Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

SIGN 163

Rapid guideline

Prevention and management of venous thromboembolism in patients with COVID-19

A national clinical guideline

December 2021

NHS SCOTLAND

Key to evidence statements and recommendations

Levels of evidence

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence; and the balance of benefits and harms of the options.

R	For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

✓	Recommended best practice based on the clinical experience of the guideline development group.

Scottish Intercollegiate Guidelines Network

Prevention and management of venous thromboembolism in patients with COVID-19

A national clinical guideline

December 2021

Scottish Intercollegiate Guidelines Network
Gyle Square, 1 South Gyle Crescent
Edinburgh EH12 9EB

www.sign.ac.uk

First published December 2021

978-1-909103-88-7

Citation text

Scottish Intercollegiate Guidelines Network (SIGN).
Prevention and management of venous thromboembolism in COVID-19. Edinburgh: SIGN; 2021. (SIGN publication 163). [December 2021]. Available from URL: http://www.sign.ac.uk

Contents

1 Introduction

1.1 The need for a guideline

Patients with COVID-19-related disease resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are at an increased risk of thrombosis and its complications. A meta-analysis of studies of rates of vascular thrombosis in patients with COVID-19 found an overall rate of venous thrombotic events of 21%, with pulmonary emboli in 13%.[1] Rates were higher in patients admitted to an intensive care unit (ICU) with venous thrombosis in 31% and pulmonary emboli in 19%. Arterial thrombotic events also occur, although with lesser frequency. The same study reported overall arterial thrombosis in 2% with a higher frequency of 5% in patients admitted to ICU. Importantly, the presence of thrombosis increased the odds of dying in patients with COVID-19 by 74% (odds ratio (OR), 1.74; 95% confidence interval (CI), 1.01 to 2.98; p=0.04).

A study in Scotland found an increased risk of non-fatal thromboembolic events for hospitalised individuals testing positive for SARS-CoV-2. The risk was particularly high for pulmonary embolism (PE) and deep vein thrombosis (DVT) in the 7 days after a positive test, with incidence rate ratios (IRR) of >27 and >17 respectively. The risk of PE remained significantly elevated up to 56 days after a positive test.[2]

Other studies have reported similar findings.[3,4] Respiratory infections with other pathogens can also lead to thrombotic complications, although the rates are much lower.[5,6] A similar prothrombotic state was noted in patients infected with the closely related coronaviruses that cause Severe Adult Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome.

Three main factors lead to venous thrombosis: endothelial damage, venous stasis, and a hypercoagulable state. These form the basis of Virchow's triad.[7] The exact pathophysiological mechanisms underlying the increased risks of thrombosis in COVID-19 are not yet fully explained. Aside from the general risks associated with lowered mobility and potential dehydration in hospitalised patients, infection with SARS-CoV-2 can produce widespread endothelial damage and a marked increase in production of pro-inflammatory cytokines that can induce a hypercoagulable state.[8,9]

SIGN guideline 122 on the prevention and management of venous thromboembolism makes recommendations on the assessment of risk of venous thrombosis, prophylactic measures, and management.[10] Given the marked increased risk of thrombosis in patients with COVID-19 and the additional factors that are involved, there is a need for a specific guideline which provides clinicians with evidence-based recommendations for the key areas of prophylaxis and management of thrombosis where these may differ from usual care in the context of COVID-19. The guideline also considers evidence for extended thromboprophylaxis. COVID-19 is a new disease, and although much information on the infection has been published, there are still areas where evidence is preliminary or lacking and this is highlighted where appropriate.

1.2 Remit of the guideline

1.2.1 Overall objectives

This guideline provides recommendations based on current evidence for best practice in the pharmacological prophylaxis and management of thrombotic complications of COVID-19. It includes advice for non-pregnant adults in hospital in ICU and non-ICU settings, as well as (non-pregnant) patients in the community. It covers all degrees of severity of COVID-19.

This guideline does not address risk assessment, diagnosis or investigation of possible thrombotic events, for which existing guidance for patients without COVID-19 should be used.[10] It excludes specific advice for the prophylaxis or management of thrombotic complications of COVID-19 in pregnancy or in patients under the age of 16. Advice on COVID-19 in pregnancy, including prevention of venous thromboembolism (VTE), is available from the guideline Coronavirus (COVID-19) Infection in Pregnancy developed collaboratively by Royal Colleges and public health agencies,[11] from the position statement Maternal Critical Care Provision developed by SIGN and the Chief Medical Officer (CMO) Clinical Cell[12] and the COVID-19 Clinical Advice Maternity Care developed by The Scottish Government.[13] The current guideline excludes advice on the management of thrombotic complications following vaccination against COVID-19. Advice on this topic is available from the British Society for Haematology guidance COVID-19 Vaccine-induced Immune Thrombocytopenia and Thrombosis[14] and the National Institute for Health and Care Excellence (NICE) COVID-19 rapid guideline Vaccine-Induced Immune Thrombocytopenia and Thrombosis.[15]

1.2.2 Target users of the guideline

This guideline will be of interest to physicians in primary and secondary care, nurses in primary and secondary care (including nurse prescribers and advanced nurse practitioners), community and hospital-based pharmacists, care co-ordinators and patients and their carers.

1.3 Definitions

For the purposes of this document, the following definitions apply.

