortality at days 15, 29, and 60
- Time from treatment start date to death
- Change in SpO2/FiO2 ratio, measured daily from randomisation to day 15, hospital discharge, or death
- Safety of candidate agents measured using:
  - physical examination
  - clinical laboratory examinations
  - vital signs (blood pressure/heart rate/temperature/respiratory rate)
  - AEs
  - duration (days) of ICU and hospitalisation
- NEWS2 assessed daily while hospitalised and on days 15 and 29
- Time to a NEWS2 of = 2, maintained for at least 24 h

Notes	ISRCTN57085639 | No data provided

aPTT: activated partial thromboplastin time; **ACS**: acute coronary syndrome; **ACCT:** Adaptive COVID-19 Treatment Trial; **AE:** adverse event; **AKI:** acute kidney injury; **AKIN:** **A**cute Kidney Injury Network; **ALT:** alanine aminotransferase; **ANC:** absolute neutrophil count; **ARDS**: acute respiratory distress syndrome; **ARs**: adverse reactions; **AST:** aspartate aminotransferase; **BARC:** Bleeding Academic Research Consortium; **BiPAP:** bilevel positive airway pressure; **BMI:** body mass index; **BP:** blood pressure; **CKI-EPI:** Chronic Kidney Disease Epidemiology Collaboration; **CNS:** central nervous system; **COPD:** chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **CPR**: cardiopulmonary resuscitation; **CrCl:** creatinine clearance; **CUS:** serial compression ultrasonography; **CT:** computed tomography; **CVVHD:** continuous veno-venous haemodialysis; **DBP:** diastolic blood pressure; **DIC:** disseminated intravascular coagulation; **DMARDs:** **d**isease-modifying antirheumatic drugs; **DOAC:** direct oral anticoagulant; **DVT:** deep vein thrombosis; **ECG:** electrocardiogram; **ECMO:** extracorporeal membrane oxygenation; **ELISA:** enzyme-linked immunosorbent assay; **ESKD:** end-stage kidney disease; **FiO2:** fraction of inspired oxygen concentration; **FSH:** follicle-stimulating hormone; **GFR**: glomerular filtration rate; **GI:** gastrointestinal; **GGT:** glutamyltransferases; **HCG:** human chorionic gonadotropin; **HFOV:** high-frequency oscillatory ventilation; **HIT:** heparin-induced thrombocytopenia **ICU:** intensive care unit; **INR:** international normalised ratio; **ISTH:** International Society on Thrombosis and Haemostasis; **IV:** intravenous(ly); **JAKi:** Janus kinase inhibitors; **LMWH:** low molecular weight heparin; **MOHFW**: Ministry of Health and Family Welfare; **MVTE:** Major vascular thrombotic events; **NEWS:** National Early Warning Score; **NIV:** non-invasive ventilation; **NOACS:** novel oral anticoagulants; **NSAIDs:** non-steroidal antiflammatory drugs; **NYHA:** New York Heart Association; **PaO2:** partial pressure of oxygen; **PCR:** polymerase chain reaction; **PD:** Pharmacodynamic; **PE:** pulmonary embolism; **PK:** Pharmacokinetic; **PRCB:** packed red blood cell; **PT(T):** partial thromboplastin (time); **RAS:** Renin-Angiotensin System; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE**: serious adverse event; **SARS:** severe acute respiratory syndrome; **SBP:** systolic blood pressure; **SC:** subcutaneous(ly);**SIC:** sepsis-induced coagulopathy;**SOFA:** sequential organ failure assessment; **SpO2:** ratio of oxygen saturation in the blood; **TB:** tuberculosis; **TIA:** transient ischaemic attack; **UFH:** unfractionated heparin; **ULN:** upper limit of normal; **VKA:** vitamin K antagonists; **VTE:** venous thromboembolism; **WBC:** white blood cells; **WHO:** World Health Organization

DATA AND ANALYSES

Comparison 1. Higher-dose anticoagulants versus lower-dose anticoagulants (short term)

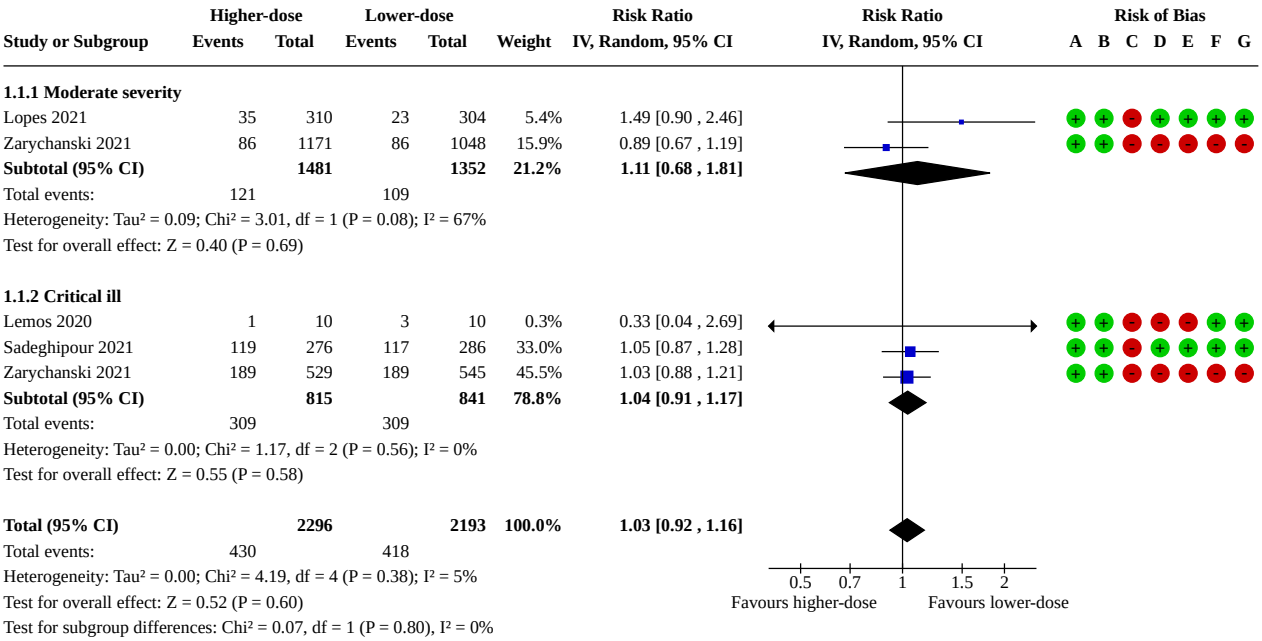
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	4	4489	Risk Ratio (IV, Random, 95% CI)	1.03 [0.92, 1.16]
1.1.1 Moderate severity	2	2833	Risk Ratio (IV, Random, 95% CI)	1.11 [0.68, 1.81]
1.1.2 Critical ill	3	1656	Risk Ratio (IV, Random, 95% CI)	1.04 [0.91, 1.17]
1.2 All-cause mortality - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	1.16 [0.86, 1.57]
1.2.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	1.49 [0.90, 2.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	1.05 [0.87, 1.28]
1.3 Necessity for additional respiratory support	3	3407	Risk Ratio (IV, Random, 95% CI)	0.54 [0.12, 2.47]
1.3.1 Moderate severity	2	2845	Risk Ratio (IV, Random, 95% CI)	0.54 [0.12, 2.47]
1.3.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.4 Necessity for additional respiratory support - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	0.16 [0.02, 1.35]
1.4.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	0.16 [0.02, 1.35]
1.4.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.5 Deep vein thrombosis	4	3422	Risk Ratio (IV, Random, 95% CI)	1.08 [0.57, 2.03]
1.5.1 Moderate severity	2	2840	Risk Ratio (IV, Random, 95% CI)	0.85 [0.38, 1.92]
1.5.2 Critically ill	2	582	Risk Ratio (IV, Random, 95% CI)	1.55 [0.56, 4.26]
1.6 Deep vein thrombosis - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	1.21 [0.53, 2.79]
1.6.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	0.98 [0.29, 3.35]
1.6.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	1.45 [0.47, 4.52]
1.7 Pulmonary embolism	4	4360	Risk Ratio (IV, Random, 95% CI)	0.46 [0.31, 0.70]
1.7.1 Moderate severity	2	2840	Risk Ratio (IV, Random, 95% CI)	0.49 [0.27, 0.88]
1.7.2 Critically ill	3	1520	Risk Ratio (IV, Random, 95% CI)	0.44 [0.25, 0.78]
1.8 Pulmonary embolism - trial at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	0.50 [0.23, 1.10]
1.8.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	0.53 [0.21, 1.31]
1.8.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	0.41 [0.08, 2.12]
1.9 Major bleeding	4	4400	Risk Ratio (IV, Random, 95% CI)	1.78 [1.13, 2.80]
1.9.1 Moderate severity	2	2841	Risk Ratio (IV, Random, 95% CI)	2.25 [1.19, 4.27]
1.9.2 Critically ill	3	1559	Risk Ratio (IV, Random, 95% CI)	1.41 [0.75, 2.67]
1.10 Major bleeding - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	2.13 [0.92, 4.90]
1.10.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	2.45 [0.78, 7.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	1.81 [0.54, 6.13]
1.11 Adverse events (minor bleeding)	3	1196	Risk Ratio (IV, Random, 95% CI)	3.28 [1.75, 6.14]
1.11.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	5.10 [1.98, 13.11]
1.11.2 Critically ill	2	582	Risk Ratio (IV, Random, 95% CI)	2.31 [1.00, 5.36]
1.12 Adverse events (minor bleeding) - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	3.67 [1.82, 7.40]
1.12.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	5.10 [1.98, 13.11]
1.12.2 Critical ill	1	562	Risk Ratio (IV, Random, 95% CI)	2.49 [0.89, 6.97]
1.13 Adverse events (stroke)	3	4349	Risk Ratio (IV, Random, 95% CI)	0.91 [0.40, 2.03]
1.13.1 Moderate severity	2	2840	Risk Ratio (IV, Random, 95% CI)	0.88 [0.13, 5.97]
1.13.2 Critical ill	2	1509	Risk Ratio (IV, Random, 95% CI)	0.91 [0.37, 2.23]
1.14 Adverse events (stroke) - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	1.62 [0.20, 13.13]
1.14.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	2.94 [0.12, 71.94]
1.14.2 Critical ill	1	562	Risk Ratio (IV, Random, 95% CI)	1.04 [0.07, 16.49]
1.15 Adverse events (major adverse limb event)	2	1176	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.99]
1.15.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.99]
1.15.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.16 Adverse events (myocardial infarction)	3	4349	Risk Ratio (IV, Random, 95% CI)	0.86 [0.48, 1.55]
1.16.1 Moderate severity	2	2840	Risk Ratio (IV, Random, 95% CI)	0.91 [0.45, 1.85]
1.16.2 Critically ill	2	1509	Risk Ratio (IV, Random, 95% CI)	0.76 [0.27, 2.17]
1.17 Adverse events (myocardial infarction) - trials at low risk of bias	2	1176	Risk Ratio (IV, Random, 95% CI)	0.91 [0.44, 1.91]
1.17.1 Moderate severity	1	614	Risk Ratio (IV, Random, 95% CI)	0.91 [0.44, 1.91]
1.17.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.18 Adverse events (atrial fibrillation)	1	562	Risk Ratio (IV, Random, 95% CI)	0.35 [0.07, 1.70]

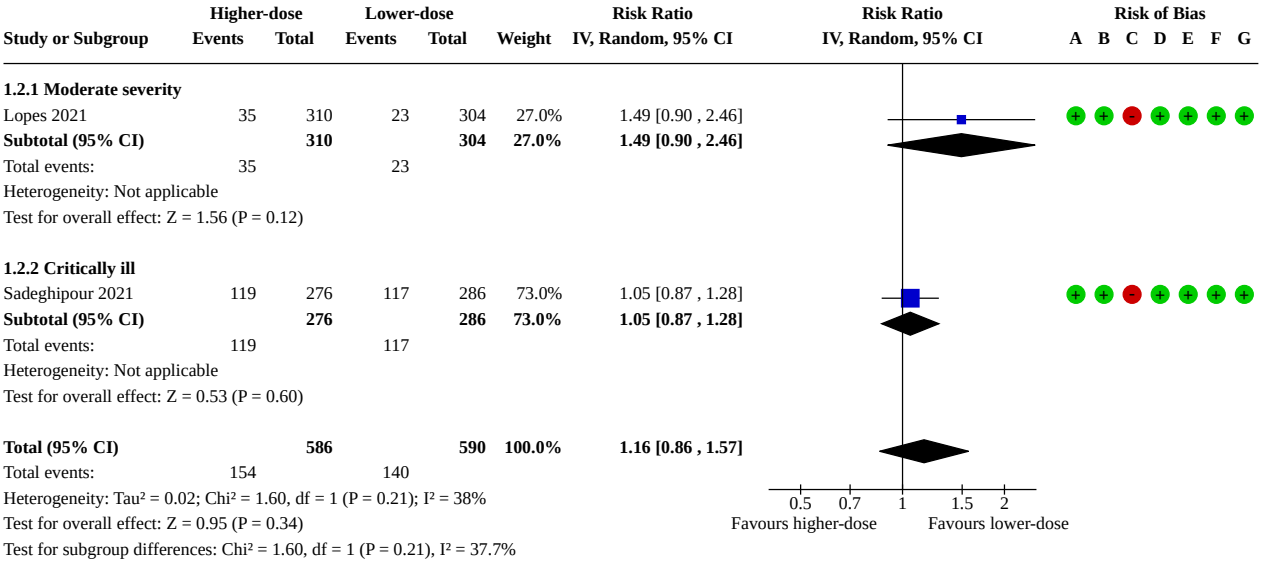
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.19 Adverse events (thrombocytopenia)	2	2789	Risk Ratio (IV, Random, 95% CI)	0.94 [0.71, 1.24]
1.19.1 Moderate severity	1	2227	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.19.2 Critically ill	1	562	Risk Ratio (IV, Random, 95% CI)	0.94 [0.71, 1.24]
1.20 Hospitalisation time	2	634	Mean Difference (IV, Random, 95% CI)	0.28 [-0.87, 1.44]
1.20.1 Moderate severity	1	614	Mean Difference (IV, Random, 95% CI)	0.30 [-0.86, 1.46]
1.20.2 Critically ill	1	20	Mean Difference (IV, Random, 95% CI)	-1.00 [-11.58, 9.58]
1.21 Hospitalisation time - trials at low risk of bias	1	614	Mean Difference (IV, Random, 95% CI)	0.30 [-0.86, 1.46]

Analysis 1.1. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 1: All-cause mortality



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

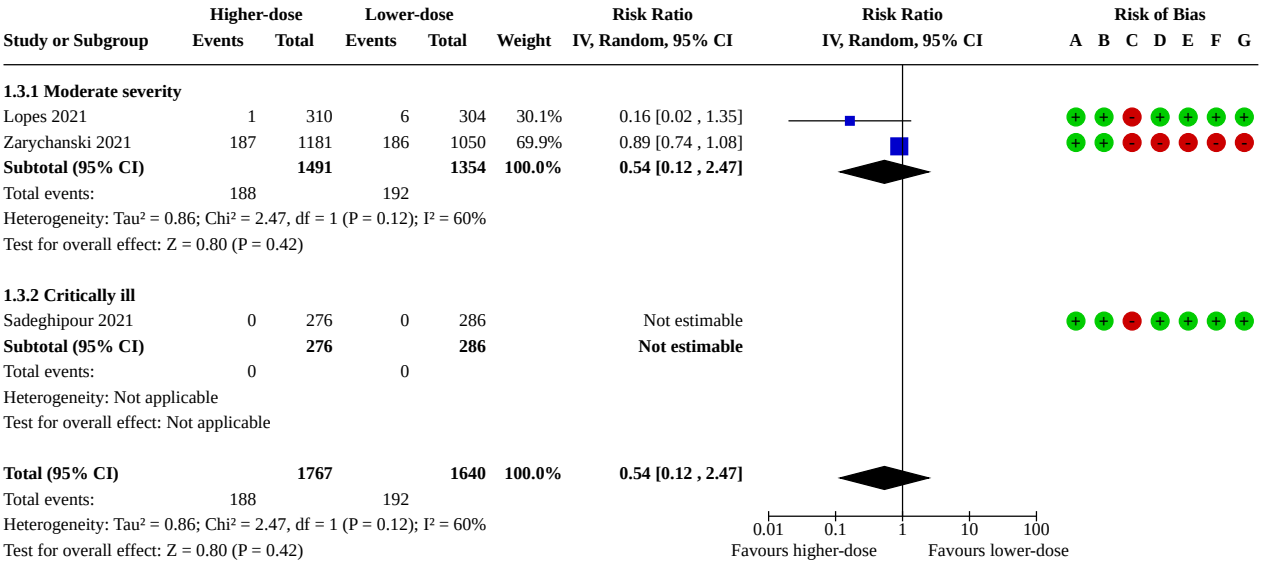
Analysis 1.2. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 2: All-cause mortality - trials at low risk of bias



