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 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?

The review protocol is shown in appendix 2.

Included studies

No studies were included for review question 2. Instead, 11 guidelines (4 UK and 7 international guidelines) were identified through a search for guidelines on pharmacological prophylaxis to reduce the risk of VTE in adults who have received care for COVID-19. One of the guidelines was subsequently excluded because it was not published in English, leaving 10 guidelines for consideration.

See appendix 5 for a brief overview of included guidelines. More details are presented in appendix 6.

Key details

The 10 English-language guidelines were checked to determine whether they provided guidance on the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults who have received care for COVID-19. Overall:

- 7 of the 10 guidelines included a recommendation on the use of pharmacological prophylaxis to reduce the risk of VTE in adults who have received care for COVID-19
- All the recommendations were consensus based
- 6 of the 7 guidelines recommend ongoing thromboprophylaxis based on individual's risk factors
- Recommended duration varied from 7 to 45 days

Strengths and limitations

The included guidelines were assessed using the AGREE II tool. The guidelines scored as either low or very low quality due to the lack of detailed methods for development provided, limited stakeholder involvement and lack of editorial independence.

Expert panel discussion

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

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

Relative value of different outcomes

No primary evidence was identified for this review question, so the relative value of different outcomes was not explicitly discussed.

Quality of the evidence

No evidence was identified for this review question, so the quality of evidence was not explicitly discussed. However, to provide some background context, the panel were presented with details of recommendations that four UK and 3 international guidelines provide in this area. The quality of the guidelines ranged from low to very low as assessed using the AGREE II tool.

Recommendations were developed by informal consensus.

The panel noted that from their clinical experience and their awareness of epidemiological studies that the rates of VTE in patients with COVID-19 who have been discharged from hospital are low. Several of these studies were in the context of not providing post-discharge thromboprophylaxis. However, the evidence appears to be conflicting and it was noted that an in-progress UK study is expected to report a higher VTE rate post-discharge in patients hospitalised with COVID-19 compared with post-discharge VTE rates reported in other studies.

The panel noted that NICE's guideline on reducing the risk of hospital-acquired venous thromboembolism in over 16s (NICE guideline NG89) recommends that acutely ill medical patients receive thromboprophylaxis for a minimum of 7 days and may be discharged with VTE prophylaxis if they are discharged before completing their hospital course. On the basis of no evidence specific for patients with COVID-19, the panel considered this guidance was appropriate for this patient group too and

would enable flexibility to prescribe a longer duration of prophylaxis if considered appropriate for the patient.

The panel discussed which type of prophylaxis should be offered noting, in their clinical experience, that LMWH may have less risk of interfering with antiviral medication. Additionally, LMWH is the first-line prophylaxis recommended in NG89 and no evidence was identified to suggest a different anticoagulant should be offered in patients discharged after treatment for COVID-19.

The panel noted that patients should be given information about continuing with thromboprophylaxis when being discharged after an inpatient stay for COVID-19. The panel agreed that provision of information for patients is important. However, the panel noted that the main message is to inform patients about risks of thromboprophylaxis in line with NICE's guideline on reducing the risk of hospital-acquired venous thromboembolism in over 16s (NICE guideline NG89).

The lack of identified studies which included prespecified subgroups meant that the panel were unable to make recommendations on thromboprophylaxis post-discharge following treatment for COVID-19 for:

- 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.

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.

Due to the lack of evidence, the panel considered it important that the guideline recommends patients have the opportunity to be recruited to available trials to inform future recommendations in this area.

Trade-off between benefits and harms

The panel recognised that patients may require different lengths of thromboprophylaxis post-discharge depending on how long they have been in hospital. For this reason, the panel indicated the importance of ensuring that patients who will be completing pharmacological VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.

Implementation and resource considerations

As the panel recommended that thromboprophylaxis post-discharge for patients that have received treatment for COVID-19 should be given in line with recommendations in NICE's guideline on reducing the risk of hospital-acquired venous thromboembolism in over 16s (NICE guideline NG89), they considered that there were no additional implementation considerations.