- Patients are classified with COVID-19-related disease if they have a positive reverse transcription polymerase chain reaction (RT-PCR) test result or show strong clinical evidence of infection with SARS-CoV-2 (eg continuous cough, fever or high temperature (≥37.8°C) or loss of, or change in, sense of smell (anosmia) or taste (ageusia)).[16]
- Patients with COVID-19 pneumonia have radiological evidence of lung infiltrates and fulfil the above criterion.
- Critical or severe COVID-19-related disease is defined as hospitalised patients who require critical care-level respiratory or cardiovascular organ support including one or more of the following:
  - high-flow nasal oxygen
  - ≥20 L/min invasive or non-invasive ventilation
  - extracorporeal life support
  - vasopressors or inotropes.
- Moderate COVID-19-related disease is defined as patients who are hospitalised for COVID-19 without the requirement for critical care-level of support (as defined above).
- COVID-19-associated VTE is defined as any VTE occurring within a month of a diagnosis of COVID-19, or within a month of discharge after a hospital admission with COVID-19.
- Extended thromboprophylaxis is defined as prophylactic-dose anticoagulation continued beyond the initial hospital course and up to 45 days following discharge.

Prophylactic-dose and therapeutic-dose anticoagulation are defined in section 4.1.

1.4 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care

evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.4.1 Influence of financial and other interests

It has been recognised that financial or academic interests may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from these sources, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial and academic interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

1.4.2 Prescribing of licensed medicines outwith their marketing authorisation

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the MA
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the MA. Such use should be supported by appropriate evidence and experience.[17]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[17]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[18]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy

- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics ((SPC) - www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[19]

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. These recommendations also highlight areas where the management of VTE in the context of COVID-19 is more likely to vary from standard (non-COVID-19 -related) practice.

2.1 Prevention of thromboembolism in patients with COVID-19 in hospital

R **Use a standard thromboprophylactic dose of a low molecular weight heparin in hospitalised patients with critical or severe COVID-19.**

R **Consider use of a therapeutic dose of a low molecular weight heparin in hospitalised patients with moderate COVID-19.**

R **In hospitalised patients with moderate COVID-19 and renal failure** (CrCl <30 mL/min) **and/or those considered at very high risk of bleeding where anticoagulation needs to be terminated very quickly, consider either:**

- **a dose-adjusted therapeutic dose of unfractionated heparin, or**
- **a dose-adjusted therapeutic dose of a low molecular weight heparin.**

R **Therapeutic-dose heparin treatment of hospitalised patients with moderate COVID-19 should be continued:**

- **for up to 14 days, or**
- **until hospital discharge, or**
- **until a discontinuation of supplemental oxygen for at least 24 hours**

whichever comes first.

2.2 Management of thromboembolism in patients with COVID-19 in hospital

R **Consider apixaban or rivaroxaban using the licensed dosing regimens as first-line anticoagulation for hospitalised patients with confirmed VTE and COVID-19.**

R **Offer anticoagulation for at least 3 months to hospitalised patients with confirmed VTE.**

3 Prevention of thromboembolism in patients with COVID-19 in community settings

Prevention of VTE in community settings is centred on identification of predisposing risk factors for development of events. The most commonly identified indications for pharmaceutical prevention of thrombotic events in the community are non-valvular atrial fibrillation and mechanical heart valve replacement.

While it is known that there is an increased risk of VTE in patients with COVID-19 admitted to hospital, no evidence was identified which addressed the question of primary prevention of thrombosis (thromboprophylaxis) in people presenting with clinical signs of COVID-19 in primary care settings. A review of current trials of antithrombotic therapy in patients with COVID-19 identified 11 ongoing RCTs in outpatients with COVID-19 which are registered in clinical trials databases.

3.1 Risk factors for VTE

A large prospective cohort study used general practice data from over 2.3 million adults aged 25–84 years in England and Wales, and a further 1.25 million adults in a validation cohort to establish a risk prediction tool (available at www.qthrombosis.org) which quantifies future absolute thrombotic risk in asymptomatic individuals in a primary care setting.[20] It does not include COVID-19 as a predictor variable.

In all men and women, risk of VTE was associated with increasing age, body mass index (BMI), and quantity of cigarettes smoked every day. The risk was also raised for those with varicose veins, congestive heart failure, chronic kidney disease (stage 4 or 5), any cancer, chronic obstructive airways disease, inflammatory bowel disease, and those admitted to hospital in the past six months (the variables for hip fracture or operation were combined with recent hospital admission to create this composite factor due to the comparability in their hazard ratios). Overall, the hazard ratios were generally similar for men and women. Risk of VTE also increased in any patients who were prescribed antipsychotic drugs, and in women who were prescribed oral contraceptives, hormone replacement therapy or tamoxifen.

The authors note that although family history was not associated with risk of VTE, this finding is likely to reflect the small numbers of patients with this information recorded in primary care databases. This does not represent a comprehensive list of all risk factors for VTE, as the methods used to develop the research tool prioritised those which are more easily quantified and extracted from general practice (GP) records. For further information on risk assessment for VTE, see SIGN 122: Prevention and management of venous thromboembolism.[10]

The tool identifies individuals at higher risk of future VTE, but is not designed to guide decision making on initiation of thromboprophylaxis in such individuals given that it neither estimates bleeding risk associated with anticoagulation nor allows a person-centred balancing of all risks (including polypharmacy and multimorbidity) and benefits associated with potential prescribing decisions. Possible uses include patient education to demonstrate components of VTE risk and to encourage lifestyle modification. Reductions in future individual risk can be quickly estimated for patient-led activities such as smoking cessation or weight loss.