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

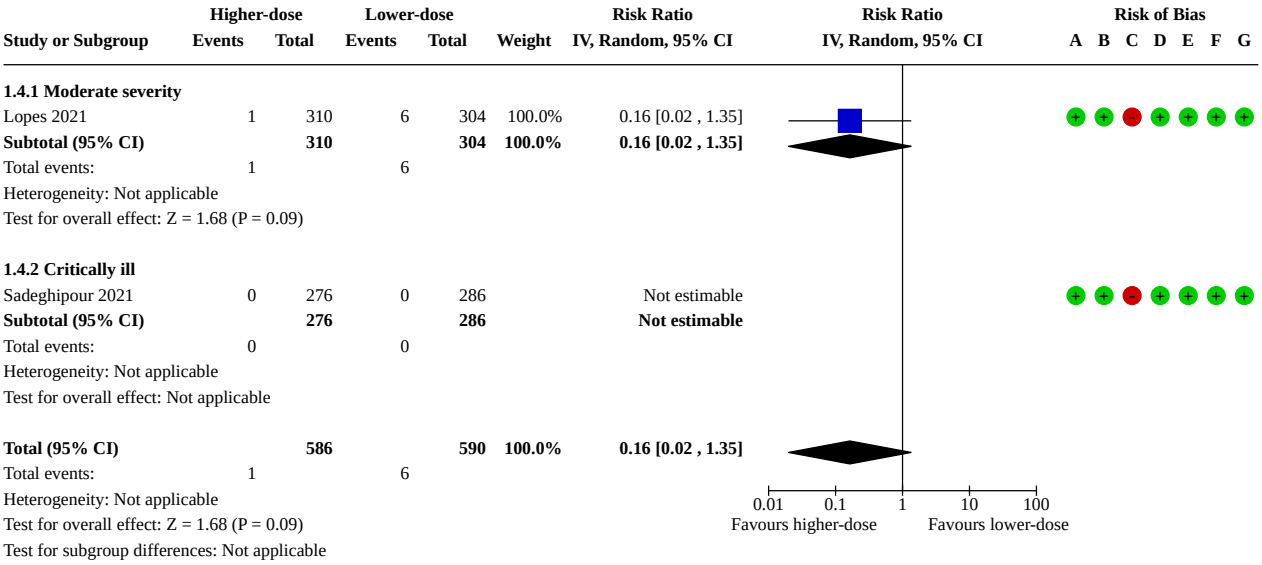
Analysis 1.3. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 3: Necessity for additional respiratory support



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

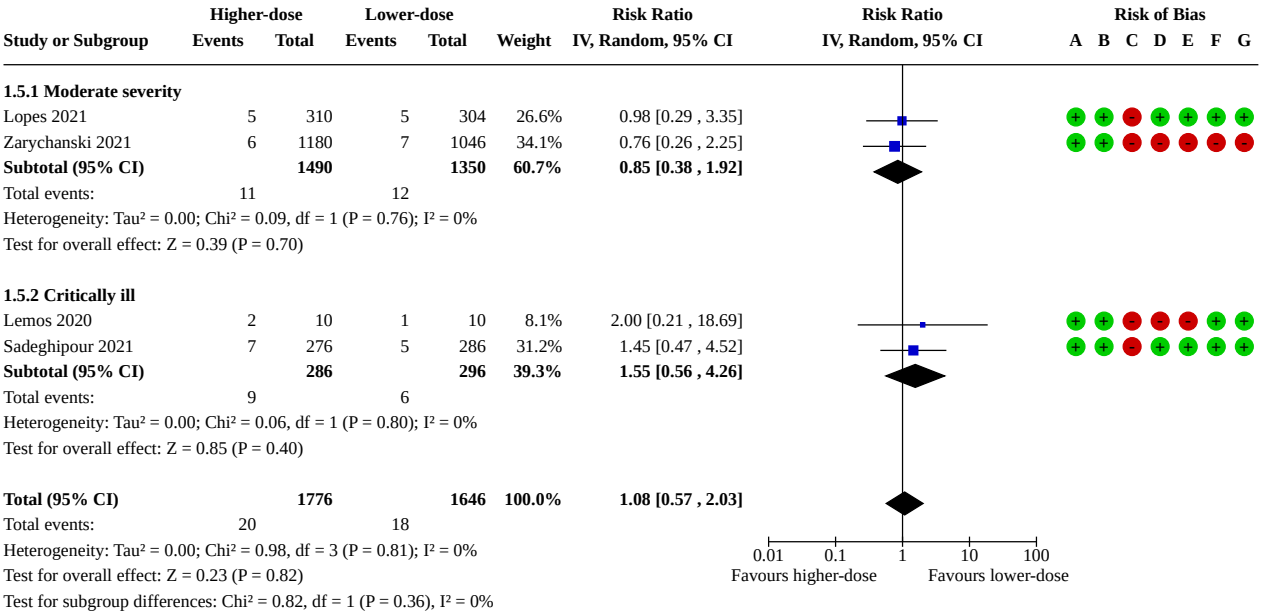
Analysis 1.4. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 4: Necessity for additional respiratory support - trials at low risk of bias



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

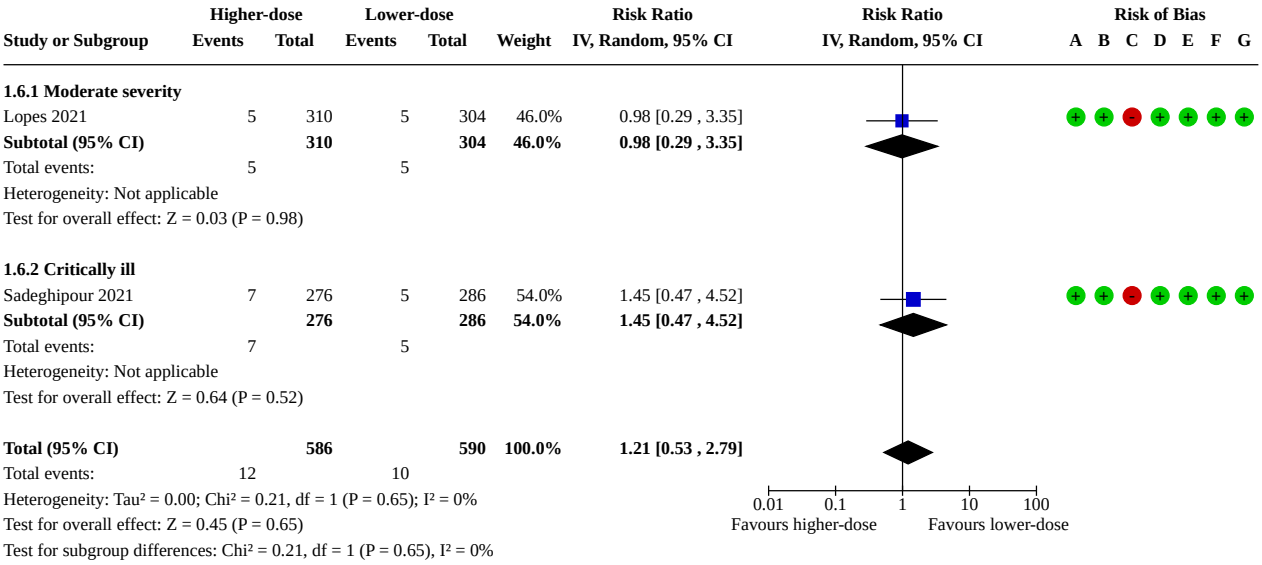
Analysis 1.5. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 5: Deep vein thrombosis



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

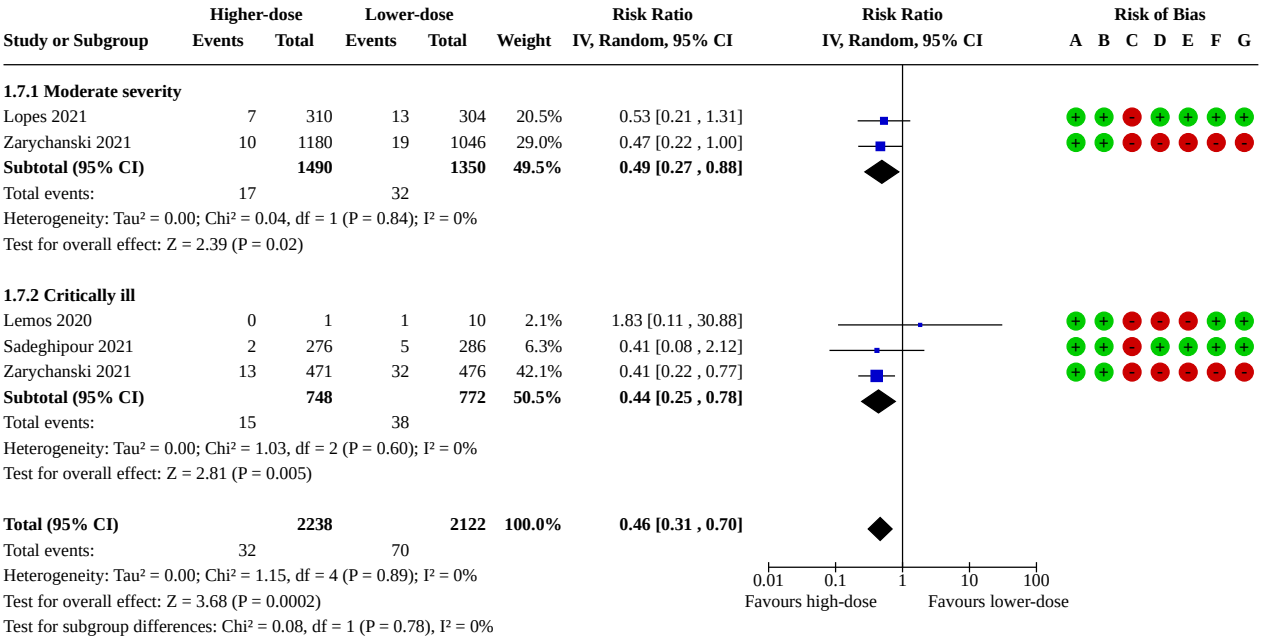
Analysis 1.6. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 6: Deep vein thrombosis - trials at low risk of bias



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

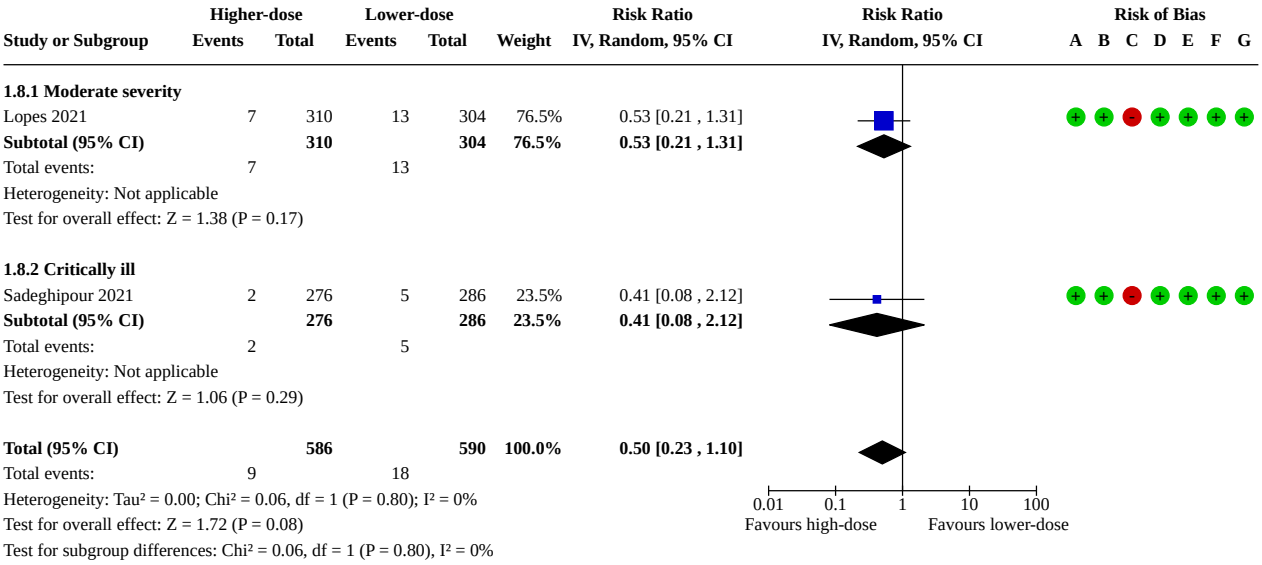
Analysis 1.7. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 7: Pulmonary embolism



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

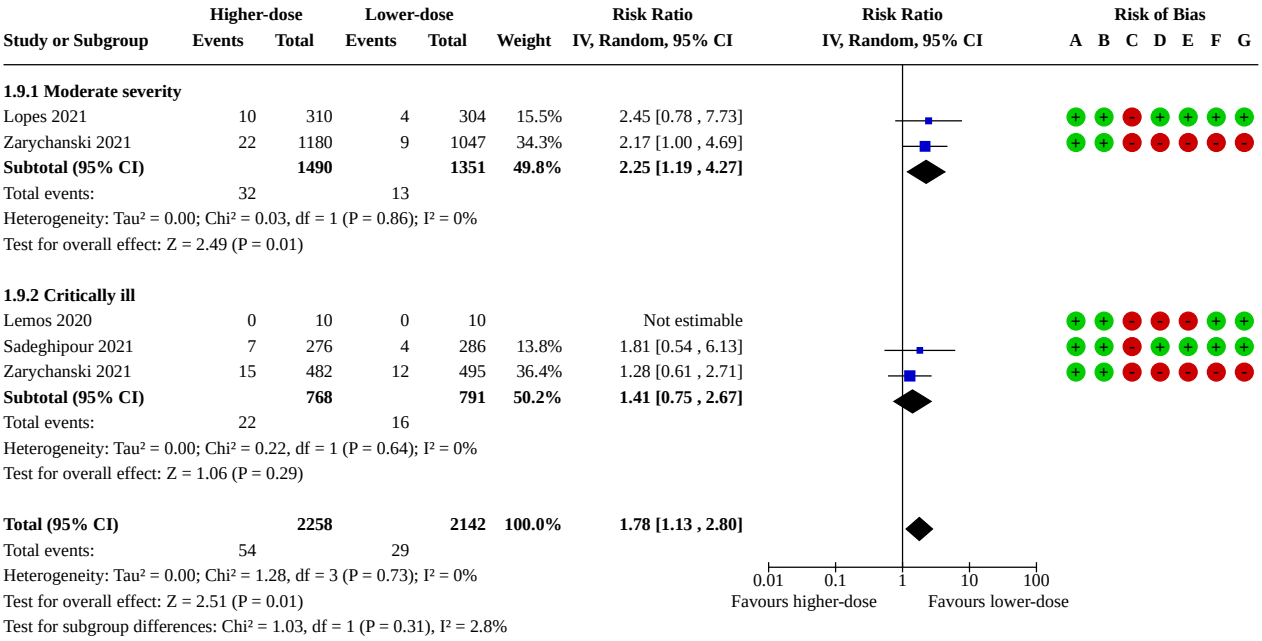
Analysis 1.8. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 8: Pulmonary embolism - trial at low risk of bias



