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Prophylactic anticoagulants for people hospitalised with COVID-19 (Review)

Flumignan RLG, Tinôco JDDS, Pascoal PIF, Areias LL, Cossi MS, Fernandes MICD, Costa IKF, Souza L, Matar CF, Tendal B, Trevisani VFM, Atallah ÁN, Nakano LCU

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[Rapid Review]

Prophylactic anticoagulants for people hospitalised with COVID-19

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ABSTRACT

Background

Coronavirus disease 2019 (COVID-19) is a serious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The primary manifestation is respiratory insufficiency that can also be related to diffuse pulmonary microthrombosis in people with COVID-19. This disease also causes thromboembolic events, such as pulmonary embolism, deep venous thrombosis, arterial thrombosis, catheter thrombosis, and disseminated intravascular coagulopathy. Recent studies have indicated a worse prognosis for people with COVID-19 who developed thromboembolism.

Anticoagulants are medications used in the prevention and treatment of venous or arterial thromboembolic events. Several drugs are used in the prophylaxis and treatment of thromboembolic events, such as heparinoids (heparins or pentasaccharides), vitamin K antagonists and direct anticoagulants. Besides their anticoagulant properties, heparinoids have an additional anti-inflammatory potential, that may affect the clinical evolution of people with COVID-19. Some practical guidelines address the use of anticoagulants for thromboprophylaxis in people with COVID-19, however, the benefit of anticoagulants for people with COVID-19 is still under debate.

Objectives

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.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS and IBECS databases, the Cochrane COVID-19 Study Register and medRxiv preprint database from their inception to 20 June 2020. We also checked reference lists of any relevant systematic reviews identified and contacted specialists in the field for additional references to trials.

Selection criteria

Randomised controlled trials (RCTs), quasi-RCTs, cluster-RCTs and cohort studies that compared prophylactic anticoagulants (heparin, vitamin K antagonists, direct anticoagulants, and pentasaccharides) versus active comparator, placebo or no intervention for the management of people hospitalised with COVID-19. We excluded studies without a comparator group. Primary outcomes were all-cause

mortality and need for additional respiratory support. Secondary outcomes were mortality related to COVID-19, deep vein thrombosis (DVT), 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 ROBINS-I to assess risk of bias for non-randomised studies (NRS) and GRADE to assess the certainty of evidence. We reported results narratively.

Main results

We identified no RCTs or quasi-RCTs that met the inclusion criteria. We included seven retrospective NRS (5929 participants), three of which were available as preprints. Studies were conducted in China, Italy, Spain and the USA. All of the studies included people hospitalised with COVID-19, in either intensive care units, hospital wards or emergency departments. The mean age of participants (reported in 6 studies) ranged from 59 to 72 years. Only three included studies reported the follow-up period, which varied from 8 to 35 days. The studies did not report on most of our outcomes of interest: need for additional respiratory support, mortality related to COVID-19, DVT, pulmonary embolism, adverse events, and quality of life.

Anticoagulants (all types) versus no treatment (6 retrospective NRS, 5685 participants)

One study reported a reduction in all-cause mortality (adjusted odds ratio (OR) 0.42, 95% confidence interval (CI) 0.26 to 0.66; 2075 participants). One study reported a reduction in mortality only in a subgroup of 395 people who required mechanical ventilation (hazard ratio (HR) 0.86, 95% CI 0.82 to 0.89). Three studies reported no differences in mortality (adjusted OR 1.64, 95% CI 0.92 to 2.92; 449 participants; unadjusted OR 1.66, 95% CI 0.76 to 3.64; 154 participants and adjusted risk ratio (RR) 1.15, 95% CI 0.29 to 2.57; 192 participants). One study reported zero events in both intervention groups (42 participants). The overall risk of bias for all-cause mortality was critical and the certainty of the evidence was very low. One NRS reported bleeding events in 3% of the intervention group and 1.9% of the control group (OR 1.62, 95% CI 0.96 to 2.71; 2773 participants; low-certainty evidence).

Therapeutic-dose anticoagulants versus prophylactic-dose anticoagulants (1 retrospective NRS, 244 participants)

The study reported a reduction in all-cause mortality (adjusted HR 0.21, 95% CI 0.10 to 0.46) and a lower absolute rate of death in the therapeutic group (34.2% versus 53%). The overall risk of bias for all-cause mortality was serious and the certainty of the evidence was low. The study also reported bleeding events in 31.7% of the intervention group and 20.5% of the control group (OR 1.8, 95% CI 0.96 to 3.37; low-certainty evidence).

Ongoing studies

We found 22 ongoing studies in hospital settings (20 RCTs, 14,730 participants; 2 NRS, 997 participants) in 10 different countries (Australia (1), Brazil (1), Canada (2), China (3), France (2), Germany (1), Italy (4), Switzerland (1), UK (1) and USA (6)). Twelve ongoing studies plan to report mortality and six plan to report additional respiratory support. Thirteen studies are expected to be completed in December 2020 (6959 participants), eight in July 2021 (8512 participants), and one in December 2021 (256 participants). Four of the studies plan to include 1000 participants or more.

Authors' conclusions

There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulants for people hospitalised with COVID-19. Since there are 22 ongoing studies that plan to evaluate more than 15,000 participants in this setting, we will add more robust evidence to this review in future updates.

PLAIN LANGUAGE SUMMARY

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

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 and blood vessels, leading to blood clots forming in the arteries, veins and lungs. These blood clots can break loose and travel to other parts of the body, where they may cause blockages leading to heart attacks or strokes. Nearly half of all people with severe COVID-19, in intensive care units, may develop clots in their veins or arteries.

What are blood thinners?

Blood thinners are medicines that prevent harmful blood clots from forming. However, they may 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 if blood clots develop and then treating them with blood thinners.

What did we want to find out?

We wanted to know whether giving people hospitalised with COVID-19 blood thinners as a preventive measure, reduced the number of deaths compared to people who received no treatment or who received a placebo treatment. We also wanted to know whether these people needed less support with breathing, whether they still developed harmful blood clots, whether they experienced bleeding and whether they experienced any other unwanted events (for example, nausea, vomiting, kidney problems and amputations).

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 (sham). 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.

Search date: 20 June 2020

What we found

We hoped to find randomised controlled trials (RCTs). RCTs allocate participants at random to receive either the treatment under investigation or the comparison treatment (another treatment, no treatment or placebo). RCTs give the best evidence.

We did not find any RCTs, so we included seven non-randomised 'retrospective' studies that looked back at treatments given to 5929 people. These studies took place in intensive care units, hospital wards and emergency departments in China, Italy, Spain and the USA. They provided evidence on deaths and bleeding but no evidence on respiratory support, blood clotting and other unwanted effects. The studies were very different from each other, so we were not able to pool their results.

Blood thinners compared with no treatment (6 studies) - One study reported a reduction in mortality and another study reported a reduction in mortality in severely ill people only. Three studies reported no difference in mortality and the remaining study reported no deaths in either group.
- One study reported major bleeding in 3% of participants who received blood thinners and 1.9% of participants who did not receive blood thinners.

Treatment dose of blood thinners compared with preventive dose (1 study) All the participants were in the intensive care unit on mechanical ventilators. They may or may not have had blood clots but were given either blood thinners in a dose usually used to treat clots (higher dose), or a dose used to prevent clots (lower dose).
- This study reported a lower rate of death in people who received the treatment dose (34.2%) compared with the preventive dose (53%).
- This study reported major bleeding in 31.7% of participants who received the treatment dose compared with 20.5% of those who received the preventive dose.

Reliability of the evidence

We do not know whether blood thinners are a useful preventive treatment for people with COVID-19 because we are very uncertain about the evidence. None of the studies randomised participants and all were retrospective. Also, they reported different results from each other and did not report their methods fully. This means our confidence (certainty) in the evidence is very low.

What happens next?

Our searches found 22 ongoing studies, 20 of which are RCTs, with 14,730 people. We plan to add the results of these studies to our review when they are published. We hope that these better quality studies will provide a conclusive answer to our review question.

SUMMARY OF FINDINGS

Summary of findings 1. Anticoagulants (all types) compared to no treatment for people hospitalised with COVID-19

Anticoagulants (all types) compared to no treatment for people hospitalised with COVID-19

Patient or population: people hospitalised with COVID-19
Setting: hospital (ICU and ward)
Intervention: anticoagulants (all types)
Comparison: no treatment

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality Follow-up: range 8 to 28 days	One study reported reduction of mortality by OR adjusted for confounding (reduction of 58% on chance of death; 2075 participants). One study reported reduction of mortality only in a subgroup of severely ill participants (HR 0.86, 95% CI 0.82 to 0.89; 395 participants). Three studies reported no differences by adjusted OR (1.64, 95% CI 0.92 to 2.92; 449 participants), unadjusted OR (1.66, 95% CI 0.76 to 3.64; 154 participants) or adjusted RR (1.15, 95% CI 0.29 to 2.57; 192 participants). One study reported zero events in both intervention groups.	5685 (6 retrospective NRS)	⊕⊖⊖⊖ Very low[a,b,c]
Necessity for additional respiratory support	No study measured this outcome		
Mortality related to COVID-19	No study measured this outcome		
Deep vein thrombosis	No study measured this outcome		
Pulmonary embolism	No study measured this outcome		
Major bleeding Follow-up: not reported	One study reported 24 (3%) bleeding events in the intervention group and 38 (1.9%) bleeding events in the control group (OR 1.62, 95% CI 0.96 to 2.71).	2773 (1 retrospective NRS)	⊕⊕⊖⊖ Low[c,d]

CI: confidence interval; **HR:** hazard ratio; **ICU:** intensive care unit; **NRS:** non-randomised studies; **OR:** odds ratio; **RR:** risk ratio

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 one level due to study limitations. Overall critical/serious risk of bias across studies, especially related to confounding.

[b]Downgraded one level due to inconsistency. We decided not to pool data due to the heterogeneity of studies (especially due to differences in interventions).
[c]Downgraded one level due to imprecision. Narrative synthesis was conducted with imprecise estimates.
[d]Downgraded one level due to study limitations. Overall serious risk of bias, especially related to confounding.

Summary of findings 2. Anticoagulants (therapeutic dose) compared to anticoagulants (prophylactic dose) for people hospitalised with COVID-19

Anticoagulants (therapeutic dose) compared to anticoagulants (prophylactic dose) for people hospitalised with COVID-19

Patient or population: people hospitalised with COVID-19
Setting: hospital (ICU and ward)
Intervention: anticoagulants (therapeutic dose)
Comparison: anticoagulants (prophylactic dose)

Outcomes	Impact	№ of participants (Studies)	Certainty of the evidence (GRADE)
All-cause mortality Follow-up: 35 days	One study reported an absolute rate of death lower in the therapeutic group (34.2% versus 53%) and an HR adjusted for confounding of 0.21 (95% CI 0.10 to 0.46).	244 (1 retrospective NRS)	⊕⊕⊖⊖ Low[a,b]
Necessity for additional respiratory support	No study measured this outcome		
Mortality related to COVID-19	No study measured this outcome		
Deep vein thrombosis	No study measured this outcome		
Pulmonary embolism	No study measured this outcome		
Major bleeding Follow-up: 35 days	One study reported 51 (31.7%) bleeding events in the intervention group and 17 (20.5%) bleeding events in the control group (OR 1.80, 95% CI 0.96 to 3.37).	244 (1 retrospective NRS)	⊕⊕⊖⊖ Low[a,b]

CI: confidence interval; **HR: h**azard ratio; **ICU:** intensive care unit; **NRS:** non-randomised studies; **OR:** odds ratio

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 one level due to study limitations. Overall serious risk of bias, especially related to selection bias.
[b]Downgraded one level due to imprecision. Narrative synthesis was conducted with imprecise estimates based on fewer than 400 participants.

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 transmittable 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; 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 can explain these haematological findings (Giannis 2020). Coagulopathy and vascular endothelial dysfunction have been proposed as complications of COVID-19. Emerging data support that asymptomatic people with COVID-19 are at risk of developing pathologic thrombosis. The association between large-vessel stroke and COVID-19 in young asymptomatic people requires further investigation (Oxley 2020), but Li 2020 found the incidence of stroke among people hospitalised with COVID-19 was 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 can 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). The decision to use, or not use, thromboprophylaxis, 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). 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 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.

OBJECTIVES

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.

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 2020).

We considered parallel or cluster-randomised controlled trials (RCTs), quasi-RCTs, and cohort studies. Cohort studies may be useful for rare adverse events and clinical decisions if there is a lack of controlled studies. We did not consider studies without a comparator group. Although cohort studies (non-randomised) were considered, we planned to limit our primary analyses to specific studies, that is, RCTs and quasi-RCTs. We did not perform a meta-analysis of non-randomised studies (NRS), and we analysed their data narratively. In future updates of this review, when at least 400 participants are included from RCTs, we will no longer consider 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
- history of venous thromboembolism

We considered only studies with a minimum duration of two weeks.

Types of participants

We included all participants eligible for prophylactic 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, independently of the disease severity (e.g. patients hospitalised in ICUs or wards). We had also considered participants with the previous history of venous thromboembolism for inclusion in this review. However, the participants with COVID-19 treated out of the hospital, i.e. 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 meets 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 the subgroup of interest's data 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. Studies in which less than 50% of the population are of interest and the subgroup of interest data are not available will be excluded.

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 comparing 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, 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 Efectiveness 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:

- early outcomes (at hospital discharge or before);
- long-term outcomes (after hospital discharge).

Our time point of primary interest is early; we, therefore, intended to produce related 'Summary of findings' tables only for this time point but we 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
  - extracorporeal membrane oxygenation

Secondary

- Mortality related to COVID-19
- Deep vein thrombosis (DVT), 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 DVT 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.

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; Appendix 2)
- MEDLINE PubMed (1946 to 20 June 2020; Appendix 3)
- Embase Wiley (1974 to 20 June 2020; Appendix 4)
- LILACS Virtual Health Library (Latin American and Caribbean Health Sciences Literature database; 1982 to 20 June 2020; Appendix 5)
- IBECS Virtual Health Library (Indice Bibliográfico Español de Ciencias de la Salud; 2015 to 20 June 2020; Appendix 5)

We adapted the preliminary search strategy for MEDLINE (PubMed; Appendix 3) for use in the other databases. We did not apply any RCT filters for any databases, but we selected the study design manually because we also considered NRS for inclusion in this review.
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.

