NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COVID-19 rapid evidence review: reducing the risk of venous thromboembolism in over 16s

November 2020

Literature search

One systematic database search was conducted to cover both review questions considered in this guideline because only the setting differed across review questions. The search for evidence was undertaken by NICE's information services team up to 19 October 2020. Studies were also considered from the NICE surveillance checks up to 27 October 2020.These search records were also subsequently assessed for inclusion (see appendix 4 for further details).

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the protocol (see appendix 2). One reviewer undertook title and abstract screening with 10% checked by a second reviewer, and all studies requiring a second opinion were considered by a second reviewer.

Full text references of potentially relevant evidence were obtained and reviewed by one reviewer to determine whether they met the inclusion criteria for this evidence review. All full text eligibility decisions were checked by a second reviewer. All uncertainties in full text selection were discussed with a second reviewer and referred to an adviser if needed.

The Information services team conducted targeted searches for grey literature (e.g. guidelines, reports and statements) that included national and international sources. The searches were conducted on 12-13 October 2020. Grey literature sources were checked weekly during development, but no additional guidelines, reports or statements were found.

See appendix 4 for search and screening details and appendix 7 for the list of excluded studies, with reasons for exclusion.

Review question 1

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?

The review protocol is shown in appendix 1.

Included studies

Three systematic reviews were included from development searches. One randomised controlled trial (RCT) and 11 cohort studies (which were not captured by these systematic reviews) were also included. An additional 2 systematic reviews and one cohort study were identified from surveillance searches and subsequently included in the evidence review. Data extraction for these 2 additional systematic reviews was limited to RCTs or cohort studies that had not already been identified in the evidence review in order to avoid double counting of studies. A final total of 18 studies were included (5 systematic reviews, 1 RCT, 12 cohort studies). See table 1 for an overview of included studies.

Table 1 Included studies for review question 1

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
Flumignan et al. 2020	Systematic review of 7 cohort studies (no meta-analysis) China (3 studies), Spain (1 study) USA (2 studies) and Italy (1 study). General hospital care Search end date 20 June 2020	People with confirmed COVID-19 infection who had been admitted to hospital with any severity of illness (n= 2470)	Pharmacological prophylaxis including heparin, low dose molecular weight heparin (LMWH), direct oral anticoagulants, treatment dose thromboprophylaxis	Another active comparator, placebo or no treatment: 6 studies used no thromboprophylaxis 1 study used standard dose thromboprophylaxis (UFH 5000 IU subcutaneously 2 to 3 times daily; or enoxaparin 40 mg twice daily if glomerular filtration rate (GFR) > 30 mL/min, or 40 mg once daily if GFR was ≤ 30 mL/min; or apixaban 2.5 mg or 5 mg twice daily)	Mortality
Kamel et al. 2020	Systematic review of 20 cohort and case-control studies (16 in quantitative synthesis) Search end date 5 July 2020 Systematic review identified from surveillance during development – 1 new cohort study included	Inpatients with confirmed COVID-19	Low-dose LMWH, high-dose LMWH	No heparin, low-dose LMWH	Mortality Major haemorrhage
Lu et al 2020	Systematic review of 5 cohort studies	People admitted to hospital with COVID-19.	Thromboprophylaxis (no drug or dosage reported)	No thromboprophylaxis (no drug or dosage reported)	Mortality

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
	China (1 study), USA (2 studies), Italy (1 study) and Spain (1 study) General hospital care 1 Jan- 4 June 2020	(n=8533)			
Mouhand et al.2020	Systematic review of 3 studies France (1 study), the Netherlands (1 study) and Belgium (1 study). Intensive care Search end date 10 July 2020	People with COVID-19 who were admitted to a hospital intensive care unit	Therapeutic dose thromboprophylaxis (no further information on drug or dosage reported)	Standard dose thromboprophylaxis (no further information on drug or dosage reported)	Incidence of venous thromboembolism
Wijaya et al. 2020	Systematic review of 8 studies Search end date 30 June 2020 Systematic review identified in surveillance during development – 2 new cohort studies included	Pregnant women with severe or critical COVID-19 (n=64) (new cohort study 1) 220 patients (38 mechanically ventilated) (new cohort study 2)	Therapeutic anticoagulation (TA) and prophylactic anticoagulation (PA) were not defined. Type of anticoagulants = heparin / LMWH. TA 16% (10/64) vs PA 58% (37/64) (new cohort study 1) TA and PA were not defined. Type and dose of anticoagulants were not defined. TA 12.3% (27/220)	Prophylactic dose anticoagulation	Mortality

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
			vs PA 79.1% (174/220) (new cohort study 2)		
Lemos et al. 2020	Randomised controlled trial Country not stated Intensive care April 2020- July 2020	People with laboratory-confirmed SARS-CoV-2 infection with respiratory failure requiring mechanical ventilation (all received mechanical ventilation) (n=20)	Therapeutic enoxaparin (subcutaneous enoxaparin with dose according to age and adjusted daily by creatinine clearance, maximum permitted dose 140 mg BID)	Standard thromboprophylaxis (subcutaneous UFH 5000 IU TID if weight < 120 kg, 7500 IU TID if weight > 120 kg), or enoxaparin (40 mg OD if weight < 120 kg and 40 mg BID if weight > 120 kg) according to clinical judgement.	Mortality Serious adverse effects: Major bleeding Bleeding requiring medical attention
Albani et al. 2020	Cohort General hospital care Italy 20 February 2020 – 10 May 2020	Adult patients admitted to hospital with RT-PCR-confirmed SARS-CoV-2 (n=1403)	Enoxaparin. Median dose of enoxaparin = 40 (40-80 mg) per day. Duration of therapy = 6 (3-9) days. 487 patients in enoxaparin cohort received prophylactic dose of 40 mg of enoxaparin per day, 312 patients received therapeutic dose of more than 40 mg of enoxaparin per day.	No enoxaparin	In-hospital mortality Admission to intensive care unit (ICU) Thrombotic events Haemorrhagic events
Jimenez-Guiu et al.2020	Cohort General hospital care Spain April 2020-April 2020	People with COVID-19 admitted to hospital but who were not critically ill (n=57)	Enoxaparin 40mg daily	Intermediate or therapeutic dose thromboprophylaxis. People with an underlying disease received therapeutic dose low molecular weight heparin (enoxaparin 1.5 mg/kg every 24 hours).	Incidence of venous thromboembolism Serious adverse effects: Bleeding complications

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
				People considered at high risk of venous thromboembolism received intermediate-dose low molecular weight heparin (enoxaparin 0.5 mg/kg every 12 hours).	
Longhitano et al. 2020	Cohort study General hospital care Italy 18 May 2020-30 May 2020	Adults with COVID-19 confirmed by clinical features and positive PCR from nasopharyngeal swab (n=74)	Anticoagulant drugs at intermediate or therapeutic dose. Therapeutic dose anticoagulation with 2 potential options: (1) heparin 12,500 U every 8-12 h (n=16) or (2) enoxaparin 100 U/kg every 12 h (n=7). Intermediate: Dose of enoxaparin (n=22) or heparin (n=1) between prophylactic and therapeutic dosage. 1 patient in this group received fondaparinux (5 mg / 24 h)	Standard antithrombotic prophylaxis: enoxaparin 80 U/kg per day (n=22) or heparin 5000 U every 8 h (n=4). 1 patient in this group received fondaparinux (2.5 mg QD)	Mortality Incidence of venous thromboembolism
Motta et al. 2020	Cohort study USA 1 April 2020- 25 April 2020 General hospital care	18 years or older, COVID positive (n=374)	Therapeutic anticoagulation Enoxaparin: 1 mg/kg subcutaneously twice daily or 1.5 mg/kg subcutaneously daily or based on renal function, or higher doses titrated to anti-Factor Xa range of 0.6 to 1 IU/mL (for twice daily dosing) and 1 to 2 IU/mL (for daily dosing)	Prophylactic anticoagulation: enoxaparin 30 or 40 mg subcutaneously every day or heparin 5000 units given subcutaneously every 8 hours	Mortality

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
			Heparin: intravenous heparin titrated to an activated partial thromboplastin time (aPTT) between 70 and 110 sec		
Nadkarni et al. 2020	Cohort study USA 1 March 2020-30 April 2020 General hospital care	All adults (aged 18 years and above) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection (n=4389)	1.Therapeutic anticoagulation: continuous intravenous infusions of bivalirudin, argatroban or unfractionated heparin (UFH), high-dose LMWH (specifically enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily), apixaban 5mg twice daily, rivaroxaban or dabigatran. patients >75 years, apixaban therapeutic at lower doses: at 2.5 mg twice a day or 5 mg once a day. 2. Prophylactic anticoagulation: subcutaneous unfractionated heparin, LMWH once daily, or apixaban (2.5 mg twice a day or 5 mg daily in patients ≤75 years)	No anticoagulation	Mortality Serious adverse effects: Major bleeding
Paolisso et al. 2020	Cohort study Italy 1 March 2020- 10 April 2020	Adult patients with confirmed COVID-19 referred to hospital (n=450)	Intermediate LMWH dosage: 40-60mg twice daily for 7 days	Standard prophylactic LMWH dosage 40-60mg once daily for 7 days	Mortality

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
	General hospital care				
Atallah et al. 2020	Cohort study Abu Dhabi 1 March 2020- 29 May 2020 Intensive care	Admission to ICU, confirmed SARS-CoV-2 infection (n=188)	Therapeutic dose heparin	Standard dose enoxaparin 40mg daily	Mortality
Ferguson et al. 2020	Cohort study USA 15 March 2020- 8 May 2020 Intensive care	People with confirmed SARS-CoV-2 by nasal/oral PCR requiring intubation for acute respiratory failure (n=141)	Therapeutic anticoagulation as either a continuous infusion of heparin dose-adjusted based on unfractionated heparin level or by subcutaneous 1mg/kg twice daily or 1.5 mg/kg daily low molecular weight heparin (LMWH).	Enoxaparin 40 mg subcutaneously daily, Enoxaparin 30 mg twice daily, Enoxaparin 0.5 mg/kg twice daily, or Heparin 5000 units subcutaneously 2 or 3 times daily.	Mortality
Jonmarker et al. 2020	Cohort study Sweden March 2020-April 2020 Intensive care	People with polymerase chain reaction confirmed COVID-19 and respiratory failure admitted to an intensive care unit (n=152)	Thromboprophylaxis dose followed local guidance and changed over time incorporating low-dose: Initial regimen tinzaparin 2500-4500 IU or dalteparin 2500-5000 IU, Medium-dose: Initial regimen tinzaparin more than 4500 IU but less than 175 IU/kg or dalteparin more than 5000 IU but less than 200 IU/kg and High-dose: Initial regimen tinzaparin 175 IU/kg	Comparisons were done between the 3 dosing strategies.	Mortality Incidence of venous thromboembolism

Study	Country, study design, dates	Population	Intervention	Control	Outcomes
			or more or dalteparin 200 IU/kg or more		
Li et al. 2020	Cohort study USA 1 March 2020- 14 April 2020 Intensive care	Adults (aged 18 years and above) with confirmed COVID-19 (n=56)	Unfractionated heparin infusion (mean lowest UFH infusion rate = 8.4 + 2.1 units/kg/ hour, mean highest UFH infusion rate =15.1 + 4 units/kg/hour)	Standard prophylaxis with subcutaneous UFH 5000 units every 8 or 12 hours, Standard prophylaxis with enoxaparin 40 mg every 24 hours No pharmacologic prophylaxis.	Mortality Serious adverse events: Major bleeding Patients requiring packed red blood cell transfusion
Pavoni 2020	Cohort study Italy Dates not reported Intensive care	Adult admitted to ICU due to COVID-19 pneumonia. Diagnosis of severe COVID-19 based on World Health Organisation (WHO) interim guidance and confirmed by RT-PCR (n=42)	Patients with D-dimer < 3000ng/mL received enoxaparin 4000UI (6000UI, body mass index>35) subcutaneously BD	Patients with D-dimer ≥3000ng/mL received enoxaparin100UI/kg every 12h All patients received aspirin once a day.	Mortality Incidence of venous thromboembolism
Taccone et al. 2020	Cohort study Belgium 10 March 2020- 30 April 2020 Intensive care	Critically ill mechanically ventilated adults with RT-PCR-confirmed COVID-19 (n=40)	High regimen thromboprophylaxis (subcutaneous enoxaparin 4,000 international units bd or therapeutic unfractionated heparin)	Standard thromboprophylaxis (subcutaneous enoxaparin 4,000 international units once daily)	Incidence of venous thromboembolism - pulmonary embolism Serious adverse events: Haemorrhagic complications

Key results

The majority of studies included people with confirmed COVID-19 infection (see Table 1).

The 5 systematic reviews had several overlapping studies so it is not appropriate to sum the number of participants across the systematic reviews because this would lead to multiple counting of data. The outcome data reported in the systematic reviews differed enough to justify extracting data from all reports individually.

Follow-up was poorly reported across the studies, with a maximum follow-up of 28 days.

The most commonly used treatments were low molecular weight heparin (often enoxaparin; tinzaparin; dalteparin in 1 study) or heparin.

