National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[D] Evidence review for VTE prevention in COVID-19

NICE guideline NG191

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Objective

This evidence aims to evaluate the clinical effectiveness and safety of pharmacological prophylaxis for reducing the risk of venous thromboembolism (VTE) in people with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of pharmacological prophylaxis to reduce the risk of venous thromboembolism in adults receiving care for suspected or confirmed COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The original NICE recommendations were published in March 2021, based on an evidence review developed by NICE. Ongoing surveillance was conducted from publication to identify any new emerging evidence to be considered for inclusion in an update.

A new RCT was published relating to the low molecular weight heparins section of the managing COVID-19 guideline (NG191). This study was highlighted by a panel member as having potential impact on current recommendations in May 2021. The surveillance decision was to update the recommendations on heparins to reconsider the effectiveness and safety of pharmacological prophylaxis to reduce the risk of venous thromboembolism in adults receiving care for suspected or confirmed COVID-19.

Initially the update focused on the recommendations for people with severe COVID-19. As the update progressed, trials covering the moderate COVID-19 population were identified through the continual weekly surveillance searches. Therefore the update was extended to cover the effectiveness and safety of pharmacological

prophylaxis to reduce the risk of venous thromboembolism in adults with moderate or severe COVID-19. Relevant references were screened against the protocol using their titles and abstracts and 1 full text reference was obtained and assessed for relevance.

Included studies

In total, 8 studies were included in this updated evidence review.

69 studies were excluded at full text screening. Details of excluded studies are in appendix C.

People with moderate severity COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Summary of included studies

Evidence comes from 3 randomised controlled trials with 3,298 participants included.

One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.

Participants in the ACTION trial had a clinical 'stable' condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically 'unstable' condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels

Study characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation <94%, pulmonary infiltrates <50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

See appendix D for full evidence tables.

People with severe COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Summary of included studies

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098)

compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.

Study characteristics

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

See appendix D for full evidence tables.

People with severe COVID-19: Intermediate dose prophylaxis vs standard dose prophylaxis

Summary of included studies

Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxoparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Summary of study characteristics

The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021). Participants were excluded if they had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

See appendix D for full evidence tables.

Results

People with moderate severity COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Key results

Mortality

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].

Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 -1.02; 465 people in 1 study].

Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 – 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].

Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.84. CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34- 4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecision (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.

Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).

See appendix E for forest plots and appendix F for GRADE profiles.

People with severe COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Key results

Mortality

All-cause mortality

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

Death in hospital

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].

Organ-support free days at 21 days

Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days

Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Adverse events

Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41,ATACC,REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).

Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

See appendix E for forest plots and appendix F for GRADE profiles.

People with severe COVID-19: Intermediate dose prophylaxis vs standard dose prophylaxis

Key results

All-cause mortality

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84— 1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding

Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 - 4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 — 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 — 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 2021). The other study was from published manuscripts that reported 30 day and 90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to

calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

See appendix E for forest plots and appendix F for GRADE profiles.

Evidence to decision

Benefits and harms

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice.

The panel also considered evidence from 6 trials evaluating whether higher doses (intermediate or treatment) of anticoagulation improve clinical outcomes in people in hospital with confirmed COVID-19.

Three of the randomised controlled trials (ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID) evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in adults in hospital with confirmed moderate COVID-19 (defined in this guideline as people receiving low-flow supplementary oxygen). The panel agreed that, for adults with moderate COVID-19, the studies showed a trend towards improved mortality outcomes with a treatment dose of an anticoagulant compared with the standard prophylactic dose. One study reported no difference in survival to hospital discharge and a statistically significant increase in survival without organ support at 28 days. The panel also emphasised a trend towards a positive effect on VTE at 30 and 90 days, and a statistically significant increase in organ-support-free days.

The panel were presented with data from 4 open-label randomised controlled trials (INSPIRATION, ATTACC, ACTIV-4a, REMAP-CAP, HESACOVID and Perepu [2021]). These trials evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19 (that is, receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation).

Two studies compared intermediate-dose anticoagulation with the standard prophylactic dose (INSPIRATION and Perepu [2021]). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality, VTE prophylaxis or ventilator-free days with an intermediate dose of an anticoagulant compared with the standard prophylactic dose. There was, however,

no indication of increased bleeding with an intermediate dose compared with the standard prophylactic dose.

Two studies compared a treatment dose of an anticoagulant with the standard prophylactic dose (HESACOVID and ATTACC-ACTIV-4a-REMAP-CAP). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality or organ support-free days with a treatment dose of an anticoagulant compared with the standard prophylactic dose. There was no sign of increased bleeding with a treatment dose compared with the standard prophylactic dose. The panel noted that 1 study showed an increase in ventilator-free days with treatment-dose anticoagulation. However, they agreed that the results were not certain enough to base a recommendation on because the study was very small.

Although the evidence did not show a statistically significantly increased risk of bleeding with higher doses of anticoagulation, the panel agreed that the occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. They therefore agreed that risk of bleeding should be assessed as soon as possible using a risk assessment tool to uncover any potential harm to people with a high risk. The panel noted that the rate of major bleeding events reported in the studies used was relatively low for adults in hospital with moderate COVID-19 (defined in this guideline as people receiving low flow supplementary oxygen) and severe COVID-19 (defined in this guideline as people receiving high-flow oxygen). Therefore, the benefits of standard-dose prophylactic anticoagulation may outweigh the potential harms in these populations. The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The panel noted that the duration of treatment recommended in NICE's guideline on VTE in over 16s is a minimum of 7 days and thought that it would be acceptable to align treatment duration of a standard prophylactic dose of a LMWH in people with moderate or severe COVID-19 with standard practice.

The panel recommended not to base prophylactic dosing of heparin on levels of D-dimer because 1 trial presented evidence showing that a person's D-dimer measurements did not influence the effects of VTE prophylaxis.

Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation, and that intermediate- or treatment-dose VTE prophylaxis should not be used apart from as part of a clinical trial.

The panel discussed what to do if someone is already on treatment-dose anticoagulation at admission. They noted that people would normally remain on their prescribed anticoagulation if they can take oral medicines. However, they would switch to a low molecular weight heparin when they could no longer take oral medicines, such as when admitted to an intensive care unit.

Certainty of the evidence

The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider standard-dose VTE prophylaxis in young people and adults with moderate or severe COVID-19 and treatment-dose VTE prophylaxis in young people and adults with moderate COVID-19.

INSPIRATION, REMAP-CAP, HESACOVID and Perepu et al. (2021) evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19. The panel noted that the interventions that people had were mixed because of the local practices of the sites taking part in the trial. The panel recognised that the HESACOVID trial was very small and likely to be

underpowered for the results it presented. Around 45% of people in INSPIRATION did not match the definition of ‘severe COVID-19’ used here. This was reflected in the lower rates of VTE than the committee expected to see in a population with severe COVID-19. The panel took these factors into account when considering the evidence.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. The panel inferred that, in view of the possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow oxygen many would choose a treatment dose of an anticoagulant in spite of a potential increased risk of bleeding. Similarly, many of those who need low-flow oxygen or high-flow oxygen would choose a standard dose of an anticoagulant.

The panel inferred that, in view of the lack of clear benefit of intermediate- or treatment-dose anticoagulation, most would choose a standard prophylactic dose of an anticoagulant.

Resources

Cost effectiveness was not assessed as part of the evidence review.

The panel did not have concerns about opportunity costs when an LMWH is being used for people who need low-flow or high-flow oxygen. The panel decided to recommend that treatment of standard dose prophylaxis is continued for up to 7 days, including after discharge. This may be a higher resource use of anticoagulation because people who are discharged before 7 days will need to learn how to self-administer LMWH at home and monitor levels. For treatment dose prophylaxis, the panel decided to recommend that treatment is continued for up to 14 days. This may be longer than the standard treatment duration for acute illness (at least 7 days), so may be a higher resource use of anticoagulation in this group. This is to reflect the duration used in the trials contributing evidence to this recommendation. For people with severe COVID-19, the panel recommended that standard prophylactic-dose

anticoagulation is used, rather than higher doses. This means there is expected to be no increase in cost related to the treatment.

Equity

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years the risk of VTE is uncertain in the context of COVID-19. The risk-benefit of VTE and dosing should be discussed by multidisciplinary teams on a case-by-case basis considering all risk factors.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is only moderate to very low. However, the panel noted that the direction of effect tended to favour treatment-dose anticoagulation for adults with COVID-19 who need low-flow supplemental oxygen.

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow or high-flow oxygen and who do not have an increased bleeding risk might favour standard-dose anticoagulation and those who need low-flow oxygen may also favour treatment-dose anticoagulation.

It is anticipated that, after considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with severe COVID-19 would choose to have standard prophylactic-dose anticoagulation.

Feasibility

Using standard prophylactic doses in young people and adults receiving low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in most centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Implementing use of treatment-dose VTE prophylaxis in young people and adults in hospital who are receiving low-flow oxygen is expected to be feasible because it represents an increase in the dose and duration of an established treatment.

Using standard prophylactic doses in young people and adults receiving high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in some centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Appendices

Appendix A: PICO table

PICO table

Criteria	Notes
Population	Adults (aged 16 years and older) being treated for suspected or confirmed COVID-19
Interventions	Pharmacological prophylaxis with: Direct oral anticoagulants (DOACs) Low molecular weight heparin (LMWH) Unfractionated heparin (UFH) Fondaparinux sodium
Comparators	To each other Placebo / no treatment Same drug with different dosing strategy
Outcomes	Incidence of venous thromboembolism (VTE, PE, DVT) Mortality (all-cause mortality, inpatient mortality, COVID-related mortality) Admission to critical care (including use of advanced organ support) Serious adverse effects (such as major bleeding or admission to hospital)
Settings	All settings
Subgroups	Subgroups of people potentially at higher risk of thromboembolism include:

	Pregnant women or women who have given birth in the past 6 weeks People receiving treatment with sex hormones People who have or have previously had cancer People receiving renal replacement therapy or extracorporeal membrane oxygenation People with clotting conditions or a history of venous thromboembolism People with obesity (BMI 30kg/m2 or higher)
Study types	RCTs Cohort studies with a comparator group Systematic reviews of RCTs and/or cohort studies Depending on the volume of evidence identified, we may prioritise inclusion based on study design. We will prioritise inclusion of RCTs and systematic reviews of RCTs but if this study type is not available we will consider cohort studies with a comparator group and appropriate adjustment for confounding variables.
Countries	Any
Timepoints	Any
Other exclusions	Studies without a comparator group
Equality issues	Religion or beliefs, people with a learning disability and disabled people.

Appendix B: Included studies

Study
Bikdeli, Behnood, Talasaz, Azita H, Rashidi, Farid et al. (2021) Intermediate vs Standard-dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to ICU: Ninety-day Results from the INSPIRATION Trial. Thrombosis and haemostasis Mohebbi, Bahram, Sadeghipour, Parham, Talasaz, Azita H. et al. (2021) Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality among Patients with COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA - Journal of the American Medical Association
Goligher Ewan, C, Bradbury Charlotte, Ann, McVerry Bryan, J et al. Therapeutic Anticoagulation in Critically Ill Patients with Covid-19-Preliminary Report. medrxiv preprint
Lemos, A.C.B., do Espirito Santo, D.A., Salvetti, M.C. et al. (2020) Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thrombosis Research 196: 359-366
Perepu U.S. EA (2021) Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomised controlled trial. Pre-publication
Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. The New England journal of medicine 2021.
Lopes RD, de Barros E Silva PGM, Furtado RHM et al. (2021) Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet (London, England)
Sholzberg, Michelle Heparin for Moderately Ill Patients with Covid-19, medRxiv preprint doi: https://doi.org/10.1101/2021.07.08.21259351; this version posted July 12, 2021

Appendix C: Excluded studies

Study	Reason for exclusion
Ayerbe, L.; Risco, C.; Ayis, S. (2020) The association between treatment with heparin and survival in patients with Covid-19. Journal of Thrombosis and Thrombolysis 50(2): 298-301	- Exclude - duplicate content *In Flumignan cochrane review*
Ayerbe, Luis; Risco, Carlos; Ayis, Salma The association between treatment with heparin and survival in patients with Covid-19. medrxiv preprint	- Exclude - duplicate content *preprint file but already have published version*
Belcaro, Gianni, Corsi, Marcello, Agus, Giovanni B et al. (2020) Thrombo-prophylaxis prevents thrombotic events in home-managed COVID patients. A registry study. Minerva medica 111(4): 366-368	- Exclude - surveillance study that would be excluded by development search filters
Belen-Apak, F Burcu and Sarialioglu, F (2020) Pulmonary intravascular coagulation in COVID-19: possible pathogenesis and recommendations on anticoagulant/thrombolytic therapy. J Thromb Thrombolysis 50(2): 278-280	- Exclude - Not a study design specified in protocol
Beun, Robert, Kusadasi, Nuray, Sikma, Maaike et al. (2020) Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. International journal of laboratory hematology 42suppl1: 19-20	- Exclude - Not a study design specified in protocol *letter to editor*
Bikdeli, Behnood, Talasaz, Azita H, Rashidi, Farid et al. (2020) Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thrombosis research 196: 382-394	- Exclude - Not a study design specified in protocol *trial protocol not results*
Birkeland, Kade, Zimmer, Raymond, Kimchi, Asher et al. (2020) Venous Thromboembolism in Hospitalized COVID-19 Patients: Systematic Review. Interactive journal of medical research 9(3): e22768	- Exclude - Not a study design specified in protocol *Only reports anticoagulation in a single group, although the text defines anticoagulation as either prophylaxis or treatment anticoagulation, but there is no way to obtain that data from this report*
Bompard, Florian, Monnier, Hippolyte, Saab, Ines et al. (2020) Pulmonary embolism in patients with COVID-19 pneumonia. The European respiratory journal 56(1)	- Exclude - Not a study design specified in protocol *comparison is not centred around use of anticoagulation, but whether PE was detected or not - everyone had the same anticoagulation*
Brouns, Steffie H, Bruggemann, Renee, Linkens, Aimee E M J H et al. (2020) Mortality and the Use of Antithrombotic Therapies Among Nursing Home Residents with COVID-19.	- Exclude - Not a study design specified in protocol *case series*

Study	Reason for exclusion
Journal of the American Geriatrics Society 68(8): 1647-1652	
Cattaneo, Marco, Bertinato, Elena M, Birocchi, Simone et al. (2020) Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified?. Thromb Haemost 120(8): 1230-1232	- Exclude - Not a study design specified in protocol
Cattaneo, Marco and Morici, Nuccia (2020) Is thromboprophylaxis with high-dose enoxaparin really necessary for COVID-19 patients? A new "prudent" randomised clinical trial. Blood transfusion = Trasfusione del sangue 18(3): 237-238	- Exclude - Not a study design specified in protocol *letter about RCT protocol*
Chang, Heepeel, Rockman, Caron B, Jacobowitz, Glenn R et al. (2020) Deep Venous Thrombosis in Hospitalized Patients with Coronavirus Disease 2019. Journal of vascular surgery. Venous and lymphatic disorders	- Exclude - Not a study design specified in protocol *Comparisons are DVT vs no DVT in people with COVID-19 and DVT vs non DVT in non COVID-19 patients. There is no analytical data for anticoagulation vs no anticoagulation or high vs standard dose. After ultrasound more people with DVT went on to therapeutic dose (which is management of DVT - not in scope) and no outcome data are reported for these groups.*
Chi, Gerald, Lee, Jane J, Jamil, Adeel et al. (2020) Venous Thromboembolism among Hospitalized Patients with COVID-19 Undergoing Thromboprophylaxis: A Systematic Review and Meta-Analysis. Journal of clinical medicine 9(8)	- Exclude - Not a study design specified in protocol *The meta-analysis / pooled results reported are not comparative*
Criel, M., Falter, M., Jaeken, J. et al. (2020) Venous thromboembolism in SARS-CoV-2 patients: Only a problem in ventilated ICU patients, or is there more to it?. European Respiratory Journal 56(1): 2001201	- Exclude - Not a study design specified in protocol *letter to editor*
Daughety, Molly M., Morgan, Andrew, Frost, Erin et al. (2020) COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated-dose Thromboprophylaxis strategy. Thrombosis Research	- Exclude - Not a study design specified in protocol *letter to editor*
Di Minno, Alessandro, Ambrosino, Pasquale, Calcaterra, Ilenia et al. (2020) COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. Seminars in thrombosis and hemostasis	- Exclude - Not a study design specified in protocol *does not report any comparative data on anticoagulation, only overall incidence of events*
Di Renzo, Gian Carlo and Giardina, Irene (2020) Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and	- Exclude - Not a study design specified in protocol