Searching other resources

We also conducted a search of the Cochrane COVID-19 Study Register (Appendix 6), and medRxiv (Appendix 7), for ongoing or unpublished studies (both searched 20 June 2020).
We checked 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, and identified and recorded reasons for exclusion of the 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 and 'Characteristics of excluded studies' table (Liberati 2009). 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 planned to use a data collection form, which we piloted on at least one study in the review, for study characteristics and outcome data. We planned that one review author (RLGF) would extract study characteristics from 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

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

Assessment of risk of bias in included studies

For data from RCTs we planned to use the 'Risk of bias' 1.0 tool to analyse the risk of bias in the underlying study results (Higgins

2017). For data from quasi-RCTs or prospective NRS, we planned to use the Risk Of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool (Sterne 2016). We also planned to use ROBINS-I to assess the risk of bias in retrospective NRS. Please refer to Appendix 1 for detailed information regarding how we planned to assess the risk of bias of RCTs, quasi-RCTs, and NRS.

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

As we included NRS only, meta-analysis was not appropriate. Instead, we narratively described and presented results per study also using tables.

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 RevMan 5 calculator to calculate missing standard deviations using other data from the trial, 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 intention-to-treat (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 of variations of intervention (all types of anticoagulants) accordingly, regardless of sparse data.

Assessment of heterogeneity

As we identified NRS only, meta-analysis was not appropriate. Instead, we narratively described and presented results per study in tables.

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

Please refer to Appendix 1 for information regarding how we had planned to synthesise data from RCTs, quasi-RCTs and NRS. We did not meta-analyse data from NRS. We reported outcome data of each included study narratively and using tables.

Synthesis without meta-analysis

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

If a meta-analysis was not possible, we explored 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 used a narrative approach to data synthesis. We planned to describe narratively skewed data reported as medians and interquartile ranges.

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
- 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. We planned to investigate the effect of variation in the intracluster correlation coefficient (ICC), and we also planned to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit. We planned 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 the early time point using the following outcomes.

- All-cause mortality
- Necessity for additional respiratory support
- Mortality related to COVID-19
- DVT
- Pulmonary embolism
- Major 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 contribute data to the analyses for the prespecified outcomes. We used methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019) using GRADEpro software (GRADEpro GDT 2015). We made a separate 'Summary of findings' table for each of the following comparisons with available data.

- Anticoagulant (all types) versus no treatment
- Anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)

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

Two review authors (RLGF, LCUN) made judgements about the certainty of the evidence, with disagreements resolved by discussion or by involving a third review author (CM, BT). We justified, documented and incorporated judgements into reporting of results for each outcome.
We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table with meta-analysis before writing the results and conclusions of future updates of our review.

RESULTS

Results of the search

We retrieved a total of 1148 records from our searches. After excluding 103 duplicate records, we screened 1045 unique records. We considered a total of 991 records not relevant at this stage and selected 54 for full-text reading. We excluded 12 studies (11 reports) (see Characteristics of excluded studies). Twenty-two studies are ongoing (see Characteristics of ongoing studies). We considered another 13 studies not relevant after a full-text analysis. For this review, we found seven non-randomised studies (NRS) with available data for inclusion. See Figure 1 for the study flow diagram (Liberati 2009).

Figure 1. Study flow diagram

RCTs: randomised controlled trials; NRS: non-randomised studies

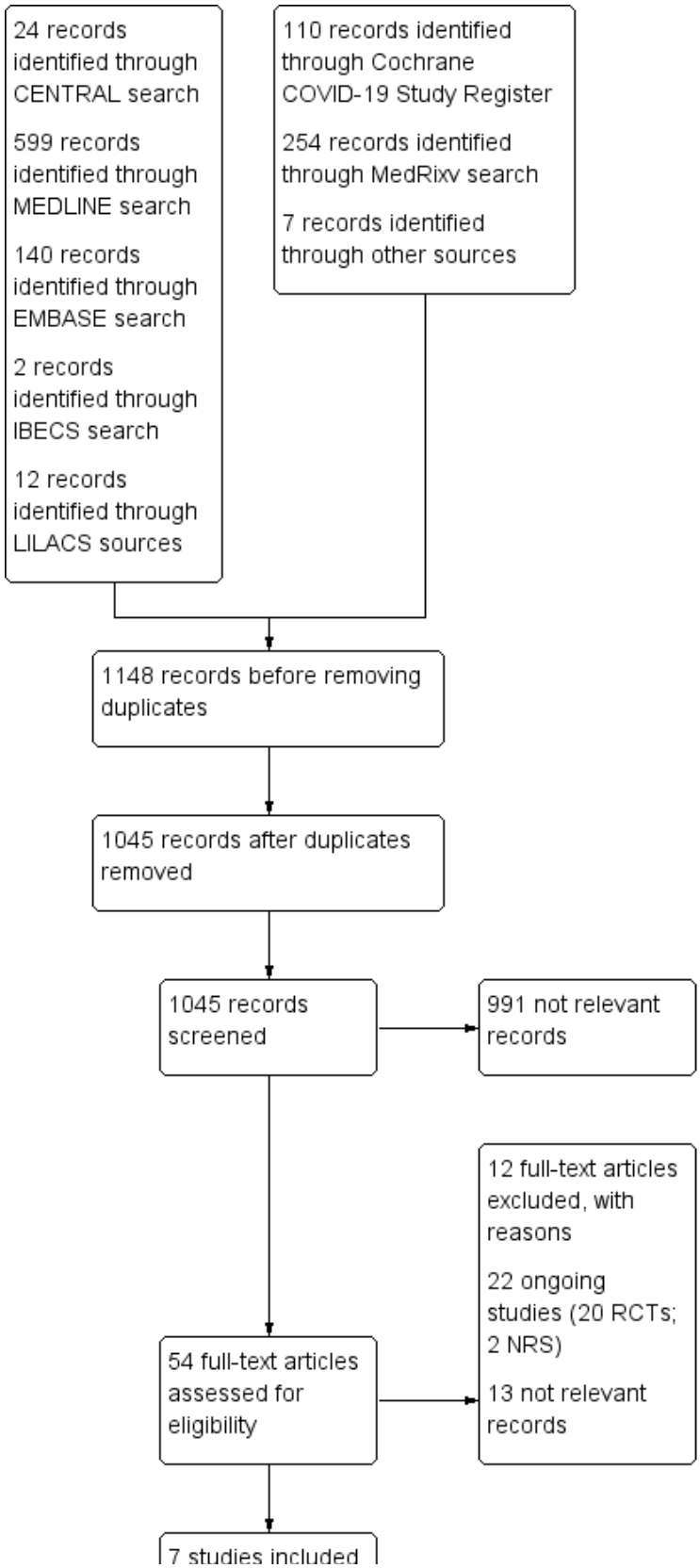
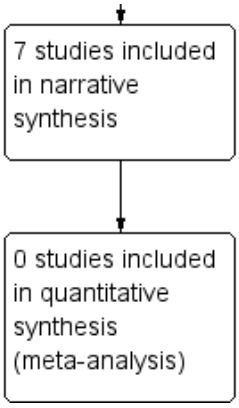


Figure 1. (Continued)



Included studies

See Table 2 for the summarised characteristics of included studies.

We included seven studies describing 5929 participants in this review, of whom at least 2888 received anticoagulants (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020; Trinh 2020). The seven included studies were all non-randomised studies (NRS) of interventions, with a comparator group. Of the seven included studies, four originated from China (Liu 2020; Shi 2020; Tang 2020; Trinh 2020), one from Italy (Russo 2020), one from Spain (Ayerbe 2020), and one from the USA (Paranjpe 2020).

Trinh 2020 compared different doses of anticoagulant (prophylactic versus therapeutic) and the six other included studies compared anticoagulation versus no anticoagulation (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). Only three included studies reported the follow-up period that varied from 8 to 35 days (Ayerbe 2020; Tang 2020; Trinh 2020). Liu 2020 compared participants from the ICU (intervention group) with participants in hospital wards (comparator group). Trinh 2020 included only participants from the ICU in both groups. The five other studies considered participants from all settings (ICU, hospital wards and emergency departments; Ayerbe 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). Paranjpe 2020 did not report data regarding age of participants. The mean age of the other six studies' participants varied from 59 to 72 years (Ayerbe 2020; Liu 2020; Russo 2020; Shi 2020; Tang 2020; Trinh 2020). Six studies reported data on mortality (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Tang 2020; Trinh 2020), and none reported data for necessity for additional respiratory support.

Paranjpe 2020 did not describe the type or dose of anticoagulation. Ayerbe 2020 and Liu 2020 used heparin in the intervention group, but they did not report details about the type of heparin or dose. Shi 2020 used low molecular weight heparin and Russo 2020 used direct oral anticoagulants in 18 participants and vitamin K antagonist in eight other participants, but neither reported more details. Tang 2020 used unfractionated heparin 10,000 IU/day to 15,000 IU/day in five participants and low molecular weight heparin (enoxaparin) 40 mg/day to 60 mg/day in 94 participants. Trinh 2020 used unfractionated heparin 15 IU/kg/hour or enoxaparin 1 mg/kg twice daily if glomerular function rate (GFR) was greater than 30 mL a minute, or once daily if GFR was 30 mL a minute or less. In addition to these anticoagulants, the comparator group in Trinh 2020 also used apixaban 2.5 mg or 5 mg twice daily.

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

Excluded studies

We excluded 12 studies for at least one reason (Characteristics of excluded studies). Eleven of the studies had an irrelevant study design because of at least one of the following reasons (Al-Samkari 2020; Artifoni 2020; EudraCT2020-001823-15; Helms 2020; Khider 2020; NCT04354155; NCT04359212; NCT04368377; NCT04394000; NCT04427098; Zhang 2020):

- 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;
- prospective cohort study without a parallel comparator group of intervention.

One study had an irrelevant intervention, that is, it is a RCT of aspirin for COVID-19, and there was no difference between the intervention groups regarding anticoagulants (NCT04365309).

Ongoing studies

Twenty-two ongoing studies met our inclusion criteria, which plan to evaluate 15,727 participants. We tried to contact study authors; we also searched by study registration number and by 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.

Four of the ongoing studies plan to include 1000 participants or more (NCT04333407; NCT04359277; NCT04366960; NCT04372589). NCT04333407 plans to compare aspirin, clopidogrel, rivaroxaban, atorvastatin, and omeprazole with no treatment in 3170 participants to assess mortality at 30 days. NCT04359277 plans to compare higher-dose versus low-dose prophylactic heparin to assess composite outcomes that include mortality in 1000 participants. NCT04366960 plans to compare 40 mg subcutaneous enoxaparin twice daily versus 40 mg subcutaneous enoxaparin once daily to assess venous thromboembolism in 2712 participants. NCT04372589 plans to compare therapeutic

anticoagulation using heparin for 14 days with prophylactic anticoagulation to assess intubation and mortality in 3000 participants. See Table 3 for a summary of the characteristics of ongoing studies.

Risk of bias in included studies

We assessed the risk of bias at the result level, in each comparison, using ROBINS-I tool (Sterne 2016). The specific judgements ('critical risk', 'serious risk', 'moderate risk', 'low risk', or 'no information') by available outcomes, in each comparison, are presented in Figure 2, Figure 3, Figure 4, Figure 5, Figure 6 and Figure 7. The support for judgement is explained in the related 'Risk of bias' tables (Table 4, Table 5, Table 6, Table 7, Table 8 and Table 9). The overall risk of bias for all-cause mortality and for hospitalisation in the comparison 'anticoagulants (all types) versus no treatment' was critical and in the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' was serious. The overall risk of bias for major bleeding was serious for both comparisons.

Figure 2. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (all-cause mortality)

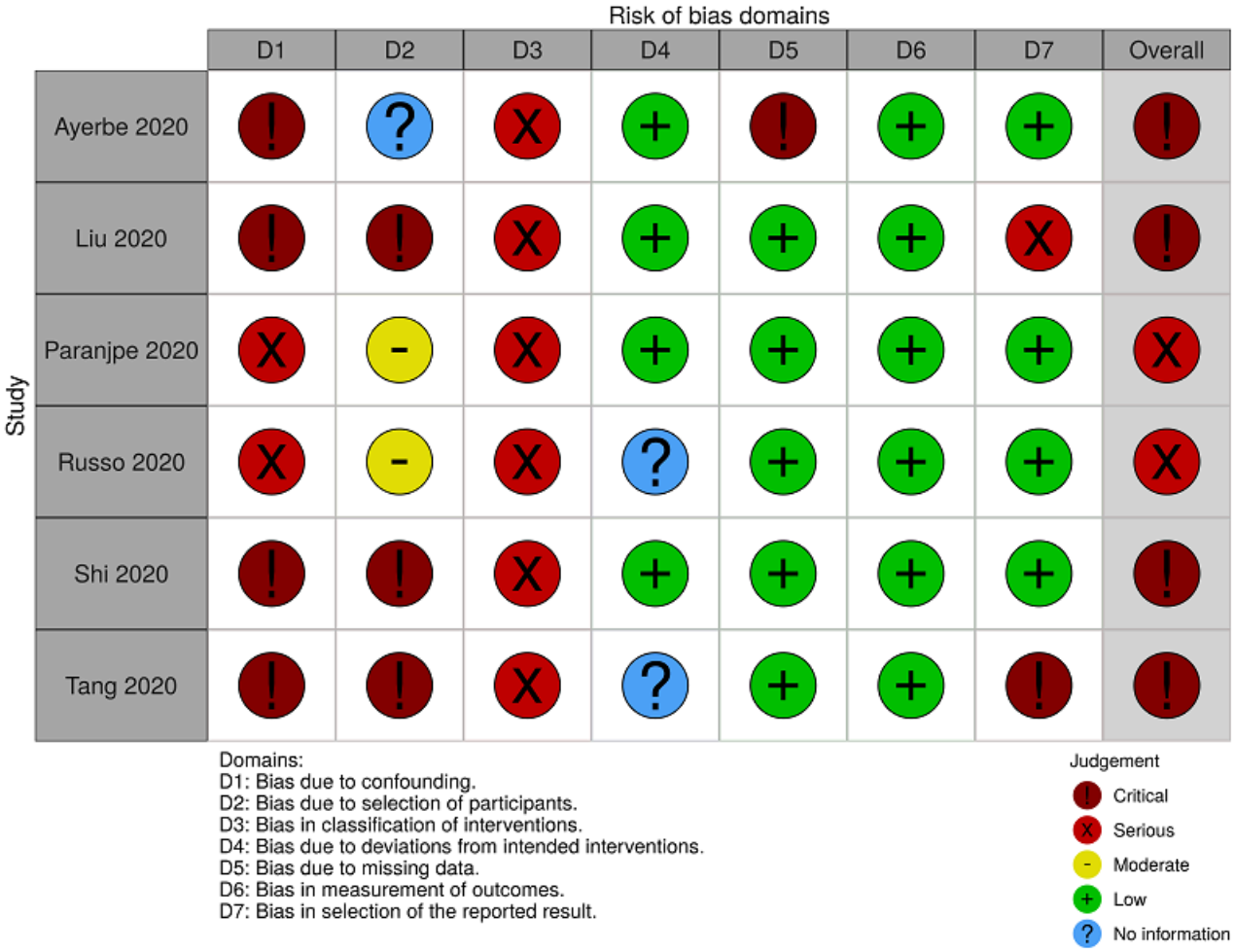


Figure 3. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (major bleeding)