Two of the 5 systematic reviews (Lu et al. 2020, Mouhand et al. 2020) did not report the drug and dosage for all thromboprophylaxis regimens used in the relevant analysis.

No studies reported outcome data for any of the subgroups of interest as specified in the scope (with the exception of a cohort study in pregnant women included in the systematic review by Wijaya et al. 2020)

Setting

The identified studies were all conducted in hospital with 9 studies in general hospital care (Flumignan et al. 2020, Kamel et al. 2020, Lu et al. 2020, Albani et al. 2020, Jimenez-Guiu et al. 2020, Longhitano et al. 2020, Motta et al. 2020, Nadkarni et al. 2020, Paolisso et al. 2020), 8 studies in intensive care units (Mouhand et al. 2020, Lemos et al. 2020, Atallah et al. 2020, Ferguson et al. 2020, Jonmarker et al. 2020, Li et al. 2020, Pavoni 2020, Taccone et al. 2020) and unclear setting in 2 cohort studies included in 1 systematic review (Wijaya et al. 2020).

No community-based studies were identified.

Results by care setting: General hospital care

Two cohort studies (Nadkarni et al. 2020, Paolisso et al. 2020) and 2 systematic reviews (Flumignan et al. 2020, Lu et al. 2020) showed a reduced risk of mortality with intermediate/therapeutic dose thromboprophylaxis compared with standard dose or no anticoagulation in the general hospital care setting.

One cohort study identified in a systematic review (Kamel et al. 2020) reported a lower risk of in-hospital mortality for patients in the high-dose heparin group compared with the no heparin and low-dose heparin groups.

One cohort study showed reduced in-hospital mortality and admissions to ICU with enoxaparin compared with no enoxaparin (Albani et al. 2020). This reduction in mortality was observed for both prophylactic and therapeutic doses of enoxaparin (Albani et al. 2020). This effect was observed in patients who had received enoxaparin for at least 2 days duration (Albani et al. 2020).

One cohort study (Longhitano et al. 2020) showed no association between intermediate/therapeutic dose thromboprophylaxis and standard dose thromboprophylaxis for mortality.

One cohort study (Motta et al. 2020) showed a significantly higher risk of mortality for patients receiving therapeutic anticoagulation compared with prophylactic anticoagulation.

Two cohort studies (Jimenez-Guiu et al. 2020, Longhitano et al. 2020) showed no association between intermediate/therapeutic dose thromboprophylaxis and standard dose thromboprophylaxis for deep vein thrombosis and venous thrombosis in the general hospital care setting.

One cohort study (Albani et al. 2020) found increased thrombotic events in people receiving therapeutic dose enoxaparin compared with prophylactic dose enoxaparin and no enoxaparin groups.

Results by care setting: Intensive care

One cohort study (Jonmarker et al.2020) showed significantly reduced mortality with high-dose thromboprophylaxis compared with medium or low-dose thromboprophylaxis

Five studies (Pavoni 2020, Lemos et al. 2020, Li et al. 2020, Ferguson et al. 2020, Atallah et al. 2020) showed no association in reduced mortality with therapeutic dose thromboprophylaxis compared with standard dose thromboprophylaxis in the intensive care setting.

Three studies (Jonmarker et al. 2020, Pavoni 2020, Taccone et al. 2020) showed an association between reduced pulmonary embolism and venous thromboembolism with therapeutic dose/high-dose thromboprophylaxis compared with standard dose/medium dose/low-dose thromboprophylaxis.

One study (Mouhand et al. 2020) showed no association in incidence of venous thromboembolism with therapeutic dose thromboprophylaxis compared with standard dose thromboprophylaxis in the intensive care setting.

One systematic review (Wijaya et al. 2020) provided evidence from 2 hospital-based cohort studies (unclear whether general hospital or intensive care setting) of no significant difference in mortality between patients receiving therapeutic compared with prophylactic anticoagulation.

Adverse events

There was limited evidence reporting adverse events across the studies.

Two studies (Ferguson et al. 2020; Li et al. 2020) showed a significant increase in the number of people on therapeutic dose thromboprophylaxis who needed a red blood cell blood transfusion compared with those receiving standard dose thromboprophylaxis.

Five studies (Lemos et al. 2020, Albani et al. 2020, Jimenez-Guiu et al. 2020, Nadkarni et al. 2020, Taccone et al. 2020) reported that the number or proportion of bleeding events was higher with intermediate or therapeutic dose

thromboprophylaxis compared with standard dose thromboprophylaxis or no prophylaxis, but statistical analyses were not reported.

There was no difference between higher or lower-dose thromboprophylaxis for bleeding complications, cerebral parenchymal bleeds, WHO grade I to IV bleeding, major bleeding and admission to critical care. A major limitation was that no statistical analysis was reported for these outcomes.

Strengths and limitations

Due to the short development timeframe of COVID-19 rapid guidelines, some development stages can be performed iteratively or in parallel. An overall summary of strengths and limitations of the included evidence was presented initially to the panel. A more detailed risk of bias assessment was then undertaken.

Risk of bias for the studies was assessed using the ROBIS checklist for systematic reviews, the Cochrane risk of bias tool for randomised controlled trials (version 2.0) or the Critical Appraisal Skills Programme (CASP) checklist for cohort studies as appropriate.

One systematic review was considered to be at low risk of bias (Flumignan et al. 2020). Two systematic reviews (Kamel et al. 2020, Wajiya et al. 2020) were rated as at moderate risk of bias. The systematic review by Lu et al. 2020 was rated as high risk of bias (with specification of study eligibility criteria, methods used to identify and select studies, and synthesis noted as areas at high risk of bias) The systematic review by Mouhand et al. 2020 was also rated as being at high risk of bias (with issues identified in specification of study eligibility criteria, methods used to identify and select studies, methods used to collect data and appraise studies and synthesis).

The one included non-UK RCT (Lemos et al. 2020) received a rating of some concerns for risk of bias.

Common issues highlighted for the included cohort studies were unclear reporting of whether potentially confounding factors were identified and taken account of, and unclear reporting of length of follow-up. All relevant included cohort studies were non-UK-based and 8 of these were single centre studies (Albani et al. 2020, Atallah

et al. 2020, Jiminez-Guiu et al., 2020, Li et al. 2020, Longhitano et al. 2020, Paolisso et al. 2020, Pavoni et al. 2020, Taccone et al. 2020).

Expert panel discussion

This section describes how the expert panel considered the evidence in relation to the recommendations within the guidance.

Relative value of different outcomes

The panel considered that the evidence base was insufficient for developing recommendations and so these were made on the basis of informal consensus. As such, the relative value of different outcomes was not explicitly discussed.

Quality of the evidence

The panel considered that the evidence base consisted largely of small single centre studies conducted early in the pandemic that had methodological problems. The panel was not confident about drawing conclusions from the body of evidence regarding using particular dosing strategies for VTE prophylaxis in people with suspected or confirmed COVID-19.

Problems with the evidence included:

- probable confounding
- selection bias (if clinicians assigned thromboprophylaxis doses based on predicting the patient's response)
- lack of detail on patients' characteristics such as pre-existing atrial fibrillation or frailty
- small sample sizes
- heterogeneity between studies making pooled analyses from published systematic reviews unreliable.

Together, the issues with the evidence base meant that it was difficult to draw definitive conclusions. In studies showing a possible effect of the intervention, the observed effect could have been due to differences in patients' characteristics rather than the VTE prophylaxis dosing strategy. In studies in which an effect was not shown, the small numbers of observed events indicate a possible lack of power to

detect an effect rather than an absence of an effect. This applied to effectiveness outcomes such as occurrence of VTE and mortality as well as safety outcomes such as bleeding events.

Therefore, recommendations were developed by informal consensus.

The panel noted that from their clinical experience and their awareness of data from epidemiological studies that the rates of VTE remained very high in patients with COVID-19 despite standard VTE prophylaxis. However, they also noted that the incidence of VTE in the second wave of infections appears to be lower than in the first wave. Possible reasons for this included:

- VTE prophylaxis may not have been offered as standard for all patients with COVID-19 in the first wave.
- Other treatments for COVID-19 that were not commonly used in the first wave such as immunotherapies and dexamethasone may have improved patient's clinical condition and thereby lowered the risk of VTE.
- Immunothrombosis could have been misdiagnosed as pulmonary embolism in the first wave because clinicians would have had little experience of immunothrombosis before the COVID-19 pandemic.
- Any studies using systematic screening for VTE were likely to report higher incidence than those with diagnosis based on clinical suspicion of significant VTE.

The committee recommended that all patients who are admitted to hospital for treatment of COVID-19 should be offered standard VTE prophylaxis taking account of bodyweight and renal function unless the patient's bleeding risk was too high to justify use of prophylaxis.

The committee noted that patients should be given information about the risks of VTE and bleeding to be able to give informed consent for VTE prophylaxis.

The committee discussed the possibility of making a weak recommendation to consider intermediate-dose VTE prophylaxis based on individual risk assessments according to local protocols. However, because of the lack of evidence available the panel considered that this would not be helpful for decision making or standardising care nationally.

The panel indicated that there was a probable difference in incidence of VTE in wards and critical care units, with critical care units generally seeing higher rates of VTE. In the absence of data about characteristics of patients with COVID-19 that indicate higher risk of VTE, the decision to provide a patient advanced respiratory support was considered to serve as an indicator of an increase in risk of VTE. There is some evidence available on the use of higher doses of anticoagulant for VTE prophylaxis. The panel agreed that based on their clinical experience, consideration should be given to increasing the standard prophylactic dose of parenteral anticoagulation, such as LMWH, to an intermediate dose to mitigate the increased risk of VTE but to minimise the risk of bleeding associated with higher doses. Therefore, the panel recommended that intermediate-dose VTE prophylaxis could be considered for people having advanced respiratory support. The panel defined an intermediate dose of VTE prophylaxis as double the standard prophylactic dose taking account of bodyweight and renal function.

Because of unknown benefit and increased bleeding risk, the panel agreed that therapeutic dose of VTE prophylaxis should be used only in research. Therapeutic dose VTE prophylaxis was defined as the standard dosage used for treating confirmed VTE.

The panel noted that the international REMAP-CAP randomised controlled trial has several participating sites in the UK. This study is assessing several treatments including therapeutic dose VTE prophylaxis compared with standard dose VTE prophylaxis.

The panel were unable to make any recommendations for people with suspected or confirmed COVID-19 who were being treated in the community. This was because no studies in this population were identified in the evidence review and the panel considered that any patients unwell enough to need VTE prophylaxis would meet the criteria for admission to hospital.

The lack of identified studies which included prespecified subgroups meant that the panel were unable to make recommendations on VTE prophylaxis in people managed in hospital for COVID-19 pneumonia in:

- 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 30 kg/m² or higher).

It was noted that these subgroups should be managed on a case-by-case basis.

One cohort study was identified which included pregnant women with COVID-19 but did not report any events for the outcome mortality in either group (therapeutic versus prophylactic dose anticoagulation). Therefore, for women with COVID-19 who are pregnant or have given birth within the past 6 weeks, the panel agreed that clinicians should follow the advice on venous thromboembolism prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus (COVID-19) in pregnancy.

Trade-off between benefits and harms

The panel recognised that the main harm from VTE prophylaxis is risk of clinically significant bleeding, and that this risk increases with increasing dose. The panel considered that the current evidence base was not strong enough to justify using therapeutic doses as VTE prophylaxis in patients with COVID-19. The panel considered that the balance of lowering the occurrence of VTE and increased risk of bleeding with intermediate doses of VTE prophylaxis could be justified in patients having advanced respiratory support.

Implementation and resource considerations

Recommendation 1.1 states that all patients admitted to hospital with COVID-19 should have a risk assessment for bleeding in line with recommendations in NICE's' guideline on reducing the risk of hospital-acquired venous thromboembolism in over 16s (NICE guideline NG89). This guideline links to a risk assessment checklist produced by Department of Health and Social Care. According to this checklist, a significant medical condition such as acute infectious disease is an indication for thromboprophylaxis.

The panel considered that by highlighting that all patients with COVID-19 should be offered VTE prophylaxis, the VTE risk assessment process would be streamlined and thus save time because clinicians could focus on evaluating bleeding risk and changes in the patient's condition when making decisions about VTE prophylaxis.

The panel noted past shortages of low molecular weight heparin products, although no current supply problems were identified.

Other considerations

Equality issues

In developing the scope of the guideline we identified the following equality issues which were addressed when developing the recommendations.

Religion / beliefs

Some pharmacological treatments for venous thromboembolism are derived from animal origin (heparins are of animal origin, and apixaban and rivaroxaban contain lactose from cow's milk). People who have concerns about using animal products because of a religious or ethical belief need to be given consideration when discussing VTE prophylaxis.

The guideline includes a recommendation for clinicians to be aware that heparins are of animal origin and cross refers to the section on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s for further information.

Disability

Some disabled people may have communication needs that need to be considered when using alternatives to face-to-face contact and also when facial masks are worn when receiving care.