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

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 venous thromboembolism 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.'

Other considerations

No other considerations were raised in the discussions.

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 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?

PICO and eligibility criteria

Criteria	Notes
Population	Adults (aged 16 years and older) who have had treatment for COVID-19
Interventions	Pharmacological prophylaxis with: Direct oral anticoagulants (DOACs) Low molecular weight heparin Unfractionated heparin Fondaparinux sodium
Comparators	To each other Placebo / no treatment
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
Subgroups	Subgroups of people potentially at higher risk of thromboembolism include: Pregnant women 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 thromboembolism People with obesity (BMI 30kg/m2 or higher)
Study types	RCTs Cohort studies with a comparator group Systematic reviews of RCTs and/or cohort studies

	Depending on the volume of evidence identified, we may prioritise inclusion based on study design. We will prioritise inclusion of RCTs and systematic reviews of RCTs but if this study type is not available we will consider cohort studies with a comparator group and appropriate adjustment for confounding variables.
Countries	Any
Timepoints	Any
Other exclusions	Studies without a comparator group
Equality issues	Religion or beliefs, people with a learning disability and disabled people.

Appendix 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 1 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 2 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 2.

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	0
Included from surveillance search after full text screening	0
Total included studies	0

Appendix 5 Included studies

No studies were included for review question 2.

Instead 10 English-language guidelines were identified which provided guidance on the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults who have received care for COVID-19. Seven of the 10 guidelines (4 UK and 3 international guidelines) included recommendations on pharmacological prophylaxis to reduce the risk of VTE in adults who have received care for COVID-19 (post-discharge prophylaxis).

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?

Guideline	Hyperlink	Type of guideline
SIGN guideline & Healthcare improvement Scotland	https://www.sign.ac.uk/media/1691/sg_prevention_of_thromboembolism_in_hospitalised_patients.pdf	UK
British Thoracic Society	BTS guidance on venous thromboembolic disease in patients with COVID-19	UK

Guideline	Hyperlink	Type of guideline
Intensive care society, Royal college of anaesthetists, Royal college of physicians London et al	Clinical guide for the prevention, detection and management of thromboembolic disease in patients with COVID-19	UK
London consensus non-trial guidelines for anticoagulation of COVID-19 positive patients	Not published as of 11 November 2020	UK
National Institute for Health	Antithrombotic therapy in patients with COVID-19	International
American college of chest physicians (CHEST)	Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report	International
Journal of the American College of Cardiology	COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up	International

Appendix 6 Evidence tables

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?

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
SIGN guideline & Healthcare improvement Scotland	UK	In the absence of evidence specifically in patients with COVID-19-related disease, it is not possible to make specific recommendations about the type and duration of extended thromboprophylaxis… there is a clinical rationale for considering it in patients at high risk for VTE and low risk of bleeding... The assessment of VTE risk can be undertaken systematically using one of the available validated scoring tools, such as International Medical Prevention Registry on Venous Thromboembolism (IMPROVE).[9] An online calculator is available to estimate the 3-month risk of VTE based on four risk factors known at or before admission (www.outcomes-umassmed. org/improve/) and a separate calculator which estimates 3-month risk of VTE based on seven factors occurring prior to and during hospital stay (www.outcomes-umassmed.org/	Consider in high-risk patients	2 weeks	Not covered	International Medical Prevention Registry on Venous Thromboembolism (IMPROVE).[9] An online calculator is available to estimate the 3-month risk of VTE based on four risk factors known at or before admission (www.outcomes-umassmed. org/improve/) and a separate calculator which estimates 3-month risk of VTE based on seven factors occurring