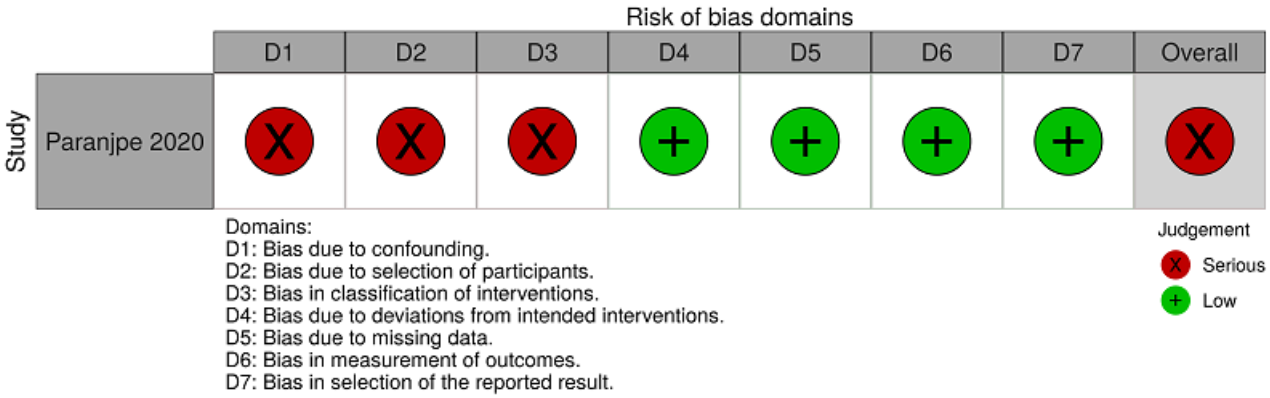


Figure 4. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (hospitalisation)

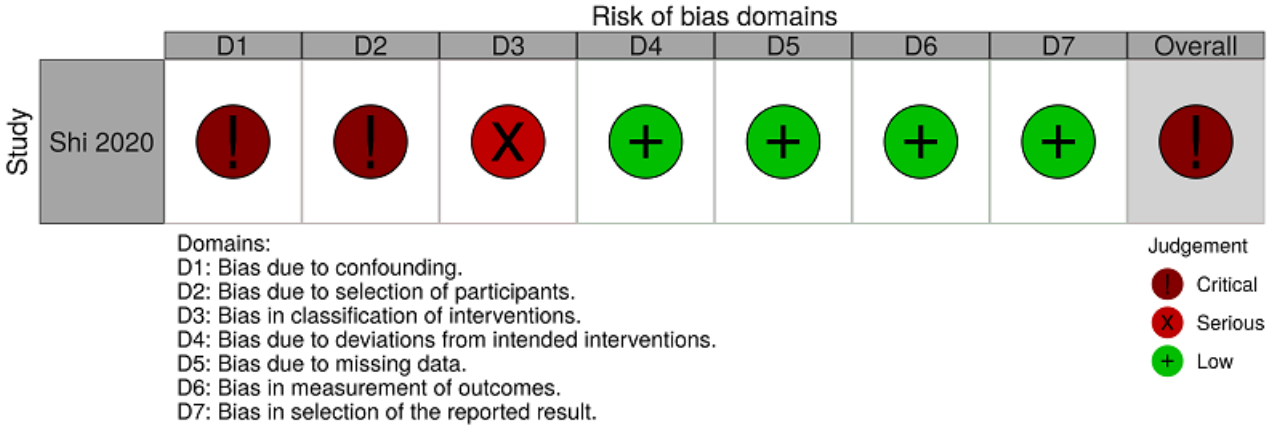


Figure 5. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) for people hospitalised with COVID-19 (all-cause mortality)

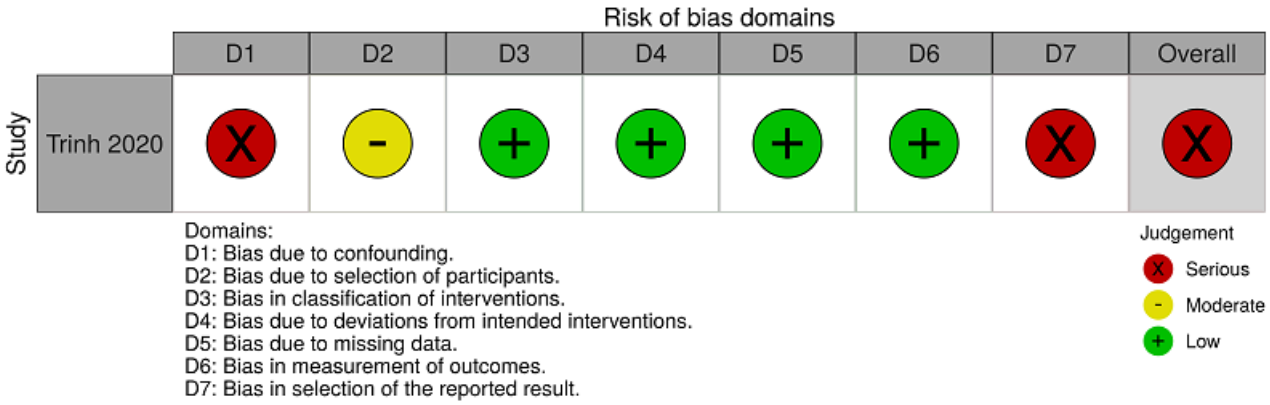


Figure 6. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) for people hospitalised with COVID-19 (major bleeding)

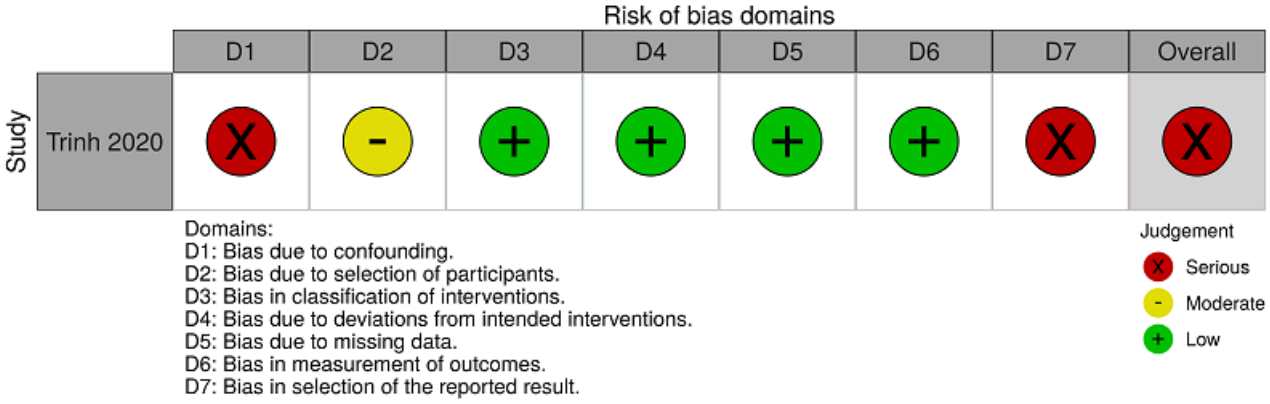
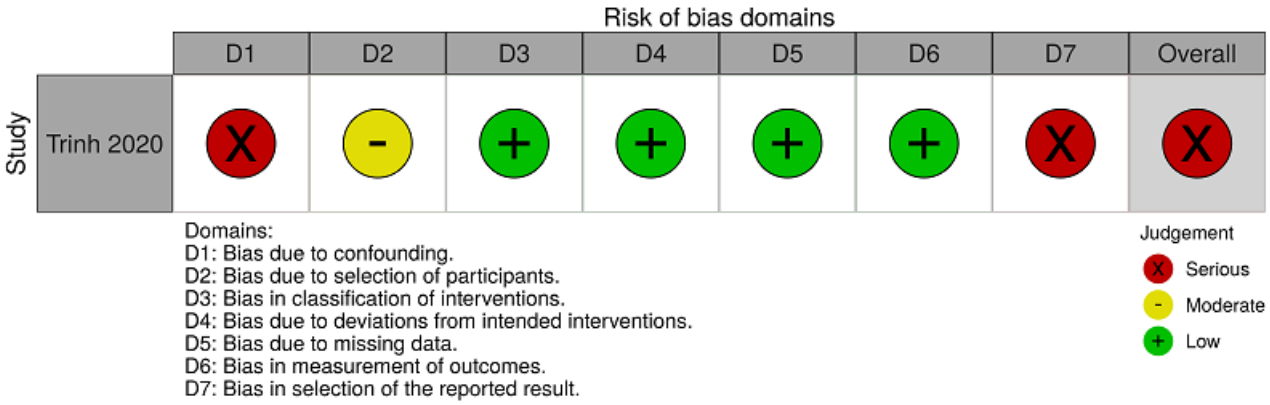


Figure 7. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) for people hospitalised with COVID-19 (hospitalisation)



Bias due to confounding

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment'. We rated four of them as critical risk because one or more prognostic variables are likely to be unbalanced between the compared groups (Ayerbe 2020; Liu 2020; Shi 2020; Tang 2020). There is not a baseline characteristics table comparing the two groups in Ayerbe 2020, Liu 2020 and Tang 2020. There is a baseline characteristics table, with limited items, comparing the two groups in Shi 2020. However, they did not consider essential characteristics, such as participants already using anticoagulants, participants who underwent surgery during hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism. In Tang 2020, the comparator group included participants who used heparin for less time or did not use heparin. These participants may be less severely ill than those in the intervention group.

We rated the other two studies as serious risk because, to minimise the impact of the absence of randomisation, the studies authors performed an adjusted analysis with propensity scores, considering confounding demographic and clinical factors, and medication use. However, neither Paranjpe 2020 nor Russo 2020 considered the confounding factors 'participants who underwent surgery during hospitalisation', 'active cancer treatment', and 'history of venous thromboembolism'. Paranjpe 2020 also did not consider 'concomitant antiplatelet use' as a confounder. See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as serious risk because, to minimise the impact of the absence of randomisation, we performed an analysis with propensity scores, considering confounding demographic, clinical, and laboratory factors, and medication use. However, Trinh 2020 did not consider the confounding factors 'participants who underwent surgery during hospitalisation', 'concomitant antiplatelet use' and 'history of venous thromboembolism'. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as serious risk because, to minimise the impact of the absence of randomisation, we performed an adjusted analysis with propensity scores, considering confounding demographic and clinical factors, and medication use. However, Paranjpe 2020 did not consider the confounding factors 'participants who underwent surgery during hospitalisation', 'active cancer treatment', 'concomitant antiplatelet use' and 'history of venous thromboembolism'. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)'. We rated this study as serious risk because, to minimise the impact of the absence of randomisation, we performed an analysis with propensity scores, considering confounding demographic, clinical, laboratory factors and medication use. However, Trinh 2020 did not consider the confounding factors 'participants who underwent surgery during hospitalisation', 'concomitant antiplatelet use' and 'history of venous thromboembolism'. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as critical risk because one or more prognostic variables are likely to be unbalanced between the compared groups. There is a baseline characteristics table, with limited items, comparing the two groups. However, Shi 2020 did not compare essential characteristics, such as participants already using anticoagulants, participants who underwent surgery during hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as serious risk because, to minimise the impact of the absence of randomisation, we performed an analysis with propensity scores,

considering confounding demographic, clinical, laboratory factors and medication use. However, Trinh 2020 did not consider the confounding factors 'participants who underwent surgery during hospitalisation', 'concomitant antiplatelet use' and 'history of venous thromboembolism'. See Figure 7 and Table 9.

Bias in selection of participants into the study

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment'. We rated three of them as critical risk (Liu 2020; Shi 2020; Tang 2020). These studies selected participants included in both groups (intervention and comparator) from a single hospital, and the studies were retrospective, so it is not possible to know whether the selection was free from bias. The selection for the studies was strongly related to both the intervention and the outcome of interest. We could not adjust the analyses for this selection bias (Liu 2020; Shi 2020; Tang 2020).

We rated Paranjpe 2020 and Russo 2020 as moderate risk because they selected the included participants in both groups from the same hospital, and selection may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for selection bias.

We rated Ayerbe 2020 as 'no information' because they selected participants included in both groups from 17 hospitals, and the study was retrospective, therefore it is not possible to know whether the selection was free from bias. See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as moderate risk because they selected the included participants in both groups from the same hospital. Trinh 2020 considered for inclusion all patients who met the inclusion criteria, and who were treated in each period. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as serious risk because they selected the included participants in both groups from the same hospital, and selection may have been related to intervention and outcome. For this outcome, the study authors did not use appropriate methods to adjust for selection bias. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)'. We rated this study as moderate risk because they selected the included participants in both groups from the same hospital. Trinh 2020 considered for inclusion all patients who met the inclusion criteria, and who were treated in each period. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as critical risk because they selected the participants of the two groups (intervention and comparator) from the same hospital, but as the study was retrospective, it is not possible to know if the selection was free from bias. The selection for the study was strongly related to both the intervention and the outcome of interest. We could not adjust the analyses for this selection bias. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as moderate risk because they selected the included participants in both groups from the same hospital. Trinh 2020 considered for inclusion all patients who met the inclusion criteria, and who were treated in each period. See Figure 7 and Table 9.

Bias in classification of interventions

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment' (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). We rated them as serious risk because there is a high risk that these studies did not standardise interventions received by participants in the same group. Ayerbe 2020 and Liu 2020 did not describe the type and doses of heparin in the intervention group. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively (Paranjpe 2020; Russo 2020; Shi 2020). Besides, in Tang 2020, the comparator group also included participants who used heparin for under seven days. This proximity to the case definition for the intervention group increases the risk of error in the classification of participants. Also, the comparator group in Tang 2020 considered two very different types of intervention. See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because intervention status was well defined based on information collected at the time of intervention. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as serious risk because there is a high risk that they did not standardise the interventions received by participants in the same group. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)'. We rated this study as low risk because intervention status was well defined based on information collected at the time of intervention. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as serious risk because there is a risk that the interventions received by participants in the same group were not standardised. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because intervention status was well defined based on information collected at the time of intervention. See Figure 7 and Table 9.