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

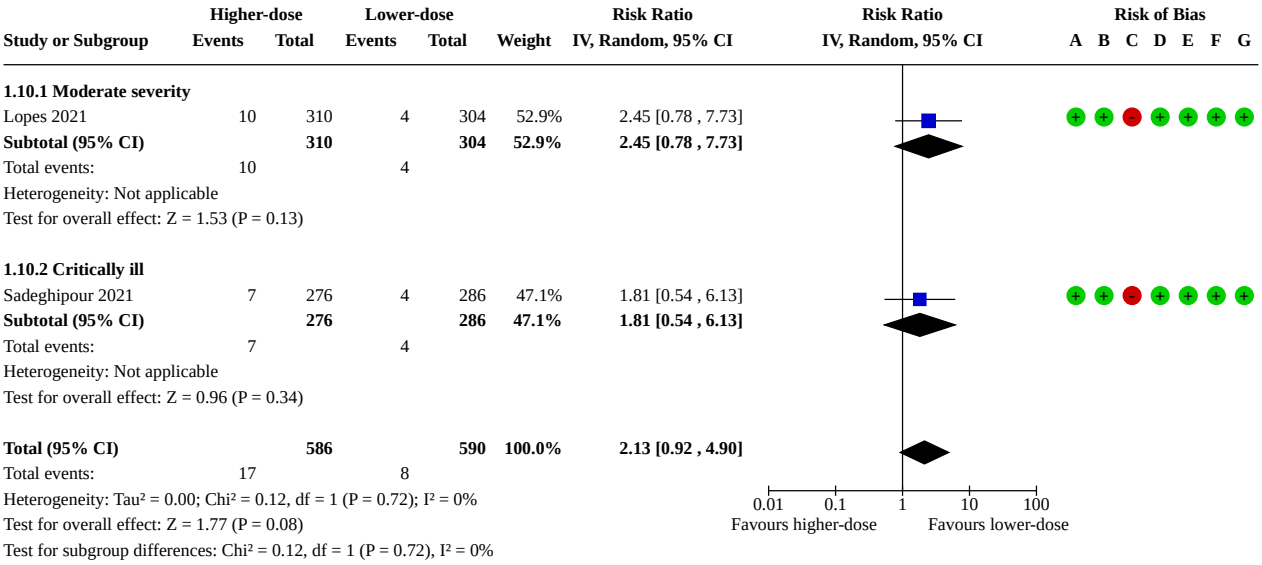
Analysis 1.9. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 9: Major bleeding



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

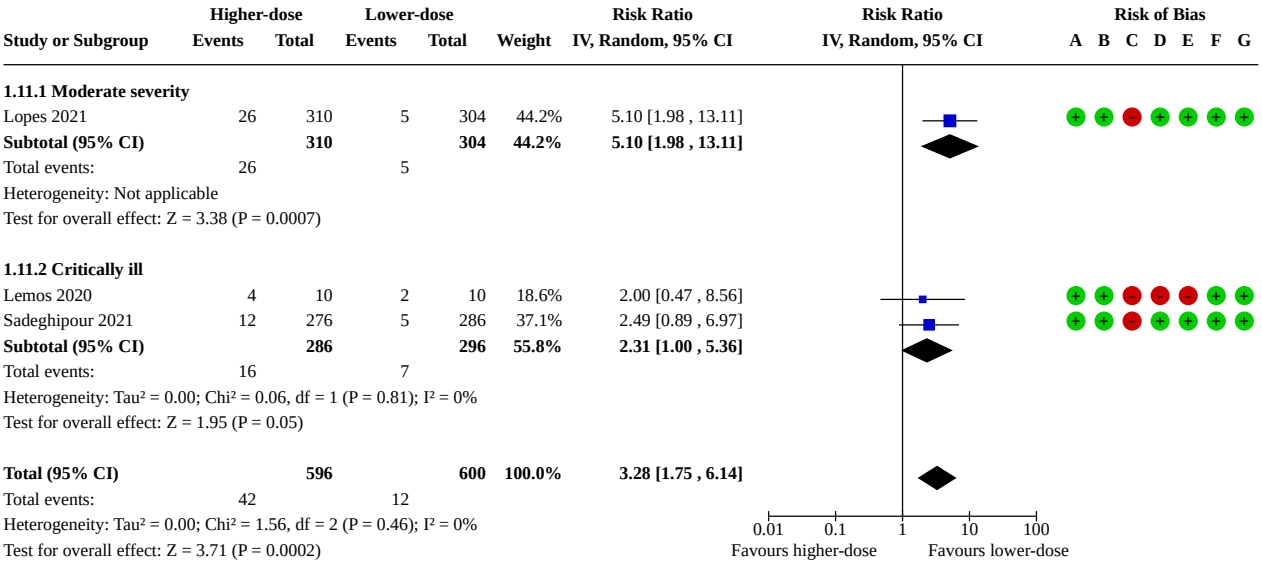
Analysis 1.10. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 10: Major bleeding - trials at low risk of bias



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

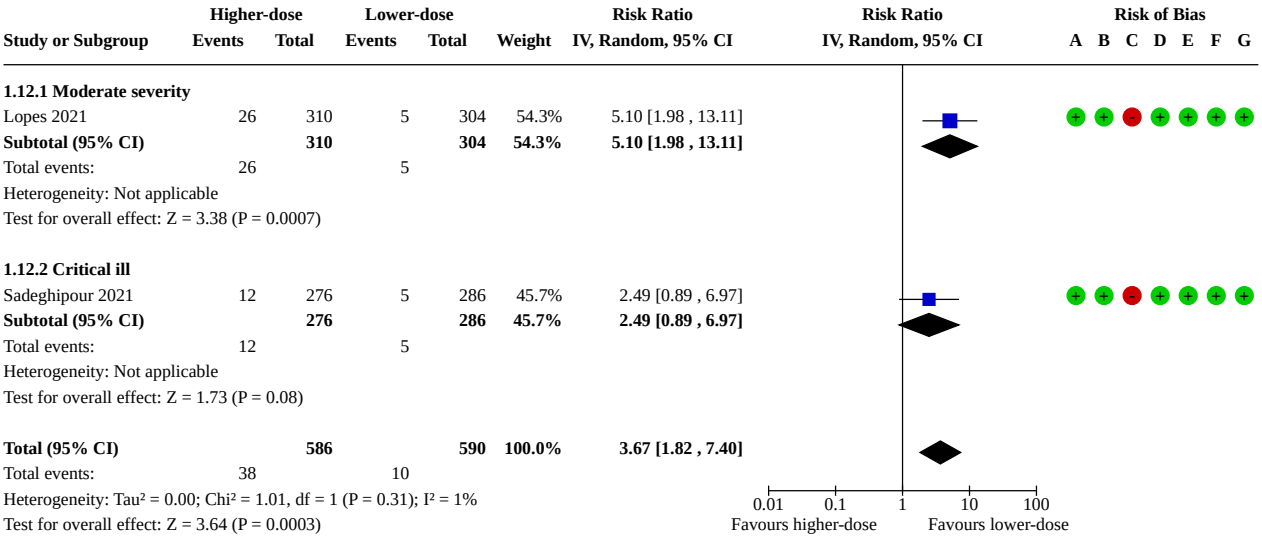
Analysis 1.11. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 11: Adverse events (minor bleeding)



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

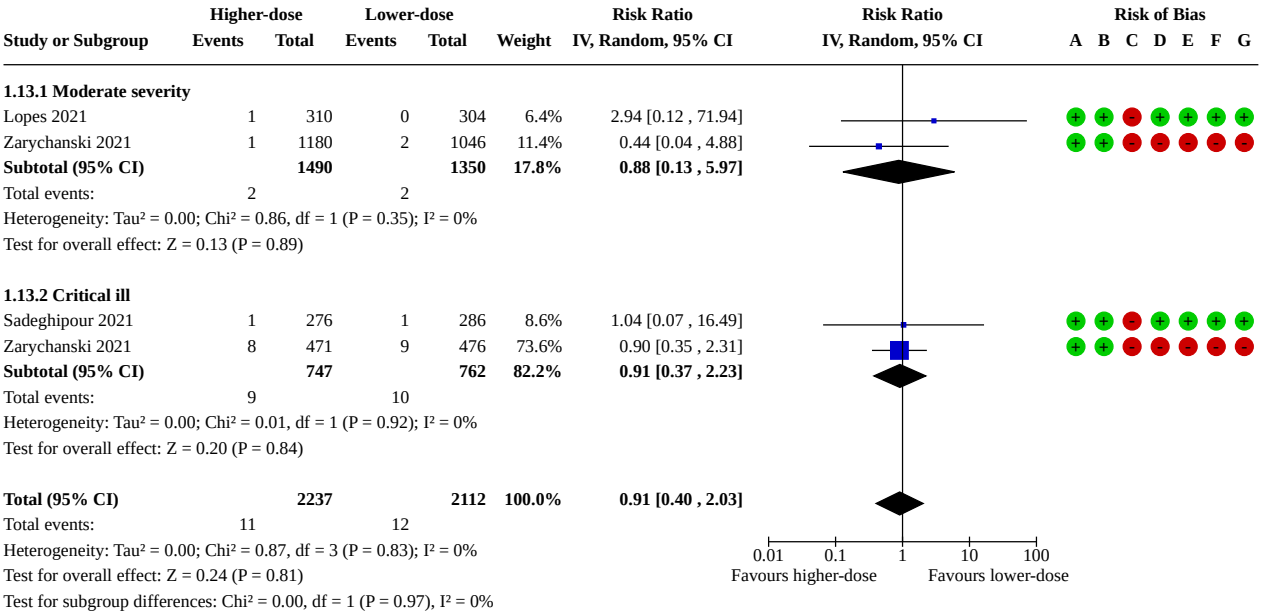
Analysis 1.12. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 12: Adverse events (minor bleeding) - trials at low risk of bias



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

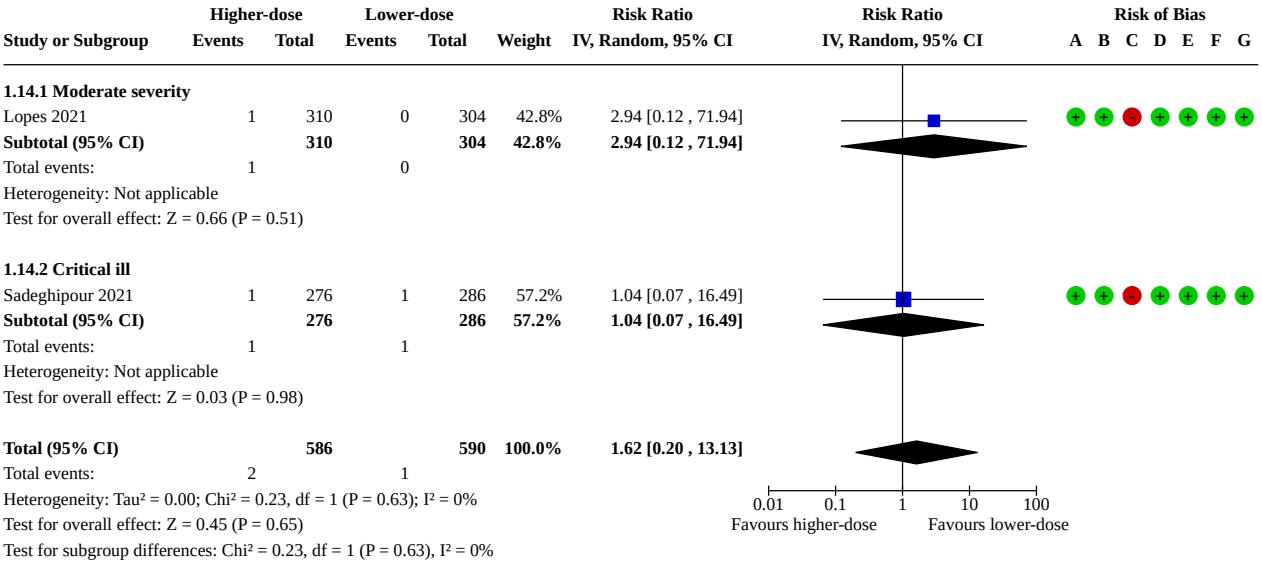
Analysis 1.13. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 13: Adverse events (stroke)



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

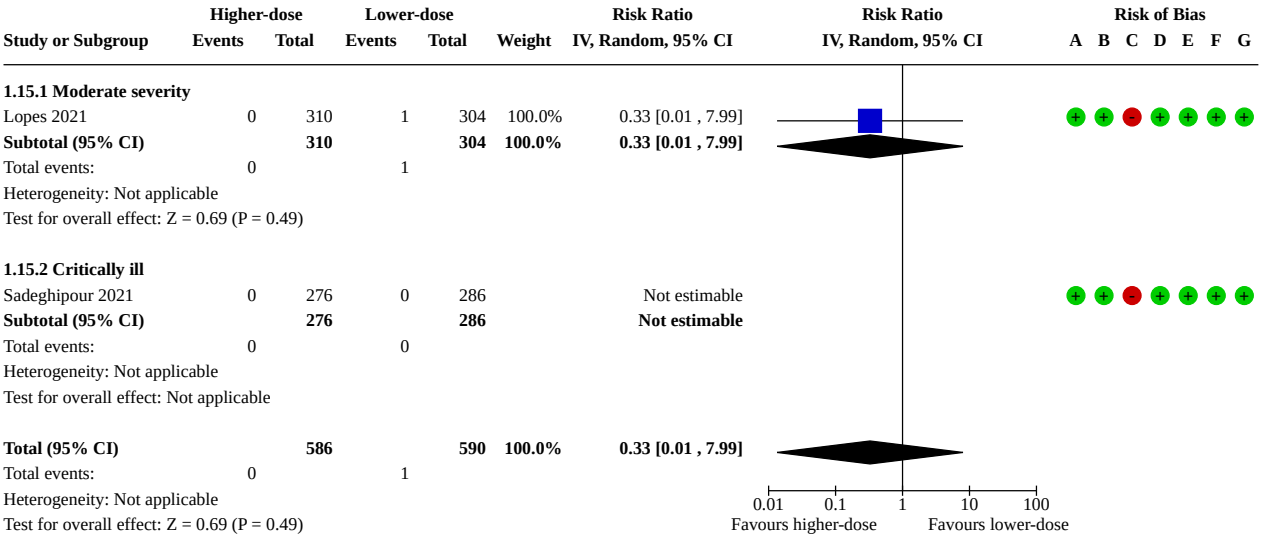
Analysis 1.14. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 14: Adverse events (stroke) - trials at low risk of bias



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

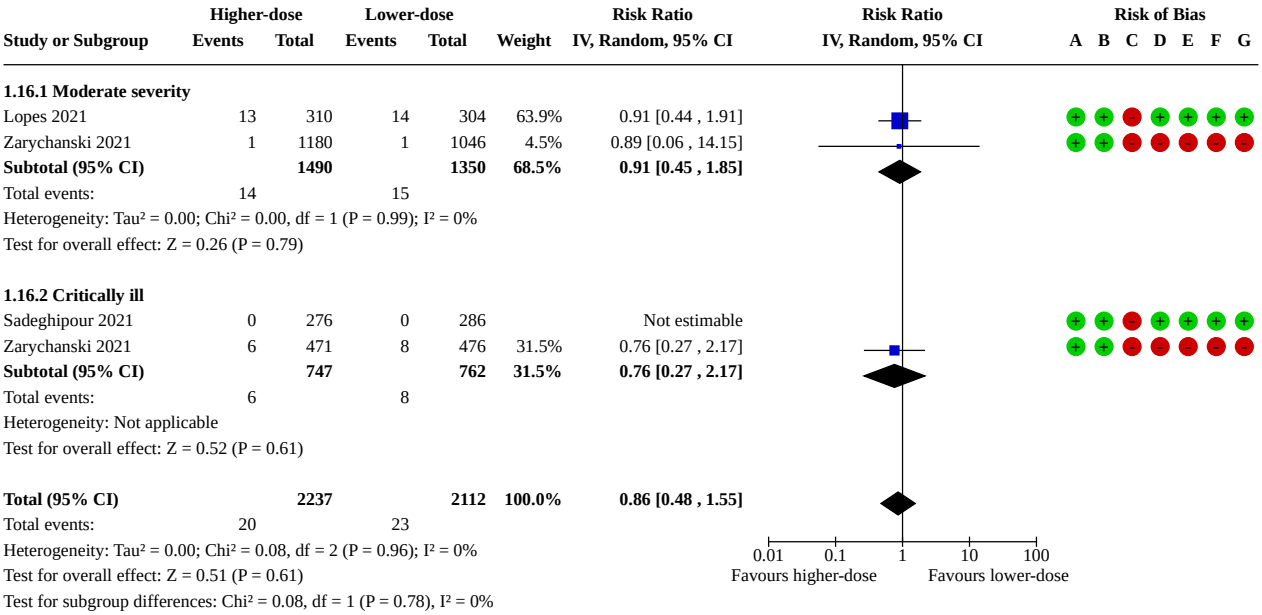
Analysis 1.15. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 15: Adverse events (major adverse limb event)



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

Analysis 1.16. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 16: Adverse events (myocardial infarction)

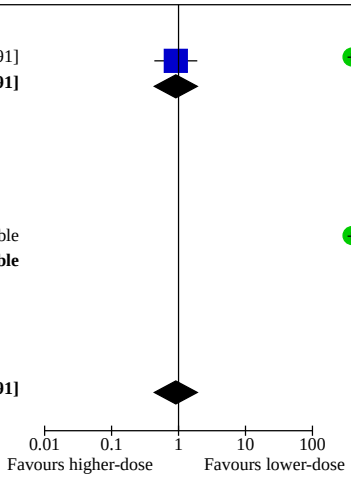


Risk of bias legend

(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

Analysis 1.17. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 17: Adverse events (myocardial infarction) - trials at low risk of bias