3.1.1 Additional modifiable risk factors particularly relevant in the context of activity restrictions

Prolonged sitting and immobility

A systematic review investigating the link between venous and arterial diseases and occupational factors among adult working populations reported conflicting results for the association between work- and computer-related seated immobility and VTE. Three case-control studies found an increased risk of VTE in workers with prolonged sitting time, while the only large prospective study did not confirm it. However, with venous stasis one of the contributing factors to development of thromboembolism, in the context of lockdowns and self isolation and reduced opportunities for physical activity, patients should be encouraged to avoid prolonged immobility. The Health and Safety Executive recommends that when individuals are working at home on a long-term basis users of display screen equipment (DSE) should complete a workstation assessment to identify any areas of personal risk.[21]

Simple steps which people can use to reduce risks from DSE include:

- breaking up long spells of DSE work with rest breaks (at least 5 minutes every hour) or changes in activity
- avoiding awkward, static postures by regularly changing position
- getting up and moving or doing stretching exercises
- avoiding eye fatigue by changing focus or blinking from time to time.

The UK Chief Medical Officers' physical activity guideline noted that above 6 to 8 hours per day of total sitting time and 3 to 4 hours per day of TV viewing time for adults are associated with greater risk of all-cause and cardiovascular disease (CVD) mortality, independently of levels of moderate-to-vigorous physical activity.[22]

✓ Encourage all individuals to remain mobile in home and work settings and to break up prolonged (>1 hour) periods of sitting with at least light physical activity, where possible.

Obesity

A Romanian case-control study analysed the association between VTE risk and obesity in 382 patients diagnosed with VTE, and 350 controls and reported associations stratified by gender, age and risk factors. Obesity was significantly associated with VTE (OR=6.22, 95% CI 4.17 to 9.28) in all patients and, independently, in males (OR=5.69, 95% CI 3.43 to 9.45) and females (OR=3.97, 95% CI 2.24 to 7.02). The risk of VTE was almost double in obese patients aged >50 years than in those aged <50 years (OR=6.14 vs 3.12).[23]

3.2 Pharmacological prevention of VTE in community settings

No evidence was identified which addressed the question of thromboprophylaxis in people presenting with clinical signs of COVID-19 in primary care settings.

Anticoagulation is generally not initiated in outpatients. For individuals with PCR-confirmed SARS-CoV-2 infection or clinically suspected COVID-19-related disease where multiple thrombotic risk factors *(see section 3.1)* cause clinical concern, primary care staff should liaise with local specialist teams.

✓ Thromboprophylaxis should not be routinely considered in patients with COVID-19 in primary care settings. Where there may be clinical concern, primary care practitioners should seek advice from their local specialist team.

- ✓ The management of patients with COVID-19 in the community should follow agreed national pathways.
- ✓ Patients with multiple risk factors for VTE should be managed holistically, with primary care practitioners having access to specialist team advice, where required, 24 hours/day.
- ✓ Care of patients with suspected VTE should follow locally agreed pathways which support early diagnosis and subsequent management.

4 Prevention of thromboembolism in patients with COVID-19 in hospital

Patients admitted to hospital with COVID-19 are at increased risk of venous thromboembolism, particularly those admitted to critical care settings.[10] Compared with non-pregnant women with COVID-19, pregnant women with COVID-19:

- have higher rates of ICU admission (this may reflect a lower threshold for admission to ICU, rather than more severe disease)
- have higher needs for ventilation and extracorporeal membrane oxygenation (ECMO)
- who require hospitalisation have overall worse maternal outcomes, including an increased risk of death, although the risk of death remains very low (the UK maternal mortality rate from COVID-19 is 2.4/100 000 maternities)
- may be at increased risk of complications in the third trimester compared with earlier in the pregnancy.

The Royal College of Obstetricians and Gynaecologists, The Royal College of Midwives, The Royal College of Paediatrics and Child Health, Public Health England and Public Health Scotland have jointly published the guideline Coronavirus (COVID-19) Infection in Pregnancy which supports the provision of safe, personalised and woman-centred care during pregnancy, birth and the early postnatal period, during the COVID-19 pandemic.[11]

Systematic reviews have assessed the overall incidence of VTE in hospitalised patients with COVID-19-related disease, with subgroup analyses for those admitted to ICU or general wards *(see Table 1)*. In all reviews, estimates of the incidence of VTE were lower when based on clinical diagnosis compared with screening or other methods of patient sampling.

More recent case series have reported a trend for lower incidence of VTE (7–14%) in ICU settings.[24-27] While the reasons for this are unclear it may reflect earlier diagnosis and improved treatment at later stages in the pandemic.