Bias due to deviations from the intended intervention

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment'. We rated four of them as low risk because they did not report any deviations from the intended intervention, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome (Ayerbe 2020; Liu 2020; Paranjpe 2020; Shi 2020). We rated Russo 2020 and Tang 2020 as 'no information' because there is insufficient information to judge. They did not report any information on whether there was deviation from the intended intervention. See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because they did not report any deviations from the intended intervention in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because they did not report any deviations from the intended intervention in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)'. We rated this study as low risk because they did not report any deviations from the intended intervention in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because they did not report any deviations from the intended intervention in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because they did not report any deviations from the intended intervention in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome. See Figure 7 and Table 9.

Bias due to missing data

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment' (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). We rated Ayerbe 2020 as critical risk because there were missing outcome data for 56 participants with no specific information or appropriate analyses. These missing data could cause a critical impact on the estimates. We rated the other five studies as low because there were no missing data for this outcome (Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because there were no missing data for this outcome. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because there were no missing data for this outcome. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)'. We rated this study as low risk because there were no missing data for this outcome. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because there were no missing data for this outcome. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because there were no missing data for this outcome. See Figure 7 and Table 9.

Bias in measurement of outcomes

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment'. We rated them as low risk because it is unlikely that the outcome assessment (death) was influenced by the knowledge of the intervention received by the study participants (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because it is unlikely that the outcome assessment (death) was influenced by the knowledge of the intervention received by the study participants. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because it is unlikely that the outcome assessment (major bleeding) was influenced by the knowledge of the intervention received by the study participants. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants

(prophylactic dose)'. We rated this study as low risk because it is unlikely that the outcome assessment (major bleeding) was influenced by the knowledge of the intervention received by the study participants. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because it is unlikely that the outcome assessment (length of hospital stay) was influenced by the knowledge of the intervention received by the study participants. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as low risk because it is unlikely that the outcome assessment (length of hospital stay) was influenced by the knowledge of the intervention received by the study participants. See Figure 7 and Table 9.

Bias in selection of the reported result

All-cause mortality

Six studies reported mortality for the comparison 'anticoagulants (all types) versus no treatment' (Ayerbe 2020; Liu 2020; Paranjpe 2020; Russo 2020; Shi 2020; Tang 2020). We rated Tang 2020 as critical risk because we did not identify the study protocol or it was not available, and it is not possible to exclude bias in selection of reported effect estimates, based on the results, from multiple measurements within the outcome domain, multiple analyses of the intervention-outcome relationship, and analyses of different subgroups. We rated Liu 2020 as serious risk because we did not identify the study protocol or it was not available (only a preprint was available), and it is not possible to exclude bias in selection of reported effect estimates, based on the results, from analyses of different subgroups. We rated the other four studies as low because we did not identify the study protocol but all reported results corresponded to the intended outcome (Ayerbe 2020; Paranjpe 2020; Russo 2020; Shi 2020). See Figure 2 and Table 4.

Trinh 2020 reported mortality for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as serious risk because we did not identify the study protocol or it was not available (only a preprint was available), and it is not possible to exclude bias. See Figure 5 and Table 7.

Major bleeding

Paranjpe 2020 reported major bleeding for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because we did not identify the study protocol but all reported results corresponded to the intended outcome. See Figure 3 and Table 5.

Trinh 2020 reported major bleeding for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)'. We rated this study as serious risk because we did not identify the study protocol or it was not available (only a preprint was available), and it is not possible to exclude bias. See Figure 6 and Table 8.

Hospitalisation

Shi 2020 reported hospitalisation for the comparison 'anticoagulants (all types) versus no treatment'. We rated this study as low risk because we did not identify the study protocol but all reported results corresponded to the intended outcome. See Figure 4 and Table 6.

Trinh 2020 reported hospitalisation for the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' and we rated this study as serious risk because we did not identify the study protocol or it was not available (only a preprint was available), and it is not possible to exclude bias. See Figure 7 and Table 9.

Effects of interventions

Since we included seven NRS of interventions and no RCTs, or quasi-RCTs, we did not perform any quantitative data analysis (meta-analysis). Otherwise, we restricted our analysis on the qualitative aspects of the results reported by the study authors.

1. Anticoagulants (all types) versus no treatment

Four studies compared heparins (Ayerbe 2020; Liu 2020; Shi 2020; Tang 2020), and Russo 2020 compared oral anticoagulants (direct oral anticoagulants or vitamin K antagonists) to no treatment. Paranjpe 2020 compared 'therapeutic anticoagulation' (including oral, subcutaneous, or intravenous forms) to no treatment, but did not describe the type or dose of the pharmacological intervention. See Summary of findings 1.

Primary outcomes

All-cause mortality

Ayerbe 2020 reported all-cause mortality as the proportion of participants and as odds ratio (OR) after adjusting for some covariates (e.g. age, gender, saturation of oxygen < 90% and temperature > 37 °C). They found 242 (13.9%) deaths in the intervention group and 44 (15.4%) deaths in the comparator group (adjusted OR 0.42, 95% confidence interval (CI) 0.26 to 0.66; P < 0.001; 2075 participants), in favour of the intervention group after all adjustments.

Liu 2020 evaluated all-cause mortality in the context of the use or not of substitutive dialysis therapy, but not comparing the use or not of heparin. In this setting, mortality in the intervention group was 22.5% and in the comparator group was 22.8%. Extracting data from the reported tables, irrespective of setting (ICU or ward), we found 35 deaths in 106 participants with anticoagulants and 11 deaths in 48 participants without anticoagulants (unadjusted OR 1.66, 95% CI 0.76 to 3.64; 154 participants).

Paranjpe 2020 reported 22.5% in-hospital mortality for the intervention group and 22.8% for the comparator group. However, in participants who required mechanical ventilation (n = 395), in-hospital mortality was 29.1% in the intervention group and 62.7% in the comparator group. In this subgroup, after a multivariate adjustment, the hazard ratio (HR) was 0.86 (95% CI 0.82 to 0.89; P < 0.001; 395 participants).

Russo 2020 reported all-cause mortality, after regression adjustment, as: risk ratio (RR) 1.15 (95% CI 0.29 to 2.57; P = 0.995; 192 participants).

Shi 2020 did not foresee this outcome but reported that no deaths occurred during the follow-up period.

Tang 2020 reported no difference in all-cause mortality between the intervention group (30.3%) and the comparator group (29.7%; P = 0.910) in general (adjusted OR 1.64, 95% CI 0.92 to 2.92; 449 participants). Among participants with a sepsis-induced coagulopathy (SIC) score of 4 or more (n = 97), mortality was 40% in the intervention group and 64.2% in the comparator group (P = 0.029). The unadjusted OR was 0.37 (95% CI 0.15 to 0.90; 97 participants). Besides, mortality among participants with high levels of D-dimer (e.g. greater than 6 times the upper limit) was 32.8% in the intervention group and 52.4% in the comparator group (P = 0.017). The unadjusted OR was 0.44 (95% CI 0.22 to 0.86; 161 participants).

It is very uncertain whether anticoagulants (all types) reduce all-cause mortality compared with no treatment because the certainty of evidence is very low.

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 (DVT)

There were no available data for this outcome.

Pulmonary embolism

There were no available data for this outcome.

Major bleeding

Liu 2020 did not define their bleeding criteria and reported bleeding in lung tissues of one participant. They did not clarify if this diagnosis was made on necropsies or clinically. Therefore, we did not consider this information as an available datum.

Paranjpe 2020 defined 'major bleeding' as:

- haemoglobin less than 7 g/dL and any red blood cell transfusion;
- at least 2 units of red blood cell transfusion within 48 hours; or
- a diagnosis code for major bleeding including intracranial haemorrhage, haematemesis, melena, peptic ulcer with haemorrhage, colon, rectal, or anal haemorrhage, haematuria, ocular haemorrhage, and acute haemorrhagic gastritis.

They reported 24 (3%) events in the intervention group and 38 (1.9%) events in the comparator group (P = 0.2). Of the 24 participants who had bleeding events in the intervention group, 15 (63%) had bleeding events after starting anticoagulation and 9 (37%) had bleeding events before starting anticoagulation. Bleeding events were more common among intubated participants (30 of 395; 7.5%) than among non-intubated participants (32 of 2378; 1.35%).

Ayerbe 2020, Russo 2020, Shi 2020 and Tang 2020 did not report data for this outcome.

Anticoagulants (all types) may make no difference in major bleeding compared with no treatment, but the certainty of evidence is low.

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

Tang 2020 reported that "the prophylactic dose of low molecular weight heparin was used in most of our heparin users, bleeding complications were unusual and commonly mild, and it is not known if higher doses would have been better." However, the trial authors did not report any related number of events or comparison between the groups. Therefore, we did not consider this information as an available datum.

Ayerbe 2020, Liu 2020, Paranjpe 2020, Russo 2020 and Shi 2020 did not report data for this outcome.

Hospitalisation time in days

Paranjpe 2020 reported 5 days (interquartile range (IQR) 3 to 8) as their median hospitalisation time, but they did not compare this outcome among the intervention and comparator groups. Therefore, we did not consider this information as an available datum.

Shi 2020 reported a median of 29 days (IQR 17 to 42) as hospitalisation time in the intervention group and 27 days (IQR 24 to 31) in the comparator group (P = 0.41). We estimated the mean difference (MD) 2 days (95% CI −0.80 to 4.80) using the method reported by Wan 2014 to convert median and IQR into MD and CI.

Tang 2020 used hospital stay of less than seven days as an exclusion criterion, but they did not report data for analysis.

Ayerbe 2020, Liu 2020 and Russo 2020 did not report data for this outcome.

It is very uncertain whether anticoagulants (all types) have any effect on hospitalisation time compared with no treatment because the certainty of evidence is very low (42 participants, 1 retrospective NRS). We downgraded the certainty of evidence by one level due to study limitations because the overall risk of bias was critical, especially related to confounding. We downgraded the certainty of evidence by two levels due to imprecision because the narrative synthesis was conducted with imprecise estimates based on few participants.

Quality of life

There were no available data for this outcome.

2. Anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)

Trinh 2020 compared heparins (unfractionated heparin or low molecular weight heparin) or direct oral anticoagulants (apixaban) in therapeutic doses (161 participants) versus heparins (unfractionated heparin or low molecular weight heparin) or direct oral anticoagulants (apixaban) in prophylactic doses (83 participants). See Summary of findings 2.

Primary outcomes

All-cause mortality

Trinh 2020 reported in-hospital mortality with a follow-up of 35 days in 43.5% of the intervention group and 74.8% of the control group (P = 0.0003). Participants in the intervention group experienced reduced mortality: HR 0.43, (95% CI 0.23 to 0.78). In the subgroup of intubated participants with mechanical ventilation, mortality was 34.2% in the intervention group and 53% in the comparative group: adjusted HR 0.21, 95% CI 0.10 to 0.46.

Anticoagulants (therapeutic dose) may reduce all-cause mortality compared with anticoagulants (prophylactic dose), but the certainty of evidence is low.

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 (DVT)

There were no available data for this outcome.

Pulmonary embolism

There were no available data for this outcome.

Major bleeding

Trinh 2020 did not define major and minor bleeding, therefore, we considered their reported bleeding as major bleeding. They reported 51 (31.7%) events of bleeding in the intervention group and 17 (20.5%) in the comparator group (OR 1.80, 95% CI 0.96 to 3.37, P = 0.07).

Anticoagulants (therapeutic dose) may lead to no difference in major bleeding compared with anticoagulants (prophylactic dose), but the certainty of evidence is low.

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

Trinh 2020 reported stroke events (intervention: 6 (3.7%) and comparator: 5 (6%), P = 0.41); renal failure requiring dialysis (intervention: 67 (42.7%) and comparator: 25 (30.9%), P = 0.08); and liver failure (intervention: 3 (1.9%) and comparator: 2 (2.4%), P = 1.00). However, they did not report any of the adverse events of interest for this review.

Hospitalisation time in days

Trinh 2020 reported hospitalisation time as mean ± SD for the intervention (23.3 ± 7.7 days) and comparator (15.7 ± 8.9 days) groups (MD 7.6 days, 95% CI 5.35 to 9.85; P < 0.001).

There was low-certainty evidence (244 participants, one retrospective NRS) that anticoagulants (therapeutic dose) may increase hospitalisation time compared with anticoagulants (prophylactic dose). We downgraded the certainty of evidence by one level due to study limitations because the overall risk of bias was serious, especially related to selection bias. We downgraded the certainty of evidence by one level due to imprecision. Narrative synthesis was conducted with imprecise estimates based on fewer than 400 participants.

Quality of life

There were no available data for this outcome.

DISCUSSION

This review aimed to assess the effects of prophylactic 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 RCTs, no quasi-RCTs, and no prospective NRS with available data assessing the effects of prophylactic anticoagulants compared to active comparator, placebo or no intervention on mortality and need for additional respiratory support for people hospitalised with COVID-19.

We found 22 ongoing studies (from Australia (1), Brazil (1), Canada (2), China (3), France (2), Germany (1), Italy (4), Switzerland (1), UK (1), and USA (6)) that plan to evaluate 15,727 participants in this setting, of whom 14,730 are from 20 RCTs, and 997 are from one prospective NRS (120 estimated participants) and one retrospective NRS (877 estimated participants). See Table 3.

Twelve ongoing studies plan to report data for mortality. Six ongoing studies plan to report data for necessity for additional respiratory support. Thirteen ongoing studies are expected to be completed in December 2020 (6959 estimated participants), eight in July 2021 (8512 estimated participants), and one in December 2021 (256 estimated participants). Four of these ongoing studies plan to include 1000 participants or more.

One of the studies plans to compare aspirin, clopidogrel, rivaroxaban, atorvastatin, and omeprazole with no treatment in 3170 participants to assess mortality at 30 days of follow-up. One study plans to compare a higher dose versus lower dose of prophylactic heparin to assess composite outcomes that include mortality in 1000 participants. One study plans to compare different doses of enoxaparin to assess venous thromboembolism in 2712 participants. Another study plans to compare therapeutic anticoagulation using heparin for 14 days with prophylactic anticoagulation to assess intubation and mortality in 3000 participants.

