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

Santos BC, Flumignan RLG, Civile VT, Atallah ÁN, Nakano LCU

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[Intervention Review]

Prophylactic anticoagulants for non-hospitalised people with COVID-19

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ABSTRACT

Background

The coronavirus disease 2019 (COVID-19) pandemic has impacted healthcare systems worldwide. Multiple reports on thromboembolic complications related to COVID-19 have been published, and researchers have described that people with COVID-19 are at high risk for developing venous thromboembolism (VTE). Anticoagulants have been used as pharmacological interventions to prevent arterial and venous thrombosis, and their use in the outpatient setting could potentially reduce the prevalence of vascular thrombosis and associated mortality in people with COVID-19. However, even lower doses used for a prophylactic purpose may result in adverse events such as bleeding. It is important to consider the evidence for anticoagulant use in non-hospitalised people with COVID-19.

Objectives

To evaluate the benefits and harms of prophylactic anticoagulants versus active comparators, placebo or no intervention, or non-pharmacological interventions in non-hospitalised people with COVID-19.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 18 April 2022.

Selection criteria

We included randomised controlled trials (RCTs) comparing prophylactic anticoagulants with placebo or no treatment, another active comparator, or non-pharmacological interventions in non-hospitalised people with COVID-19. We included studies that compared anticoagulants with a different dose of the same anticoagulant. We excluded studies with a duration of under two weeks.

Data collection and analysis

We used standard Cochrane methodological procedures. Our primary outcomes were all-cause mortality, VTE (deep vein thrombosis (DVT) or pulmonary embolism (PE)), and major bleeding. Our secondary outcomes were DVT, PE, need for hospitalisation, minor bleeding, adverse events, and quality of life. We used GRADE to assess the certainty of the evidence.

Main results

We included five RCTs with up to 90 days of follow-up (short term). Data were available for meta-analysis from 1777 participants.

Anticoagulant compared to placebo or no treatment

Five studies compared anticoagulants with placebo or no treatment and provided data for three of our outcomes of interest (all-cause mortality, major bleeding, and adverse events). The evidence suggests that prophylactic anticoagulants may lead to little or no difference in all-cause mortality (risk ratio (RR) 0.36, 95% confidence interval (CI) 0.04 to 3.61; 5 studies; 1777 participants; low-certainty evidence)

and probably reduce VTE from 3% in the placebo group to 1% in the anticoagulant group (RR 0.36, 95% CI 0.16 to 0.85; 4 studies; 1259 participants; number needed to treat for an additional beneficial outcome (NNTB) = 50; moderate-certainty evidence). There may be little to no difference in major bleeding (RR 0.36, 95% CI 0.01 to 8.78; 5 studies; 1777 participants; low-certainty evidence). Anticoagulants probably result in little or no difference in DVT (RR 1.02, 95% CI 0.30 to 3.46; 3 studies; 1009 participants; moderate-certainty evidence), but probably reduce the risk of PE from 2.7% in the placebo group to 0.7% in the anticoagulant group (RR 0.25, 95% CI 0.08 to 0.79; 3 studies; 1009 participants; NNTB 50; moderate-certainty evidence). Anticoagulants probably lead to little or no difference in reducing hospitalisation (RR 1.01, 95% CI 0.59 to 1.75; 4 studies; 1459 participants; moderate-certainty evidence) and may lead to little or no difference in adverse events (minor bleeding, RR 2.46, 95% CI 0.90 to 6.72; 5 studies, 1777 participants; low-certainty evidence).

Anticoagulant compared to a different dose of the same anticoagulant

One study compared anticoagulant (higher-dose apixaban) with a different (standard) dose of the same anticoagulant and reported five relevant outcomes. No cases of all-cause mortality, VTE, or major bleeding occurred in either group during the 45-day follow-up (moderate-certainty evidence). Higher-dose apixaban compared to standard-dose apixaban may lead to little or no difference in reducing the need for hospitalisation (RR 1.89, 95% CI 0.17 to 20.58; 1 study; 278 participants; low-certainty evidence) or in the number of adverse events (minor bleeding, RR 0.47, 95% CI 0.09 to 2.54; 1 study; 278 participants; low-certainty evidence).

Anticoagulant compared to antiplatelet agent

One study compared anticoagulant (apixaban) with antiplatelet agent (aspirin) and reported five relevant outcomes. No cases of all-cause mortality or major bleeding occurred during the 45-day follow-up (moderate-certainty evidence). Apixaban may lead to little or no difference in VTE (RR 0.36, 95% CI 0.01 to 8.65; 1 study; 279 participants; low-certainty evidence), need for hospitalisation (RR 3.20, 95% CI 0.13 to 77.85; 1 study; 279 participants; low-certainty evidence), or adverse events (minor bleeding, RR 2.13, 95% CI 0.40 to 11.46; 1 study; 279 participants; low-certainty evidence).

No included studies reported on quality of life or investigated anticoagulants compared to a different anticoagulant, or anticoagulants compared to non-pharmacological interventions.

Authors' conclusions

We found low- to moderate-certainty evidence from five RCTs that prophylactic anticoagulants result in little or no difference in major bleeding, DVT, need for hospitalisation, or adverse events when compared with placebo or no treatment in non-hospitalised people with COVID-19. Low-certainty evidence indicates that prophylactic anticoagulants may result in little or no difference in all-cause mortality when compared with placebo or no treatment, but moderate-certainty evidence indicates that prophylactic anticoagulants probably reduce the incidence of VTE and PE.

Low-certainty evidence suggests that comparing different doses of the same prophylactic anticoagulant may result in little or no difference in need for hospitalisation or adverse events. Prophylactic anticoagulants may result in little or no difference in risk of VTE, hospitalisation, or adverse events when compared with antiplatelet agents (low-certainty evidence). Given that there were only short-term data from one study, these results should be interpreted with caution.

Additional trials of sufficient duration are needed to clearly determine any effect on clinical outcomes.

PLAIN LANGUAGE SUMMARY

Prophylactic blood thinners for the prevention of death and venous thromboembolism in COVID-19 outpatients

Key messages

- When used in the outpatient setting, anticoagulants (blood thinners) probably reduce venous thromboembolism (VTE) and pulmonary embolism (PE) when compared with placebo or no treatment in people with COVID-19. However, these drugs seem to have little or no effect in reducing death, major bleeding, need for hospitalisation, or adverse events.

What is VTE?

Venous thromboembolism, which includes both deep vein thrombosis (DVT) and PE, is a condition where a blood clot forms in a vein and may migrate to another location (e.g. the lung). DVT occurs when a blood clot forms inside a deep vein and blocks the blood flow. PE occurs when (part of) a blood clot detaches from the deep vein and ends up in the lung blood vessels, blocking the blood supply of the lungs.

How are COVID-19 and VTE related?

COVID-19 typically affects the lungs and airways; however, in addition to respiratory problems, people with COVID-19 can also experience problems with their blood vessels, leading to blood clots forming in the veins and lungs.

How is VTE treated and how can VTE be prevented in people who are at risk?

The initial treatment includes drugs such as anticoagulants to prevent the formation of further new blood clots. Patients may also receive compression stockings and clinical care (e.g. physical exercise, skin hydration, and physical therapy). Anticoagulants such as rivaroxaban and apixaban act by inhibiting the blood elements involved in the formation of blood clots. For this reason, they are also used to prevent blood clots from forming in people who are considered to be at risk, such as people with COVID-19. This is known as prophylactic treatment. However, the use of anticoagulants can cause side effects such as bleeding.

What did we want to find out?

We wanted to find out whether giving anticoagulants to non-hospitalised people with COVID-19 reduced the number of deaths or new blood clots compared to people who received placebo (an identical-seeming medicine but with no active properties) or no intervention; a different dose or formulation of the same anticoagulant; antiplatelet agents (medications that prevent blood clots from forming); or non-drug treatments. We also wanted to know the effects of anticoagulants on the need for hospitalisation; major bleeding or adverse events; and quality of life.

What did we do?

We searched for studies, giving preference to randomised controlled trials (studies where participants are randomly assigned to one of two or more treatment groups), that evaluated prophylactic anticoagulants given to people with COVID-19 in the outpatient setting, compared with placebo or no treatment, a different dose of the same anticoagulant, or antiplatelet agents. We pooled the results when appropriate.

What did we find?

The results were based on five studies with a total of 1777 participants from the USA, Switzerland, Germany, Belgium, Brazil, India, South Africa, Spain, and the UK. Two large groups of participants were studied: those with COVID-19 who did not require hospitalisation, and people with COVID-19 who had been discharged from hospital. Five studies compared anticoagulants versus placebo or no treatment, and one study also compared a prophylactic anticoagulant with a different dose of the same anticoagulant as well as versus antiplatelet agents. Each comparison investigated the effects of anticoagulants on death, VTE, major bleeding, need for hospitalisation, and adverse events.

We have low confidence that prophylactic anticoagulants compared with placebo or no treatment for non-hospitalised people with COVID-19 have little or no effect on reducing the risk of death or adverse events. Prophylactic anticoagulants probably decrease the risk of VTE; 50 patients would need to be treated to avoid one VTE event.

There may be little or no difference in hospitalisation rates between people who receive prophylactic anticoagulants and those who receive a different dose of the same anticoagulant. Moreover, prophylactic anticoagulants may lead to little or no difference in reducing VTE when compared with antiplatelet agents.

What are the limitations of the evidence?

We have low confidence in the evidence due to issues with study methods and sizes. In the future, high-quality studies may produce important data, especially regarding outcomes such as death, DVT, and PE.

How up-to-date is this evidence?

The evidence is current as of 18 April 2022.

Summary of findings 1. Anticoagulant compared to placebo or no treatment for non-hospitalised people with COVID-19

Anticoagulant versus placebo or no treatment for non-hospitalised people with COVID-19

Patient or population: non-hospitalised people with COVID-19
Setting: outpatient
Intervention: anticoagulant
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with anticoagulant				
All-cause mortality Follow-up: from 30 to 90 days	Study population		RR 0.36 (0.04 to 3.61)	1777 (5 RCTs)	⊕⊕⊝⊝ Low [a b]	
	6 per 1000	2 per 1000 (0 to 20)				
Venous thromboembolism Follow-up: from 30 to 90 days	Study population		RR 0.36 (0.16 to 0.85)	1259 (4 RCTs)	⊕⊕⊕⊝ Moderate [a c]	NNTB = 50
	31 per 1000	11 per 1000 (5 to 26)				
Major bleeding Follow-up: from 30 to 90 days	Study population		RR 0.36 (0.01 to 8.78)	1777 (5 RCTs)	⊕⊕⊝⊝ Low [a b]	
	1 per 1000	0 per 1000 (0 to 10)				
Deep vein thrombosis Follow-up: from 30 to 90 days	Study population		RR 1.02 (0.30 to 3.46)	1009 (3 RCTs)	⊕⊕⊕⊝ Moderate [a c]	
	10 per 1000	10 per 1000 (3 to 34)				
Pulmonary embolism Follow-up: from 30 to 90 days	Study population		RR 0.25 (0.08 to 0.79)	1009 (3 RCTs)	⊕⊕⊕⊝ Moderate [a c]	NNTB = 50
	27 per 1000	7 per 1000 (2 to 22)				
Need for hospitalisation Follow-up: from 30 to 90 days	Study population		RR 1.01 (0.59 to 1.75)	1459 (4 RCTs)	⊕⊕⊕⊝ Moderate [a c]	
	34 per 1000	34 per 1000				

	(20 to 59)				
Adverse events (minor bleeding) Follow-up: from 30 to 90 days	Study population		RR 2.46 (0.90 to 6.72)	1777 (5 RCTs)	⊕⊕⊖⊖ Low [a b]
	6 per 1000	14 per 1000 (5 to 37)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **RCT:** randomised controlled trial; **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]Although we judged some included studies as having a high risk of selection, performance, and reporting bias, the estimates did not significantly differ after sensitivity analysis, therefore we did not downgrade due to risk of bias.
[b]Downgraded two levels due to imprecision (fewer than 300 events included in the analysis and very wide CI).
[c]Downgraded one level due to imprecision (fewer than 300 events included in the analysis).

Summary of findings 2. Anticoagulant compared to different dose of the same anticoagulant for non-hospitalised people with COVID-19

Anticoagulant versus different dose of the same anticoagulant for non-hospitalised people with COVID-19

Patient or population: non-hospitalised people with COVID-19
Setting: outpatient
Intervention: higher-dose anticoagulant
Comparison: standard dose of the same anticoagulant

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard dose of the same anticoagulant	Risk with higher-dose anticoagulant				
All-cause mortality Follow-up: 45 days	Study population		Not estimable	278 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	There were no cases of mortality.
	-					

Venous thromboembolism Follow-up: 45 days	Study population -		Not estimable	278 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	There were no cases of venous thromboembolism.
Major bleeding Follow-up: 45 days	Study population -		Not estimable	278 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	There were no cases of major bleeding.
Deep vein thrombosis	This outcome was not measured.					
Pulmonary embolism	This outcome was not measured.					
Need for hospitalisation Follow-up: 45 days	Study population 7 per 1000	14 per 1000 1 to 152	RR 1.89 (0.17 to 20.58)	278 (1 RCT)	⊕⊕⊖⊖ Low [b]	
Adverse events (minor bleeding) Follow-up: 45 days	Study population 30 per 1000	14 per 1000 3 to 75	RR 0.47 (0.09 to 2.54)	278 (1 RCT)	⊕⊕⊖⊖ Low [b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **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 imprecision (fewer than 300 events included in the analysis).
[b]Downgraded two levels due to imprecision (fewer than 300 events included in the analysis and very wide CI).

Summary of findings 3. Anticoagulant compared to antiplatelet agent for non-hospitalised people with COVID-19

Anticoagulant versus antiplatelet agent for non-hospitalised people with COVID-19

Patient or population: non-hospitalised people with COVID-19
Setting: outpatient setting
Intervention: anticoagulant
Comparison: antiplatelet agent

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with antiplatelet agents (short term)	Risk with anticoagulant				
All-cause mortality Follow-up: 45 days	Study population -		Not estimable	279 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	There were no cases of mortality.
Venous thromboembolism Follow-up: 45 days	Study population 7 per 1000	2 per 1000 (0 to 60)	RR 0.36 (0.01 to 8.65)	279 (1 RCT)	⊕⊕⊖⊖ Low [b]	
Major bleeding Follow-up: 45 days	Study population -		Not estimable	279 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	There were no cases of major bleeding.
Deep vein thrombosis	This outcome was not measured.					
Pulmonary embolism	This outcome was not measured.					
Need for hospitalisation Follow-up: 45 days	Study population 0 out of 144	1 out of 135	RR 3.20 (0.13 to 77.85)	279 (1 RCT)	⊕⊕⊖⊖ Low [b]	
Adverse events **(minor bleeding)** Follow-up: 45 days	Study population 14 per 1000	30 per 1000 (6 to 159)	RR 2.13 (0.40 to 11.46)	279 (1 RCT)	⊕⊕⊖⊖ Low [b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **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.

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[a]Downgraded one level due to imprecision (fewer than 300 events included in the analysis).
[b]Downgraded two levels due to imprecision (fewer than 300 events included in the analysis and very wide CI).

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) describes both the formation of a thrombus (blood clot) in the deep veins, most commonly in the legs (deep vein thrombosis (DVT)), or the subsequent embolisation of all or part of the thrombus to the pulmonary circulation (pulmonary embolism (PE)) (Cogo 1993; Kakkos 2021). DVT of the lower limbs may be associated with localised pain, swelling and erythema, as well as the development of pulmonary emboli, and the later occurrence of post-thrombotic syndrome (persistent swelling, erythema, and ulceration), regardless of the treatment (Broderick 2021; Flumignan 2015; Flumignan 2022a; Flumignan 2023; Hirsh 1986). PE presents acutely, with shortness of breath, pain on inspiration, tachycardia, and right heart overload. If left untreated, it can lead to circulatory collapse and death (Stein 1991). It can also cause chronic post-thrombotic pulmonary hypertension in the longer term. In the era of more liberal central venous catheterisation, DVT may increasingly involve the upper extremities (Verso 2003). Rarely, other parts of the venous circulation such as the cerebral, portal, and mesenteric veins can be affected (Acosta 2008; Saposnik 2011; Valla 2002).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for coronavirus disease 2019 (COVID-19), which since 2020 has grown rapidly into a pandemic affecting people worldwide, leading to intense demand on healthcare systems (Phelan 2020). Since the beginning of the COVID-19 pandemic, multiple reports of thromboembolic complications related to COVID-19 have been published worldwide (Lodigiani 2020; Tang 2020), and people with COVID-19 have been described as being at high risk for the development of VTE (COVIDSurg 2022a; Flumignan 2021; Flumignan 2022b; Klok 2020a; Middeldorp 2020). Recent data show that the most frequently reported thrombotic events directly related to morbidity and mortality are DVT and PE (COVIDSurg 2022a; Hanff 2020). The incidence of thromboembolic events has been reported to range from 20% to 30% in people hospitalised due to COVID-19 (Flumignan 2021; Flumignan 2022b; Klok 2020b; Middeldorp 2020). Recent studies have described hypercoagulability and endothelial dysfunction as hallmarks of COVID-19 (Kelliher 2022), which could be explained by the association of SARS-CoV-2 infection with changes in the host's coagulation profile (Zehra 2022). This phenomenon is still unclear, but could be related to high levels of inflammatory mediators that cause damage to both arterial and venous walls, leading to platelet aggregation and, consequently, causing coagulation and thrombosis (Matos 2011; Varga 2020). Another theory is that the entry of SARS-CoV-2 through the angiotensin-converting enzyme 2 (ACE-2) receptor on cells can trigger a secondary increase in tissue factor, ultimately leading to endothelial dysregulation and thrombosis (Bautista-Vargas 2020).

VTE, which can present as DVT or PE (or both), can occur spontaneously. However, there are many risk factors for VTE, including periods of inactivity or being confined to bed, dehydration, hospitalisation, trauma, clotting disorders and previous superficial or deep vein thrombosis, pregnancy, oral combined hormonal contraceptives, malignancy, obesity, smoking, and age (Anderson 2003; Barbar 2010; Kakkos 2021; Kearon 2016; NICE 2019; Spyropoulos 2011). Regarding people with COVID-19, the main risk factors described are immobilisation, hypoxia, endothelial cell activation or damage, and acute inflammation (Ortega-Paz 2021; Tsaplin 2021).

Data regarding non-hospitalised people with COVID-19 are limited; some reports show that the incidence of thromboembolic events in this group of people is of possible concern and presents a higher thrombotic risk than has been acknowledged (Benzakoun 2020; Giannis 2021).

Description of the intervention

Prophylactic anticoagulation strategies in those deemed to be at risk (such as those undergoing surgical procedures or prolonged hospital inpatient stays) are recommended by national guidelines, such as those published by the National Institute for Health and Care Excellence (NICE) in the UK and the American College of Chest Physicians in the USA (Guyatt 2012; Kahn 2014; NICE 2019; NICE 2020). These include the use of both mechanical methods such as compression stockings and intermittent pneumatic compression devices (IPC), and pharmacological methods, including parenteral anticoagulation (e.g. low-molecular-weight heparin (LMWH)) (Alikhan 2014; Kakkos 2022; Sachdeva 2014).

The most used pharmacological interventions for preventing arterial and venous thrombosis are anticoagulants such as heparin, pentasaccharides, vitamin K antagonists, and direct oral anticoagulants (Amaral 2022; Biagioni 2020; Flumignan 2021; Flumignan 2022b; Flumignan 2023; Righini 2006). Because there is a high prevalence of vascular thrombosis and associated mortality in people with COVID-19, physicians prescribe prophylactic anticoagulants untimely – for example, during the prehospital or ambulatory phase of COVID-19 (Hippensteel 2020; Spyropoulos 2022). When used prophylactically, anticoagulant doses are usually one-third or one-half of those given for therapeutic purposes. Nevertheless, adverse events such as bleeding may have a significant impact on patient care (Flumignan 2021; Flumignan 2022b; Paranjpe 2020).

How the intervention might work

The COVID-19 pandemic remains a global health issue. However, non-transmissible circulatory diseases remain the leading cause of disease burden worldwide (Logue 2021). The risk of thromboembolic events in people with COVID-19, even if they are receiving prophylactic anticoagulation, can reach 69% in severely ill hospitalised people when screening strategies are implemented, exceeding that observed in clinically ill people (0.42%) (Llitjos 2020; Spyropoulos 2020). Lodigiani 2020 found a cumulative rate of VTE of 21% in 388 severely ill people with COVID-19, and half of the VTE events were diagnosed upon hospital admission, suggesting that these events developed in the early symptomatic phase, before clinical deterioration. Optimising measures to prevent vascular thrombosis is therefore essential in the management of people with COVID-19 (Hippensteel 2020). The high prevalence of thrombosis in severely ill people with COVID-19 led the American Society of Hematology, the International Society on Thrombosis and Haemostasis, and the American College of Chest Physicians to recommend that all people hospitalised with COVID-19 should receive prophylactic anticoagulation (Cuker 2021; Moores 2020; Spyropoulos 2020). However, there is no consensus and there are no recommendations regarding outpatient prevention of thrombosis. Research on the prevention of vascular thrombosis has mainly concentrated on

pharmacological interventions (Spyropoulos 2018). It is possible that starting anticoagulants earlier may have a role in this setting during the pre-hospitalised phase in people with COVID-19 (Barco 2020; Capell 2021).

Current recommendations regarding thromboprophylaxis while treating people with COVID-19 are based on expert consensus, and the majority of scientific societies suggest that if there are no contraindications and after a careful evaluation of bleeding risk, adults hospitalised with COVID-19 should receive thromboprophylaxis (Bikdeli 2020; Moores 2020; Spyropoulos 2020). However, there is no consensus concerning thromboprophylaxis in the outpatient setting. Some studies suggest that physicians should stratify the risk for thrombotic and haemorrhagic events individually, but the topic is still under discussion (Emert 2020; Sobreira 2020).

Why it is important to do this review

Research has shown an increase in cases of VTE during the COVID-19 quarantine period (Tomidokoro 2021). Other studies have shown late arterial and venous thrombosis in people with COVID-19. Prophylactic measures such as anticoagulation can reduce these effects (Benson 2021). However, there is no consensus about the impact of these interventions in managing outpatients with COVID-19, and the effects of prophylactic anticoagulants in people with COVID-19 in an ambulatory setting are still under discussion. Identifying strategies to prevent coagulopathy will be crucial to reduce COVID-19 hospitalisation rates and related outcomes such as VTE and death. There is an urgent need for evidence to inform healthcare decision-making during the COVID-19 pandemic. Randomised controlled trials (RCTs) analysing the use of anticoagulants in outpatients with COVID-19 are ongoing (Barco 2020; Capell 2021; NCT04542408). If performed appropriately, RCTs provide the best evidence for experimental therapies in highly controlled therapeutic settings. Non-randomised studies (NRS) of interventions can be developed faster and may represent the only available evidence to guide decision-making at this point. To ensure that we captured all relevant evidence, we planned to include RCTs and NRS, as we do not expect to find adequate RCT evidence for some time (Reeves 2021). In this Cochrane Review, we aimed to identify and synthesise the available evidence on the effectiveness and safety of prophylactic anticoagulants in non-hospitalised people with COVID-19, and so aid decision-making for clinicians and their patients.

OBJECTIVES

To evaluate the benefits and harms of prophylactic anticoagulants versus active comparators, placebo or no intervention, or non-pharmacological interventions in non-hospitalised people with COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

To ensure that we captured all relevant study types, we planned to consider a broad range of empirical studies of any size that provided a quantitative measure of impact (Reeves 2021). To assess the effects of prophylactic anticoagulants on non-hospitalised people with COVID-19, we included RCTs (parallel, cluster, individual, or cross-over design). In the case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs to address the objective of this review, we planned to include quasi-RCTs (e.g. assignment to treatment by alternation, medical register, or by date of birth) and prospective controlled cohort studies of interventions (non-randomised studies (NRS)). As we identified sufficient RCTs (at least 400 participants), we did not include quasi-RCTs or NRS. Details on planned methods for accessing non-RCTs can be found in our protocol (Santos 2022). We only considered studies with a minimum duration of two weeks.

Types of participants

We included non-hospitalised participants of both sexes and any age with a COVID-19 diagnosis. COVID-19 infection was confirmed by reverse transcription polymerase chain reaction (RT-PCR) (WHO 2020). We excluded people receiving treatment for current VTE because they were receiving an anticoagulant regimen. We included participants with a previous diagnosis of VTE who had finished VTE treatment, regardless of the time of the VTE diagnosis compared with the COVID-19 diagnosis. We considered participants with a previous history of hospitalisation, amputation, or any other outcome of interest for inclusion in the review. We excluded studies involving hospitalised participants with COVID-19, as these participants are covered in another Cochrane Review (Flumignan 2022b).

When we found studies with mixed populations (e.g. hospitalised and non-hospitalised participants), and only a subset of the participants met our inclusion criteria, we attempted to obtain data for the subgroup of interest from the study authors to permit inclusion in the review. If we were not able to obtain separate data for the subgroup of interest from a mixed population, but at least 50% of the study population were of interest, we included all participants in our analysis. We planned to explore the effect of this decision in a sensitivity analysis if needed. We excluded studies with mixed populations in which less than 50% of the population was of interest and data for the subgroup of interest were not available.

Types of interventions

We included studies that compared prophylactic anticoagulants with either placebo, no treatment, a pharmacological (active) comparator, or a non-pharmacological comparator. We included studies with any combination of interventions providing the 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 planned to undertake the following comparisons in the review.

- Anticoagulant versus placebo or no treatment (we planned to pool all anticoagulants together, i.e. heparin, 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.

We considered the following pharmacological interventions:

- both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), heparinoids and pentasaccharides (synthetic and selective anticoagulant drugs);
- vitamin K antagonists; and
- direct anticoagulants, including factor Xa inhibitors and direct thrombin inhibitors, i.e. direct oral anticoagulants and non-oral direct anticoagulants (e.g. bivalirudin).

We included 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 LMWH, such as enoxaparin 30 mg twice a day or 40 mg daily, and UFH 5000 international units three times a day. However, all doses of anticoagulants were eligible for our review, when they were used for primary or secondary prophylaxis of thromboembolism (e.g. previous VTE event, high risk of a new event, presence of active cancer and thrombophilia) (Fernandes 2019; Weitz 2017).

Types of outcome measures

We evaluated core outcomes as predefined by the Core Outcome Measures in Effectiveness Trials Initiative for people with COVID-19 (COMET 2021). We presented the outcomes at two different time points following the start of the intervention, if data were available:

- short-term outcomes (at 90 days or less after the start of the intervention); and
- long-term outcomes (more than 90 days after the start of the intervention).

The short-term time points include the time frame from the start of the intervention up to 90 days, and the long-term time points include the time frame after this period. We included studies in the review irrespective of whether the measured outcome data had been reported in a useable way.