A self-controlled case series study using a national, general population cohort included all patients who received both a positive diagnosis of SARS-CoV-2 and also experienced a thromboembolic event in Scotland up to October 2020. The risk of non-fatal thromboembolism was significantly higher over the whole risk interval (between 5 days before and 54 days after the sample was obtained for the patient's first positive SARS-CoV-2 test) than the control interval (a period from March 2018 to October 2020 excluding the risk interval), and highest within the 7 days following the positive test (IRR 12.01, 95% CI 9.91 to 14.56). The study reported a decline in VTE risk from the peak at 0–7 days after the positive SARS-CoV-2 test, however composite risk of myocardial infarction, ischaemic stroke, PE or DVT remained significantly elevated above control levels at 56 days after the positive test suggesting that VTE risk remains a serious concern for all hospitalised patients.[2] **(EVIDENCE LEVEL 3)**

Table 1: Pooled incidence of VTE in patients hospitalised with COVID-19

Review	Pooled incidence of VTE in all hospitalised patients with COVID-19 (%)	Pooled incidence of VTE in ICU patients with COVID-19 (%)	Pooled incidence of VTE in non-ICU patients with COVID-19 (%)
Jiminez, et al 2021[28]	17.0 (95% CI 13.4 to 20.9)	27.9 (95% CI 22.1 to 34.1)	7.1 (95% CI 4.8 to 9.8)
Porfidia, et al 2020[29]	26 (95% PI 6 to 66)	24 (95% PI 5 to 66)	9 (95% PI 0 to 94)
Zhang, et al 2021[30]	13 (95% CI 5 to 24)	31 (95% CI 22 to 42	7 (95% CI 1 to 18)
Mansory, et al 2021[31]	12.8 (95% CI 11.1 to 14.6)	24.1 (95% CI 20.07 to 28.28)	7.7 (95% CI 5.96 to 9.70)

Abbreviations: PI – prediction interval

Randomised controlled trials[32,33] have shown that a prophylactic dose of low molecular weight heparin (LMWH) significantly reduces the risk of VTE in medical inpatients and this has become standard clinical practice for management of these patients. There was concern in the early stages of the pandemic that prophylactic-dose LMWH might be insufficient to prevent VTE in patients with COVID-19 and that higher doses of LMWH should be considered. However, such a strategy has the potential to increase bleeding risk.

This section describes the evidence and recommendations for doses of anticoagulation that should be considered in patients admitted to hospital with COVID-19-related disease.

4.1 Definitions

Prophylactic-dose anticoagulation in medical patients is considered to include any of the following regimens: unfractionated heparin (UFH) 5,000 units every 8–12 hours, enoxaparin 40 mg once daily, dalteparin 5,000 units every 24 hours, or fondaparinux 2.5 mg once daily. All of these medications require dose adjustment to account for patients' weight and renal function.

Therapeutic-dose anticoagulation is considered as the dose used to treat acute venous thrombosis and would include any of the following regimens: enoxaparin 1.5 mg/kg every 24 hours (in uncomplicated patients with low risk of recurrence) or enoxaparin 1 mg/kg every 12 hours (in patients with risk factors such as obesity, cancer, recurrent VTE etc), dalteparin 200 units/kg once daily (banded dosing – see British National Formulary[17] or local protocols), tinzaparin 175 units/kg (banded dosing), fondaparinux 7.5 mg every 24 hours (dose adjusted for extremes of body weight), UFH by intravenous (IV) infusion (IV loading dose (5,000 units or 75 units/kg) followed by subcutaneous injection (15,000 units/12 hours)) or continuous IV infusion (18 units/kg/hour) with dose alterations based on activated partial thromboplastin time (APTT) measurement (usual range 1.5–2.5 seconds).

Adults with SARS-CoV-2 infection can be grouped into categories based on the severity of COVID-19-related disease ranging from asymptomatic to critically ill. Categories have been defined differently by national and international organisations (eg the World Health Organization[34] and National Institutes of Health[35]) and within protocols for individual clinical trials, with the result that criteria for each category may overlap or vary across different sources. A patient's clinical status may also change over time and caution is required in the interpretation of evidence.

In this section evidence and recommendations are considered together for the combined category of patients with either critical or severe COVID-19-related disease and for patients with moderate COVID-19.

Critical or severe COVID-19-related disease is defined as hospitalised patients who require critical care-level respiratory or cardiovascular organ support including one or more of the following:

- high-flow nasal oxygen
- ≥20 L/min invasive or non-invasive ventilation
- extracorporeal life support
- vasopressors or inotropes.

Moderate COVID-19 disease is defined as patients who are hospitalised for COVID-19 without the requirement for critical care-level support (as defined above).

4.2 Contraindications to pharmacological prophylaxis with heparins

Contraindications to pharmacological thromboprophylaxis with heparins in patients with COVID-19 include:

- platelet count ≤25 x 10^9/L (≤50 x 10^9/L for therapeutic-dose or intermediate-dose thromboprophylaxis) (note that these reduced platelet count thresholds apply specifically to patients with COVID-19-related disease)
- receiving anticoagulation for another reason
- patient considered to be at high bleeding risk, for example recent intracranial haemorrhage, untreated inherited/acquired bleeding disorders
- major trauma with high bleeding risk
- active bleeding
- heparin-induced thrombocytopenia (HIT)
- acute stroke (use intermittent pneumatic leg compression if immobile and contact the stroke team for guidance)
- immediately before and after procedures, for example surgery, lumbar puncture (individual heparins have distinct pharmacokinetics and cannot be used interchangeably. See the SPC for specific advice on appropriate timing of administration.)
- acute bacterial endocarditis.

Cautions for pharmacological thromboprophylaxis with heparins include:

- liver failure and prothrombin time ratio >2
- persistent hypertension (blood pressure ≥230/120 mm Hg).