The guideline overview section includes the following standard text that is considered to address equality issues regarding disability: 'When using this guideline, follow the usual professional guidelines, standards and laws (including those on equalities, safeguarding, communication and mental capacity), as described in making decisions using NICE guidelines.'

Appendix 1 Methods used to develop the guidance

Methods used to develop this guideline can be found in Developing NICE guidelines: the manual. Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies

Appendix 2 Review protocol

Review question 1: 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?

PICO and eligibility criteria

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/m^2 or higher)
Study types	RCTs Cohort studies with a comparator group Systematic reviews of RCTs and/or cohort studies

Criteria	Notes
	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 3 Literature search strategy

One search was carried out for both review questions:

Review question 1: What is the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults receiving care for suspected or confirmed COVID-19?

Review question 2: What is the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults who have received care for COVID-19?

Table 2 Search strategy for the review questions

Database	Platform	Segment searched
MEDLINE ALL	Ovid	1946 to October 16, 2020
Embase	Ovid	1974 to 2020 October 15
Cochrane Library	Wiley	Issue 10 of 12, October 2020
Pre-prints – bioRxiv and medRxiv	RIS via EPPI	RIS file received on 19/10/2020, 8:32 AM
WHO COVID-19 database	WHO website	19/10/2020
Surveillance	-	23 oct 2020 12:38 last modified Search date: 27th October

Database strategies

Full details are available on request.

Table 3 World Health Organization COVID-19 database strategy

Variable	Details
Name	World Health Organization Global research on coronavirus disease (COVID-19)
URL	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
Notes	"WHO is gathering the latest scientific findings and knowledge on coronavirus disease (COVID-19) and compiling it in a database. We update the database daily from searches of bibliographic databases, hand searches of the table of contents of relevant journals, and the addition of other relevant scientific articles that come to our attention."
Search terms	(tw:(anticoagula* OR antithromb* OR antiemboli* or thrombin* OR thromboprophyla* OR fibrinolytic* OR DOAC OR DOACs)) AND (tw:(thrombosis OR thromboses OR thrombus OR thromboembolism OR VTE OR DVT)) (tw:(apixaban OR eliquis OR rivaroxaban OR xarelto OR edoxaban OR lixiana OR savaysa OR fondaparinux OR arixtra OR aspirin OR acetylsalicylic)) (tw:(warfarin OR marevan OR acenocoumarol OR nicoumalone OR sinthrome OR phenindione OR dicumarol OR phenprocoumon OR biscoumacetate))
How the results were selected	Searched terms and selected relevant ones from the list
Results	125 – added to EPPI

Appendix 4 Search and screening information

Evidence selection to completion of draft evidence review (26 October 2020) for expert panel meeting 1.

Stage	Number of references
Included for screening after deduplication and reference clean up	321
Included from title and abstract screening	82
Included from full text screening	15
Included from surveillance search after full text screening	3
Total included studies	18

Appendix 5 Included studies

Systematic reviews

Flumignan, R.L.G., Tinoco, J.D.D.S.a., Pascoal, P.I.F. et al. (2020) Prophylactic anticoagulants for people hospitalised with COVID-19. Cochrane Database of Systematic Reviews 2020(9): cd013739

Kamel, A.M., Sobhy, M., Magdy, N. et al. (2020) Anticoagulation outcomes in hospitalized Covid-19 patients: A systematic review and meta-analysis of case-control and cohort studies. Reviews in Medical Virology

Lu, Ying-Feng, Pan, Li-Ya, Zhang, Wen-Wu et al. (2020) A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 100: 34-41

Mohamed Mouhand, F.H., Shokri Shaikha D., Al-Shokri, Shunnar Khaled, M. et al. Prevalence of Venous Thromboembolism in Critically-ill COVID-19 Patients: Systematic Review and Meta-analysis. medrxiv preprint

Wijaya, Indra; Andhika, Rizky; Huang, Ian (2020) The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 26: 1076029620960797

Randomised controlled trials

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

Cohort studies

Albani, Filippo, Sepe, Lilia, Fusina, Federica et al. (2020) Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study. EClinicalMedicine 27: 100562

Atallah, B, Sadik, Z G, Salem, N et al. (2020) The impact of protocol-based high-intensity pharmacological thromboprophylaxis on thrombotic events in critically ill COVID-19 patients. Anaesthesia

Ferguson, John, Volk, Stacy, Vondracek, Thomas et al. (2020) Empiric Therapeutic Anticoagulation and Mortality in Critically Ill Patients With Respiratory Failure From SARS-CoV-2: A Retrospective Cohort Study. Journal of clinical pharmacology 60(11): 1411-1415

Jimenez-Guiu, Xavier, Huici-Sanchez, Malka, Romera-Villegas, Antonio et al. (2020) Deep vein thrombosis in non-critically ill patients with coronavirus disease 2019 pneumonia: deep vein thrombosis in non-intensive care unit patients. Journal of vascular surgery. Venous and lymphatic disorders

Jonmarker, Sandra, Hollenberg, Jacob, Dahlberg, Martin et al. Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients. medrxiv preprint

Li, Matthew, Gitarts, Steven, Nyabera, Akwe et al. (2020) Continuous Infusion Low-Dose Unfractionated Heparin for the Management of Hypercoagulability Associated With COVID-19. Journal of Pharmacy Practice

Longhitano, Yaroslava, Racca, Fabrizio, Zanza, Christian et al. (2020) Venous Thrombo-Embolism in Hospitalized SARS-CoV-2 Patients Treated with Three Different Anticoagulation Protocols: Prospective Observational Study. Biology 9(10)

Motta, K, Ogunnaike Rahila, O, Shah, Rutvik et al. Clinical Outcomes With the Use of Prophylactic Versus Therapeutic Anticoagulation in COVID-19. medrxiv preprint

Nadkarni, G.N., Lala, A., Bagiella, E. et al. (2020) Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. Journal of the American College of Cardiology 76(16): 1815-1826

Paolisso, Pasquale, Bergamaschi, Luca, D'Angelo, Emanuela Concetta et al. (2020) Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients. Frontiers in pharmacology 11: 1124

Pavoni, V., Gianesello, L., Pazzi, M. et al. (2020) Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: A call to action. Thrombosis Research 196: 313-317

Taccone, Fabio Silvio, Gevenois, Pierre Alain, Peluso, Lorenzo et al. (2020) Higher Intensity Thromboprophylaxis Regimens and Pulmonary Embolism in Critically Ill Coronavirus Disease 2019 Patients. Critical care medicine 48(11): e1087-e1090

Appendix 6 Evidence tables

Systematic reviews

Flumignan, 2020

Bibliographic Reference	Flumignan, R.L.G.; Tinoco, J.D.D.S.a.; Pascoal, P.I.F.; Areias, LL; Cossi, M.S.; Fernandes, M.I.C.D.; Costa, I.K.F.; Souza, L.; Matar, C.F.; Tendal, B.; Trevisani, V.F.M.; Atallah, A.N.; Nakano, L.C.U.; Prophylactic anticoagulants for people hospitalised with COVID-19; Cochrane Database of Systematic Reviews; 2020; vol. 2020 (no. 9); cd013739

Study details

Study design	Systematic review
Protocol registration (if reported)	The protocol for this review was prospectively registered with the Open Science Framework. Flumignan RL, Tinôco JD, Pascoal PI, Areias LL, Cossi MS, Fernandes MI et al. Prophylactic anticoagulants for patients hospitalised with COVID-19 (Protocol). Available from doi.org/10.17605/OSF.IO/8PRXW (registered 7 August 2020).
Search end date	20-Jun-2020
Aim of the study	The systematic review assessed the effects of pharmacological thromboprophylaxis compared with active comparator, placebo or no intervention in people with COVID-19 admitted to hospital.
Country/ Geographical location	Included studies were conducted in China (3 studies), Spain (1 study) USA (2 studies) and Italy (1 study).
Study setting	All studies were in people admitted to hospital. One study compared ICU and ward-based prophylactic strategies.
Population description	People with confirmed COVID-19 infection who had been admitted to hospital with any severity of illness.
Inclusion criteria	People with COVID-19 admitted to hospital who were eligible for pharmacological thromboprophylaxis.

	The review included parallel or cluster-randomised controlled trials (RCTs), quasi-RCTs, and cohort studies. Studies had to adjust for existing thromboprophylaxis use, surgery during hospital admission, current cancer treatment, antiplatelet use, and history of venous thromboembolism. Studies with a minimum duration of 2 weeks. Eligible interventions were heparinoids, vitamin K antagonists, direct anticoagulants and studies could compare different formulations, doses, and schedules of the same intervention.
Exclusion criteria	People with COVID-19 treated in the community.
Intervention	Pharmacological prophylaxis (other potential interventions such as antiplatelet agents, elastic stockings, intermittent pneumatic compression were allowed as additional interventions). The included studies used: heparin (type and dose not described; 2 studies) low molecular weight heparin (dose not reported; 1 study) low molecular weight heparin (40 to 60 mg enoxaparin daily; 94 of 99 participants) or unfractionated heparin (10,000-15,000 IU daily; 5 of 99 participants) (both in 1 study) direct oral anticoagulants (18 of 26 participants) or vitamin K antagonists (8 of 26 participants) (both in 1 study); treatment dose thromboprophylaxis (type and dose not described; 1 study) treatment dose thromboprophylaxis (unfractionated heparin, infusion of ≥ 15 IU/kg/h with or without a heparin bolus of 80 IU/kg aiming for activated prothrombin time of 70-100 s based on institutional protocol; or enoxaparin 1 mg/kg twice daily if GFR> 30 ml/min, or once daily if GFR was 30 ml/min or less; or apixaban 10 mg (no prior anticoagulation) or 5 mg (prior anticoagulation) twice daily)
Comparator	Another active comparator, placebo or no treatment (other potential interventions such as antiplatelet agents, elastic stockings, intermittent pneumatic compression were allowed as comparators). The included studies used: no thromboprophylaxis (6 studies) standard dose thromboprophylaxis (UFH 5000 IU subcutaneously 2 to 3 times daily; or enoxaparin 40 mg twice daily if GFR > 30 mL/min, or 40 mg once daily if GFR was ≤ 30 mL/min; or apixaban 2.5 mg or 5 mg twice daily; 1 study)
Methods of data analysis	Meta-analysis of non-randomised studies was not done.
Source of funding	No sources of financial support were reported.
Study limitations (Author)	Overall a small number of small studies were identified. 'Very little' evidence on adverse effects of thromboprophylaxis was reported. No studies reported on need for additional respiratory support (a predefined primary outcome), occurrence of deep vein thrombosis or pulmonary embolism. The methods of included studies including drug dosages and assessment of confounding variables differed substantially, and many did not report complete and clear information about their data. The authors also noted: 'Social and cultural aspects of the evaluated interventions can also interfere with their acceptability and effectiveness...' The certainty of evidence was rated as low to very low. The certainty of evidence was downgraded due to inconsistency, imprecision, and risk of bias, particularly overall

	critical or serious risk of bias, particularly confounding or selection bias, across studies. The authors conclude that the external validity of the overall evidence should be considered with caution.
Other details	Risk of bias was assessed using the Risk Of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool. The authors concluded: 'It is very uncertain if anticoagulants (all types) compared with no treatment, reduce all-cause mortality at 28 days after the intervention (5685 participants, 6 retrospective non-randomised studies), or have any effect on hospitalisation time (42 participants, 1 retrospective non-randomised study, follow-up not reported)... Anticoagulants (all types) may make no difference in major bleeding compared with no treatment, but the certainty of evidence is low (2773 participants, 1 retrospective non-randomised study (NRS), follow-up not reported).' Therapeutic dose thromboprophylaxis compared with standard dose thromboprophylaxis may reduce all-cause mortality with no difference in major bleeding but may increase time spent in hospital, but the certainty of evidence is low (244 participants, 1 retrospective NRS, follow-up 35 days).