Primary outcomes

- All-cause mortality.
- VTE: DVT or PE, symptomatic or asymptomatic, first episode or recurrent, and fatal or non-fatal. The diagnosis had to be confirmed by clinical examination and at least one additional objective diagnostic test. We accepted ultrasonography or angiography (e.g. by computed tomography (CT), magnetic resonance imaging (MRI), or digital subtraction) for the DVT diagnosis from any site (e.g. lower limbs, upper limbs, abdomen). We accepted angiography by any described method and ventilation-perfusion scan for confirmation of PE. We also considered postmortem examination as an objective confirmation of DVT and PE. If the participant had both DVT and PE events, we counted this as one unique event of VTE in our analysis.
- 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 the International Society on Thrombosis and Haemostasis (ISTH) (Schulman 2010).

Secondary outcomes

- DVT: symptomatic or asymptomatic, and first episode or recurrent. The diagnosis had to be confirmed by ultrasonography or angiography (e.g. by CT, MRI, or digital subtraction) from any site (e.g. lower limbs, upper limbs, abdomen).
- PE: symptomatic or asymptomatic, first episode or recurrent, and fatal or non-fatal. The diagnosis had to be confirmed by angiography (e.g. by CT, MRI, or digital subtraction) and ventilation-perfusion scan, or both. We also considered postmortem examination as an objective confirmation of DVT and PE.
- Need for hospitalisation (yes or no).
- Adverse events (AE): minor bleeding/clinically relevant non-major bleeding defined as an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following: a hospital admission for bleeding, or a physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy (including interruption or discontinuation of study drug). In addition, we considered bleeding events that led to participant's discomfort and impairment of activities of daily life as clinically relevant non-major bleeding.
- AE: all possible AEs separately, as individual outcomes, such as thrombocytopenia, gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, abdominal pain), allergic reactions, renal failure, acute limb ischaemia, need for surgical peripheral revascularisation, and amputations. We only considered the AEs described in the included studies.
- Quality of life based on the participant's subjective perception of improvement (yes or no) as reported by the study authors or using any validated scoring system such as the 36-Item Short Form Health Survey (SF-36) (Ware 1992).

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for RCTs and controlled clinical trials without language, publication year, or publication status restrictions:

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 4) via the Cochrane Register of Studies Online (CRSO);
- Cochrane COVID-19 Study Register via the CRSO;
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE);
- Embase Ovid;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature); and
- LILACS (Latin American and Caribbean Health Science Information database) (via Virtual Health Library).

We developed search strategies for other databases based on the search strategy designed for MEDLINE. Where appropriate, we combined these strategies with adaptations of the Highly Sensitive Search Strategy designed by the Cochrane to identify RCTs and

controlled clinical trials (as described in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Lefebvre 2022). Search strategies for the major databases are provided in Appendix 1.

We searched the following trial registries:

- World Health Organization International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform); and
- ClinicalTrials.gov (clinicaltrials.gov).

The most recent searches were carried out on 18 April 2022.

Searching other resources

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

Data collection and analysis

Selection of studies

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

Two review authors (BCS and LCUN) independently screened the titles and abstracts of all articles identified as a result of the search; we coded these as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (non-relevant) using the Covidence tool (Covidence). In the case of disagreement, we asked a third review author to arbitrate (RLGF). We retrieved the full-text study reports/publications, and two review authors (BCS and VTC) independently screened the full texts and identified studies for inclusion, and identified and recorded the reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (RLGF) if required. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We illustrated the study selection process in a PRISMA flow diagram (Liberati 2009). We listed all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table and provided the reasons for their exclusion. 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 useable data.

Data extraction and management

We managed and synthesised the available data using Review Manager Web (RevMan Web 2022). 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 used the article published for numerical analysis, and we reported the differences and considered any impact on the certainty of evidence (Schünemann 2021a). We used a data collection form that had been piloted on at least one study in the review for study characteristics and outcome data. Two review authors (BCS and VTC) extracted data from the included studies. Any disagreements were resolved by discussion. We extracted the following study characteristics.

- Methods: study design, duration of the study, number of study centres and location, study setting, and date of the study.
- Participants: comorbidities, pregnancy, number randomised, exclusions postrandomisation, number lost to follow-up/withdrawn, number analysed, number of interest, mean age, age range, gender, severity of the condition, inclusion criteria, and exclusion criteria.
- Interventions: intervention and comparison characteristics (e.g. manufacturer, dosage, additional procedures, method of administration), concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected (e.g. how outcomes were measured) and time points reported.
- Funding for the trial, conflicts of interest of study authors, and registration number.

One review author (BCS) transferred data into Review Manager Web (RevMan Web 2022). We double-checked that the data had been entered correctly by comparing the data presented in the systematic review with the data extraction form. Two review authors (RLGF and LCUN) spot-checked the study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (BCS and VTC) assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* for RCTs (RoB 1) (Higgins 2017). Any disagreements were resolved by discussion within the review team. We assessed 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; and
- other bias.

We graded each potential source of bias as low, high, or unclear and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. Where there was information on risk of bias relating to unpublished data or correspondence with a study author, we noted this in the risk of bias table.

When evaluating treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

We based the overall bias judgement of included RCTs on the following three domains of RoB 1, namely:

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

We labelled an RCT at low risk in all of these domains as a low-risk study. We labelled an RCT at high risk in one of these domains as a high-risk study. We indicated that the risk of bias in the study was unclear if there was no clear information on risk of bias for one or more key domains, but the RCT was not at high risk for any key domain.

Details on how we planned to assess risk of bias in cluster-randomised trials, quasi-RCTs, and NRS can be found in the protocol (Santos 2022).

Measures of treatment effect

Dichotomous data

We calculated the risk ratio (RR) and 95% confidence intervals (CIs) for dichotomous variables.

Continuous data

We calculated the mean differences (MD) and 95% CIs between treatment groups when studies reported the same outcomes for continuous data. When studies reported similar outcomes on different scales, we calculated the standardised mean difference (SMD) and 95% CIs. If standard deviations (SDs) or standard errors (SEs) were not available, we attempted to extract P values from the available data. We estimated the MD using the method reported by Wan 2014 to convert the median and interquartile range into MD and CI. When this was not possible, we narratively described skewed data reported as medians and interquartile ranges. To interpret SMD, we used the following thresholds, as recommended in Section 15.5.3.1 of the *Cochrane Handbook for Systematic Reviews of Intervention* (Schünemann 2021b):

- SMD < 0.2 = trivial or no effect;
- SMD ≥ 0.2 and < 0.5 = small effect;
- SMD ≥ 0.5 and < 0.8 = medium effect; and
- SMD ≥ 0.8 = large effect.

We also calculated the number needed to treat for an additional beneficial outcome (NNTB) for the primary outcomes (all-cause mortality and VTE), using NNTB = 1/risk difference (RD). We also calculated the number needed to treat for an additional harmful outcome (NNTH) for the primary outcome major bleeding, using NNTH = 1/RD. We calculated the RD using Review Manager Web (RevMan Web 2022). We expressed the NNTB and NNTH to indicate the direction of effect, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021a).

Unit of analysis issues

We considered each participant as the unit of analysis for the outcomes all-cause mortality, VTE, major bleeding, DVT, PE, need for hospitalisation, AEs (e.g. minor bleeding, thrombocytopenia, gastrointestinal AE, allergic reactions, renal failure), and quality of life. We considered each limb as the unit of analysis for AEs such as amputation rate. If trials included multi-arm interventions, we considered only the arms relevant to the scope of our review.

We did not include any cross-over or cluster-randomised trials in the review. Details of how we planned to address any unit of analysis issues can be found in the protocol (Santos 2022).

Dealing with missing data

We included all available data from the included studies. We described missing data for each study in the 'Characteristics of included studies' table and risk of bias table, and discussed the extent to which the missing data could alter the results of the review. We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). Where possible, we used the Review Manager Web calculator to calculate missing SDs by using other data from the trial, such as CIs (RevMan Web 2022). We estimated the MD using the method reported by Wan 2014 to convert the median and interquartile range into MD and CI. When data were only reported in graphs, we extracted the data of interest (such as mean, SD or SE) using Graphreader software (Graphreader 2022). We identified translators for foreign languages with which we were unfamiliar (e.g. Chinese and Japanese). When translation was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results using a sensitivity analysis. For all outcomes, we followed the intention-to-treat (ITT) principle to the greatest degree possible, that is we analysed participants in the group to which they had been randomised regardless of what intervention they actually received. We used available-case data for the denominator if ITT data were not available. In trials with a large proportion of missing data (more than 20%), we assessed the impact of this with sensitivity analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Assessment of heterogeneity

We visually inspected forest plots to consider the direction and magnitude of effects and the degree of overlap between CIs. We used the I^2 statistic to measure heterogeneity among the trials in each analysis; we acknowledge that there is substantial uncertainty in the value of I^2 when there is only a small number of studies. If we identified substantial heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis. As strict thresholds for the interpretation of I^2 are not recommended, we used the rough guide to interpretation provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

When I^2 was in an area of overlap between two categories (e.g. between 50% and 60%), we considered differences in participants and interventions among the trials contributing data to the analysis (Deeks 2021).

Assessment of reporting biases

We performed searches in multiple sources to reduce the chance of reporting biases. We planned to assess the presence of publication bias and other reporting bias using funnel plots if we identified a sufficient number of studies (i.e. more than 10) for inclusion in the meta-analysis (Sterne 2017). If asymmetry was present, we would explore possible causes, including publication bias,

poor methodological quality, and true heterogeneity (Sterne 2017). We also planned to perform additional statistical analysis for continuous outcomes with intervention effects measured as MD to assess reporting biases, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*; however, as the meta-analysis included fewer than 10 studies, it was not possible to perform this analysis (Sterne 2017).

Data synthesis

We synthesised the data by using Review Manager Web (RevMan Web 2022). We undertook meta-analysis only when this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. If we were confident that the trials had estimated the same underlying treatment effect (i.e. that the population, interventions, comparators, and outcome characteristics of the included studies were homogenous), we used a fixed-effect meta-analysis model. If clinical heterogeneity was sufficient to expect that underlying treatment effects differed between trials, or if we identified at least substantial heterogeneity, we used a random-effects meta-analysis model. We planned that if there was substantial clinical, methodological, or statistical heterogeneity across trials that precluded the pooling of data, we would use a narrative approach for data synthesis (Deeks 2021).

We addressed all outcomes listed in the Types of outcome measures section, in the order in which they were shown, in the Effects of interventions section of the Results. In addition, we presented one summary of findings table for each comparison, in which we summarised the main outcomes. We included the results of individual studies and any statistical summary of these in the Data and analyses tables in the review.

In preparation for synthesis (either meta-analyses or synthesis without meta-analysis), we assessed how much data were available for each of our comparisons using the following method:

- table to compare PICO elements/study design features;
- conversion of numerical data for meta-analysis;
- forest plots;
- qualitative synthesis; and
- synthesis without meta-analysis.

We performed a pooled analysis for RCTs and undertook sensitivity analysis if sufficient data were available. When possible, we summarised effect estimates graphically using forest plots (McKenzie 2021).

Subgroup analysis and investigation of heterogeneity

We did not have sufficient data to undertake the planned analyses. We plan to perform the following subgroup analyses for all outcomes if sufficient data become available:

- type of anticoagulants (e.g. heparin, heparinoids, vitamin K antagonists, direct anticoagulants);
- antiplatelet therapy (yes or no);
- duration of prophylaxis (e.g. up to 30 days after the start of intervention or more);
- time of starting prophylaxis (e.g. days since positive COVID-19 diagnosis);
- age (e.g. children less than 18 years, adults (18 to 74 years), and seniors (75 years and older));
- comorbidities, i.e. we assessed participants with previous risk factors for outcomes of interest for this review separately (e.g. previous VTE, cardiovascular comorbidities, and thrombophilia);
- illness severity (e.g. symptomatic versus asymptomatic or minimally symptomatic); and
- different doses of drugs.

We performed additional subgroup analysis to investigate if there was a difference in effect between participants who had never been hospitalised and those who started treatment after discharge from hospital (COVID-19-related hospitalisation).

We used the formal test for subgroup differences in Review Manager Web (RevMan Web 2022) and based our interpretation on the results.

Sensitivity analysis

As we identified sufficient RCTs, we only undertook preplanned sensitivity analyses relevant to these. See Santos 2022 for details on planned sensitivity analyses relevant to NRS. We planned to carry out the following sensitivity analyses to test whether critical methodological factors or decisions affected the main result.

- Only including studies with a low overall risk of bias by RoB 1 (see Assessment of risk of bias in included studies).
- We planned to examine both the fixed-effect model and random-effects model meta-analyses, and explore the differences between the two estimates. However, we only used random-effects model meta-analyses because of clinical heterogeneity.
- We planned to explore the decision to include all participants when at least 50% were of interest in a study with a mixed population. However, this was not necessary because there were no mixed populations.
- We planned to explore the impact of including studies with missing data (proportion of more than 20%) in the overall assessment of results. If we identified studies with missing data that were unobtainable, we would repeat the analyses excluding these studies in order to determine their impact on the primary analyses. However, this sensitivity analysis was unnecessary because no studies had more than 20% of data missing.

We planned to present these results and compare them with the overall findings; however, this was not possible given the available data. We planned to justify in the final report any post hoc sensitivity analyses that arose during the review process. We did not undertake any unplanned sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We prepared summary of findings tables using GRADEpro GDT software (GRADEpro GDT), and presented the main findings of the review for the short time point (90 days or less) (Atkins 2004). The population consisted of non-hospitalised people with COVID-19, and we compared the effects of prophylactic anticoagulants versus active comparator, placebo, or no intervention on the most clinically relevant outcomes for these participants. We created one table for each separate comparison, in order of importance for decision makers: Anticoagulant compared

to placebo or no treatment for non-hospitalised people with COVID-19; Anticoagulant compared to a different dose of the same anticoagulant for non-hospitalised people with COVID-19; and Anticoagulant compared to antiplatelet agents for non-hospitalised people with COVID-19. We included the following outcomes in each table.

- All-cause mortality
- VTE
- Major bleeding
- DVT
- Pulmonary embolism
- Need for hospitalisation
- Adverse events: minor bleeding

We evaluated the certainty of the evidence using the GRADE approach (Atkins 2004; Schünemann 2021a). We assigned one of four levels of certainty: high, moderate, low, or very low, based on the overall risk of bias, directness of the evidence, inconsistency of results, precision of the estimates, and risk of publication bias, as described in the Assessment of risk of bias in included studies section (Atkins 2004; Schünemann 2021a).

Reaching conclusions

We based our conclusions only on findings from the quantitative synthesis of studies included in this review. We avoided making any recommendations for practice, suggested priorities for future research, and outlined what the remaining uncertainties are in the area.

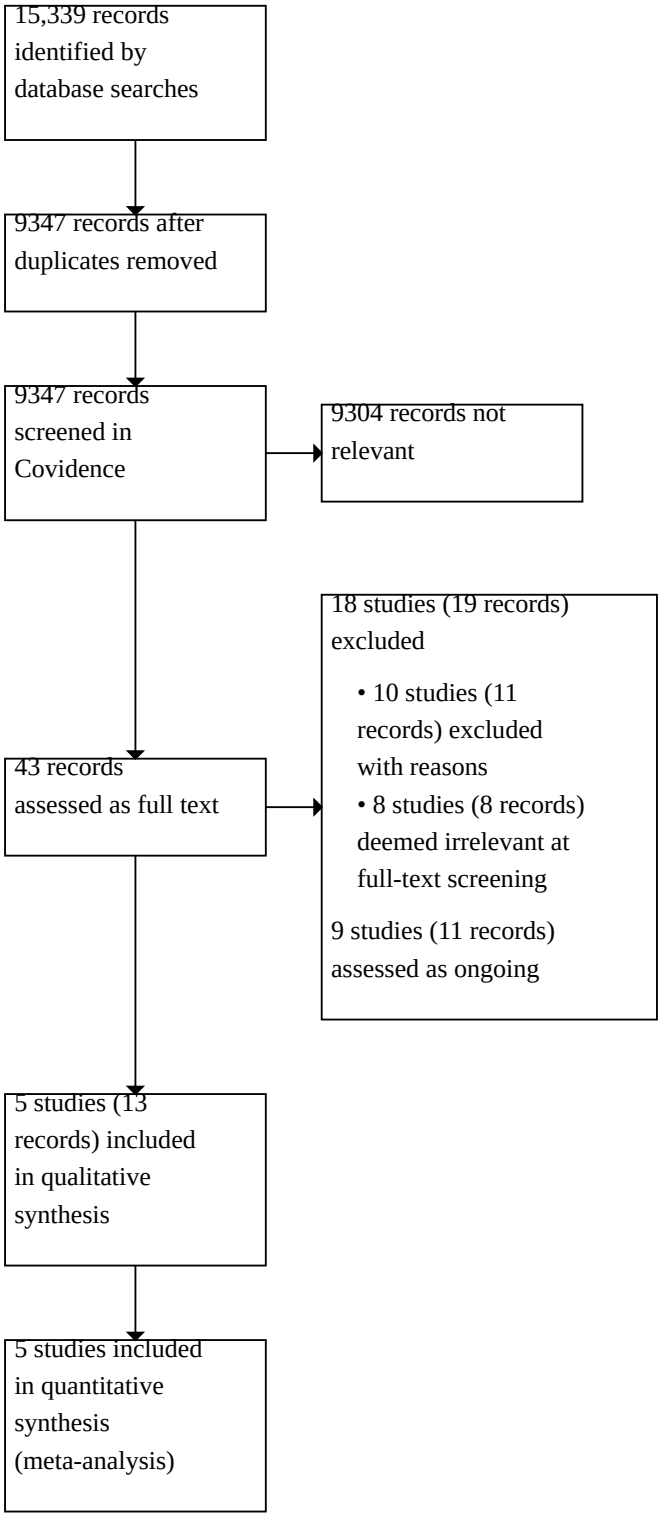
RESULTS

Description of studies

Results of the search

Our searches of the databases identified 15,339 records. After de-duplication, 9347 records were screened in Covidence (Covidence). We assessed 9304 of these records as not relevant for this review for different reasons (e.g. inadequate population of interest, inadequate study design, inadequate condition, etc.). We assessed the remaining 43 records (30 studies) by full text for eligibility. We identified five RCTs (13 records) that met our inclusion criteria (Characteristics of included studies). As a result, we did not include NRS as planned in our protocol. We excluded 10 studies (11 records); the reasons for their exclusion are summarised in Characteristics of excluded studies. We further assessed eight studies (eight reports) as irrelevant at full-text review. We assessed nine studies (11 records) as ongoing (Characteristics of ongoing studies). See Figure 1.

Figure 1. PRISMA flow diagram.



We contacted authors of all the included studies, as well as pharmaceutical companies and authors of the ongoing studies, in an attempt to locate any ongoing studies or data for inclusion in the review. When we received a response, it was negative for new data.

Included studies

See Characteristics of included studies.

Design and setting

We found five studies (20 records) with 1777 participants eligible for inclusion in our analysis (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). All five included studies were parallel RCTs.

- Ananworanich 2021 evaluated a group with prophylactic rivaroxaban and a group that received placebo, but the study authors did not assess VTE, DVT, or PE as outcomes.
- Barco 2022 evaluated a group receiving prophylactic enoxaparin and a group that received standard care (no treatment).
- Connors 2021 evaluated people with COVID-19 diagnosed by polymerase chain reaction (PCR) or antigen test in the outpatient setting who received either apixaban at different doses, aspirin, or placebo; however, the authors did not provide separate data for the groups with DVT and PE.
- The ETHIC trial evaluated a group of COVID-19 patients in the outpatient setting who received prophylactic enoxaparin and a group who received standard care, but the study authors did not provide information on DVT and PE participants separately (Cools 2022).
- Ramacciotti 2022 evaluated participants receiving prophylactic rivaroxaban compared with participants receiving no treatment. The study did not report on the need for hospitalisation.

The five included studies provided data for three different comparisons:

- anticoagulant versus placebo or no treatment (1777 participants; Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022);
- anticoagulant versus a different dose of the same anticoagulant (278 participants; Connors 2021); and
- anticoagulant versus antiplatelet agents (279 participants; Connors 2021).

Ananworanich 2021 reported in their study protocol that the recruitment of participants began in September 2020 and concluded in March 2021, and was performed in 47 USA states. Barco 2022 also provided information about the study duration (between June 2020 and April 2022), with participants recruited from eight centres in Switzerland and Germany. Connors 2021 conducted their study between September 2020 and August 2021 and enrolled participants from 52 centres in the USA. In the ETHIC trial (Cools 2022), the study lasted from October 2020 to November 2021, with recruitment performed in 15 centres in six countries (Belgium, Brazil, India, South Africa, Spain, and the UK). Ramacciotti 2022 provided information about study duration (October 2020 to June 2021) and indicated that participants were enrolled from 14 medical centres in Brazil.

Participants

We included a total of 1777 participants in our analysis. All participants analysed in this review had been diagnosed with COVID-19 confirmed by an objective investigation such as PCR or an antigen test. Currently hospitalised patients or those with a history of current active pathological bleeding were excluded from the studies. All studies included men and women, age 18 years or older, with the majority older than 50 years. Two studies had a majority of female participants (60% in Ananworanich 2021 and 59.1% in Connors 2021). The three remaining studies had more male participants (54% in Barco 2022, 60% in Ramacciotti 2022, and 55% in Cools 2022).

Ananworanich 2021 reported the enrolment of participants with mild COVID-19 at screening and high risk for severe COVID-19. Barco 2022 reported that outpatients with acute COVID-19 were eligible if they presented with respiratory symptoms or body temperature higher than 37.5 °C. Connors 2021 considered newly diagnosed symptomatic participants with SARS-CoV-2 infection with positive PCR or antigen test results. Cools 2022 described the enrolment of participants who had not received a COVID-19 vaccine and had symptomatically confirmed COVID-19 (i.e. with a positive SARS-CoV-2 reverse transcription-quantitative polymerase chain reaction (RT-qPCR)) in the outpatient setting plus at least one risk factor for severe disease. In the initial protocol, they planned to enrol patients aged at least 55 years and with at least two predefined risk factors: older age (≥ 70 years), a body mass index greater than 25 kg/m^2, chronic lung disease, diabetes, cardiovascular disease, or corticosteroid use. Ramacciotti 2022 included postdischarge patients who had been hospitalised with COVID-19 for at least three days.

All studies reported that patients with severe renal impairment, thrombocytopenia, or any clinical condition that prohibited anticoagulation were excluded from participation.

Only one of the five included studies replied to our request for more information, but they were unable to provide any additional data. No trialist provided additional data beyond the data already published.

Interventions and co-treatments

All included studies evaluated prophylactic anticoagulants in the intervention group, with some differences between protocols. Ananworanich 2021 and Connors 2021 compared prophylactic anticoagulants versus placebo. Barco 2022, Cools 2022, and Ramacciotti 2022 compared prophylactic anticoagulants versus no treatment. Connors 2021 made two additional comparisons: prophylactic anticoagulants versus the same anticoagulant at a different dose, and prophylactic anticoagulants versus antiplatelet agents.

Ananworanich 2021 described prophylaxis with anticoagulants for participants with COVID-19 in the outpatient setting. The 497 participants were randomised into two groups:

- rivaroxaban (one 10 mg tablet) once a day for 21 consecutive days; or
- placebo equivalent (multivitamin, one tablet) orally daily for 21 consecutive days.

Barco 2022 described prophylaxis with anticoagulant agents for participants with a positive test for SARS-CoV-2 eligible for ambulatory treatment, with the presence of respiratory symptoms or a body temperature greater than 35.7 °C. They randomised 472 participants into two groups:

- enoxaparin 40 mg/0.4 mL daily subcutaneously for 14 days; or
- standard care (no thromboprophylaxis).

Connors 2021 evaluated 657 participants with newly diagnosed COVID-19 with positive PCR or antigen test results. Participants were randomised into four groups:

- apixaban 2.5 mg orally twice a day for 45 days;
- apixaban 5.0 mg orally twice a day for 45 days;
- aspirin 81 mg orally twice a day for 45 days; or
- placebo orally twice a day for 45 days.

Cools 2022 enrolled 219 participants who had not received a COVID-19 vaccine and had symptomatically COVID-19 confirmed with positive PCR in the outpatient setting associated with at least one risk factor for severe disease. Participants were randomised into two groups:

- enoxaparin for 21 days (40 mg once daily if weight < 100 kg; 40 mg twice daily if weight ≥ 100 kg); or
- standard care (without thromboprophylaxis).

Ramacciotti 2022 considered participants at discharge who were hospitalised with COVID-19 (confirmed by reverse transcription polymerase chain reaction (RT-PCR), antigen, or immunoglobulin M (IgM) tests) for at least three days. They randomised 320 participants into two groups:

- rivaroxaban 10 mg/day for 35 days; or
- standard care (no thromboprophylaxis) for 35 days.

Sample size calculations

We were able to include participants from all studies in our analysis (see the numbers above) (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). Ananworanich 2021 described a sample size calculation with 80% power to detect a relative risk reduction (RRR) of 35% in favour of anticoagulation compared with placebo. Barco 2022 calculated that 920 patients would be required for 80% power to show superiority of enoxaparin versus standard of care (no thromboprophylaxis) with a two-sided significance level of 5%. Connors 2021 estimated 80% to 90% power to detect an RRR between 33% and 50% in the primary outcome between each active drug (apixaban or aspirin) and placebo, with an alpha error of 2.5% (one-sided). Cools 2022 calculated the sample size based on an alpha level of 5% and an event rate of 25% in the standard care group, based on 80% power. Ramacciotti 2022 assumed 80% power with an RRR of 67%. Only Ramacciotti 2022 reached the calculated sample size. The remaining four studies did not reach the calculated sample size due to recommendations from the Independent Data Monitoring Committee to stop enrolment because the event rate was lower than anticipated (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022).

Length of follow-up

Ananworanich 2021 randomised participants with acute COVID-19 stratified by site and symptom duration (< 6 days versus ≥ 6 days). The study authors performed 12 telemedicine visits (days 1, 4, 6, 8, 10, 12, 14, 18, 21, 24, 28, and 35), and AEs and bleeding events based on standardised definitions were recorded by the investigator.

Barco 2022 performed block-stratified randomisation (by age group 50 to 70 versus > 70 years and by study centre). Follow-up was performed through telephone follow-up visits by trained personnel 3, 7, 14, 30, and 90 days following randomisation.

Connors 2021 studied participants with newly diagnosed (by PCR or antigen test) symptomatic COVID-19, and participants were contacted weekly using text links to the REDCap survey or by the Research Communication Center staff telephone calls during the 45-day randomised treatment period to capture relevant clinical outcomes and again after a subsequent 30-day safety follow-up.

Cools 2022 evaluated symptomatic, PCR-confirmed COVID-19 participants, and data were collected at 21, 50, and 90 days following randomisation by the treating physician using an electronic case report form designed by the Thrombosis Research Institute.

Ramacciotti 2022 analysed participants at discharge after hospitalisation with COVID-19. The first follow-up was on day 7 after randomisation either at an outpatient clinic or by telephone. The second follow-up was performed on day 35 at an outpatient clinic or hospital.

Outcomes

Ananworanich 2021 presented data on the frequency of AEs resulting in discontinuation; serious AEs and hypersensitivity; major bleeding events; the proportion of participants who progressed to a moderate or severe disease category; the incidence of hospitalisation and the proportion of participants with disease progression; disease resolution; and time to disease resolution. The study reported no deaths during the follow-up period; however, there were no data regarding the number of participants diagnosed with VTE events such as DVT and PE. Despite our attempts to contact the study authors, we did not receive any additional data that could be analysed in the review.