Source – NHS Greater Glasgow and Clyde Adult Therapeutics Handbook

4.3 Patients hospitalised with critical or severe COVID-19

4.3.1 Dose of anticoagulation

Two RCTs, one multiplatform RCT (mpRCT) and two systematic reviews of observational data provide evidence on dose of anticoagulation in hospitalised patients with critical or severe COVID-19.

Three international multisite RCTs (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), Accelerating COVID-19 Therapeutic interventions and Vaccines-4 Antithrombotics Inpatient platform trial (ACTIV-4a) and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)) aligned their trial design, eligibility criteria, interventions, outcome measures and statistical analyses to allow results to be pooled (mpRCT).

The trial was conducted in 408 sites across 14 countries, and compared the effect of therapeutic anticoagulation and standard thromboprophylaxis. Patients were stratified by disease severity, with severe disease defined as in section 4.1. Therapeutic dosing and usual care pharmacological thromboprophylaxis of LMWH or UFH were guided by local protocols. In the therapeutic and standard prophylactic-dose groups patients received LMWH (89% and 90%, respectively) or UFH (10.9% and 5.6%, respectively). Recruitment to the trial was stopped after interim analyses met the threshold for futility.

From per protocol analysis (n=1,098) the median composite ordinal score (-1 to 21) of inhospital mortality (score of -1) and organ support free days (OSFD) (score of 0 to 21) over a 21-day period was 1 day (interquartile range –1 to 16) in the therapeutic-dose group compared with 4 days (interquartile range –1 to 16) in the standard thromboprophylaxis group (median adjusted OR 0.83, 95% credible interval (CrI)) 0.67 to 1.03). Inhospital survival was similar in the therapeutic-dose group (62.7%) and the standard thromboprophylaxis group (64.5%), (median adjusted OR 0.84, 95% CrI 0.64 to 1.11). Major bleeding was also comparable: 3.8% in the therapeutic group compared with 2.3% in the standard thromboprophylaxis group (OR 1.48, 95% CrI 0.75 to 3.04). Descriptively, there were fewer thrombotic events in the therapeutic group compared with the standard thromboprophylaxis group (6.4% vs 10.4%, no OR calculated). The OR for major thrombotic events or mortality combined was 1.04 (95% CrI 0.79 to 1.35). This OR is likely to be weighted by the larger number of deaths (n=399) compared with thrombotic events (n=92).[36] **(EVIDENCE LEVEL 1+)**

It remains unclear whether the mpRCT indicated a significantly decreased risk of thrombosis associated with therapeutic-dose anticoagulation. Given the size of the trial it might be assumed that a 4% absolute decrease in VTE with the use of therapeutic LMWH compared with standard dose would indicate a statistically significant decrease in odds of VTE. However, this cannot be confirmed as an OR was not calculated. The authors of the mpRCT calculated that their results for the primary outcome reflect a 99.9% chance of futility (no difference between the therapeutic- and prophylactic-dose effects) and a 95.0% chance of inferiority (the therapeutic dose is harmful).

Two further RCTs, conducted in Brazil with small samples sizes of critically/severely ill patients with COVID-19, reported conflicting results.

The first trial compared therapeutic with prophylactic anticoagulation in patients stratified by clinical stability.[37] Those categorised as clinically unstable (n=39) had COVID-19-related critical illness, a life-threatening condition, a requirement for mechanical ventilation or vasopressors, or were unable to take oral medication. The only outcome stratified by clinical stability was a hierarchical composite of time to death, duration of hospitalisation, or duration of supplemental oxygen use through 30 days (win ratio method). In the clinically unstable group there was no difference between those receiving a therapeutic dose and a prophylactic dose in the win ratio for the hierarchical outcomes of 30-day mortality, length of stay and oxygen support; (clinically unstable win ratio therapeutic (n=23) vs prophylactic (n=16) 1.12, 95% CI 0.44 to 2.82) (a different 95% CI of 0.57 to 1.21 was reported in a figure in the supplementary material). The applicability of these results are limited by the fact that the hierarchical composite outcome cannot be separated into individual outcomes restricting comparison with other studies. The results from the clinically unstable cohort are also less applicable due to the small sample size. **(EVIDENCE LEVEL 1+)**

The second trial (n=20) compared therapeutic with prophylactic anticoagulation in patients with severe/critical COVID-19.[38] Over a 28-day period, patients receiving therapeutic dose had more OSFD (15 days [interquartile range 6 to 16]) compared with 0 days ([interquartile range 0 to 11], p=0.028) in patients who received prophylactic dose. There was no statistically significant difference in inhospital mortality rate (p=0.160) or all-cause 28-day mortality rate (p=0.264), but patients in the therapeutic group were four times more likely to be released

from mechanical ventilation during the 28-day follow up compared with the prophylactic group (hazard ratio (HR) 4.0, 95% CI 1.03 to 15.05, p=0.031). No major bleeding was reported in either group. Two patients in the therapeutic group experienced minor bleeding. Four patients had bleeding which required medical attention in the therapeutic group and two patients in the prophylactic group. There was one DVT and one PE in the prophylactic group and two DVTs in the therapeutic group. **(EVIDENCE LEVEL 1+)**

Two high-quality systematic reviews identified the same retrospective cohort study which reported a decrease in mortality in mechanically ventilated patients who received a therapeutic dose of heparin or enoxaparin for >5 days compared with a prophylactic dose (HR 0.21, 95% CI 0.10 to 0.46), p<0.001).[39,40] One of these reviews included a further cohort study which reported no difference in mortality between dosing in critically ill pregnant women with COVID-19 (all patients survived).[40] **(EVIDENCE LEVEL 2++)**

In summary, the evidence for therapeutic or prophylactic dose anticoagulation on clinical outcomes reports inconsistent findings. The largest trials which collectively include 1,113 patients with critical or severe COVID-19 report that therapeutic anticoagulation did not improve survival or OSFD compared with prophylactic anticoagulation. A smaller RCT (n=20) suggests that therapeutic anticoagulation may improve OSFD and one retrospective cohort study reported reduction in mortality. Confidence in the collective quality of evidence is limited by a range of factors affecting individual studies such as small sample sizes and risk of confounding.