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		IMPROVE/risk_score/index.html). When extended thromboprophylaxis is considered to be appropriate, ie in a patient with COVID-19-related disease who is at high risk of thrombosis and low risk of bleeding, it is recommended that the choice of agent and duration of treatment be decided on a case by case basis after discussion between the patient and the clinician. Options for treatment may include a LMWH or DOAC for 14 days following discharge in patients without contraindications.				prior to and during hospital stay (www.outcomes-umassmed.org/IMPROVE/risk_score/index.html).
British Thoracic Society	UK	Although LMWH is therefore recommended in patients who commence anticoagulation for suspected or proven VTE during their in-patient stay, it seems reasonable to switch to a DOAC on discharge. Extended thromboprophylaxis on discharge can be considered if the patient is considered at high risk of VTE (e.g. past history VTE, cancer, significantly reduced mobility, critical care admission) and the risk of VTE is felt to outweigh the risk of bleeding. The nature and duration of thromboprophylaxis in patients recovering from COVID-19 pneumonia is not clear	Consider in high-risk patients	4 weeks	Not covered	Not covered

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		but a standard prophylactic dose of LMWH or DOAC for 4 weeks may be a reasonable approach.				
Intensive care society, Royal college of anaesthetists, Royal college of physicians London et al	UK	There is currently no specific evidence on the use of thromboprophylaxis following discharge from hospital following COVID-19 infection. Extended thromboprophylaxis may be considered on discharge in those patients who are high risk, including those with a critical care admission and reduced pre-admission mobility. 14 to 28 days of thromboprophylaxis with LMWH may be considered in such patients.	Consider in high-risk patients	2 to 4 weeks	Not covered	Not covered
London consensus non-trial guidelines for anticoagulation of COVID-19 positive patients	UK	No routine thromboprophylaxis BUT consider high risk patients on a case by case basis.	Consider in high-risk patients	1 to 2 weeks	Not covered	Not covered
National Institute for Health	International	Routine post-discharge VTE prophylaxis is not recommended for patients with COVID-19 (AIII). However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the Food and Drug Administration approval of two regimens: rivaroxaban 10 mg daily	Consider in high-risk patients	6 weeks	Not covered	Modified IMPROVE score

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days.16,17 Inclusion criteria for the trials that studied these regimens included: Modified IMPROVE-VTE score ≥4; or Modified IMPROVE-VTE score ≥2 and D-dimer level >2 times the upper limit of normal;16 or Age ≥75 years; or Age >60 years and D-dimer level >2 times the upper limit of normal; or Age 40 to 60 years, D-dimer level >2 times the upper limit of normal, and previous VTE event or cancer.17 Any decision to use post-discharge VTE prophylaxis should consider the individual patient's risk factors, including reduced mobility, bleeding risks, and feasibility.				
American college of chest physicians (CHEST)	International	Duration of Thromboprophylaxis: Our search identified no study reporting incidence of VTE or major bleeding after hospital discharge in patients with COVID-19. In non-COVID patients, a significant proportion of VTE events associated with hospitalization occur after discharge.28-30,51 Anticoagulant thromboprophylaxis up to 45 days	Consider in high-risk patients	5 to 6 weeks	Not covered	Modified IMPROVE score

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		after discharge reduces the risk of VTE following hospital admission (RR, 0.61; 95% CI, 0.44-0.83) but increases the risk of major bleeding (RR, 2.04; 95% CI, 1.42- 2.91).52 A post hoc analysis of the MAGELLAN trial suggests that extended thromboprophylaxis is associated with a net benefit in patients at high risk of VTE as per modified IMPROVE score and low risk of bleeding (ie, absence of active cancer, dual antiplatelet therapy, history of bronchiectasis or pulmonary cavitation, active gastroduodenal ulcer, or any bleeding in the previous 3 months).53 However, in the MARINER trial of 12,069 patients at risk of VTE as per modified IMPROVE score, rivaroxaban 10 mg daily for 45 days after hospital discharge did not reduce symptomatic VTE.54 The 2018 American Society of Hematology practice guideline recommends against the use of extended thromboprophylaxis, because they determined a net harm associated with extended thromboprophylaxis.22 Many hospitalized patients with COVID-19 would likely have been eligible for randomized controlled trials assessing extended thromboprophylaxis, and it appears therefore justified to extrapolate relative treatment effects				