Barco 2022 described the majority of our outcomes of interest. The primary outcome reported was a composite of any untoward hospitalisation and all-cause death within the 30 days following randomisation. They also reported cardiovascular events including DVT, PE, myocardial infarction or myocarditis, peripheral arterial ischaemic events, acute splanchnic vein thrombosis, and ischaemic stroke. They reported information regarding major bleeding and non-major clinically relevant bleeding and serious AEs. The authors reported no deaths within the 30 days following randomisation.

Connors 2021 described some of our outcomes of interest. The primary outcome was the composite of symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, ischaemic stroke, hospitalisation for cardiovascular or pulmonary events, and all-cause mortality. They also reported data on the individual components of the primary study endpoint, mortality without antecedent hospitalisation, major bleeding, clinically relevant non-major bleeding as defined by the International Society on

Thrombosis and Haemostasis (ISTH) criteria, and any events of disseminated intravascular coagulation. However, the authors did not provide separate data regarding DVT and PE events (combined data only reported). Despite our attempts to contact the study authors, we did not receive any additional data that could be analysed in the review. There were no deaths during the follow-up period.

Cools 2022 presented data on all-cause death and hospitalisation; they also reported data regarding diagnosis of VTE and bleeding events. The study authors did not provide separate data for DVT and PE during the complete follow-up period (90 days). It was only possible to collect information at the first time point of 21 days.

Ramacciotti 2022 evaluated several relevant outcomes for this review: all-cause mortality, VTE, DVT, PE, major bleeding, and AEs. However, the study authors did not provide data on the need for hospitalisation. Despite our attempts to contact the study authors, we did not receive any additional data regarding this outcome. They also reported data on myocardial infarction, non-haemorrhagic stroke, and major adverse limb events.

Excluded studies

See Characteristics of excluded studies. We excluded a total of 10 studies (Aghamohammadi 2020; Borghi 2021; ChiCTR2000034796; JPRN-UMIN000042489; Kuno 2022; Lisker 2021; Rivera-Caravaca 2021; Sharma 2021; Spyropoulos 2021; Vergori 2021).

We excluded three studies because the participants were hospitalised patients (Sharma 2021; Spyropoulos 2021; Vergori 2021). As we had sufficient information from RCTs, we excluded seven studies that were not randomised (Aghamohammadi 2020; Borghi 2021; ChiCTR2000034796; JPRN-UMIN000042489; Kuno 2022; Lisker 2021; Rivera-Caravaca 2021).

Ongoing studies

We identified nine ongoing RCTs that met our inclusion criteria (Capell 2021; EUCTR2020-005884-29-IT; NCT04542408; NCT04650087; NCT04715295; NCT04746339; NCT04757857; Ramos-Peñafiel 2020; RBR-7nzwkpg). The RCTs plan to evaluate 8197 participants in total. Seven studies are comparing prophylactic anticoagulants versus placebo or no treatment (Capell 2021; NCT04542408; NCT04650087; NCT04746339; NCT04757857; Ramos-Peñafiel 2020; RBR-7nzwkpg); one is comparing a prophylactic anticoagulant versus a different dose of the same anticoagulant (EUCTR2020-005884-29-IT); and one is comparing prophylactic anticoagulants versus other pharmacological intervention (NCT04715295). We contacted the study authors and also searched by study registration number and title of the study on all databases of interest for this review. However, we did not receive any response, and there are no additional data from the ongoing studies. For further details, see Characteristics of ongoing studies.

Risk of bias in included studies

See Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

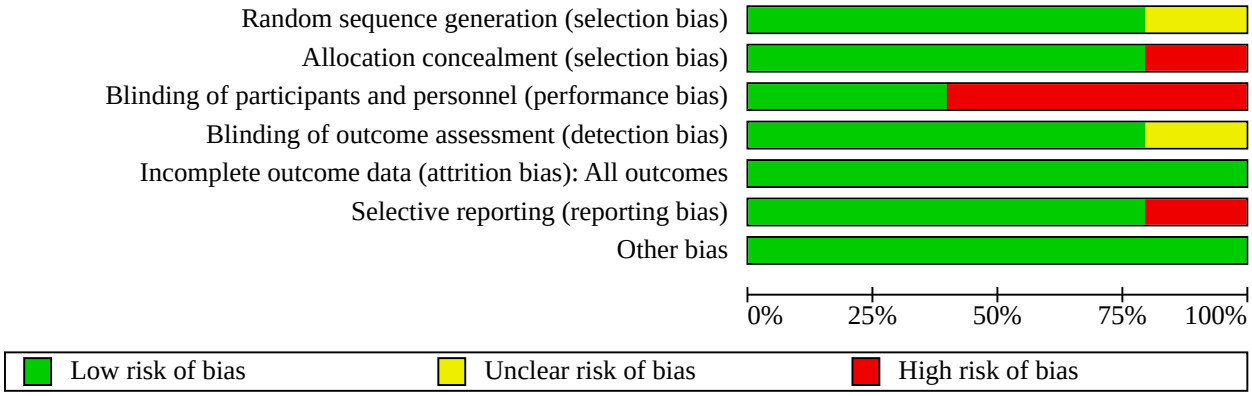
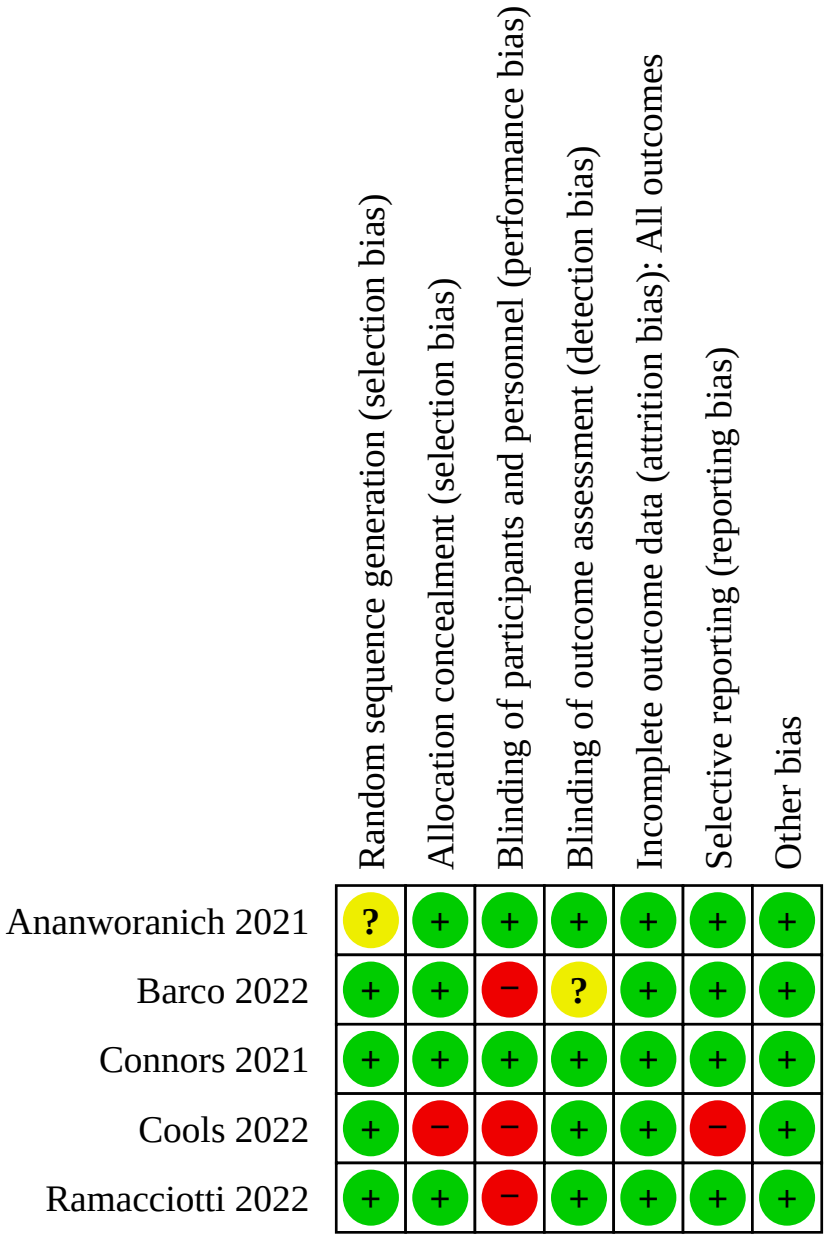


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We used RoB 1 to assess risk of bias as all included studies were RCTs. We judged the overall risk of bias as high for Cools 2022. We judged Ananworanich 2021 and Barco 2022 as at unclear risk of bias, and Connors 2021 and Ramacciotti 2022 as at low risk of bias.

Allocation

Ananworanich 2021 did not provide details on how the randomisation sequence was generated. The authors stated that participants were randomised with a 1:1 proportion to receive either rivaroxaban or placebo equivalent. We therefore assessed this study as at unclear risk of bias for random sequence generation, and low risk of bias for allocation concealment.

We assessed Barco 2022 as at low risk for selection bias. The study authors described randomisation by a computer-generated approach and integrated into the electronic data capture software REDCap (Vanderbilt University, version 9.1.24), and the participants underwent block-stratified randomisation in a 1:1 ratio.

We assessed Connors 2021 as at low risk of selection bias. The study authors reported that randomisation code lists were computer generated, and participants were randomised in a 1:1:1:1 proportion to receive aspirin with matching placebo, prophylactic-dose apixaban, apixaban at therapeutic dose, or placebo.

We assessed Ramacciotti 2022 as at low risk of selection bias. The study authors stated that randomisation was carried out using a central, concealed, web-based, automated randomisation system, and participants were randomly allocated in a 1:1 ratio to receive either thromboprophylaxis with rivaroxaban or regular follow-up.

Although Cools 2022 described that the randomisation sequence was established using a prespecified, secure, central, web-based randomisation system, the study authors stated that the study was unblinded and that no allocation concealment was applied. We therefore assessed the study as at high risk of selection bias due to lack of allocation concealment.

Blinding

Ananworanich 2021 divided participants into a treatment group (rivaroxaban) and a control group (placebo). They reported that participants and personnel were blinded, so we judged this study as at low risk for both performance and detection bias.

Despite the fact that an independent data and safety monitoring board monitored the trials by Barco 2022, Cools 2022, and Ramacciotti 2022, they were classified as open-label trials, in which participants and study personnel were aware of treatment allocation, but not of the allocation sequence. We assessed all three studies as at high risk of performance bias because personnel and participants were not blinded (Barco 2022; Cools 2022; Ramacciotti 2022). However, we assessed Cools 2022 and Ramacciotti 2022 as at low risk of detection bias since they used an independent data evaluating or monitoring committee. We judged Barco 2022 as at unclear risk of detection bias because insufficient details were provided.

Connors 2021 stated that participants were randomly assigned (double-blind), and all tablets in the four groups were taken two times a day. In addition, personnel were unaware of randomised drug assignment. We therefore assessed this study as at low risk of both performance and detection bias.

Incomplete outcome data

We assessed Ananworanich 2021, Barco 2022, and Cools 2022 as having a low risk of attrition bias because the study authors described dropouts, and numbers were similar between groups. The study authors used an ITT approach, reported and analysed AEs.

We assessed Connors 2021 as at low risk of attrition bias because the authors described dropouts, which were similar between groups, and AEs.

We assessed Ramacciotti 2022 as at low risk of attrition bias. The study authors described all losses/exclusions, and all participants were analysed by an ITT approach.

Selective reporting

The protocols of Ananworanich 2021, Barco 2022, and Connors 2021 were available, and all prespecified (primary and secondary) outcomes of interest in the review were reported as prespecified. We therefore assessed these studies as at low risk of reporting bias.

We assessed Cools 2022 as at high risk of reporting bias because although the protocol was available, the study authors made adjustments to the inclusion criteria during the course of the study because enrolment was slower than expected. Moreover, they reported that "due to the very low number of events and the study's early termination, only the primary efficacy outcome was tested for statistical significance".

We judged the study by Ramacciotti 2022 as at low risk of reporting bias because the full protocol was available, and all prespecified (primary and secondary) outcomes of interest in the review were reported.

Other potential sources of bias

We assessed all five included studies as at low risk of other bias as we identified no other reasons for bias (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022).

Effects of interventions

See: **Summary of findings 1** Anticoagulant compared to placebo or no treatment for non-hospitalised people with COVID-19; **Summary of findings 2** Anticoagulant compared to different dose of the same anticoagulant for non-hospitalised people with COVID-19; **Summary of findings 3** Anticoagulant compared to antiplatelet agent for non-hospitalised people with COVID-19

See Summary of findings 1; Summary of findings 2; Summary of findings 3.

The included studies provided sufficient short-term (90 days or less) follow-up data. There were no available data regarding long-term follow-up (> 90 days). We calculated number needed to treat for an additional beneficial outcome (NNTB) for outcomes with clinically important differences. None of the included studies compared anticoagulant versus a different anticoagulant, or anticoagulant versus non-pharmacological interventions.

Anticoagulant versus placebo or no treatment

Five studies with a follow-up duration ranging from 21 to 90 days reported this comparison (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). Ananworanich 2021 compared a group that received prophylactic rivaroxaban (10 mg daily) with placebo; Barco 2022 compared enoxaparin 40 mg daily with standard care (no treatment); Connors 2021 compared apixaban 2.5 mg twice a day with placebo; Cools 2022 compared enoxaparin 40 mg once daily if body weight was < 100 kg and 40 mg twice daily if body weight was ≥ 100 kg with standard care (no treatment); and Ramacciotti 2022 compared rivaroxaban 10 mg daily with no treatment.

Primary outcomes

All-cause mortality

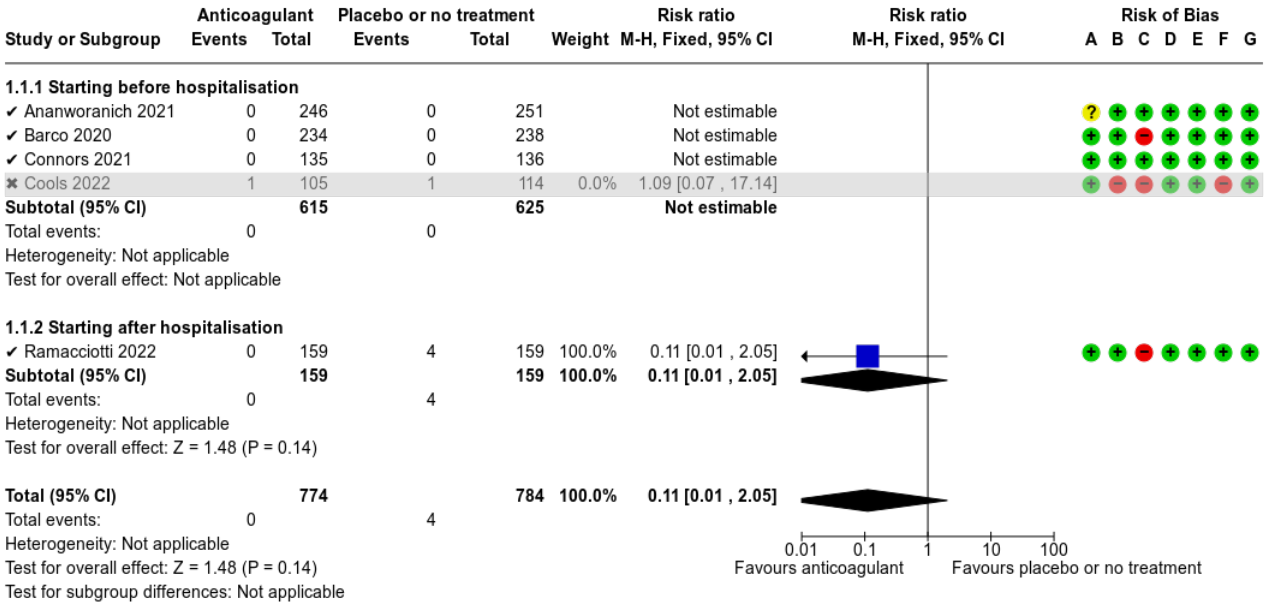
All studies reported this outcome (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). Ananworanich 2021, Barco 2022, and Connors 2021 reported no deaths during the follow-up period. Combining the data, overall there was little or no difference in all-cause mortality between anticoagulants and either placebo or no treatment (risk ratio (RR) 0.36, 95% confidence

interval (CI) 0.04 to 3.61; 5 studies; 1777 participants; P = 0.39; low-certainty evidence) (Analysis 1.1). We detected no important heterogeneity (I^2 = 24%). We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

The test for subgroup differences suggests that starting prophylaxis as an outpatient versus after discharge does not have a modifying effect on all-cause mortality (P = 0.27) (Analysis 1.1).

Sensitivity analyses including only trials at low risk of bias did not change the effect estimate substantially (RR 0.11, 95% CI 0.01 to 2.05) (Figure 4).

Figure 4. Sensitivity analysis (All-cause mortality): only trials at low risk of bias.



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

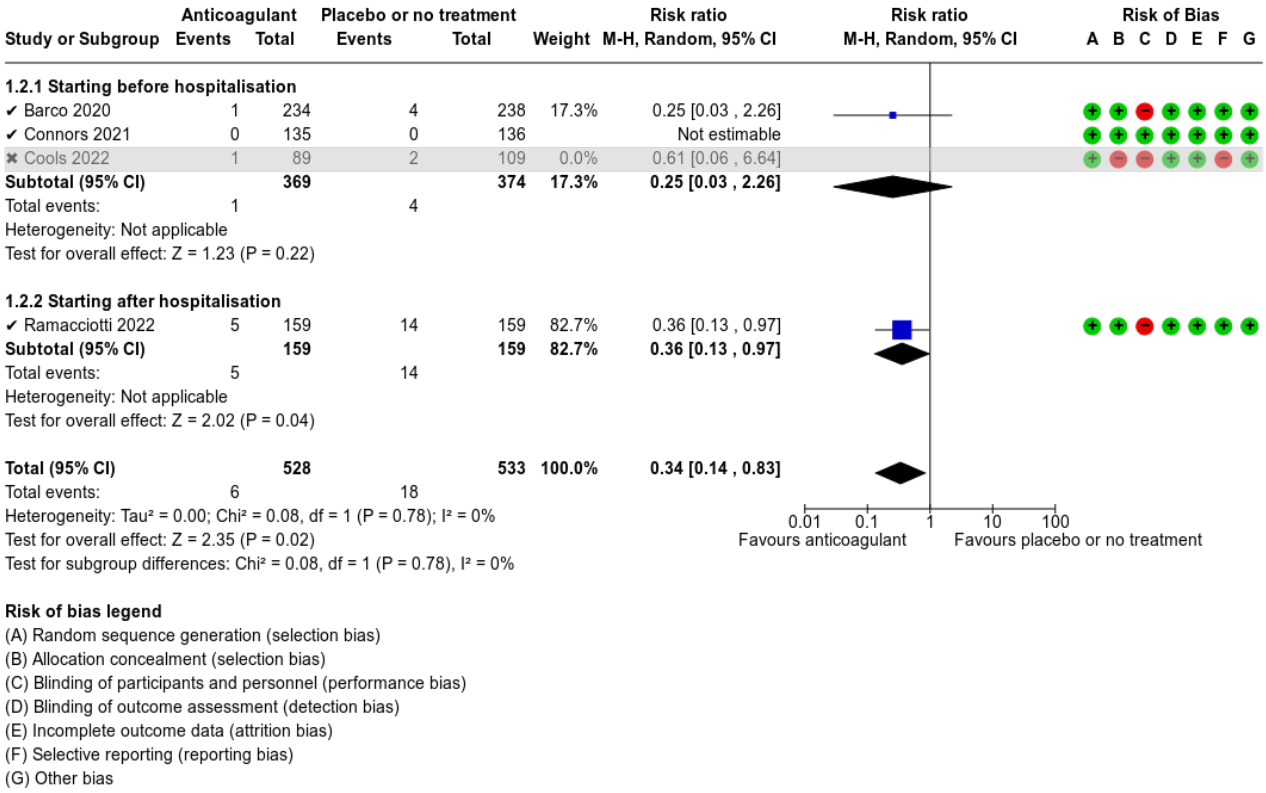
Venous thromboembolism (VTE)

Ananworanich 2021 did not report data on VTE events, therefore four studies provided data for this outcome (Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). Connors 2021 reported no VTE during the follow-up period. Barco 2022; Cools 2022, and Ramacciotti 2022 reported VTE data. Overall, our analysis shows that anticoagulants probably decrease VTE compared with placebo or no treatment (RR 0.36, 95% CI 0.16 to 0.85; 4 studies; 1259 participants; P = 0.02; NNTB = 50; moderate-certainty evidence; Analysis 1.2). We detected no heterogeneity (I^2 = 0%). We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

The test for subgroup differences suggests that starting prophylaxis as an outpatient versus after discharge does not have a modifying effect on VTE (P = 0.95) (Analysis 1.2).

Sensitivity analyses including only trials at low risk of bias did not change the effect estimate substantially (RR 0.34, 95% CI 0.14 to 0.83) (Figure 5).

Figure 5. Sensitivity analysis (Venous thromboembolism): only trials at low risk of bias.

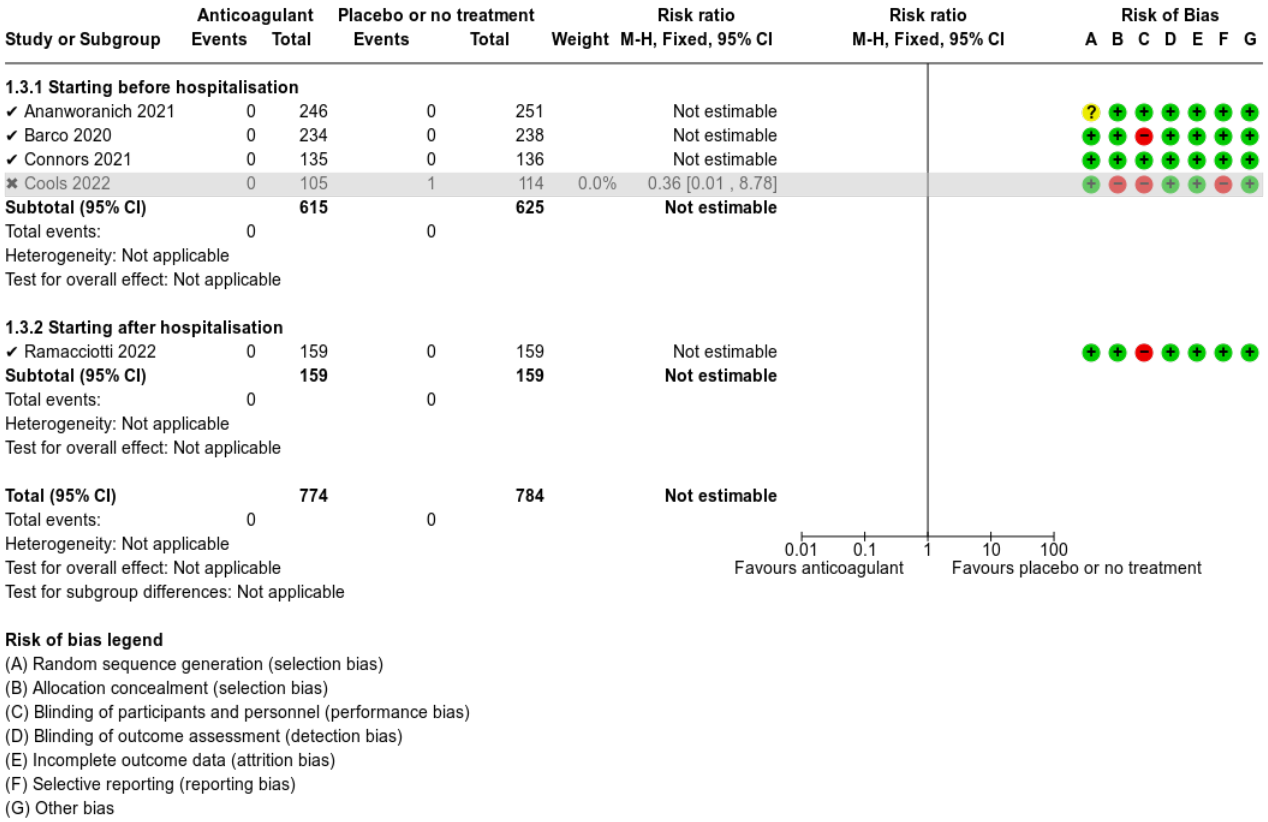


Major bleeding

Ananworanich 2021, Barco 2022, Connors 2021, and Ramacciotti 2022 reported that no major bleeding occurred during the follow-up period, therefore we could not estimate the effect of this outcome. Cools 2022 reported data, and overall there was little or no difference in major bleeding between anticoagulant use and placebo or no treatment (RR 0.36, 95% CI 0.01 to 8.78; 5 studies; 1777 participants; I^2 = not applicable; P = 0.53; low-certainty evidence; Analysis 1.3). We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

The test for subgroup differences was not applicable because there was no event in the subgroup 'after discharge' (Analysis 1.3). Sensitivity analyses including only trials at low risk of bias were not estimable because there was no event in any of the included studies (Figure 6).

Figure 6. Sensitivity analysis (Major bleeding): only trials at low risk of bias.



Secondary outcomes

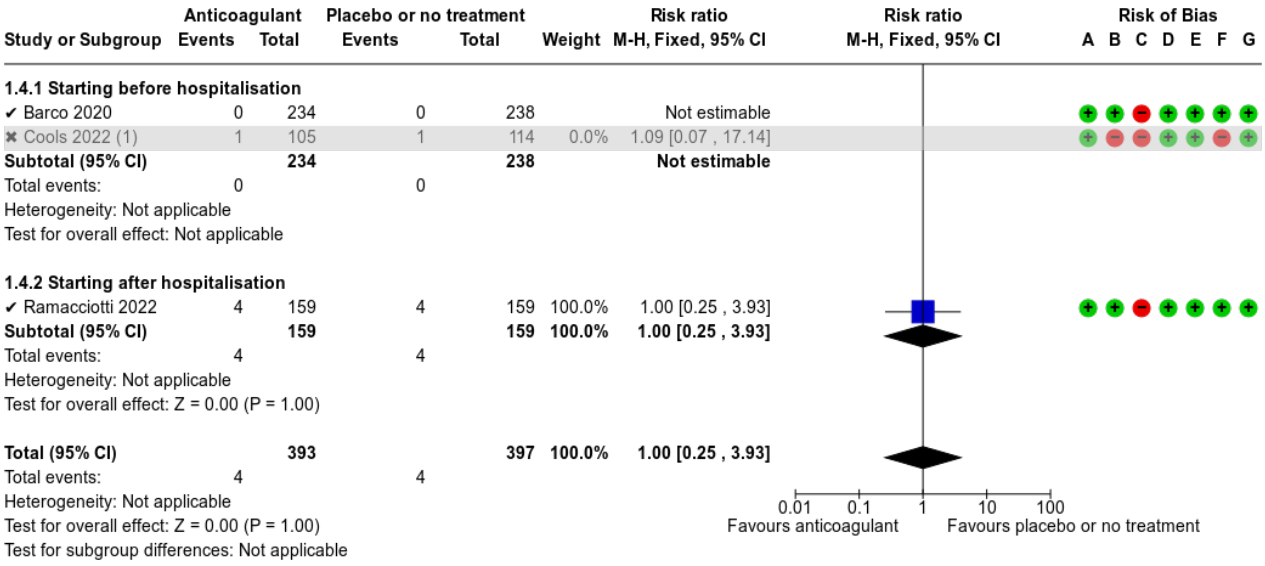
Deep vein thrombosis (DVT)

Ananworanich 2021 and Connors 2021 did not report this outcome. Barco 2022 reported no DVT during follow-up. Cools 2022 and Ramacciotti 2022 reported data that overall showed little or no difference in DVT between anticoagulation use and placebo or no treatment (RR 1.02, 95% CI 0.30 to 3.46; 3 studies; 1009 participants; P = 0.98; moderate-certainty evidence; Analysis 1.4). There was no heterogeneity among the different anticoagulant subgroups ($I^2 = 0$). Cools 2022 reported one DVT event in the anticoagulation group at 30-day follow-up. The authors reported another VTE event in the standard care group at 90-day follow-up, but as it was not possible to establish whether it was DVT or PE, we did not include this event in our analysis. We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

The test for subgroup differences suggests that starting prophylaxis as an outpatient versus after discharge does not have a modifying effect on DVT (P = 0.96) (Analysis 1.4).