Study arms

Thromboprophylaxis (N = NR)
No thromboprophylaxis (N = NR)

Characteristics

Study-level characteristics

Age	Range of means across studies = 59 to 72 years
Gender	Range of proportion male across studies = 60% to 66%
Ethnicity	Not reported

Outcomes

Study timepoints	8 (day) Not reported in most studies

Effect of thromboprophylaxis

	Thromboprophylaxis vs No thromboprophylaxis
	8 (day)
	N1 = NR, N2 = NR
Mortality All-cause, adjusted, n=2,075 *Polarity: Lower values are better*	
Odds ratio/95% CI	0.42 (0.26 to 0.66)
Mortality In hospital, people on mechanical ventilation, adjusted, n=395 *Polarity: Lower values are better*	
Hazard ratio/95% CI	0.86 (0.82 to 0.89)

	Thromboprophylaxis vs No thromboprophylaxis
	8 (day)
	N1 = NR, N2 = NR
Mortality All-cause, adjusted, n=192 *Polarity: Lower values are better*	
Relative risk/95% CI	1.15 (0.29 to 2.57)
Mortality All-cause, adjusted, n=449 *Polarity: Lower values are better*	
Odds ratio/95% CI	1.64 (0.92 to 2.92)
Sepsis-induced coagulopathy score of 4 or more Unadjusted, n=97	
Odds ratio/95% CI	0.37 (0.15 to 0.9)
D-dimer more than 6 times the upper limit Unadjusted, n=161	
Odds ratio/95% CI	0.44 (0.22 to 0.86)

Kamel, 2020

Bibliographic Reference	Kamel, A.M.; Sobhy, M.; Magdy, N.; Sabry, N.; Farid, S.; Anticoagulation outcomes in hospitalized Covid-19 patients: A systematic review and meta-analysis of case-control and cohort studies; Reviews in Medical Virology; 2020

Study details

Study design	Systematic review
Protocol registration (if reported)	NR
Search end date	05-Jul-2020
Aim of the study	To study the association between anticoagulation and outcomes in hospitalised COVID-19 patients.
Country/ Geographical location	Gonzalez-Porras: Spain (retrospective cohort)
Study setting	Gonzalez-Porras: hospital

Population description	Hospitalised adult patients with confirmed or suspected COVID-19 eligible in review Gonzalez-Porras: Inpatients with confirmed COVID-19
Inclusion criteria	Case-control or cohort studies, hospitalised adult patients with confirmed or suspected COVID-19, use of therapeutic or prophylactic anticoagulation (AC).
Exclusion criteria	Studies with no control group or outcome data
Intervention	Gonzalez-Porras: Low-dose LMWH, high-dose LMWH
Comparator	Gonzalez-Porras: No heparin, low-dose LMWH
Methods of data analysis	Narrative synthesis and meta-analysis
Other details	20 studies were included in the narrative synthesis. 16 studies were included in the meta-analysis. 4 studies had not already been identified in the evidence review for this guideline (Giacomelli, Sivaloganathan, Bousquet, Gonzalez-Porras). Sivaloganathan and Giacomelli not eligible for evidence review based on study design. Bousquet not eligible as mixed AC population. Remaining 1 (Gonzalez-Porras) data extracted. Risk of bias was assessed using the Newcastle Ottawa Scale. Gonzalez-Porras: NOS=7 Results for Gonzalez-Porras were summarised in a review evidence table: Adjusted risk for in-patient mortality in non-heparin group higher (OR 6·2, 95% CI: 2·6–14.6) compared with high-heparin group. Receipt of low-dose heparin increased in-patient mortality (OR 2·0, 95% CI: 1·1–3.6) compared with the high-dose. 24 patients (3·4%) had major haemorrhage (fatal in 1) (14 receiving high-dose heparin).

Characteristics

Study-level characteristics

Age	
Gonzalez-Porras	
Median IQR	72.48 (64 to 85)
Gender	
Gonzalez-Porras Male	
No of events	n = 413 ; % = 59.8
Ethnicity	
Gonzalez-Porras	
No of events	n = NR ; % = NR

Lu, 2020

Bibliographic Reference	Lu, Ying-Feng; Pan, Li-Ya; Zhang, Wen-Wu; Cheng, Fang; Hu, Sha-Sha; Zhang, Xue; Jiang, Hai-Yin; A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19.; International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases; 2020; vol. 100; 34-41

Study details

Study design	Meta-analysis
Protocol registration (if reported)	Not reported
Search start date	01-Jan-2020
Search end date	04-Jun-2020
Aim of the study	Assessing the pooled incidence of venous thromboembolism in people admitted to hospital with COVID-19 and determining whether thromboprophylaxis affected mortality. Only the second aim is relevant to the guideline review question.
Country/ Geographical location	The included studies were conducted in China (1 study), USA (2 studies), Italy (1 study) and Spain (1 study)
Study setting	Not reported for the studies in the pooled analysis of interest.
Population description	People admitted to hospital with COVID-19.
Inclusion criteria	For the studies assessing the effects of thromboprophylaxis, case-control and cohort studies were included. No people in the control group could have received thromboprophylaxis. Reports in English only were included and needed to report adequate date to allow estimates of risk to be calculated.
Intervention	Thromboprophylaxis (no further information on drug or dosage reported)
Comparator	No thromboprophylaxis (no further information on drug or dosage reported)
Methods of data analysis	Random effects meta-analysis
Source of funding	Natural Science Foundation of Zhejiang Province (Grant No. LY20H090012)
Study limitations (Author)	Overall the authors' assessment of limitations was short, and did not specifically address any limitations of the analysis of thromboprophylaxis compared with no thromboprophylaxis. The authors recognised limitations were that the included studies included a patients with 'widely varying characteristics'; the studies also differed in country conducted, definition of thromboprophylaxis exposure and design, which the authors concluded could have affected the results.

Other details	The authors stated that they followed Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Study arms

Thromboprophylaxis (N = 2886)
No thromboprophylaxis (N = 5647)

Characteristics

Study-level characteristics

Age	range of means across studies = 57 to 68 years
Gender	range of proportion male across studies = 55% to 61%
Ethnicity	Not reported

Outcomes

Study timepoints	Timepoints for included studies not reported

Thromboprophylaxis compared with no prophylaxis (meta-analysis)

	Thromboprophylaxis vs No thromboprophylaxis
	N1 = 5647, N2 = 2886
Mortality Unadjusted *Polarity: Lower values are better*	
Relative risk/95% CI	0.86 (0.69 to 1.09)
Adjusted data	
Relative risk/95% CI	0.84 (0.63 to 1.13)
Excluding preadmission antithrombotic treatment	
Relative risk/95% CI	0.79 (0.48 to 1.31)

Mohamed Mouhand et al.

Bibliographic Reference	Mohamed Mouhand, F.H.; Shokri Shaikha D., Al-Shokri; Shunnar Khaled, M.; Mohamed Sara, F.; Najim Mostafa, S.; Ibrahim Shahd, I.; Elewa, Hazem; Dousa Khalid, M.; Abdalla Lina, O.; Bardissy Ahmed, El-Bardissy; Elshafei Mohamed, Nabil; Abubeker Ibrahim, Y.; Danjuma, Mohammed; Yassin Mohamed, A; Prevalence of Venous Thromboembolism in Critically-ill COVID-19 Patients: Systematic Review and Meta-analysis; medrxiv preprint

Study details

Study design	Meta-analysis

Protocol registration (if reported)	The protocol was registered on PROSPERO (CRD42020185916).
Search end date	10-Jul-2020
COVID-19 prevalence at the time of the study	Higher prevalence (e.g. during peak of first wave)
Aim of the study	This systematic aimed to assess: the prevalence of venous thromboembolism in critically ill patients with COVID-19; the yield of systematic screening and its effect on the prevalence of VTE; and the odds of VTE with standard dose thromboprophylaxis compared with therapeutic dose thromboprophylaxis.
Country/ Geographical location	The included studies were conducted in France (1 study), the Netherlands (1 study) and Belgium (1 study).
Study setting	Hospital intensive care units
Population description	People with COVID-19 who were admitted to a hospital intensive care unit.
Inclusion criteria	Observational studies including (cohort, cross-sectional and case-series designs). English language studies only were included.
Exclusion criteria	Studies in which the proportion of venous thromboembolism could not be calculated. Studies with participants who were not admitted to an intensive care unit.
Intervention	Standard dose thromboprophylaxis (no further information on drug or dosage reported)
Comparator	Therapeutic dose thromboprophylaxis (no further information on drug or dosage reported)
Methods of data analysis	Random effects meta-analysis
Source of funding	The authors reported that they had no sources of funding.
Study limitations (Author)	The authors noted that their funnel plot suggested publication bias, but no accompanying image was provided. The authors also noted variations in reporting of type of venous thromboembolism, method of diagnosis and dosing of thromboprophylaxis varied across studies. Other limitations recognised by the authors were not directly relevant to the analysis of interest. The authors noted that they could not address the safety of therapeutic dose thromboprophylaxis because of a lack of data.
Other details	The authors reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Quality assessment of included studies was based on the following source: Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater agreement. J. Clin. Epidemiol. 320 2012;65(9):934–939

Study arms

Therapeutic dose thromboprophylaxis (N = 83)
Standard dose prophylaxis (N = 479)

Characteristics

Study-level characteristics

Age	Range of means or medians across studies = 62 to 70 years
Gender	Range of proportion male across studies = 57% to 77%
Ethnicity	Not reported

Outcomes

Study timepoints	Timepoints for included studies not reported

Standard dose thromboprophylaxis compared with therapeutic dose thromboprophylaxis

	Standard dose prophylaxis vs Therapeutic dose thromboprophylaxis
Occurrence of venous thromboembolism *Polarity: Lower values are better*	
Odds ratio/95% CI	2.34 (0.77 to 7.14)
Studies with systematic screening for venous thromboembolism	
Odds ratio/95% CI	5.45 (1.9 to 15.57)

Wijaya, 2020

Bibliographic Reference	Wijaya, Indra; Andhika, Rizky; Huang, Ian; The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review.; Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis; 2020; vol. 26; 1076029620960797

Study details

Study design	Systematic review
Protocol registration (if reported)	NR
Search start date	01-Dec-2019
Search end date	30-Jun-2020
Aim of the study	To assess association between therapeutic dose anticoagulation and impact on mortality in people with COVID-19

Country/ Geographical location	Pierce-Williams: USA Khalil: UK
Study setting	NR
Population description	Pierce-Williams: 64 pregnant women with severe or critical COVID-19 Khalil: 220 patients (38 mechanically ventilated)
Inclusion criteria	Research studies including adult COVID-19 patients with available data on the use of therapeutic dose anticoagulation and reporting all-cause mortality
Exclusion criteria	Review articles, non-research letters, case reports, commentaries or perspectives, non-English language articles, studies in paediatric patients (< 18 years old)
Intervention	Therapeutic dose anticoagulation Review authors defined therapeutic dose anticoagulation treatment as use of any therapeutic-range anticoagulation therapies (either unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or direct oral anticoagulants [DOAC]). Pierce-Williams study: TA and PA were not defined. Type of anticoagulants = heparin / LMWH. TA 16% (10/64) vs PA 58% (37/64) Khalil study: TA and PA were not defined. Type and dose of anticoagulants were not defined. TA 12.3% (27/220) vs PA 79.1% (174/220)
Comparator	Prophylactic dose anticoagulation
Methods of data analysis	Narrative synthesis. No meta-analysis.
Other details	8 studies were included in this systematic review. 2 of these studies (Pierce-Williams [retrospective cohort], Khalil [prospective cohort]) had not previously been identified in the evidence review for this guideline. Data for these 2 studies are extracted. Quality of included studies was assessed using the Newcastle Ottawa Scale. Pierce-Williams: NOS=9 Khalil: NOS=8

Study arms

Therapeutic dose anticoagulation
Prophylactic dose anticoagulation

Characteristics

Study-level characteristics

Age	
Pierce-Williams	
Mean/SD	33 (NR)
Khalil	
Mean/SD	66.9 (NR)
Gender	

Pierce-Williams Male	
No of events	n = 0; % = 0
Khalil Male	
No of events	n = NR; % = 59.1
Ethnicity	
Pierce-Williams	
No of events	n = NR; % = NR
Khalil	
No of events	n = NR; % = NR

Outcomes

Mortality

	Therapeutic dose anticoagulation	**Prophylactic dose anticoagulation**
Mortality		
Pierce-Williams		
No of events	n = 0; % = 0	n = 0; % = 0
P value	NA	NA
Khalil		
No of events	n = NR; % = 8.6	n = NR; % = 13.6
P value	0.323	NA

Randomised controlled trials

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
Aim of the study	To assess whether therapeutic anticoagulation improves gas exchange compared with standard anticoagulant thromboprophylaxis
County/ Geographical location	Not reported
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, prespecified 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, indication for therapeutic anticoagulation due to pulmonary embolism, and acute coronary syndrome. 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 BID)

Comparator (where applicable)	Standard thromboprophylaxis (subcutaneous UFH 5000 IU TID if weight < 120 kg, 7500 IU TID if weight > 120 kg), or enoxaparin (40 mg OD if weight < 120 kg and 40 mg BID 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

	Therapeutic enoxaparin (N = 10)	Standard thromboprophylaxis (N = 10)
Age *(years)*		
Mean/SD	55 (10)	58 (16)
Gender		
Male		
No of events	n = 9; % = 90	n = 7; % = 70
Ethnicity		
No of events	Not reported	Not reported

Outcomes

Study timepoints	28 (day)

Mortality

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

Adverse effects

	Therapeutic enoxaparin	Standard thromboprophylaxis
	28 (day)	28 (day)
	N = 10	N = 10
Major bleeding		

	Therapeutic enoxaparin	Standard thromboprophylaxis
	28 (day)	28 (day)
	N = 10	N = 10
No of events	n = 0; % = 0	n = 0; % = 0
Bleeding requiring medical attention		
No of events	n = 4; % = 40	n = 2; % = 20

Cohort studies

Albani, 2020

Bibliographic Reference	Albani, Filippo; Sepe, Lilia; Fusina, Federica; Prezioso, Chiara; Baronio, Manuela; Caminiti, Federica; Di Maio, Antonella; Faggian, Barbara; Franceschetti, Maria Elena; Massari, Marco; Salvaggio, Marcello; Natalini, Giuseppe; Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study.; EClinicalMedicine; 2020; vol. 27; 100562