Study	Reason for exclusion
thromboprophylaxis. Am J Obstet Gynecol 223(1): 135-135	
Falcoz, P.-E., Monnier, A., Puyraveau, M. et al. (2020) Extracorporeal membrane oxygenation for critically ill patients with COVID-19-related acute respiratory distress syndrome: Worth the effort?. American Journal of Respiratory and Critical Care Medicine 202(3): 460-463	- Exclude - Not a study design specified in protocol *Not comparative*
Ferrandis, Raquel, Llau, Juan V, Quintana, Manuel et al. (2020) COVID-19: opening a new paradigm in thromboprophylaxis for critically ill patients?. Crit Care 24(1): 332-332	- Exclude - Not a study design specified in protocol
Frydman, Galit H, Boyer, Edward W, Nazarian, Rosalynn M et al. (2020) Coagulation Status and Venous Thromboembolism Risk in African Americans: A Potential Risk Factor in COVID-19. Clin Appl Thromb Hemost 26: 1076029620943671-1076029620943671	- Exclude - Not a study design specified in protocol
Hanif, Ahmad, Khan, Sumera, Mantri, Nikhitha et al. (2020) Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience. Annals of hematology 99(10): 2323-2328	- Exclude - Intervention does not match that specified in the protocol *The type of anticoagulation in the group of interest (prophylaxis) dose not seem to be reported*
Hasan, Syed Shahzad, Radford, Sam, Kow, Chia Siang et al. (2020) Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis. Journal of thrombosis and thrombolysis	- Exclude - Not a study design specified in protocol *Only reports incidence of VTE, not any comparative data*
Hekimian, G., Lebreton, G., Brechot, N. et al. (2020) Severe pulmonary embolism in COVID-19 patients: A call for increased awareness. Critical Care 24: 274	- Exclude - Not a study design specified in protocol *letter to editor*
Ho, K.S., Herrera, Y., Pattupara, A. et al. (2020) ANTICOAGULATION AND COVID-19: A META-ANALYSIS. Chest 158(4supplement): a2205	- Exclude - surveillance study that would be excluded by development search filters
Huang, Yongshent, Lyu, Xiaoyu, Li, Dan et al. A cohort study of 223 patients explores the clinical risk factors for the severity diagnosis of COVID-19. medrxiv preprint	- Exclude - Not a study design specified in protocol
Huette, P., Beyls, C., Guilbart, M. et al. (2020) Extracorporeal membrane oxygenation for respiratory failure in COVID-19 patients: outcome and time-course of clinical and biological parameters. Canadian Journal of Anesthesia 67(10): 1486-1488	- Exclude - Not a study design specified in protocol *letter, case series*

Study	Reason for exclusion
Klok, F A, Kruip, M J H A, van der Meer, N J M et al. (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research 191: 145-147	- Exclude - Not a study design specified in protocol
Kumar, Poornima; Mediwake, Rapti; Rhead, Camilla (2020) A matter of time: duration and choice of venous thromboprophylaxis in patients diagnosed with COVID-19. Br J Hosp Med (Lond) 81(5): 1-2	- Exclude - Not a study design specified in protocol
Kwok, Benjamin, Brosnahan, Shari B, Amoroso, Nancy E et al. (2020) Pulmonary Embolism Response Team activation during the COVID-19 pandemic in a New York City Academic Hospital: a retrospective cohort analysis. Journal of thrombosis and thrombolysis	- Exclude - Intervention does not match that specified in the protocol
Lachant, D.J., Lachant, N.A., Kouides, P. et al. (2020) Chronic therapeutic anticoagulation is associated with decreased thrombotic complications in SARS-CoV-2 infection. Journal of Thrombosis and Haemostasis 18(10): 2640-2645	- Exclude - Not a study design specified in protocol *Looks at people who were on anticoagulation BEFORE admission for COVID-19 so is not telling us about prophylaxis because of COVID-19 and has no comparator group*
Liao, S.-C., Shao, S.-C., Chen, Y.-T. et al. (2020) Incidence and mortality of pulmonary embolism in COVID-19: A systematic review and meta-analysis. Critical Care 24(1): 464	- Exclude - Not a study design specified in protocol *no comparative data*
Llitjos, Jean-Francois, Leclerc, Maxime, Chochois, Camille et al. (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of thrombosis and haemostasis : JTH 18(7): 1743-1746	- Exclude - duplicate content *In McBane, Mouhand systematic reviews*
Lucarelli, E., Behn, C., Lashley, S. et al. (2020) Mechanical Ventilation in Pregnancy Due to COVID-19: A Cohort of Three Cases. American Journal of Perinatology 37(1): 1066-1069	- Exclude - Not a study design specified in protocol *case series*
Maldonado, Edward; Tao, Derrick; Mackey, Katherine (2020) Antithrombotic Therapies in COVID-19 Disease: a Systematic Review. Journal of general internal medicine 35(9): 2698-2706	- Exclude - duplicate content *The eligible study has been picked up in other systematic reviews that better match the PICO*
Manolis, A.S., Manolis, T.A., Manolis, A.A. et al. (2020) COVID-19 Infection: Viral Macro- and Micro-Vascular Coagulopathy and Thromboembolism/Prophylactic and Therapeutic Management. Journal of Cardiovascular Pharmacology and Therapeutics	- Exclude - Not a study design specified in protocol
Mattioli, M., Benfaremo, D., Mancini, M. et al. (2020) Safety of intermediate dose of low	- Exclude - Not a study design specified in protocol

Study	Reason for exclusion
molecular weight heparin in COVID-19 patients. Journal of Thrombosis and Thrombolysis	*Think this is non-comparative - all patients received 'intermediate' dose LMWH but the dose for each patient differed depending on bodyweight or renal impairment so it looks like 3 doses. It does not appear to be possible to extract outcome data for individual dosages. Finally, because of the different clinical characteristics of the 3 groups such a comparison is unlikely to be appropriate.*
Maurer, L.R., Luckhurst, C.M., Hamidi, A. et al. (2020) A low dose heparinized saline protocol is associated with improved duration of arterial line patency in critically ill COVID-19 patients. Journal of Critical Care 60: 253-259	- Exclude - Intervention does not match that specified in the protocol
McBane, Robert D., Torres Roldan, Victor D., Niven, Alexander S. et al. (2020) Anticoagulation in COVID-19: A Systematic Review, Meta-Analysis and Rapid Guidance From The Mayo Clinic. Mayo Clinic Proceedings	- Exclude - duplicate content *The analysis of interest included 4 studies, 3 of which have been included in other systematic reviews that have been included. On investigation of the relevance of the 4th study (Yin 2020 Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2), it has been determined to be a duplicate report of data from Tang 2020 (Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy) – same number of participants, identical top-line results.*
Mortus, J.R., Manek, S.E., Brubaker, L.S. et al. (2020) Thromboelastographic Results and Hypercoagulability Syndrome in Patients with Coronavirus Disease 2019 Who Are Critically Ill. JAMA Network Open 3(6): e2011192	- Exclude - Outcome does not match that specified in the protocol
Nahum, J., Morichau-Beauchant, T., Daviaud, F. et al. (2020) Venous Thrombosis among Critically Ill Patients with Coronavirus Disease 2019 (COVID-19). JAMA Network Open 3(5): 10478	- Exclude - Not a study design specified in protocol *Letter, case series*
NCT04401293 (2020) Full Dose Heparin Vs. Prophylactic Or Intermediate Dose Heparin in High Risk COVID-19 Patients. https://clinicaltrials.gov/show/NCT04401293	- Exclude - Not a study design specified in protocol
NCT04408235 (2020) High Versus Low LMWH Dosages in Hospitalized Patients With Severe COVID-19 Pneumonia and Coagulopathy. https://clinicaltrials.gov/show/NCT04408235	- Exclude - Not a study design specified in protocol *protocol, no results*
NCT04409834 (2020) Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients Trial. https://clinicaltrials.gov/show/NCT04409834	- Exclude - Not a study design specified in protocol

Study	Reason for exclusion
NCT04508439 (2020) Effect of the Use of Anticoagulant Therapy During Hospitalization and Discharge in Patients With COVID-19 Infection. https://clinicaltrials.gov/show/NCT04508439	- Exclude - Not a study design specified in protocol
Nopp, Stephan, Moik, Florian, Jilma, Bernd et al. (2020) Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Research and practice in thrombosis and haemostasis	- Exclude - Intervention does not match that specified in the protocol
Pawlowski, Colin, Venkatakrishnan, AJ, Kirkup, Christian et al. Enoxaparin is associated with lower rates of thrombosis, kidney injury, and mortality than Unfractionated Heparin in hospitalized COVID patients. medrxiv preprint	- Exclude - Intervention does not match that specified in the protocol
Piagnerelli, Michaël; Cauchie, Philippe; Wautrecht, Jean-Claude (2020) Optimizing the Risk-Benefit Balance of Thromboprophylaxis in Critically Ill Patients With Coronavirus Disease 2019. Crit Care Med 48(10): e988-e989	- Exclude - Not a study design specified in protocol *is a letter*
Piazza, Ornella (2020) Should ICU COVID-19 patients empirically receive therapeutic doses of anticoagulant?. Infez Med 28(suppl1): 4-5	- Exclude - Not a study design specified in protocol *editorial*
Pooni, Rajan S (2020) Research in brief: Coagulopathy in COVID-19: Determining and managing thrombotic risk in COVID-19 infection. Clinical medicine (London, England) 20(4): e59	- Exclude - Not a study design specified in protocol
Porfidia, Angelo and Pola, Roberto (2020) Venous Thromboembolism and Heparin Use in COVID-19 Patients: Juggling between Pragmatic Choices, Suggestions of Medical Societies and the Lack of Guidelines. J Thromb Thrombolysis 50(1): 68-71	- Exclude - Not a study design specified in protocol
Prandoni, P., Cattelan, A.M., Carrozzi, L. et al. (2020) The hazard of fondaparinux in non-critically ill patients with COVID-19: Retrospective controlled study versus enoxaparin. Thrombosis Research 196: 395-397	- Exclude - Not a study design specified in protocol *letter to editor*
Roberts, Lara N, Whyte, Martin B, Georgiou, Loizos et al. (2020) Postdischarge venous thromboembolism following hospital admission with COVID-19. Blood 136(11): 1347-1350	- Exclude - Not a study design specified in protocol *The only comparison is post-discharge VTE rate in COVID-19 patients compared with historical controls, but data on continuing prophylaxis is absent so can't answer our ongoing prophylaxis question*
Russo, Vincenzo, Cardillo, Giuseppe, Viggiano, Giuseppe Vito et al. (2020) Fondaparinux Use in Patients With COVID-19: A Preliminary	- Exclude - Outcome does not match that specified in the protocol

Study	Reason for exclusion
Multicenter Real-World Experience. Journal of cardiovascular pharmacology 76(4): 369-371	
Savioli, Felicio (2020) Is there a rationale for heparin use among severe COVID-19 patients?. Einstein (Sao Paulo) 18: eed5758-eed5758	- Exclude - Not a study design specified in protocol
Schiavone, M., Gasperetti, A., Mancone, M. et al. (2020) Oral anticoagulation and clinical outcomes in COVID-19: An Italian multicenter experience. International Journal of Cardiology	- Exclude - Intervention does not match that specified in the protocol
Shah, Akshay, Donovan, Killian, McHugh, Anna et al. (2020) Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study. Critical care (London, England) 24(1): 561	- Exclude - Not a study design specified in protocol *No comparative data on prophylaxis strategy, all patients had standard low molecular weight heparin. Only comparative data is mortality in VTE compared with no VTE*
Spyropoulos, Alex C; Ageno, Walter; Barnathan, Elliot S (2020) Hospital-based use of thromboprophylaxis in patients with COVID-19. Lancet 395(10234): e75-e75	- Exclude - Not a study design specified in protocol
Stattin, K., Lipcsey, M., Andersson, H. et al. (2020) Inadequate prophylactic effect of low-molecular weight heparin in critically ill COVID-19 patients. Journal of Critical Care 60: 249-252	- Exclude - Not a study design specified in protocol
Stessel, Bjorn, Vanvuchelen, Charlotte, Bruckers, Liesbeth et al. (2020) Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study. Thrombosis research 194: 209-215	- Exclude - duplicate content *In Mouhand systematic review*
Susen, Sophie, Tacquard, Charles Ambroise, Godon, Alexandre et al. (2020) Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. Crit Care 24(1): 364-364	- Exclude - Not a study design specified in protocol
Tang, Ning, Bai, Huan, Chen, Xing et al. (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of thrombosis and haemostasis : JTH 18(5): 1094-1099	- Exclude - duplicate content *In Flumignan Cochrane review and Lu, McBane systematic reveiws*
Trigonis, Russell A, Holt, Daniel B, Yuan, Rebecca et al. (2020) Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. Critical care medicine 48(9): e805-e808	- Exclude - Not a study design specified in protocol *The overall comparison is DVT versus no DVT rather than comparing thromboprophylaxis strategies. Data on 6 different strategies is reported but the only statistical analysis is one overall p-value. To extract this data in line with the guideline review question, we'd need to*

Study	Reason for exclusion
	create 6 arms but there is no other useful data reported for those 6 arms for the data extraction wouldn't really give useful information
Trimaille, Antonin, Curtiaud, Anais, Marchandot, Benjamin et al. (2020) Venous thromboembolism in non-critically ill patients with COVID-19 infection. Thrombosis research 193: 166-169	- Exclude - Not a study design specified in protocol *is a letter with cohort data however the data comparison was not by use or type of anticoagulation but be presence of VTE or not*
Tritschler, T., Mathieu, M.-E., Skeith, L. et al. (2020) Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. Journal of Thrombosis and Haemostasis	- Exclude - Not a study design specified in protocol
Turan, O., Hakim, A., Dashraath, P. et al. (2020) Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: A systematic review. International Journal of Gynecology and Obstetrics 151(1): 7-16	- Exclude - Outcome does not match that specified in the protocol
Viecca, Maurizio, Radovanovic, Dejan, Forleo, Giovanni Battista et al. (2020) Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacological research 158: 104950	- Exclude - Not a study design specified in protocol
Zermatten, M.G., Pantet, O., Gomez, F. et al. (2020) Utility of D-dimers and intermediate-dose prophylaxis for venous thromboembolism in critically ill patients with COVID-19. Thrombosis Research 196: 222-226	- Exclude - Not a study design specified in protocol *letter to editor*
Zhang, Chi, Shen, Long, Le, Ke-Jia et al. (2020) Incidence of Venous Thromboembolism in Hospitalized Coronavirus Disease 2019 Patients: A Systematic Review and Meta-Analysis. Frontiers in cardiovascular medicine 7: 151	- Exclude - Not a study design specified in protocol *No comparative data for anticoagulation - only comparison is VTE incidence in severe vs not-severe disease*
Zhang, Li, Feng, Xiaokai, Zhang, Danqing et al. (2020) Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation 142(2): 114-128	- Exclude - Not a study design specified in protocol *cross-sectional survey*

Appendix D: Evidence tables

Goligher Ewan et al.