Sensitivity analyses including only trials at low risk of bias did not change the effect estimate substantially (RR 1.00, 95% CI 0.25 to 3.93) (Figure 7).

Figure 7. Sensitivity analysis (Deep vein thrombosis): only trials at low risk of bias.



Footnotes

(1) Cools 2022 reported 1 event in the anticoagulation group at 30 days. At 90 days follow-up the study reported another VTE event, but it was not possible to establis

Risk of bias legend

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

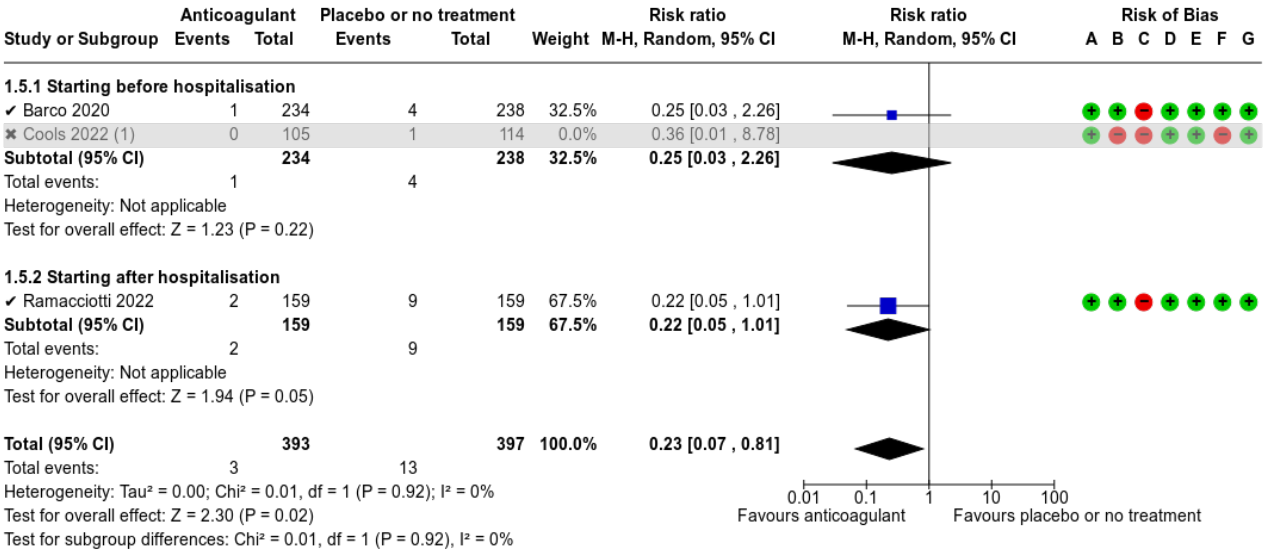
Pulmonary embolism (PE)

Ananworanich 2021 and Connors 2021 did not report this outcome. Barco 2022, Cools 2022, and Ramacciotti 2022 reported data. Combining the data showed that anticoagulants probably decrease PE compared with placebo or no treatment (RR 0.25, 95% CI 0.08 to 0.79; 3 studies; 1009 participants; P = 0.02; NNTB = 50; moderate-certainty evidence). We detected no heterogeneity (I^2 = 0%). Cools 2022 reported one PE in the anticoagulation group at 30-day follow-up. The authors reported another VTE event in the standard care group at 90-day follow-up, but as it was not possible to establish whether it was DVT or PE, we did not include this event in our analysis. We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

The test for subgroup differences suggests that starting prophylaxis as an outpatient versus after discharge does not have a modifying effect on PE (P = 0.84) (Analysis 1.5).

Sensitivity analyses including only trials at low risk of bias did not change the effect estimate substantially (RR 0.23, 95% CI 0.07 to 0.81) (Figure 8).

Figure 8. Sensitivity analysis (Pulmonary embolism): only trials at low risk of bias.



Footnotes

(1) Cools 2022 reported one event at the no treatment group on the 30 days follow-up. At 90 days follow-up the authors reported another VTE event, but it was not possi

Risk of bias legend

(A) Random sequence generation (selection bias)
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(F) Selective reporting (reporting bias)
(G) Other bias

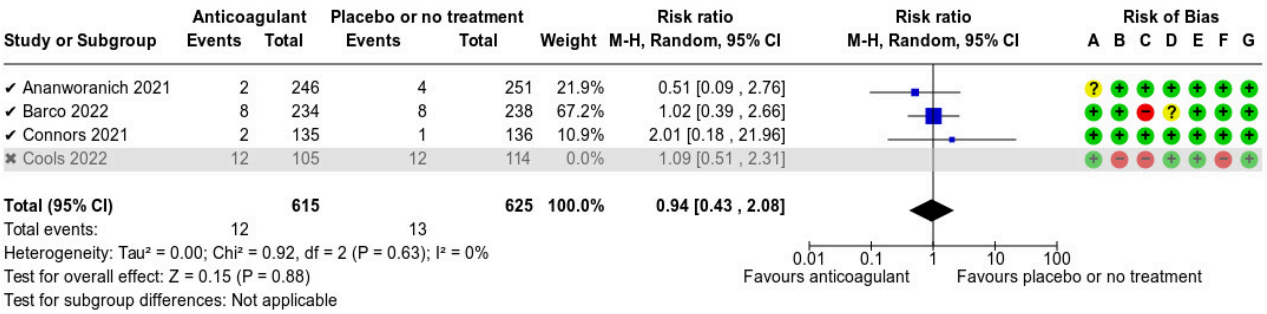
Need for hospitalisation

Ramacciotti 2022 did not report this outcome. The remaining four studies reported data (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022). Overall, there was little or no difference in need for hospitalisation with anticoagulant use compared with placebo or no treatment (RR 1.01, 95% CI 0.59 to 1.75; 4 studies; 1459 participants; P = 0.96; moderate-certainty evidence; Analysis 1.6).

There was no heterogeneity among the different anticoagulant groups (I^2 = 0%). We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

Lack of available data precluded subgroup analysis. Sensitivity analyses including only trials at low risk of bias did not change the effect estimate substantially (RR 0.94, 95% CI 0.43 to 2.08) (Figure 9).

Figure 9. Sensitivity analysis (Need for hospitalisation): only trials at low risk of bias.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
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(F) Selective reporting (reporting bias)
(G) Other bias

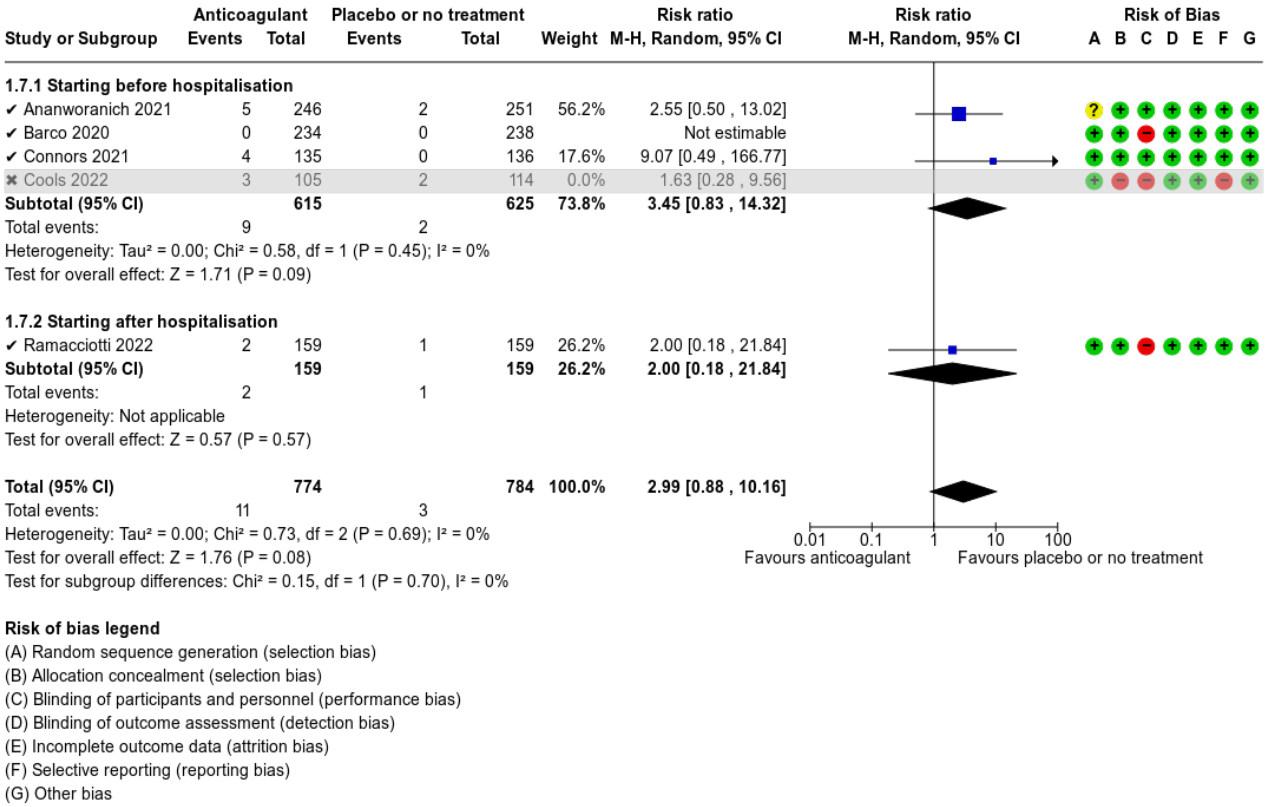
Adverse events – minor bleeding

All included studies reported this outcome. Ananworanich 2021 reported 5/246 minor bleeding events in the intervention group and 2/251 in the placebo group during the follow-up period. Barco 2022 reported that no minor bleeding occurred during the follow-up period. Connors 2021 reported 4/135 minor bleeding events in the anticoagulant group and 0/136 in the placebo group. Cools 2022 reported that 3/105 participants in the intervention group and 2/114 participants in the standard care group (no treatment) had minor bleeding. Ramacciotti 2022 reported 2/159 minor bleeding events in the anticoagulant group and 1/159 in the no-treatment group. The overall effect estimate of this outcome showed little or no difference between anticoagulants and placebo or no treatment (RR 2.46, 95% CI 0.90 to 6.72; 5 studies; 1777 participants; P = 0.08; low-certainty evidence; Analysis 1.7). We detected no heterogeneity among the studies (I^2 = 0%). We used a random-effects model for this analysis because of clinical heterogeneity among the included studies.

The test for subgroup differences suggests that starting prophylaxis as an outpatient versus after discharge does not have a modifying effect on minor bleeding (P = 0.85) (Analysis 1.7).

Sensitivity analyses including only trials at low risk of bias did not change the effect estimate substantially (RR 2.99, 95% CI 0.88 to 10.16) (Figure 10).

Figure 10. Sensitivity analysis (Adverse events (minor bleeding)): only trials at low risk of bias.



Adverse events – all

All included studies reported adverse events (AEs), but all studies reported AEs combined, therefore we could not analyse each type of adverse event separately. Ananworanich 2021 reported 35/246 AEs in the intervention group and 36/251 in the placebo group during the follow-up period. Barco 2022 reported a total of 17 serious AEs, 8/234 in the intervention group and 9/238 in the control group. Connors 2021 reported 10/135 AEs in the anticoagulant group and 3/136 in the placebo group. Cools 2022 reported that 22/105 participants in the intervention group and 13/114 participants in the standard care group (no treatment) experienced AEs; the most common AE in both groups was COVID-19-related pneumonia. Ramacciotti 2022 reported 4/159 AEs in the anticoagulant group and 3/159 AEs in the no-treatment group. The overall effect estimate of this outcome did not show a clear difference between anticoagulants and placebo or no treatment when all AEs were pooled together (RR 1.32, 95% CI 0.88 to 1.98; 5 studies; 1777 participants; P = 0.18; I^2 = 25%; low-certainty evidence; Analysis 1.8).

Quality of life

There were no available data for this outcome.

Higher-dose anticoagulant versus standard dose of the same anticoagulant

Connors 2021 compared apixaban 5 mg twice daily (higher dose; intervention group) versus apixaban 2.5 mg twice daily (standard dose; control group) with a 45-day follow-up.

Primary outcomes

All-cause mortality

Connors 2021 reported no deaths during the follow-up period, therefore we could not estimate this effect with the available data (Analysis 2.1). Insufficient data precluded subgroup or sensitivity analysis.

Venous thromboembolism (VTE)

Connors 2021 reported no VTE during the follow-up period, therefore we could not estimate this effect (Analysis 2.2). Insufficient data precluded subgroup or sensitivity analysis.

Major bleeding

Connors 2021 reported no major bleeding during the follow-up period, therefore we could not estimate this effect (Analysis 2.3). Insufficient data precluded subgroup or sensitivity analysis.

Secondary outcomes

Deep vein thrombosis (DVT)

Connors 2021 reported no DVT during the follow-up period, therefore we could not estimate this effect (Analysis 2.4). Insufficient data precluded subgroup or sensitivity analysis.

Pulmonary embolism (PE)

Connors 2021 reported no PE during the follow-up period, therefore we could not estimate this effect (Analysis 2.5). Insufficient data precluded subgroup or sensitivity analysis.

Need for hospitalisation

Connors 2021 reported 2/143 hospitalisations in the higher-dose group and 1/135 hospitalisations in the standard-dose group. There was little or no difference between higher dose and standard dose of the same anticoagulant in need for hospitalisation (RR 1.89, 95% CI 0.17 to 20.58; 1 study; 278 participants; low-certainty evidence; Analysis 2.6). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Adverse events – minor bleeding

Connors 2021 reported 2/143 events in the higher-dose group and 4/135 events in the standard-dose group. There was little or no difference between higher dose and standard dose of the same anticoagulant in minor bleeding (RR 0.47, 95% CI 0.09 to 2.54; 1 study; 278 participants; low-certainty evidence; Analysis 2.7). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Adverse events – all

Connors 2021 also reported different AEs combined as 13/143 events in the intervention group and 9/135 events in the control group. Data were insufficient to analyse other AEs individually. The effect estimate did not show a clear difference between higher dose and standard dose of the same anticoagulant when all AEs were pooled together (RR 1.36, 95% CI 0.60 to 3.09; 1 study; 278 participants; I^2 = not applicable; moderate-certainty evidence; Analysis 2.8).

Quality of life

There were no available data for this outcome.

Anticoagulant versus antiplatelet agent

Connors 2021 compared apixaban 2.5 mg twice daily (intervention group) versus aspirin 81 mg once daily (control group) with 45-day follow-up data.

Primary outcomes

All-cause mortality

Connors 2021 reported no deaths during the follow-up period, therefore we could not estimate this effect (Analysis 3.1). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Venous thromboembolism (VTE)

Connors 2021 reported little or no difference in VTE between anticoagulant and antiplatelet agent (RR 0.36, 95% CI 0.01 to 8.65; 1 study; 279 participants; low-certainty evidence; Analysis 3.2). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Major bleeding

Connors 2021 reported no major bleeding during the follow-up period, therefore we could not estimate this effect (Analysis 3.3). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Secondary outcomes

Deep vein thrombosis (DVT)

Connors 2021 did not report data on this outcome.

Pulmonary embolism (PE)

Connors 2021 did not report data on this outcome.

Need for hospitalisation

Data from Connors 2021 showed little or no difference in need for hospitalisation between anticoagulant and antiplatelet agent (RR 3.20, 95% CI 0.13 to 77.85; 1 study; 279 participants; low-certainty evidence; Analysis 3.4). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Adverse events – minor bleeding

Connors 2021 reported 4/135 events in the experimental group and 2/144 events in the control group. There was no clear difference between anticoagulant and antiplatelet agent (RR 2.13, 95% CI 0.40 to 11.46; 1 study; 279 participants; low-certainty evidence; Analysis 3.5). Insufficient data precluded assessment of heterogeneity or performance of subgroup or sensitivity analysis.

Adverse events – all

Connors 2021 also reported different AEs combined as 9/135 events in the anticoagulant group and 6/144 events in the antiplatelet agent group, but did not provide details. Data were insufficient to analyse other AEs individually. The effect estimate did not show a clear difference between groups (RR 1.35, 95% CI 0.60 to 3.06; 1 study; 279 participants; moderate-certainty evidence; Analysis 3.6).

Quality of life

Connors 2021 did not report data on this outcome.

DISCUSSION

Summary of main results

Since 2020, the COVID-19 pandemic has affected people worldwide and has led to intense demand on healthcare systems (COVER 2022; COVIDSurg 2021a; COVIDSurg 2021b; COVIDSurg 2022a; COVIDSurg 2022b; NIHR 2022; Phelan 2020). Thromboembolic complications related to COVID-19 have been reported worldwide throughout the entire pandemic (Lodigiani 2020; Tang 2020), and it is known that people with COVID-19 are at high risk for VTE (Correia 2022; COVIDSurg 2022a; Flumignan 2021; Flumignan 2022b; Klok 2020a; Middeldorp 2020). The most frequently reported thrombotic events directly related to morbidity and mortality have been DVT and PE (COVIDSurg 2022a; Hanff 2020).

Current data regarding non-hospitalised people with COVID-19 are limited, but the incidence of thromboembolic events in this group is of possible concern and likely presents a higher thrombotic risk than has been acknowledged (Benzakoun 2020; Giannis 2021). We identified five RCTs involving a total of 1777 participants that investigated the benefits and harms of prophylactic anticoagulants in non-hospitalised people with COVID-19. The studies provided data on three possible comparisons: 1) anticoagulant versus placebo or no treatment; 2) anticoagulant versus a different dose of the same anticoagulant; and 3) anticoagulant versus antiplatelet agents.

Anticoagulant versus placebo or no treatment

See Summary of findings 1. All five included studies compared anticoagulants with placebo or no treatment and provided data for three of our outcomes of interest (all-cause mortality, major bleeding, and AEs) at short-term follow-up (90 days) (Ananworanich 2021; Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). Data reported by Barco 2022, Cools 2022, and Ramacciotti 2022 should be interpreted with caution given that each study was at high risk of bias for at least one of seven risk of bias domains.

Meta-analysis showed that prophylactic anticoagulants may lead to little or no difference in reducing the risk of death, but the evidence was of low certainty. We pooled data from four studies to assess VTE (Barco 2022; Connors 2021; Cools 2022; Ramacciotti 2022). The meta-analysis showed that anticoagulants probably decrease VTE slightly compared with placebo or no treatment (moderate-certainty evidence). Three studies reported data on DVT and PE (Barco 2022; Cools 2022; Ramacciotti 2022). Data reported by Cools 2022 and Ramacciotti 2022 showed that anticoagulants probably result in little or no difference in DVT (moderate-certainty evidence). Pooling data from three studies suggests that prophylactic anticoagulants probably reduce PE when compared with placebo or no treatment (moderate-certainty evidence) (Barco 2022; Cools 2022; Ramacciotti 2022).

Four studies reported no cases of major bleeding during the study period, while one study reported no clear difference between anticoagulant prophylaxis and placebo or no treatment (low-certainty evidence). Results showed that prophylactic anticoagulants may lead to little or no difference in minor bleeding when compared to placebo or no treatment (low-certainty evidence). Pooling data for all AEs from five studies showed little or no difference between intervention and control groups (low-certainty evidence).

None of the included studies reported data on quality of life.

We undertook subgroup analysis to investigate effect differences between participants when prophylaxis started before or after hospitalisation. The small number of participants and studies contributing data to each subgroup meant that the analysis was unable to produce any useful findings. No difference was detected by the test for subgroup differences for any outcome.

Anticoagulant versus a different dose of the same anticoagulant

See Summary of findings 2. One study with a 45-day follow-up provided data for five of our outcomes of interest (all-cause mortality, VTE, major bleeding, need for hospitalisation, and AEs) in this comparison (Connors 2021). The study authors reported no deaths, no VTE, and no major bleeding during study follow-up in either group, therefore we could not estimate the effect on all-cause mortality, VTE, or major bleeding. Our analysis showed that prophylactic anticoagulants probably lead to little or no difference in reducing the need for hospitalisation (low-certainty evidence) and all AEs (moderate-certainty evidence) when comparing apixaban 2.5 mg twice daily with a different dose of the same anticoagulant; anticoagulants may lead to little or no difference in reducing minor bleeding events (low-certainty evidence) for this comparison.

Anticoagulant versus antiplatelet agent

See Summary of findings 3. One study with a 45-day follow-up provided data for five of our outcomes of interest (all-cause mortality, VTE, major bleeding, need for hospitalisation, and AEs) in this comparison (Connors 2021). The study authors reported no deaths and no major bleeding during follow-up, therefore we could not estimate the effects of all-cause mortality and major bleeding. Anticoagulants may lead to little or no difference in reducing VTE or the need for hospitalisation when compared to antiplatelet agents (low-certainty evidence). Prophylactic apixaban may lead to little or no difference in reducing minor bleeding events when compared to aspirin (low-certainty evidence). Apixaban may lead to little or no difference in reducing all AEs when compared with aspirin (moderate-certainty evidence).

Overall completeness and applicability of evidence

We assessed whether the use of prophylactic anticoagulants for the treatment of people with COVID-19 in the outpatient setting could reduce all cause-mortality, VTE, and the need for hospitalisation safely without causing major bleeding or AEs. We also planned to evaluate other relevant parameters such as quality of life, but none of the studies reported data on this outcome.

The overall evidence was based on five studies involving 1777 eligible participants from the USA, Switzerland, Germany, Belgium, Brazil, India, South Africa, Spain, and the UK. All five studies provided data for the first comparison with placebo or no treatment as the control group. All included studies evaluated at least one of our primary outcomes. However, there were no mortality events in the studies by Ananworanich 2021, Barco 2022, and Connors 2021; no VTE in the study by Connors 2021; no major bleeding in the studies by Ananworanich 2021, Barco 2022, Connors 2021, and Ramacciotti 2022; and no DVT in the study by Barco 2022. We were only able to analyse a portion of the data from the study by Cools 2022 in the review as the study authors did not provide information

regarding DVT and PE separately, therefore we could not use the complete data in our subsequent analysis of DVT and PE for the entire follow-up period. The number of studies for each possible comparison was small, ranging from one to five studies. However, the included studies had relatively large primary sample sizes (all five studies had 219 or more participants).

We did not identify any studies comparing an anticoagulant versus a different anticoagulant or an anticoagulant versus non-pharmacological interventions.

It is noteworthy that the studies included in this review were conducted in nine different countries, most of which (55%) were high-income countries. Social and cultural aspects of these regions related to the evaluated interventions can also interfere with their acceptability and effectiveness for the treatment of people non-hospitalised with COVID-19. The external validity of the overall evidence presented in this review should therefore be interpreted with caution.

The key limitations of this review are presented below.

- Some of the included studies presented a high risk of bias (Barco 2022; Cools 2022; Ramacciotti 2022).
- None of the included studies presented quality of life data.
- Some data were not available. We did not have access to all data in the study by Ananworanich 2021 regarding the diagnosis of VTE, DVT, and PE, therefore we did not include data for these outcomes from this study in the review. We also did not have access to all data in Connors 2021 on the occurrence of DVT and PE, therefore we did not include data for these outcomes from this study in the review. Ramacciotti 2022 did not provide data on the need for hospitalisation, therefore we did not include data for this outcome from this study in the review. Furthermore, we did not have access to all the data of interest regarding DVT and PE during the entire follow-up period from Cools 2022.
- Follow-up was relatively short (from 35 to 90 days).
- Only Connors 2021 made comparisons between anticoagulants versus a different dose of the same anticoagulant, and anticoagulants versus antiplatelet agents.

The short follow-up (35 to 90 days) prevented long-term analysis and impacted data for chronic complications of COVID-19. Recent data have shown that some patients have persistent symptoms that continue or develop after the acute SARS-CoV-2 infection phase; this condition is known as 'long COVID' (Lee 2021; Shah 2021). Moreover, Townsend 2021 demonstrated that these individuals have prolonged elevation of D-dimer, with an increase in serious thromboembolic events. It would therefore be important to consider a longer follow-up to assess these outcomes in people with long COVID.

Quality of the evidence

We created a summary of findings table for each comparison using GRADEpro GDT software (GRADEpro GDT).

For the comparison prophylactic anticoagulant versus placebo or no treatment in non-hospitalised people with COVID-19 (Summary of findings 1), we found moderate-certainty evidence for the majority of outcomes of interest (VTE, DVT, PE, and need for hospitalisation), and low-certainty evidence for three of our outcomes of interest (all-cause mortality, major and minor bleeding). We downgraded the certainty of the evidence by one either one level or two levels due to imprecision, as fewer than 300 events were included in the analysis and confidence intervals were wide. We identified high risk of bias due to a lack of allocation concealment and blinding in three studies (Barco 2022; Cools 2022; Ramacciotti 2022). However, we decided not to downgrade for risk of bias, as the effect estimate did not significantly differ after removing these studies in a sensitivity analysis. In addition, Cools 2022 adjusted the inclusion criteria during the study, but the estimates did not significantly differ after sensitivity analysis. Following GRADE recommendations, we did not downgrade for inconsistency and indirectness because heterogeneity among studies was low, and we did not find any differences in outcome measures.

For the comparison prophylactic anticoagulant versus a different dose of the same anticoagulant for non-hospitalised people with COVID-19 (Summary of findings 2), we found moderate-certainty evidence for the outcomes all-cause mortality, VTE, and major bleeding and low-certainty evidence for need for hospitalisation and minor bleeding up to 45-day follow-up (short term). Following GRADE recommendations, we downgraded by one level or two levels due to imprecision, as fewer than 300 events were included in the analysis and confidence intervals were wide. The single study in this comparison demonstrated a low risk of bias (Connors 2021), therefore we did not downgrade based on risk of bias. Moreover, we did not downgrade for inconsistency because there was only one study.