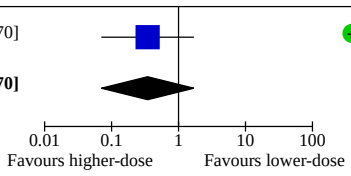
Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
1.17.1 Moderate severity							
Lopes 2021	13	310	14	304	100.0%	0.91 [0.44 , 1.91]	+ + - + + + +
Subtotal (95% CI)		**310**		**304**	**100.0%**	**0.91 [0.44 , 1.91]**	
Total events:	13		14				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
1.17.2 Critically ill							
Sadeghipour 2021	0	276	0	286		Not estimable	+ + - + + + +
Subtotal (95% CI)		**276**		**286**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**586**		**590**	**100.0%**	**0.91 [0.44 , 1.91]**	
Total events:	13		14				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
Test for subgroup differences: Not applicable							



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

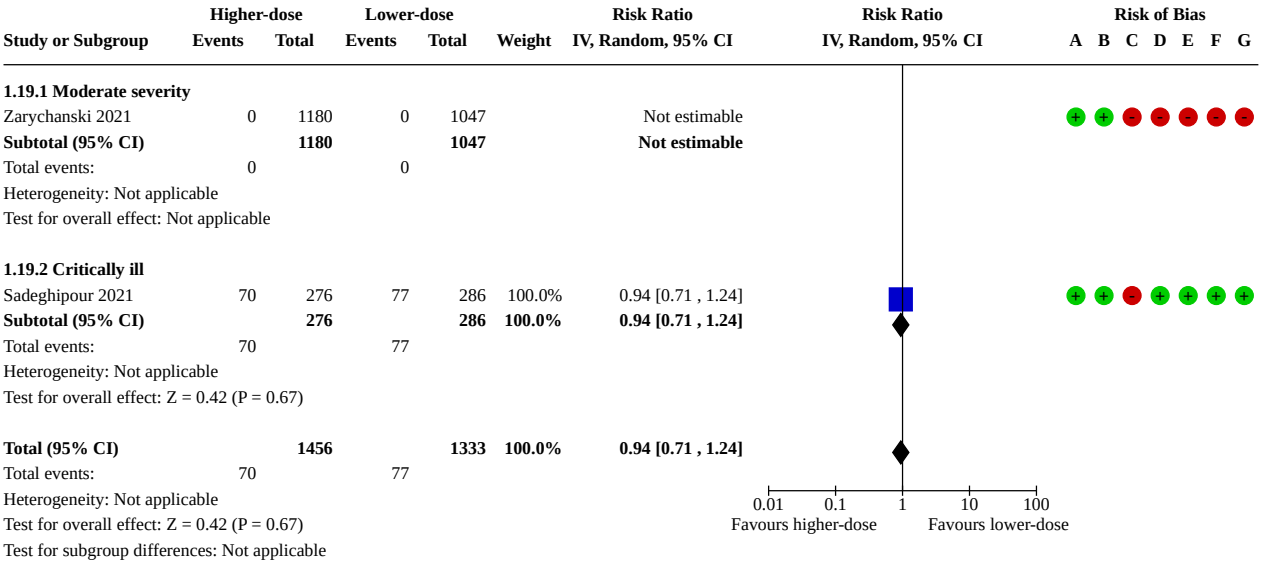
Analysis 1.18. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 18: Adverse events (atrial fibrillation)

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
Sadeghipour 2021	2	276	6	286	100.0%	0.35 [0.07 , 1.70]	+ + - + + + +
Total (95% CI)		**276**		**286**	**100.0%**	**0.35 [0.07 , 1.70]**	
Total events:	2		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.31 (P = 0.19)							
Test for subgroup differences: Not applicable							



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

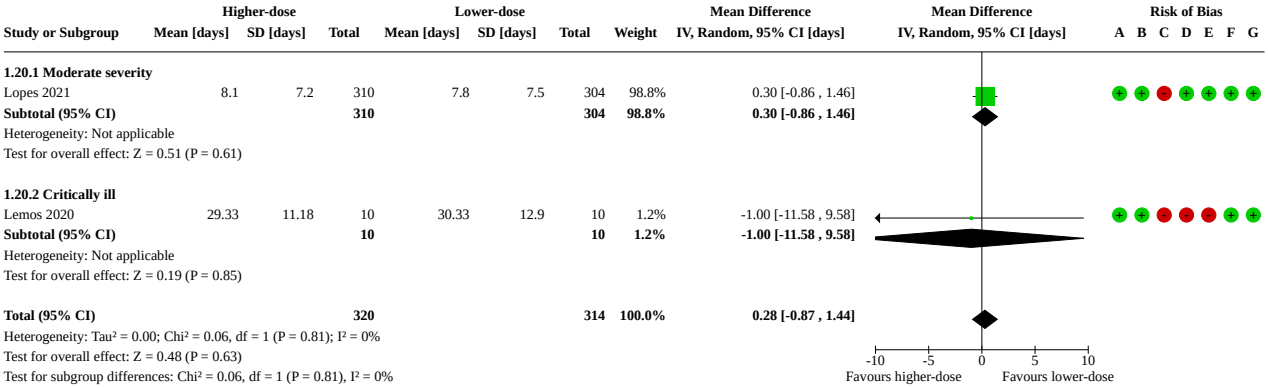
Analysis 1.19. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 19: Adverse events (thrombocytopenia)



Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI
1.19.1 Moderate severity						
Zarychanski 2021	0	1180	0	1047		Not estimable
Subtotal (95% CI)		**1180**		**1047**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.19.2 Critically ill						
Sadeghipour 2021	70	276	77	286	100.0%	0.94 [0.71 , 1.24]
Subtotal (95% CI)		**276**		**286**	**100.0%**	**0.94 [0.71 , 1.24]**
Total events:	70		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
Total (95% CI)		**1456**		**1333**	**100.0%**	**0.94 [0.71 , 1.24]**
Total events:	70		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Not applicable						

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

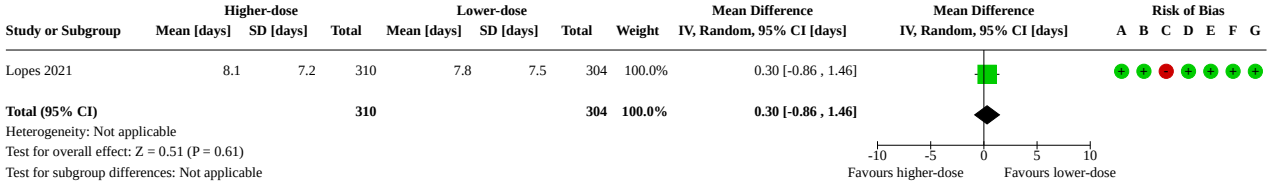
Analysis 1.20. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 20: Hospitalisation time



Study or Subgroup	Higher-dose Mean [days]	Higher-dose SD [days]	Higher-dose Total	Lower-dose Mean [days]	Lower-dose SD [days]	Lower-dose Total	Weight	Mean Difference IV, Random, 95% CI [days]
1.20.1 Moderate severity								
Lopes 2021	8.1	7.2	310	7.8	7.5	304	98.8%	0.30 [-0.86 , 1.46]
Subtotal (95% CI)			**310**			**304**	**98.8%**	**0.30 [-0.86 , 1.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.51 (P = 0.61)								
1.20.2 Critically ill								
Lemos 2020	29.33	11.18	10	30.33	12.9	10	1.2%	-1.00 [-11.58 , 9.58]
Subtotal (95% CI)			**10**			**10**	**1.2%**	**-1.00 [-11.58 , 9.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.19 (P = 0.85)								
Total (95% CI)			**320**			**314**	**100.0%**	**0.28 [-0.87 , 1.44]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%								
Test for overall effect: Z = 0.48 (P = 0.63)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								

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

Analysis 1.21. Comparison 1: Higher-dose anticoagulants versus lower-dose anticoagulants (short term), Outcome 21: Hospitalisation time - trials at low risk of bias



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

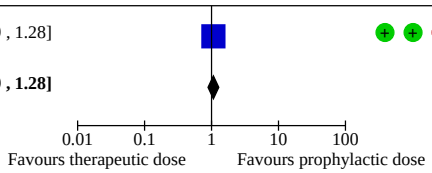
Comparison 2. Higher-dose anticoagulants versus lower-dose anticoagulants (long term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	1	590	Risk Ratio (IV, Random, 95% CI)	1.07 [0.89, 1.28]
2.2 Necessity for additional respiratory support	1	590	Risk Ratio (IV, Random, 95% CI)	Not estimable
2.3 Deep vein thrombosis	1	590	Risk Ratio (IV, Random, 95% CI)	1.39 [0.45, 4.33]
2.4 Pulmonary embolism	1	590	Risk Ratio (IV, Random, 95% CI)	0.40 [0.08, 2.03]
2.5 Major bleeding	1	590	Risk Ratio (IV, Random, 95% CI)	1.74 [0.51, 5.87]
2.6 Adverse events (minor bleeding)	1	590	Risk Ratio (IV, Random, 95% CI)	2.32 [0.90, 5.95]
2.7 Adverse events (stroke)	1	590	Risk Ratio (IV, Random, 95% CI)	0.99 [0.06, 15.80]
2.8 Adverse events (acute peripheral arterial thrombosis)	1	590	Risk Ratio (IV, Random, 95% CI)	Not estimable
2.9 Adverse events (myocardial infarction)	1	590	Risk Ratio (IV, Random, 95% CI)	Not estimable
2.10 Adverse events (atrial fibrillation)	1	590	Risk Ratio (IV, Random, 95% CI)	0.50 [0.13, 1.97]
2.11 Adverse events (thrombocytopenia)	1	590	Risk Ratio (IV, Random, 95% CI)	12.91 [0.73, 228.18]

Analysis 2.1. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 1: All-cause mortality

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
Sadeghipour 2021	132	296	123	294	100.0%	1.07 [0.89 , 1.28]		+ + - + + + +
Total (95% CI)		**296**		**294**	**100.0%**	**1.07 [0.89 , 1.28]**		
Total events:	132		123					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

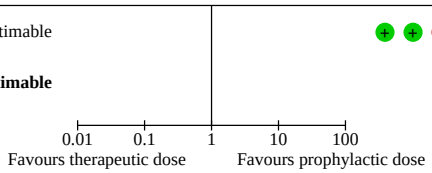


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.2. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 2: Necessity for additional respiratory support

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
Sadeghipour 2021	0	296	0	294		Not estimable		+ + - + + + +
Total (95% CI)		**296**		**294**		**Not estimable**		
Total events:	0		0					

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

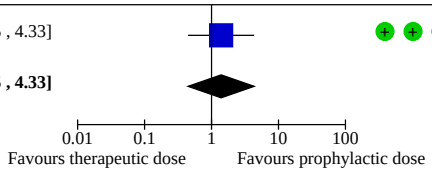


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.3. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 3: Deep vein thrombosis

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
Sadeghipour 2021	7	296	5	294	100.0%	1.39 [0.45 , 4.33]		+ + - + + + +
Total (95% CI)		**296**		**294**	**100.0%**	**1.39 [0.45 , 4.33]**		
Total events:	7		5					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable

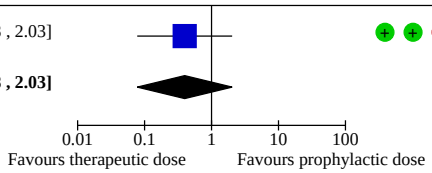


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.4. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 4: Pulmonary embolism

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
Sadeghipour 2021	2	296	5	294	100.0%	0.40 [0.08 , 2.03]		+ + - + + + +
Total (95% CI)		**296**		**294**	**100.0%**	**0.40 [0.08 , 2.03]**		
Total events:	2		5					

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable

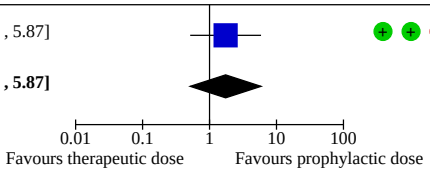


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.5. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 5: Major bleeding

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI
Sadeghipour 2021	7	296	4	294	100.0%	1.74 [0.51 , 5.87]
Total (95% CI)		**296**		**294**	**100.0%**	**1.74 [0.51 , 5.87]**
Total events:	7		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

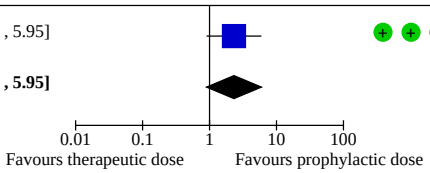


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.6. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 6: Adverse events (minor bleeding)

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI
Sadeghipour 2021	14	296	6	294	100.0%	2.32 [0.90 , 5.95]
Total (95% CI)		**296**		**294**	**100.0%**	**2.32 [0.90 , 5.95]**
Total events:	14		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable

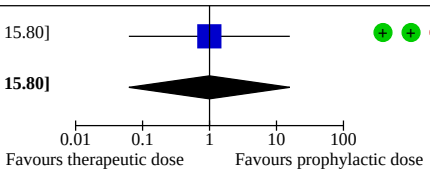


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.7. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 7: Adverse events (stroke)

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI
Sadeghipour 2021	1	296	1	294	100.0%	0.99 [0.06 , 15.80]
Total (95% CI)		**296**		**294**	**100.0%**	**0.99 [0.06 , 15.80]**
Total events:	1		1			

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

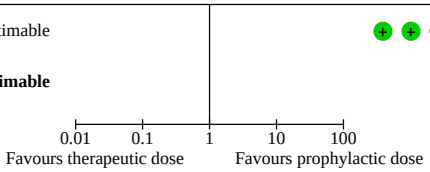


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.8. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 8: Adverse events (acute peripheral arterial thrombosis)

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI
Sadeghipour 2021	0	296	0	294		Not estimable
Total (95% CI)		**296**		**294**		**Not estimable**
Total events:	0		0			

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

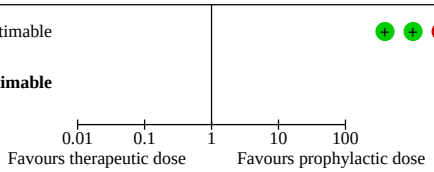


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.9. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 9: Adverse events (myocardial infarction)

Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
Sadeghipour 2021	0	296	0	294		Not estimable	+	+	-	+	+	+	+
Total (95% CI)		**296**		**294**		**Not estimable**							
Total events:	0		0										

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

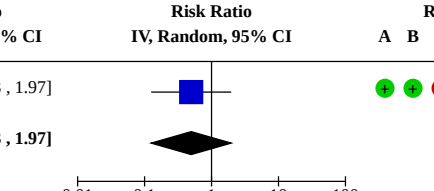


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.10. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 10: Adverse events (atrial fibrillation)

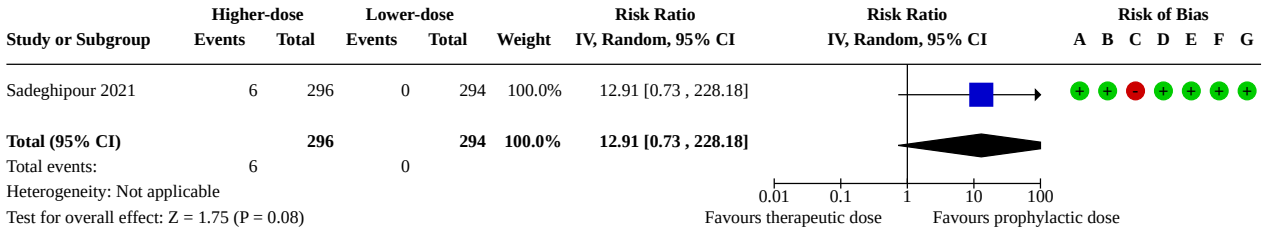
Study or Subgroup	Higher-dose Events	Higher-dose Total	Lower-dose Events	Lower-dose Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
Sadeghipour 2021	3	296	6	294	100.0%	0.50 [0.13 , 1.97]	+	+	-	+	+	+	+
Total (95% CI)		**296**		**294**	**100.0%**	**0.50 [0.13 , 1.97]**							
Total events:	3		6										

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



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

Analysis 2.11. Comparison 2: Higher-dose anticoagulants versus lower-dose anticoagulants (long term), Outcome 11: Adverse events (thrombocytopenia)