Bibliographic Reference	Goligher Ewan, C; Bradbury Charlotte, Ann; McVerry Bryan, J; Lawler Patrick, R; Berger Jeffrey, S; Gong Michelle, N; Carrier, Marc; Reynolds Harmony, R; Kumar, Anand; Turgeon Alexis, F; Kornblith Lucy, Z; Kahn Susan, R; Marshall John, C; Kim Keri, S; Houston Brett, L; Derde Lennie P., G.; Cushman, Mary; Tritschler, Tobias; Angus Derek, C; Godoy Lucas, C; McQuilten, Zoe; Kirwan, Bridget-Anne; Farkouh Michael, E; Brooks Maria, M; Lewis Roger, J; Gordon, Anthony; Berry, Scott; McArthur Colin, J; Neal Matthew, D; Hochman Judith, S; Webb Steven, A; Zarychanski, Ryan; Therapeutic Anticoagulation in Critically Ill Patients with Covid-19-Preliminary Report; medrxiv preprint

Study details

Trial registration (if reported)	NCT02735707 NCT 04505774 NCT 04359277 NCT04372589
Study start date	21-Apr-2020
Study end date	19-Dec-2020
Aim of the study	To determine whether therapeutic dose anticoagulation improves survival and reduces the duration of organ support compared to usual care pharmacological thromboprophylaxis in critically ill patients with COVID-19.
County/ Geographical location	Multicenter: Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, USA
Study setting	Intensive care units in hospitals
Population description	Patients with confirmed infection of covid-19, assessed as severe.
Inclusion criteria	Hospitalized adult patients; confirmed Covid-19; severe Covid-19: provision of intensive care unit-level respiratory or cardiovascular organ support (high flow nasal oxygen ≥ 20 L/min, non-invasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes)
Exclusion criteria	Admitted to the ICU with Covid-19 for more than 48 hours (REMAP-CAP) or to hospital for more than 72 hours (ACTIV-4a, ATTACC) prior to randomization; at imminent risk of death without an ongoing commitment to full organ support; at high risk of bleeding; receiving dual antiplatelet therapy; had a separate clinical indication for therapeutic anticoagulation; history of heparin sensitivity including heparin-induced thrombocytopenia.

Intervention/test/approach	Therapeutic anticoagulation (unfractionated or low molecular weight heparin)
Comparator (where applicable)	Prophylactic anticoagulation (usual care)
Methods for population selection/allocation	Selection methods unclear. Random allocation (with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention)
Methods of data analysis	Bayesian cumulative logistic model that calculated the posterior probability distribution for the proportional odds ratio. Adjusted for age, sex, site, time period.
Attrition/loss to follow-up	1205 randomised, 1074 analysed. 11% attrition.
Source of funding	European Union, National Health and Medical Research Council (NHMRC) (Australia), Health Research Council (HRC) (New Zealand), Canadian Institute of Health Research, Strategy for Patient-Oriented Research (CIHR-SPOR) (Canada).
Study limitations (Author)	Open-label design (authors state that although clinician or participant awareness likely had little or no impact on the primary outcome that incorporated mortality and duration of organ support). Clinicians employed local site practice in usual care arm. A substantial majority of enrollment in the severe patient group was in the United Kingdom where national practice guidelines changed during the trial to recommend that Covid-19 patients admitted to an ICU receive intermediate (rather than low) dose anticoagulation for thromboprophylaxis. Many participants in the usual care arm therefore received an intermediate dose of thromboprophylaxis. Subgroup analysis indicated that treatment effect of intervention did not vary meaningfully based on whether sites used low or intermediate dose thromboprophylaxis.
Study limitations (Reviewer)	**None**
Other details	**None**

Study arms

Therapeutic heparin (N = 532)

Aim of the study	To determine whether therapeutic dose anticoagulation improves survival and reduces the duration of organ support compared to usual caer pharmacological thromboprophylaxis in critically ill patients with COVID-19.
Exclusion criteria	Admitted to the ICU with Covid-19 for more than 48 hours (REMAP-CAP) or to hospital for more than 72 hours (ACTIV-4a, ATTACC) prior to randomization; at imminent risk of death without an ongoing commitment to full organ support; at high risk of bleeding; receiving dual antiplatelet therapy; had a separate clinical indication for therapeutic anticoagulation; history of heparin sensitivity including heparin-induced thrombocytopenia
Intervention/test/approach	Therapeutic anticoagulation
Comparator (where applicable)	Prophylactic anticoagulation
Attrition/loss to follow-up	590 randomised, 529 analysed. 10% attrition.
Study limitations (Author)	None specific to therapeutic arm.

Therapeutic anticoagulation according to local practice (IV unfractionated heparin or SC low molecular weight heparin) for up to 14 days or until hospital discharge or liberation from the need for supplemental oxygen, whichever comes first For UFH, suggested target for aPTT of 1.5 to 2.5 times the upper limit of normal or therapeutic anti-Xa levels Low molecular weight heparin dosed according to patient weight and creatinine clearance.

Prophylactic heparin (N = 557)

Aim of the study	To determine whether therapeutic dose anticoagulation improves survival and reduces the duration of organ support compared to usual caer pharmacological thromboprophylaxis in critically ill patients with COVID-19.
Exclusion criteria	Admitted to the ICU with Covid-19 for more than 48 hours (REMAP-CAP) or to hospital for more than 72 hours (ACTIV-4a, ATTACC) prior to randomization; at imminent risk of death without an ongoing commitment to full organ support; at high risk of bleeding; receiving dual antiplatelet therapy; had a separate clinical indication for therapeutic anticoagulation; history of heparin sensitivity including heparin-induced thrombocytopenia
Intervention/test/approach	Therapeutic anticoagulation

Comparator (where applicable)	Prophylactic anticoagulation
Attrition/loss to follow-up	615 randomised, 545 analysed. 11% attrition.
Study limitations (Author)	Clinicians employed local site practice in usual care arm.

Characteristics

Arm-level characteristics

Characteristic	Therapeutic heparin (N = 532)	Prophylactic heparin (N = 557)
Age Mean (SD)	60.2 (13.1)	61.6 (12.5)
Gender Male No of events	n = 383 ; % = 72	n = 379 ; % = 68
White No of events	n = 314 ; % = 74.2	n = 326 ; % = 73.6
Asian No of events	n = 69 ; % = 16.3	n = 71 ; % = 16
Black No of events	n = 24 ; % = 5.7	n = 20 ; % = 4.5
Other No of events	n = 16 ; % = 3.8	n = 26 ; % = 5.9

Characteristic	Therapeutic heparin (N = 532)	Prophylactic heparin (N = 557)
No oxygen/supplemental oxygen Sample size	n = 8 ; % = 1.5	n = 7 ; % = 1.3
High flow nasal oxygen Sample size	n = 172 ; % = 32.3	n = 188 ; % = 33.8
Non-invasive ventilation Sample size	n = 214 ; % = 40.2	n = 200 ; % = 35.9
Vasopressors/inotropes Sample size	n = 87 ; % = 16.7	n = 100 ; % = 18.2
Invasive mechanical ventilation Sample size	n = 138 ; % = 25.9	n = 162 ; % = 29.1
Diabetes mellitus (type 1 or 2) Sample size	n = 168 ; % = 32.1	n = 182 ; % = 33.3
Severe cardiovascular disease Sample size	n = 36 ; % = 7.3	n = 34 ; % = 6.6
Chronic kidney disease Sample size	n = 56 ; % = 11.2	n = 40 ; % = 8
Chronic respiratory disease Sample size	n = 121 ; % = 24.1	n = 125 ; % = 24.2

Characteristic	Therapeutic heparin (N = 532)	Prophylactic heparin (N = 557)
Chronic liver disease Sample size	n = 6 ; % = 1.2	n = 2 ; % = 0.4

Outcomes

Survival

Outcome	Therapeutic heparin vs Prophylactic heparin, , N2 = 557, N1 = 529
Survival to hospital discharge Odds ratio/95% CI	0.88 (0.67 to 1.16)

Survival

Outcome	Therapeutic heparin, , N = 532	Prophylactic heparin, , N = 557
Survival to hospital discharge No of events	n = 340 ; % = 64.3	n = 356 ; % = 65.3

Survival to hospital discharge - Polarity - Higher values are better

Organ support-free days

Outcome	Therapeutic heparin vs Prophylactic heparin, , N2 = 557, N1 = 532
Organ support-free days to 21 Odds ratio/95% CI	0.87 (0.7 to 1.08)

Organ support-free days

Outcome	Therapeutic heparin, , N = 532	Prophylactic heparin, , N = 557
Organ support-free days to 21 Median (IQR)	3 (-1 to 16)	5 (-1 to 16)

Organ support-free days to 21 - Polarity - Higher values are better

Major thrombotic events or death

Outcome	Therapeutic heparin vs Prophylactic heparin, , N2 = 532, N1 = 557
Major thrombotic events or death Odds ratio/95% CI	1.05 (0.79 to 1.4)

Major thrombotic events or death

Outcome	Therapeutic heparin, , N = 532	Prophylactic heparin, , N = 557
Major thrombotic events No of events	n = 27 ; % = 5.7	n = 49 ; % = 10.3
Death in hospital No of events	n = 189 ; % = 35.7	n = 189 ; % = 34.7
Major thrombotic events or death No of events	n = 200 ; % = 41.4	n = 211 ; % = 42.7

Major thrombotic events - Polarity - Lower values are better

Death in hospital - Polarity - Lower values are better

Major thrombotic events or death - Polarity - Lower values are better

Major bleeding

Outcome	Therapeutic heparin vs Prophylactic heparin, , N2 = 532, N1 = 557
Major bleeding **Odds ratio/95% CI**	**1.19 (0.57 to 2.49)**

Major bleeding

Outcome	Therapeutic heparin, , N = 532	Prophylactic heparin, , N = 557
Major bleeding No of events	n = 15 ; % = 3.1	n = 12 ; % = 2.4

Major bleeding - Polarity - Lower values are better

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes *(Using central web-based systems)*
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No *(Baseline characteristics comparable)*
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No *(The analysis did not include people who withdrew consent after randomisation (10 in intervention group, 15 in control group). Likely to have a small effect.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No *(Small number of participants excluded post-randomisation, unlikely to affect overall results.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Due to potential deviations arising from experimental context and exclusion of participants who withdrew from the analysis.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No information *(Prophylactic heparin given according to local protocols. Various settings within the study.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No information *(Intervention implementation success not reported)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	No information *(Not reported)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Probably no
Domain 2b: Risk of bias due to deviations from the intended	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns

Section	Question	Answer
interventions (effect of adhering to intervention)		
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lawler, 2021

Bibliographic Reference	Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. The New England journal of medicine 2021.

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT02735707, NCT04505774, NCT04359277, NCT04372589
Study start date	21-Apr-2020
Study end date	22-Jan-2021

COVID-19 prevalence at the time of the study	Higher prevalence (e.g. during peak of first wave)
Aim of the study	Investigate if therapeutic-dose anticoagulation improves outcomes in non-critically ill patients hospitalized for Covid-19
County/ Geographical location	Multiple: UK, US, Canada, Brazil
Study setting	Hospital
Population description	Those with moderate disease severity- defined as hospitalization for Covid-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU.
Inclusion criteria	SEE TABLE PG.41 SUPPLEMENTARY MATERIAL FOR SUMMARY ATTACC: Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours, for microbiologically confirmed COVID-19, enrolled < 72 hours of hospital admission or of COVID-19 confirmation ACTIV-4a: As per ATTACC REMAP-CAP: Patients will be eligible for this domain if:

	• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Exclusion criteria	SEE TABLE PG.41 SUPPLEMENTARY MATERIAL FOR SUMMARY ATTACC: Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization 2. Patients for whom the intent is to notuse pharmacologic thromboprophylaxis 3. Active bleeding 4. Risk factors for bleeding, including: a. intracranial surgery or stroke within 3 months; b. history of intracerebral arteriovenous malformation; c. cerebral aneurysm or mass lesions of the central nervous system;intracranial malignancy e. history of intracranial bleeding f. history of bleeding diatheses (e.g., hemophilia) g. history of gastrointestinal bleeding within previous 3 months h. thrombolysis within the previous 7 days i. presence of an epidural or spinal catheter j. recent major surgery <14 days k. uncontrolled hypertension (sBP >200mmHg, dBP >120 mmHg) l. other physician-perceived contraindicationsto anticoagulation 5. Platelet count <50 x109/L, INR >2.0, or baseline aPTT >50 6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur) 7. Acute or subacute bacterial endocarditis 8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity 9. Current use of dual antiplatelet therapy 10. Patients with an independent indication for therapeutic anticoagulation 11. Patients in whom imminent demise is anticipated and there is no commitment toactive ongoing intervention 12. Anticipated transfer to another hospital thatis not a study site within 72 hours 13. Enrollment in other trials related to anticoagulation or antiplatelettherapy ACTIV-4a: Not stated

	REMAP-CAP: More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement oforgan failure support) • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual antiplatelet therapy • Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decisionhas been made to commence therapeutic anticoagulation • Enrollment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial • Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT). • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention/test/approach	Summary table pg. 43 supplementary material REMAP-CAP: Unfractionated heparin or low molecular weight heparin • Patients may be switched between unfractionated heparin and low molecular weight heparin. Dosing: Dosed according to local hospital policy, practice, and guidelines for treatment of venous thromboembolism • For UFH, suggested target for aPTT of 1.5 to 2.5 times the upper limit of normal or therapeutic anti-Xa levels • Low molecular weight heparin dosed according to patient weight. Duration: Up to 14 days or to hospital discharge, whichever comes first • For ICU patients, therapeutic anticoagulation could be discontinued at ICU discharge.

	ACTIV-4a: Unfractionated heparin or low molecular weight heparin • Patients may be switched between unfractionated heparin and low molecular weight heparin • Patients with impaired renal function were stipulated to received unfractionated heparin. Dosing: Low molecular weight heparin dosed according to patient weight and creatinine clearance • For UFH, suggested target of anti-Xa of 0.3-0.7 IU/ml or aPTT 1.5 to 2.5 times the upper limit of normal. Duration: Up to 14 days or to hospital discharge, whichever comes first ATTACC: Unfractionated heparin or low molecular weight heparin • Either agent permitted and patients may be switched between unfractionated heparin and low molecular weight heparin. Dosing: Low molecular weight heparin dosed according to patient weight and creatinine clearance according to local practice and policy • For UFH, suggested target of aPTT 1.5 to 2.5 times the upper limit of normal or therapeutic anti-Xa levels. Duration: Up to 14 days or until hospital discharge or recovery (defined as liberation from supplemental oxygen>24 hours, provided oxygen was required), whichever comes first
Comparator (where applicable)	REMAP-CAP: Standard venous thromboprophylaxis according to local guidelines or usual practice. Dose of chosen agent should not be sufficient to result in therapeutic anticoagulation. Up to 14 days or hospital discharge, whichever comes first • After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician. ACTIV-4a: Any one of enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin according to local preference. Dose of agent specified to be consistent with guidelines for low dose thromboprophylaxis. Up to 14 days or

	hospital discharge, whichever comes first • After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician. ATTAC: Standard venous thromboprophylaxis according to local guidelines or usual practice. Dose of chosen agent should not be more than half of the approved therapeutic dose for the treatment of venous thromboembolism. Up to 14 days or hospital discharge, whichever comes first • After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician.
Methods for population selection/allocation	The design prospectively stratified participants into severe (ICU-level of care; critically ill) and moderate (hospitalized; non-critically ill) disease severity states at enrolment.
Methods of data analysis	Method of randomisation: Computer generated randomisation, response-adaptive randomisation. Statistical analysis: Bayesian cumulative logistic model that calculated the posterior probability distribution for the proportional odds ratio. Adjusted for age, sex, site, time period.
Attrition/loss to follow-up	Intervention arms: 1190 participants randomised to intervention arms, 1171 participants included in the primary analysis. Usual care arms: 1055 participants randomised to usual care arms, 1048 partipants included in the primary analysis.
Source of funding	ATTACC - The ATTACC platform was supported by grants from the Canadian Institutes of Health Research, LifeArc Foundation, Thistledown Foundation, Research Manitoba, Ontario Ministry of Health, Peter Munk Cardiac Centre, Cancercare Manitoba Foundation, and Victoria General Hospital Foundation. ACTIV-4a - The ACTIV-4a platform was sponsored by the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda and administered through OTA-20-011. The research was, in part, funded by the National Institutes of Health (NIH) Agreement 1OT2HL156812-01. REMAP-CAP - Supported by the European Union

Study limitations (Author)	• The open-label design of the mpRCT represents a potential limitation • The potential for ascertainment bias cannot be excluded for the secondary outcomes of major bleeding or thrombosis • This, along with the absence of protocolized screening for venous thrombosis, exclusion of patients at increased bleeding risk, and changing disease epidemiology over time may have contributed to lower thrombotic event rates than have been previously reported • The treatment effect was attenuated in the final analysis relative to the adaptive stopping results; nevertheless, a high probability of benefit persisted in all D-dimer groups.
Study limitations (Reviewer)	None to add
Other details	None to add.