Study details

Study design	Cohort study
Study start date	20-Feb-2020
Study end date	10-May-2020
Aim of the study	To assess the impact of thromboprophylaxis with enoxaparin on outcomes in patients admitted with COVID-19
County/ Geographical location	Italy
Study setting	Hospital inpatient setting
Population description	Adult patients admitted to hospital with RT-PCR-confirmed SARS-CoV-2.
Inclusion criteria	Patients admitted with RT-PCT-confirmed SARS-CoV-2.
Exclusion criteria	Aged less than18 years, or being still admitted to hospital (hence definitive outcome not available at time of analysis)

Intervention/test/approach	Enoxaparin. Median dose of enoxaparin = 40 (40-80 mg) per day. Duration of therapy = 6 (3-9) days. 487 patients in enoxaparin cohort received prophylactic dose of 40 mg of enoxaparin per day, 312 patients received therapeutic dose of more than 40 mg of enoxaparin per day.
Comparator (where applicable)	No enoxaparin
Methods for population selection/allocation	Prescription of thromboprophylaxis was the responsibility of the attending clinician.
Methods of data analysis	Propensity score calculation and multivariate logit regression modelling the primary outcome
Other details	Patients in enoxaparin cohort were significantly older, significantly more likely to be male and higher BMI

Study arms

Enoxaparin (N = 799)
No enoxaparin (N = 604)

Characteristics

Arm-level characteristics

	Enoxaparin (N = 799)	**No enoxaparin (N = 604)**
Age		
Median IQR	69 (60 to 77)	72 (59.8 to 80)
Gender		

	Enoxaparin (N = 799)	No enoxaparin (N = 604)
Male		
No of events	n = 545; % = 68.2	n = 379; % = 62.7
Ethnicity		
No of events	n = NR; % = NR	n = NR; % = NR

Outcomes

Mortality

	Enoxaparin vs No enoxaparin
	N1 = 604, N2 = 799
In-hospital mortality	
Odds ratio/95% CI	0.53 (0.4 to 0.7)
Enoxaparin prophylactic dose 40 mg of enoxaparin per day	
Odds ratio/95% CI	0.5 (0.36 to 0.69)
Enoxaparin therapeutic dose more than 40 mg of enoxaparin per day	
Odds ratio/95% CI	0.54 (0.38 to 0.76)
Enoxaparin for 1-2 days	
Odds ratio/95% CI	1.41 (0.96 to 2.08)

	Enoxaparin vs No enoxaparin
	N1 = 604, N2 = 799
Enoxaparin for 2-4 days	
Odds ratio/95% CI	0.52 (0.35 to 0.79)
Enoxaparin for more than 4 days	
Odds ratio/95% CI	0.34 (0.24 to 0.48)

Critical care outcomes

	Enoxaparin vs No enoxaparin
Admission to ICU Odds ratio/95% CI	0.48 (0.32 to 0.69)

Vascular events

	Enoxaparin	No enoxaparin
	N = 799	N = 604
Thrombotic events		
Enoxaparin prophylactic dose		
No of events	n = 12; % = 2.5	NR
Enoxaparin therapeutic dose		
No of events	n = 51; % = 16	NR
No enoxaparin		
No of events	n = 13; % = 2.2	*NR*

	Enoxaparin	No enoxaparin
	N = 799	N = 604
Haemorrhagic events		
Enoxaparin prophylactic dose		
No of events	n = 6; % = 1.2	*NR*
Enoxaparin therapeutic dose		
No of events	n = 10; % = 3.2	*NR*
No enoxaparin		
No of events	n = 15; % = 2.5	*NR*

Atallah, 2020

Bibliographic Reference	Atallah, B; Sadik, Z G; Salem, N; El Nekidy, W S; Almahmeed, W; Park, W M; Cherfan, A; Hamed, F; Mallat, Jihad; The impact of protocol-based high-intensity pharmacological thromboprophylaxis on thrombotic events in critically ill COVID-19 patients.; Anaesthesia; 2020

Study details

Study start date	01-Mar-2020
Study end date	29-May-2020
Aim of the study	To explore the incidence of thrombotic events in critically ill COVID-19 patients To assess factors that are independently associated with thrombotic events To evaluate the incidence of the occurrence of haemorrhagic events.
County/ Geographical location	Abu Dhabi
Study setting	Hospital, ICU
Population description	There are no baseline characteristics at arm level reported in this study. Characteristics are reported based on outcome. No significant differences were found in baseline characteristics between patients who did and did not experience thrombotic events except for the

	D-dimer level, which was significantly higher in the thrombotic events group
Inclusion criteria	Admission to ICU, confirmed SARS-CoV-2 infection as detected by a real-time reverse transcription-polymerase chain reaction assay
Exclusion criteria	Patients were excluded if they had a high risk of bleeding, a brief (< 24 h) ICU stay or if the COVID-19 infection was deemed to be incidental and did not impact their ICU admission who had a confirmed thrombotic event diagnosis before ICU admission
Intervention/test/approach	therapeutic dose heparin high-intensity thromboprophylaxis
Comparator (where applicable)	standard dose enoxaparin 40mg daily
Methods for population selection/allocation	Those admitted to ICU
Methods of data analysis	Multivariate logistic regression analysis

Study arms

patients with thrombotic events (N = 21) Arms are documented by outcome, rather than by intervention as the paper reports results in this way
patients with non-thrombotic events (N = 167)

Characteristics

Study-level characteristics

	Study (N = 188)
Age	
Median IQR	49 (40 to 61)
Gender	
Male	
Sample Size	n = 154; % = 82
Female	
Sample Size	n = 34; % = 18
Ethnicity	Not reported
D-dimer	
Median IQR	1.8 (0.8 to 3.9)

Outcomes

Mortality

ICU mortality 0.77

	patients with thrombotic events	patients with non-thrombotic events
	N = 21	N = 167
ICU mortality *Polarity: Not set*		
No of events	n = 5; % = 24	n = 33; % = 20

Incidence of VTE

Overall p value for comparison of thromboprophylaxis strategy, p 0.46

	patients with thrombotic events	patients with non-thrombotic events
	N = 21	N = 167
Standard prophylactic dose		
No of events	n = 11; % = 52	n = 72; % = 43
High-intensity prophylactic dose		
No of events	n = 6; % = 29	n = 69; % = 41
Therapeutic anticoagulation		
No of events	n = 4; % = 19	n = 20; % = 12

Ferguson, 2020

Bibliographic Reference	Ferguson, John; Volk, Stacy; Vondracek, Thomas; Flanigan, John; Chernaik, Andrew; Empiric Therapeutic Anticoagulation and Mortality in Critically Ill Patients With Respiratory Failure From SARS-CoV-2: A Retrospective Cohort Study.; Journal of clinical pharmacology; 2020; vol. 60 (no. 11); 1411-1415

Study details

Study start date	15-Mar-2020
Study end date	08-May-2020
Aim of the study	To determine if therapeutic anticoagulation for respiratory failure caused by SARS-CoV-2 leads to improved survival in intubated patients.
County/ Geographical location	USA
Study setting	Hospital, ICU
Population description	Patients with confirmed SARS-CoV-2 by nasal/oral PCR requiring intubation for acute respiratory failure. Baseline demographics, comorbidities, and laboratory investigations were similar between groups.
Inclusion criteria	Patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 respiratory failure necessitating invasive mechanical ventilation were included in the study. Patients who received empiric therapeutic

	anticoagulation prior to the time of intubation were included in the study group. Adjuvant treatments included hydroxychloroquine, azithromycin, convalescent plasma, sarilumab/placebo, remdesivir. Adjuvant therapies were administered at the discretion of the treating physician based on preferences and drug availability.
Exclusion criteria	Not specified.
Intervention/test/approach	Therapeutic anticoagulation was administered as either a continuous infusion of heparin dose-adjusted based on unfractionated heparin level or by subcutaneous 1mg/kg twice daily or 1.5 mg/kg daily low molecular weight heparin (LMWH). LMWH dose adjustments were made based on anti-Xa levels in the event of renal insufficiency. Patients who were receiving oral anticoagulation prior to admission and remaining on anticoagulation were included in the therapeutic anticoagulation group.
Comparator (where applicable)	All patients in the control group received DVT chemoprophylaxis in the form of enoxaparin 40 mg subcutaneously daily, enoxaparin 30 mg twice daily, enoxaparin 0.5 mg/kg twice daily, or heparin 5000 units subcutaneously 2 or 3 times daily.
Methods for population selection/allocation	A retrospective cohort of adult patients admitted to the intensive care unit at 3 hospitals between March 15, 2020 and May 8, 2020.
Methods of data analysis	Kaplan-Meier survival analysis was performed at 28 days for all patients and for the prespecified cohort of patients with a baseline D-dimer > 2 µg/mL. Proportional Cox hazard ratio was used to compare survival between groups. Multivariate logistic regression analysis was performed using adjuvant treatment as independent variables to model survival.
Source of funding	There was no funding for this research.
Study limitations (Author)	The study did not evaluate all general medical ward patients who received empiric therapeutic anticoagulation. Whether empiric anticoagulation at the time of diagnosis reduces progression to intubation is uncertain. The study authors chose time zero to be the day of intubation rather than hospital admission. Second, there was a difference between groups in adjuvant therapies administered. More patients who received therapeutic anticoagulation received convalescent plasma than those who received only prophylactic dose anticoagulation. Last, because of the prolonged duration of illness associated with SARS-CoV-2 infection, 28-day mortality may be an insufficient length of time to recognise significant differences in outcomes.
Other details	The 28-day mortality was 26.1% (95%CI, 12.9%-39.3%) in patients who received therapeutic anticoagulation and 29.5% (95%CI, 20.2%-38.8%) in those who received a prophylaxis dose for DVT prevention (HR, 0.52; 95%CI, 0.26-1.04; P = .055). In a multivariate logistic regression analysis, empiric therapeutic anticoagulation was associated with an odds ratio of death at 28 days of 0.73 (95%CI, 0.33-1.76), P = .48. In the prespecified subgroup with a serum D-dimer ≥ 2 µg/ml, the 28-day mortality was 25% (95%CI, 6.3%-43.7%) in patients who received therapeutic anticoagulation (n = 24) and 23.8% (95%CI, 13.1%-34.6%) in those who received a prophylactic dose for DVT prevention (n = 63): HR, 0.67; 95%CI, 0.26%-1.74%; P = .41. There were no fatal bleeding events in either group. Twelve patients who received empiric therapeutic anticoagulation (25.5%) required a packed red blood cell (PRBC) transfusion for a haemoglobin below 7

	g/dL, whereas 8 who were treated with DVT prophylaxis alone (7.6%) received a PRBC transfusion (P = .01).

Study arms

Therapeutic dose anticoagulation (N = 46)
Prophylactic dose anticoagulation (N = 95)

Characteristics

Study-level characteristics

Age	65 (56-73)	63 (52-71)
Male, n (%)	24 (52.2)	54 (56.8)
Ethnicity	Not reported	Not reported

Outcomes

Study timepoints	28 (day)

28-day mortality

	28 (day)	
	Therapeutic dose anticoagulation	Prophylactic dose anticoagulation
	N = NR	N = NR
28-day mortality *Polarity: Lower values are better*		
No of events	n = NR; % = 26.1	n = NR; % = 29.5
Prespecified subgroup with a serum D-dimer≥ 2 µg/mL		
No of events	n = NR; % = 25	n = NR; % = 23.8

Jimenez-Guiu, 2020

Bibliographic Reference	Jimenez-Guiu, Xavier; Huici-Sanchez, Malka; Romera-Villegas, Antonio; Izquierdo-Miranda, Alexandre; Sancho-Cerro, Ana; Vila-Coll, Ramon; Deep vein thrombosis in non-critically ill patients with coronavirus disease 2019 pneumonia: deep vein thrombosis in non-intensive care unit patients.; Journal of vascular surgery. Venous and lymphatic disorders; 2020

Study details

Trial registration (if reported)	Not reported
Study start date	Apr-2020
Study end date	Apr-2020

Aim of the study	To describe the prevalence of DVT in people admitted to hospital with COVID-19 and to correlate these findings with the type of thromboprophylaxis used.
County/ Geographical location	Spain
Study setting	Hospital wards
Population description	People with COVID-19 admitted to hospital with unilateral or bilateral pneumonia caused by COVI-19 but who were not critically ill
Inclusion criteria	People who had COVID-19 pneumonia confirmed by polymerase chain reaction testing of nasopharyngeal specimen who presented to the emergency department and were admitted to hospital.
Exclusion criteria	People who were receiving palliative treatment, were pregnant, had diagnosis of a thromboembolic event before hospital admission, needed treatment in an intensive care unit, and those who declined to participate in the present study.
Intervention/test/approach	Standard dose thromboprophylaxis (enoxaparin 40 mg daily).
Comparator (where applicable)	Intermediate or therapeutic dose thromboprophylaxis. People with an underlying disease (such as atrial fibrillation or prosthetic heart valve) received therapeutic dose low molecular weight heparin (enoxaparin 1.5 mg/kg every 24 hours). People considered at high risk of venous thromboembolism (for example, body mass index >30 kg/m^2, thrombophilia, a history of thromboembolism, active cancer) received intermediate-dose low molecular weight heparin (enoxaparin 0.5 mg/kg every 12 hours).
Methods for population selection/allocation	Not reported clearly.
Methods of data analysis	Logistic regression; X^2 test; Student t test
Attrition/loss to follow-up	None reported.
Source of funding	Author contributions indicated that funding was obtained but the source of funding was not reported.
Study limitations (Author)	The authors recognised that the small sample size in their study could affect the ability to statistically detect a difference between the groups. The authors noted that the treatments given for COVID-19 (no further details reported) changed frequently as understanding of the disease increased, which could mean that the results are not widely applicable.