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		from those studies to hospitalized patients with COVID-19. Assuming that patients with COVID-19 incur the same risk of bleeding as patients without COVID-19 at high risk of VTE (ie, 0.7% at 35 days after discharge without extended thromboprophylaxis in patients at low risk of bleeding)53 and that symptomatic VTE is associated with a similar burden to patients as major bleeding,22 the panel suggests that extended thromboprophylaxis would result in a net benefit in patients with COVID-19 at low bleeding risk, if the risk of symptomatic VTE would be above 1.8% at 35 to 42 days after hospital discharge. Despite evidence suggesting a higher risk of VTE during hospitalization in patients with COVID-19 than in patients without COVID-19, the panel recommends only inpatient anticoagulant thromboprophylaxis, because post discharge VTE and major bleeding rates in COVID-19 patients are currently unknown. In patients with COVID-19, we recommend inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge. Remarks: Extended thromboprophylaxis in patients with COVID-19 at low risk of bleeding should be considered, if				

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis. See text for assumptions indicating net benefit.				
Journal of the American College of Cardiology	International	Extended (post-discharge) VTE prophylaxis. After hospital discharge from acute medical illness, extended prophylaxis with LMWH (70) or direct oral anticoagulants (DOACs) (71-74) can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding (75,76). While no data specific to COVID19 exist, it is reasonable to employ individualized risk stratification for thrombotic and haemorrhagic risk, followed by consideration of extended prophylaxis (for up to 45 days) for patients with elevated risk of VTE (e.g., reduced mobility, co-morbidities such as active cancer, 15 and [according to some authors in the writing group], elevated D-dimer >2 times the upper normal limit) who have low risk of bleeding (74,77,78). The role of thromboprophylaxis for quarantined patients with mild COVID-19 but significant co-morbidities, or for patients without COVID-19 who are less active because of quarantine is uncertain. These patients should be	Consider in high-risk patients	Up to 45 days	Not covered	Specified characteristics (e.g., reduced mobility, co-morbidities such as active cancer, 15 and [according to some authors in the writing group], elevated D-dimer >2 times the upper normal limit)

Source	Type of guideline	Consensus / expert opinion recommendations on continuing thromboprophylaxis on discharge from hospital (patients without VTE)	Summary of approach	Duration	Monitoring	Method of risk assessment
		advised to stay active at home. In the absence of high-quality data, pharmacological prophylaxis should be reserved for those at highest risk patients, including those with limited mobility and history of prior VTE or active malignancy.				

Appendix 7 Excluded studies

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?

Study	Reason for exclusion
Ayerbe, L.; Risco, C.; Ayis, S. (2020) The association between treatment with heparin and survival in patients with Covid-19. Journal of Thrombosis and Thrombolysis 50(2): 298-301	- Exclude - duplicate content
Ayerbe, Luis; Risco, Carlos; Ayis, Salma The association between treatment with heparin and survival in patients with Covid-19. medrxiv preprint	- Exclude - duplicate content
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
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
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 patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thrombosis research 196: 382-394	- Exclude - Not a study design specified in protocol
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 - systematic review of non-controlled studies
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

Study	Reason for exclusion
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 (*case series)*
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
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	- Exclude - Not a study design specified in protocol

Study	Reason for exclusion
thromboprophylaxis. Am J Obstet Gynecol 223(1): 135-135	
Falcoz, P.-E., Monnier, A., Puyraveau, M. et al. (2020) Extracorporeal membrane oxygenation for critically ill patients with COVID-19-related acute respiratory distress syndrome: Worth the effort?. American Journal of Respiratory and Critical Care Medicine 202(3): 460-463	- Exclude - Not a study design specified in protocol
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
Hekimian, G., Lebreton, G., Brechot, N. et al. (2020) Severe pulmonary embolism in COVID-19 patients: A call for increased awareness. Critical Care 24: 274	- Exclude - Not a study design specified in protocol
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