Study arms

Treatment dose anticoagulation (N = 1181)

usual care thromboprophylaxis (N = 1050)

Characteristics

Arm-level characteristics

Characteristic	Treatment dose anticoagulation (N = 1181)	usual care thromboprophylaxis (N = 1050)
Age Mean (SD)	59 (14.1)	58.8 (13.9)
Gender Male Sample size	n = 713 ; % = 60.4	n = 597 ; % = 56.9
White Sample size	n = 622 ; % = 62.6	n = 564 ; % = 66.7
Asian Sample size	n = 41 ; % = 4.1	n = 43 ; % = 5.1

Characteristic	Treatment dose anticoagulation (N = 1181)	usual care thromboprophylaxis (N = 1050)
Black Sample size	n = 219 ; % = 22	n = 162 ; % = 19.2
Hispanic / Latino Sample size	n = 574 ; % = 57.2	n = 537 ; % = 61.1
Hypertension Sample size	n = 546 ; % = 53.4	n = 447 ; % = 50.1
Diabetes mellitus Sample size	n = 352 ; % = 29.8	n = 311 ; % = 29.6
Antiplatelet agent Sample size	n = 148 ; % = 13	n = 111 ; % = 11
remdesivir Sample size	n = 428 ; % = 36.3	n = 383 ; % = 36.5
corticosteroids Sample size	n = 479 ; % = 60.6	n = 415 ; % = 63.3
tocilzumab Sample size	n = 6 ; % = 0.5	n = 7 ; % = 0.7
None Sample size	n = 156 ; % = 13.2	n = 123 ; % = 11

Characteristic	Treatment dose anticoagulation (N = 1181)	usual care thromboprophylaxis (N = 1050)
low flow nasal cannula/face mask Sample size	n = 789 ; % = 66.8	n = 696 ; % = 66.3
high flow nasal cannula Sample size	n = 25 ; % = 2.1	n = 28 ; % = 2.7
Non-invasive mechanical ventilation Sample size	n = 21 ; % = 1.8	n = 24 ; % = 2.3
Unspecified in REMAP-CAP levels of oxygen support, including no support, below high flow nasal cannula were not differentiated Sample size	n = 190 ; % = 16.1	n = 179 ; % = 17.1
ATTACC Sample size	n = 650 ; % = 55	n = 509 ; % = 48.5
ACTIV-4a Sample size	n = 387 ; % = 32.8	n = 392 ; % = 37.3
REMAP-CAP Sample size	n = 144 ; % = 12.2	n = 149 ; % = 14.2

Outcomes

Organ support free days

Outcome	Treatment dose anticoagulation vs usual care thromboprophylaxis, , N2 = , N1 =
Organ support free days at day 21 All moderate participants Odds ratio/95% CI	1.29 (1.04 to 1.61)

Survival

Outcome	Treatment dose anticoagulation vs usual care thromboprophylaxis, , N2 = , N1 =
Survival without organ support 28 days all moderate patients Odds ratio/95% CI	1.3 (1.05 to 1.61)
Survival to hospital discharge all moderate patients Odds ratio/95% CI	1.21 (0.87 to 1.68)
Survival to hospital discharge without major thrombotic events all moderate patients. Odds ratio/95% CI	1.39 (1.02 to 1.88)
survival without any macrovascular thrombotic events Odds ratio/95% CI	1.41 (1.04 to 1.92)

Outcome	Treatment dose anticoagulation vs usual care thromboprophylaxis, , N2 = , N1 =
28 Day survival Hazard ratio/95% CI	1.2 (0.88 to 1.61)

Survival without organ support 28 days - Polarity - Higher values are better
Survival to hospital discharge - Polarity - Higher values are better
Survival to hospital discharge without major thrombotic events - Polarity - Higher values are better
survival without any macrovascular thombotic events - Polarity - Higher values are better
28 Day survival - Polarity - Higher values are better

Survival

Outcome	Treatment dose anticoagulation, , N = NA	usual care thromboprophylaxis, , N = NA
Survival to hospital discharge No of events	n = 1085 ; % = 92.7	n = 962 ; % = 91.8
Survival to hospital discharge Total number of pts in analysis	n = 1171 ; % = NA	n = 1048 ; % = NA
Survival without organ support 28 days No of events	n = 932 ; % = 79.8	n = 789 ; % = 75.4
Survival without organ support 28 days total number of pts in analysis	n = 1175 ; % = NA	n = 1046 ; % = NA
Survival to hospital discharge No of events	n = 1085 ; % = 92.7	n = 962 ; % = 91.8

Outcome	Treatment dose anticoagulation, , N = NA	usual care thromboprophylaxis, , N = NA
Survival to hospital discharge total number of patients in analysis	n = 1171 ; % = NA	n = 1048 ; % = NA
Survival to hospital discharge without major thrombotic events major thrombotic events was defined by a composite of myocardial infarction, pulmonary embolism, ischemic stroke, and systemic arterial embolism events; No of events	n = 1086 ; % = 92	n = 942 ; % = 90.1
Survival to hospital discharge without major thrombotic events major thrombotic events was defined by a composite of myocardial infarction, pulmonary embolism, ischemic stroke, and systemic arterial embolism events; Sample size	n = 1180 ; % = NA	n = 1046 ; % = NA
survival to hospital discharge without any macrovascular thrombotic events defined by the composite of major thrombotic events plus deep venous thrombosis; No of events	n = 1084 ; % = 91.9	n = 938 ; % = 89.7
survival to hospital discharge without any macrovascular thrombotic events defined by the composite of major thrombotic events plus deep venous thrombosis; Sample size	n = 1180 ; % = NA	n = 1046 ; % = NA
Mortality Mortality was calculated by NICE by subtracting survival until discharge from total number of events No of events	n = 86 ; % = 7.34	n = 86 ; % = 8.21

Survival to hospital discharge - Polarity - Higher values are better
Survival to hospital discharge - Polarity - Higher values are better
Survival to hospital discharge without major thrombotic events - Polarity - Higher values are better
survival to hospital discharge without any macrovascular thombotic events - Polarity - Higher values are better
Mortality - Polarity - Lower values are better
Major bleeding

Outcome	Treatment dose anticoagulation, , N = 1180	usual care thromboprophylaxis, , N = 1047
Major bleeding No of events	n = 22	n = 9

Major bleeding - Polarity - Lower values are better
Confirmed ISTH major bleeding events

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes *(Using central web-based systems)*
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No information
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No information *(Intervention implementation success not reported)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	No *(Adherence to protocol-assigned anticoagulation dose on the day following randomization was 88.3% in the therapeutic-dose anticoagulation arm and 98.3% in the thromboprophylaxis arm. Among participants randomized to therapeutic-dose heparin,*

Section	Question	Answer
		94.7% (1035/1093) received a low molecular weight heparin, most commonly enoxaparin. Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes *(Loss to follow up <20%)*
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lemos, 2020

Bibliographic Reference	Lemos, A.C.B.; do Espirito Santo, D.A.; Salvetti, M.C.; Gilio, R.N.; Agra, L.B.; Pazin-Filho, A.; Miranda, C.H.; Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID); Thrombosis Research; 2020; vol. 196; 359-366

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	REBEC RBR-949z6v (HESACOVID phase II RCT)
Study start date	Apr-2020
Study end date	Jul-2020
COVID-19 prevalence at the time of the study	Unclear
Aim of the study	To assess whether therapeutic anticoagulation improves gas exchange compared with standard anticoagulant thromboprophylaxis
County/ Geographical location	Not stated (single-centre study with authors based in Brazil)
Study setting	Single-centre study. Presumed set in critical care (patients requiring mechanical ventilation)
Population description	Patients with laboratory-confirmed SARS-CoV-2 infection with respiratory failure requiring mechanical ventilation (all received mechanical ventilation)

	Age, gender and ethnicity are summarised below. Other key baseline characteristics: prophylactic anticoagulation before enrolment = 4 (40%) in therapeutic enoxaparin group, 7 (70%) in standard thromboprophylaxis group therapeutic anticoagulation before enrolment = 0 in therapeutic enoxaparin group , 0 in standard thromboprophylaxis group D-dimer (micrograms/litre, mean (95% CI) = 4176 (1986 to 6365) in therapeutic enoxaparin group, 3408 (1283 to 5532) in standard thromboprophylaxis group
Inclusion criteria	Patients aged over 18 years-old, RT-PCR-confirmed SARS-CoV-2 infection, acute respiratory distress syndrome according to Berlin definition, severe clinical presentation with respiratory failure requiring mechanical ventilation, pre-specified levels of D-dimer, prothrombin, activated partial thromboplastin time/ratio and platelet count .
Exclusion criteria	Key exclusion criteria: people aged over 85 years. Patients receiving renal replacement therapy and people with active cancer were excluded
Intervention/test/approach	Therapeutic enoxaparin (subcutaneous enoxaparin with dose according to age and adjusted daily by creatinine clearance, maximum permitted dose 140 mg twice daily)
Comparator (where applicable)	Standard thromboprophylaxis (subcutaneous UFH 5000 IU three times daily if weight < 120 kg, 7500 IU three times daily if weight > 120 kg), or enoxaparin (40 mg once daily if weight < 120 kg and 40 mg twice daily if weight > 120 kg) according to clinical judgement

Study arms

Therapeutic enoxaparin (N = 10)

Standard thromboprophylaxis (N = 10)

Unfractionated heparin (N=5), low molecular weight heparin (N=5)

Characteristics

Arm-level characteristics

Characteristic	Therapeutic enoxaparin (N = 10)	Standard thromboprophylaxis (N = 10)
Age (years) Mean (SD)	55 (10)	58 (16)
Male No of events	n = 9 ; % = 90	n = 7 ; % = 70
Ethnicity No of events	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

28 day

Mortality

Outcome	Therapeutic enoxaparin, 28 day, N = 10	Standard thromboprophylaxis, 28 day, N = 10
All cause 28 day mortality No of events	n = 1 ; % = 10	n = 3 ; % = 30
All cause 28 day mortality P value	0.264	NA
In-hospital mortality No of events	n = 2 ; % = 20	n = 5 ; % = 50
In-hospital mortality P value	0.160	NA

Adverse effects

Outcome	Therapeutic enoxaparin, 28 day, N = 10	Standard thromboprophylaxis, 28 day, N = 10
Major bleeding No of events	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Therapeutic enoxaparin, 28 day, N = 10	Standard thromboprophylaxis, 28 day, N = 10
Bleeding requiring medical attention No of events	n = 4 ; % = 40	n = 2 ; % = 20

Ventilator-free days

Outcome	Therapeutic enoxaparin, 28 day, N =	Standard thromboprophylaxis, 28 day, N =
Ventilator-free days Median (IQR)	15 (6 to 16)	0 (0 to 11)

Ventilator-free days - Polarity - Lower values are better

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes *(Limited reporting of details. Opaque envelopes used)*
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes *(open label)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes *(open label)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended	2.1. Were participants aware of their assigned intervention during the trial?	Yes

Section	Question	Answer
interventions (effect of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes *(Table of characteristics provides some data on other interventions e.g. drugs received)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably no
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lopes, 2021

Bibliographic Reference	Lopes RD; de Barros E Silva PGM; Furtado RHM; Macedo AVS; Bronhara B; Damiani LP; Barbosa LM; de Aveiro Morata J; Ramacciotti E; de Aquino Martins P; de Oliveira AL; Nunes VS; Ritt LEF; Rocha AT; Tramujas L; Santos SV; Diaz DRA; Viana LS; Melro LMG; de Alcântara Chaud MS; Figueiredo EL; Neuenschwander FC; Dracoulakis MDA; Lima RGSD; de Souza Dantas VC; Fernandes ACS; Gebara OCE; Hernandes ME; Queiroz DAR; Veiga VC; Canesin MF; de Faria LM; Feitosa-Filho GS; Gazzana MB; Liporace IL; de Oliveira Twardowsky A; Maia LN; Machado FR; de Matos Soeiro A; Conceição-Souza GE; Armaganijan L; Guimarães PO; Rosa RG; Azevedo LCP; Alexander JH; Avezum A; Cavalcanti AB; Berwanger O; ; Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial.; Lancet (London, England); 2021

Study details

Trial registration (if reported)	NCT04394377
Study start date	24-Jun-2020
Study end date	26-Feb-2021
Aim of the study	To assess whether in-hospital anticoagulation with rivaroxaban (20 mg once daily) for patients with a stable condition or enoxaparin (1 mg/kg twice daily) for patients with an unstable condition, followed by rivaroxaban for

	30 days, compared with in-hospital prophylactic anticoagulation with heparin decreased the time to death, duration of hospitalisation, or duration of supplemental oxygen support and to assess the effect on major or clinically relevant non-major bleeding through 30 days.
County/ Geographical location	31 sites in Brazil
Study setting	Hospital
Population description	Patients hospitalised with COVID-19 and elevated D-dimer concentration (above the upper limit of normal reference range per local laboratory). Moderate severity COVID-19 group of patients based on the information in the paper- only around 14% of the participants were on high-flow oxygen, the rest are either on no oxygen or low-flow.
Inclusion criteria	Patients hospitalised with COVID-19 and elevated D-dimer concentration (above the upper limit of normal reference range per local laboratory).
Exclusion criteria	Formal indication for therapeutic anticoagulation Contraindications to rivaroxaban or heparin Conditions placing patients at high risk for bleeding.
Intervention/test/approach	Therapeutic anticoagulation- rivaroxaban at 20 mg daily (and enoxaparin 1 mg/kg twice daily for clinically unstable patients) Therapeutic anticoagulation, either: a) For stable patients: oral rivaroxaban 20 mg or 15 mg daily (a reduced dose of 15 mg once daily was used in patients with a creatinine clearance of 30–49 mL/min or those taking azithromycin). All patients in the therapeutic anticoagulation group continued treatment to day 30 with the same dose of rivaroxaban.

	b) For unstable patients: initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0·3–0·7 IU/mL anti-Xa concentration). When these patients became stable, they were transitioned to oral rivaroxaban (20 mg or 15 mg) to day 30. Patients were clinically unstable if they had COVID-19-related critical illness, a life threatening condition, a requirement for mechanical ventilation or vasopressors, or were unable (based on investigator assessment) to take oral medication.
Comparator (where applicable)	Prophylactic anticoagulation with heparin/enoxaparin according to local hospital practices.
Methods for population selection/allocation	Random allocation to both groups. There was no masking of patients or investigators to group allocation. Randomisation was done in a 1:1 ratio in permuted blocks of variable size, stratified according to clinical condition (stable or unstable), using a central, concealed, web-based, automated randomisation system
Methods of data analysis	Intention-to-treat principle, including all randomly allocated participants.
Attrition/loss to follow-up	One (<1%) patient, in the therapeutic group, was lost to follow-up because of withdrawal of consent and was not included in the primary analysis
Source of funding	COVID-19 Brazil Coalition, Bayer SA.
Study limitations (Author)	The open label design has a potential risk of bias, especially with respect to clinical event ascertainment. Adherence to the medication at the end of the study was assessed through pill count done by patients via telephone call and not in an in-person medical evaluation. The results apply mainly to the use of rivaroxaban in clinically stable patients hospitalised with confirmed COVID-19 within 14 days from symptom onset, elevated D-dimer concentration, and without indication for therapeutic anticoagulation.
Study limitations (Reviewer)	Deviation from intended intervention: The comparison was therapeutic-dose anticoagulation for 30 days versus usual care anticoagulation during hospitalization. Both arms received anticoagulation, but the majority of the

	intervention group (94.8%) received therapeutic dose anticoagulation while the majority of the control group received prophylactic dose anticoagulation during hospitalization (99.5%), while 13% were prescribed extended prophylaxis beyond hospital discharge.