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

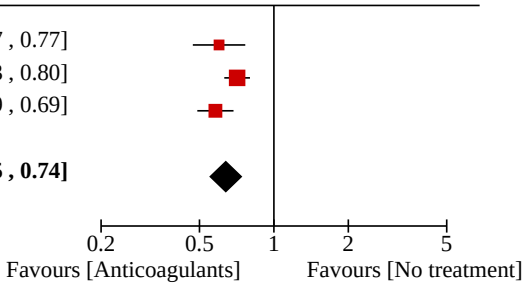
Comparison 3. Anticoagulants versus no treatment (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	3		Risk Ratio (IV, Random, 95% CI)	0.64 [0.55, 0.74]
3.2 Deep vein thrombosis	1	1403	Risk Ratio (IV, Random, 95% CI)	5.67 [1.30, 24.70]
3.3 Pulmonary embolism	1	1403	Risk Ratio (IV, Random, 95% CI)	24.19 [3.31, 176.53]
3.4 Major bleeding	2	7218	Risk Ratio (IV, Random, 95% CI)	1.19 [0.66, 2.12]
3.5 Adverse events (stroke)	1	1403	Risk Ratio (IV, Random, 95% CI)	1.13 [0.32, 4.00]
3.6 Adverse events (myocardial infarction)	1	1403	Risk Ratio (IV, Random, 95% CI)	15.88 [0.93, 270.48]
3.7 Hospitalisation time	1	1376	Mean Difference (IV, Random, 95% CI)	5.00 [4.47, 5.53]

Analysis 3.1. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 1: All-cause mortality

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Albani 2020	-0.5108	0.1246	22.3%	0.60 [0.47 , 0.77]
Rentsch 2020	-0.3425	0.061	44.0%	0.71 [0.63 , 0.80]
Santoro 2020	-0.5447	0.086	33.7%	0.58 [0.49 , 0.69]
Total (95% CI)			**100.0%**	**0.64 [0.55 , 0.74]**

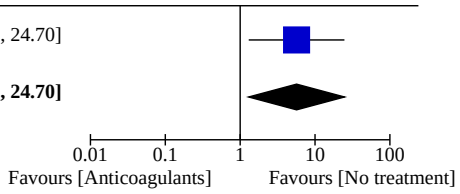
Heterogeneity: Tau² = 0.01; Chi² = 4.24, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 6.14 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 2: Deep vein thrombosis

Study or Subgroup	Anticoagulants Events	Anticoagulants Total	No treatment Events	No treatment Total	Weight	Risk Ratio IV, Random, 95% CI
Albani 2020	15	799	2	604	100.0%	5.67 [1.30 , 24.70]
Total (95% CI)		**799**		**604**	**100.0%**	**5.67 [1.30 , 24.70]**
Total events:	15		2			

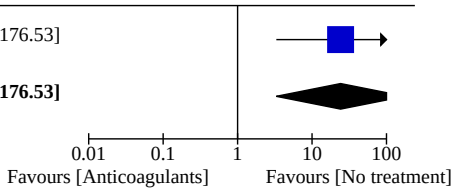
Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 3: Pulmonary embolism

Study or Subgroup	Anticoagulants Events	Anticoagulants Total	No treatment Events	No treatment Total	Weight	Risk Ratio IV, Random, 95% CI
Albani 2020	32	799	1	604	100.0%	24.19 [3.31 , 176.53]
Total (95% CI)		**799**		**604**	**100.0%**	**24.19 [3.31 , 176.53]**
Total events:	32		1			

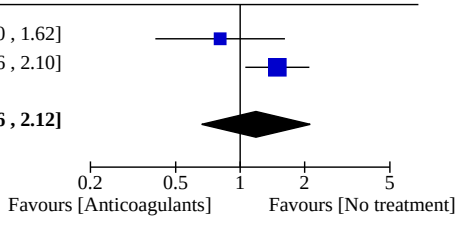
Heterogeneity: Not applicable
Test for overall effect: Z = 3.14 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 4: Major bleeding

Study or Subgroup	Anticoagulants Events	Anticoagulants Total	No treatment Events	No treatment Total	Weight	Risk Ratio IV, Random, 95% CI
Albani 2020	16	799	15	604	37.4%	0.81 [0.40 , 1.62]
Santoro 2020	70	2601	58	3214	62.6%	1.49 [1.06 , 2.10]
Total (95% CI)		**3400**		**3818**	**100.0%**	**1.19 [0.66 , 2.12]**
Total events:	86		73			

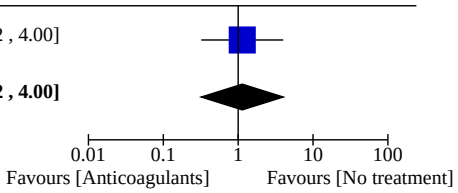
Heterogeneity: Tau² = 0.11; Chi² = 2.41, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 5: Adverse events (stroke)

Study or Subgroup	Anticoagulants Events	Anticoagulants Total	No treatment Events	No treatment Total	Weight	Risk Ratio IV, Random, 95% CI
Albani 2020	6	799	4	604	100.0%	1.13 [0.32 , 4.00]
Total (95% CI)		**799**		**604**	**100.0%**	**1.13 [0.32 , 4.00]**
Total events:	6		4			

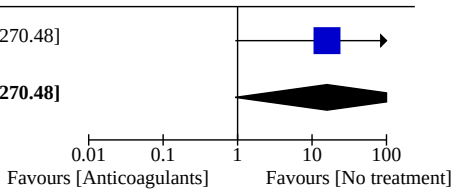
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 6: Adverse events (myocardial infarction)

Study or Subgroup	Anticoagulants Events	Anticoagulants Total	No treatment Events	No treatment Total	Weight	Risk Ratio IV, Random, 95% CI
Albani 2020	10	799	0	604	100.0%	15.88 [0.93 , 270.48]
Total (95% CI)		**799**		**604**	**100.0%**	**15.88 [0.93 , 270.48]**
Total events:	10		0			

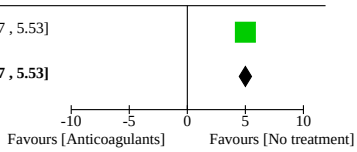
Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Anticoagulants versus no treatment (short term), Outcome 7: Hospitalisation time

Study or Subgroup	Anticoagulants Mean [days]	Anticoagulants SD [days]	Anticoagulants Total	No treatment Mean [days]	No treatment SD [days]	No treatment Total	Weight	Mean Difference IV, Random, 95% CI [days]
Albani 2020	10	6.68	780	5	2.97	596	100.0%	5.00 [4.47 , 5.53]
Total (95% CI)			**780**			**596**	**100.0%**	**5.00 [4.47 , 5.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 18.63 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Anticoagulants	Drugs that suppress, delay or prevent blood clots
Antiplatelet agents	Drugs that prevent blood clots by inhibiting platelet function
Arterial thrombosis	An interruption of blood flow to an organ or body part due to a blood clot blocking the flow of blood
Body mass index (BMI)	Body mass divided by the square of the body height, universally expressed in units of kg/m^2

Table 1. Glossary of terms *(Continued)*

Catheters	Medical devices (tubes) that can be inserted in the body for a broad range of functions, such as to treat diseases, to perform a surgical procedure, and to provide medicine, fluids and food
COVID-19	An infectious disease caused by SARS-CoV-2 virus
Deep vein thrombosis (DVT)	Coagulation or clotting of the blood in a deep vein, that is, far beneath the surface of the skin
Disseminated intravascular coagulopathy	A severe condition in which blood clots form throughout the body, blocking small blood vessels and that may lead to organ failure. As clotting factors and platelets are used up, bleeding may occur, throughout the body (e.g. in the urine, in the stool, or bleeding into the skin)
Duplex ultrasound	Non-invasive evaluation of blood flow through the arteries and veins by ultrasound devices
Heparin (also known as unfractionated heparin (UFH))	A drug used to prevent blood clotting (anticoagulant, blood thinner)
Hypercoagulability	An abnormality of blood coagulation that increases the risk of blood clot formation in blood vessels (thrombosis)
Low-molecular-weight heparin	A drug used to prevent blood clotting (anticoagulant)
Obesity	Amount of body fat beyond healthy conditions (BMI > 30 kg/m^2)
Placebo	Substance or treatment with no active effect, like a sugar pill
Platelet	Colourless blood cells that help blood to clot by clumping together
Pulmonary embolism (PE)	Blood clot in the lung or blood vessel leading to the lung. The clot originates in a vein (e.g. deep vein thrombosis) and travels to the lung
Quasi-randomised controlled trial (quasi-RCT)	A study in which participants are divided by date of birth or by hospital register number, i.e. not truly randomly divided into separate groups to compare different treatments
Randomised controlled trial (RCT)	A study in which participants are divided randomly into separate groups to compare different treatments
Respiratory failure	An abnormality that results from inadequate gas exchange by the respiratory system
SARS-CoV-2	The virus (coronavirus 2) that causes COVID-19
Thrombosis	Local coagulation of blood (clot) in a part of the circulatory system
Vascular	Relating to blood vessels (arteries and veins)
Venous	Relating to a vein
Venous thromboembolism (VTE)	A condition that involves a blood clot that forms in a vein and may migrate to another location (e.g. the lung)

Table 2. Summary of characteristics of included studies

Study (design)	Country	Participant age (mean ± SD)	Setting	Intervention type (dose)	Comparator	All-cause mortality	Necessity for additional respiratory support	Follow-up time (mean days)	Total participants allocated	Intervention group participants (anticoagulant)
Albani 2020 (Prospective cohort)	Italy	68.66 ± 12.62 (experimental), 70.6 ± 15.01 (comparator)	Hospital[a]	Enoxaparin (40-80 mg once daily, duration 3-9 days)	NA	In-hospital mortality: aOR 0.53 (95% CI 0.10 to 0.70), in favour of intervention group	NR	Until death or hospital discharge (time in days NR)	1403	799
Lemos 2020 (RCT)	Brazil	55 ± 10 (experimental), 58 ± 16 (comparator)	Hospital[a]	Therapeutic anticoagulation: heparin (SC enoxaparin, adjusted-dose by age and CrCl (maximum dose allowed 140 mg twice daily)	Prophylactic anticoagulation: SC UFH 5000 IU three times/day (if weight < 120 kg) and 7500 IU 3 times/day (if weight > 120 kg) or enoxaparin 40 mg once daily (if weight < 120 kg) and 40 mg twice daily (if weight > 120 kg) according to the doctor's judgment	RR 0.33 (95% CI 0.04 to 2.69)	NR	28	20	10
Lopes 2021	Brazil	56.7 ± 14.1 (experimental),	Hospital[a]	Therapeutic anticoagulation:	Prophylactic anticoagulation: enoxa-	RR 1.49 (95% CI 0.90 to 2.46)	RR 0.16 (95% CI	30	615	310

Table 2. Summary of characteristics of included studies *(Continued)*

(RCT)		56.5 ± 14.5 (comparator)		stable participants = rivaroxaban 20 mg once daily; unstable participants = enoxaparin 1 mg/kg twice daily. Followed by rivaroxaban for 30 days, irrespective of the duration of hospitalisation	parin 40 mg once daily		0.02 to 1.35)			
Rentsch 2020 (Prospective cohort)	USA	67.03 ± 12.31 (experimental), 67.83 ± 13.74 (comparator)	Hospital[a]	• SC UFH (5000 IU twice daily or 3 times/day (1094 participants; 30.2%) • LMWH (enoxaparin 40 mg once or twice daily (2506 participants; 69.1%), fondaparinux 2.5 mg once daily (4 participants; 0.1%), dalteparin 2500-5000 IU once daily, all SC) • DOACs (apixaban 2.5 mg twice daily (21 participants; 0.6%), rivaroxaban 10 mg once daily or 2.5 mg twice daily (2 participants; 0.1%), dabigatran 220 mg once daily, all orally)	NA	Inpatient mortality: aHR 0.69 (95% CI 0.61 to 0.77) 30-day mortality: aHR 0.73 (95% CI 0.66 to 0.81)	NR	30	4297	3627
Sadeghipour 2021 (RCT)	Iran	61.23 ± 14.68 (experimental), 59.66 ± 17.88 (comparator)	Hospital[a]	Higher-dose anticoagulation: enoxaparin 1 mg/kg once daily, modified according to body weight and CrCl	Lower-dose anticoagulation: enoxaparin 40 mg once daily, modified according to body weight and CrCl	Short-term time point: RR 1.05 (95% CI 0.87 to 1.28) Long-term time point: RR 1.07 (95% CI 0.89 to 1.29)	Short-term time point: no events in both groups Long-term time point: no	90	562	276

Table 2. Summary of characteristics of included studies *(Continued)*

						events in both groups				
Santoro 2020 (Prospective cohort)	Spain, Italy, Ecuador, Cuba, Germany, China, Canada, Serbia, USA, Chile, and Colombia	66 ± 15 (experimental), 63 ± 27 (comparator)	Hospital[a]	Anticoagulant (oral, SC, or IV): • 327 (12%) participants = previous anticoagulation treatment • 1888 (72%) participants = prophylactic (lower-dose) during hospitalisation • 341 (13%) participants = therapeutic (higher-dose) LMWH • 23 (0.75%) oral anticoagulation with VKA • 23 (0.75%) DOACs	NA	RR 0.91 (95% CI 0.89 to 0.93), in all participants (N = 3089) RR 0.58 (95% CI 0.49 to 0.67), in those non-anticoagulated before admission (N = 2695) RR 0.50 (95% CI 0.37 to 0.70), in those undergoing invasive ventilation (N = 391) RR 0.72 (95% CI 0.51 to 1.01), in those undergoing non-invasive ventilation (N = 583)	NR	15	5838	2601
Zarychanski 2021 (RCT)	UK, USA, Canada, Brazil, Ireland, Netherlands, Australia, Nepal, Saudi Arabia, and Mexico	Critically ill: 60.2 ± 13.1 (experimental), 61.6 ± 12.5 (comparator)	Hospital[a]	Therapeutic anticoagulation: LMWH or UFH according to local protocols used for the treatment of acute VTE for up to 14 days or until recovery (defined as hospital discharge, or liberation from supplemental oxygen for ≥ 24 h)	Prophylactic anticoagulation: LMWH or UFH according to local practice or with guidance from the trial protocol on max-	Short-term time point: moderate-severity RR 0.89 (95% CI 0.67 to 1.19), critically ill RR 1.03 (95% CI 0.88 to 1.21)	Short-term time point: moderate-severity RR 0.89 (95% CI 0.74 to 1.08), critically ill: NR	90	3450	1780

Table 2. Summary of characteristics of included studies *(Continued)*

		Moderate-severity illness: 59.0 ± 14.1 (experimental), 58.8 ± 13.9 (comparator)			imum dosing, which included either standard low-dose thromboprophylaxis or enhanced intermediate dose thromboprophylaxis	Long-term time point: NR	Long-term time point: NR			
Total	Australia: 1 Brazil: 3 Canada: 2 Chile: 1 China: 1 Colombia: 1 Cuba: 1 Ecuador: 1 Germany: 1 Iran: 1 Ireland: 1 Italy: 2 Mexico: 1 Nepal: 1 Netherlands: 1 Saudi Arabia: 1 Serbia:1 Spain: 1 UK: 1 USA: 3	55 to 68.66 (mean, 7 studies)	-	-	-	7 studies considered mortality	4 studies considered additional respiratory support	15 to 90 (7 studies)	16,185	9403

aHR: adjusted hazard ratio; **aOR:** adjusted odds ratio; twice daily**:** twice a day; **CI:** confidence interval; **CrCl:** creatinine clearance; **DOACs:** direct oral anticoagulants; **GFR:** glomerular filtration rate;**HR:** hazard ratio; **ICU:** intensive care units; **IU:** international unit;**LMWH**: low-molecular-weight heparin; **NA:** no anticoagulation; **NR:** not reported; **NRS:** non-randomised study;**OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio; **SC:** subcutaneous; **SD:** standard deviation; **SIC**: sepsis-induced coagulopathy; **TID:** three times a day; **UFH:** unfractionated heparin; **VKA**: vitamin K antagonist

[a]Hospital: includes intensive care unit, hospital wards or emergency department.
[b]Anticoagulation used twice daily if glomerular filtration rate (GFR) was > 30 mL/min, or once daily if GFR was 30 mL/min or less.