4.3.2 Choice of anticoagulant

Fondaparinux is an effective agent for thromboprophylaxis in acutely ill medical inpatients but it has a long half-life.[32] A LMWH with a shorter half-life than fondaparinux, such as enoxaparin or dalteparin, may be preferable due to a perceived increased risk of bleeding in patients with COVID-19 disease, particularly those who are critically ill.

It has been suggested that inflammation and associated endothelial injury and platelet activation may be an important cause of thromboembolism in patients hospitalised with COVID-19. A large open-label platform RCT conducted mostly in the UK has shown that aspirin use in patients hospitalised with COVID-19 did not reduce 28-day mortality or progression to invasive mechanical ventilation or death, irrespective of other anticoagulation status.

The RECOVERY trial allocated 14,892 patients hospitalised with COVID-19 to 150 mg aspirin once daily plus usual care (n=7,351) or usual care alone (n=7,541).[41] At randomisation, 5,035 patients (34%) were receiving thromboprophylaxis with higher-dose LMWH, 8,878 (60%) with standard-dose LMWH, and 979 (7%) were not receiving thromboprophylaxis. There was no difference in death within 28 days between those allocated to aspirin or usual care (16.6% vs 17.2%; rate ratio 0.96, 95% CI 0.89 to 1.04). The incidence of thrombotic events was lower (4.6% vs 5.3%; absolute difference 0.6%, standard error (SE) 0.4%) and the incidence of major bleeding events was higher (1.6% vs 1.0%; absolute difference 0.6%, SE 0.2%) in the aspirin group.

There was no significant difference in 28-day mortality between the aspirin group and usual-care group for patients who were also receiving higher dose LMWH (rate ratio 0.96, 95% CI 0.85 to 1.09), standard-dose LMWH (rate ratio 1.02, 95% CI 0.91 to 1.15) or no thromboprophylaxis (rate ratio 0.83, 95% CI 0.66 to 1.04).

Low molecular weight heparins are associated with a lower risk of heparin-induced thrombocytopenia than unfractionated heparin.[17]

Patients with abnormal renal function are at an increased risk of both thrombosis and bleeding. In contrast to UFH, LMWHs and direct oral anticoagulants (DOACs) are primarily cleared via renal excretion. Therefore, care is required if these anticoagulants are given to patients with

renal insufficiency (creatinine clearance (CrCl) <30 mL/min) because they can accumulate and increase the risk of bleeding. While marketing authorisation for some LMWHs recommend that they are not used in patients with end stage renal failure (CrCl <15 mL/min), local thrombosis protocols may support careful use of dose-adjusted LMWH with anti-Xa monitoring in those with severe renal impairment (CrCl 15–30 mL/min). As the indications and dose alterations of LMWHs differ for individual drugs when used in patients with renal failure,[42] in the context of COVID-19 where rapid reversal of anticoagulation may be required, either dose-adjusted UFH or dose-adjusted LMWH may be considered as an option for thromboprophylaxis. The choice of an LMWH in patients with end stage renal failure is an off-label use *(see section 1.4.2)* and any such use should be supported by local prescribing protocols.

R **Use a standard thromboprophylactic dose of a low molecular weight heparin in hospitalised patients with critical or severe COVID-19.**

R **In hospitalised patients with critical or severe COVID-19 and renal failure** (CrCl <30 mL/min) **and/or those considered at very high risk of bleeding where anticoagulation needs to be terminated very quickly, use either:**

- **a dose-adjusted standard thromboprophylactic dose of unfractionated heparin, or**
- **a dose-adjusted standard thromboprophylactic dose of a low molecular weight heparin.**

4.4 Patients hospitalised with moderate COVID-19

4.4.1 Dose of anticoagulation

Two RCTs described in section 4.3.1 also provided results for the effects of therapeutic-dose anticoagulation compared with standard prophylactic dose in patients with moderate COVID-19 disease severity.

In the mpRCT, among 2,219 participants with moderate COVID-19 in the final analysis, a therapeutic-dose improved OSFD compared with a standard prophylactic dose (OR 1.27, 95% CrI 1.03 to 1.58).[43] This equated to a median adjusted absolute improvement in reaching 21 days without organ support of 4.0% (95% CrI 0.5 to 7.2) in the therapeutic-dose group compared with the standard-dose group (80.2% vs 76.4% respectively). Compared with standard thromboprophylaxis, patients receiving a therapeutic dose also had a higher chance of survival without organ support at 28 days (OR 1.3, 95% CrI 1.05 to 1.61), and were at lower risk of experiencing major thrombotic events or death (OR 0.72, 95% CrI 0.53 to 0.98) and lower risk of experiencing any thrombotic event or death (OR 0.71, 95% CrI 0.52 to 0.96). There was no difference in 28-day survival in the therapeutic-dose group compared with the standard-dose group (OR 1.20, 95% CI 0.88 to 1.61) or in major bleeding (1.9% and 0.9% respectively, OR 1.80, 95% CI 0.90 to 3.74). There was no difference in any results when stratified by D-dimer level. Around 20% of participants assigned to the therapeutic arm received lower than therapeutic-dose intensity anticoagulation and around 30% in the prophylactic arm received higher than prophylactic-dose intensity anticoagulation. This reflected the fact that intermediate-dose anticoagulation was considered usual care for ICU-level prophylaxis in some hospitals participating in the trial. **(EVIDENCE LEVEL 1+)**