We found six retrospective NRS (5685 participants) with limited evidence of anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (Table 2). The overall risk of bias for all-cause mortality and for hospitalisation was critical and for major bleeding was serious in this comparison. Two studies reported reduction of mortality by odds ratio (reduction of 58% on chance of death) or hazard ratio (HR 0.86, 95% CI 0.82 to 0.89; 395 participants), both adjusted for confounding. Another study reported reduction of mortality only in a subgroup of severely ill participants, two studies reported no differences by unadjusted OR 1.66 (95% confidence interval (CI) 0.76 to 3.64) or adjusted risk ratio (RR) 1.15 (95% CI 0.29 to 2.57), and another study reported zero events in both intervention groups. One study reported 3% of bleeding events in the intervention group and 1.9% in the control group (OR 1.62, 95% CI 0.96 to 2.71). One study reported a median

of 29 days of hospitalisation (IQR 17 to 42) in the intervention group and 27 days (IQR 24 to 31) in the control group (MD 2 days, 95% CI −0.80 to 4.80). See Summary of findings 1.

We found one retrospective NRS (244 participants) with limited evidence about anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) for people hospitalised with COVID-19. One study reported an absolute rate of death lower in the intervention group (34.2% versus 53%) and an adjusted HR 0.21 (95% CI 0.10 to 0.46) for confounding. One study reported 31.7% of bleeding events in the intervention group and 20.5% in the control group (OR 1.8, 95% CI 0.96 to 3.37). One study reported a mean increase of 7.6 days of hospitalisation (95% CI 5.35 to 9.85) in length of hospital stay. See Summary of findings 2.

Overall completeness and applicability of the evidence

While most of the studies reported our primary outcome of all-cause mortality, we identified very little evidence relating to adverse effects of anticoagulants. It is also noteworthy that none of the studies measured our other primary outcome (necessity for additional respiratory support) or our secondary outcomes such as mortality related to COVID-19, DVT, pulmonary embolism and quality of life.

There was substantial heterogeneity in the methods of the included studies and many of them 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 many studies.

The number of studies for each of the possible comparisons was small, ranging from one to six studies. Moreover, the included studies had small primary sample sizes, except for only two included studies that evaluated more than 2000 participants. The largest study involved 2773 participants treated with anticoagulation, but did not provide details about the type or dose of the pharmacological interventions. Another issue is the poor reporting quality of most of these studies, which directly affects data extraction and judgement of risk of bias.

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

It is noteworthy that the studies included in this review were conducted in four different countries, most of which (75%) 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 no available evidence based on RCTs or quasi-RCTs to support their use. This reinforces the importance of this review and serves as an incentive for further investigation.

Certainty of the evidence

We found no RCTs, quasi-RCTs or prospective NRS with available data that were eligible for this review, and we included only seven retrospective NRS.

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 and for hospitalisation in the comparison 'anticoagulants (all types) versus no treatment' was critical and in the comparison 'anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose)' was serious. The overall risk of bias for major bleeding was serious for the both comparisons with available data. 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. There was no information from three included studies for the all-cause mortality assessment in the comparison 'anticoagulants (all types) versus no treatment'.

The certainty of evidence is low to very low. We downgraded the certainty of evidence due to risk of bias, particularly with regard to overall critical/serious risk of bias across studies, especially related to confounding or selection bias. We downgraded the certainty of evidence due to inconsistency and we decided not to pool data due to heterogeneity of studies (especially due to differences in the interventions). We also downgraded the certainty of evidence by one or two levels due to imprecision because the narrative synthesis was conducted with an imprecise estimate based on fewer than 400 participants (in some cases in very few participants).

It is very uncertain if anticoagulants (all types) compared with no treatment, reduce all-cause mortality at 28 days after the intervention (5685 participants, 6 retrospective NRS), or have any effect on hospitalisation time (42 participants, 1 retrospective NRS, follow-up not reported) because the certainty of evidence is very low for both outcomes. Anticoagulants (all types) may make no difference in major bleeding compared with no treatment, but the certainty of evidence is low (2773 participants, 1 retrospective NRS, follow-up not reported). See Summary of findings 1.

Anticoagulants (therapeutic dose), compared with anticoagulants (prophylactic dose), may reduce all-cause mortality, may make no difference in major bleeding or may increase hospitalisation time, but the certainty of evidence is low (244 participants, 1 retrospective NRS, follow-up 35 days) for all these outcomes. See Summary of findings 2.

Potential biases in the review process

We performed a comprehensive search of the literature, and we performed study selection according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). We believe that we identified all the relevant studies that met our inclusion criteria. However, the possibility remains that we may have missed some studies, particularly in the grey literature. We adhered to the inclusion and exclusion criteria prespecified in the protocol in order to limit subjectivity (Flumignan 2020). We made efforts to obtain additional relevant data from study authors but were unable to do so. If we can source supplementary data, we will consider them in future updates. Two review authors selected studies in

duplicate, independently, to reduce potential bias of the review process. One review author extracted data and assessed risk of bias of the included studies, and another review author checked the data extraction and 'Risk of bias' judgements, to accelerate the process and also to reduce potential bias of the review process.

Agreements and disagreements with other studies or reviews

A systematic review of 'potential rapid diagnostics, vaccine and therapeutics for COVID-19' searched for published articles in PubMed, Embase and Cochrane Library, and found 27 studies for inclusion, but none of them regarding anticoagulants (Pang 2020).

A systematic review of 'therapeutic management of patients with COVID-19' searched for studies published in English in Embase, MEDLINE and Google Scholar between 1 December 2019 and 31 March 2020, without any criteria regarding study design. Tobaiqy 2020 included 41 studies (three clinical studies, seven case reports, 10 case series, and 11 retrospective and 10 prospective observational studies) in their review. However, none of their included studies evaluated anticoagulants.

A systematic review of 'hypercoagulation and antithrombotic treatment in coronavirus 2019' searched for studies published in English in PubMed, ISI Web of Science, SCOPUS, and Cochrane Library on 28 March 2020, without any restrictions on publication date or publication status (Violi 2020). They excluded studies without a control group, animal studies, case reports, editorials, commentaries, letters, review articles, and guidelines from their analysis. No additional criteria for the included studies were described. Violi 2020 included nine NRS, which reported measures of clotting activation and their relationship with COVID-19 clinical severity. However, no included study evaluated prophylactic anticoagulants for people hospitalised with COVID-19.

Two narrative reviews regarding 'pharmacologic treatments for COVID-19' and 'management of critically ill adults with COVID-19' analysed several pharmacological interventions for the management of these people, but neither addressed prophylactic anticoagulants directly (Poston 2020; Sanders 2020).

In order to prevent microvascular thrombosis, some clinicians use higher-dose anticoagulation rather than prophylactic 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, all 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).

AUTHORS' CONCLUSIONS

Implications for practice

We found no randomised controlled trials (RCTs), no quasi-RCTs, and no prospective non-randomised studies (NRS) with available data addressing the effects of prophylactic anticoagulants on mortality and need for additional respiratory support for people hospitalised with COVID-19. There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulants for people hospitalised with COVID-19; we found low- to very low-certainty evidence from seven retrospective NRS.

Implications for research

High-quality RCTs that compare prophylactic anticoagulants for people hospitalised with COVID-19 are needed. Since there are 22 ongoing studies (20 RCTs) that plan to evaluate 15,727 participants in this setting, robust evidence may be available soon. Thirteen ongoing studies with an estimated 6959 participants, including one large RCT with 2712 participants comparing different doses of enoxaparin, are planned to be completed by the end of 2020. Other large RCTs, with an estimated 1000, 3000 and 3170 participants are planned to be completed by July 2021. From these three additional RCTs, two compare different doses of heparin (total of 4000 participants), and one compares oral anticoagulants and other drugs to no treatment (3170 participants). There is a need for RCTs with high methodological quality, that is, adequate reporting of randomisation, allocation concealment, blinding, assessing the effects on this population prospectively in an unconfounded randomised study of prophylactic anticoagulants for people hospitalised with COVID-19.

The most notable outcomes to be measured are death and necessity 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ayerbe 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: peer-reviewed journal publication • Setting and dates: hospital, 1 March 2020-20 April 2020 • Country: Spain • Language: English • Number of centres: 17 • Trial registration number: NR
Participants	• Number of participants: 2075 allocated (intervention = 1734; comparator = 341) • Age: 67.6 ± 15.5 years (mean ± SD) • Gender: 1256 (60%) male • Comorbidities: NR • Confounding factors: prior anticoagulation (NR), surgery (NR), cancer (NR), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: NR Inclusion criteria • COVID-19 confirmed by a PCR test Exclusion criteria • NR
Interventions	• Intervention of interest: anticoagulation with heparin (type and dose not described) • Comparator: without anticoagulation • Concomitant therapy: hydroxychloroquine, azithromycin, steroids, tocilizumab, a combination of lopinavir with ritonavir, and oseltamivir. Proportion of participants with each medication not described. • Duration of follow-up: 8 days (median, IQR 5–12)
Outcomes	There is no differentiation between primary and secondary outcomes. • Mortality
Notes	• Sponsor/funding: the study authors declare that they have no financial support. • COIs: Salma Ayis was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London

Liu 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: preprint • Setting and dates: ICU (intervention); hospital ward (comparator), 8 February 2020-3 April 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR
Participants	• Number of participants: 154 allocated (intervention = 61; comparator = 93) • Age: 72.41 ± 10.4 years (mean ± SD) in intervention group, 70.1 ± 11.01 years (mean ± SD) in comparator group • Gender: 94 (61%) male • Comorbidities: NR • Confounding factors: prior anticoagulation (NR), surgery (NR), cancer (NR), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: NR Inclusion criteria • COVID-19 confirmed by a PCR test Exclusion criteria • NR
Interventions	• Intervention of interest: with anticoagulation (heparin). Type and dose were not described • Comparator: without anticoagulation • Concomitant therapy: possible use of tocilizumab, but the proportion of participants was not described • Duration of follow-up: NR
Outcomes	There is no differentiation between primary and secondary outcomes. • Mortality • Laboratorial parameters (blood routine characteristics, coagulation parameters) • Thrombocytopenia
Notes	• Sponsor/funding: grants 2016CB02400 and 2017YFC1201103 from the National Major Research and Development Program of China. The study authors declare that "The founder of this study did not contributed to data collection, analysis, and interpretation, and the manuscript preparation." • COIs: all study authors declare no competing interests

Paranjpe 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: peer-reviewed journal publication • Setting and dates: hospital, 14 March 2020-11 April 2020 • Country: USA

Paranjpe 2020 *(Continued)*

	• Language: English • Number of centres: 1 • Trial registration number: NR
Participants	• Number of participants: 2773 allocated (intervention = 786; comparator = 1987) • Age: NR • Gender: NR • Comorbidities: NR • Confounding factors: prior anticoagulation (proportion NR, but adjusted), surgery (NR), cancer (NR), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: intubation and mechanical ventilation Inclusion criteria • COVID-19 confirmed by a PCR test Exclusion criteria • NR
Interventions	• Intervention of interest: treatment-dose anticoagulation (including oral, SC, or IV forms). There is no detail about dose and type of anticoagulant. • Comparator: without anticoagulation • Concomitant therapy: NR • Duration of follow-up: NR (data reported from the period of hospitalisation)
Outcomes	There is no differentiation between primary and secondary outcomes. • Mortality • Laboratorial parameters (blood routine characteristics, coagulation parameters, CPR levels) • Bleeding
Notes	• Sponsor/funding: the work was supported by U54 TR001433-05, National Center for Advancing Translational Sciences, National Institutes of Health • COIs: Dr. Fayad has received consulting fees from Alexion and GlaxoSmithKline; has received research funding from Daiichi-Sankyo, Amgen, Bristol-Myers Squibb, and Siemens Healthineers; and has received financial compensation as a board member and advisor to and owns equity as a co-founder of Trained Therapeutix Discovery. Dr. Nadkarni has received financial compensation as a consultant and Advisory Board member for and owns equity in RenalytixAI; is a scientific co-founder of RenalytixAI and Pensieve Health; has received operational funding from Goldfinch Bio; and has received consulting fees from BioVie Inc., AstraZeneca, Reata, and GLG consulting in the past 3 years. All other study authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Russo 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: peer-reviewed journal publication • Setting and dates: hospital, February 2020-April 2020 • Country: Italy • Language: English • Number of centres: 5 • Trial registration number: NR

Russo 2020 *(Continued)*

Participants	• Number of participants: 192 allocated (intervention = 26; comparator = 166) • Age: 67.7 ± 15.2 years (mean ± SD) • Gender: 115 (60%) male • Comorbidities: hypertension (57.8%), diabetes (21.9%), heart failure (10.4%) • Confounding factors: prior anticoagulation (13.5%), surgery (NR), cancer (NR), antiplatelet use (28.6%), history of VTE (NR) • Type of ventilator support: NR Inclusion criteria • Adults (age > 18 years) with severe COVID-19 confirmed by a PCR test Exclusion criteria • Discontinuation of antithrombotic therapy during hospitalisation

Interventions	• Intervention of interest: anticoagulation at hospital admission
	  * DOACS in 18 participants, or
	  * VKA (well controlled) in 8 participants
	• Comparator: without anticoagulation
	• Concomitant therapy: antiplatelet therapy in 28.6% of participants
	• Duration of follow-up: NR (data reported from the period of hospitalisation)

Outcomes	There is no a differentiation between primary and secondary outcomes. • Mortality • ARDS risk
Notes	• Sponsor/funding: the study authors declare that they have no financial support. • COIs: the study authors declare that they have no conflicts of interest.