For the comparison prophylactic anticoagulants versus antiplatelet agents in non-hospitalised people with COVID-19 (Summary of findings 3), we found moderate-certainty evidence for the outcomes all-cause mortality and major bleeding and low-certainty evidence for VTE, need for hospitalisation, and minor bleeding up to 45-day follow-up (short term). Following GRADE recommendations, we downgraded by one level or two levels due to imprecision, as fewer than 300 events were included in the analysis and confidence intervals were wide. The study in this comparison demonstrated a low risk of bias (Connors 2021), therefore we did not downgrade based on risk of bias. Furthermore, we did not downgrade for inconsistency because there was only one study.

The risk of bias differed substantially among the included studies (Figure 2; Figure 3), and it did not affect the overall certainty of the evidence. High risk of bias in some studies was due to a lack of blinding of personnel and participants (Barco 2022; Cools 2022; Ramacciotti 2022), while in one study it was related to selective reporting (Cools 2022). We pursued a sensitivity analysis and found that excluding studies at high risk of bias did not result in changes in any of the predefined outcomes for the comparison anticoagulant versus placebo or no treatment.

Moderate–certainty evidence means that our confidence in the effect estimates is reduced because the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Including additional studies in future versions of this review will help strengthen our confidence in the findings.

Potential biases in the review process

We believe that we have identified and included all relevant RCTs by using a search methodology that included multiple sources,

without restricting language, date, or status of publication. When we identified additional reports of the same study during the study selection process, we utilised the best information.

Given that we found RCTs answering our review question, we decided not to include NRS following our protocol (Santos 2022). This decision improved our evidence quality because we considered only better study designs. However, this decision may impair the estimates of rare events.

We requested additional relevant data from the study authors, but received no response to our queries. We rigorously observed the criteria described in the protocol to include or exclude participants to limit any type of non-compliance with the protocol (Santos 2022).

We performed double data extraction to reduce bias in the review process and ensure the quality of assessment of included RCTs.

We were able to include all participants from each included study because the study authors reported the majority of our outcomes of interest.

We did not perform a funnel plot assessment because of the insufficient number of included studies (fewer than 10) in each comparison.

Agreements and disagreements with other studies or reviews

We did not find another systematic review of RCTs assessing the effects of prophylactic anticoagulants for the treatment of non-hospitalised people with COVID-19. Two systematic reviews assessed the effects of anticoagulant interventions for the treatment of people with COVID-19 in the outpatient setting (Kyriakoulis 2022; Tunjungputri 2022); however, they included both NRS and RCTs, a significant difference from our review.

Kyriakoulis 2022 performed a systematic review aiming to identify published guidance reports regarding thromboprophylaxis in people with COVID-19 in different settings (outpatients, hospitalised, and postdischarge). The authors considered only full-text articles in English found in PubMed/Embase, and identified reports on people with COVID-19 postdischarge (75%) and little information regarding the outpatient scenario (34%). The majority of these documents (63%) recommended thromboprophylaxis for people with a high VTE risk after hospital discharge. In the outpatient scenario, a minority of the documents (28%) recommended pharmacological thromboprophylaxis for people with a high VTE risk. However, the authors did not perform meta-analysis and concluded that their recommendations were derived from limited evidence.

Tunjungputri 2022 aimed to provide an update on the available evidence regarding the clinical benefits and risk of oral and parenteral anticoagulants in people with COVID-19 during hospitalisation and after discharge. They compared the use of parenteral anticoagulants with standard treatment, a comparison also made in our review. Their main outcomes included mortality and survival rates, requirement for intensive care unit and mechanical ventilation. Tunjungputri 2022 performed a systematic review searching within the Cochrane Library, EBSCO, PubMed, and Embase databases. However, they limited their search to reports in English. Of the 32 included studies, only seven were RCTs, and the population of interest was hospitalised patients with COVID-19, which differs from our review. The study results suggest that anticoagulation may have an impact on reducing mortality in hospitalised patients (RR 0.55, 95% CI 0.43 to 0.66; P < 0.001). The other studies they considered were observational studies and case reports. Furthermore, they did not find any data regarding postdischarge COVID-19 patients and did not include the Ramacciotti 2022 trial, one of our included studies.

It is well established that hypercoagulability is an essential hallmark of COVID-19, and people with COVID-19 are at higher risk of developing thromboembolic complications (Correia 2022; COVIDSurg 2022a; Kelliher 2022). In addition, several studies demonstrated that the SARS-CoV-2 virus causes a high level of inflammatory mediators that lead to arterial and venous wall damage, resulting in endothelial dysregulation. This process ultimately leads to coagulation and thrombosis (Goshua 2020; Matos 2011; Varga 2020).

Flumignan 2022b performed a Cochrane Review that aimed to assess the effects of prophylactic anticoagulants versus an active comparator, placebo, or no intervention, on mortality and the need for respiratory support in people hospitalised with COVID-19. The authors stated that, when compared to a lower-dose regimen, higher-dose anticoagulants result in little or no difference in all-cause mortality and increase minor bleeding in people hospitalised with COVID-19 at 30-day follow-up. They also suggested that anticoagulants possibly reduce PE, but slightly increase major bleeding. However, there may be little or no difference in hospitalisation time, DVT, stroke, major adverse limb events, myocardial infarction, atrial fibrillation, and thrombocytopenia. These results in hospitalised people with COVID-19 are similar to the results found in our analysis of non-hospitalised people with COVID-19.

Since the beginning of the COVID-19 pandemic, researchers have hypothesised that anticoagulants may have a role in preventing thromboembolic events in symptomatic patients with COVID-19 (Cuker 2021; Moores 2020; Spyropoulos 2020). The current guidelines do not recommend initiation of antiplatelet or direct oral anticoagulant therapy in non-hospitalised symptomatic patients with COVID-19, and also do not recommend their continuation after hospital discharge (NIH 2022; Schulman 2022). Ramacciotti 2020 recommended that VTE prophylaxis should be considered after discharge based on risk stratification for thrombotic and haemorrhagic risk for each case. Moreover, patients with an elevated risk of VTE and a low risk of bleeding should be considered for extended prophylaxis (up to 45 days). That recommendation is similar to the Italian Society on Thrombosis and Haemostasis (SISET) guidelines, which state that thromboprophylaxis should be maintained at home for 7 to 14 days postdischarge or in the pre-hospital scenario in the case of pre-existing or persisting VTE risk factors (Marietta 2020). Our certainty of evidence shows that prophylactic anticoagulants probably decrease the risk of VTE in non-hospitalised people with COVID-19 when compared with placebo or no treatment; however, the true effect may be substantially different from the estimated effect.

AUTHORS' CONCLUSIONS

Implications for practice

We found moderate- to low-certainty evidence that prophylactic anticoagulants result in little or no difference in mortality, major bleeding, deep vein thrombosis (DVT), need for hospitalisation, or adverse events (AEs) when compared with placebo or no treatment for non-hospitalised people with COVID-19. Moderate-certainty evidence shows that prophylactic anticoagulants probably reduce the incidence of venous thromboembolism (VTE) and pulmonary embolism (PE) compared with placebo or no treatment.

We found moderate- to low-certainty evidence that there is little or no difference between prophylactic anticoagulants and a different dose of the same anticoagulant in need for hospitalisation or AEs up to 45-day follow-up. Prophylactic anticoagulants may result in little or no difference in VTE, need for hospitalisation, or AEs when compared with antiplatelet agents (low-certainty evidence). These results should be interpreted with caution given that we had only short-term data from one study.

None of the included studies reported quality of life or compared prophylactic anticoagulant use to a different anticoagulant, or anticoagulants versus non-pharmacological interventions. None of the included studies reported on long-term outcomes, which could produce substantial differences in the results.

Implications for research

Although the majority of the studies included in the review are small trials, the topic of our review is important to investigate (Handoll 2015). However, our review has limitations such as high risk of selection, performance, and reporting bias in the included studies and a very small number of less-frequent (rare) events (e.g. VTE, DVT, PE, mortality, and AEs). To increase our confidence in the results, future trials should include the main clinical outcomes (all-cause mortality, VTE, and major bleeding); report the outcomes separately (e.g. with DVT and PE as separate events, not VTE in general or composite scores); and be large enough to detect significant clinical outcomes. Ideally, trials should have long-term follow-up periods (over three years) so the long-term effects of prophylactic anticoagulants can be investigated. This would facilitate reporting on rare outcomes, such as AEs related to anticoagulants. It could also highlight long-term effects on chronic COVID-19 complications because some patients have persistent symptoms that continue or develop after the acute SARS-CoV-2 infection phase (Lee 2021; Shah 2021). Future trials on VTE should include quality of life assessment, especially regarding long COVID, which has a major impact on quality of life.

To limit risk of performance and detection bias, the control groups should use a placebo with the same posology of the intervention. A placebo control is feasible and also improves the methodological quality of the study; we therefore hope, in the future, to include more randomised controlled trials with placebo or other active drug control.

It is of interest to differentiate the effects of anticoagulant agents in younger and older people, and in those with or without comorbidities. The use of previous antiplatelet therapy is a potential confounder and should also be reported. Large, well-reported studies should record and report data to allow these factors to be accounted for.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ananworanich 2021

Study characteristics	
Methods	Prospective, multicentre, 2-armed, parallel-assignment RCT
Participants	**Number of participants**: 497 **Age**: ≥ 18 years **Gender:** female (267 participants) and male (177 participants) **Inclusion criteria**

Ananworanich 2021 *(Continued)*

- Participants must be at high risk for COVID-19 disease progression by fulfilling at least 1 of the following criteria at screening:
  - Presence of chronic pulmonary disease, COPD, pulmonary hypertension
  - DM (type 1 or type 2), requiring oral medication or insulin for treatment
  - Hypertension, requiring at least 1 oral medication for treatment
  - Immunocompromised status due to disease (e.g. those living with HIV with a CD4 T-cell count of < 200/mm^3)
  - Immunocompromised status due to medication (e.g. taking 20 mg or more of prednisone equivalents a day, anti-inflammatory monoclonal antibody therapies, cancer therapies)
  - Any chronic disease that is associated with high risk for severe COVID in the opinion of the site investigator
  - BMI ≥ 35 kg/m^2 (based on self-reported weight and height)
- Documented SARS-CoV-2 positive diagnostic test of ≤ 7 days at the time of screening
- Symptomatic for COVID-19 for ≤ 72 hours at the time of screening (defined as having at least 2 of the following symptoms of COVID-19 that is of new onset or has worsened from baseline: fever, chills, myalgia, arthralgia, headache, fatigue, cough, sore throat, nasal congestion, anosmia, ageusia, nausea, vomiting, or diarrhoea. If only 2 symptoms are present, they cannot both be anosmia and ageusia.)
- Capable of giving informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in the protocol
- Agree to participate in all remote, in-person, or home visits as required in the protocol and provide updated contact information as necessary
- Female of childbearing potential must agree to practise adequate contraception during the study

Exclusion criteria

- Currently hospitalised or under immediate consideration for hospitalisations at screening and Day 1
- Have new-onset shortness of breath or increased shortness of breath from pre-COVID-19 (for people with known COPD) at screening and Day 1
- Hypoxaemia (oxygen saturation < 94% in ambient air or oxygen saturation below pre-COVID-19 level for people with known COPD) at Day 1
- Require supplemental oxygen (new requirement or increase in requirement from pre-COVID-19 condition) at screening and Day 1
- Have a history of (in the past 3 months) or current active pathological bleeding
- Have a history of haemorrhagic stroke or intracranial haemorrhage
- Have a recent severe head trauma within 30 days which includes concussion, skull fracture, or hospitalisation for head injury
- Have known intracranial neoplasm, cerebral metastases, arteriovenous malformation, or aneurysm
- Have history of pregnancy-related haemorrhage
- Have active gastroduodenal ulcer or other GI bleeding diagnosed in the past 3 months
- Currently are in a haemodynamically unstable state
- Currently require thrombolysis or pulmonary embolectomy
- Have history of severe hypersensitivity reaction to rivaroxaban (Xarelto)
- Currently have a prosthetic heart valve
- Have known diagnosis of triple positive antiphospholipid syndrome
- Have known diagnosis of chronic kidney disease (stage IV or receiving dialysis)
- Have a history of thrombocytopenia or known platelet count < 100,000 cells/mm^3
- Have history of bronchiectasis and pulmonary cavitation
- Have active cancer (e.g. receiving chemotherapy or treatment for complication of the active cancer)
- Had epidural or neuraxial anaesthesia or spinal puncture in the past 2 weeks and plan to undergo these procedures during the study
- Had surgery in the past 4 weeks or plan to undergo surgery during the study
- Currently is pregnant or plans to become pregnant
- Currently is breastfeeding
- Share household with an enrolled participant in this study

Ananworanich 2021 *(Continued)*

- Co-enrolment in any clinical trial that includes prohibited procedures (spinal puncture or surgery) or that includes treatments within the same drug class as rivaroxaban or treatments for which co-administration with rivaroxaban are prohibited. Note that any co-enrolment other than this requires approval by the Sponsor. For any co-enrolled study, the total volume of blood samples collected across the studies should not exceed 275 mL in 4 weeks.
- Currently using and plan to use the following medications during the study:
  - Rivaroxaban or drugs in the same class
  - Dual antiplatelets therapy
  - Other anticoagulants
  - Combined P-gp and CYP3A inhibitors and inducers

Interventions	**Intervention**: rivaroxaban (one 10 mg tablet), orally daily for 21 consecutive days **Control**: placebo-equivalent (multivitamin, 1 tablet), orally daily for 21 consecutive days
Outcomes	**Primary outcomes** • Frequency of AE including Grades 3 and 4, resulting in discontinuation through day 35 • Number of participants with AE resulting in study intervention discontinuation through day 35 • Number of participants with serious AE through day 35 • Hypersensitivity and major bleeding events through Day 35 • Proportion of participants who progressed to moderate or severe disease category **Secondary outcomes** • Time to disease resolution • Incidence of hospitalisation • Proportion of participants with disease progression • Proportion of participants with disease resolution
Funding	Bill & Melinda Gates Medical Research Institute
Declaration of interest	EG reports support from AstraZeneca, Genentech, Regeneron, TEVA, and DBV; consulting fees from P&T AscellaHealth; payment/honoraria from TEVA (Digihaler) and Genentech (omalizumab); and serving on Regeneron Pediatric Asthma Advisory Board and ACAAI Patient Advocacy Board. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation is not specified
Allocation concealment (selection bias)	Low risk	Quote: 'Participants were randomised 1:1, stratified by site and symptom duration (< 6 days vs ≥ 6 days), to receive either rivaroxaban (one 10-mg tablet) or placebo equivalent (multivitamin, 1 tablet) orally daily for 21 consecutive days.' Quote: 'Participants received a box delivered to their home that contained the study drug (e.g., either rivaroxaban or placebo), thermometer, pulse oximeter, nasal swab test kit and labels, and personal protective equipment. There were 12 telemedicine visits (days 1, 4, 6, 8, 10, 12, 14, 18, 21, 24, 28, and 35)'

Ananworanich 2021 *(Continued)*

		Comment: information from study article
Blinding of participants and personnel (performance bias)	Low risk	Quote: 'The bottle of medication the participants receive will not identify the treatment allocation. The active or placebo bottles will be labeled for investigational use with a randomized number to maintain blinding.' Quote: 'This randomization strategy can easily be generalized beyond 3 contemporaneously available interventions and will ensure approximately equal randomization of each intervention to control, while helping to maintain blinding and minimize possible bias.' Comment: from supplementary data of the study report.
Blinding of outcome assessment (detection bias)	Low risk	Quote: 'Independent data monitoring committee will be convened for this study with expertise in COVID-19 or respiratory viruses and emerging epidemics as well as biostatistics'. Comment: data from supplementary data of the study report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: 'Between 16 August 2020 and 3 February 2021, 538 adults were screened and 497 were enrolled (246 in rivaroxaban and 251 in placebo). The numbers of participants in each analysis population were similar between treatment groups. Sixty-four participants discontinued the study and 89 discontinued the study drug (similar between groups).' Comment: information from study article
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported as prespecified
Other bias	Low risk	We did not find other bias in the study.

Barco 2022

Study characteristics	
Methods	Prospective, 2-armed, open-label, parallel-group, multicentre RCT
Participants	**Number of participants:** 472 **Age:** ≥ 50 years **Gender**: male (255 participants) and female (217 participants) **Inclusion criteria** • Patients aged 50 years or older with a positive test for SARS-CoV-2 in the past 5 days and eligible for ambulatory treatment • Presence of respiratory symptoms (i.e. cough, sore throat, or shortness of breath) or body temperature > 37.5 °C. • Ability of the patient to travel to the study centre by private transportation, performed either by accompanying person from same household or by the patient him/herself • Ability to comply with standard hygiene requirements at the time of in-hospital visit, including a face mask and hand disinfectant • Ability to walk from car to study centre or reach it using a wheelchair transport with the help of an accompanying person from the same household also complying with standard hygiene requirements

Barco 2022 *(Continued)*

- Ability to self-administer prefilled enoxaparin injections after instructions received at the study centre, or availability of a person living with the patient to administer enoxaparin

Exclusion criteria

- Any acute or chronic condition posing an indication for anticoagulant treatment, e.g. atrial fibrillation, prior VTE, acute confirmed symptomatic VTE, acute coronary syndrome
- Anticoagulant thromboprophylaxis deemed necessary in view of the patient's history, comorbidity, or predisposing strong risk factors for thrombosis:
  - Any of the following events occurring in the prior 30 days: fracture of lower limb, hospitalisation for heart failure, hip/knee replacement, major trauma, spinal cord injury, stroke
  - Previous VTE
  - Histologically confirmed malignancy that was diagnosed or treated (surgery, chemotherapy, radiotherapy) in the past 6 months, or is recurrent, metastatic, or inoperable
- Any clinically relevant bleeding (defined as bleeding requiring hospitalisation, transfusion, surgical intervention, invasive procedures, occurring in a critical anatomical site, or causing disability) within 30 days prior to randomisation or sign of acute bleeding
- Intracerebral bleeding at any time in the past or signs/symptoms consistent with acute intracranial haemorrhage
- Haemoglobin < 8 g/dL and platelet count < 50 x 10^9 cells/L confirmed by recent laboratory test (< 90 days)
- Patients with any known coagulopathy or bleeding diathesis, including known significant liver disease associated with coagulopathy
- Severe renal insufficiency (baseline creatinine clearance < 30 mL/min calculated using the Cockcroft-Gault formula) confirmed by recent laboratory test (< 90 days)
- Contraindications to enoxaparin therapy, including prior heparin-induced thrombocytopenia and known hypersensitivity
- Current use of dual antiplatelet therapy
- Participation in other interventional studies over the past 30 days
- Non-compliance or inability to adhere to treatment or lack of a family environment or support system for home treatment

Interventions	**Intervention**: enoxaparin 40 mg/0.4mL syringe daily sc for 14 days **Control**: standard of care (no thromboprophylaxis)
Outcomes	**Planned and reported primary outcomes** • Hospitalisations (time frame: 30 days) • All-cause death (time frame: 30 days) **Planned and reported secondary outcomes** • Number of cardiovascular events (time frame: within 14 days, 30 days, and 90 days of randomisation) including DVT (including catheter-associated), PE, myocardial infarction/myocarditis, arterial ischaemia including mesenteric and extremities, acute splanchnic vein thrombosis, or ischaemic stroke • Any hospitalisations (time frame: within 14 days, 30 days, and 90 days of randomisation) • All-cause death (time frame: within 14 days, 30 days, and 90 days of randomisation) • Net clinical benefit (time frame: within 14 days, 30 days, and 90 days of randomisation) measured by number of cardiovascular events, and major bleeding • Disseminated intravascular coagulation (time frame: within 14 days, 30 days, and 90 days of randomisation) ISTH criteria, in-hospital diagnosis
Funding	National Research Programme COVID-19, University Hospital Zurich, University of Zurich, Dr-Ing Georg Pollert, Johanna Dürmüller-Bol Foundation
Declaration of interest	SB reports institutional research grants from Concept Medical, Bard, Bentley, Boston Scientific, INARI, Sanofi, and Bayer; and personal fees from Concept Medical, Bayer, Boston Scientific, and INARI. BG re-

Barco 2022 *(Continued)*

	ports non-financial support and funding for an accredited continuing medical education programme from Axonlab and Thermo Fisher Scientific; personal fees and funding for an accredited continuing medical education programme from Alnylam, Pfizer, and Sanofi; funding for an accredited continuing medical education programme from Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Takeda, Octapharma, SOBI, Janssen, Novo Nordisk, Mitsubishi Pfizer, Tanabe Pharma, outside the submitted work. SVK reports grants or contracts from Bayer AG; consulting fees from Bayer, Daiichi-Sankyo, and Boston Scientific; and payment or honoraria from Bayer, INARI Medical, MSD, Pfizer, and Bristol Myers Squibb. SS reports research grants from Edwards Lifesciences to the institution, research grants from Medtronic to the institution, research grants from Boston Scientific to the institution, research grants from Abbott to the institution, personal fees from Boston Scientific, Teleflex, BTG -Boston Scientific outside the submitted work. HRE reports speaker honoraria from Daiichi-Sankyo and Bayer. DS reports employment by Sanofi-Aventis Switzerland. DD reports research support from German Research Foundation, CytoSorbents, Haemonetic; consulting and speaker's fees from Bayer Healthcare, Daiichi-Sankyo, LEO Pharma, AstraZeneca, Boston Scientific, and BMS-Pfizer. NK reports institutional research grants from Concept Medical, Bard, Bentley, Boston Scientific, INARI, Sanofi, and Bayer; and personal fees from Concept Medical, Bayer, Boston Scientific, and INARI
Notes	Quote: "The funder of the study had no role in study design, data collection, management, data analysis, data interpretation, or writing of the report." Comment: information from study article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation sequence was computer-generated and integrated into the electronic data capture software RedCAP (Vanderbild University, version 9.1.24)." Comment: information from the study article
Allocation concealment (selection bias)	Low risk	Quote: "Eligible participants underwent block-stratified randomisation (by age group 50 – 70 vs > 70 years and by study centre) in a 1:1 ratio to receive either enoxaparin or standard of care (no thromboprophylaxis). " Quote: ''Participants and study personnel were aware of treatment allocation, but not of the allocation sequence." Comment: information from the study article
Blinding of participants and personnel (performance bias)	High risk	Quote: 'Participants and study personnel were aware of treatment allocation, but not of the allocation sequence.' Comment: information from the study article
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: 'An independent data and safety monitoring board (DSMB) composed of a vascular medicine specialist, a respiratory physician, and a clinical biostatistician monitored the trial.' Quote: 'At the beginning of the study, the sponsor planned independent monitoring of the trial in collaboration with the deputed division of the Clinical Trial Centre of the University Hospital Zurich. Monitoring was done remotely during the lockdown periods, or by visiting study sites thereafter, and consisted of a site initiation visit followed by regular visits based on the number of patients enrolled.' Comment: information from the study article
Incomplete outcome data (attrition bias)	Low risk	Between Aug 15, 2020 and Jan, 14, 2022, from 3319 participants prescreened, 475 with acute symptomatic COVID-19 scheduled for an ambulatory treatment

Barco 2022 *(Continued)*

All outcomes		were enrolled in the trial and randomly assigned to receive prophylactic-dose enoxaparin versus standard of care (no anticoagulation). Quote: 'The final intention-to-treat population consisted of 472 patients: 234 received enoxaparin and 238 no thromboprophylaxis.' Comment: information from the study article
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported as prespecified
Other bias	Low risk	We did not find other bias in the study.

Connors 2021

Study characteristics	
Methods	Prospective, multicentre, double-blind, placebo-controlled RCT
Participants	**Number of participants:** 657 **Age**: between 40 and 80 years **Gender:** female (388 participants) and male (269 participants) **Inclusion criteria** • Ambulatory patients • COVID-19 positive in past 14 days • Platelets > 100,000/mm^3 • eGFR > 30 mL/min **Exclusion criteria** • Hospitalised • Contraindication/other indication for anticoagulation • Pregnancy • Active cancer
Interventions	**Intervention 1**: apixaban 2.5 mg orally twice a day for 45 days **Intervention 2**: apixaban 5.0 mg orally twice a day for 45 days **Intervention 3**: aspirin 81 mg orally twice a day for 45 days **Control**: placebo orally twice a day for 45 days
Outcomes	**Planned primary outcome** • Need for hospitalisation for cardiovascular/pulmonary events: composite endpoint of need for hospitalisation for cardiovascular/pulmonary events, symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, ischaemic stroke, and all-cause mortality for up to 45 days after initiation of assigned treatment **Reported primary outcomes** • Composite of symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, ischaemic stroke, hospitalisation for cardiovascular or pulmonary events, and all-cause mortality for up to 45 days after treatment initiation **Secondary outcomes**

Connors 2021 *(Continued)*

- Individual components of the primary study endpoint
- Mortality without antecedent hospitalisation
- Major bleeding
- Clinically relevant non-major bleeding as defined by ISTH

Funding	Funded in part by NIH Agreement 1OT2HL156812-01. Specifically, the ACTIV-4B trial was supported by Other Transition Authorities from the NHLBI. Grantee institutions included the University of Pittsburgh; the University of Illinois Chicago; and the Brigham and Women's Hospital. The trial drugs and matching placebo were donated by the Bristol Myers Squibb-Pfizer Alliance.
Declaration of interest	Dr Connors reported receiving personal fees from Bristol Myers Squibb, Pfizer, Abbott, Alnylam, Takeda, Roche, and Sanofi, and that his institution has received research funding from CSL Behring. Dr Brooks reported receiving personal fees for data and safety monitoring board membership from Cerus Corporation. Dr Krishnan reported receiving grants from Sergey Brin Family Foundation Research in COVID. Dr Bledsoe reported receiving grants payable to his institution from the NIH for clinical trial work and receiving consulting fees from JAJ LLC. Dr Kirwan reported receiving grants from SOCAR Research SA. Dr Everett reported receiving consulting fees from Johnson & Johnson, Gilead, and Merck. Dr Hou reported receiving grants from Brigham and Women's Hospital, NIH, Novartis, and CalciMedica. Dr Haight reported receiving grants and non-financial support from OneFlorida. Dr Wilson reported receiving personal fees from Pfizer, Bristol Myers Squibb, Alexion, Janssen, and Paratek and receiving grants from Gilead. Dr Ridker reported receiving grants from Bristol Myers Squibb and Pfizer and serving as a consultant for work unrelated to this study for Corvidia, Novartis, Flame, Agepha, Inflazome, AstraZeneca, Janssen, Civi Biopharm, SOCAR, Novo Nordisk, Uptton, Omeicos, and Boehringer Ingelheim. No other authors reported disclosures.
Notes	Quote: "The trial drugs and matching placebo were donated by the Bristol Myers Squibb-Pfizer Alliance." Quote: "The National Heart, Lung, and Blood Institute had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication." Comment: information from the study article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'Randomisation code lists were computer generated using permuted blocks with block size equal to 4 during the process of drug labelling and then implemented electronically through the central electronic data-capture system.' Comment: information from the study article.
Allocation concealment (selection bias)	Low risk	Quote: 'Participants were randomised centrally in a 1:1:1:1 ratio to receive aspirin (81 mg once daily) with matching placebo, prophylactic-dose apixaban (2.5 mg twice daily), apixaban at therapeutic dose (5 mg twice daily), or placebo twice daily.' Quote: 'After randomisation, drug was shipped directly to the participant's home with subsequent follow-up conducted by the RCC central study staff.' Comment: information from the study article.
Blinding of participants and personnel (performance bias)	Low risk	Quote: 'To try to ensure consistency across sites in the setting of an outpatient COVID-19 trial, all post-randomisation participant contact was conducted by weekly electronic links to REDCap surveys or by the Research Communication Center (RCC) at the University of Illinois Chicago with live telephone calls by call centre agents and research pharmacists in Chicago and Pittsburgh. Direct

Connors 2021 *(Continued)*

		shipment of study drug to participants homes, end point and safety adjudication, and 24-hour emergency and unblinding services were provided by investigators at the Brigham and Women's Hospital in Boston.' Comment: information from the study article.
Blinding of outcome assessment (detection bias)	Low risk	Quote: 'Medical records were sent to the Clinical Endpoints Committee, who adjudicated events using standardized criteria. Both the medical monitors and the end points committee were unaware of randomised drug assignment.' Comment: information from the study article.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers of participants in each analysis population were similar between treatment groups. Also, the dropouts were reported and also similar between groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported as-prespecified.
Other bias	Low risk	We did not find other bias in the study.