A further RCT, conducted in Brazil, compared therapeutic with prophylactic anticoagulation in patients stratified by clinical stability.[37] Those categorised as clinically stable (n=576) meet the definition for moderate COVID-19 disease severity *(see section 4.1)*. The only outcome stratified by clinical stability was a hierarchical composite of time to death, duration of hospitalisation, or duration of supplemental oxygen use through 30 days (win ratio method). In the clinically stable group there was no difference between those receiving a therapeutic dose and a

prophylactic dose in the win ratio for the hierarchical outcome of 30-day mortality, length of stay and oxygen support (win ratio therapeutic vs prophylactic dose 0.84, 95% CI 0.64 to 1.11). The authors note that the lack of any effect in this patient group with moderate COVID-19 disease conflicts with the results from the mpRCT which indicate benefits for a therapeutic-dose strategy. Most patients in this trial received the DOAC rivaroxaban while most patients in the mpRCT received heparins. The authors note that heparins, which inhibit multiple coagulation proteases, might have other anti-inflammatory and antiviral effects, some of which may be specific to COVID-19. In addition the route of administration, oral versus subcutaneous may have an impact. **(EVIDENCE LEVEL 1+)**

The RAPID trial randomised 465 patients hospitalised with moderate COVID-19-related disease who had elevated D-dimer to therapeutic dose or prophylactic dose heparin. The primary outcome was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or ICU admission, and was not statistically significantly different between the two arms (OR, 0.69, 95% CI 0.43 to 1.10), although the odds of death at 28 days was decreased in the therapeutic dose arm (OR 0.22, 95% CI 0.07 to 0.65).[44] There was a numeric decrease in the number of VTEs with two events in the therapeutic-dose arm and seven events in the standard prophylactic-dose arm. There was no difference in bleeding. The authors hypothesise the significant reduction in mortality associated with therapeutic-dose anticoagulation in this trial compared with the mpRCT may be explained by a stronger contrast between experimental and control arms in the RAPID trial. In the mpRCT there was some variation in intensity of anticoagulation delivered to participants in each arm due to trial protocols and variation in local prescribing policies *(see above)*. The authors also acknowledge that the primary outcome, which did not demonstrate a statistically significant difference between anticoagulation dosages was underpowered. **(EVIDENCE LEVEL 1+)**

Responses to the trial have suggested that the use of relative efficacy metrics (odds ratios) for the primary outcome[45] and use of a composite outcome[46] may underestimate the effect of therapeutic anticoagulation. When considered with Bayesian analysis, it has been suggested that the results of this trial demonstrate a 94% probability that therapeutic anticoagulation yields a benefit.[45]

The guideline development group were aware that patients discharged from critical care to general ward care are assumed to be recovering and are likely to be transitioning from critical or severe COVID-19-related disease to moderate COVID-19-related disease. The recommendations for different dosage of anticoagulation in these two groups are not intended to support the increase of anticoagulation intensity when stepping patients down in this way. On discharge from critical care, the patient's condition is generally less inflammatory, and, as they have received prophylactic-dose anticoagulation during the period of critical care, the guideline development group discussed that they are less likely to benefit from therapeutic-dose anticoagulation than patients admitted with moderate COVID-19-related disease in the absence of any anticoagulation. The group noted that in the available RCTs therapeutic anticoagulation was not given after recovery from critical illness but before. In the mpRCT patients were assigned to experimental groups based on COVID-19-related disease severity at enrolment, underlining that this evidence does not directly apply to intensification or reduction of anticoagulation in recovering or deteriorating patients. In line with standard practice, patients should be reviewed on step down from critical care to ward-level care and risks of VTE and bleeding assessed.

In summary, in moderately ill patients, there appears to be evidence of benefit for therapeutic doses over standard prophylactic dose LMWH on organ support free days, survival without organ support at 28 days and incidence of the composite outcome of thrombotic events or death in one mpRCT. This benefit may or may not be considered compelling for an individual patient. However, identifying which patients would benefit is challenging, as the studies within

the mpRCT had different inclusion criteria regarding time from hospital admission to enrolment. Primary composite outcomes in other trials and evidence from what might be considered standard outcomes (for example, 28-day mortality, major bleeding, length of stay and time to discharge) do not show a benefit for therapeutic-dose anticoagulation, although results may be influenced by underpowering and later introduction of adjunctive therapies in patients hospitalised with COVID-19.

R **Consider use of a therapeutic dose of a low molecular weight heparin in hospitalised patients with moderate COVID-19.**

R **In hospitalised patients with moderate COVID-19 and renal failure** (CrCl <30 mL/min) **and/or those considered at very high risk of bleeding where anticoagulation needs to be terminated very quickly, consider either:**

- **a dose-adjusted therapeutic dose of unfractionated heparin, or**
- **a dose-adjusted therapeutic dose of a low molecular weight heparin.**

✓ Bleeding risk should be considered when making decisions regarding intensity of anticoagulation.