Shi 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: preprint • Setting and dates: hospital, 1 February 2020-15 March 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR
Participants	• Number of participants: 42 allocated (intervention = 21; comparator = 21) • Age: 69 years (mean; from 40-91 years) • Gender: 28 (66%) male • Comorbidities: hypertension (30.9%), diabetes (19%), chronic kidney disease (0%). All comorbidities were equivalent between the groups. • Confounding factors: prior anticoagulation (NR), surgery (NR), cancer (no difference), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: NR Inclusion criteria

Shi 2020 *(Continued)*

	• Adults (age > 18 years) with COVID-19 confirmed by a PCR test • Experienced any of the following: shortness of breath, respiration rate ≥ 30 breaths/min; resting oxygen saturation ≤ 93%; PaO_2/FiO_2 ≤ 300 mmHg; lung imaging showing significant lesion progression of > 50% within 24 h-48 h, and a severe clinical classification • No previous history of bronchiectasis, bronchial asthma, or other respiratory diseases • No immunosuppressant or glucocorticoid use during treatment Exclusion criteria • Patients with severe systemic diseases and other acute or chronic infectious diseases • Patients with liver and kidney insufficiency or congenital heart disease • Patients who had been treated with LMWH in the previous 3 months • Patients with a prior history of mental illness • Pregnant or lactating women • Patients clinically classified as critically ill or housed in the ICU • Patients allergic to LMWH or contraindicated for LMWH
Interventions	• Intervention of interest: with anticoagulation. LMWH (dose NR) • Comparator: without anticoagulation • Concomitant therapy: no difference between the groups about antiviral treatment • Duration of follow-up: NR. The length of hospital stay varied from 17-42 days (interquartile range)
Outcomes	There is no differentiation between primary and secondary outcomes. • Mortality • Laboratorial parameters (blood routine characteristics, coagulation parameters, CPR levels, cytokine levels) • General length of stay (hospitalisation time in days)
Notes	• Sponsor/funding: National Natural Science Foundation of China 303 (No. 81603037 to SC) and the National Key Research and Development Plan of 304 China (2017YFC0909900) • COIs: all study authors declare no competing interests

Tang 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: peer-reviewed journal publication • Setting and dates: hospital, 1 January 2020-13 February 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR
Participants	• Number of participants: 449 allocated (intervention = 99; comparator = 350) • Age: 65.1 ± 12.0 years (mean ± SD) • Gender: 268 (60%) male • Comorbidities: hypertension (39.4%), diabetes (20.7%), heart diseases (9.1%) • Confounding factors: prior anticoagulation (NR), surgery (NR), cancer (NR), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: NR

Tang 2020 *(Continued)*

	Inclusion criteria • Adults (age > 18 years) with severe COVID-19 confirmed by a PCR test Exclusion criteria • Bleeding diathesis • Hospital stay < 7 days • Lack of information about coagulation parameters and medications • Age < 18 years

Interventions	• Intervention of interest: anticoagulation for ≥ 7 days
	  * UFH (10,000-15,000 IU/d) in 5 participants, or
	  * LMWH (40-60 mg enoxaparin/d) in 94 participants
	• Comparator: no anticoagulants
	• Concomitant therapy: all participants received antiviral
	• Duration of follow-up: 28 days after ICU admission

Outcomes	There is no differentiation between primary and secondary outcomes. • Mortality • Coagulation parameters
Notes	• Sponsor/funding: National Mega Project on Major Infectious Disease Prevention of China, Grant/Award Number: 2017ZX10103005-007 • COIs: the study authors declare that they have no conflicts of interest.

Trinh 2020

Study characteristics	
Methods	• Study design: retrospective cohort • Type of publication: preprint • Setting and dates: ICU, 1 March 2020-11 April 2020 • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NR
Participants	• Number of participants: 244 allocated (intervention = 161; comparator = 83) • Age: 59.6 ± 13.2 years (mean ± SD) • Gender: 161 (66%) male • Comorbidities: hypertension (50%), diabetes (36.9%), chronic kidney disease (9.8%), asthma (12.3%). All comorbidities were equivalent between the groups, except asthma (intervention = 8.1%; comparator = 20.5%) • Confounding factors: prior anticoagulation (intervention = 1.9%; comparator = 6%), surgery (NR), cancer (intervention = 6.8%; comparator = 9.6%), antiplatelet use (NR), history of VTE (NR) • Type of ventilator support: intubation and mechanical ventilation Inclusion criteria • Adults (age > 18 years) with COVID-19 confirmed by a PCR test Exclusion criteria

Trinh 2020 *(Continued)*

	• Patients who died within 5 days of ICU admission

Interventions	• Intervention of interest: therapeutic anticoagulation
	  * UFH, infusion of ≥ 15 IU/kg/h with or without a heparin bolus of 80 IU/kg with the goal to achieve an activated prothrombin time of 70-100 s based on institutional protocol; or
	  * Enoxaparin 1 mg/kg twice daily if GFR > 30 ml/min, or once daily if GFR was 30 ml/min or less; or
	  * Apixaban 10 mg (no prior anticoagulation) or 5 mg (prior anticoagulation) twice daily
	• Comparator: prophylaxis anticoagulation
	  * UFH 5000 IU SC 2-3 times daily; or
	  * Enoxaparin 40 mg twice daily if GFR > 30 mL/min, or 40 mg once daily if GFR was ≤ 30 mL/min; or
	  * Apixaban 2.5 mg or 5 mg twice daily
	• Concomitant therapy: the majority of participants received a combination of enoxaparin and UFH; all participants were in mechanical ventilation support
	• Duration of follow-up: 35 days after ICU admission

Outcomes	There is no a differentiation between primary and secondary outcomes. • Survival probability • Stroke • Bleeding • End-stage renal disease • Liver failure • ICU length of stay (days) • General length of stay (hospitalisation time in days)
Notes	• Sponsor/funding: NR • COIs: NR

ARDS: acute respiratory distress syndrome; **COI:** conflict of interest; **CPR:** cardiopulmonary resuscitation; **DOACS:** direct oral anticoagulants; **FiO_2:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HIT:** heparin-induced thrombocytopenia; **ICU:** intensive care unit; **IQR:** interquartile range; **IU:** international unit; **IV:** intravenous(ly); **LMWH:** low molecular weight heparin; **NR:** not reported; **PaO_2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **SC:** subcutaneous(ly); **SD:** standard deviation; **UFH:** unfractionated heparin; **ULN:** upper limit of normal; **VKA:** vitamin K antagonists; **VTE:** venous thromboembolism

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

Study	Reason for exclusion
Al-Samkari 2020	Irrelevant study design. Retrospective cohort study without a parallel comparator group of intervention
Artifoni 2020	Irrelevant study design. Retrospective cohort study without a comparator group (single-arm study)
EudraCT2020-001823-15	Irrelevant study design. Prospective cohort study without a comparator group (single-arm study).
Helms 2020	Irrelevant study design. Prospective cohort study without an intervention purpose
Khider 2020	Irrelevant study design. Prospective cohort study without a parallel comparator group of intervention
NCT04354155	Irrelevant study design. Prospective cohort study without a comparator group (single-arm study)
NCT04359212	Irrelevant study design. Prospective cohort study without a parallel comparator group of intervention

Study	Reason for exclusion
NCT04365309	Irrelevant intervention. RCT of aspirin for COVID-19. There is no difference between the intervention groups regarding anticoagulants.
NCT04368377	Irrelevant study design. Prospective cohort study without a comparator group (single-arm study).
NCT04394000	Irrelevant study design. Prospective before-after cohort study without a parallel comparator group
NCT04427098	Irrelevant study design. Prospective cohort study without a comparator group (single-arm study)
Zhang 2020	Irrelevant study design. Retrospective cases series. Description of 7 participants without a consistent comparator group

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	Multicenter, prospective, randomised controlled, 2-armed, parallel assignment study
Participants	172 participants, ≥ 18 years, female and male 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 per 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

ACTRN12620000517976 *(Continued)*

	• 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 to 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

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 RCT; open label, 1:1; 2-armed, parallel-assignment study
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

ChiCTR2000030700 *(Continued)*

- 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 (creatinine clearance (CcCl) < 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 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

ChiCTR2000030701 *(Continued)*	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 • 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 alanine aminotransferase (ALT) / aspartate aminotransferase (AST) increased > 5 times of the ULN • Patients known to have severe renal impairment (creatinine clearance (CcCl) < 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, two 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 fifth 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 (Ccr ≤ 15mL/min) • 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

Marietta 2020

Study name	Randomised controlled trial comparing high versus low LMWH dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation
Starting date	1 June 2020

Marietta 2020 *(Continued)*

Contact information	Marco Marietta, MD Azienda Ospedaliero-Universitaria di Modena, Italy 0594224640 ext +39 | marco.marietta@unimore.it
Methods	Multicentre, open-label, investigator-sponsored, two arms, 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 mm3)
	• 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

Marietta 2020 *(Continued)*

- Need for invasive mechanical ventilation for participants, who are in non-invasive mechanical ventilation at randomisation

Secondary

- 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 RCT with 2 parallels arms, 1:1, open label
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

NCT04333407 *(Continued)*

	• 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 • 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

NCT04344756 *(Continued)*

	Exclusion criteria
	• Participants with contraindications to anticoagulation
	  * Congenital hemorrhagic disorders
	  * 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 creatinine clearance 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 of care • Control participants will receive the best standard of 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 creatinine clearance (Cockcroft) ≥ 30 mL/min or UFH 5000 IU/12 h if creatinine clearance < 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 Acute Kidney Injury 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)

NCT04344756 *(Continued)*

	• 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) • 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 adverse events (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	Multicenter, prospective, 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

NCT04345848 *(Continued)*

	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 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 of 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 • Sequential organ failure assessment 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 • Hospitalized, COVID-19-positive, between 18 and ≤ 85 years of age • Signed informed consent form

NCT04352400 *(Continued)*

- 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
  * 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/m2 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

NCT04352400 *(Continued)*

- 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

- 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
- pO2/FiO2 ratio (time frame: day 1 until day 28). Change in pO2/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

NCT04359277

Study name	A randomized trial of anticoagulation strategies in COVID-19
Starting date	21 April 2020
Contact information	Jeffrey Berger NYU Langone Health, New York, USA 212-263-4004 | PROTECT.COVID19@nyulangone.org
Methods	Open-label, 2-armed, parallel-assignment, RCT
Participants	1000 participants, ≥ 18 years, female and male Inclusion criteria • ≥ 18 years • Hospitalised patient with a diagnosis of COVID-19 • Elevated D-dimer within prior 48 h. Definition of elevated D-dimer is site-determined Exclusion criteria • Meeting alternative indication for higher-dose anticoagulation • Prevalent blood clot at the time of enrolment • D-dimer > 10,000 ng/mL • Rapidly rising D-dimer (change in D-dimer > 10 x over the prior 48 h) • Prior VTE • Atrial fibrillation (with a CHADS2 Score > 1*) • Renal failure (creatinine clearance < 15 and/or requirement of renal replacement therapies) • HIT within 100 days • Stroke within 30 days • Hemorrhagic stroke (ever)

NCT04359277 *(Continued)*

- GI bleed within 6 months
- Platelet count < 100,000
- Anemia with a haemoglobin < 9 mg/dL
- Pregnancy
- Signs of active bleeding (e.g. a whole blood or PRBC transfusion in the past 30 days)
- Other high bleeding risk (i.e. trauma, use of dual antiplatelet therapy)
- Congestive heart failure, hypertension,
- Age > 75 years
- Diabetes
- Prior stroke or TIA symptoms

Interventions	Experimental: higher-dose anticoagulation Drug: enoxaparin higher dose • Enoxaparin in participants with a creatine clearance of > 30 • Enoxaparin 1 mg/kg every 12 h SC for weight 50-150 kg • Enoxaparin 0.75 mg/kg every 12 h SC for weight > 150 kg or BMI > 40 • UFH IV titrated to a goal antiXa of 0.3-0.5 unit/mL (may be used as an alternative) For enoxaparin, antiXA testing will be done after fourth injection only for participants with BMI > 40 or weight > 150 kg as per institutional policy Comparator: lower-dose prophylactic anticoagulation Drug: lower-dose prophylactic anticoagulation • Heparin 5000 units every 12 or every 8 h or 7500 units every 8 h for BMI > 40 or weight > 150 kg, or • Enoxaparin 40 mg every 24 h or 30 mg every 12 h or every 24 h (with Creatine Clearance < 30 mL/min) SQ or • Enoxaparin 40 mg every 12 h SC for weight >150kg or BMI > 40-50 • Enoxaparin 60 mg every 12 h SC for BMI > 50 For enoxaparin, antiXA testing will be done after fourth injection only for participants with BMI > 40 or weight > 150 kg as per institutional policy. For participants who develop AKI, and received enoxaparin, transition to IV UFH by checking antiXa when next dose of enoxaparin would be due and initiating IV heparin when antiXa < 0.7 IU/mL
Outcomes	Primary • Composite incidence of: all-cause mortality, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, stroke, or shock (time frame: 30 days) Secondary • Score on WHO Ordinal Scale (time frame: 30 days) • Incidence of AKI (KDIGO criteria for Acute Kidney Injury (time frame: 30 days) • Requirement of invasive mechanical ventilation or ECMO (time frame: 30 days) • Cardiac injury (time frame: 30 days) measured by troponin and NT proBNP levels • Hypercoagulability (time frame: 30 days) measured by D-dimer and fibrinogen levels • DIC score (time frame: 30 days) • Length of Hospital Stay (time frame: 30 days)
Notes	NCT04359277 | No data provided

NCT04360824

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 University of Iowa, Iowa City, Iowa, USA 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 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/mm3) • Increased risk of bleeding, as assessed by the investigator • Acute or chronic renal insufficiency with creatinine clearance < 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/m2 or 0.5 mg/kg SC twice daily if BMI ≥ 30 kg/m2) Comparator: standard of care. Standard prophylactic dose enoxaparin (40 mg SC daily if BMI < 30 kg/m2 and 30 mg SC twice daily or 40 mg SC twice daily if BMI ≥ 30 kg/m2)
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

NCT04360824 *(Continued)*

- 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.