Cools 2022

Study characteristics	
Methods	Prospective, open-label, multicentre, multinational RCT

Participants	**Number of participants**: 219
	
	Age: ≥ 50 years
	
	Gender: male (122 participants) and female (97 participants)
	
	Planned inclusion criteria
	
	• Signed informed consent
	• Confirmed COVID-19 (i.e. symptoms and positive test for SARS-CoV-2)
	• Male or female, age ≥ 55 years
	• At least 2 of the following additional risk factors:
	  ○ Age ≥ 70 years
	  ○ BMI > 25 kg/m^2
	  ○ COPD
	  ○ DM
	  ○ Cardiovascular disease
	  ○ Corticosteroid use
	
	Exclusion criteria
	
	• Contraindications to UFH or LMWH
	• Recent (< 48 hours) or planned spinal or epidural anaesthesia or puncture, PCI, or thrombolytic therapy within the preceding 24 hours
	• Increased risk for bleeding complications
	• Pregnant women
	• Severe renal impairment (GFR < 30 mL/min)
	• Receiving any antiplatelet therapy (except for low-dose (≤ 100 mg) aspirin) or anticoagulant therapy (e.g. VKA, DOAC)

Cools 2022 *(Continued)*

- Patients participating in an interventional study that is outside the purview of TRI sponsored studies

Reported inclusion criteria

- Confirmed COVID-19 (symptoms + positive test for SARS-CoV-2)
- Male or female, age ≥ 30 years
- Allow current clopidogrel (≤ 75 mg) monotherapy
- At least 1 of the following additional risk factors:
  - Age ≥ 70 years
  - BMI ≥ 25 kg/m^2
  - Chronic lung disease (chronic obstructive lung disease, chronic bronchitis, chronic obstructive asthma, interstitial lung disease)
  - DM
  - Cardiovascular disease (coronary artery disease, PAD, heart valve disease, treated arrhythmia, heart failure, hypertension, congenital heart disease, prior stroke or transient ischaemic attack, carotid artery disease)
  - Previous VTE (DVT or PE)
  - Liver disease (alcoholic cirrhosis, non-alcoholic cirrhosis, chronic non-alcoholic liver disease, chronic hepatitis C, chronic hepatitis B, cryptogenic cirrhosis)
  - Immunocompromised state (due to blood or bone marrow transplant, immunodeficiencies, HIV infection, systemic corticosteroid use or other medication that weakens the immune system (e.g. active cancer treatment))
  - Anaemia of chronic disease or sickle cell disease

Interventions	**Intervention**: enoxaparin 40 mg once daily sc if weight < 100 kg and 40 mg twice daily if weight ≥ 100 kg for 21 days **Control**: current standard of care (without enoxaparin)

Outcomes	**Planned primary outcomes**
	• Hospital admission (time frame: 21 days, 50 days, and 90 days), including the following:
	  ○ Pneumonia
	  ○ Acute respiratory distress syndrome
	  ○ Admission to ICU
	  ○ Mechanical ventilation/intubation requirement
	  ○ Continuous positive airway pressure
	  ○ Non-invasive ventilation
	  ○ Extracorporeal membrane oxygenation
	• Death (time frame: 21 days, 50 days, and 90 days)
	  ○ All-cause
	  ○ Cardiovascular
	  ○ Non-cardiovascular
	  ○ Specific causes
	  ○ Fatal bleed
	Secondary outcomes
	• Bleeding as defined by ISTH criteria (time frame: 21 and 50 days)
	  ○ Frequency
	  ○ Location
	  ○ Treatment (transfusion and units of blood products transfused)
	  ○ Severity (classified as major, clinically relevant non-major and minor)
	• Diagnosis of VTE (time frame: 21 days, 50 days, and 90 days)
	  ○ DVT or PE
	Reported primary outcomes

Cools 2022 *(Continued)*

- Composite of all-cause death and all-cause admission to hospital (hospitalisation) at 21 days after randomisation (with further assessments at days 50 and 90)

Secondary outcomes

- Diagnosis of VTE at days 21, 50, and 90
- Bleeding events at days 21 and 50
- Bleeding events at day 90 was added as a post hoc outcome

Funding	The Thrombosis Research Institute and Sanofi UK
Declaration of interest	FC reports speaker fees from Boehringer Ingelheim Pharma, Bayer, Pfizer, and Daiichi-Sankyo Europe, and a modest research grant from Daiichi-Sankyo Europe. JS reports personal fees from Pfizer, AstraZeneca, Novartis, Sanofi, BMS, Dr Reddy's Laboratory, Lupin, and Abbott. RDL reports research grants from Bristol Myers Squibb, Pfizer, Amgen, GlaxoSmithKline, Medtronic, and Sanofi Aventis, and personal fees from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Bayer, outside the submitted work. BJ reports personal fees from Bayer Healthcare and Sanofi-Aventis. JIA reports speaker fees from Sanofi, Rovi, Bayer, and Aspen. FDRH acknowledges part support as Director of the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Oxford Thames Valley and Theme Lead of the NIHR Oxford University Hospital Biomedical Research Centre, and has also received occasional fees or expenses for speaking or consultancy from AstraZeneca, Boehringer Ingelheim, Bayer, BMS/Pfizer, and Novartis. HG reports personal fees from Pfizer, Bayer, and Boehringer Ingelheim. PM reports honoraria from Bayer Pharma and Portolo. SS reports speaker fees from Bayer Pharma, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Sanofi Aventis, and Pfizer, and consultancy fees from Bayer Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Sanofi Aventis, Aspen, and Pfizer. SH reports personal fees from Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Portola, and Sanofi, outside the submitted work. AGGT reports grants from Bayer Healthcare and personal fees from Bayer Healthcare, Bristol Myers Squibb/Pfizer, Daiichi-Sankyo, and Boehringer Ingelheim, outside the submitted work. WA reports honoraria from Bayer Pharma, Bristol Myers Squibb, Pfizer, Daiichi-Sankyo, Portola, Aspen, Sanofi, Leo Pharma, Norgine, and Werfen. ATR reports consultancy fees from Bayer Pharma, Daiichi-Sankyo, Sanofi, Aspen, and Pfizer. KP reports a consultancy fee from Johnson & Johnson. AKK reports research grants from Anthos, Bayer, and Sanofi and personal fees from Anthos Therapeutics, Bayer, and Sanofi. All other authors declare no competing interests.
Notes	Quote: "Sanofi funded this investigator-sponsored study and provided enoxaparin free of charge. The Thrombosis Research Institute had input in study design, data collection, data analysis, data interpretation, and writing of the report." Comment: information from the study article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'The randomisation sequence was established before enrolment of the first patient and was done by use of a prespecified, secure, central, web-based randomisation system.' Quote: 'Randomisation was generated with a random block design (block size either 2 or 4), blocking within each site to allow equal allocation of the two treatments within each site.' Comment: information from the study article.
Allocation concealment (selection bias)	High risk	Quote: 'The study was unblinded and therefore no allocation concealment was applied.' Comment: information from the study article.

Cools 2022 *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	Quote: 'The study was unblinded and therefore no allocation concealment was applied.' Comment: information from the study article.
Blinding of outcome assessment (detection bias)	Low risk	Quote: 'The Clinical Events Committee were responsible for systematically adjudicating death, hospitalisation, and the classification of bleeding in a blinded way to the treatment assignment according to predefined clinical outcome definitions.' Comment: information from the study article.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: 'Of 230 patients with COVID-19 assessed for eligibility, 219 were randomly assigned to receive either standard of care (114 (52%) - 109 (95%)) included in per-protocol analysis) or enoxaparin (105 (48%)) - 89 (85%) included in per-protocol analysis). At 21 days, in the intention-to-treat analysis, the composite of all-cause mortality and all-cause hospitalisation was observed in 12 (11%) of 105 patients in the enoxaparin group and in 12 (11%) of 114 patients in the standard-of-care group (unadjusted hazard ratio 1.09 [95% CI 0·49 – 2·43); log-rank P = 0·83; figure 2; table 2)''. Comment: information from the study article.
Selective reporting (reporting bias)	High risk	Quote: 'Due to the very low number of events and the study's early termination, only the primary efficacy outcome was tested for statistical significance. Median follow-up for the primary efficacy outcome was 21 days (IQR 21–21) for both groups.' Quote: 'Adjustments to the inclusion criteria were made during the course of the study.' Comment: information from the study article.
Other bias	Low risk	We did not find other bias in the study.

Ramacciotti 2022

Study characteristics	
Methods	Prospective, open-label, multicentre RCT
Participants	**Number of participants**: 320 **Age**: between 18 and 90 years old **Gender**: male (191 participants) and female (127 participants) **Inclusion criteria** • Male and non-pregnant female patients 18 years of age or older • Positive RT-PCR assay for SARS-CoV-2 in a respiratory tract sample • Pneumonia confirmed by chest imaging • Additional risk factors for VTE, as indicated by a total modified IMPROVE risk score of 4 or higher • Have received thromboprophylaxis with LMWH, fondaparinux, or UFH during the index hospitalisation **Exclusion criteria**

Ramacciotti 2022 *(Continued)*

- Age < 18 years
- Refusal of informed consent
- Physician decision that involvement in the trial was not in the patient's best interest
- Patients with a medical indication for anticoagulation therapy at the time of inclusion (e.g. diagnosis of VTE, atrial fibrillation, mechanical valve prosthesis)
- Platelets < 50,000/mm^3
- Patients with contraindications to anticoagulation (active bleeding, liver failure, blood dyscrasia, or prohibitive haemorrhagic risk in the investigator's assessment)
- 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
- Use of strong inhibitors of CYP3A4 and/or P-gp (e.g. protease inhibitors, ketoconazole, itraconazole) and/or use of P-gp and strong inducers of CYP3A4 (e.g. rifampicin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's wort)
- Creatinine clearance < 30 mL/min
- Pregnancy or breastfeeding
- Known HIV infection
- Presence of 1 of the following uncontrolled or unstable cardiovascular diseases: stroke, ECG-confirmed acute ischaemia or myocardial infarction, and/or clinically significant dysrhythmia

Interventions	**Intervention**: rivaroxaban 10 mg once daily for 35 days post-hospital discharge **Control**: no intervention
Outcomes	**Planned and reported** **Primary outcomes**: • VTE and VTE-related death (time frame: at day 35 post-hospital discharge) **Secondary outcomes**: • Major bleeding (time frame: at day 35 post-hospital discharge) **Other outcomes**: • A composite of myocardial infarction, stroke, arrhythmias, heart failure, VTE, and all-cause death (time frame: at day 35 post-hospital discharge) • Days alive out of the hospital at 35 days (time frame: at day 35 post-hospital discharge • D-dimer (time frame: at day 35 post-hospital discharge) • C-reactive protein (time frame: at day 35 post-hospital discharge)
Funding	Bayer
Declaration of interest	ER reports grants and consulting fees from Bayer and Pfizer; grants from the Brazilian Ministry of Science and Technology; and personal fees from Aspen Pharma, Biomm Pharma, and Daiichi-Sankyo, outside of the submitted work. LBA reports grants from Bayer, Pfizer, and the Brazilian Ministry of Science and Technology. DC reports personal fees from Bayer, Janssen, Daiichi-Sankyo, and Pfizer; and grants from Stago. ACS reports consulting fees from Janssen Research & Development, Bayer, Portola, Boehringer Ingelheim, Bristol Myers Squibb, and ATLAS group; and grants from Janssen and Boehringer Ingelheim. MLS reports personal fees from Bayer, Pfizer, and Sanofi. EEJ reports consulting and personal fees form Bayer. CD reports consulting and personal fees from Bayer, Novartis, and Daiichi-Sankyo. SMVS reports personal fees from Bayer. RCC reports personal fees from Boehringer Ingelheim and AstraZeneca. ATaf reports personal fees from Janssen and Recovery Force and grants from Bio Tap, Idorsia, Bristol Myers Squibb, Novo Nordisk, Janssen, and Doasense. RDL reports grants and personal fees from Bristol Myers Squibb, Pfizer, GlaxoSmithKline, Medtronic PLC, and Sanofi; and personal fees from Amgen, Bayer, and Boehringer Ingelheim, outside of the submitted work. All other authors declare no competing interests.

Ramacciotti 2022 *(Continued)*

Notes	Quote: "The study funder had no role in the planning and design of the study, data collection, analysis, and interpretation, nor writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'Randomisation was done in permuted blocks of variable size, using a central, concealed, web-based, automated randomisation system (RedCap, version 11.0.3).' Comment: information from the study article.
Allocation concealment (selection bias)	Low risk	Quote: 'Patients were randomly allocated in a 1:1 ratio to receive either thromboprophylaxis with rivaroxaban 10 mg/day or regular follow-up (no anticoagulation) for 35 days.' Quote: 'Randomisation was done in permuted blocks of variable size, using a central, concealed, web-based, automated randomisation system (RedCap, version 11.0.3).' Comment: information from the study article.
Blinding of participants and personnel (performance bias)	High risk	Quote: 'The MICHELLE trial was an open-label study, with no masking of investigators or patients to group allocation.' Comment: information from the study article.
Blinding of outcome assessment (detection bias)	Low risk	Quote: 'An independent clinical events classification committee, whose members were unaware of the study treatment assignment, adjudicated all venous and arterial thromboembolic and bleeding events, and causes of death. ' Comment: information from the study article.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote 'From Oct 8, 2020, to June 29, 2021, 997 patients were screened. Of these patients, 677 did not meet eligibility criteria; the remaining 320 patients were enrolled and randomly assigned to receive rivaroxaban (n = 160 (50%)) or no anticoagulation (n = 160 (50%). Thus, 159 patients per group were included in the intention-to-treat analysis.'
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	We did not find other bias in the study.

AE: adverse events
BMI: body mass index
CD4: cluster of differentiation 4
COPD: chronic obstructive pulmonary disease
COVID-19: coronavirus disease 2019
CYP3A: cytochrome P450 3A
DOAC: direct oral anticoagulant
DM: diabetes mellitus
DVT: deep vein thrombosis
ECG: electrocardiogram
eGFR: estimated glomerular filtration rate
GI: gastrointestinal
GFR: glomerular filtration rate

ICU: intensive care unit
IMPROVE: International Medical Prevention Registry on Venous Thromboembolism
ISTH: International Society on Thrombosis and Haemostasis
LMWH: low-molecular-weight heparin
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institutes of Health
PAD: peripheral artery disease
PCI: percutaneous coronary intervention
PE: pulmonary embolism
P-gp: permeability glycoprotein
RCT: randomised controlled trial
RT-PCR: reverse transcription polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
sc: subcutaneously
TRI: Translational Research Institute
UFH: unfractionated heparin
VKA: vitamin K antagonist
VTE: venous thromboembolism

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

Study	Reason for exclusion
Aghamohammadi 2020	Ineligible study design: case report
Borghi 2021	Ineligible study design: case report
ChiCTR2000034796	Ineligible study design: non-RCT and observational study
JPRN-UMIN000042489	Ineligible study design: non-RCT
Kuno 2022	Ineligible study design: non-RCT and observational study
Lisker 2021	Ineligible study design: non-RCT
Rivera-Caravaca 2021	Ineligible study design: non-RCT
Sharma 2021	Ineligible study design: hospitalised patients
Spyropoulos 2021	Ineligible study design: hospitalised patients
Vergori 2021	Ineligible study design: non-RCT and hospitalised patients

RCT: randomised controlled trial

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

Capell 2021

Study name	A study of rivaroxaban to reduce the risk of major venous and arterial thrombotic events, hospitalisation and death in medically ill outpatients with acute, symptomatic coronavirus disease 2019 (COVID-19) infection (PREVENT-HD)
Methods	Double-blind, placebo-controlled, pragmatic, event-driven RCT
Participants	**Number of participants**: 4000 **Age:** ≥ 18 years

Capell 2021 *(Continued)*

Gender: male or female

Inclusion criteria

- COVID-19 positive diagnosis by locally obtained viral diagnostic test (e.g. PCR). This may be nasal swab or saliva test or other available technology to demonstrate current infection. (Note: this is not an antibody test or serology test that just indicates prior exposure to the disease. In the case of multiple positive COVID-19 PCR tests, only the date of the first test may be used.)
- Confirm that participant is known to health system, with at least 1 contact in EMR prior to screening
- Symptoms attributable to COVID-19 (e.g. fever, cough, loss of taste or smell, muscle aches, shortness of breath, fatigue)
- Initial treatment plan does not include hospitalisation
- Presence of at least 1 additional risk factor:
  - Age ≥ 60 years
  - Prior history of VTE
  - History of thrombophilia
  - History of CAD
  - History of PAD
  - History of cerebrovascular disease or ischaemic stroke
  - History of cancer (other than basal cell carcinoma)
  - History of diabetes requiring medication
  - History of heart failure
  - BMI ≥ 35 kg/m^2
  - D-dimer > ULN for local laboratory (within 2 weeks of the date of the COVID-19 test and prior to randomisation)
- Must provide consent via eConsent indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study, including follow-up
- Willing and able to adhere to the lifestyle restrictions specified in the protocol

Exclusion criteria

- Increased risk of bleeding, such as i) significant bleeding in the last 3 months, ii) active gastroduodenal ulcer in the last 3 months, iii) history of bronchiectasis or pulmonary cavitation, iv) need for dual antiplatelet therapy or anticoagulation, v) prior intracranial haemorrhage, vi) known severe thrombocytopenia (platelet count < 50 × 10^9/L), or vii) active cancer and undergoing treatment
- Any illness or condition that in the opinion of the investigator would significantly increase the risk of bleeding (e.g. recent trauma, recent surgery, severe uncontrolled hypertension, gastrointestinal cancer, renal failure requiring dialysis, severe liver disease, known bleeding diathesis)
- Known allergies, hypersensitivity, or intolerance to rivaroxaban or its excipients
- Positive COVID-19 antibody or serology test after 2-week period of acute, symptomatic COVID-19 infection
- Known diagnosis of triple positive (i.e. positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies) antiphospholipid syndrome
- Recently taken, or required to take, any disallowed therapies as noted in the protocol (Disallowed Concomitant Therapy) before the planned first dose of study intervention or required during the study (e.g. need for the use of strong CYP 3A4 inhibitor or inducer per local prescribing information)
- Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study intervention or is currently enrolled in an experimental, investigational study. (Note: participation in an observational registry is allowed.)
- Women who are pregnant or breastfeeding, and women of childbearing potential without proper contraceptive measures

Interventions	**Intervention:** rivaroxaban 10 mg once daily for 35 days

Capell 2021 *(Continued)*

	Control: placebo once daily for 35 days
Outcomes	**Primary outcomes** • Time to first occurrence of a composite endpoint of symptomatic VTE, MI, ischaemic stroke, acute limb ischaemia, non-CNS systemic embolisation, all-cause hospitalisation, and all-cause mortality up to day 35 **Secondary outcomes** • Time to first occurrence of a composite endpoint of symptomatic VTE, MI, ischaemic stroke, acute limb ischaemia, non-CNS systemic embolisation, and all-cause mortality up to day 35 • Time to first occurrence of all-cause hospitalisation up to day 35 • Time to first occurrence of symptomatic VTE up to day 35 • Time to first occurrence of an ER visit up to day 35 • Time to first occurrence of symptomatic VTE, MI, ischaemic stroke, acute limb ischaemia, non-CNS systemic embolisation, and all-cause hospitalisation up to day 35 • Incidence of participants who are hospitalised or dead from any cause on day 35 • Time to all-cause mortality up to day 35
Starting date	13 August 2020
Contact information	warren.capell@cuanschutz.edu
Notes	

EUCTR2020-005884-29-IT

Study name	Role of heparin in the prevention of thromboembolism in patients with COVID-19 and respiratory failure
Methods	Prospective, multicentre, 2-armed, parallel-assignment RCT
Participants	**Number of participants**: 652 **Age:** ≥ 18 years **Gender:** female and male **Inclusion criteria** • Confirmed or suspected COVID-19 infection • Endotracheal tube in place • Intubated yesterday or today • PaO_2 to FIO_2 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 thrombocytopenia • aPTT > 120 s and not due to anticoagulant therapy • Platelet count < 20 x 10^9/L • Pulmonary bleeding • Uncontrolled bleeding • Obvious or suspected pregnancy

EUCTR2020-005884-29-IT *(Continued)*

	• 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-Barré syndrome) • Usually receives home oxygen • Dependent on others for personal care due to physical or cognitive decline • Death is imminent or inevitable within 24 h • The clinical team would not be able to set up the study nebuliser and ventilator circuit as required including with active humidification • Clinician objection
Interventions	**Intervention:** parnaparin, dalteparin, nadroparin, bemiparin, reviparin, or enoxaparin **Control:** standard LMWH prophylaxis
Outcomes	**Primary outcomes** • To assess whether intermediate-dose LMWH is more effective than standard LMWH prophylaxis in reducing the composite of all-cause death or invasive mechanical ventilation or venous thromboembolic events. Time point of evaluation of this endpoint: 28 days • To assess whether intermediate-dose LMWH is more effective than standard LMWH prophylaxis in reducing venous thromboembolic events • To assess the safety of intermediate-dose LMWH in comparison to standard LMWH prophylaxis in incidence of major or clinically relevant non-major bleedings **Secondary outcomes** • Confirmed VTE within 28 days from randomisation • Major or clinically relevant non-major bleedings within 28 days from randomisation • Confirmed VTE or persistent respiratory failure with need for oxygen therapy at 3 months from randomisation
Starting date	28 April 2021
Contact information	mariacristina.vedovati@unipg.it
Notes	

NCT04542408

Study name	Hamburg edoxaban for anticoagulation in COVID-19 study (HERO-19)
Methods	Prospective, double-blind RCT
Participants	**Number of participants:** 172 **Age:** ≥ 18 years **Gender:** male and female **Inclusion criteria** • Diagnosis of COVID-19 and hospitalisation on ICU • Diagnosis of COVID-19 and hospitalisation on normal ward • Diagnosis of COVID-19 (within 10 days) and troponin ≥ ULN and/or D-dimer ≥ 0.5 mg/L **Exclusion criteria**

NCT04542408 *(Continued)*

	• Age below 18 • Life expectancy less than 3 months before COVID-19 • Resuscitation > 30 minutes • Hypersensitivity to the active substance, to edoxaban or any of its excipients • Significantly increased bleeding risk • Other indication for anticoagulation beyond COVID-19 • GFR < 15 mL/min • Planned transfer of the patient to another clinic within the next 42 days
Interventions	**Intervention:** therapeutic anticoagulation using LMWH body weight-adapted during course of hospital stay and oral anticoagulation using edoxaban according to summary of product characteristics (60 mg once a day) after being discharged from hospital/outpatient course **Control:** prophylactic anticoagulation using LMWH as part of standard of care while inpatient course, and placebo after discharge/outpatient course
Outcomes	**Primary outcomes** • Combined endpoint: all-cause mortality and/or venous thromboembolism and/or arterial thromboembolism (time frame: 42 days) **Secondary outcomes** • All-cause mortality (time frame: 42 days) • Mortality related to VTE (time frame: 42 days) • Mortality related to arterial thromboembolism (time frame: 42 days) • Rate of venous and/or arterial thromboembolism (time frame: 42 days) • Rate and length of mechanical ventilation (time frame: 42 days) • Length of initial stay at ICU after application of IMP (time frame: 42 days) • Rehospitalisation (time frame: 42 days) • Rate and length of renal replacement therapy (time frame: 42 days) • Cardiac arrest/cardiopulmonary resuscitation (time frame: 42 days)
Starting date	12 November 2020
Contact information	s.kluge@uke.de m.karakas@uke.de
Notes	

NCT04650087

Study name	COVID-19 thrombosis prevention trials: post-hospital thromboprophylaxis
Methods	Prospective, double-blind RCT
Participants	**Number of participants:** 1223 **Age:** ≥ 18 years **Gender:** male or female **Inclusion criteria** • PCR-positive COVID-19 infection • Hospitalised for 2 or more days

NCT04650087 *(Continued)*

	Exclusion criteria • Pre-existing indication for anticoagulation (e.g. PE or DVT; atrial fibrillation; mechanical cardiac valve) • Contraindication to antithrombotic therapy (e.g. known bleeding within the last 30 days requiring emergency room presentation or hospitalisation; major surgery within 14 days; ischaemic stroke, intracranial bleed, or neurosurgery within 3 months) • Platelet count < 50,000/μL • Haemoglobin < 8 g/dL • Renal insufficiency (GFR < 30 mL/min/1.73 m^2) • Pregnancy • Prison inmate • Life expectancy less than 90 days • Unwilling or unable to provide informed consent/unwilling or unable to complete the study protocol • Dual antiplatelet therapy that cannot be discontinued • Concomitant need for strong inducers/inhibitors of P-gp or CYP3A4
Interventions	**Intervention:** apixaban 2.5 mg twice a day, once in the morning and once in the evening for 30 days **Control:** placebo twice a day, once in the morning and once in the evening for 30 days
Outcomes	**Primary outcomes** • Composite outcome of symptomatic DVT, PE, other VTE, ischaemic stroke, MI, other arterial thromboembolism, and all-cause mortality as measured by hospital records (time frame: 30 days after hospital discharge) **Secondary outcomes** • Composite outcome of all-cause mortality and the EQ-5D index score (time frame: 30 days after hospital discharge) • Composite outcome of symptomatic DVT, PE, other VTE, ischaemic stroke, MI, other arterial thromboembolism, and all-cause mortality as measured by hospital records (time frame: 45 days and 90 days after hospital discharge) • New, symptomatic VTE for up to 30 days after randomisation as measured by hospital records (time frame: 30 days after randomisation) • New, symptomatic arterial thromboembolism (inclusive of ischaemic stroke, MI, or peripheral arterial thromboembolism) for up to 30 days after randomisation as measured by hospital records (time frame: 30 days after randomisation) **Other outcomes** • Incidence of all-cause mortality (time frame: 30 days after hospital discharge) • Incidence of all-cause rehospitalisation for up to 90 days after randomisation (time frame: 30 days after hospital discharge) • Individual domains of EQ-5D and the EQ-5D visual analogue scale for 30 and 90 days after randomisation (time frame: 30 and 90 days after hospital discharge)
Starting date	15 February 2021
Contact information	tracy.wang@duke.edu
Notes	