Study arms

Standard dose thromboprophylaxis (N = 37)
Intermediate or therapeutic dose thromboprophylaxis (N = 20)

Characteristics

Study-level characteristics

Age	
Mean/SD	71.3 (12.7)
Gender	Proportion male = 50.9%

Ethnicity	Not reported

Outcomes

Risk of deep vein thrombosis with intermediate or therapeutic dose thromboprophylaxis compared with standard dose prophylaxis

	Intermediate or therapeutic dose thromboprophylaxis vs Standard dose thromboprophylaxis
Deep vein thrombosis Risk of deep vein thrombosis with intermediate or therapeutic dose thromboprophylaxis compared with standard dose prophylaxis *Polarity: Lower values are better*	
Odds ratio/95% CI	0.19 (0.08 to 0.46)

Absolute numbers of deep vein thrombosis with intermediate or therapeutic dose thromboprophylaxis compared with standard dose prophylaxis

	Standard dose thromboprophylaxis	Intermediate or therapeutic dose thromboprophylaxis
	N = 37	N = 20
Deep vein thrombosis Deep vein thrombosis confirmed by compression duplex ultrasonography in symptomatic patients *Polarity: Lower values are better*		
No of events	n = 6; % = 16	n = 0; % = 0
Bleeding complications Recorded according to a consensus report from the Bleeding Academic Research Consortium *Polarity: Lower values are better*		
No of events	n = 0; % = 0	n = 1; % = 5

Jonmarker et al.

Bibliographic Reference	Jonmarker, Sandra, Hollenberg, Jacob, Dahlberg, Martin et al. Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients.; medrxiv preprint

Study details

Trial registration (if reported)	Retrospectively registered on Clinicaltrials.gov (NCT04412304)
Study start date	Mar-2020
Study end date	Apr-2020

Aim of the study	To assess the effects of 3 thromboprophylaxis dosing strategies in critically ill patients with COVID-19
County/ Geographical location	Sweden
Study setting	Hospital intensive care unit
Population description	People with polymerase chain reaction confirmed COVID-19 and respiratory failure admitted to an intensive care unit
Inclusion criteria	People with polymerase chain reaction confirmed COVID-19 and respiratory failure admitted to an intensive care unit. Pre-existing thromboprophylaxis because of any indication other than previous deep vein thrombosis or pulmonary embolism.
Exclusion criteria	Discharge from intensive care unit on the same day as admission. Pre-existing thromboprophylaxis because of previous deep vein thrombosis or pulmonary embolism. No initial thromboprophylaxis in the intensive care unit.
Intervention/test/approach	The choice of dosing strategy followed local guidance and changed over time. In March, low-dose thromboprophylaxis was recommended for all COVID-19 patients at both participating intensive care units. In April, the recommendations changed to medium-dose and then to high-dose thromboprophylaxis. This strategy continued throughout the study period in one intensive care unit. In the other intensive care unit, full-dose thromboprophylaxis was only used for one week, and then recommendations changed back to medium-dose thromboprophylaxis. Patients who received an adjusted dose because of reduced kidney function were classified according to the intended dose.
Comparator (where applicable)	Comparisons were done between the 3 dosing strategies.
Methods for population selection/allocation	The authors noted that thromboprophylaxis dosage was based on local standardised recommendations, not on degree of critical illness or risk of thrombosis.
Methods of data analysis	Differences over categories of the exposure were tested with Kruskal-Wallis for continuous data, and Fisher's exact for categorical data. In the survival analyses, participants could accrue follow-up time from date of admission to the intensive care unit until the date of death or 28 days after admission, whichever occurred first. In analyses of thromboembolic and bleeding events, the date of that event also led to censoring of follow-up time. Kaplan-Meier curves were used to estimate the cumulative risk of death, thromboembolic event, and bleeding event, and the log-rank test was used to compare the initial dosing strategies. Cox proportional hazards regression was used to estimate hazard ratios with corresponding 95% confidence intervals of death within 28 days from admission to the intensive care unit. Multivariable models were adjusted for sex, age, body mass index, Simplified Acute Physiology Score III (SAPS III), use of invasive respiratory support, and initial dosing strategy of thromboprophylaxis (low, medium and high-dose thromboprophylaxis). Analysis was performed using STATA 13.1 (StataCorp), and R v 3.5.1 (R Core Team (2017).

Attrition/loss to follow-up	All participants were analysed.
Source of funding	The authors reported that they had no external funding for this study.
Study limitations (Author)	The authors recognised limitations of the cohort design. This included that other treatments for COVID-19 changed over the period of the study and could have affected the results. The authors highlighted changes in ventilation strategy from low tidal volumes, fluid restriction and heavy sedation to higher tidal volumes, more fluids and less sedation. The authors reported that many patients had dose changes because of the changes in dosing protocol during their stay in the intensive care unit; this included more than one dosage change in some patients including dose increases, reductions, or both. The authors also recognised a limitation in that the groupings were on initial dose rather than total dose received. The authors also noted that fewer people on high-dose thromboprophylaxis received 'invasive' ventilation, however they also noted that this was not a statistically significant difference and that it was adjusted for in the analysis. During the pandemic it was not always possible to do computed tomography (CT) to diagnose pulmonary embolism, so the incidence may have been underestimated so the primary outcome was set as mortality. The authors additionally noted that the results for bleeding should be interpreted with caution because of low numbers of events.

Study arms

Low-dose thromboprophylaxis (N = 67) Initial regimen tinzaparin 2500-4500 IU or dalteparin 2500-5000 IU
Medium-dose thromboprophylaxis (N = 48) Initial regimen tinzaparin more than 4500 IU but less than 175 IU/kg or dalteparin more than 5000 IU but less than 200 IU/kg
High-dose thromboprophylaxis (N = 37) Initial regimen tinzaparin 175 IU/kg or more or dalteparin 200 IU/kg or more

Characteristics

Study-level characteristics

	Study (N = 152)
Age	
Median IQR	61 (52 to 69)
Gender	Number and proportion male = 125 (82%)
Ethnicity	Not reported

Arm-level characteristics

	Low-dose thromboprophylaxis (N = 67)	Medium-dose thromboprophylaxis (N = 48)	High-dose thromboprophylaxis (N = 37)
Age *(years)*			
Median IQR	63 (52 to 71)	58 (51 to 66)	63 (54 to 70)
Gender			

	Low-dose thromboprophylaxis (N = 67)	Medium-dose thromboprophylaxis (N = 48)	High-dose thromboprophylaxis (N = 37)
Custom value	Number and proportion male = 59 (88%)	35 (73%)	31 (84%)

Outcomes

Study timepoints	28 (day) Outcomes were measured until 28 days after admission to the intensive care unit or death.

Outcome data by initial thromboprophylaxis strategy

	Low-dose thromboprophylaxis	Medium-dose thromboprophylaxis	High-dose thromboprophylaxis
	28 (day)	28 (day)	28 (day)
	N = 67	N = 48	N = 37
Mortality 28-day *Polarity: Lower values are better*			
No of events	n = 26; % = 39	n = 12; % = 25	n = 5; % = 14
Custom value	analysis of difference across exposure categories: p = 0.02	analysis of difference across exposure categories: p = 0.02	analysis of difference across exposure categories: p = 0.02
Thromboembolic events Within 28 days; includes ischaemic stroke and peripheral arterial embolism which are out of scope for this review question. These groups are removed in the subgroup analyses. *Polarity: Lower values are better*			
No of events	n = 12; % = 18	n = 9; % = 19	n = 1; % = 3
Custom value	analysis of difference across exposure categories: p = 0.04	analysis of difference across exposure categories: p = 0.04	analysis of difference across exposure categories: p = 0.04
Pulmonary embolism verified by computed tomography or by clinical suspicion of PE as cause of deterioration combined with findings of acute strain of the right heart on echocardiography			
No of events	n = 10; % = 15	n = 6; % = 13	n = 1; % = 3

	Low-dose thromboprophylaxis	Medium-dose thromboprophylaxis	High-dose thromboprophylaxis
	28 (day)	28 (day)	28 (day)
	N = 67	N = 48	N = 37
Custom value	analysis of difference across exposure categories: p = 0.15	analysis of difference across exposure categories: p = 0.15	analysis of difference across exposure categories: p = 0.15
Deep vein thrombosis verified by ultrasound			
No of events	n = 1; % = 2	n = 3; % = 6	n = 0; % = 0
Custom value	analysis of difference across exposure categories: p = 0.21	analysis of difference across exposure categories: p = 0.21	analysis of difference across exposure categories: p = 0.21
Bleeding complications Within 28 days; categorised according to WHO bleeding scale *Polarity: Lower values are better*			
No of events	n = 8; % = 12	n = 7; % = 15	n = 1; % = 3
Custom value	analysis of difference across exposure categories: p = 0.16	analysis of difference across exposure categories: p = 0.16	analysis of difference across exposure categories: p = 0.16
Cerebral parenchymal bleed			
No of events	n = 2; % = 3	n = 0; % = 0	n = 0; % = 0
Custom value	analysis of difference across exposure categories: p = 0.50	analysis of difference across exposure categories: p = 0.50	analysis of difference across exposure categories: p = 0.50
WHO grade I bleed (minor)			
No of events	n = 3; % = 5	n = 4; % = 8	n = 1; % = 3
Custom value	analysis of difference across exposure categories: p = 0.58	analysis of difference across exposure categories: p = 0.58	analysis of difference across exposure categories: p = 0.58
WHO grade II bleed (moderate)			
No of events	n = 2; % = 3	n = 1; % = 2	n = 0; % = 0
Custom value	analysis of difference across exposure categories: p = 0.79	analysis of difference across exposure categories: p = 0.79	analysis of difference across exposure categories: p = 0.79
WHO grade III bleed (major)			
No of events	n = 1; % = 2	n = 1; % = 2	n = 0; % = 0
Custom value	analysis of difference across exposure categories: p = 0.99	analysis of difference across exposure categories: p = 0.99	analysis of difference across exposure categories: p = 0.99

	Low-dose thromboprophylaxis	Medium-dose thromboprophylaxis	High-dose thromboprophylaxis
	28 (day)	28 (day)	28 (day)
	N = 67	N = 48	N = 37
WHO Grade IV bleed (severe)			
No of events	n = 2; % = 3	n = 1; % = 2	n = 0; % = 0
Custom value	analysis of difference across exposure categories: p = 0.79	analysis of difference across exposure categories: p = 0.79	analysis of difference across exposure categories: p = 0.79

Risk of death by thromboprophylaxis dosing strategy

	Medium-dose thromboprophylaxis vs Low-dose thromboprophylaxis	High-dose thromboprophylaxis vs Low-dose thromboprophylaxis
	28 (day)	28 (day)
	N1 = 67, N2 = 48	N1 = 67, N2 = 37
Mortality within 28 days *Polarity: Lower values are better*		
Univariable model		
Hazard ratio/95% CI	0.59 (0.3 to 1.16)	0.31 (0.12 to 0.82)
Multivariable model Adjusted for sex, age (continuously), body mass index (</≥30 kg/m^2 and missing [n=6]), use of invasive mechanical ventilation, and Simplified Acute Physiology Score III (continuously)		
Hazard ratio/95% CI	0.88 (0.43 to 1.83)	0.33 (0.13 to 0.87)
Multivariable imputed model Adjusted as the multivariable model but with body mass index imputed due to missing values (n=6), and flexibly modelled with restricted cubic splines at 3 knots over the percentile (10th, 50th, and 90th) distribution of body mass index in the population.		
Hazard ratio/95% CI	0.87 (0.42 to 1.82)	0.3 (0.11 to 0.81)

Li, 2020

Bibliographic Reference	Li, Matthew; Gitarts, Steven; Nyabera, Akwe; Kondaveeti, Ravali; Hammudeh, Yousef; Gonzalez, Carlos; Trandafirescu, Theo; Penumadu, Arunakumari; Lopez, Ricardo; Sahibzada, Asad; La Cruz, Angel De; Rahman, Habibur; Continuous

Infusion Low-Dose Unfractionated Heparin for the Management of Hypercoagulability Associated With COVID-19; Journal of Pharmacy Practice; 2020

Study details

Study start date	01-Mar-2020
Study end date	14-Apr-2020
Aim of the study	1) To compare incidence of thromboembolic events in patients treated with the low-dose UFH infusion versus those with routine prophylactic dosing. 2) to assess the efficacy and safety of the UFH infusion
County/ Geographical location	USA
Study setting	Community teaching hospital in New York City. ICU management: UFH = 57%, control = 29%
Population description	Adults (aged 18 years and above) with confirmed COVID-19
Exclusion criteria	Pregnant or incarcerated, ICU length of stay of less than 48 hours, UFH duration of less than 48 hours, transferred to another institution, alternative indication for therapeutic anticoagulation
Intervention/test/approach	Unfractionated heparin infusion (mean lowest UFH infusion rate = 8.4 + 2.1 units/kg/ hour, mean highest UFH infusion rate =15.1 + 4 units/kg/hour)
Comparator (where applicable)	Control. 14 (50%) received standard prophylaxis with subcutaneous UFH 5000 units every 8 or 12 hours, 12 (42.9%) received standard prophylaxis with enoxaparin 40 mg every 24 hours, 2 (7.1%) patients did not receive any pharmacologic prophylaxis.
Methods for population selection/allocation	Choice of UFH or standard prophylaxis at clinical discretion
Methods of data analysis	Propensity score calculation and propensity score matched cohort used. Timepoint not reported.