Notes	NCT04360824 | No data provided

NCT04362085

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 • One 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/m2 or ≥ 40 kg/m2 • Haemoglobin < 80 g/L in the last 72 h

NCT04362085 *(Continued)*

- 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)
- 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)

NCT04362085 *(Continued)*

	• Changes in D-dimer up to day 3 (time frame: up to day 3)
Notes	NCT04362085 | 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	Multicentre, prospective, 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 creatinine clearance < 15 mL/min/1.73 m2 • 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 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

NCT04366960 *(Continued)*

	• 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 trans-thoracic 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	Single-centre, prospective, single-blinded (outcomes assessor), 2-armed, cluster, parallel-assignment 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 • Contraindication to anticoagulation in the opinion of the treating clinician including overt bleeding platelet count < 50,000; Bleeding Academic Research Consortium (BARC) major bleeding in the past 30 days; GI bleeding within 3 months; history of intracranial hemorrhageIschemic 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 (aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin) 5 times > ULN

NCT04367831 *(Continued)*

	• 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 • Enrollment 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/m2: enoxaparin 40 mg SC daily • BMI 40-50 kg/m2: enoxaparin 40 mg SC every 12 h • BMI > 50 kg/m2: 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 of 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 • Hospital length of stay (time frame: discharge from hospital or 30 days). Length of stay measured in days
Notes	NCT04367831 | No data provided

NCT04372589

Study name	Antithrombotic therapy to ameliorate complications of COVID-19
Starting date	20 May 2020
Contact information	Ryan Zarychanski

NCT04372589 *(Continued)*	University of Manitoba, Canada 204-787-2993 | rzarychanski@cancercare.mb.ca
Methods	Multicentre, prospective, open-label, 1:1. 2-armed, parallel-assignment RCT
Participants	3000 participants, ≥ 18 years, female and male Inclusion criteria • Patients ≥ 18 years providing (possibly through a substitute decision maker) informed consent who require hospitalisation anticipated to last ≥ 72 h, with microbiologically-confirmed COVID-19, enrolled < 72 h of hospital admission or of COVID-19 confirmation Exclusion criteria • Receiving invasive mechanical ventilation • Patients for whom the intent is to not use pharmacologic thromboprophylaxis • 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 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, DBP > 120 mmHg); other physician-perceived contraindications to anticoagulation • Platelet count < 50 x10^9/L, INR > 2.0, or baseline aPTT > 50 • Haemoglobin < 80 g/L (to minimise the likelihood of requiring red blood cell transfusion if potential bleeding were to occur) • Acute or subacute bacterial endocarditis • History of HIT or other heparin allergy including hypersensitivity • Current use of dual antiplatelet therapy • Patients with an independent indication for therapeutic anticoagulation • Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention • Pregnancy • Anticipated transfer to another hospital that is not a study site within 72 h • Enrollment in other studies related to anticoagulation or antiplatelet therapy
Interventions	Experimental: therapeutic heparin Therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from supplemental oxygen > 24 h if previously required, whichever comes first) with heparin, with preference for SC LMWH (enoxaparin preferred, although dalteparin or tinzaparin are also acceptable, as available) if no contraindication is present; alternatively, IV UFH infusion may be used. Comparator: prophylactic anticoagulation Participants will receive usual care of thromboprophylactic dose anticoagulation according to local practice.
Outcomes	Primary • Intubation and mortality (time frame: 30 days). The primary endpoint is an ordinal endpoint with 3 possible outcomes based on the worst status of each participant through day 30: no requirement for invasive mechanical ventilation, invasive mechanical ventilation, or death Secondary • All-cause mortality (time frame: 30 days and 90 days)

NCT04372589 *(Continued)*

- Intubation (time frame: 30 days). Invasive mechanical ventilation
- Hospital-free days (time frame: 30 days). Days alive outside of the hospital through 30 days following randomisation
- ICU-free days (time frame: 30 days). Number of days alive outside of the ICU through 30 days following randomisation
- Ventilator-free days (time frame: 30 days). Number of days alive without the use of a ventilator through 30 days following randomisation
- Non-invasive ventilation (time frame: 30 days). The use of non-invasive mechanical ventilation or high-flow nasal cannula
- Organ support-free days (time frame: 21 days). Number of days alive without the use of vasopressors/inotropes and ventilation (including high-flow nasal cannula > 30 L/min and FIO2 > 40%) through 21 days following randomisation, ranked with death at anytime during 21 days as -1
- Myocardial infarction (time frame: 30 days and 90 days)
- Ischaemic stroke (time frame: 30 days and 90 days)
- VTE (time frame: 30 days and 90 days)
- Major bleeding (time frame: Intervention period (maximum 14 days)). As defined by the ISTH
- HIT (time frame: Intervention period (maximum 14 days)). Laboratory-confirmed

Notes	NCT04372589 | 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	Multicenter, 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

NCT04373707 *(Continued)*

	• 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 • 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

NCT04377997 *(Continued)*

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, 100.4F), pneumonia, symptoms of lower respiratory illness (e.g. cough, difficulty breathing), loss of smell or taste, myalgias, pharyngitis, or diarrhoea • 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/uL • 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, nonsteroidal anti-inflammatory drugs (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 of 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)

NCT04377997 *(Continued)*

	• Risk of major bleeding event according to the ISTH definition (time frame: 12 weeks) Secondary There is no description.
Notes	NCT04377997 | No data provided

NCT04393805

Study name	Heparins for thromboprophylaxis in COVID-19 patients: HETHICO study in Veneto
Starting date	1 June 2020
Contact information	Paolo Simioni Department of Medicine, University of Padua, Italy +39 0498212667 | paolo.simioni@unipd.it
Methods	Multicentre, retrospective cohort, open label, investigator-sponsored, two hospitalised population arms (ICU and wards). A comparison of anticoagulant types and doses is foreseen as secondary analysis.
Participants	877 participants, ≥ 18 years, female and male Inclusion criteria • proved SARS-COVID-2 infection Exclusion criteria • none
Interventions	ICU group: thromboprophylaxis with LMWH, mostly enoxaparin Ward group: thromboprophylaxis with LMWH, mostly enoxaparin
Outcomes	Primary • Bleeding (time frame: 28 days). Collect and evaluate in real-life the safety data of the anticoagulant treatments used by estimating the incidence of bleeding complications during hospitalisation. • Thrombosis (time frame: 28 days). Collect and evaluate in real-life the efficacy data of the anti-coagulant treatments used by estimating the incidence of DVT and/or PE during hospitalisation. • Mortality (time frame: 28 days). Collect and evaluate in real-life the data by estimating incidence of intra-hospital death. Secondary • Worsening (time frame: 28 days). Clinical worsening with transfer to the intensive/sub-intensive clinical care unit • Length of stay (time frame: 60 days)
Notes	NCT04393805 | No data provided

NCT04394377

Study name	Randomized clinical trial to evaluate a routine full anticoagulation strategy in patients with coronavirus (COVID-19) - COALIZAO ACTION Trial
Starting date	21 June 2020
Contact information	Renato Delascio Lopes, MD, PhD Brazilian Clinical Research Institute, Sao Paulo, Brazil +55 11 5904 7339 | renato.lopes@duke.edu
Methods	Multicentre, quadruple masking (participant, care provider, investigator, outcomes assessor), investigator-sponsored, 2-armed, parallel-assignment RCT
Participants	600 participants, ≥ 18 years, female and male 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/mm3 • 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 SBP of ≥ 180 mmHg or DBP 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 • Creatinine clearance < 30 mL/min according to the Cockcroft-Gault Formula • Pregnancy or breastfeeding
Interventions	Experimental: routine full anticoagulation strategy. Rivaroxaban 20 mg/d followed by enoxaparin/UFH when needed Comparator: usual standard of care and currently have no indication of full anticoagulation. Control group with enoxaparin 40 mg/d

NCT04394377 *(Continued)*

Outcomes	Primary • 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. Secondary • 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
Notes	NCT04394377 | 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 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

NCT04397510 *(Continued)*

	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

NCT04401293

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	Multicenter, prospective, 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

NCT04401293 *(Continued)*

	• 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 * creatine clearance < 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 creatinine clearance ≥ 30 mL/min (or enoxaparin 0.5 mg/kg SC twice a day for creatinine clearance ≥ 15 mL/min and < 30 mL/min) during the course of their hospitalisation. Comparator: prophylactic/intermediate-dose LMWH or UFH therapy Participants in this study arm will be treated with local institutional standard of 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, 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. Secondary • Major bleeding (time frame: day 30 ± 2 days). Risk of major bleeding defined using the ISTH criteria • Composite outcome of arterial thromboembolic events, venous thromboembolic events and all-cause mortality at hospital day 10 + 4 (time frame: day 10 + 4). The composite 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 hospital day 10 + 4 • SIC score (time frame: day 30 ± 2 days). SIC score based on ISTH guidelines. Platelets, K/uL (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

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	Multicenter, prospective, 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 hs-cTnT > 2.0 ULN * at least one of the following conditions: known coronary artery disease; known diabetes mellitus; active smoking • 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 months 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

NCT04416048 *(Continued)*

- 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 vitamin K antagonists, 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 m2 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. ASS > 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 breast-feeding
- Known intolerance or history of hypersensitivity to the active substance or to any of the excipients of the Investigational Medicinal Product (IMP)
- Participants who are legally detained in an official institution
- Participants who may be dependent on the sponsor, the investigator or the trial sites, are not eligible to enter the trial

Interventions	Experimental: rivaroxaban Treatment with rivaroxaban 20 mg (15 mg for participants with an estimated GFR ≥ 30 mL/min/1.73 m2 and < 50 mL/min/1.73 m2) 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

NCT04416048 *(Continued)*	• 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

APTT: activated partial thromboplastin time; **ACS**: acute coronary syndrome; **AKI:** acute kidney injury; **ARDS**: acute respiratory distress syndrome; **BARC:** Bleeding Academic Research Consortium; **BMI:** body mass index; **BP:** blood pressure; **CKI-EPI:** Chronic Kidney Disease Epidemiology Collaboration; **CPAP:** continuous positive airway pressure; **CPR**: cardiopulmonary resuscitation; **CT:** computed tomography;**DBP:** diastolic blood pressure; **DIC:** disseminated intravascular coagulation; **DVT:** deep vein thrombosis; **ECMO:** extracorporeal membrane oxygenation; **ELISA:** enzyme-linked immunosorbent assay; **GFR**: glomerular filtration rate; **GI:** gastrointestinal; **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); **LMWH:** low molecular weight heparin; **NIV:** non-invasive ventilation; **PCR:** polymerase chain reaction; **PE:** pulmonary embolism; **PRCB:** packed red blood cell; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SARS:** severe acute respiratory syndrome; **SBP:** systolic blood pressure; **SC:** subcutaneous(ly);**SIC:** sepsis-induced coagulopathy;**SOFA:** sequential organ failure assessment; **TIA:** transient ischaemic attack; **UFH:** unfractionated heparin; **ULN:** upper limit of normal; **WHO:** World Health Organization

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
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, i.e. 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)

Table 1. Glossary of terms *(Continued)*

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 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)	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)
Ayerbe 2020 (Retrospective cohort)	Spain	67	Hospital[a]	Heparin (NR)	NA	OR 0.42 (95% CI 0.26 to 0.66) P < 0.001, in favour of intervention group	NR	8	2075	1734
Liu 2020 (Retrospective cohort)	China	72	ICU (intervention) vs hospital ward (comparator)	Heparin (NR)	NA	Unadjusted OR 1.66, 95% CI 0.76 to 3.64	NR	NR	154	61
Paranjpe 2020 (Retrospective cohort)	USA	NR	Hospital[a]	Treatment dose anticoagulation	NA	In-hospital mortality: intervention 22.5% versus comparator 22.8% In subgroup who required mechanical ventilation: intervention 29.1% versus comparator 62.7% (adjusted HR 0.86, 95% CI 0.82 to 0.89; 395 participants, P < 0.001)	NR	NR	2773	786
Russo 2020 (Retrospective cohort)	Italy	67	Hospital[a]	DOACS (NR) in 18 participants and VKA (NR) in 8 participants	NA	RR 1.15 (95% CI 0.29 to 2.57), P = 0.995	NR	NR	192	26
Shi 2020 (Retrospective cohort)	China	69	Hospital[a]	LMWH	NA	Reported no deaths in both groups	NR	NR	42	21

Table 2. Summary of characteristics of included studies *(Continued)*

Tang 2020 (Retrospective cohort)	China	65	Hospital[a]	UFH (10,000 to 15,000 IU/d in 5 participants and LMWH (40 mg/d to 60 mg/d) in 94 participants	NA	No difference (general mortality): (adjusted OR 1.64, 95% CI 0.92 to 2.92; 449 participants) Subgroup analysis: participants with SIC score of ≥ 4(unadjusted OR 0.37, 95% CI 0.15 to 0.90; 97 participants) Participants with D-dimer > 6 times the ULN (unadjusted OR 0.44, 95% CI 0.22 to 0.86; 161 participants)	NR	28	449	99
Trinh 2020 (Retrospective cohort)	USA	59	ICU	UFH 15 IU/kg/h; or enoxaparin 1 mg/kg twice or once daily; or apixaban 10 mg (if no prior anticoagulation) or 5 mg (if prior anticoagulation) twice daily[b]	UFH 5000 IU two to three times daily; or enoxaparin 40 mg twice or once daily; or apixaban 2.5 mg or 5 mg twice daily[b]	Reduction in all-cause mortality (adjusted HR 0.21, 95% CI 0.10 to 0.46) and a lower absolute rate of death in the therapeutic group (34.2% versus 53%)	NR	35	244	161
Total	China: 3 Italy: 1 Spain: 1 USA: 2	-	-	-	-	6 studies considered mortality; 1 study did not report mortality data	No study considered additional respiratory support	8 to 35 (3 studies)	5929	2888

Table 2. Summary of characteristics of included studies *(Continued)*

CI: confidence interval; **DOACS:** direct oral anticoagulants; **GFR:** glomerular filtration rate;**HR:** hazard ratio; **ICU:** intensive care units;**LMWH**: low molecular weight heparin; **NA:** no anticoagulation; **NR:** not reported; **NRS:** non-randomised study;**OR:** odds ratio; **RR:** risk ratio; **SIC**: sepsis-induced coagulopathy; **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 greater than 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	Primary outcomes	Estimated number of participants	Estimated primary completion date
ACTRN12620000517976	Australia	RCT	Time to separation from invasive ventilation	172	25 July 2021
ChiCTR2000030700	China	RCT	Time to virus eradication	60	30 September 2020
ChiCTR2000030701	China	RCT	Time to virus eradication	60	30 September 2020
ChiCTR2000030946	China	Prospective cohort	Biochemical indicators	120	24 April 2020
Marietta 2020	Italy	RCT	Clinical worsening (includes death and necessity for additional respiratory support)	300	June 2021
NCT04333407	UK	RCT	All-cause mortality at 30 days after admission	3170	30 March 2021
NCT04344756	France	RCT	Survival without ventilation	808	31 July 2020
NCT04345848	Switzerland	RCT	Composite outcome of arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality	200	30 November 2020
NCT04352400	Italy	RCT	Time to clinical improvement	256	December 2021
NCT04359277	USA	RCT	Composite incidence of: all-cause mortality, cardiac arrest, symptomatic deep venous thrombosis, PE, arterial thromboembolism, myocardial infarction, stroke, or shock	1000	21 April 2021
NCT04360824	USA	RCT	Risk of all-cause mortality	170	16 April 2021
NCT04362085	Canada	RCT	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	November 2020
NCT04366960	Italy	RCT	Incidence of VTE detected by imaging	2712	August 2020
NCT04367831	USA	RCT	Total number of patients with clinically relevant venous or arterial thrombotic events in ICU	100	November 2020
NCT04372589	Canada	RCT	Intubation and mortality	3000	January 2021
NCT04373707	France	RCT	VTE	602	September 2020
NCT04377997	USA	RCT	• Risk of composite efficacy endpoint of death, cardiac arrest, symptomatic deep	300	1 January 2021