Table 3. Summary of characteristics of ongoing studies

Study	Country	Design	Experimental intervention	Comparator intervention	Primary outcomes	Estimated number of participants	Estimated primary completion date
ACTRN12620000517976	Australia	RCT	Nebulised heparin (UFH)	Standard care (without anticoagulants)	Time to separation from invasive ventilation	172	25 July 2021
Busani 2020	Italy	RCT	Enoxaparin	UFH	All-cause mortality at day 28, defined as the comparison of proportions of patients' deaths for any cause at day 28 from randomisation	210	6 May 2021
Chambers 2020	USA	RCT	Intermediate-dose enoxaparin	Standard prophylactic dose enoxaparin	Risk of all-cause mortality (time frame: 30 days post-intervention)	170	16 April 2021
ChiCTR2000030700	China	RCT	Enoxaparin	Standard care (without anticoagulants)	Time to virus eradication	60	30 September 2020
ChiCTR2000030701	China	RCT	Enoxaparin	Standard care (without anticoagulants)	Time to virus eradication	60	30 September 2020
ChiCTR2000030946	China	Prospective cohort	LMWH	Mechanical prevention	Biochemical indicators	120	24 April 2020
CTRI/2020/06/026021	India	RCT	Nafamostat (synthetic serine proteinase inhibitor)	Standard care (without anticoagulants)	Proportion of patients showing clinical improvement	40	27 January 2021
CTRI/2020/08/027023	India	RCT	Enoxaparin	Standard care (without anticoagulants)	Reduction in clinical symptoms and RT-PCR test negative	100	27 January 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

CTRI/2020/11/029173	India	RCT	Nebulised heparin	Standard care (without anticoagulants)	Time to separation from mechanical ventilation (duration of mechanical ventilation) up to day 28	58	27 January 2021
CTRI/2020/11/029345	India	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin; apixaban	Time to first event rate within 30 days of randomisation of the composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism (including PE) confirmed by imaging or requiring surgical intervention or ischaemic stroke confirmed by imaging	3600	27 January 2021
EUCTR2020-001302-30-AT	Austria	RCT	Rivaroxaban	Standard care (without anticoagulants)	Time to sustained improvement of one category from admission	500	11 January 2021
EUCTR2020-001708-41-IT	Italy	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	Incidence of VTE (a composite of incident asymptomatic and symptomatic proximal DVT diagnosed by serial compression ultrasonography, and symptomatic PE diagnosed by CT scan), in patients with SARS-CoV-2 infection	2000	30 October 2020
EUCTR2020-001709-21-FR	France	RCT	Higher-dose LMWH	Lower-dose LMWH	VTE (causing death or not)	230	11 May 2020
EUCTR2020-001891-14-ES	Spain	RCT	Enoxaparin	Standard care (without anticoagulants)	Need for oxygen therapy escalation due to oxygen saturation (Sat O_2) = 92% with FiO_2 = 0.5 and respiratory rate = 30 (IROX index = $SatO_2/FiO_2$)/FR < 5.5) or invasive mechanical ventilation or mortality during admission	140	16 November 2020
EUCTR2020-002234-32-IT	Switzerland	RCT	Higher-dose edoxaban	Lower-dose edoxaban	Major vascular thrombotic events at 25 (+/-3) days defined as a composite of: • Asymptomatic proximal DVT • Symptomatic proximal or distal DVT • Symptomatic PE or thrombosis • Myocardial infarction • Ischaemic stroke • Non-CNS systemic embolism • Death	420	11 January 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

EUC-TR2020-002504-39-DE	Germany	RCT	Edoxaban	Fondaparinux	Composite of all-cause mortality and/or VTE and/or arterial thromboembolism within 42 days	172	5 January 2021
EUC-TR2020-003349-12-IE	Ireland	RCT	Heparin	Standard care (without anti-coagulants)	D-dimer profile, with data collected on days 1, 3, 5 and 10	40	19 October 2020
Goldin 2020	USA	RCT	Higher-dose LMWH	Lower-dose LMWH	Composite outcome of arterial thromboembolic events, venous thromboembolic events and all-cause mortality at day 30 ± 2 days (time frame: day 30 ± 2 days). Risk of arterial thromboembolic events (including myocardial infarction, stroke, systemic embolism), VTE (including symptomatic DVT of the upper or lower extremity, asymptomatic proximal DVT of the lower extremity, non-fatal PE), and all-cause mortality at day 30 ± 2 days	308	26 April 2021
IRC-T20200515047456N1	Iran	RCT	UFH	Standard care (without anti-coagulants)	Decrease D-dimer level Improve compliance Improve of oxygenation Improve SOFA score	15	13 July 2020
ISRCTN14212905	UK	RCT	Nafamostat (synthetic serine proteinase inhibitor)	Standard care (without anti-coagulants)	Safety of candidate agents as add-on therapy to standard care in patients with COVID-19 measured at 30, 60 and 90 days post-treatment	100	3 August 2020
Kharma 2020	Qatar	RCT	Bivalirudin (DOAC)	LMWH or UFH	PaO_2/FiO_2 ratio (time frame: 3 days of intervention)	100	24 June 2020
Lasky 2021	USA	RCT	Dociparstat (heparinoid)	Placebo	Proportion of participants who are alive and free of invasive mechanical ventilation	525	17 February 2021
Lins 2020	Brazil	RCT	UFH	Standard care (without UFH)	The percentage of clotted dialysers within 72 h in each of the studied groups	90	27 July 2020
Marietta 2020	Italy	RCT	Higher-dose LMWH	Lower-dose LMWH	Clinical worsening (includes death and necessity for additional respiratory support)	300	June 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

NCT04333407	UK	RCT	Rivaroxaban	Standard care (without anticoagulants)	All-cause mortality at 30 days after admission	3170	30 March 2021
NCT04344756	France	RCT	Higher-dose LMWH or UFH	Lower-dose LMWH or UFH	Survival without ventilation	808	31 July 2020
NCT04345848	Switzerland	RCT	Higher-dose LMWH or UFH	Lower-dose LMWH or UFH	Composite outcome of arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality	200	30 November 2020
NCT04352400	Italy	RCT	Nafamostat (synthetic serine proteinase inhibitor)	Placebo	Time to clinical improvement	256	December 2021
NCT04366960	Italy	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	Incidence of VTE detected by imaging	2712	August 2020
NCT04367831	USA	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	Total number of patients with clinically relevant venous or arterial thrombotic events in ICU	100	November 2020
NCT04373707	France	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	VTE	602	September 2020
NCT04377997	USA	RCT	Higher-dose LMWH or UFH	Lower-dose LMWH or UFH	Risk of composite efficacy endpoint of death, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, or haemodynamic shock Risk of major bleeding event according to the ISTH definition	300	1 January 2021
NCT04397510	USA	RCT	Nebulised heparin	Placebo	Mean daily PaO_2/FiO_2	50	31 December 2020
NCT04406389	USA	RCT	Higher-dose heparinoid or fondaparinux	Lower-dose heparinoid or fondaparinux	30-day mortality	186	December 2021
NCT04409834	USA	RCT	Higher-dose heparinoid plus an-	Lower-dose heparinoid without an-	Venous or arterial thrombotic events	750	May 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

			tiplatelet agent	tiplatelet agent			
NCT04416048	Germany	RCT	Higher-dose DOAC (rivaroxaban)	Lower-dose heparinoid	Composite endpoint of VTE (DVT and/or fatal or non-fatal PE), arterial thromboembolism, new myocardial infarction, non-haemorrhagic stroke, all-cause mortality or progression to intubation and invasive ventilation (time frame: 35 days post-randomisation)	400	30 May 2021
NCT04420299	Spain	RCT	Higher-dose heparin	Lower-dose heparin	Combined worsening variable. Presence of any of the following will be considered worsening • Death • ICU admission • Need for either non-invasive or invasive mechanical ventilation • Progression to moderate/severe respiratory distress syndrome according to objective criteria (Berlin definition) • VTE (DVT or PE) or arterial (acute myocardial infarction or stroke) • Proportion of patients that worsen	120	31 March 2021
NCT04444700	Brazil	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	Composite outcome of ICU admission (yes/no), non-invasive positive pressure ventilation (yes/no), invasive mechanical ventilation (yes/no), or all-cause death (yes/no) up to 28 days	462	31 December 2020
NCT04485429	Brazil	RCT	Higher-dose heparin	Lower-dose heparin	Rate of invasive mechanical ventilation	268	31 December 2020
NCT04508439	Mexico	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	Ventilatory support time Thrombotic complications Length of hospital stay Mortality rate	130	30 December 2020
NCT04511923	Ireland	RCT	Nebulised heparin	Standard care (without anticoagulants)	D-dimer profile up to day 10 Frequency of severe adverse outcomes up to day 60	40	January 2022

Table 3. Summary of characteristics of ongoing studies *(Continued)*

NCT04512079	USA	RCT	Apixaban (DOAC)	Lower-dose enoxaparin; higher-dose enoxaparin	Time to first event (time frame: 30 days) Number of in-hospital rate of BARC 3 or 5 (time frame: 30 days) Number of in-hospital rate of BARC 3 or 5 bleeding (binary). BARC Type 3: a. Overt bleeding plus haemoglobin drop of 3 to < 5 g/dL (provided haemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus haemoglobin drop < 5 g/dL (provided haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial haemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision	3600	March 2022
NCT04530578	Argentina	RCT	Nebulised heparin	Enoxaparin	Percentage of patients requiring mechanical ventilation (time frame: 15 days)	200	1 June 2021
NCT04542408	Germany	RCT	Higher-dose LMWH	Lower-dose LMWH	Combined endpoint: all-cause mortality and/or VTE and/or arterial thromboembolism (time frame: 42 days) • All-cause mortality and/or VTE and/or arterial thromboembolism during follow-up (42 days). Thromboembolisms will be detected by duplex ultrasonography of arms and legs	172	30 September 2021
NCT04545541	USA	RCT	Nebulised heparin	Placebo	Alive and Ventilator-Free Score (time frame: day 28)	300	June 2022
NCT04584580	Egypt	RCT	Higher-dose LMWH	Lower-dose LMWH	Mortality (time frame: until patient is discharged or up to 4 weeks whichever comes first) Occurrence of venous and/or arterial thrombosis (time frame: until patient is discharged or up to 4 weeks whichever comes first)	50	31 December 2020

Table 3. Summary of characteristics of ongoing studies *(Continued)*

NCT04600141	Brazil	RCT	Higher-dose LMWH or UFH	Lower-dose LMWH or UFH	Proportion of patients with clinical improvement (time frame: 30 days) • Not hospitalised, with no limitations on activities • Not hospitalised, but limited to activities • Hospitalised, with no need for supplemental oxygen • Hospitalised, needing supplemental oxygen • Hospitalised, requiring high-flow oxygen therapy, non-invasive mechanical ventilation or both • Hospitalised, requiring ECMO, invasive mechanical ventilation or both • Death	308	31 December 2020
NCT04604327	Spain	RCT	Higher-dose LMWH	Lower-dose LMWH	Clinical deterioration (time frame: 10 days) Combined outcome that includes number of patients who suffer any of the following: death, ICU admission, mechanical ventilatory support, progression to moderate or severe ARDS (according to Berlin criteria) or arterial or venous thrombosis	164	31 July 2021
NCT04623177	Spain	Prospective cohort	Higher-dose LMWH	Lower-dose LMWH; no anticoagulation	ICU mortality rate (time frame: from admission to ICU discharge, an average of 1 month)	950	30 September 2020
NCT04640181	USA	RCT	Rivaroxaban at low, intermediate or therapeutic dose	Enoxaparin at low, intermediate or therapeutic dose	Death or 30-day all-cause mortality (time frame: 30 days) Mechanical ventilation, intubation (time frame: 30 days) Transfer to an ICU setting (time frame: 30 days)	150	31 July 2021
NCT04646655	Italy	RCT	Higher-dose enoxaparin	Lower-dose enoxaparin	Mortality rate (time frame: 30 days from enrolment) Progression of respiratory failure (time frame: 30 days from enrolment) Progression of respiratory failure (time frame: 30 days from enrolment)	300	31 July 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

					Progression of respiratory failure (time frame: 30 days from enrolment) Number of major bleeding episodes (time frame: up to 6 months from randomisation)		
NCT04655586	USA	RCT	Higher-dose heparin	Lower-dose heparin	Change in D-dimer level from baseline to day 8, or day of discharge if prior to day 8 Number of major or non-major clinically relevant bleeding events within 8 days of randomisation Time to recovery within 30 days of randomisation	100	31 May 2021
NCT04723563	USA	RCT	Nebulised heparin	Placebo	Need for mechanical ventilation at day 28	50	29 May 2021
NCT04730856	Spain	RCT	Higher-dose heparin	Lower-dose heparin	Reduction of suspicion of systemic thrombotic symptomatic events (time frame: 30 days) Use of mechanical ventilation (time frame: 30 days) Progression on the WHO Progression Scale during follow-up (time frame: 30 days) Overall survival at 30 days (time frame: 30 days) Length of hospital stay (days) (time frame: 30 days) Length of ICU stay (days) (time frame: 30 days)	600	31 July 2021
NCT04743011	Brazil	RCT	Nebulised heparin	Placebo	Change in aPTT > 1.5 (time frame: immediately or up to 8 days after starting treatment) Viral load in nasal swab RT-PCR (time frame: immediately or up to 8 days after starting treatment)	50	31 December 2021
NCT04745442	Spain	RCT	Heparin	No anticoagulant	Combined variable: mortality or worsening rate with need for non-invasive mechanical ventilation or with need for invasive mechanical ventilation (time frame: at day 31 after randomisation or hospital discharge (whichever occurs first)	48	15 January 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

PACTR202007606637743	Egypt	RCT	Nebulised heparin	No anticoagulant	The average daily ratio of partial pressure of oxygen to FiO2 (PaO2/FiO2) while the patient is on room air for 7 days	100	22 February 2021
RBR-7y8j2bs	Brazil	RCT	Nebulised heparin	Placebo	Efficacy: relative to the proposed treatment, through the analysis of the viral load of the SARS-CoV-2 virus in the participants treated by the sequential evaluation of the viral load in RT-PCR of nasal swab. Safety: related to the use of inhalational high-molecular-weight heparin in patients with SARS-CoV-2 through the assessment of haemorrhagic events of any nature, alteration of the coagulogram that indicates an increase in aPTT > 1.5 and HIT	40	11 October 2021
Sholzberg 2021a	Canada	RCT	Higher-dose heparinoids	Lower-dose heparinoids	Composite outcome of ICU admission (yes/no), non-invasive positive pressure ventilation (yes/no), invasive mechanical ventilation (yes/no), or all-cause death (yes/no) up to 28 days	462	April 2022
Vanassche 2020	Belgium	RCT	LMWH	DOAC plus aprotinin	The overall objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to standard care in patients hospitalised with COVID-19	210	18 August 2020
Van Haren 2020	Argentina	RCT	Nebulised heparin	No anticoagulant	Intubation rate (time frame: day 28) Proportion of patients requiring invasive mechanical ventilation	712	1 June 2021
Wilkinson 2020	UK	RCT	Anticoagulants (no details)	NA	Time to clinical improvement of at least 2 points (from randomisation) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by day 29 (this will also define the 'responder' for the response rate analyses)	1800	04 September 2021
Total number of studies	Argentina: 2 Australia: 1 Austria: 1	Prospective cohort: 2 RCT: 60			35 studies considered mortality 26 studies considered additional respiratory support	35,470 participants (120 from NRS; 35,350 from RCTs)	58 studies to December 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

	Belgium: 1 Brazil: 6 Canada: 1 China: 3 Egypt: 2 France: 3 Germany: 3 India: 4 Iran: 1 Ireland: 2 Italy: 6 Mexico: 1 Qatar: 1 Spain: 6 Switzerland: 2 UK: 3 USA: 13	Four studies to July 2022

aPTT: activated partial thromboplastin time; **ARDS:** acute respiratory distress syndrome; **BARC:** Bleeding Academic Research Consortium; **CNS:** central nervous system; **DOACs:** direct oral anticoagulants; **DVT**: deep vein thrombosis; **ECMO:** extracorporeal membrane oxygenation; **FiO_2:** fraction of inspired oxygen; **HIT:** heparin-induced thrombocytopenia; **ICU:** intensive care unit; **ISTH:** International Society on Thrombosis and Haemostasis; **LMWH**: low-molecular-weight heparin; **NA:** not available; **NRS:** non-randomised studies; **PaO_2:** arterial oxygen pressure;**PE:** pulmonary embolism; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SOFA:** sequential organ failure assessment; **UFH:** unfractionated heparin; **VKA**: vitamin K antagonist; **VTE:** venous thromboembolism; **WHO:** World Health Organization

Table 4. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (all-cause mortality)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the in-	Bias due to missing data	Bias in measure-	Bias in selection of the reported result	Overall risk of bias

Table 4. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (all-cause mortality) *(Continued)*

				tended intervention		ment of outcomes		
Albani 2020	**Serious risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Serious risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. To minimise the impact of the absence of randomisation, an adjusted analysis with propensity scores was performed considering age, sex, disease severity, admission to ICU and COVID-19 treatment. However, the essential confounding factors: 'participants already using anticoagulants', 'participants who underwent surgery during the hospitalisation', 'active cancer treatment', 'concomitant antiplatelet use' and 'history of venous thromboembolism' were not considered.	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days after hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used. It is not clear how prevalent use of anticoagulation was handled.	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	There were missing outcome data for 27 participants (1.9% of the total) and balanced between the groups. These missing data possibly could not cause an important impact on the estimate.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study has some important problems.
Rentsch 2020	**Moderate risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Moderate risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, and history of venous thromboembolism, were not considered. However, an appropriate analysis method to control for measured confounders was used (inverse probability of treatment weighting), and all the im-	Participants included in both groups were selected from a nationwide cohort of patients receiving care in the Department of Veterans Affairs in the USA, and selection may have not been related to intervention and outcome. The start of follow-up and start of intervention coin-	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	No missing data were reported for the outcome.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-

Table 4. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (all-cause mortality) *(Continued)*

	portant confounding domains for this study were probably controlled.	cided for most participants (the first 24 h of hospitalisation).	the risk of the outcome.			participants.		performed randomised trial.
Santoro 2020	**Critical risk**	**No information**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Serious risk**	**Critical risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, and antiplatelet use were not considered. The Cox's multivariable regression analysis was performed to define independent risk factors for the mortality outcome, but only for participants with respiratory failure.	Insufficient information to judge. There was insufficient information if the start of follow-up and the start of intervention coincided for most participants.	The intervention groups were not clearly defined and recorded at the start of the intervention. Information about frequency and dose was not provided.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	No missing data were reported for the outcome.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was available, but it is not possible to exclude bias in selection of reported effect estimate, based on the results, from multiple outcome measurements within the outcome domain (mortality), and multiple effect estimates for different subgroups were provided, omitting varying proportions of the original cohort.	The study is too problematic to provide useful evidence.