Study arms

Therapeutic anticoagulation (N = 311)

Prophylactic anticoagulation (N = 304)

303 received prophylactic anticoagulation, 1 received therapeutic anticoagulation

Characteristics

Arm-level characteristics

Characteristic	Therapeutic anticoagulation (N = 311)	Prophylactic anticoagulation (N = 304)
Age Mean (SD)	56.7 (14.1)	56.5 (14.5)
Male Sample size	n = 192 ; % = 62	n = 176 ; % = 58

Characteristic	Therapeutic anticoagulation (N = 311)	Prophylactic anticoagulation (N = 304)
Female Sample size	n = 119 ; % = 38	n = 128 ; % = 42
Asthma Sample size	n = 18 ; % = 6	n = 11 ; % = 4
Diabetes Sample size	n = 83 ; % = 27	n = 67 ; % = 22
Hypertension Sample size	n = 151 ; % = 49	n = 151 ; % = 50
Chronic lung disease Sample size	n = 7 ; % = 2	n = 12 ; % = 4
Coronary disease Sample size	n = 12 ; % = 4	n = 16 ; % = 5
Catheter or oxygen mask Sample size	n = 185 ; % = 59	n = 184 ; % = 61
high-flow nasal cannula Sample size	n = 26 ; % = 8	n = 22 ; % = 7
tracheal intubation Sample size	n = 23 ; % = 7	n = 15 ; % = 5

Characteristic	Therapeutic anticoagulation (N = 311)	Prophylactic anticoagulation (N = 304)
Non-invasive ventilation Sample size	n = 2 ; % = 1	n = 3 ; % = 1
No oxygen support Sample size	n = 75 ; % = 6	n = 80 ; % = 26
Mild Sample size	n = 30 ; % = 10	n = 39 ; % = 13
Moderate moderate disease was characterised by an oxygen saturation <94%, pulmonary infiltrates >50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300; Sample size	n = 257 ; % = 83	n = 249 ; % = 82
Severe severe disease was defined as respiratory failure, haemodynamic instability, or multiple organ dysfunction. Sample size	n = 24 ; % = 8	n = 16 ; % = 5
Antiplatelet agent Sample size	n = 22 ; % = 7	n = 26 ; % = 9
Vasopressor Sample size	n = 16 ; % = 5	n = 8 ; % = 3
Systemic corticosteroids	n = 257 ; % = 83	n = 253 ; % = 83

Characteristic	Therapeutic anticoagulation (N = 311)	Prophylactic anticoagulation (N = 304)
Sample size		
>1 x upper limit of normal Sample size	n = 311 ; % = 100	n = 304 ; % = 100
>3 x upper limit of normal Sample size	n = 84 ; % = 27	n = 83 ; % = 27
Unstable Unstable clinical condition was defined as the presence of a COVID-19- related critical illness with an immediately life-threatening condition that would typically lead to intensive care unit admission. Sample size	n = 23 ; % = 7	n = 16 ; % = 5
Stable Sample size	n = 288 ; % = 93	n = 288 ; % = 95

Outcomes

Study timepoints

30 day

Mortality

Outcome	Therapeutic anticoagulation, 30 day, N = 311	Prophylactic anticoagulation, 30 day, N = 304
Death 30 days Sample size	n = 35 ; % = 11	n = 23 ; % = 8
cardiovascular cause of death Sample size	n = 6 ; % = 2	n = 0 ; % = 0
non-cardiovascular cause of death Sample size	n = 84 ; % = 27	n = 83 ; % = 27
Composite thrombotic outcome Sample size	n = 23 ; % = 7	n = 30 ; % = 10
Venous thromboembolism Sample size	n = 11 ; % = 4	n = 18 ; % = 6

Death - Polarity - Lower values are better

Serious adverse events

Outcome	Therapeutic anticoagulation, 30 day, N = 311	Prophylactic anticoagulation, 30 day, N = 304
Major bleeding or clinically relevant non-major bleeding (ISTH definitions). Defined as symptomatic and/or Fatal bleeding, and/or Bleeding in a critical area or organ, and/or bleeding causing a fall in haemoglobin level of 20 g L1(1.24 mmol L1) or more, or leading to transfusion of two or more units of whole blood or red cells. International Society on Thrombosis and Haemostasis. Sample size	n = 26 ; % = 8	n = 7 ; % = 2
Major bleeding Sample size	n = 10 ; % = 3	n = 4 ; % = 1
Clinically relevant non-major bleeding Sample size	n = 16 ; % = 5	n = 3 ; % = 1

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No *(No masking to group allocation)*

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	No *(Mean 30-day adherence to the study intervention was 94·8% (SD 15·2) in patients allocated to therapeutic anticoagulation group and 99·5% (6·2) in the prophylactic group)*

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes *(ITT analysis used)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Mohebbi, 2021

Bibliographic Reference	Mohebbi, Bahram; Sadeghipour, Parham; Talasaz, Azita H.; Hajighasemi, Alireza; Sadeghian, Saeed; Rashidi, Farid; Rezaeifar, Parisa; Tahamtan, Ouria; Matin, Samira; Sharif-Kashani, Babak; Shafaghi, Shadi; Beigmohammadi, Mohammad Taghi; Ghazi, Samrand Fattah; Farrokhpour, Mohsen; Yadollahzadeh, Mahdi; Sadeghipour, Pardis; Abri, Homa; Sezavar, Seyed Hashem; Payandemehr, Pooya; Shahmirzaei, Shaghayegh; Najafi, Atabak; Dabbagh, Ali; Moghadam, Keivan Gohari; Jamalkhani, Sepehr; Khalili, Hossein; Riahi, Taghi; Tabrizi, Sanaz; Mousavian, Seyed Masoud; Abedini, Atefeh;

Lookzadeh, Somayeh; Rahmani, Hamid; Zoghi, Elnaz; Mohammadi, Keyhan; Kakavand, Hessam; Hosseini, Seyed Hossein; Bakhshandeh, Hooman; Amin, Ahmad; Rafiee, Farnaz; Baghizadeh, Elahe; Parhizgar, Seyed Ehsan; Hadavand, Naser; Maleki, Majid; Aliannejad, Rasoul; Eslami, Vahid; Kashefizadeh, Alireza; Jimenez, David; Madhavan, Mahesh V.; Sethi, Sanjum S.; Parikh, Sahil A.; Kirtane, Ajay J.; Gupta, Aakriti; Monreal, Manuel; Piazza, Gregory; Goldhaber, Samuel Z.; Bikdeli, Behnood; Van Tassell, Benjamin W.; Dobesh, Paul P.; Stone, Gregg W.; Lip, Gregory Y. H.; Krumholz, Harlan M.; Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality among Patients with COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial; JAMA - Journal of the American Medical Association; 2021

Study details

Trial registration (if reported)	NCT04486508
Study start date	29-Jul-2020
Study end date	19-Nov-2020
Aim of the study	Evaluate the effects of intermediate dose vs standard dose prophylactic anticoagulation among adult patients admitted to the ICU with COVID-19.
County/ Geographical location	Multicentre: 10 academic centres in Iran
Study setting	ICU
Inclusion criteria	Adult patients (≥18 years) ; PCR-confirmed COVID-19 and admitted to ICU within 7 days of initial hospitalisation; no other firm indication for anticoagulation (such as mechanical valve, high-risk AF, VTE, or left ventricular thrombus) ; not enrolled in another blinded randomized trial ; willing to participate in the study and provide informed consent ; estimated survival of at least 24 hours at the discretion of enrolling physician.
Exclusion criteria	Weight <40Kg ; use of systemic anticoagulation for another indication (mechanical valve, ECMO, AF, left ventricular thrombus, or diagnosed VTE) ; overt bleeding at the day of enrolment ; known major bleeding within 30 days (according to the Bleeding Academic Research Consortium (BARC) definition, Appendix A) ; platelet count <50,000/Fl ; pregnancy (as confirmed by beta-HCG testing among female patients <50 years) ; history of heparin induced thrombocytopenia or immune thrombocytopenia ; ischemic stroke within the past 2 weeks ; major head or spinal trauma in the past 30 days ; craniotomy/major neurosurgery within the past 3 months ; known brain metastases or vascular malformations (aneurysm) ; presence of an epidural, spinal or pericardial

	catheter ; major surgery other than neurosurgery within 14 days prior to enrolment ; coexistence of severe obesity (weight >120Kg or BMI>35Kg/M2 along with severe renal insufficiency defined as CrCl<30 mL/min) ; allergic reaction to study medications ; lack or withdrawal of informed consent.
Intervention/test/approach	Intermediate dose enoxaparin 1mg/kg daily
Comparator (where applicable)	standard dose enoxaparin 40mg daily
Source of funding	Rajaie Cardiovascular Medical and Research centre.

Study arms

Intermediate dose enoxaparin (N = 276)

Intermediate-Dose prophylactic anticoagulation Enoxaparin: 1 mg/kg once daily for 30 days (if weight < 120kg and creatinine clearance > 30 ml/min).

Standard dose (N = 286)

Enoxaparin 40mg daily

Characteristics

Arm-level characteristics

Characteristic	Intermediate dose enoxaparin (N = 276)	Standard dose (N = 286)
Age Median (IQR)	62 (51 to 70.7)	61 (47 to 71)

Characteristic	Intermediate dose enoxaparin (N = 276)	Standard dose (N = 286)
Male Sample size	n = 162 ; % = 58.7	n = 163 ; % = 57
Female Sample size	n = 114 ; % = 41.3	n = 123 ; % = 43
nasal cannula Sample size	n = 10 ; % = 3.6	n = 14 ; % = 4.9
face mask Sample size	n = 33 ; % = 12	n = 27 ; % = 9.4
reservoir mask Sample size	n = 76 ; % = 27.5	n = 96 ; % = 33.6
high flow nasal cannula Sample size	n = 9 ; % = 3.3	n = 6 ; % = 2.1
non-invasive positive pressure ventilation Sample size	n = 93 ; % = 33.7	n = 85 ; % = 29.7
Invasive positive pressure ventilation Sample size	n = 55 ; % = 19.9	n = 58 ; % = 20.3
Hypertension Sample size	n = 131 ; % = 48	n = 118 ; % = 41.2

Characteristic	Intermediate dose enoxaparin (N = 276)	Standard dose (N = 286)
Diabetes Sample size	n = 82 ; % = 29.7	n = 73 ; % = 25.6
Hyperlipidaemia Sample size	n = 75 ; % = 27.2	n = 68 ; % = 23.8

Outcomes

Study timepoints

30 day

90 day

Mortality

Outcome	Intermediate dose enoxaparin vs Standard dose, , N2 = 276, N1 = 286
Mortality No OR for mortality at 90 days Odds ratio/95% CI	1.09 (0.78 to 1.53)

Mortality - Polarity - Lower values are better

Mortality

Outcome	Intermediate dose enoxaparin, 30 day, N = 276	Intermediate dose enoxaparin, 90 day, N = 276	Standard dose, 30 day, N = 286	Standard dose, 90 day, N = 286
Mortality No of events	n = 119 ; % = 43.1	n = 127 ; % = 46	n = 117 ; % = 40.9	n = 123 ; % = 43

Mortality - Polarity - Lower values are better

Venous thromboembolism

Outcome	Intermediate dose enoxaparin vs Standard dose, , N2 = 276, N1 = 286
Venous thromboembolism no OR results reported at 90 days Odds ratio/95% CI	0.93 (0.37 to 2.32)

Venous thromboembolism

Outcome	Intermediate dose enoxaparin, 30 day, N = 276	Intermediate dose enoxaparin, 90 day, N = 276	Standard dose, 30 day, N = 286	Standard dose, 90 day, N = 286
Venous thromboembolism No of events	n = 9 ; % = 3.3	n = 9 ; % = 3.3	n = 10 ; % = 3.5	n = 10 ; % = 3.5

Venous thromboembolism - Polarity - Lower values are better

All venous thromboembolism events were diagnosed by the online clinical event committee. Each event was confirmed only if guideline-recommended imaging tests were presented.

Advanced organ support

Outcome	Intermediate dose enoxaparin, 30 day, N = 276	Intermediate dose enoxaparin, 90 day, N =	Standard dose, 30 day, N = 286	Standard dose, 90 day, N =
Ventilator-free days No results for this outcome at 90 days. difference between the total number of days alive after enrolment and the total number of days receiving invasive mechanical ventilation Median (IQR)	30 (3 to 30)	*empty data* (*empty data* to *empty data*)	30 (1 to 30)	*NR*

Ventilator-free days - Polarity - Higher values are better

Serious adverse events

Outcome	Intermediate dose enoxaparin vs Standard dose, 30 day, N2 = 276, N1 = 286	Intermediate dose enoxaparin vs Standard dose, 90 day, N2 = , N1 =
Major bleeding No OR reported at 90days.Major bleeding consisted of Bleeding Academic Research Consortium (BARC) type 3 and 5, which defines type 3a as overt bleeding plus haemoglobin drop of 3 to 5 g/dL or any transfusion with overt bleeding; type 3b as overt bleeding plus haemoglobin drop 5 g/dL, cardiac tamponade, or bleeding requiring surgical intervention for control; type 3c as intracranial haemorrhage; and type 5 as fatal bleeding Odds ratio/95% CI	1.83 (0.53 to 5.93)	*NR*

Major bleeding - Polarity - Lower values are better

Serious adverse events

Outcome	Intermediate dose enoxaparin, 30 day, N = 276	Intermediate dose enoxaparin, 90 day, N = 276	Standard dose, 30 day, N = 286	Standard dose, 90 day, N = 286
Major bleeding Major bleeding consisted of Bleeding Academic Research Consortium (BARC) type 3 and 5, which defines type 3a as overt bleeding plus haemoglobin drop of 3 to 5 g/dL or any transfusion with overt bleeding; type 3b as overt bleeding plus haemoglobin drop 5 g/dL, cardiac tamponade, or bleeding requiring surgical intervention for control; type 3c as intracranial haemorrhage; and type 5 as fatal bleeding No of events	n = 7 ; % = 2.5	n = 7 ; % = 2.5	n = 4 ; % = 1.4	n = 4 ; % = 1.4

Major bleeding - Polarity - Lower values are better

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes *(open label)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes *(open label)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably no

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Perepu, 2021

Bibliographic Reference	Perepu U.S. EA; Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomised controlled trial; Pre-publication; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	
Study start date	26-Apr-2020
Study end date	06-Jan-2021
COVID-19 prevalence at the time of the study	Unclear
Aim of the study	To compare standard prophylactic and intermediate dosing of the LMWH enoxaparin in adults hospitalised with severe COVID-19, defined as requiring intensive care or manifested by laboratory criteria for coagulopathy.
County/ Geographical location	USA
Study setting	Hospitals
Population description	Adults hospitalised with COVID-19 and admitted to an intensive care unit (ICU) and/or had laboratory evidence of coagulopathy.
Inclusion criteria	Adults 18 years of age or older with SARS-CoV-2 infection confirmed by nasopharyngeal swab polymerase chain reaction and requiring hospitalisation were eligible if they were admitted to an ICU and/or had a modified ISTH Overt DIC score ≥3.
Exclusion criteria	Patients were excluded if there was an indication for full therapeutic dose anticoagulation or they had active major bleeding, severe thrombocytopenia (platelet count <25,000/microlitre), current pregnancy, a history of acute venous or arterial thrombosis within the prior 3 months, or acute or chronic renal insufficiency with an estimated creatinine clearance less than 30 mL/min calculated by the modified Cockcroft and Gault formula.
Intervention/test/approach	The intermediate dose was 1 mg/kg SC daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30.
Comparator (where applicable)	The standard dose was 40 mg SC daily if the body-mass index (BMI) was less than 30 kg/m2 and 30 mg SC twice daily for non-ICU patients or 40 mg SC twice daily for ICU patients if the BMI was ≥ 30.