Table 3. Summary of characteristics of ongoing studies *(Continued)*

			venous thrombosis, PE, arterial thromboembolism, myocardial infarction, or haemodynamic shock • Risk of major bleeding event according to the ISTH definition		
NCT04393805	Italy	Retrospective cohort	• Bleeding • Thrombosis • Mortality	877	December 2020
NCT04394377	Brazil	RCT	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	600	December 2020
NCT04397510	USA	RCT	Mean daily PaO_2:FiO_2	50	31 December 2020
NCT04401293	USA	RCT	Composite outcome of arterial thromboembolic events, venous thromboembolic events and all-cause mortality at day 30 ± 2 days	308	22 October 2020
NCT04416048	Germany	RCT	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	400	30 April 2021
Total number of studies	Australia: 1 Brazil: 1 Canada: 2 China: 3 France: 2 Germany: 1 Italy: 4 Switzerland: 1 UK: 1 USA: 6	Prospective cohort: 1 RCT: 20 Retrospective cohort: 1	12 studies considered mortality Six studies considered additional respiratory support	15,727 participants • 997 from NRS • 14,730 from RCTs	13 studies to December 2020 8 studies to July 2021 1 study to December 2021

DVT: deep vein thrombosis; **FiO_2:** fraction of inspired oxygen; **ISTH:** International Society on Thrombosis and Haemostasis; **NRS:** non-randomised studies; **PaO_2:** arterial oxygen pressure;**PE:** pulmonary embolism; **RCT:** randomised controlled trial; **VTE:** venous thromboembolism

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 intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ayerbe 2020	Critical risk	No information	Serious risk	Low risk	Critical risk	Low risk	Low risk	Critical risk
Judgement	One or more prognostic variables are likely to be unbalanced between the compared groups. There is no baseline characteristics table comparing the two groups. Essential characteristics, such as participants already using anticoagulants, 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 17 hospitals, and the study was retrospective, therefore it is not possible to know whether the selection was free from bias.	As this was a retrospective study, there is a high risk that the interventions received by participants in the same group were not standardised. The type and doses of heparin in the intervention group were not described.	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 56 participants with no specific information or appropriate analyses. These missing data could cause a critical impact on the estimates.	It is unlikely that the outcome assessment (death) 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.
Liu 2020	Critical risk	Critical risk	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. There is no baseline characteristics table comparing the two groups. Essential characteristics, such as participants already using anticoagulants, 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 study was retrospective, therefore it is not possible to know whether the selection was free from bias. The selection for the study was strongly related to both the intervention and the outcome of interest. We cold not adjust	As this was a retrospective study, there is a high risk that the interventions received by participants in the same group were not standardised. The type and doses of heparin in the intervention group were not described.	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 was reported for this outcome.	It is unlikely that the outcome assessment (death) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified or was not available or both (only a preprint was available), and it is not possible to exclude bias in selection of reported effect estimate, based on the results, from different sub-	The study is too problematic to provide useful evidence.

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

		the analyses for this selection bias.					groups analyses.	
Paranjpe 2020	Serious risk	Moderate risk	Serious risk	Low risk	Low risk	Low risk	Low risk	Serious risk
Judgement	To minimise the impact of the absence of randomisation, an adjusted analysis with propensity scores was performed considering confounding demographic, clinical, and medication use. However, the confounding factors 'participants who underwent surgery during the hospitalisation', 'active cancer treatment', 'concomitant antiplatelet use' and 'history of venous thromboembolism' were not considered.	The included participants in both groups were selected from the same hospital, and selection may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for selection bias.	There is a high risk that the interventions received by participants in the same group were not standardised. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively.	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 this outcome.	It is unlikely that the outcome assessment (death) 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
Russo 2020	Serious risk	Moderate risk	Serious risk	No information	Low risk	Low risk	Low risk	Serious risk
Judgement	To minimise the impact of the absence of randomisation, we performed an analysis with propensity scores, considering confounding demographic and clinical factors, and medication use. However, the study did not consider confounding factors 'participants who underwent a surgery during the hospitalisation', 'active cancer treatment' and 'history of venous thromboembolism'.	The included participants in both groups were selected from the same hospital, and selection may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for selection bias.	There is a high risk that the interventions received by participants in the same group were not standardised. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively.	Insufficient information to judge. No information is reported on whether there was deviation from the intended intervention.	No missing data were reported for this outcome.	It is unlikely that the outcome assessment (death) 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
Shi 2020	Critical risk	Critical risk	Serious risk	Low risk	Low risk	Low risk	Low risk	Critical risk
Judgement	One or more prognostic variables are likely to be unbal-	The participants of the two groups	There is a risk that the interventions	No deviations from	No missing data were	It is unlikely that the	The study protocol was	The study is too prob-

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

	anced between the compared groups. There is a baseline characteristics table comparing the two groups with limited items. However, the study did not compare essential characteristics, such as participants already using anticoagulants, participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism.	(intervention and comparator) were selected from the same hospital, but as the study was retrospective, it is not possible to know if the selection was free from bias. The selection for the study was strongly related to both the intervention and the outcome of interest. We could not adjust the analyses for this selection bias.	received by participants in the same group were not standardised. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively.	the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlikely to impact on the outcome.	reported for this outcome.	outcome assessment (death) was influenced by the knowledge of the intervention received by the study participants.	not identified but all reported results corresponded to the intended outcome.	lematic to provide useful evidence.
Tang 2020	Critical risk	Critical risk	Serious risk	No information	Low risk	Low risk	Critical risk	Critical risk
Judgement	One or more prognostic variables are likely to be unbalanced among the compared groups. There was no table comparing the characteristics of the two groups at baseline. The comparator group included participants who used heparin for less time or did not use heparin. These participants may be less severely ill than those in the intervention group.	Participants included in both groups were selected from the same hospital, but as the study was retrospective, it is not possible to know whether the selection was free from bias. The selection for the study was strongly related to both the intervention and the outcome of interest. We could not adjust the analyses for this selection bias.	As this was a retrospective study, there is a high risk that the interventions received by participants in the same group were not standardised. Besides, the comparator group also included participants who used heparin for less than seven days. This proximity to the case definition for the intervention group increases the risk of error in the classification of participants. Also, the comparator	Insufficient information to judge. No information is reported on whether there was deviation from the intended intervention.	No missing data were reported for this outcome.	It is unlikely that the outcome assessment (death) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified or was not available or both, and it is not possible to exclude bias in selection of reported effect estimate, based on the results, from multiple measurements within the outcome domain, multiple analyses of the intervention-outcome rela-	The study is too problematic to provide useful evidence.

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

			group considered two very different types of intervention.			tionship, and different subgroups analyses.		

Table 5. 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
Paranjpe 2020	Serious risk	Serious risk	Serious risk	Low risk	Low risk	Low risk	Low risk	Serious risk
Judgement	To minimise the impact of the absence of randomisation, we performed an adjusted analysis with propensity scores considering confounding demographic and clinical factors, and medication use. However, the study did not consider confounding factors 'participants who underwent surgery during the hospitalisation', 'active cancer treatment', 'concomitant antiplatelet use' and 'history of venous thromboembolism'.	The included participants in both groups were selected from the same hospital, and selection may have been related to intervention and outcome. For this outcome, the authors did not use appropriate methods to adjust for selection bias.	There is a high risk that the interventions received by participants in the same group were not standardised. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively.	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 this outcome.	It is unlikely that the outcome assessment (major bleeding) 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

Table 6. 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 6. ROBINS-I assessments: anticoagulants (all types) versus no treatment for people hospitalised with COVID-19 (hospitalisation) *(Continued)*

Shi 2020	Critical risk	Critical risk	Serious 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. There is a baseline characteristics table comparing the two groups with limited items. However, the study did not compare essential characteristics, such as participants already using anticoagulants, participants who underwent surgery during the hospitalisation, concomitant antiplatelet use, and history of venous thromboembolism.	The participants of the two groups (intervention and comparator) were selected from the same hospital, but as the study was retrospective, it is not possible to know if the selection was free from bias. The selection for the study was strongly related to both the intervention and the outcome of interest. We could not adjust the analyses for this selection bias.	There is a risk that the interventions received by participants in the same group have not been standardised. There is a high risk of differential classification errors because the information on the status of the interventions was obtained retrospectively.	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 this outcome.	It is unlikely that the outcome assessment (length of hospital stay) 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 7. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) 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 intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Trinh 2020	Serious risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Serious risk
Judgement	To minimise the impact of the absence of randomisation, we performed an analysis with propensity scores considering confounding demographic, clinical and laboratory factors, and medication use. However, the study did not consider confounding factors 'participants who underwent a surgery during the hospitalisation', 'con-	The included participants in both groups were selected from the same hospital. The study authors considered for inclusion all patients who met the inclusion criteria and who were	Intervention status was well defined based on information collected at the time of intervention.	No deviations from the intended intervention were reported in the study, and if any deviation occurred from usual practice, it was unlike-	No missing data were reported for this outcome.	It is unlikely that the outcome assessment (death) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified or was not available or both (only a preprint was available), and it is not possible to exclude bias.	The study has some important problems

Table 7. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) for people hospitalised with COVID-19 (all-cause mortality) *(Continued)*

	comitant antiplatelet use' and 'history of venous thromboembolism'.	treated in each period.		ly to impact on the outcome.				

Table 8. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) 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
Trinh 2020	Serious risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Serious risk
Judgement	To minimise the impact of the absence of randomisation, we performed an analysis with propensity scores considering confounding demographic, clinical and laboratory factors, and medication use. However, the study did not consider confounding factors 'participants who underwent surgery during the hospitalisation', 'concomitant antiplatelet use' and 'history of venous thromboembolism'.	The included participants in both groups were selected from the same hospital. The study authors considered for inclusion all patients who met the inclusion criteria and who were treated in each period.	Intervention status was well defined based on information collected at the time of intervention.	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 this outcome.	It is unlikely that the outcome assessment (major bleeding) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified or was not available or both (only a preprint was available), and it is not possible to exclude bias.	The study has some important problems

Table 9. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) 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
Trinh 2020	Serious risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Serious risk

Table 9. ROBINS-I assessments: anticoagulants (therapeutic dose) versus anticoagulants (prophylactic dose) for people hospitalised with COVID-19 (hospitalisation) *(Continued)*

Judgement	To minimise the impact of the absence of randomisation, we performed an analysis with propensity scores considering confounding demographic, clinical and laboratory factors, and medication use. However, the study did not consider confounding factors 'participants who underwent a surgery during the hospitalisation', 'concomitant antiplatelet use' and 'history of venous thromboembolism'.	The included participants in both groups were selected from the same hospital. The study authors considered for inclusion all patients who met the inclusion criteria and who were treated in each period.	Intervention status was well defined based on information collected at the time of intervention.	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 this outcome.	It is unlikely that the outcome assessment (length of hospital stay) was influenced by the knowledge of the intervention received by the study participants.	The study protocol was not identified or was not available or both (only a preprint was available), and it is not possible to exclude bias.	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 whole 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 no evidence from RCTs, quasi-RCTs, and prospective NRS, we included retrospective NRS and followed the methodology as specified in the protocol (Flumignan 2020).

Data extraction and management

Assessment of risk of bias in included studies

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* (Higgins 2017) for RCTs (RoB1 tool). 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*: 1) recruitment bias; 2) baseline imbalance; 3) loss of clusters; 4) incorrect analysis; and 5) 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 RoB1 tool: 1) adequate sequence generation, 2) blinding of outcome assessors, and 3) 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 is no clear information on the risk of bias for one or more key domains, but the RCT is not at high risk for any domain, we planned to indicate that the risk of bias in the study is unclear.

Non-randomised studies

Using the ROBINS-I tool, 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 the outcomes, 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.

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 (Adriana Sanudo, Federal University of Sao Paulo, Brazil) 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 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 is little heterogeneity between the study designs, and we consider 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 I^2 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 identify substantial heterogeneity, we planned to report it and explore possible causes by prespecified subgroup analysis.

As strict thresholds for interpretation of I^2 are not recommended, we intend to follow the rough guide to interpretation in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020).

- 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 I^2 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 2020).

Data synthesis

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

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. CENTRAL (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

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

1-3 / OR

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

5-32 / OR

34

4 AND 33

Appendix 4. Embase (Wiley) 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 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)

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"))

Appendix 6. Cochrane COVID-19 search strategy

Anticoagulant* or Heparin* or Rivaroxaban or Warfarin or Enoxaparin or DOAC or LMWH

Appendix 7. medRxiv search strategy

Anticoagulant OR anticoagulants OR Heparin OR Rivaroxaban OR Warfarin OR Enoxaparin OR DOAC OR LMWH

HISTORY

Review first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

RLGF: clinical and methodological expertise, development of the search strategy and conception and writing of the review
JDST: clinical and methodological expertise and advice
PP: clinical expertise and advice
LLA: development of the search strategy
MC: clinical expertise and advice
MIF: clinical expertise and advice
IC: clinical expertise and advice
LS: clinical expertise and advice

CM: clinical expertise and advice
BT: methodological expertise and advice
VT: methodological expertise and advice
AA: clinical and methodological expertise and advice
LCUN: clinical and methodological expertise and writing of the review

DECLARATIONS OF INTEREST

RLGF: none known
JDST: none known
PP: none known
LLA: none known
MC: none known
MIF: none known
IC: none known
LS: none known
CM: none known
BT: none known
VT: none known
AA: none known
LCUN: none known

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  Non-financial internal sources.
- Cochrane Brazil, Brazil

  Non-financial internal sources.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies

We did not include retrospective non-randomised studies (NRS) in our protocol. However, as there was no evidence from randomised controlled trials (RCTs), quasi-RCTs, and prospective NRS, we included retrospective NRS with a control group and followed the methodology as specified in the protocol (Flumignan 2020).

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.

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 2020):

- participants already using anticoagulants (e.g. atrial fibrillation);
- participants who underwent surgery during the hospitalisation;
- active cancer treatment;
- concomitant antiplatelet use;
- history of venous thromboembolism.

However, we included all retrospective 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).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects] [*therapeutic use]; Bias; Cause of Death; COVID-19 [*complications] [mortality]; Hemorrhage [chemically induced]; Hospitalization; Retrospective Studies; *SARS-CoV-2; Thromboembolism [etiology] [mortality] [*prevention & control]

MeSH check words

Aged; Humans; Middle Aged