COVID-19: coronavirus disease 2019; **ICU:** intensive care unit

Table 5. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (deep vein thrombosis)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Albani 2020	**Critical risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Critical risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism, were not considered. The outcome was reported without any adjustment.	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days after hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used.	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	There were missing outcome data for 27 participants (1.9% of the total), balanced between the groups. These missing data would probably not have an important impact on the estimate.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study is too problematic to provide useful evidence.

Table 6. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (pulmonary embolism)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Albani 2020	**Critical risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Critical risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days af-	The intervention groups were clearly defined and recorded at the start of the in-	No deviations from the intended intervention were reported in the study, and	There were missing outcome data for 27 participants (1.9% of the total),	It is unlikely that the outcome assessment (objective outcome)	The study protocol was not identified but all reported re-	The study is too problematic to provide useful evidence.

Table 6. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (pulmonary embolism) *(Continued)*

	participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism, were not considered. The outcome was reported without any adjustment.	ter hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used.	tervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	balanced between the groups. These missing data would probably not have an important impact on the estimate.	was influenced by the knowledge of the intervention received by the study participants.	sults corresponded to the intended outcome.	

Table 7. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (major bleeding)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Albani 2020	**Critical risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Critical risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism, were not considered. The outcome was reported without any adjustment.	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days after hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used.	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	There were missing outcome data for 27 participants (1.9% of the total) and balanced between the groups. These missing data would probably not have an important impact on the estimate.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study is too problematic to provide useful evidence.
Santoro 2020	**Critical risk**	**No information**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Critical risk**

Table 7. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (major bleeding) *(Continued)*

Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, and antiplatelet use were not considered. The Cox's multivariable regression analysis was performed to define independent risk factors only for the mortality outcome.	Insufficient information to judge. There was insufficient information if the start of follow-up and the start of intervention coincided for most participants.	The intervention groups were not clearly defined and recorded at the start of the intervention. Information about frequency and dose was not provided.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	No missing data were reported for the outcome.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was available, and the reported results corresponded to the intended outcome.	The study is too problematic to provide useful evidence.

Table 8. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (adverse events (stroke))

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Albani 2020	**Critical risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Critical risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism, were not considered. The outcome was reported	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days after hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used.	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	There were missing outcome data for 27 participants (1.9% of the total), balanced between the groups. These missing data would probably not have an important impact on the estimate.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study is too problematic to provide useful evidence.

Table 8. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (adverse events (stroke)) *(Continued)*

								without any adjustment.

Table 9. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (adverse events (myocardial infarction))

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Albani 2020	**Critical risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Critical risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism, were not considered. The outcome was reported without any adjustment.	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days after hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used.	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	There were missing outcome data for 27 participants (1.9% of the total), balanced between the groups. These missing data would probably not have an important impact on the estimate.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study is too problematic to provide useful evidence.

Table 10. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (hospitalisation)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias

Table 10. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (hospitalisation) *(Continued)*

Albani 2020	**Serious risk**	**Serious risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Serious risk**
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. Essential characteristics, such as participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism, were not considered.	Participants included in both groups were selected from a single hospital, and the first dose of anticoagulant was administered between 0 and 3 days after hospital admission. The start of follow-up and start of intervention possibly did not coincide for most participants, and adjustment techniques to correct the presence of selection bias were not used.	The intervention groups were clearly defined and recorded at the start of the intervention. Intervention status was probably not affected by knowledge of the outcome or the risk of the outcome.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	There were missing outcome data for 27 participants (1.9% of the total) and balanced between the groups. These missing data would probably not have an important impact on the estimate.	It is unlikely that the outcome assessment (objective outcome) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified but all reported results corresponded to the intended outcome.	The study has some important problems.

APPENDICES

Appendix 1. Planned methodology for randomised controlled trials (RCTs) and non-randomised studies (NRS) of interventions

Types of studies

We planned to use the *Cochrane Handbook for Systematic Reviews of Interventions* to guide the whole of this review process (Higgins 2020a). To assess the effects of prophylactic anticoagulants for people hospitalised with COVID-19 we had planned to include randomised controlled trials (RCTs) only, as such studies if performed appropriately, currently give the best evidence for experimental therapies in highly controlled therapeutic settings.

In case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs to answer this review's questions, we had planned to include prospective controlled non-randomised studies (NRS) of interventions, including quasi-randomised controlled trials (e.g. assignment to treatment by alternation, medical register or by date of birth).

In case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs, quasi-RCTs, and prospective NRS, we planned to include retrospective observational studies with a control group.

As there was evidence from RCTs, and prospective NRS, we no longer included retrospective NRS and followed the methodology as specified in the protocol (Flumignan 2020a).

Measures of treatment effect

Dichotomous data

For dichotomous variables, we planned to calculate the risk ratio (RR) and 95% confidence intervals (CIs).

Continuous data

For continuous data, we planned to calculate mean differences (MD) and 95% CIs between treatment groups where studies reported the same outcomes. Where similar outcomes are reported on different scales, we planned to calculate the standardised mean difference (SMD) and 95% CI. To interpret SMD, we planned to use the following thresholds.

- SMD less than 0.2 = trivial or no effect
- SMD equal to or greater than 0.2 and less than 0.5 = small effect
- SMD equal to or greater than 0.5 and less than 0.8 = medium effect
- SMD equal to or greater than 0.8 = large effect

Unit of analysis issues

We planned to seek advice from a statistician (VTC) to address issues relating to double-counting, correlation or unit of analysis posed by the following.

- Cluster-RCTs
- Episodes of disease
- Multi-arm studies

We planned for individuals to be our unit of analysis. If studies included multi-arm interventions, we planned to consider only the arms relevant to the scope of our review.

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised RCTs. We planned to adjust their sample sizes using the methods described in Section 23.1.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or a study of a similar population. If we used ICCs from other sources, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually randomised trials, we planned to synthesise the relevant information. We planned to consider it reasonable to combine the results from both types of studies if there was little heterogeneity between the study designs, and we considered the interaction between the effect of the intervention and the choice of randomisation unit to be unlikely. We also planned to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Assessment of heterogeneity

We planned to inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We planned to use the I^2 statistic (Higgins 2003), to measure heterogeneity among the studies in each analysis, but acknowledge that there is substantial uncertainty in the value of the I^2 statistic when there is only a small number of studies: we therefore also planned to consider the P value from the Chi^2 test. If we identified substantial heterogeneity, we planned to report it and explore possible causes by prespecified subgroup analysis.

As strict thresholds for interpretation of the I^2 statistic are not recommended, we intended to follow the rough guide to interpretation in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

When the I^2 statistic lies in an area of overlap between two categories (e.g. between 50% and 60%), we planned to consider differences in participants and interventions among the studies contributing data to the analysis (Deeks 2021).

Data synthesis

In preparation for synthesis (either meta-analyses or synthesis without meta-analysis), we planned to assess how much data are available for each of our comparisons by the following.

- Table to compare PICO elements/study design features
- Conversion of numerical data for meta-analysis
- Forest plots
- Qualitative synthesis
- Synthesis without meta-analysis

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL; via the Cochrane Library) search strategy

#1(2019 novel coronavirus infection) or (COVID-19 pandemic) or (coronavirus disease-19) or (COVID19) or (2019 novel coronavirus disease) or (coronavirus disease 2019) or COVID-19

#2MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees

#3(Wuhan coronavirus) or (Wuhan seafood market pneumonia virus) or (COVID19 virus) or (COVID-19 virus) or (coronavirus disease 2019 virus) or (SARS-CoV-2) or (SARS2) or (2019 novel coronavirus)

#4MeSH descriptor: [Coronavirus] explode all trees

#5Coronavirus* or Deltacoronavirus* or Deltacoronavirus*

#6#1 OR #2 OR #3 OR #4 OR #5

#7MeSH descriptor: [Antithrombins] explode all trees

#8(Direct Thrombin Inhibitor*) or (Direct Antithrombin*) or (thrombin inhibitor)

#9MeSH descriptor: [Coumarins] explode all trees

#10Coumarin* or (Benzopyran 2 ones) or (Coumarin Derivative*)

#11MeSH descriptor: [Dabigatran] explode all trees

#12Pradaxa or (Dabigatran Etexilate) or (Dabigatran Etexilate Mesylate)

#13MeSH descriptor: [Anticoagulants] explode all trees
#14(Anticoagulation Agent*) or (Anticoagulant Drug*) or Anticoagulant* or (Indirect Thrombin Inhibitor*)
#15MeSH descriptor: [Heparin] explode all trees
#16(Unfractionated Heparin) or (Heparinic Acid) or Liquaemin or (Sodium Heparin) or alpha-Heparin or (alpha Heparin) or UFH or heparin*
#17MeSH descriptor: [Fondaparinux] explode all trees
#18(Fondaparinux Sodium) or Quixidar or Arixtra
#19MeSH descriptor: [Hirudin Therapy] explode all trees

#20Leeching or Hirudin*
#21MeSH descriptor: [Phenindione] explode all trees
#22Phenylindanedione or Phenyline or Pindione or Fenilin or Dindevan
#23MeSH descriptor: [Polysaccharides] explode all trees
#24Glycans
#25MeSH descriptor: [Rivaroxaban] explode all trees
#26Xarelto or Rivaroxaban
#27MeSH descriptor: [Warfarin] explode all trees
#28Apo-Warfarin or Aldocumar or Gen-Warfarin or Warfant or Coumadin* or Marevan or Tedicumar or warfarin*
#29MeSH descriptor: [Factor Xa Inhibitors] explode all trees
#30(factor Xa inhibitor*)
#31MeSH descriptor: [Enoxaparin] explode all trees
#32Enoxaparin* or Lovenox or Clexane
#33reviparin* or Clivarine or reviparin-sodium or (reviparin sodium) or Clivarin
#34MeSH descriptor: [Dalteparin] explode all trees
#35Tedelparin or (Dalteparin Sodium) or Fragmin or Fragmine
#36danaproid or Orgaran or Lomoparan or (danaparoid sodium) or (danaproid sodium) or danaparoid* or DOAC or embolex or Liquemine or (oral anticoagulants) or Pentasaccharide* or (vitamin k antagonist) or Savaysa or (edoxaban tosylate) or edoxaban or xi-melagatran or Exanta
#37MeSH descriptor: [Phenprocoumon] explode all trees
#38Phenylpropylhydroxycumarinum or Phenprocoumalol or Phenprocoumarol or Phenprogramma or Marcoumar or Marcumar or Falithrom or Liquamar or Oligosaccharides or (idraparinux sodium)
#39MeSH descriptor: [Tinzaparin] explode all trees
#40(Tinzaparin Sodium) or Innohep
#41MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees
#42(Heparin Low Molecular Weight) or LMWH or (Low-Molecular-Weight Heparin) or parnaparin or Azetidines or Benzylamines
#43MeSH descriptor: [Nadroparin] explode all trees
#44Nadroparin* or Fraxiparin*#45MeSH descriptor: [Acenocoumarol] explode all trees
#46Nicoumalone or Acenocoumarin or Sinthrome or Synthrom or Syncoumar or Syncumar or Sinkumar or Sintrom or Mini-Sintrom or (Mini Sintrom) or MiniSintrom or Lactones or Pyridines
#47#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48#6 AND #47
#49#48 AND trials
#50#49 AND Filter: Custom date range 20/06/2020 to 14/04/2021

Appendix 3. MEDLINE (PubMed) search strategy

1 "COVID-19" [Supplementary Concept] or (2019 novel coronavirus infection) or (2019-nCoV infection) or (COVID-19 pandemic) or (coronavirus disease-19) or (2019-nCoV disease) or (COVID19) or (2019 novel coronavirus disease) or (coronavirus disease 2019) or COVID-19

2 "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] or (Wuhan coronavirus) or (Wuhan seafood market pneumonia virus) or (COVID19 virus) or (COVID-19 virus) or (coronavirus disease 2019 virus) or (SARS-CoV-2) or (SARS2) or (2019-nCoV) or (2019 novel coronavirus)

3 "Coronavirus"[Mesh] or Coronavirus* or Deltacoronavirus*

4 #1 OR #2 OR #3

5 "Antithrombins"[Mesh] or (Direct Thrombin Inhibitor*) or (Direct Antithrombin*) or (thrombin inhibitor)

6 "Coumarins"[Mesh] or Coumarin* or (1,2-Benzopyrone Derivative*) or (1,2 Benzopyrone Derivative*) or Benzopyran-2-ones or (Benzopyran 2 ones) or (Coumarin Derivative*) or (1,2-Benzopyrones) or (1,2 Benzopyrones) or (1,2-Benzo-Pyrones) or (1,2 Benzo Pyrones)

7 "Dabigatran"[Mesh] or Pradaxa or Dabigatran*

8 "Anticoagulants"[Mesh] or Anticoagulant* or (Indirect Thrombin Inhibitor*)

9 "Heparin"[Mesh] or (Unfractionated Heparin) or (Heparinic Acid) or Liquaemin or (Sodium Heparin) or alpha-Heparin or (alpha Heparin) or UFH or heparin*

10 "Fondaparinux"[Mesh] or (Fondaparinux Sodium) or Quixidar or Arixtra

11 "Hirudin Therapy"[Mesh] or Leeching or Hirudin*

12 "Phenindione"[Mesh] or Phenylindanedione or Phenyline or Pindione or Fenilin or Dindevan

13 "Polysaccharides"[Mesh] or Glycans

14 "Rivaroxaban"[Mesh] or Xarelto or Rivaroxaban

15 "Warfarin"[Mesh] or Apo-Warfarin or Aldocumar or Gen-Warfarin or Warfant or Coumadin* or Marevan or Tedicumar or warfarin*

16 "Factor Xa Inhibitors" [Pharmacological Action] or (factor Xa inhibitor*)

17 "Enoxaparin"[Mesh] or Enoxaparin* or Lovenox or Clexane

18 "reviparin" [Supplementary Concept] or reviparin* or Clivarine or reviparin-sodium or (reviparin sodium) or Clivarin

19 "Dalteparin"[Mesh] or Tedelparin or (Dalteparin Sodium) or Fragmin*

20 "danaparoid" [Supplementary Concept] or danaproid* or Orgaran or Lomoparan or danaparoid*

21 DOAC or embolex or Liquemine or (oral anticoagulants) or Pentasaccharide* or (vitamin k antagonist)

22 "edoxaban" [Supplementary Concept] or Savaysa or (edoxaban tosylate) or edoxaban

23 "ximelagatran" [Supplementary Concept] or xi-melagatran or Exanta

24 "Phenprocoumon"[Mesh] or Phenylpropylhydroxycumarinum or Phenprocoumalol or Phenprocoumarol or Phenprogramma or Marcoumar or Marcumar or Falithrom or Liquamar