Methods for population selection/allocation	Patients hospitalised with a diagnosis of COVID-19 were screened for eligibility. Using the Research Electronic Capture (REDCap) platform, patients were randomly assigned in a 1:1 ratio to receive either a standard prophylactic dose or an intermediate dose of enoxaparin.
Methods of data analysis	Demographic and clinical measures collected were summarized and tested for differences. Continuous measures were displayed as medians and interquartile ranges. Tests for differences used the Wilcoxon rank sum test. Categorical measures were displayed as counts and percentages. Tests for differences used Pearson's chi-square and Fisher's exact tests, where appropriate. Analysis of the primary and secondary outcome measures was performed on the intention-to-treat population, defined as all patients who provided informed consent and underwent randomisation (N = 173). The primary outcome measure was assessed as both (1) the 30-day all-cause mortality and (2) the time to death with censoring at 30 days. They hypothesized that the intermediate dose enoxaparin group (intervention arm) had a mortality rate below (and time-to-death above) the standard prophylactic dose enoxaparin group (standard of care arm). Estimates for the 30-day mortality odds ratio, confidence interval, and Pearson's chi-square p-value, testing for a difference between doses, were provided. For the time-to-death analysis, differences between doses were analysed using Cox proportional hazard modelling and reported as hazard ratios with 95% confidence intervals, along with their p-values. They used log(-log(survival)) plots to verify the proportional hazards assumption. Raw proportional hazards models were fit on five samples: all patients, patients with BMI less than 30, BMI greater than 30, admitted to ICU, and not admitted to ICU. Additional models were fit in both the intention-to-treat and Per-protocol populations, adjusting for age, gender, BMI, and ICU admission. They estimated that the risk of death within 30 days would be 40% in the standard dose enoxaparin group. Assuming the risk would be reduced to 20% in the intermediate dose enoxaparin group, they calculated that the assignment of 164 patients with 1:1 randomisation would provide 80% power for a two-sided test to detect such a difference in the primary outcome between the two arms with alpha of 0.05. Secondary outcomes included arterial or venous thromboembolism and major bleeding. Like the dichotomous primary outcome, secondary outcome comparisons are reported as estimates for the odds ratios, confidence intervals, and p-values. Additional analyses were performed on the per protocol population, defined as all

	randomised patients who received the assigned treatment, to assess the sensitivity of their results after removing untreated patients. SAS 9.4 was used for all calculations and data analysis.
Attrition/loss to follow-up	2 withdrew consent in the standard dose arm and 1 withdrew consent in the intermediate dose arm. These occurred before the initiation of treatment.
Source of funding	National Institutes of Health Clinical and Translational Science Award.
Study limitations (Author)	"One limitation of our study is that the trial design was based on data available in early 2020 that suggested a mortality of up to 40% in hospitalized patients with severe COVID-19 who were treated with standard prophylactic dose LMWH. Studies performed later in the pandemic suggested a lower in-hospital mortality of 15 to 20%, which is in agreement with our finding of 18% all-cause mortality at 30 days. Another limitation is that the results of our study cannot be extrapolated to all patients hospitalized with COVID-19, since over 85% of screened patients did not meet the eligibility criteria. The most frequent reasons for screen failure were lack of laboratory evidence for coagulopathy, renal insufficiency, or a clinical indication for therapeutic dose anticoagulation. Finally, our study was not designed to examine outcomes beyond 30 days. Therefore, additional studies are needed to confirm our findings and assess the impact of anticoagulation therapy on the long-term effects of COVID-19."
Study limitations (Reviewer)	This was an open-label study. Therefore, there is a risk of bias when measuring outcomes that involve a degree of subjectivity.
Other details	None

Study arms

Intermediate enoxaparin (N = 87)

Standard enoxaparin (N = 86)

Characteristics

Arm-level characteristics

Characteristic	Intermediate enoxaparin (N = 87)	Standard enoxaparin (N = 86)
median age (years) Nominal	65	63.5
% Female (%) Nominal	46	42
Admitted to ICU (%) Nominal	61	63
Cancer Nominal	8	15
Diabetes mellitus Nominal	34	40

Characteristic	Intermediate enoxaparin (N = 87)	Standard enoxaparin (N = 86)
Heart disease Nominal	31	31
Hypertension Nominal	59	62
Lung disease Nominal	23	22
Obesity Nominal	52	45

Outcomes

Study timepoints

30 day

Outcome	Intermediate enoxaparin, 30 day, N = 87	Standard enoxaparin, 30 day, N = 86
All-cause mortality 30 days (number) Nominal	13	18
Major bleeding (number) Nominal	2	2
VTE 30 days (number)	7	6

Outcome	Intermediate enoxaparin, 30 day, N = 87	Standard enoxaparin, 30 day, N = 86
Nominal		

All-cause mortality 30 days - Polarity - Lower values are better
Major bleeding - Polarity - Lower values are better
VTE 30 days - Polarity - Lower values are better

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No *(Azithromycin used in more of*

Section	Question	Answer
interventions (effect of adhering to intervention)		*the intermediate group than the standard group.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably no
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably yes
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sholzberg et al.

Bibliographic Reference	Sholzberg, Michelle; Heparin for Moderately Ill Patients with Covid-19; (no. Pre-print)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04362085 - registration for US, Canada, Ireland, Saudi Arabia, UAE NCT04444700 - registration for Brazil (for administrative reasons could not be registered with the rest
Study start date	11-May-2020
Study end date	10-May-2021
COVID-19 prevalence at the time of the study	Unclear As study was conducted through various centres around the world, it is difficult to accurately determine COVID-19 prevalence overall.
Aim of the study	To determine whether early initiation of therapeutic heparin guided by D-Dimer levels could reduce the risk of critical illness or death in moderately ill COVID-19 patients
County/ Geographical location	USA, Canada, Brazil, Ireland, KSA, UAE
Study setting	Multi-centre, open label, randomized control trial.
Population description	Hospitalised patients with confirmed SARS-CoV-2 infection and elevated D-dimer levels
Inclusion criteria	Patients were eligible if they were admitted to hospital wards for Covid-19 with laboratory confirmed SARS-CoV-2 infection and elevated D-dimer levels within the first 5 days of admission. D-dimer levels were required to be above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation.
Exclusion criteria	Participants were excluded if they had substantial bleeding risks, an absolute indication for or any contraindication against heparin anticoagulation based on care team judgment, were pregnant or if they had already met, or would imminently meet any component of the primary outcome.

Intervention/test/approach	Patients allocated to therapeutic heparin received therapeutic doses of low molecular weight heparin (LMWH) or unfractionated heparin (UFH). Study treatment continued until the first of hospital discharge, day 28, study withdrawal or death.
Comparator (where applicable)	Patients allocated to prophylactic heparin received dose-capped prophylactic subcutaneous heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance
Methods for population selection/allocation	Included participants were randomized using a web-based central randomization (a computer-generated random sequence) with variable block sizes stratified by site and age (≤65 versus >65 years). Patients were assigned in 1:1 ratio to therapeutic or prophylactic heparin. Patients allocated to therapeutic heparin received therapeutic doses of low molecular weight heparin (LMWH) or unfractionated heparin (UFH), patients allocated to prophylactic heparin received dose-capped prophylactic subcutaneous heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance. Study treatment was started within 24 hours after randomization, and continued until the first of hospital discharge, day 28, study withdrawal or death.
Methods of data analysis	The primary analysis of the primary composite outcome was based on the intention-to-treat (ITT) principle using logistic regression. Participants who did not have a 28-day assessment, but discharged from hospital alive prior to day 28, were assumed to be event-free up to day 28.
Attrition/loss to follow-up	In therapeutic heparin 11 participants and in prophylactic dose 12 participants - did not meet component of primary composite outcome, were discharged from hospital alive and were lost to telephone follow-up.
Source of funding	Task 54, Defence Research Development Canada, Department of National Defence, Ottawa, Canada; St. Michael's Hospital Foundation, Toronto, Canada; St. Joseph's Health Centre Foundation, Toronto, Canada; 2020 TD Community Health Solutions Fund – COVID-19 Research Grant; Michael Garron Hospital, Toronto, Canada; The Ottawa Hospital Foundation COVID-19 Emergency Response Fund, Ottawa, Canada; International Network of Venous Thromboembolism Clinical Research Networks (INVENT) Kickstarter Award; Science Foundation Ireland, Enterprise Ireland, IDA Ireland COVID-19 Rapid Response Funding Call 20/COV/0157; SEAMO (Southeastern Ontario Academic Medical Organization) COVID-19 Innovation Fund; P20 GM135007 from the National Institute of General Medical Sciences, NIH; University of Vermont Medical Center Fund Grant; College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia
Study limitations (Author)	Our trial has two major limitations. First, RAPID had an adaptive design. The protocol prespecified that the sample size would be increased if the conditional power at 75% of the original sample size was between 60 and 80%. 21 However, the conditional power was below 60%, therefore the sample size was not increased, thus

	RAPID remained underpowered. Second, the trial had an open-label design, but all relevant outcomes were blindly adjudicated by an independent clinical events committee.
Study limitations (Reviewer)	The study had an open-label design and so outcomes or effects may not be certain. Moreover, the study included a small number of participants and so its effect in the wider population cannot be translated easily.

Study arms

Therapeutic heparin (N = 228)

Prophylactic heparin (N = 237)

Characteristics

Arm-level characteristics

Characteristic	Therapeutic heparin (N = 228)	Prophylactic heparin (N = 237)
Age Mean (SD)	60.4 (14.1)	59.6 (15.5)
Male No of events	n = 123 ; % = 53.9	n = 141 ; % = 59.5
Female No of events	n = 105 ; % = 46.1	n = 96 ; % = 40.5

Characteristic	Therapeutic heparin (N = 228)	Prophylactic heparin (N = 237)
White Includes European, Middle Eastern and North African No of events	n = 162 ; % = 73	n = 163 ; % = 69.4
Asian No of events	n = 27 ; % = 12.2	n = 38 ; % = 16.2
Black or African American No of events	n = 18 ; % = 8.1	n = 23 ; % = 9.8
Hispanic or Latino No of events	n = 14 ; % = 6.3	n = 10 ; % = 4.3
Native Hawaiian or other Pacific Islander No of events	n = 1 ; % = 0.5	n = 0 ; % = 0
Body mass index (kg/m²) Mean (SD)	30.3 (6.4)	30.2 (7)
Duration of symptoms prior to hospitalisation (days) Mean (SD)	7.1 (5.1)	7.1 (5.2)

Outcomes

Event data

Outcome	Therapeutic heparin, , N = 228	Prophylactic heparin, , N = 237
Death / respiratory support / ICU admission (Events) Up to 28 days No of events	n = 37 ; % = 16.2	n = 52 ; % = 21.9
All-cause mortality (Events) 28 days No of events	n = 4 ; % = 1.8	n = 18 ; % = 7.6
Respiratory support (Events) Moving onto invasive or non-invasive support. 28 days No of events	n = 21 ; % = 9.2	n = 26 ; % = 11
ICU admission (Events) 28 days No of events	n = 33 ; % = 14.5	n = 42 ; % = 17.7
All-cause mortality and IV/NIV (composite) (Events) 28 days No of events	n = 23 ; % = 10.1	n = 38 ; % = 16
VTE events (Events) in 28 days No of events	n = 2 ; % = 0.9	n = 7 ; % = 3

Outcome	Therapeutic heparin, , N = 228	Prophylactic heparin, , N = 237
Major bleeding (Events) 28 days No of events	n = 2 ; % = 0.9	n = 4 ; % = 1.7

Death / respiratory support / ICU admission - Polarity - Lower values are better
All-cause mortality - Polarity - Lower values are better
Respiratory support - Polarity - Lower values are better
ICU admission - Polarity - Lower values are better
All-cause mortality and IV/NIV (composite) - Polarity - Lower values are better
VTE events - Polarity - Lower values are better
Major bleeding - Polarity - Lower values are better
Up to 28 days

Continuous data

Outcome	Therapeutic heparin, , N = 228	Prophylactic heparin, , N = 237
Number of ventilator-free days (Mean) mean Mean (SD)	26.5 (5.6)	24.7 (8.5)
Number of organ-support free days (Mean (SD)) mean Mean (SD)	25.8 (6.2)	24.1 (8.8)

Number of ventilator-free days - Polarity - Higher values are better
Number of organ-support free days - Polarity - Higher values are better

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - RQ1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No *(23 participants lost to*

Section	Question	Answer
		follow up (11 T group, 12 S group))
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Probably no
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Probably yes
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No *(objective, or done by blinded committee)*
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes *(But adjudicated by blinded committees to mitigate)*
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

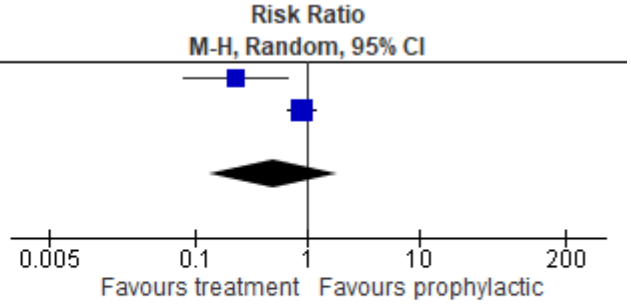
Appendix E: Forest Plots

People with moderate severity COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Mortality

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RAPID 2021 (1)	4	228	18	237	42.6%	0.23 [0.08, 0.67]
REMAP-CAP 2021 (2)	86	1171	86	1048	57.4%	0.89 [0.67, 1.19]
Total (95% CI)		**1399**		**1285**	**100.0%**	**0.50 [0.13, 1.88]**
Total events	90		104			

Heterogeneity: Tau² = 0.77; Chi² = 5.83, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 1.02 (P = 0.31)

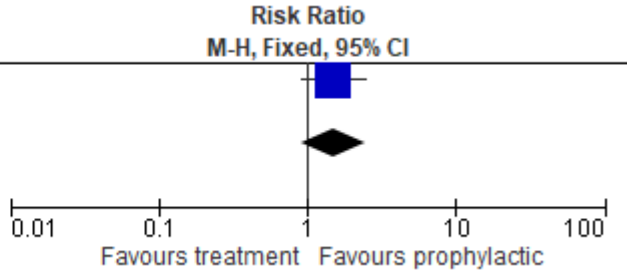


Footnotes
(1) 28 days
(2) CAVEAT - Mortality was calculated by subtracting survival from total number of events in moderate patients with no macrovascular thrombotic events.