Study	Reason for exclusion
Klok, F A, Kruip, M J H A, van der Meer, N J M et al. (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research 191: 145-147	- Exclude - Not a study design specified in protocol
Kumar, Poornima; Mediwake, Rapti; Rhead, Camilla (2020) A matter of time: duration and choice of venous thromboprophylaxis in patients diagnosed with COVID-19. Br J Hosp Med (Lond) 81(5): 1-2	- Exclude - Not a study design specified in protocol
Kwok, Benjamin, Brosnahan, Shari B, Amoroso, Nancy E et al. (2020) Pulmonary Embolism Response Team activation during the COVID-19 pandemic in a New York City Academic Hospital: a retrospective cohort analysis. Journal of thrombosis and thrombolysis	- Exclude - Intervention does not match that specified in the protocol
Lachant, D.J., Lachant, N.A., Kouides, P. et al. (2020) Chronic therapeutic anticoagulation is associated with decreased thrombotic complications in SARS-CoV-2 infection. Journal of Thrombosis and Haemostasis 18(10): 2640-2645	- Exclude - Not a study design specified in protocol
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
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Study	Reason for exclusion
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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
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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
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Nopp, Stephan, Moik, Florian, Jilma, Bernd et al. (2020) Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Research and practice in thrombosis and haemostasis	- Exclude - Intervention does not match that specified in the protocol
Pawlowski, Colin, Venkatakrishnan, AJ, Kirkup, Christian et al. Enoxaparin is associated with lower rates of thrombosis, kidney injury, and	- Exclude - Intervention does not match that specified in the protocol

Study	Reason for exclusion
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Study	Reason for exclusion
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Stattin, K., Lipcsey, M., Andersson, H. et al. (2020) Inadequate prophylactic effect of low-molecular weight heparin in critically ill COVID-19 patients. Journal of Critical Care 60: 249-252	- Exclude - Not a study design specified in protocol
Stessel, Bjorn, Vanvuchelen, Charlotte, Bruckers, Liesbeth et al. (2020) Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study. Thrombosis research 194: 209-215	- Exclude - duplicate content
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Trigonis, Russell A, Holt, Daniel B, Yuan, Rebecca et al. (2020) Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. Critical care medicine 48(9): e805-e808	- Exclude - Not a study design specified in protocol
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Tritschler, T., Mathieu, M.-E., Skeith, L. et al. (2020) Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. Journal of Thrombosis and Haemostasis	- Exclude - Not a study design specified in protocol
Turan, O., Hakim, A., Dashraath, P. et al. (2020) Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: A systematic review. International	- Exclude - Outcome does not match that specified in the protocol

Study	Reason for exclusion
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Viecca, Maurizio, Radovanovic, Dejan, Forleo, Giovanni Battista et al. (2020) Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacological research 158: 104950	- Exclude - Not a study design specified in protocol
Zermatten, M.G., Pantet, O., Gomez, F. et al. (2020) Utility of D-dimers and intermediate-dose prophylaxis for venous thromboembolism in critically ill patients with COVID-19. Thrombosis Research 196: 222-226	- Exclude - Not a study design specified in protocol
Zhang, Chi, Shen, Long, Le, Ke-Jia et al. (2020) Incidence of Venous Thromboembolism in Hospitalized Coronavirus Disease 2019 Patients: A Systematic Review and Meta-Analysis. Frontiers in cardiovascular medicine 7: 151	- Exclude - Not a study design specified in protocol
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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	- Exclude – relevant for review question 1
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	- Exclude – relevant for review question 1

Study	Reason for exclusion
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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	- Exclude – relevant for review question 1
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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	- Exclude – relevant for review question 1
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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	- Exclude – relevant for review question 1

Study	Reason for exclusion
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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	- Exclude – relevant for review question 1
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	- Exclude – relevant for review question 1