25 "idrabiotaparinux" [Supplementary Concept] or (Biotin/analogs and derivatives) or Oligosaccharides

26 "idraparinux" [Supplementary Concept] or (idraparinux sodium)

27 "Tinzaparin"[Mesh] or (Tinzaparin Sodium) or Innohep

28 "Heparin, Low-Molecular-Weight"[Mesh] or (Heparin Low Molecular Weight) or LMWH or (Low-Molecular-Weight Heparin) or parnaparin

29 "melagatran" [Supplementary Concept] or Azetidines or Benzylamines

30 "Nadroparin"[Mesh] or Nadroparin* or Fraxiparin or Fraxiparine

31 "Acenocoumarol"[Mesh] or Nicoumalone or Acenocoumarin or Sinthrome or Synthrom or Syncoumar or Syncumar or Sinkumar or Sintrom or Mini-Sintrom or (Mini Sintrom) or MiniSintrom

32 "vorapaxar" [Supplementary Concept] or Lactones or Pyridines

33 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32

34 #4 AND #33

35 #34 AND Filters: from 2020/6/20 - 2021/4/14

Appendix 4. Embase.com (Elsevier) search strategy

1 ('coronavirus disease 2019'/exp or (2019 novel coronavirus infection) or (COVID-19 pandemic) or (coronavirus disease-19) or (COVID19) or (2019 novel coronavirus disease) or (coronavirus disease 2019) or COVID-19 OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR (Wuhan coronavirus) or (Wuhan seafood market pneumonia virus) or (COVID19 virus) or (COVID-19 virus) or (coronavirus disease 2019 virus) or (SARS-CoV-2) or (SARS2) or (2019 novel coronavirus) OR 'Coronavirus infection'/exp OR Coronavirus* or Deltacoronavirus* or Deltacoronavirus*) AND ('antithrombin'/exp OR (Direct Thrombin Inhibitor*) or (Direct Antithrombin*) or (thrombin inhibitor) OR 'coumarin derivative'/exp OR Coumarin* or (Benzopyran 2 ones) or (Coumarin Derivative*) OR 'dabigatran'/exp OR Pradaxa or (Dabigatran Etexilate) or (Dabigatran Etexilate Mesylate) OR 'anticoagulant agent'/exp OR (Anticoagulation Agent*) or (Anticoagulant Drug*) or Anticoagulant* or (Indirect Thrombin Inhibitor*) OR 'heparin derivative'/exp OR (Unfractionated Heparin) or (Heparinic Acid) or Liquaemin or (Sodium Heparin) or alpha-Heparin or (alpha Heparin) or UFH or heparin* OR 'fondaparinux'/exp OR (Fondaparinux Sodium) or Quixidar or Arixtra OR 'anticoagulant therapy'/exp OR Hirudins or Leeching or Hirudin* OR 'phenindione'/exp OR Phenylindanedione or Phenyline or Pindione or Fenilin or Dindevan OR 'polysaccharide'/exp OR Glycans OR 'rivaroxaban'/exp OR Xarelto or Rivaroxaban OR 'warfarin'/exp OR Apo-Warfarin or Aldocumar or Gen-Warfarin or Warfant or Coumadin* or Marevan or Tedicumar or warfarin* OR 'blood clotting factor 10a

inhibitor'/exp OR (factor Xa inhibitor*) OR 'enoxaparin'/exp OR Enoxaparin* or Lovenox or Clexane OR reviparin* or Clivarine or reviparin-sodium or (reviparin sodium) or Clivarin OR 'dalteparin'/exp OR Tedelparin or (Dalteparin Sodium) or Fragmin* OR danaproid or Orgaran or Lomoparan or danaparoid* or DOAC or embolex or Liquemine or (oral anticoagulants) or Pentasaccharide* or (vitamin k antagonist) or Savaysa or (edoxaban tosylate) or edoxaban or xi-melagatran or Exanta OR 'phenprocoumon h 3'/exp OR Phenylpropylhydroxycumarinum or Phenprocoumalol or Phenprocoumarol or Phenprogramma or Marcoumar or Marcumar or Falithrom or Liquamar or Oligosaccharides or (idraparinux sodium) OR 'tinzaparin'/exp OR (Tinzaparin Sodium) OR 'low molecular weight heparin'/exp OR (Heparin Low Molecular Weight) or LMWH or (Low-Molecular-Weight Heparin) or parnaparin or Azetidines or Benzylamines OR 'nadroparin'/exp OR Nadroparin* or Fraxiparin or Fraxiparine OR 'acenocoumarol'/exp OR Nicoumalone or Acenocoumarin or Sinthrome or Synthrom or Syncoumar or Syncumar or Sinkumar or Sintrom or Mini-Sintrom or (Mini Sintrom) or MiniSintrom or Lactones or Pyridines)

2 #1 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

3 #2 AND (2020:py OR 2021:py)

Appendix 5. LILACS and IBECS (Virtual Health Library) search strategy

tw:((tw:(mh: "Coronavirus Infections" OR mh: "Infecciones por Coronavirus" OR mh: "Infecções por Coronavirus" OR covid-19 OR (coronavirus infection*) OR mers OR (middle east respiratory syndrome) OR (novel coronavirus pneumonia) OR (wuhan seafood market pneumonia) OR (brote por el nuevo coronavirus 2019) OR (brote por el coronavirus de wuhan) OR (epidemia de neumonía por coronavirus de wuhan) OR (síndrome respiratório de oriente medio) OR (síndrome respiratorio de oriente medio por coronavirus) OR (epidemia de pneumonia por coronavirus de wuhan) OR (epidemia de pneumonia por coronavírus de wuhan) OR (epidemia de pneumonia por coronavírus de wuhan de 2019-2020) OR mh: betacoronavirus OR (2019 new coronavirus) OR (2019 novel coronavirus) OR betacoronavirus* OR sars-cov-2 OR (severe acute respiratory syndrome coronavirus 2) OR (wuhan coronavirus) OR (wuhan seafood market pneumonia virus) OR (coronavirus de wuhan) OR (coronavirus del síndrome respiratorio agudo grave 2) OR (nuevo coronavirus 2019) OR (virus de la neumonía del mercado de pescado y marisco de wuhan) OR (wuhan coronavirus) OR (coronavírus da síndrome respiratória aguda grave 2) OR (coronavírus de wuhan) OR (vírus de pneumonia no mercado de frutos do mar de wuhan) OR mh: coronavirus OR (coronavirus* rabbit) OR coronavirus* OR deltacoronavirus* OR (coronavirus del conejo) OR (coronavirus do coelho))) AND (tw:(tw:((tw:(mh: antithrombins OR mh: antitrombinas OR (direct antithrombins) OR (direct thrombin inhibitors) OR (antitrombinas directas) OR (antitrombinas diretas) OR d27.505.519.389.745.800.449 OR d27.505.954.502.119.500)) OR (tw:(mh: coumarins OR mh: cumarinas OR mh: cumarínicos OR (coumarin derivative*) OR coumarin* OR cumarina* OR d03.383.663.283.446 OR d03.633.100.150.446)) OR (tw:(mh: dabigatran OR mh: dabigatrán OR mh: dabigatrana OR (dabigatran* etexilat*) OR (dabigatran etexilate mesylate) OR pradaxa OR (etexilato de dabigatrana) OR d03.383.725.192 OR d03.633.100.103.280)) OR (tw:(mh: anticoagulants OR mh: anticoagulantes OR (agent* anticoagulant*) OR anticoagulant* OR (anticoagulant drug*) OR (anticoagulation agents) OR (indirect thrombin inhibitor*) OR (agentes anticoagulantes) OR (agentes de anticoagulación) OR anticoagulante*)) OR (tw:(mh: heparin OR mh: heparina OR (heparin sodium) OR (heparin unfractionated) OR (heparinic acid) OR liquaemin OR (alpha heparin) OR alpha-heparin OR alfa-heparina OR (ácido heparínico) OR (heparina alfa) OR heparina-alfa)) OR (tw:(mh: fondaparinux OR arixtra OR (fondaparinux sodium) OR quixidar OR (fondaparinux sódico))) OR (tw:(mh: "Hirudin Therapy" OR mh: "Terapia con Hirudina" OR mh: "Terapia com Hirudina")) OR (tw:(mh: phenindione OR mh: fenindiona OR dindevan OR fenilin OR phenylindanedione OR phenyline OR pindione OR d02.455.426.559.847.486.487.750 OR d04.615.486.487.750)) OR (tw:(mh: polysaccharides OR mh: polisacáridos OR mh: polissacarídeos OR glycans OR glican*)) OR (tw:(mh: rivaroxaban OR mh: rivaroxabán OR mh: rivaroxabana OR xarelto OR d02.886.778.727 OR d03.383.533.640.713 OR d03.383.903.727)) OR (tw:(mh: warfarin OR mh: warfarina OR mh: varfarina OR aldocumar OR apo-warfarin OR coumadin OR coumadine OR gen-warfarin OR marevan OR tedicumar OR warfant OR (warfarin potassium) OR (warfarin sodium) OR d03.383.663.283.446.520.914 OR d03.633.100.150.446.520.914)) OR (tw:(mh: "Factor Xa Inhibitors" OR mh: "Inhibidores del Factor Xa" OR mh: "Inibidores do Fator Xa" OR (anticoagulant* direct-acting oral) OR (direct acting oral anticoagulant*) OR (direct factor xa inhibitor*) OR d27.505.519.389.745.800.449.500 OR d27.505.954.502.119.500.500 OR (anticoagulantes orales de acción directa) OR (inhibidor del factor xa) OR (inhibidores directos del factor xa) OR (anticoagulantes orais de ação direta) OR (inibidor do fator xa) OR (inibidores diretos do fator xa))) OR (tw:(mh: enoxaparin OR mh: enoxaparin* OR clexane OR lovenox)) OR (tw:(mh: dalteparin OR mh: dalteparina OR (dalteparin sodium) OR fragmin* OR tedelparin*)) OR (tw:(doac OR embolex OR liquemine OR (oral anticoagulants) OR pentasaccharide* OR (vitamin k antagonist) OR savaysa OR (edoxaban tosylate) OR edoxaban OR xi-melagatran OR exanta OR danaproid* OR orgaran OR lomoparan OR danaparoid* OR reviparin* OR clivarine OR reviparin-sodium OR (reviparin sodium) OR clivarin OR azetidines OR benzylamines OR lactones OR pyridines)) OR (tw:(mh: phenprocoumon OR mh: fenprocumón OR mh: femprocumona OR falithrom OR liquamar OR marcoumar OR marcumar OR phenprocoumalol OR phenprocoumarol OR phenprogramma OR phenylpropylhydroxycumarinum OR d03.383.663.283.446.520.750 OR d03.633.100.150.446.520.750 OR fenilpropilhidroxicumarina OR fenprocumalol OR fenprocumarol OR femprocumalol OR femprocumarol OR fenilpropilidroxicumarina OR (feno procumarol) OR fenoprocumalol OR fenoprocumona)) OR (tw:(mh: tinzaparin OR mh: tinzaparina OR innohep OR (tinzaparin sodium) OR (tinzaparina sódica))) OR (tw:(mh: "Heparin, Low-Molecular-Weight" OR mh: "Heparina de Bajo-Peso-Molecular" OR mh: "Heparina de Baixo Peso Molecular" OR (heparin low molecular weight) OR lmwh OR (low molecular weight heparin) OR (low-molecular-weight heparin) OR hbpm)) OR (tw:(mh: nadroparin OR mh: nadroparina OR (calcium nadroparin) OR fraxiparin* OR nadroparin*)) OR (tw:(mh: acenocoumarol OR mh: acenocumarol OR acenocoumarin OR (mini sintrom) OR mini-sintrom OR minisintrom OR nicoumalone OR sinkumar OR sinthrome OR sintrom* OR syncoumar OR syncumar OR synthrom OR d03.383.663.283.446.520.079 OR d03.633.100.150.446.520.079 OR acenocumarina OR nicumalon*)))))) AND (db:("LILACS" OR "IBECS")) AND (year_cluster:[2020 TO 2021])

Appendix 6. Cochrane COVID-19 Study Register search strategy

"Anticoagulant* or Heparin* or Rivaroxaban or Warfarin or Enoxaparin or DOAC or LMWH" AND Filter created: 20 Jun '20 - 14 Apr '21

Appendix 7. medRxiv search strategy

"Anticoagulant OR anticoagulants OR Heparin OR Rivaroxaban OR Warfarin OR Enoxaparin OR DOAC OR LMWH" (match whole all) and posted between "20 Jun, 2020 and 14 Apr, 2021"

WHAT'S NEW

Date	Event	Description
13 January 2022	New search has been performed	Search updated to 14 April 2021; new studies incorporated
14 April 2021	New citation required and conclusions have changed	Updated search. Conclusions changed

HISTORY

Review first published: Issue 10, 2020

Date	Event	Description
2 October 2020	New citation required but conclusions have not changed	First version published

CONTRIBUTIONS OF AUTHORS

RLGF: clinical and methodological expertise, development of the search strategy and conception and writing of the review
VTC: methodological expertise and advice
JDST: clinical and methodological expertise and advice
PIFP: clinical expertise and advice
LLA: development of the search strategy
CM: clinical expertise and advice
BT: methodological expertise and advice
VFMT: methodological expertise and advice
ANA: clinical and methodological expertise and advice
LCUN: clinical and methodological expertise and writing of the review

DECLARATIONS OF INTEREST

RLGF: none known
VTC: none known
JDST: none known
PIFP: none known
LLA: none known
CM: none known
BT: none known
VFMT: none known
ANA: none known
LCUN: none known

SOURCES OF SUPPORT

Internal sources

- Division of Vascular and Endovascular Surgery, Universidade Federal de São Paulo, Brazil

  Non-financial internal sources.
- Cochrane Brazil, Brazil

  Non-financial internal sources.

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Title and Objectives

We amended the title from 'Prophylactic anticoagulants for people hospitalised with COVID-19' at the protocol stage (Flumignan 2020a) and the previous version of this review (Flumignan 2020b) to 'Anticoagulants for people hospitalised with COVID-19' in this version to better reflect the purposes of the review. The objectives were amended from 'To assess the effects of prophylactic anticoagulants versus active comparator, placebo or no intervention, on mortality and the need for respiratory support in people hospitalised with COVID-19' in the protocol and previous version to 'To assess the benefits and harms of anticoagulants versus active comparator, placebo or no intervention in people hospitalised with COVID-19.' in this version.

Types of studies

At the protocol stage, we had planned to narratively describe skewed data reported as medians and interquartile ranges. However, in our review, we estimated the mean difference (MD) using the method reported by Wan 2014 to convert median and interquartile range (IQR) into MD and confidence intervals (CI). When this was not possible, we narratively described the skewed data as originally planned. We planned to limit our primary analyses to specific studies, that is, randomised controlled trials (RCTs) and quasi-RCTs, but we performed meta-analyses for all included studies (RCTs or non-randomised studies (NRS)) with available data to follow Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021).

Subgroup analysis and investigation of heterogeneity

At the protocol stage, we had planned subgroup analysis but did not include illness severity. However, in this review version, we performed a subgroup analysis by illness severity when possible. Since venous thromboembolism is more prevalent in more severely ill people with COVID-19, we considered it clinically relevant to present the results by this subgroup analysis.

Data extraction and management

Assessment of risk of bias in included studies

We planned to include only studies that used statistical adjustment for baseline factors using multivariate analyses for the following confounding factors in our protocol (Flumignan 2020a): participants already using anticoagulants (e.g. atrial fibrillation); participants who underwent surgery during the hospitalisation; active cancer treatment; concomitant antiplatelet use; and history of venous thromboembolism. However, we included all prospective NRS that met our inclusion criteria, irrespective of the 'statistical adjustment for baseline factors' and assessed the confounders at the 'bias due to confounding' domain of the ROBINS-I tool in this review (Sterne 2016).

Summary of findings and assessment of the certainty of the evidence

Although we had already included major bleeding as a particular outcome, we amended the summary of findings tables to include adverse events (minor bleeding) in this review version.

Authors' contributions

Some review authors (Marcelly S Cossi, Maria ICD Fernandes, Isabelle KF Costa, and Larissa Souza) were not available to contribute to this review version; therefore, we moved them to the 'Acknowledgment' section. In addition, we incorporated Vinicius T Civile into the review authors' team due to his amount of contribution.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects]; *COVID-19 [complications]; Heparin [adverse effects]; SARS-CoV-2; *Thromboembolism

MeSH check words

Aged; Humans; Middle Aged