Mortality – rivaroxaban

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTION 2021	35	310	23	304	100.0%	1.49 [0.90, 2.46]
Total (95% CI)		**310**		**304**	**100.0%**	**1.49 [0.90, 2.46]**
Total events	35		23			

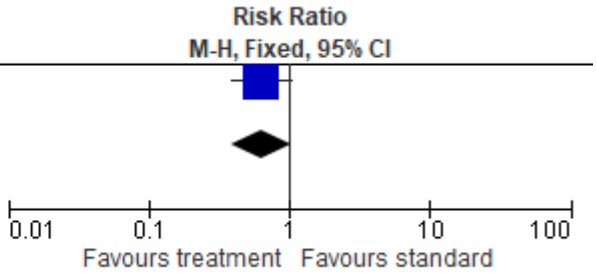
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)



All-cause mortality or need for IV or NIV

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RAPID 2021	23	228	38	237	100.0%	0.63 [0.39, 1.02]
Total (95% CI)		**228**		**237**	**100.0%**	**0.63 [0.39, 1.02]**
Total events	23		38			

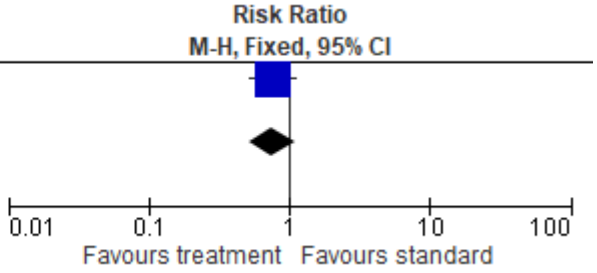
Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)



Death / need for IV or NIV / ICU admission

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RAPID 2021	37	228	51	237	100.0%	0.75 [0.51, 1.11]
Total (95% CI)		**228**		**237**	**100.0%**	**0.75 [0.51, 1.11]**
Total events	37		51			

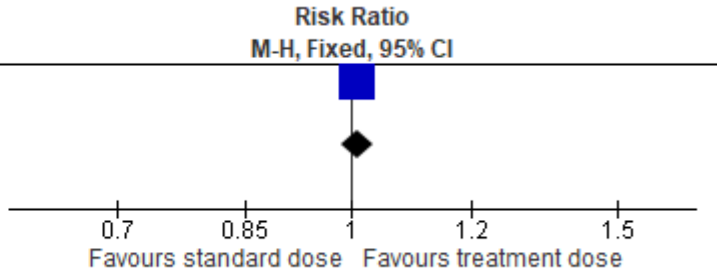
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)



Survival to hospital discharge

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
REMAP-CAP 2021	1085	1171	962	1048	100.0%	1.01 [0.99, 1.03]
Total (95% CI)		**1171**		**1048**	**100.0%**	**1.01 [0.99, 1.03]**
Total events	1085		962			

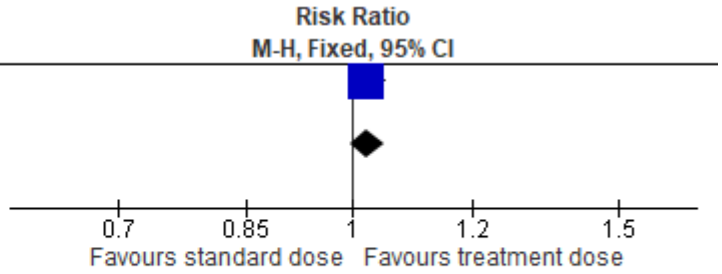
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)



Survival to hospital discharge without major thrombotic events

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
REMAP-CAP 2021 (1)	1086	1180	942	1046	100.0%	1.02 [1.00, 1.05]
Total (95% CI)		**1180**		**1046**	**100.0%**	**1.02 [1.00, 1.05]**
Total events	1086		942			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.10)



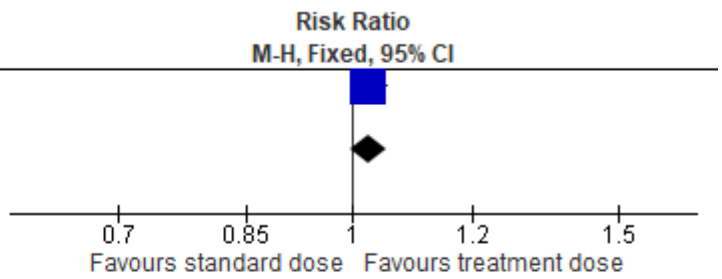
Footnotes

(1) major thrombotic events was defined by a composite of myocardial infarction, pulmonary embolism, ischaemic stroke and systemic arterial embolism...

Survival to hospital discharge without any macrovascular thrombotic events

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
REMAP-CAP 2021 (1)	1084	1180	938	1046	100.0%	1.02 [1.00, 1.05]
Total (95% CI)		**1180**		**1046**	**100.0%**	**1.02 [1.00, 1.05]**
Total events	1084		938			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)

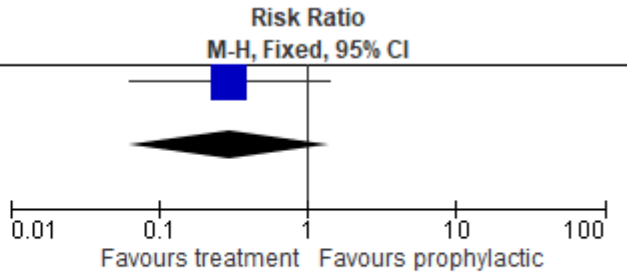


Footnotes
(1) major thrombotic events was defined by a composite of major thrombotic events plus deep vein thrombosis

Venous thromboembolism

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RAPID 2021 (1)	2	228	7	237	100.0%	0.30 [0.06, 1.41]
Total (95% CI)		**228**		**237**	**100.0%**	**0.30 [0.06, 1.41]**
Total events	2		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)

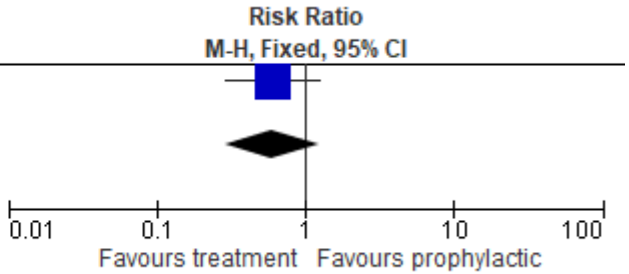


Footnotes
(1) 28 days

Venous thromboembolism – rivaroxaban

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTION 2021	11	311	18	304	100.0%	0.60 [0.29, 1.24]
Total (95% CI)		**311**		**304**	**100.0%**	**0.60 [0.29, 1.24]**
Total events	11		18			

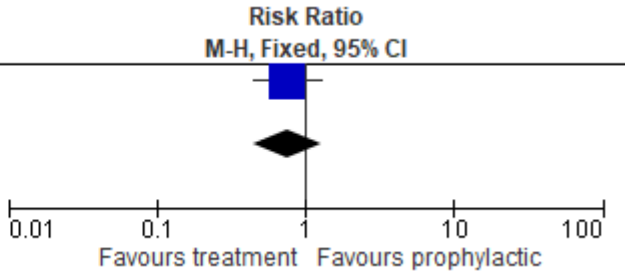
Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)



Composite Thrombotic Outcome

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTION 2021	23	310	30	304	100.0%	0.75 [0.45, 1.26]
Total (95% CI)		**310**		**304**	**100.0%**	**0.75 [0.45, 1.26]**
Total events	23		30			

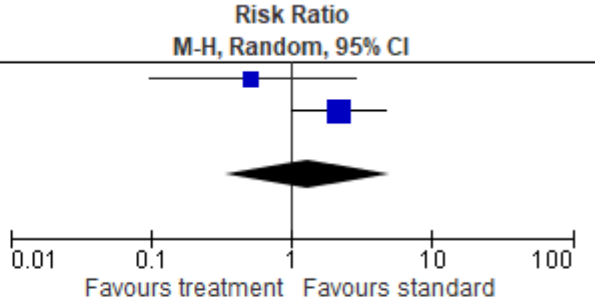
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



Major bleeding

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RAPID 2021	2	228	4	237	35.6%	0.52 [0.10, 2.81]
REMAP-CAP 2021 (1)	22	1180	9	1047	64.4%	2.17 [1.00, 4.69]
Total (95% CI)		**1408**		**1284**	**100.0%**	**1.30 [0.34, 4.98]**
Total events	24		13			

Heterogeneity: Tau² = 0.57; Chi² = 2.28, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.39 (P = 0.70)

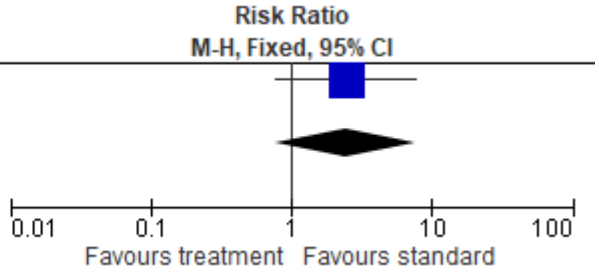


Footnotes
(1) Major bleeding in ACTION and REMAP-CAP defined according to the International Society onThrombosis and Haemostasis

Major bleeding – rivaroxaban

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTION 2021	10	310	4	304	100.0%	2.45 [0.78, 7.73]
Total (95% CI)		**310**		**304**	**100.0%**	**2.45 [0.78, 7.73]**
Total events	10		4			

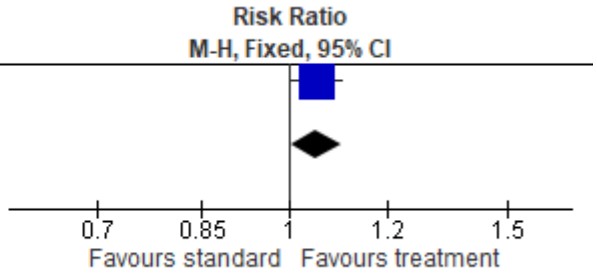
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)



Survival without organ support

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
REMAP-CAP 2021	932	1175	789	1046	100.0%	1.05 [1.01, 1.10]
Total (95% CI)		**1175**		**1046**	**100.0%**	**1.05 [1.01, 1.10]**
Total events	932		789			

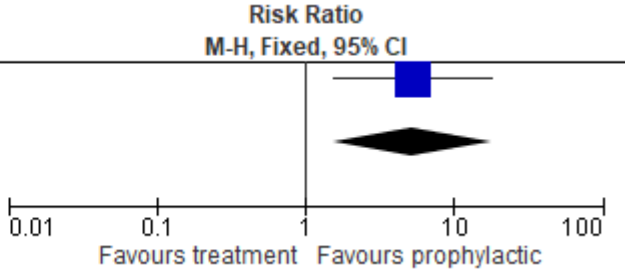
Heterogeneity: Not applicable
Test for overall effect: Z = 2.18 (P = 0.03)



Clinically relevant non-major bleeding – rivaroxaban

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTION 2021	16	310	3	304	100.0%	5.23 [1.54, 17.77]
Total (95% CI)		**310**		**304**	**100.0%**	**5.23 [1.54, 17.77]**
Total events	16		3			

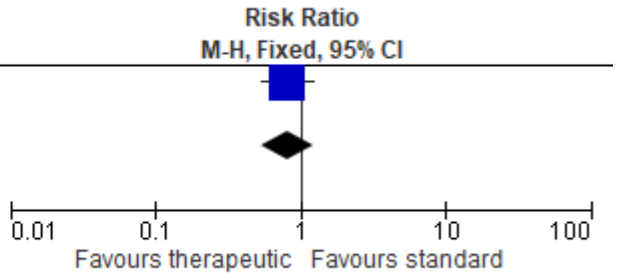
Heterogeneity: Not applicable
Test for overall effect: Z = 2.65 (P = 0.008)



ICU admission

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RAPID 2021	33	228	42	237	100.0%	0.82 [0.54, 1.24]
Total (95% CI)		**228**		**237**	**100.0%**	**0.82 [0.54, 1.24]**
Total events	33		42			

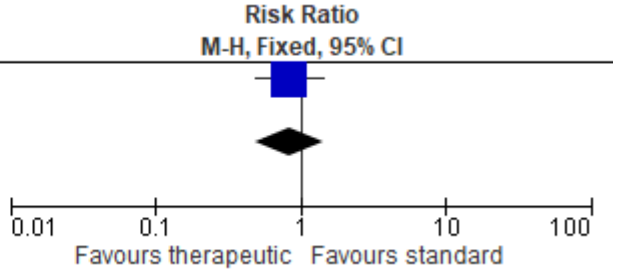
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



Need for IV or NIV

Study or Subgroup	Treatment dose Events	Total	Standard dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RAPID 2021	21	228	26	237	100.0%	0.84 [0.49, 1.45]
Total (95% CI)		**228**		**237**	**100.0%**	**0.84 [0.49, 1.45]**
Total events	21		26			

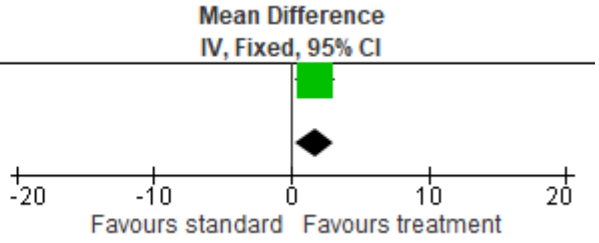
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)



Organ support-free days

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
RAPID 2021	25.8	6.2	228	24.1	8.8	237	100.0%	1.70 [0.32, 3.08]
Total (95% CI)			**228**			**237**	**100.0%**	**1.70 [0.32, 3.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)

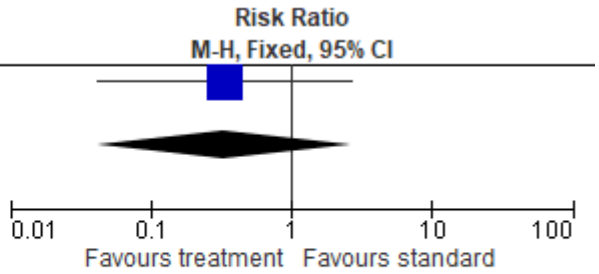


People with severe COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

All-cause mortality

Study or Subgroup	Treatment Events	Treatment Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HESACOVID 2020 (1)	1	10	3	10	100.0%	0.33 [0.04, 2.69]
Total (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.04, 2.69]**
Total events	1		3			

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

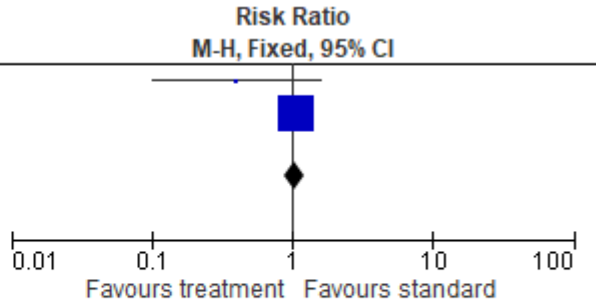


Footnotes
(1) At 28 days. Therapeutic enoxaparin 1mg/kg twice daily vs unfractionated heparin OR enoxaparin 40mg daily

Death in hospital

Study or Subgroup	Treatment Events	Treatment Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HESACOVID 2020 (1)	2	10	5	10	2.5%	0.40 [0.10, 1.60]
REMAP-CAP 2021 (2)	199	534	200	564	97.5%	1.05 [0.90, 1.23]
Total (95% CI)		**544**		**574**	**100.0%**	**1.03 [0.89, 1.21]**
Total events	201		205			

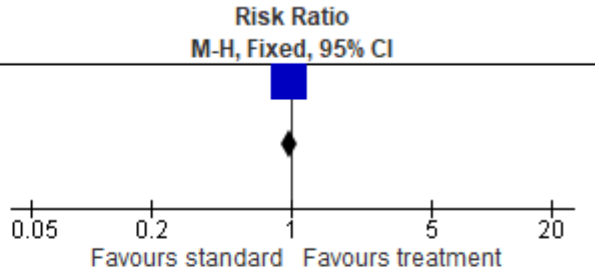
Heterogeneity: Chi² = 1.84, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.43 (P = 0.67)



Footnotes
(1) Therapeutic enoxaparin 1mg/kg twice daily vs unfractionated heparin OR enoxaparin 40mg daily
(2) Treatment (dose varies across study sites) vs standard dose venous thromboprophylaxis (dose and treatment varies across study sites)

Survival to hospital discharge

Study or Subgroup	Treatment Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
REMAP-CAP 2021 (1)	335	534	364	564	100.0%	0.97 [0.89, 1.06]
Total (95% CI)		**534**		**564**	**100.0%**	**0.97 [0.89, 1.06]**
Total events	335		364			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						

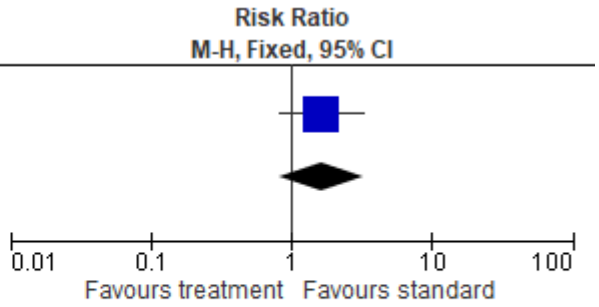


Footnotes

(1) Treatment (dose varies across study sites) vs standard dose venous thromboprophylaxis (dose and treatment varies across study sites)

Major bleeding

Study or Subgroup	Treatment Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HESACOVID 2020 (1)	0	10	0	10		Not estimable
REMAP-CAP 2021 (2)	20	529	13	562	100.0%	1.63 [0.82, 3.25]
Total (95% CI)		**539**		**572**	**100.0%**	**1.63 [0.82, 3.25]**
Total events	20		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						



Footnotes

(1) At 28 days. Therapeutic enoxaparin 1mg/kg twice daily vs unfractionated heparin OR enoxaparin 40mg daily

(2) During treatment period. Treatment (dose varies across study sites) vs standard dose venous thromboprophylaxis (dose and treatment...