Study arms

Unfractionated heparin infusion (N = 28)
Control (N = 28)

Characteristics

Arm-level characteristics

	Unfractionated heparin infusion (N = 28)	Control (N = 28)
Age (Mean/SD)	63.8 (13.6)	65.3 (12.7)
Gender (Male)		
No of events	n = 18; % = 64	n = 20; % = 71
Ethnicity	Not reported	Not reported

Outcomes

Cases of thromboembolism

	Unfractionated heparin infusion	Control
	N = 28	N = 28
Cases of venous thromboembolism		
No of events	n = 2; % = 7	n = 0; % = 0
Cases of catheter-related thromboembolism		
No of events	n = 1; % = 3	n = 0; % = 0

Mechanical ventilation

	Unfractionated heparin infusion	Control
	N = 28	N = 28
Patients requiring mechanical ventilation		
No of events	n = 21; % = 75	n = 7; % = 25
P value	≤0.005	NR
Duration of mechanical ventilation *(days)*		
Mean/SD	13.7 (7.4)	1.7 (3.8)
P value	≤0.005	NR
ICU length of stay *(days)*		
Mean/SD	12 (9.2)	1 (2.9)
P value	≤0.005	NR

Mortality

	Unfractionated heparin infusion	Control
	N = 28	N = 28
7 day mortality		
No of events	n = 5; % = 17.9	n = 9; % = 32.1
P value	0.36	NR

Adverse events

	Unfractionated heparin infusion	Control
	N = 28	N = 28
Major bleeding		
No of events	n = 2; % = 7.1	n = 0; % = 0
P value	0.49	NR
Patients requiring packed red blood cell transfusion		
No of events	n = 10; % = 35.7	n = 0; % = 0
Custom value	≤0.005	NR

Longhitano, 2020

Bibliographic Reference	Longhitano, Yaroslava; Racca, Fabrizio; Zanza, Christian; Muncinelli, Marina; Guagliano, Alberto; Peretti, Elisa; Minerba, Anna Chiara; Mari, Marta; Boverio, Riccardo; Salio, Mario; Chichino, Guido; Franceschi, Francesco; Piccioni, Andrea; Abenavoli, Ludovico; Salvini, Mauro; Artico, Marco; Venous Thrombo-Embolism in Hospitalized SARS-CoV-2 Patients Treated with Three Different Anticoagulation Protocols: Prospective Observational Study.; Biology; 2020; vol. 9 (no. 10)

Study details

Study start date	18-May-2020
Study end date	30-May-2020
Aim of the study	(1) to analyse risk of vein thrombosis and pulmonary embolism in patients affected by pneumonia due to Covid-19; (2) evaluate conditions increasing risk; (3) to assess efficacy of different doses of antithrombotic drugs
County/ Geographical location	Italy
Study setting	Teaching hospital in Alessandria, Italy (3 medical wards and general ICU) ICU: Higher dose group = 25%, Standard dose group = 22% General ward: Higher dose group = 75%, Standard dose group = 78%
Population description	Adults with COVID-19 confirmed by clinical features and positive PCR from nasopharyngeal swab. No significant differences between higher dose and standard prophylaxis groups in: age, gender, presence of comorbidities, laboratory values including D-dimer
Inclusion criteria	All consecutive patients referred for acute respiratory failure due to COVID-19 pneumonia screened for asymptomatic DVT and recruited. Adults aged 18 years and above included.
Exclusion criteria	Patients with previous coagulative disorders, polyglobulia, anticoagulant chronic therapy, previous DVT diagnosis or diagnosis of cancer-related DVT
Intervention/test/approach	All patients received anticoagulant drugs at prophylactic, intermediate or therapeutic dose (according to clinical judgement). Patients receiving intermediate and therapeutic doses combined in the higher dose group. Therapeutic dose (full-dose) anticoagulation protocol with 2 potential options: (1) heparin 12,500 U every 8-12 h (n=16) or (2) enoxaparin 100 U/kg every 12 h (n=7). Intermediate: Dose of enoxaparin (n=22) or heparin (n=1) between prophylactic and therapeutic dosage. 1 patient in this group received fondaparinux (5 mg / 24 h)
Comparator (where applicable)	Standard antithrombotic prophylaxis: enoxaparin 80 U/kg per day (n=22) or heparin 5000 U every 8 h (n=4). 1 patient in this group received fondaparinux (2.5 mg QD)
Methods for population selection/allocation	Prospective observational study

Study arms

Higher dose antithrombotic prophylaxis (N = 47) Patients receiving intermediate and therapeutic doses
Standard antithrombotic prophylaxis (N = 27)

Characteristics

Study-level characteristics

	Study (N = 74)
Age	
Mean/SD	68.65 (15.12)
Gender (Male)	
No of events	n = 44; % = 59.5
Ethnicity	Not reported

Outcomes

Thrombotic events

	Higher dose antithrombotic prophylaxis	Standard antithrombotic prophylaxis
	N = 47	N = 27
Venous thrombotic events		
No of events	n = 11; % = 23	n = 10; % = 37
Odds ratio	0.516 (0.189 to 1.429)	NA
P value	0.210	NA

Mortality

	Higher dose antithrombotic prophylaxis	Standard antithrombotic prophylaxis
	N = 47	N = 27
Mortality		
No of events	n = 10; % = 21	n = 2; % = 7
Odds ratio	3.38 (0.78 to 14.67)	NA
P value	0.119	NA

Motta et al.

Bibliographic Reference	Motta Jishu, K; Ogunnaike Rahila, O; Shah, Rutvik; Stroever, Stephanie; Cedeno Harold, V; Thapa Shyam, K; Chronakos John, J; Jimenez Eric, J; Petrini, Joann; Hegde, Abhijith; Clinical Outcomes With the Use of Prophylactic Versus Therapeutic Anticoagulation in COVID-19; medrxiv preprint

Study details

Study start date	01-Apr-2020
Study end date	25-Apr-2020
Aim of the study	To determine the impact of anticoagulation on in-hospital mortality among COVID-19 positive patients in terms of in-hospital mortality with use of pre-emptive therapeutic over prophylactic dose enoxaparin or heparin
County/ Geographical location	USA
Study setting	Hospital, 2 large acute care hospitals
Population description	Adult patients admitted with a diagnosis of COVID 19 (ICD-10 code B97.29, 113 J12.89, J18.9, U07.1) between April 1 and April 25, 2020, and treated with anticoagulation during their inpatient stay.
Inclusion criteria	18 years or older Confirmed SARS-CoV-2 infection treated with therapeutic or prophylactic use of enoxaparin or heparin, both regimens started preemptively upon admission
Exclusion criteria	Patients were excluded if they did not take enoxaparin or heparin during their inpatient stay or if they were on other forms of AC prior to or during their hospitalisation
Intervention/test/approach	Therapeutic anticoagulation
Comparator (where applicable)	Prophylactic anticoagulation
Methods for population selection/allocation	Not reported
Methods of data analysis	multivariable logistic regression model to determine risk differences in mortality given AC dosage. missing data was accounted for sensitively analysis
Study limitations (Author)	The patients in this sample were selected from 2 institutions in Western Connecticut and were predominantly older, non-Hispanic, and White- only generalisable to similar populations
Other details	To input into outcomes table: The risk of in-hospital mortality was 2.3 times greater (adjusted risk ratio 2.3 in patients receiving pre-emptive therapeutic anticoagulation, 95% CI = 1.0, 4.9; p = 0.04).

Study arms

prophylactic anticoagulation (N = 299) Prophylactic dosage for enoxaparin was defined as 30 or 40 mg subcutaneously every day.
therapeutic anticoagulation (N = 75) Enoxaparin: 1 mg/kg subcutaneously twice daily or 1.5 mg/kg subcutaneously daily or based on renal function, or higher doses titrated to anti-Factor Xa range of 0.6 to 1 IU/mL (for twice daily dosing) and 1 to 2 IU/mL (for daily dosing) Heparin: For heparin, therapeutic dosage was defined as

intravenous heparin titrated to an activated partial thromboplastin time (aPTT) between 70 and 110 sec, and prophylactic dosage was defined as 5000 units given subcutaneously every 8 hours.

Characteristics

Arm-level characteristics

	prophylactic anticoagulation (N = 299)	therapeutic anticoagulation (N = 75)
Age		
Mean/SD	64.2 (17.9)	66.9 (18.6)
Gender		
Female		
Mean/SD	122 (79.2)	32 (20.8)
Ethnicity		
White		
Mean/SD	159 (78.7)	43 (21.3)
African-American		
Mean/SD	30 (81.1)	7 (18.9)
Hispanic		
Mean/SD	104 (83.2)	21 (16.8)
Other		
Mean/SD	25 (83.3)	5 (16.7)

Outcomes

Mortality

RR 2.3, 95% C.I 1.0-4.9, p value 0.04

	prophylactic anticoagulation	therapeutic anticoagulation
	N = 299	N = 75
Mortality		
No of events	n = 43; % = 14.4	n = 29; % = 38.6

Nadkarni, 2020

Bibliographic Reference	Nadkarni, G.N.; Lala, A.; Bagiella, E.; Chang, H.L.; Moreno, P.R.; Pujadas, E.; Arvind, V.; Bose, S.; Charney, A.W.; Chen, M.D.; Cordon-Cardo, C.; Dunn, A.S.; Farkouh, M.E.; Glicksberg, B.S.; Kia, A.; Kohli-Seth, R.; Levin, M.A.; Timsina, P.; Zhao, S.; Fayad, Z.A.; Fuster, V.; Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19; Journal of the American College of Cardiology; 2020; vol. 76 (no. 16); 1815-1826

Study details

Study start date	01-Mar-2020
Study end date	30-Apr-2020
Aim of the study	To examine association of anticoagulation with in-hospital outcomes
County/ Geographical location	USA
Study setting	5 hospitals in New York City
Population description	All adults (aged 18 years and above) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection. D-dimer concentrations were highest in patients who received therapeutic AC (median 2.3mg/ml; interquartile range:1.2 to 5.8mg/ml)
Exclusion criteria	Patients who left hospital within 24 h of admission, patients treated with both therapeutic and prophylactic regimens of AC during hospitalisation excluded
Intervention/test/approach	1) Therapeutic anticoagulation, 2) Prophylactic anticoagulation From online appendix: Patients classed as on therapeutic AC if on continuous intravenous infusions of bivalirudin, argatroban or unfractionated heparin (UFH), high-dose LMWH (specifically enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily), apixaban 5mg twice daily, rivaroxaban or dabigatran. For patients >75 years, apixaban therapeutic at lower doses: at 2.5 mg twice a day or 5 mg once a day. Patients classed as on prophylactic AC if on subcutaneous unfractionated heparin, LMWH once daily, or apixaban (2.5 mg twice a day or 5 mg daily in patients ≤75 years)
Comparator (where applicable)	No anticoagulation
Methods of data analysis	Retrospective analysis
Other details	Adjusted hazard ratios are presented (as below in outcome tables) for in-hospital mortality and intubation. Among patients on single therapeutic agent bleeding rates higher for low molecular weight heparin (LMWH) compared with direct oral anticoagulants (DOACs) (2.6% vs. 1.3%, respectively). Among patients on single prophylactic agent, bleeding rates higher for unfractionated heparin (UFH) compared with LMWH (1.7%vs. 0.7%, respectively). Many patients were on more than 1 AC agent over the course of their hospitalisation, preventing direct comparisons between anticoagulants. Data suggest that therapeutic DOACs may be associated with better survival and lower intubation rates compared with LMWH (UFH were not included due to small sample size). Additional sensitivity analysis in online appendix (not extracted here)

Study arms

Therapeutic anticoagulation (N = 900)
Prophylactic anticoagulation (N = 1959)
No anticoagulation (N = 1530)