NCT04715295

Study name	Safety and efficacy of doxycycline and rivaroxaban in COVID-19 (DOXYCOV)
Methods	Prospective, open-label RCT
Participants	**Number of participants**: 200 **Age:** ≥ 18 years **Gender:** male or female **Inclusion criteria** • COVID-19 infection confirmed by SARS-CoV-2 RT-PCR, as per protocol • Able to start treatment within 24 hours from time of diagnosis • Patient with mild symptoms as defined by WHO, with PaO_2 > 93% • Signed written consent of the patient • Accepts and has the ability to be reached by phone during the study duration, plus a designated contact person who can be contacted in case of emergency **Exclusion criteria** • Blood pressure < 90/60 mmHg • Respiratory rate ≥ 30/min • Known cardiac condition • Known G6PD deficiency • Patients with < 45 kg body mass • eGFR < 30 mL/min or ALT ≥ 3N or body temperature ≥ 38 °C or any life-threatening comorbidity • Any reason that makes it impossible to monitor the patient during the study period • Baseline ECG prior to randomisation showing QTc > 500 ms • Ongoing treatment other than symptomatic • History of retinopathy • Absolute contraindication to treatment with hydroxychloroquine (known hypersensitivity, concomitant treatment at risk of torsades de pointes) • Contraindication to any study medication including allergy • Ongoing treatment with high-dose systemic chronic corticosteroid (> 40 mg) • Patients treated with immunosuppressants at the time of randomisation • Known pregnant women and breastfeeding women
Interventions	**Intervention:** doxycycline 200 mg daily for 7 days with or without rivaroxaban 15 mg tablets daily from day 1 to day 10 **Control**: hydroxychloroquine 400 mg daily for 5 days in combination with azithromycin 500 mg on day 1 and 250 mg daily from day 2 through day 5 Comment: the trial plan is to use a factorial design to compare anticoagulant and control group. The co-treatment seems to be balanced across arms.
Outcomes	**Primary outcomes** • Clinical (time frame: day 1 to 10) • Virological (time frame: day 1 to 10) **Secondary outcomes** • Symptom remission (time frame: day 1 to 10) • Hospitalisation (time frame: day 1 to 10) • Mortality (time frame: day 1 to 10)

NCT04715295 *(Continued)*

	• Biological variables (time frame: day 1 to day 7 and day 10)
Starting date	5 October 2020
Contact information	sobngwieugene@yahoo.fr
Notes	

NCT04746339

Study name	Apixaban for prophylaxis of thromboembolic outcomes in COVID-19 (APOLLO)
Methods	Prospective, multicentre, quadruple-blind RCT

Participants	**Number of participants:** 1000
	
	Age: ≥ 18 years
	
	Gender: male and female
	
	Inclusion criteria
	
	• Outpatients with symptomatic laboratory-proven diagnosis of COVID-19 (any exam that shows acute infection as positive PCR or IgM in the context of acute symptoms ≤ 10 days) AND
	• Negative pregnancy test for women in childbearing period
	• D-dimer level ≥ 2 x ULN or
	• C-reactive protein ≥ 10 mg/L or
	• At least 2 of the following risk factors:
	  ◦ D-dimer level ≥ ULN
	  ◦ C-reactive protein ≥ ULN
	  ◦ Age ≥ 65
	  ◦ Diabetes
	  ◦ Chronic kidney disease stage 3
	  ◦ Cardiopulmonary disease (e.g. PAD, CAD, heart failure, COPD)
	  ◦ History of PE/DVT
	  ◦ Nursing home/skilled nursing facility resident or severely restricted mobility
	  ◦ BMI ≥ 30 kg/m^2
	
	Exclusion criteria
	
	• Age < 18 years
	• Patients with indication for full anticoagulation during inclusion (e.g. diagnosis of VTE, atrial fibrillation, MVP)
	• Platelets < 50,000/mm^3
	• Use of acetylsalicylic acid > 100 mg per day
	• Use of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor)
	• Chronic use of non-steroidal anti-inflammatory drugs
	• Hypersensitivity to apixaban
	• Creatinine clearance < 30 mL/min
	• Pregnancy or breastfeeding
	• Contraindication to anticoagulation (active bleeding, recent major surgery, blood dyscrasia, or prohibitive haemorrhage risk as evaluated by the investigator)
	• 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 malformation, or aneurysm

NCT04746339 *(Continued)*

	• Use of strong inhibitors of CYP P450 3A4 and/or 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)
Interventions	**Intervention:** apixaban 2.5 mg twice daily for 30 days **Control:** placebo twice daily for 30 days
Outcomes	**Primary outcomes** • Number of days alive and out of hospital or emergency department (time frame: in 30 days) **Secondary outcomes** • Hospitalisation due to bleeding (time frame: in 30 days) • Hospitalisations for cardiopulmonary causes (time frame: in 30 days) • All-cause hospitalisation (time frame: in 30 days) • All-cause death (time frame: in 30 days) • Days free of VTE (time frame: in 30 days) • MACE (time frame: in 30 days)
Starting date	4 March 2021
Contact information	renato.lopes@duke.edu
Notes	

NCT04757857

Study name	COVID-19 antithrombotic rivaroxaban evaluation (CARE)
Methods	Prospective, pragmatic, open-label RCT

Participants	**Number of participants:** 660
	
	Age: ≥ 18 years
	
	Gender: male and female
	
	Inclusion criteria
	
	• Adults ≥ 18 years old
	• Evaluated in the emergency unit with probable or confirmed infection by COVID-19
	• Time between symptoms and inclusion ≤ 7 days
	• Present mild or moderate signs and symptoms, with no clear indication for hospitalisation
	• Present at least 2 risk factors for complication:
	  ○ 65 years
	  ○ Hypertension
	  ○ Diabetes mellitus
	  ○ Asthma
	  ○ COPD or other chronic lung diseases
	  ○ Smoking
	  ○ Immunosuppression
	  ○ Obesity (BMI > 30)
	  ○ History of non-active cancer
	  ○ Bed restriction or reduced mobility (≥ 50% of wake time without walking)

NCT04757857 *(Continued)*

- Previous history of VTE
- Use of oral hormonal contraceptives

Exclusion criteria

- Patients < 18 years old
- Hospitalisation indication upon first medical care
- Positive test for influenza in the first visit
- Any known liver disease associated with coagulopathy; INR > 1.5
- Pregnant, lactating, or with the possibility of becoming pregnant and not using an adequate contraceptive method
- High risk of bleeding:
  - History of bronchiectasis or pulmonary cavitation
  - Significant bleeding in the last 3 months
  - Active gastroduodenal ulcer
  - History of recent bleeding (within 3 months) or a high risk of bleeding
- Stroke within 1 month or any history of haemorrhagic or lacunar stroke or any intracranial bleeding or any intracranial neoplasia, brain metastasis, arteriovenous malformation, or brain aneurysm
- Severe heart failure with left ventricular ejection fraction < 30% (echocardiogram or other validated methods previously documented) or symptoms of heart failure NYHA class III or IV
- Estimated GFR < 30 mL/min
- Clinical indication for dual antiplatelet therapy or anticoagulation therapy (VTE, atrial fibrillation/flutter, MVP)
- Marked thrombocytopenia (platelets < 50,000/mm^3)
- Non-cardiovascular disease that is associated with a poor prognosis, e.g. active cancer (excluding non-melanoma skin cancer) defined as cancer without remission or requiring active chemotherapy or adjuvant therapies such as immunotherapy or radiation therapy or that increases the risk of an adverse reaction to the evaluated interventions
- History of hypersensitivity or known contraindication to rivaroxaban
- Systemic treatment with strong inhibitors of CYP3A4 and P-gp (e.g. systemic azole antimycotics such as ketoconazole, and HIV protein inhibitors such as ritonavir) or strong inducers of CYP 3A4 (i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine)
- Current treatment being tested
- Concomitant participation in another study with experimental drugs in the context of COVID
- Use of chloroquine or hydroxychloroquine associated with azithromycin
- Active cancer
- Other contraindications to rivaroxaban

Interventions	**Interventions:** rivaroxaban 10 mg orally once a day for 14 days **Control:** no intervention, receive best local standardised care
Outcomes	**Primary outcomes** • VTE within 30 days from randomisation. Defined as DVT, acute PE, other major venous thrombotic events • Mechanical ventilation free-survival within 30 days from randomisation. Defined as survival without requirement of mechanical ventilation • MACE within 30 days from randomisation. Defined as acute MI, stroke, or acute limb ischaemia • Out-of-hospital death not attributed to major injury within 30 days from randomisation. Death that occurred out of hospital due to any cause not related to trauma or other major injury **Secondary outcomes** • Time from randomisation to hospitalisation within 30 days from randomisation. Defined as time elapsed since randomisation to hospital admission

NCT04757857 *(Continued)*

	• Length of hospitalisation within 30 days from randomisation. To assess the duration of hospitalisation (length of hospital stay) • Hospitalisation in ICU within 30 days from randomisation. Requirement of admission to ICU for intensive care • Clinical requirement of mechanical ventilation within 30 days from randomisation. Requirement of oxygen supplementation through invasive or non-invasive mechanical ventilation • Clinical duration of mechanical ventilation within 30 days from randomisation. Total time on oxygen supplementation through invasive or non-invasive mechanical ventilation • Composite vascular endpoint within 30 days from randomisation (non-fatal MI, non-fatal ischaemic stroke or cardiovascular death, VTE) • Composite vascular endpoint II within 30 days from randomisation (cardiovascular death, non-fatal MI, non-fatal ischaemic stroke or acute limb ischaemia, VTE) • Major bleeding within 30 days from randomisation. Defined by ISTH criteria • Mortality within 30 days from randomisation. Defined by all-cause deaths
Starting date	29 September 2020
Contact information	dvilanova@haoc.com.br
Notes	

Ramos-Peñafiel 2020

Study name	Effect of the use of anticoagulant therapy during hospitalisation and discharge in patients with COVID-19 infection
Methods	Prospective, double-blind RCT
Participants	**Number of participants:** 130 **Age:** between 18 and 90 years old **Gender**: male and female **Inclusion criteria** • Patients with a diagnosis of COVID-19 infection confirmed by PCR requiring hospital care for the administration of supplemental oxygen **Exclusion criteria** • Patients with life expectancy less than 48 h • Patients who require ventilatory support upon admission • Age over 75 years or with a history of atrial fibrillation • History of venous or arterial thrombosis • Severe neurological impairment • Absence of a primary caregiver to supervise the administration of medication • History of cerebral haemorrhage • History of previous use of oral anticoagulants • History of major surgery 30 days prior to admission • Uncontrolled systemic arterial hypertension • KDIGO stage III chronic kidney disease or less • Haemodialysis or peritoneal dialysis treatment • History of active or inactive cancer • Pregnant or postpartum patients

Ramos-Peñafiel 2020 *(Continued)*

Interventions	**Intervention:** prophylactic enoxaparin arm 1 mg/kg/dose daily **Control**: enoxaparin therapeutic regimen arm at doses of 1 mg/kg/dose twice daily during in-hospital stay Patients who are discharged will be randomised into the following 2 treatment arms: **Intervention**: rivaroxaban 10 mg orally every 24 hours **Control**: clinical follow-up only
Outcomes	**Primary outcomes** • LMWH (enoxaparin) and ventilatory support time (time frame: 30 days) • Thrombotic complications and rivaroxaban (time frame: 30 days) • LMWH (enoxaparin) and length of hospital stay (time frame: 30 days) • LMWH (enoxaparin) and mortality rate (time frame: 30 days)
Starting date	20 June 2020
Contact information	christian.ramos.penafiel@gmail.com
Notes	

RBR-7nzwkpg

Study name	Effects of treatment with oral anticoagulant associated with antibiotic therapy in COVID-19
Methods	Prospective, double-blind RCT
Participants	**Number of participants:** 160 **Age:** ≥ 18 years **Gender**: male and female **Inclusion criteria** • Clinical suspicion of COVID-19 • Oxygen saturation between 93% and 97% • At least 1 more symptom according to the Ministry of Health criteria including tiredness or shortness of breath, fever and chills, cough, and loss of smell or taste • Positive result for the D-dimer test **Exclusion criteria** • Patients with active infectious diseases, immunosuppressive diseases, or active cancer • Pregnant or lactating women • Known renal failure • Current use of anticoagulants • Contraindication to the use of edoxaban or moxifloxacin
Interventions	**Intervention:** 1 non-transparent bottle containing 28 tablets of edoxaban 60 mg. The prescription will obey the following dosage: 1 tablet, once daily, for 28 days. **Control:** 1 non-transparent bottle containing 28 non-transparent capsules. The capsules will contain standard placebo formulation, consisting of 0.5% magnesium stearate, 1.0% Aerosil, 30%

RBR-7nzwkpg *(Continued)*

	pharmaceutical talc + starch q.s.p. The prescription will obey the following dosage: 1 capsule, once daily, for 28 days.
Outcomes	**Primary outcome** • Frequency of individuals who required hospitalisation after starting treatment **Secondary outcomes** • Secondary outcomes are not expected
Starting date	24 January 2021
Contact information	anna.piovezan@unisul.br
Notes	

ALT: alanine transaminase
aPTT: activated partial thromboplastin clotting time
BMI: body mass index
CAD: coronary artery disease
CNS: central nervous system
COPD: chronic obstructive pulmonary disease
CYP3A4: cytochrome P450 3A4
DVT: deep vein thrombosis
ECG: electrocardiogram
ECMO: extracorporeal membrane oxygenation
EMR: electronic medical record
ER: emergency room
eGFR: estimated glomerular filtration rate
FIO_2: fraction of inspired oxygen
G6PD: glucose-6-phosphate dehydrogenase
GFR: glomerular filtration rate
HFOV: high-frequency oscillatory ventilation
ICU: intensive care unit
IgM: immunoglobulin M
IMP: investigational medicinal product
INR: international normalised ratio
ISTH: International Society of Thrombosis and Haemostasis
LMWH: low-molecular-weight heparin
MACE: major cardiovascular events
MI: myocardial infarction
MVP: mechanical valve prosthesis
N: normal
NYHA: New York Heart Association
PAD: peripheral artery disease
PaO_2: partial pressure of arterial oxygen
PE: pulmonary embolism
P-gp: P-glycoprotein
PCR: polymerase chain reaction
QTc: corrected QT interval
RCT: randomised controlled trial
RT-PCR: reverse transcription polymerase chain reaction
ULN: upper limit of normal
VTE: venous thromboembolism
WHO: World Health Organization

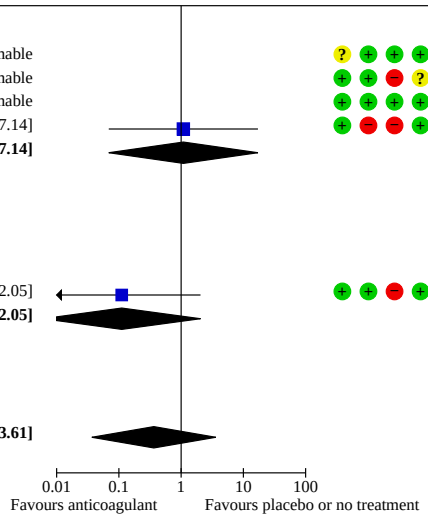
DATA AND ANALYSES

Comparison 1. Anticoagulant versus placebo or no treatment (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	5	1777	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.61]
1.1.1 As an outpatient	4	1459	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.07, 17.14]
1.1.2 After discharge	1	318	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.05]
1.2 Venous thromboembolism	4	1259	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.16, 0.85]
1.2.1 As an outpatient	3	941	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.90]
1.2.2 After discharge	1	318	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.13, 0.97]
1.3 Major bleeding	5	1777	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.01, 8.78]
1.3.1 As an outpatient	4	1459	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.01, 8.78]
1.3.2 After discharge	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Deep vein thrombosis	3	1009	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.30, 3.46]
1.4.1 As an outpatient	2	691	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.07, 17.14]
1.4.2 After discharge	1	318	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.25, 3.93]
1.5 Pulmonary embolism	3	1009	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.79]
1.5.1 Starting before hospitalisation	2	691	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.05, 1.72]
1.5.2 Starting after hospitalisation	1	318	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 1.01]
1.6 Need for hospitalisation	4	1459	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.59, 1.75]
1.7 Adverse events (minor bleeding)	5	1777	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.90, 6.72]
1.7.1 As an outpatient	4	1459	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.85, 7.79]
1.7.2 After discharge	1	318	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.18, 21.84]
1.8 Adverse events (all)	5	1777	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.88, 1.98]
1.8.1 As an outpatient	4	1459	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.83, 2.20]
1.8.2 After discharge	1	318	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.30, 5.86]

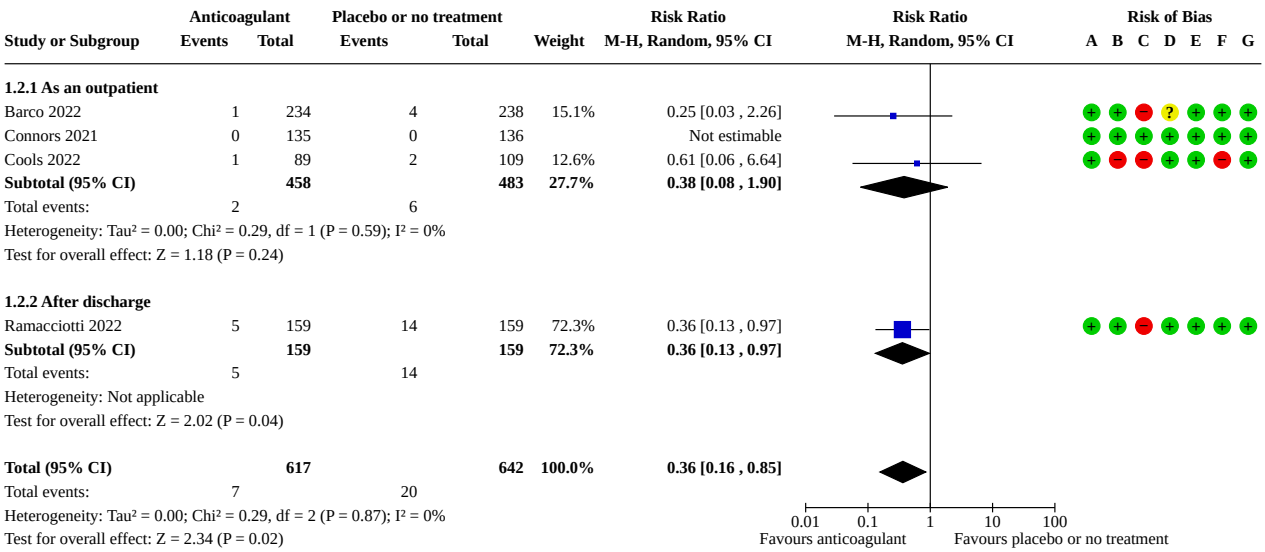
Analysis 1.1. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 1: All-cause mortality

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.1.1 As an outpatient							
Ananworanich 2021	0	246	0	251		Not estimable	? + + + + + +
Barco 2022	0	234	0	238		Not estimable	+ + − ? + + +
Connors 2021	0	135	0	136		Not estimable	+ + + + + + +
Cools 2022	1	105	1	114	52.1%	1.09 [0.07 , 17.14]	+ − − + + − +
Subtotal (95% CI)		**720**		**739**	**52.1%**	**1.09 [0.07 , 17.14]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.06 (P = 0.95)							
1.1.2 After discharge							
Ramacciotti 2022	0	159	4	159	47.9%	0.11 [0.01 , 2.05]	+ + − + + + +
Subtotal (95% CI)		**159**		**159**	**47.9%**	**0.11 [0.01 , 2.05]**	
Total events:	0		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Total (95% CI)		**879**		**898**	**100.0%**	**0.36 [0.04 , 3.61]**	
Total events:	1		5				
Heterogeneity: Tau² = 0.65; Chi² = 1.31, df = 1 (P = 0.25); I² = 24%							
Test for overall effect: Z = 0.86 (P = 0.39)							
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.3%							



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

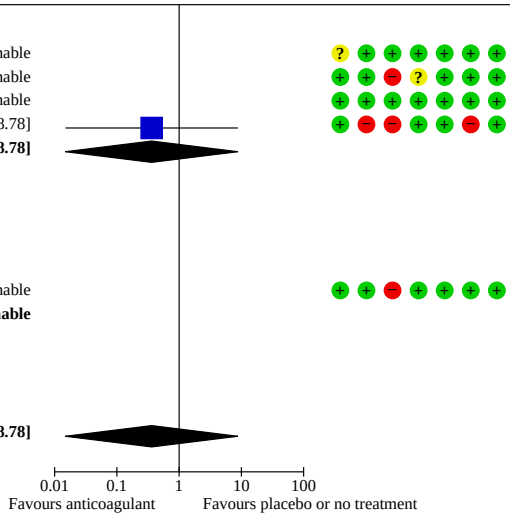
Analysis 1.2. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 2: Venous thromboembolism



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

Analysis 1.3. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 3: Major bleeding

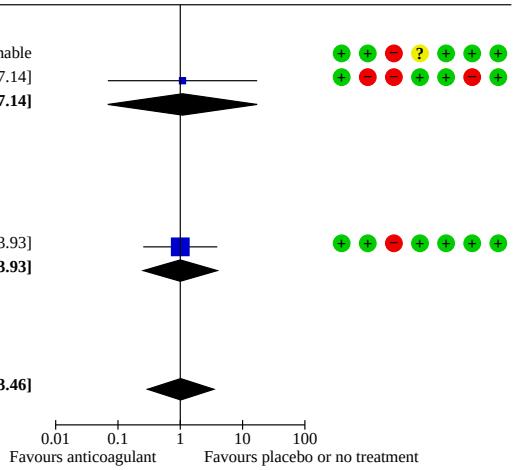
Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.3.1 As an outpatient							
Ananworanich 2021	0	246	0	251		Not estimable	? + + + + + +
Barco 2022	0	234	0	238		Not estimable	+ + − ? + + +
Connors 2021	0	135	0	136		Not estimable	+ + + + + + +
Cools 2022	0	105	1	114	100.0%	0.36 [0.01 , 8.78]	+ − − + + − +
Subtotal (95% CI)		**720**		**739**	**100.0%**	**0.36 [0.01 , 8.78]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.62 (P = 0.53)							
1.3.2 After discharge							
Ramacciotti 2022	0	159	0	159		Not estimable	+ + − + + + +
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**879**		**898**	**100.0%**	**0.36 [0.01 , 8.78]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.62 (P = 0.53)							
Test for subgroup differences: Not applicable							



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

Analysis 1.4. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 4: Deep vein thrombosis

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 As an outpatient						
Barco 2022	0	234	0	238		Not estimable
Cools 2022 (1)	1	105	1	114	19.7%	1.09 [0.07 , 17.14]
Subtotal (95% CI)		**339**		**352**	**19.7%**	**1.09 [0.07 , 17.14]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.4.2 After discharge						
Ramacciotti 2022	4	159	4	159	80.3%	1.00 [0.25 , 3.93]
Subtotal (95% CI)		**159**		**159**	**80.3%**	**1.00 [0.25 , 3.93]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**498**		**511**	**100.0%**	**1.02 [0.30 , 3.46]**
Total events:	5		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%						



Footnotes

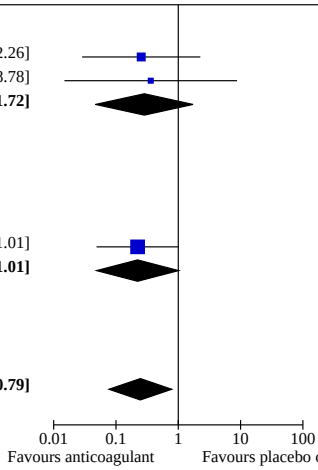
(1) Cools 2022 reported 1 event in the anticoagulation group at 30 days. At 90 days follow-up the study reported another VTE event, but it was not possible to establish if it was DVT or PE

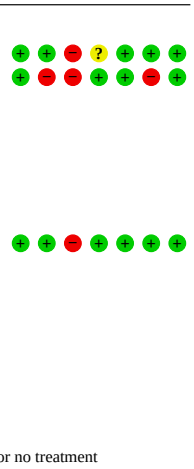
Risk of bias legend

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

Analysis 1.5. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 5: Pulmonary embolism

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Starting before hospitalisation						
Barco 2022	1	234	4	238	28.2%	0.25 [0.03 , 2.26]
Cools 2022 (1)	0	105	1	114	13.2%	0.36 [0.01 , 8.78]
Subtotal (95% CI)		**339**		**352**	**41.5%**	**0.28 [0.05 , 1.72]**
Total events:	1		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.5.2 Starting after hospitalisation						
Ramacciotti 2022	2	159	9	159	58.5%	0.22 [0.05 , 1.01]
Subtotal (95% CI)		**159**		**159**	**58.5%**	**0.22 [0.05 , 1.01]**
Total events:	2		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
Total (95% CI)		**498**		**511**	**100.0%**	**0.25 [0.08 , 0.79]**
Total events:	3		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						





Footnotes

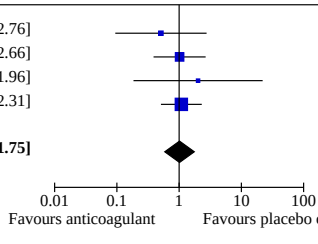
(1) Cools 2022 reported one event at the no treatment group on the 30 days follow-up. At 90 days follow-up the authors reported another VTE event, but it was not possible to stablish if it was

Risk of bias legend

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

Analysis 1.6. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 6: Need for hospitalisation

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Ananworanich 2021	2	246	4	251	10.4%	0.51 [0.09 , 2.76]
Barco 2022	8	234	8	238	32.1%	1.02 [0.39 , 2.66]
Connors 2021	2	135	1	136	5.2%	2.01 [0.18 , 21.96]
Cools 2022	12	105	12	114	52.2%	1.09 [0.51 , 2.31]
Total (95% CI)		**720**		**739**	**100.0%**	**1.01 [0.59 , 1.75]**
Total events:	24		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Not applicable						