Organ support free days

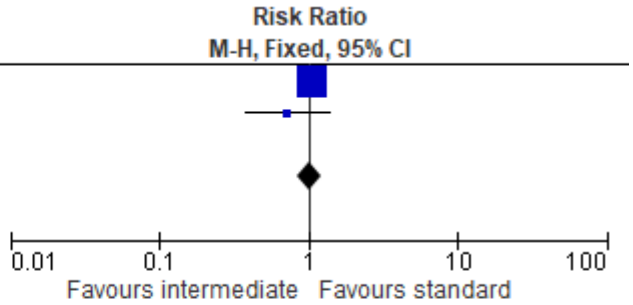
No forest plot. Odds ratio and 95% credible interval as reported in paper.

People with severe COVID-19: Intermediate dose prophylaxis vs standard dose prophylaxis

All-cause mortality (30 days)

Study or Subgroup	Intermediate Events	Intermediate Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
INSPIRATION 2021 (1)	119	276	117	286	86.4%	1.05 [0.87, 1.28]
Perepu 2021 (2)	13	87	18	86	13.6%	0.71 [0.37, 1.37]
Total (95% CI)		**363**		**372**	**100.0%**	**1.01 [0.84, 1.21]**
Total events	132		135			

Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%
Test for overall effect: Z = 0.08 (P = 0.94)

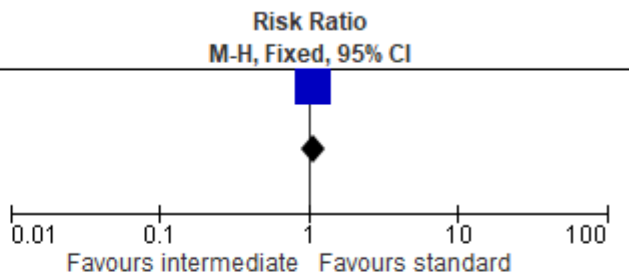


Footnotes
(1) At 30 days. Intermediate enoxaparin 1mg/kg daily for 30 days vs enoxaparin 40mg daily
(2) At 30 days. Intermediate enoxaparin 1mg/kg daily for 30 days if BMI <30kg/m2 or 0.5mg/kg twice a day if BMI was 30 or more vs enoxaparin...

All-cause mortality (90 days)

Study or Subgroup	Intermediate Events	Intermediate Total	Standard aparin Events	Standard aparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
INSPIRATION 2021 (1)	127	276	123	286	100.0%	1.07 [0.89, 1.29]
Total (95% CI)		**276**		**286**	**100.0%**	**1.07 [0.89, 1.29]**
Total events	127		123			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

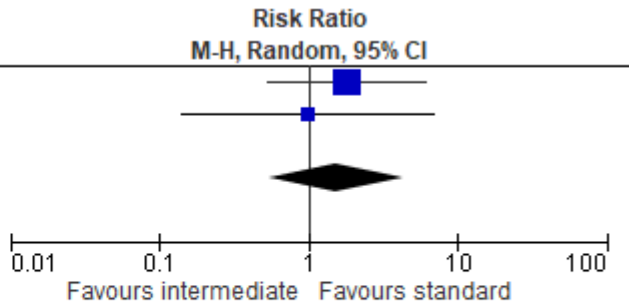


Footnotes
(1) At 30 days. Intermediate enoxaparin 1mg/kg daily for 30 days vs enoxaparin 40mg daily

Major bleeding

Study or Subgroup	Intermediate Events	Intermediate Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI
INSPIRATION 2021 (1)	7	276	4	286	71.7%	1.81 [0.54, 6.13]
Perepu 2021 (2)	2	87	2	86	28.3%	0.99 [0.14, 6.86]
Total (95% CI)		**363**		**372**	**100.0%**	**1.53 [0.54, 4.28]**
Total events	9		6			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0\%$
Test for overall effect: Z = 0.81 (P = 0.42)

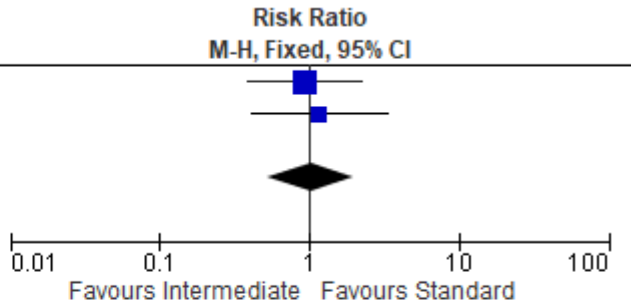


Footnotes
(1) At 30 days. Intermediate enoxaparin 1mg/kg daily for 30 days vs enoxaparin 40mg daily
(2) At 30 days. Intermediate enoxaparin 1mg/kg daily for 30 days if BMI <30kg/m2 or 0.5mg/kg twice a day if BMI was 30 or more vs enoxaparin...

VTE 30 days

Study or Subgroup	Intermediate Events	Intermediate Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
INSPIRATION 2021	9	276	10	286	61.9%	0.93 [0.38, 2.26]
Perepu 2021 (1)	7	87	6	86	38.1%	1.15 [0.40, 3.29]
Total (95% CI)		**363**		**372**	**100.0%**	**1.02 [0.52, 2.00]**
Total events	16		16			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



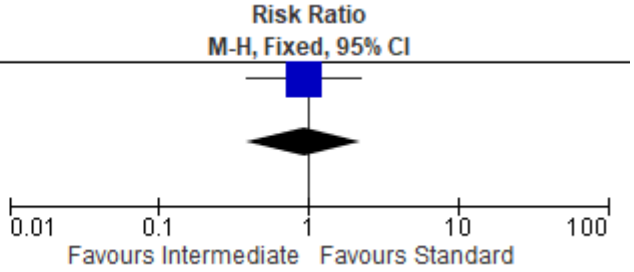
Footnotes

(1) At 30 days. Intermediate enoxaparin 1mg/kg daily for 30 days if BMI <30kg/m2 or 0.5mg/kg twice a day if BMI was 30 or more vs...

VTE 90 days

Study or Subgroup	Intermediate Events	Intermediate Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Fixed, 95% CI
INSPIRATION 2021	9	276	10	286	100.0%	0.93 [0.38, 2.26]
Total (95% CI)		**276**		**286**	**100.0%**	**0.93 [0.38, 2.26]**
Total events	9		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)



Appendix F: GRADE profiles

People with moderate severity COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard dose VTE prophylaxis	With treatment dose VTE prophylaxis	Relative effect (95% CI)	Risk with standard dose VTE prophylaxis	Risk difference with treatment dose VTE prophylaxis
Mortality 30 days											
2684 (2 RCTs)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	104/1285 (8.1%)	90/1399 (6.4%)	**RR 0.50** (0.13 to 1.88)	81 per 1,000	**40 fewer per 1,000** (from 70 fewer to 71 more)
Mortality 30 days - rivaroxaban											
614 (1 RCT)	serious[d]	not serious	not serious	serious[c]	none	Low	23/304 (7.6%)	35/310 (11.3%)	**RR 1.49** (0.90 to 2.46)	76 per 1,000	**37 more per 1,000** (from 8 fewer to 110 more)
All-cause mortality or need for IV or NIV											
465 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	38/237 (16.0%)	23/228 (10.1%)	**RR 0.63** (0.39 to 1.02)	160 per 1,000	**59 fewer per 1,000** (from 98 fewer to 3 more)
Death / need for IV or NIV / ICU admission											

Certainty assessment							Summary of findings				
465 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	52/237 (21.9%)	37/228 (16.2%)	**RR 0.74** (0.51 to 1.08)	219 per 1,000	**57 fewer per 1,000** (from 108 fewer to 18 more)

Survival without organ support 28 days

2221 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	789/1046 (75.4%)	932/1175 (79.3%)	**RR 1.05** (1.01 to 1.10)	754 per 1,000	**38 more per 1,000** (from 8 more to 75 more)

Venous thromboembolism 30 days

465 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	7/237 (3.0%)	2/228 (0.9%)	**RR 0.30** (0.06 to 1.41)	30 per 1,000	**21 fewer per 1,000** (from 28 fewer to 12 more)

Survival to hospital discharge without major thrombotic events

2226 (1 RCT)	serious[a]	not serious	not serious	serious[c]	none	Low	942/1046 (90.1%)	1086/1180 (92.0%)	**RR 1.02** (1.00 to 1.05)	901 per 1,000	**18 more per 1,000** (from 0 fewer to 45 more)

Survival to hospital discharge without any macrovascular thrombotic events

2226 (1 RCT)	serious[a]	not serious	not serious	serious[c]	none	Low	938/1046 (89.7%)	1084/1180 (91.9%)	**RR 1.02** (1.00 to 1.05)	897 per 1,000	**18 more per 1,000** (from 0 fewer to 45 more)

Venous thromboembolism 30 days rivaroxaban

Certainty assessment							Summary of findings				
615 (1 RCT)	serious[e]	not serious	not serious	serious[c]	none	Low	18/304 (5.9%)	11/311 (3.5%)	**RR 0.60** (0.29 to 1.24)	59 per 1,000	**24 fewer per 1,000** (from 42 fewer to 14 more)

Survival to hospital discharge

2219 (1 RCT)	serious[a]	not serious	not serious	serious[c]	none	Low	962/1048 (91.8%)	1085/1171 (92.7%)	**RR 1.01** (0.99 to 1.03)	918 per 1,000	**9 more per 1,000** (from 9 fewer to 28 more)

Composite Thrombotic Outcome- Defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

614 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	30/304 (9.9%)	23/310 (7.4%)	**RR 0.75** (0.45 to 1.26)	99 per 1,000	**25 fewer per 1,000** (from 54 fewer to 26 more)

Major bleeding rivaroxaban

614 (1 RCT)	serious[e]	not serious	not serious	serious[c]	none	Low	4/304 (1.3%)	10/310 (3.2%)	**RR 2.45** (0.78 to 7.73)	13 per 1,000	**19 more per 1,000** (from 3 fewer to 89 more)

Major bleeding

2692 (2 RCTs)	serious[a]	not serious	not serious	serious[c]	none	Low	13/1284 (1.0%)	24/1408 (1.7%)	**RR 1.30** (0.34 to 4.98)	10 per 1,000	**3 more per 1,000** (from 7 fewer to 40 more)

Clinically relevant non-major bleeding

Certainty assessment							Summary of findings				
614 (1 RCT)	serious[f]	not serious	not serious	not serious	none	Moderate	3/304 (1.0%)	16/310 (5.2%)	**RR 5.23** (1.54 to 17.77)	10 per 1,000	**42 more per 1,000** (from 5 more to 165 more)

ICU admission

465 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	42/237 (17.7%)	33/228 (14.5%)	**RR 0.82** (0.54 to 1.24)	177 per 1,000	**32 fewer per 1,000** (from 82 fewer to 43 more)

Need for IV or NIV

465 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	26/237 (11.0%)	21/228 (9.2%)	**RR 0.84** (0.49 to 1.45)	110 per 1,000	**18 fewer per 1,000** (from 56 fewer to 49 more)

Organ support-free days

465 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	237	228	-		MD 1.7 higher (0.32 higher to 3.08 higher)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis)
b. Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events)
c. 95% CI crossed line of no effect
d. Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients
e. Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients
f. 13% were prescribed treatment beyond hospital discharge

People with severe COVID-19: Treatment dose prophylaxis vs standard dose prophylaxis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Standard dose VTE prophylaxis	With Treatment dose VTE prophylaxis	Relative effect (95% CI)	Risk with Standard dose VTE prophylaxis	Risk difference with Treatment dose VTE prophylaxis
All-cause mortality 28 days											
20 (1 RCT)	serious[a]	not serious	not serious	very serious[b]	none	Very low	3/10 (30.0%)	1/10 (10.0%)	**RR 0.33** (0.04 to 2.69)	300 per 1,000	**201 fewer per 1,000** (from 288 fewer to 507 more)
Organ support free days											
0 (1 RCT)	serious[a]	not serious	not serious	serious[c]	none	Low	NR	NR	**OR 0.83** (0.67 to 1.03)	NR	NR
Death in hospital											
1118 (2 RCTs)	serious[a]	not serious	not serious	serious[c]	none	Low	205/574 (35.7%)	201/544 (36.9%)	**RR 1.03** (0.89 to 1.21)	357 per 1,000	**11 more per 1,000** (from 39 fewer to 75 more)
Survival to hospital discharge											
1098 (1 RCT)	serious[a]	not serious	not serious	serious[c]	none	Low	364/564 (64.5%)	335/534 (62.7%)	**RR 0.97** (0.89 to 1.06)	645 per 1,000	**19 fewer per 1,000** (from 71 fewer to 39 more)

Certainty assessment							Summary of findings				
Major bleeding											
1111 (2 RCTs)	serious[a]	not serious	not serious	serious[c]	none	Low	13/572 (2.3%)	20/539 (3.7%)	**RR 1.63** (0.82 to 3.25)	23 per 1,000	**14 more per 1,000** (from 4 fewer to 51 more)

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis)
b. No statistically significant effect, and low number of patients
c. CI includes line of no effect

People with severe COVID-19: Intermediate dose prophylaxis vs standard dose prophylaxis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Standard dose VTE prophylaxis	With Intermediate dose VTE prophylaxis	Relative effect (95% CI)	Risk with Standard dose VTE prophylaxis	Risk difference with Intermediate dose VTE prophylaxis
All-cause mortality 30 days											
735 (2 RCTs)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	135/372 (36.3%)	132/363 (36.4%)	**RR 1.01** (0.84 to 1.21)	363 per 1,000	**4 more per 1,000** (from 58 fewer to 76 more)
Major bleeding											
735 (2 RCTs)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	6/372 (1.6%)	9/363 (2.5%)	**RR 1.53** (0.55 to 4.26)	16 per 1,000	**9 more per 1,000** (from 7 fewer to 53 more)
All-cause mortality 90 days											
562 (1 RCT)	not serious	not serious	serious[d]	serious[c]	none	Low	123/286 (43.0%)	127/276 (46.0%)	**RR 1.07** (0.89 to 1.29)	430 per 1,000	**30 more per 1,000** (from 47 fewer to 125 more)
VTE 30 days											

Certainty assessment							Summary of findings				
735 (2 RCTs)	serious[a]	not serious	serious[b]	serious[c]	none	Very low	16/372 (4.3%)	16/363 (4.4%)	**RR 1.02** (0.52 to 2.00)	43 per 1,000	**1 more per 1,000** (from 21 fewer to 43 more)

VTE 90 days

562 (1 RCT)	not serious	not serious	serious[d]	serious[c]	none	Low	10/286 (3.5%)	9/276 (3.3%)	**RR 0.93** (0.38 to 2.26)	35 per 1,000	**2 fewer per 1,000** (from 22 fewer to 44 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Co-interventions (azithromycin) used more in intervention group in one study
b. Some patients in one study have moderate, not severe COVID-19
c. No statistically significant effect
d. Differences between the population of interest and those studied.

Appendix H: Recommendations for research

Question	**What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?**
Population	Patients 18 years and under who have COVID-19 pneumonia
Intervention(s)	Treatment-dose LMWH
Comparator(s)	Standard prophylaxis with LMWH
Outcomes	• incidence of VTE • mortality (all-cause, inpatient, COVID-19 related) • admission to critical care (including use of advanced organ support) • serious adverse events such as major bleeding or admission to hospital

Question	**What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?**
Population	Patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

Intervention(s)	Extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose: • low molecular weight heparins • unfractionated heparins • fondaparinux sodium • direct-acting anticoagulant • vitamin K antagonists
Comparator(s)	No extended pharmacological VTE prophylaxis
Outcomes	• incidence of VTE • mortality (all-cause, inpatient, COVID-19 related) • serious adverse events such as major bleeding or admission to hospital

Question	**What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?**
Population	Patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:

	• no additional risk factors for VTE • additional risk factors for VTE
Intervention(s)	Intermediate dose: • low molecular weight heparins (LMWH) • unfractionated heparin (UFH) • fondaparinux sodium • direct-acting anticoagulant • vitamin K antagonists
Comparator(s)	Standard-dose: • LMWH UFH • fondaparinux sodium • direct-acting anticoagulants vitamin K antagonists antiplatelets
Outcomes	• incidence of VTE • mortality (all-cause, inpatient, COVID-19 related) • admission to critical care (including use of advanced organ support) • serious adverse events such as major bleeding or admission to hospital