Characteristics

Arm-level characteristics

	Therapeutic anticoagulation (N = 900)	Prophylactic anticoagulation (N = 1959)	No anticoagulation (N = 1530)
Age			
Median IQR	70 (59 to 80)	65 (54 to 76)	61 (45 to 75)
Gender			
Female			
No of events	n = 353; % = 39.2	n = 851; % = 43.4	n = 728; % = 47.6
Ethnicity			
Black			
No of events	n = 228; % = 25.3	n = 567; % = 28.9	n = 357; % = 23.3
Hispanic			
No of events	n = 222; % = 24.7	n = 523; % = 26.7	n = 427; % = 27.9
White			
No of events	n = 234; % = 26	n = 432; % = 22.1	n = 394; % = 25.8
Asian			
No of events	n = 38; % = 4.2	n = 94; % = 4.8	n = 69; % = 4.5
Other			
No of events	n = 178; % = 19.8	n = 343; % = 17.5	n = 283; % = 18.5

Outcomes

Mortality - therapeutic anticoagulation

	Therapeutic anticoagulation vs No anticoagulation
	N1 = 1530, N2 = 900
In-hospital mortality	
Hazard ratio/95% CI	0.53 (0.45 to 0.62)

Mortality - prophylactic anticoagulation

	Prophylactic anticoagulation vs No anticoagulation
	N1 = 1530, N2 = 1959
In-hospital mortality	
Hazard ratio/95% CI	0.5 (0.45 to 0.57)

Intubation - therapeutic anticoagulation

	Therapeutic anticoagulation vs No anticoagulation
	N1 = 1530, N2 = 900
Intubation	
Hazard ratio/95% CI	0.69 (0.51 to 0.94)

Intubation - prophylactic anticoagulation

	Prophylactic anticoagulation vs No anticoagulation
	N1 = 1530, N2 = 1959
Intubation	
Hazard ratio/95% CI	0.72 (0.58 to 0.89)

Major bleeding

	Therapeutic anticoagulation	Prophylactic anticoagulation	No anticoagulation
	N = 900	N = 1959	N = 1530
Major bleeding			
No of events	n = 27; % = 3	n = 33; % = 1.7	n = 29; % = 1.9

Paolisso, 2020

Bibliographic Reference	Paolisso, Pasquale; Bergamaschi, Luca; D'Angelo, Emanuela Concetta; Donati, Francesco; Giannella, Maddalena; Tedeschi, Sara; Pascale, Renato; Bartoletti, Michele; Tesini, Giulia; Biffi, Mauro; Cosmi, Benilde; Pizzi, Carmine; Viale, Pierluigi; Galie, Nazzareno; Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients.; Frontiers in pharmacology; 2020; vol. 11; 1124

Study details

Study start date	01-Mar-2020
Study end date	10-Apr-2020
Aim of the study	Investigate the association between different dosages of low molecular weight heparin (LMWH) and mortality among COVID-19 hospitalised patients
County/ Geographical location	Italy
Study setting	Hospital
Inclusion criteria	Consecutive adult patients with confirmed COVID-19 referred to hospital
Exclusion criteria	Those treated with warfarin, new oral anticoagulation and enoxaparin 100mg twice daily were excluded, bleeding diathesis, hospital stay < 5 days, lack of information about coagulation parameters and medications, age <18 years and any disease dictating anticoagulation, such as atrial fibrillation, prosthetic heart valves, or venous thromboembolic disease.
Intervention/test/approach	Intermediate LMWH dosage: 40-60mg twice daily for 7 days

Comparator (where applicable)	Standard prophylactic LMWH dosage" 40-60mg once daily for 7 days
Methods for population selection/allocation	Those presenting with confirmed COVID-19 diagnosis at hospital
Methods of data analysis	logistic regression analysis with propensity score adjustment was used, to control for the imbalance in the group characteristics. The propensity score, i.e. the conditional probability of being treated with the intermediate LMWH dosage given the set of variables that differed significantly between the dosage groups, was estimated using a multiple logistic regression model.

Study arms

Standard prophylactic LMWH (N = 361) Dosage 40-60 daily for 7 days
Intermediate LMWH (N = 89) Dosage 40-60mg twice daily for 7 days

Study design	Retrospective cohort study

Characteristics

Study-level characteristics

	Study (N = 450)
Ethnicity	Not reported

Arm-level characteristics

	Standard prophylactic LMWH (N = 361)	Intermediate LMWH (N = 89)
Age (median)	55 to 79	54 to 74
Gender		
Male		
Sample Size	n = 227; % = 63	n = 56; % = 63
Female		
Sample Size	n = 134; % = 37	n = 33; % = 37
BMI >30 *(kg/m^2)*		
Median IQR	26 (24 to 29.7)	26 (24 to 29)
D-dimer		
Median IQR	0.8 (0.5 to 1.6)	0.7 (0.5 to 1.2)
hydroxychloroquine 400mg twice daily for day 1, followed by 400mg/day in 2 divided doses for total of 5 days		
Sample Size	n = 283; % = 78.4	n = 80; % = 89.9

Outcomes

Mortality

All-cause mortality. p value 0.001

	Standard prophylactic LMWH	Intermediate LMWH
	N = 361	N = 89
All-cause mortality *Polarity: Not set*		
Sample Size	n = 75; % = 20.8	n = 4; % = 4.5

Admission to critical care

admission to critical care p value 0.8

Standard prophylactic LMWH	Intermediate LMWH
N = 57 (15.8%)	N = 13 (14.6%)

Pavoni, 2020

Bibliographic Reference	Pavoni, V.; Gianesello, L.; Pazzi, M.; Stera, C.; Meconi, T.; Frigieri, F.C.; Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: A call to action; Thrombosis Research; 2020; vol. 196; 313-317

Study details

Aim of the study	1) to evaluate outcome of severe COVID-19 based on prothrombotic risk factors, 2) assess impact of different doses of LMWH on incidence of bleeding
County/ Geographical location	Italy
Study setting	Single centre study in hospital, ICU
Population description	Adult (aged 18 years and above) patients admitted to ICU due to COVID-19 pneumonia. Diagnosis of severe COVID-19 based on WHO interim guidance and confirmed by RT-PCR
Exclusion criteria	Patients at time of admission already on vitamin K antagonists, direct oral anticoagulants (DOAC), or antiplatelet treatment with known bleeding diathesis or coagulation disorder excluded
Intervention/test/approach	Group 1: On ICU admission, patients with D-dimer < 3000ng/mL received enoxaparin 4000UI (6000UI, body mass index>35) subcutaneously b.i. All patients received aspirin once a day.
Comparator (where applicable)	Group 2: On ICU admission, patients with D-dimer ≥3000ng/mL received enoxaparin100UI/kg every 12h All patients received aspirin once a day.
Methods for population selection/allocation	Retrospective observational study

Study arms

Group 1 (N = 22) See intervention description
Group 2 (N = 20) See comparator description

Characteristics

Arm-level characteristics

	Group 1 (N = 22)	Group 2 (N = 20)
Age		
P value Mean/SD	0.150 60 (14.4)	NA 64.8 (7.8)
Gender		
Male		
No of events P value	n = 16; % = 72.7 P=0.231	n = 11; % = 55 NA
Ethnicity	Not reported	Not reported

Outcomes

Cases of VTE

	Group 1	Group 2
	N = 22	N = 20
VTE		
No of events	n = 3; % = 13.6	n = 13; % = 65
P value	0.001	NA
PE		
No of events	n = 1; % = 4.5	n = 2; % = 10
P value	NR	NA
Proximal DVT		
No of events	n = 2; % = 9.1	n = 11; % = 55
P value	NR	NA
Perivascular thrombosis		
No of events	n = 9; % = 40.9	n = 6; % = 30
P value	0.461	NA

Mortality

	Group 1	Group 2
	N = 22	N = 20
ICU mortality		
No of events	n = 2; % = 9.1	n = 5; % = 25

	Group 1	Group 2
	N = 22	N = 20
P value	0.167	NA
Hospital mortality		
No of events	n = 4; % = 18.1	n = 5; % = 25
P value	0.590	NA

Admission to critical care

	Group 1	Group 2
	N = 22	N = 20
Length of ICU stay *(days)*		
Mean/SD	9 (4.8)	11.5 (5.6)
P value	0.040	NA

Adverse effects

	Group 1	Group 2
	N = 22	N = 20
Major bleeding events	n = 0; % = 0	n = 0; % = 0

Taccone, 2020

Bibliographic Reference	Taccone, Fabio Silvio; Gevenois, Pierre Alain; Peluso, Lorenzo; Pletchette, Zoe; Lheureux, Olivier; Brasseur, Alexandre; Garufi, Alessandra; Talamonti, Marta; Motte, Serge; Nobile, Leda; Grimaldi, David; Creteur, Jacques; Vincent, Jean-Louis; Higher Intensity Thromboprophylaxis Regimens and Pulmonary Embolism in Critically Ill Coronavirus Disease 2019 Patients.; Critical care medicine; 2020; vol. 48 (no. 11); e1087-e1090

Study details

Trial registration (if reported)	Not reported
Study start date	10-Mar-2020
Study end date	30-Apr-2020
Aim of the study	To assess effect of thromboprophylaxis regimens on occurrence of pulmonary embolism in COVID-19
County/ Geographical location	Belgium
Study setting	ICU of University hospital
Population description	Critically ill mechanically ventilated adults with RT-PCR-confirmed COVID-19 Baseline characteristics not reported by arm.

	Study level: age (assumed median, IQR) 61 (57 to 66) years, 70% male, ethnicity not reported, D-dimer level on admission (ng/ml) (assumed median, IQR) 1896 (1131 to 3248)
Inclusion criteria	Critically ill mechanically ventilated adults with COVID-19 eligible if they underwent CT pulmonary angiography as part of routine management in case of persistent hypoxaemia or respiratory deterioration.
Intervention/test/approach	High regimen thromboprophylaxis (subcutaneous enoxaparin 4,000 international units bid or therapeutic unfractionated heparin)
Comparator (where applicable)	Standard thromboprophylaxis (subcutaneous enoxaparin 4,000 international units once daily)
Methods of data analysis	Timepoint unclear. All patients followed up to 30 April 2020. Retrospective analysis of prospectively collected data. Included adjustment for confounders

Study arms

High regimen thromboprophylaxis (N = 13)
Standard regimen thromboprophylaxis (N = 27)

Characteristics

Study-level characteristics

	High regimen thromboprophylaxis N = 13	Standard regimen thromboprophylaxis N = 27
Age (yrs)	58 [53-61]	63 [58-68]
Male Gender, n (%)	11 (85)	17 (63)
Ethnicity	Not reported	Not reported

Outcomes

Occurrence of pulmonary embolism

	High regimen thromboprophylaxis	Standard regimen thromboprophylaxis
	N = 13	N = 27
Occurrence of pulmonary embolism		
No of events	n = 2; % = 11	n = 11; % = 50

Occurrence of pulmonary embolism

	High regimen thromboprophylaxis vs Standard regimen thromboprophylaxis
Occurrence of pulmonary embolism	
P value	0.02
Odds ratio/95% CI	0.13 (0.02 to 0.69)
Occurrence of pulmonary embolism (multivariate analysis)	

	High regimen thromboprophylaxis vs Standard regimen thromboprophylaxis
P value	0.01
Odds ratio/95% CI	0.09 (0.02 to 0.57)

Haemorrhagic complications (patients receiving enoxaparin)

Total number of patients in each arm receiving enoxaparin was unclear

	High regimen thromboprophylaxis	Standard regimen thromboprophylaxis
	N = NR	N = NR
Haemorrhagic complications		
No of events	n = 3; % = NR	n = 2; % = NR

Appendix 7 Excluded studies

Study	Reason
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 (included in Cochrane review by Flumignan et al. 2020)
Ayerbe, Luis; Risco, Carlos; Ayis, Salma The association between treatment with heparin and survival in patients with Covid-19. medrxiv preprint	- Exclude - duplicate content
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
Bikdeli, Behnood, Talasaz, Azita H, Rashidi, Farid et al. (2020) Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill	- Exclude - Not a study design specified in protocol

Study	Reason
patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thrombosis research 196: 382-394	
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
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
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. Journal of the American Geriatrics Society 68(8): 1647-1652	- Exclude - Not a study design specified in protocol
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
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
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
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

Study	Reason
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
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
Di Renzo, Gian Carlo and Giardina, Irene (2020) Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. Am J Obstet Gynecol 223(1): 135-135	- Exclude - Not a study design specified in protocol
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
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
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 (does not include comparative data)
Hekimian, G., Lebreton, G., Brechot, N. et al. (2020) Severe pulmonary embolism in COVID-	- Exclude - Not a study design specified in protocol

Study	Reason
19 patients: A call for increased awareness. Critical Care 24: 274	
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
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
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 (does not include comparative data)
Llitjos, Jean-Francois, Leclerc, Maxime, Chochois, Camille et al. (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients.	- Exclude - duplicate content

Study	Reason
Journal of thrombosis and haemostasis : JTH 18(7): 1743-1746	
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
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
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 molecular weight heparin in COVID-19 patients. Journal of Thrombosis and Thrombolysis	- Exclude - Not a study design specified in protocol
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
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
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

Study	Reason
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
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
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
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