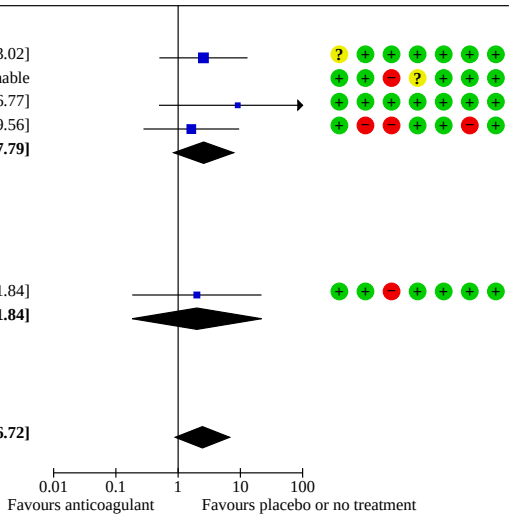


Risk of bias legend

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

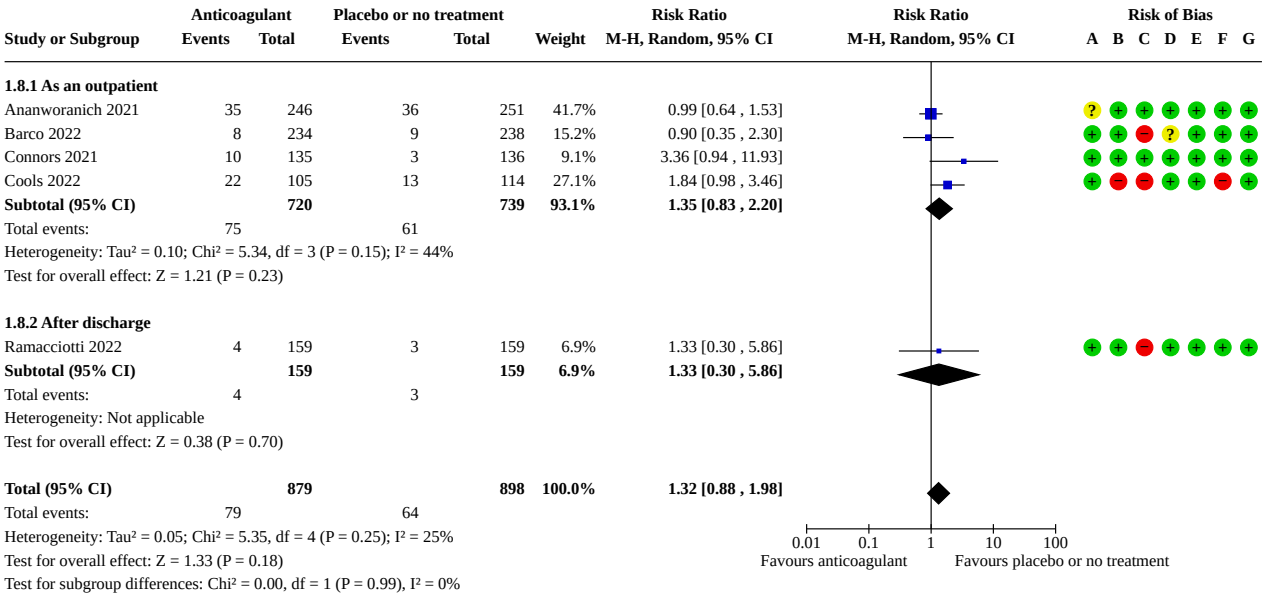
Analysis 1.7. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 7: Adverse events (minor bleeding)

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Placebo or no treatment Events	Placebo or no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 As an outpatient						
Ananworanich 2021	5	246	2	251	38.1%	2.55 [0.50 , 13.02]
Barco 2022	0	234	0	238		Not estimable
Connors 2021	4	135	0	136	11.9%	9.07 [0.49 , 166.77]
Cools 2022	3	105	2	114	32.3%	1.63 [0.28 , 9.56]
Subtotal (95% CI)		**720**		**739**	**82.3%**	**2.57 [0.85 , 7.79]**
Total events:	12		4			
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.10)						
1.7.2 After discharge						
Ramacciotti 2022	2	159	1	159	17.7%	2.00 [0.18 , 21.84]
Subtotal (95% CI)		**159**		**159**	**17.7%**	**2.00 [0.18 , 21.84]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**879**		**898**	**100.0%**	**2.46 [0.90 , 6.72]**
Total events:	14		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 3 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%						



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

Analysis 1.8. Comparison 1: Anticoagulant versus placebo or no treatment (short term), Outcome 8: Adverse events (all)



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

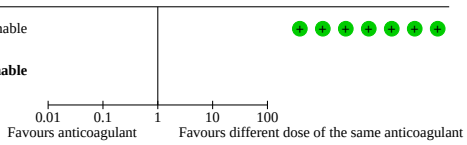
Comparison 2. Anticoagulant versus a different dose of the same anticoagulant (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Venous thromboembolism	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Major bleeding	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4 Deep vein thrombosis	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.5 Pulmonary embolism	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.6 Need for hospitalisation	1	278	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.17, 20.58]
2.7 Adverse events (minor bleeding)	1	278	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.09, 2.54]
2.8 Adverse events (all)	1	278	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.60, 3.09]

Analysis 2.1. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 1: All-cause mortality

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Different dose of the same anticoagulant Events	Different dose of the same anticoagulant Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	0	135	0	143		Not estimable		+ + + + + + +
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events:	0		0					

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

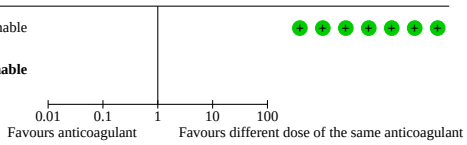


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.2. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 2: Venous thromboembolism

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Different dose of the same anticoagulant Events	Different dose of the same anticoagulant Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	0	135	0	143		Not estimable		+ + + + + + +
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events:	0		0					

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

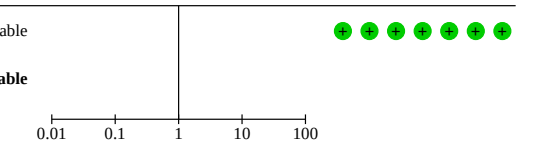


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.3. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 3: Major bleeding

Study or Subgroup	[Not identical] Events	[Not identical] Total	[Not identical] Events	[Not identical] Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	0	135	0	143		Not estimable		+ + + + + + +
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events:	0		0					

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

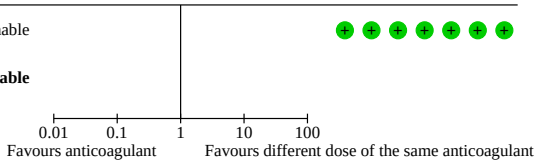


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.4. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 4: Deep vein thrombosis

Study or Subgroup	[Not identical] Events	Total	[Not identical] Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Connors 2021	0	135	0	143		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

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

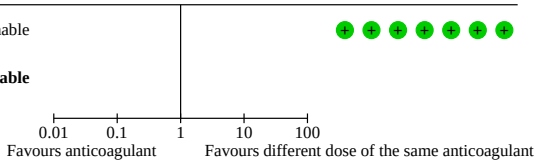


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.5. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 5: Pulmonary embolism

Study or Subgroup	[Not identical] Events	Total	[Not identical] Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Connors 2021	0	135	0	143		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

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

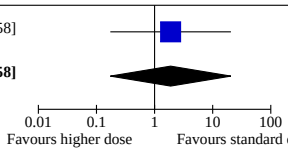


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 2.6. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 6: Need for hospitalisation

Study or Subgroup	Higher dose anticoagulant Events	Total	Standard dose anticoagulant Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Connors 2021	2	143	1	135	100.0%	1.89 [0.17 , 20.58]
Total (95% CI)		**143**		**135**	**100.0%**	**1.89 [0.17 , 20.58]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



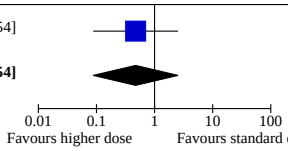
Risk of Bias: A B C D E F G

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

Analysis 2.7. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 7: Adverse events (minor bleeding)

Study or Subgroup	Higher dose anticoagulant Events	Total	Standard dose anticoagulant Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Connors 2021	2	143	4	135	100.0%	0.47 [0.09 , 2.54]
Total (95% CI)		**143**		**135**	**100.0%**	**0.47 [0.09 , 2.54]**
Total events:	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



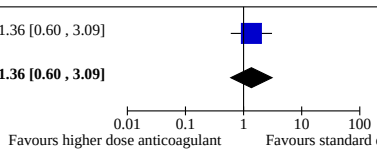
Risk of Bias: A B C D E F G

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

Analysis 2.8. Comparison 2: Anticoagulant versus a different dose of the same anticoagulant (short term), Outcome 8: Adverse events (all)

Study or Subgroup	Higher dose anticoagulant Events	Total	Standard dose anticoagulant Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Connors 2021	13	143	9	135	100.0%	1.36 [0.60 , 3.09]
Total (95% CI)		**143**		**135**	**100.0%**	**1.36 [0.60 , 3.09]**
Total events:	13		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Risk of Bias: A B C D E F G

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

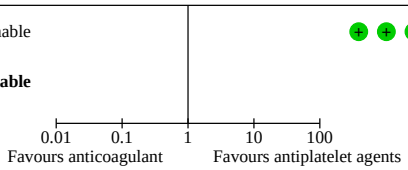
Comparison 3. Anticoagulant versus antiplatelet agents (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Venous thromboembolism	1	279	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.65]
3.3 Major bleeding	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Need for hospitalisation	1	279	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [0.13, 77.85]
3.5 Adverse events (minor bleeding)	1	279	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.40, 11.46]
3.6 Adverse events (all)	1	279	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.60, 3.06]

Analysis 3.1. Comparison 3: Anticoagulant versus antiplatelet agents (short term), Outcome 1: All-cause mortality

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Antiplatelet agents Events	Antiplatelet agents Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	0	135	0	144		Not estimable		+ + + + + + +
Total (95% CI)		**0**		**0**		**Not estimable**		
Total events:	0		0					

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

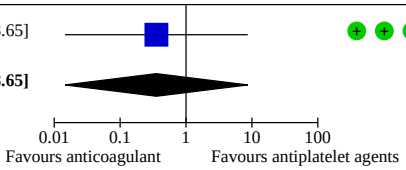


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 3.2. Comparison 3: Anticoagulant versus antiplatelet agents (short term), Outcome 2: Venous thromboembolism

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Antiplatelet agents Events	Antiplatelet agents Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	0	135	1	144	100.0%	0.36 [0.01 , 8.65]	+ + + + + + +
Total (95% CI)		**135**		**144**	**100.0%**	**0.36 [0.01 , 8.65]**	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.53)
Test for subgroup differences: Not applicable

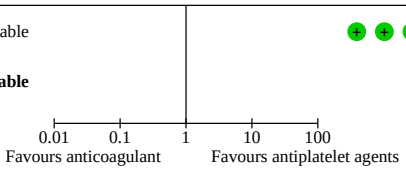


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 3.3. Comparison 3: Anticoagulant versus antiplatelet agents (short term), Outcome 3: Major bleeding

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Antiplatelet agents Events	Antiplatelet agents Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	0	135	0	144		Not estimable	+ + + + + + +
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				

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

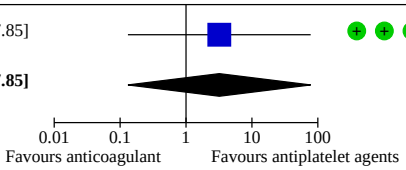


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 3.4. Comparison 3: Anticoagulant versus antiplatelet agents (short term), Outcome 4: Need for hospitalisation

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Antiplatelet agents Events	Antiplatelet agents Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	1	135	0	144	100.0%	3.20 [0.13 , 77.85]	+ + + + + + +
Total (95% CI)		**135**		**144**	**100.0%**	**3.20 [0.13 , 77.85]**	
Total events:	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable

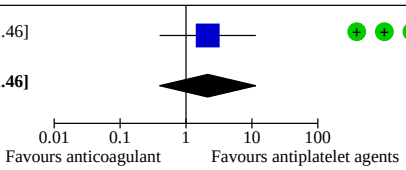


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 3.5. Comparison 3: Anticoagulant versus antiplatelet agents (short term), Outcome 5: Adverse events (minor bleeding)

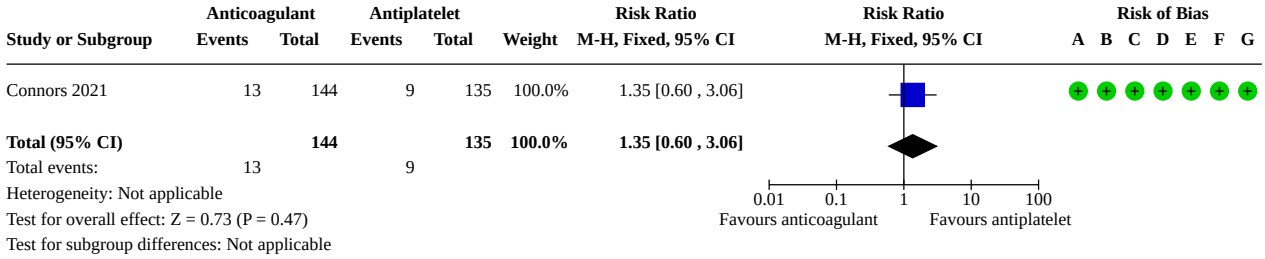
Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Antiplatelet agents Events	Antiplatelet agents Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Connors 2021	4	135	2	144	100.0%	2.13 [0.40 , 11.46]	+ + + + + + +
Total (95% CI)		**135**		**144**	**100.0%**	**2.13 [0.40 , 11.46]**	
Total events:	4		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



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

Analysis 3.6. Comparison 3: Anticoagulant versus antiplatelet agents (short term), Outcome 6: Adverse events (all)



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

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present (Date of most recent search: 18 April 2022)	1 exp COVID-19/ 2 COVID-19.ti,ab. 3 COVID19.ti,ab. 4 2019 novel coronavirus infection.ti,ab. 5 coronavirus disease 19.ti,ab. 6 2019 novel coronavirus disease.ti,ab. 7 coronavirus disease 2019.ti,ab. 8 exp Coronavirus/ 9 Coronavirus*.ti,ab. 10 Deltacoronavirus*.ti,ab. 11 Delta-coronavirus*.ti,ab. 12 or/1-11 13 exp Anticoagulants/ 14 (anticoagul* or anti-coagu*).ti,ab. 15 exp Heparin/ 16 heparin*.ti,ab. 17 UFH.ti,ab.	April 2022: 3892

(Continued)

18 LMWH.ti,ab.

19 LMH.ti,ab.

20 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren).ti,ab.

21 (Clexane or klexane or lovenox).ti,ab.

22 Fragmin.ti,ab.

23 Innohep.ti,ab.

24 clivarin*.ti,ab.

25 (danaproid or danaparoid).ti,ab.

26 antixarin.ti,ab.

27 (Zibor or cy 222 or embolex or monoembolex).ti,ab.

28 (rd 11885 or RD1185).ti,ab.

29 (Kabi-2165 or Kabi 2165).ti,ab.

30 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169).ti,ab.

31 (fr-860 or fr860 or cy-216 or cy216).ti,ab.

32 (kb101 or lomoparan or orgaran).ti,ab.

33 (fluxum or lohepa or lowhepa).ti,ab.

34 (op 2123 or op2123).ti,ab.

35 (ave 5026 or ave5026).ti,ab.

36 (M118 or RO-1).ti,ab.

37 coumar*.ti,ab.

38 (warfarin or (vitamin adj3 antagonist*)).ti,ab.

39 (VKA or coumadin* or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab.

40 exp Antithrombins/

41 exp Hirudin Therapy/

42 (thrombin adj3 inhib*).ti,ab.

43 hirudin*.ti,ab.

44 (dabigatran or Pradaxa or Rendix).ti,ab.

45 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab.

46 (ximelagatran or Exanta or Exarta or melagatran).ti,ab.

47 (AZD0837 or AZD-0837).ti,ab.

48 (S35972 or S-35972).ti,ab.

(Continued)

	49 Factor Xa Inhibitors/ 50 Xarelto.ti,ab. 51 (Bay-597939 or Bay597939).ti,ab. 52 PRT054021.ti,ab. 53 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab. 54 (DU-176b or DU176b).ti,ab. 55 (PRT-054021 or PRT054021).ti,ab. 56 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab. 57 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab. 58 etexilate.ti,ab. 59 agatroban.ti,ab. 60 or/13-59 61 12 and 60	
2. EMBASE via Ovid (Date of most recent search: 18 April 2022)	1 exp COVID-19/ 2 COVID-19.ti,ab. 3 COVID19.ti,ab. 4 2019 novel coronavirus infection.ti,ab. 5 coronavirus disease 19.ti,ab. 6 2019 novel coronavirus disease.ti,ab. 7 coronavirus disease 2019.ti,ab. 8 exp Coronavirus/ 9 Coronavirus*.ti,ab. 10 Deltacoronavirus*.ti,ab. 11 Delta-coronavirus*.ti,ab. 12 or/1-11 13 Anticoagulants/ 14 (anticoagul* or anti-coagu*).ti,ab. 15 exp Heparin/ 16 heparin*.ti,ab. 17 UFH.ti,ab. 18 LMWH.ti,ab. 19 LMH.ti,ab.	April 2022: 7555

(Continued)

20 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren).ti,ab.

21 (Clexane or klexane or lovenox).ti,ab.

22 Fragmin.ti,ab.

23 Innohep.ti,ab.

24 clivarin*.ti,ab.

25 (danaproid or danaparoid).ti,ab.

26 antixarin.ti,ab.

27 (Zibor or cy 222 or embolex or monoembolex).ti,ab.

28 (rd 11885 or RD1185).ti,ab.

29 (Kabi-2165 or Kabi 2165).ti,ab.

30 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169).ti,ab.

31 (fr-860 or fr860 or cy-216 or cy216).ti,ab.

32 (kb101 or lomoparan or orgaran).ti,ab.

33 (fluxum or lohepa or lowhepa).ti,ab.

34 (op 2123 or op2123).ti,ab.

35 (ave 5026 or ave5026).ti,ab.

36 (M118 or RO-1).ti,ab.

37 coumar*.ti,ab.

38 (warfarin or (vitamin adj2 antagonist*)).ti,ab.

39 (VKA or coumadin* or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab.

40 exp Antithrombins/

41 exp Hirudin Therapy/

42 (thrombin adj3 inhib*).ti,ab.

43 hirudin*.ti,ab.

44 (dabigatran or Pradaxa or Rendix).ti,ab.

45 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab.

46 (ximelagatran or Exanta or Exarta or melagatran).ti,ab.

47 (AZD0837 or AZD-0837).ti,ab.

48 (S35972 or S-35972).ti,ab.

49 Factor Xa Inhibitors/

50 Xarelto.ti,ab.

(Continued)

	51 (Bay-597939 or Bay597939).ti,ab. 52 PRT054021.ti,ab. 53 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab. 54 (DU-176b or DU176b).ti,ab. 55 (PRT-054021 or PRT054021).ti,ab. 56 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab. 57 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab. 58 etexilate.ti,ab. 59 agatroban.ti,ab. 60 or/13-59 61 12 and 60	
3. CINAHL via Ebsco (Date of most recent search: 18 April 2022)	S40 S13 AND S39 S39 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 S38 TX agatroban S37 TX etexilate S36 TX Xarelto S35 TX Factor Xa Inhibitor* S34 TX dabigatran or Pradaxa or Rendix S33 TX hirudin* S32 TX thrombin inhib* S31 TX Antithrombins S30 TX VKA or coumadin* or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcumar or Falithrom or AVK or phenprocoumon* or al-documar or carfin or jantoven or kumatox or lawarin or marevan or prothro-madin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin S29 TX vitamin K antagonist* S28 TX warfarin S27 TX coumar* S26 TX danaproid or danaparoid S25 TX clivarin* S24 TX Innohep S23 TX Fragmin S22 TX Clexane or klexane or lovenox	April 2022: 725

(Continued)

	S21 TX Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren S20 TX LMH S19 TX LMWH S18 TX UFH S17 TX heparin* S16 (MH "Heparin+") S15 TX anticoagul* or anti-coagu* S14 (MH "Anticoagulants+") S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 S12 TX Delta-coronavirus*. S11 TX Deltacoronavirus* S10 TX Coronavirus* S9 (MH "Coronavirus+") S8 (MH "SARS-CoV-2") S7 TX coronavirus disease 2019 S6 TX 2019 novel coronavirus disease S5 TX coronavirus disease 19 S4 TX 2019 novel coronavirus infection S3 TX COVID19 S2 TX COVID-19 S1 (MH "COVID-19")	
4. VASCULAR REGISTER IN CRSW (Date of most recent search: 18 April 2022)	#1 COVID-19 OR COVID19 OR 2019 novel coronavirus infection OR coronavirus disease 19 OR 2019 novel coronavirus disease OR coronavirus disease 2019 OR Coronavirus* OR Deltacoronavirus* OR Delta-coronavirus* AND INREGISTER	April 2022: 45
5. CENTRAL via CRSO (Date of most recent search: 18 April 2022)	#1 MESH DESCRIPTOR COVID-19 EXPLODE ALL TREES 1004 #2 COVID-19:TI,AB,KY 8293 #3 COVID19:TI,AB,KY 408 #4 (2019 novel coronavirus infection):TI,AB,KY 3 #5 (coronavirus disease 19):TI,AB,KY 49 #6 (2019 novel coronavirus disease):TI,AB,KY 4 #7 (coronavirus disease):TI,AB,KY 3060 #8 MESH DESCRIPTOR Coronavirus EXPLODE ALL TREES 616	April 2022: **279**

(Continued)

#9 Coronavirus*:TI,AB,KY 5137

#10 Deltacoronavirus*:TI,AB,KY 1

#11 Deltacoronavirus*:TI,AB,KY 1

#12 Delta-coronavirus*:TI,AB,KY 0

#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 8923

#14 MESH DESCRIPTOR Anticoagulants EXPLODE ALL TREES 11803

#15 (anticoagul* or anti-coagu*):TI,AB,KY 14242

#16 MESH DESCRIPTOR Heparin EXPLODE ALL TREES 4863

#17 heparin*:TI,AB,KY 12316

#18 UFH:TI,AB,KY 751

#19 LMWH:TI,AB,KY 1453

#20 LMH:TI,AB,KY 9

#21 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren):TI,AB,KY 14

#22 (Clexane or klexane or lovenox):TI,AB,KY 177

#23 Fragmin:TI,AB,KY 224

#24 Innohep:TI,AB,KY 37

#25 clivarin*:TI,AB,KY 22

#26 (danaproid or danaparoid):TI,AB,KY 54

#27 antixarin:TI,AB,KY 2

#28 (Zibor or cy 222 or embolex or monoembolex):TI,AB,KY 38

#29 (fluxum or lohepa or lowhepa):TI,AB,KY 15

#30 coumar*:TI,AB,KY 389

#31 warfarin:TI,AB,KY 4906

#32 (vitamin k antagonist*):TI,AB,KY 1064

#33 (VKA or coumadin* or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin):TI,AB,KY 945

#34 MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES 2289

#35 MESH DESCRIPTOR Hirudin Therapy EXPLODE ALL TREES 75

#36 (thrombin inhib*):TI,AB,KY 546

#37 hirudin*:TI,AB,KY 483

#38 (dabigatran or Pradaxa or Rendix):TI,AB,KY 1068

(Continued)

	#39 (ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY 182 #40 MESH DESCRIPTOR Factor Xa Inhibitors EXPLODE ALL TREES 1091 #41 Xarelto:TI,AB,KY 85 #42 etexilate:TI,AB,KY 327 #43 agatroban:TI,AB,KY 2 #44 #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 28554 #45 #13 AND #44 279	
6. Clinicaltrials.gov (Date of most recent search: 18 April 2022)	COVID-19 OR COVID19 OR 2019 novel coronavirus infection OR coronavirus disease 19 OR 2019 novel coronavirus disease OR coronavirus disease 2019 OR Coronavirus* OR Deltacoronavirus* OR Delta-coronavirus* | Anticoagulants* OR Heparin OR LMWH OR warfarin OR Factor Xa Inhibitors OR Antithrombins OR coumarin	April 2022: 117
7. ICTRP Search Portal (Date of most recent search: 18 April 2022)	COVID-19 OR COVID19 OR 2019 novel coronavirus infection OR coronavirus disease 19 OR 2019 novel coronavirus disease OR coronavirus disease 2019 OR Coronavirus* OR Deltacoronavirus* OR Delta-coronavirus* | Anticoagulants* OR Heparin OR LMWH OR warfarin OR Factor Xa Inhibitors OR Antithrombins OR coumarin	April 2022: 80
8. LILACS (Date of most recent search: 18 April 2022)	COVID-19 OR COVID19 OR Coronavirus OR Deltacoronavirus OR Delta-coronavirus [Palavras] and Anticoagulants OR Heparin OR LMWH OR warfarin OR Factor Xa Inhibitors OR Antithrombins OR coumarin [Palavras]	April 2022: **75**
9. COVID Cochrane Register (Date of most recent search: 18 April 2022)		April 2022: 2571
TOTAL before de-duplication		April 2022: 15339
TOTAL after de-duplication		April 2022: 9347

HISTORY

Protocol first published: Issue 4, 2022

CONTRIBUTIONS OF AUTHORS

BCS: drafting of protocol, study selection, data extraction, risk of bias assessment, data analysis, and drafting of final review
RLGF: drafting of protocol, study selection, data extraction, data analysis, drafting of final review, and acting as guarantor of the review
VTC: drafting of protocol, data extraction, risk of bias assessment, data analysis, and drafting of final review
ANA: drafting of protocol, data analysis, and drafting of final review
LCUN: drafting of protocol, study selection, data extraction, data analysis, and drafting of final review

DECLARATIONS OF INTEREST

BCS: none known; BCS has declared that she works as a private practice vascular surgeon, dealing with both venous and arterial diseases.
RLGF: none known; RLGF has declared he is professor of vascular surgery at Universidade Federal de São Paulo, Brazil.
VTC: none known

ANA: none known; ANA has declared he is director of Cochrane Brazil.
LCUN: none known

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Internal sources

- Division of Vascular and Endovascular Surgery, Universidade Federal de Sao Paulo, Brazil

  This project received methodological support from a collaboration between Cochrane Brazil and the Division of Vascular and Endovascular Surgery.

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol (Santos 2022), we planned the objectives of this review as: to assess the benefits and harms of prophylactic anticoagulants versus active comparator, placebo, or no intervention in non-hospitalised people with COVID-19. However, in the review we amended the objective as follows: to assess the benefits and harms of prophylactic anticoagulants versus active comparator, placebo or no intervention, or non-pharmacological interventions in non-hospitalised people with COVID-19, because it better reflects what we performed.

In our protocol we planned to perform subgroup analyses for all outcomes comparing different doses of drugs. At the review stage, we decided to perform an isolated comparison for this purpose because we considered it a clinical relevant comparison, and the included studies compared different doses of drugs in different groups. In our protocol we planned to perform subgroup analyses for 'days since positive COVID-19 diagnosis'; however, at the review stage we performed subgroup analysis for 'starting prophylaxis before hospitalisation and postdischarge' because we considered this to be clinically relevant.

In our protocol we planned to include additional study types to randomised controlled trials (RCTs) if we did not identify sufficient RCT data (e.g. non-randomised studies, cohort, retrospective, etc.). Given that we found five RCTs with more than 400 participants, we did not include any non-RCTs.

In our protocol we planned to include number needed to treat for an additional beneficial outcome (NNTB) for the primary outcomes (all-cause mortality, venous thromboembolism, and major bleeding), but at the review stage we reported all clinically important differences using NNTB.

We planned to report all adverse events separately; however, this was not possible due to how these were reported by the included studies. We have now reported minor bleeding as a separate outcome, as well as all other adverse events combined.

NOTES

Parts of the Methods section of this protocol are based on a standard template established by Cochrane Vascular.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects]; Aspirin; *COVID-19; Platelet Aggregation Inhibitors; *Pulmonary Embolism [prevention & control]; *Venous Thromboembolism [prevention & control]

MeSH check words

Humans