R **Therapeutic-dose heparin treatment of hospitalised patients with moderate COVID-19 should be continued:**

- **for up to 14 days, or**
- **until hospital discharge, or**
- **until a discontinuation of supplemental oxygen for at least 24 hours**

whichever comes first.

✓ For all patients hospitalised with COVID-19, it is important that both anticoagulation dose and purpose of anticoagulation are recorded in the patient's notes, medicines chart or appropriate local system in order to differentiate individuals receiving therapeutic doses of anticoagulation for different indications.

✓ Care of patients with suspected VTE should follow locally agreed pathways which support early diagnosis and subsequent management.

4.5 Intermediate-dose thromboprophylaxis

Many centres have developed protocols for intermediate-dose thromboprophylaxis (doses higher than standard, but below normal treatment doses). No evidence was found comparing intermediate dosing with therapeutic-dose prophylaxis and it is not possible to develop recommendations either in favour or against this approach. There is considerable inconsistency in the definition of intermediate dosing, ranging from simple increases in standard dosing, dosing by weight, and dosing based on anti-Xa activity, and also variable consideration of renal function and BMI. Further studies are needed to establish whether this approach has any merit.

A multicentre RCT compared intermediate-dose anticoagulation (n=276) with standard prophylactic-dose anticoagulation (n=286) in adult patients admitted to ICU with COVID-19. Intermediate-dose anticoagulation, compared with standard prophylactic-dose anticoagulation, did not result in a significant difference in the primary outcome of a composite of venous or arterial thrombosis, treatment with ECMO, or mortality within 30 days. The authors note that these results do not support the routine empirical use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the ICU with COVID-19.[47]

5 Management of thromboembolism in patients with COVID-19 in hospital

No primary evidence was identified on the duration, dose or choice of anticoagulant for patients who are hospitalised with COVID-19 and diagnosed with any venous or arterial thrombosis. In the absence of specific evidence on the management of VTE in individuals with COVID-19 in hospital, the guideline development group endorses the same approach for the treatment of VTE in individuals infected with COVID-19 as for non-infected individuals with VTE.

There appears to be no difference in efficacy between anticoagulants used to treat COVID-19-associated VTE (defined in section 1.3) in any given clinical setting, nor the dose used. However, close clinical review is necessary to ensure an adequate response to anticoagulation given the highly prothrombotic nature of COVID-19 infection *(see section 4)*.

5.1 Choice of anticoagulant

One systematic review was identified which addressed the questions of choice, duration and dose of anticoagulant for patients who are hospitalised with COVID-19 and diagnosed with any venous or arterial thrombosis. This review found no evidence and used expert consensus to recommend that such patients be treated using standard care.[48] No RCTs or preprint studies were identified. Therefore, in the absence of evidence matching the population component of this key question *(see Annex 1)*, the guideline development group agreed that the treatment of acute VTE in hospitalised patients with COVID-19 should follow the recommendations for treatment of VTE in acutely ill medical inpatients.

The National Institute for Health and Care Excellence (NICE) clinical guideline 158 (NG158) Venous thromboembolic diseases: diagnosis, management and thrombophilia testing addressed the treatment of VTE in all patients, without a focus on COVID-19.[49] The evidence review for NG158 included a de novo network meta-analysis (NMA) which included 34 RCTs that examined initial treatment (3–12 months) of all VTE, DVT and PE. Outcomes explored were VTE recurrence, major bleeding, clinically relevant non-major bleeding and all-cause mortality. The following drugs, or combinations of drugs were compared with each other: LMWH and vitamin K antagonist (VKA); fondaparinux and VKA; UFH and VKA; apixaban; dabigatran; edoxaban; and rivaroxaban. **(EVIDENCE LEVEL 1++)**

5.1.1 Initial treatment of all VTE

The NMA reported that apixaban, rivaroxaban, edoxaban and the combination of LMWH + VKA were each superior to UFH + VKA for the prevention of VTE recurrence (pooled data of DVT, PE and unspecified VTE). No significant differences were noted between any other drugs or combinations for this outcome *(see Table 2)*.

Apixaban was superior (ie less bleeding) to all other comparators except rivaroxaban for the outcome of major bleeding. There was no significant difference between apixaban and rivaroxaban for this outcome *(see Table 2)*.

Apixaban was superior (ie less bleeding) to all other comparators except dabigatran for the outcome of clinically relevant non-major bleeding. There was no significant difference between apixaban and dabigatran, or between any other comparators for this outcome *(see Table 2)*.

There were no significant differences between any comparator for the outcome of VTE-related mortality. The combination of fondaparinux + VKA was inferior (higher risk of death) to both the combination of LMWH + VKA and rivaroxaban for the outcome of all-cause mortality.

There were no significant differences between any other comparators for all-cause mortality *(see Table 2)*.

Further results for the initial treatment of DVT, initial treatment of PE, initial treatment of VTE in older adults, initial treatment of VTE in people with obesity and initial treatment of VTE in people with cancer are shown in Annex 2.

Based on the NMA results, the preferred option for first-line anticoagulation is with either of the two DOACs, apixaban or rivaroxaban, due to the lower risk of bleeding complications with these two agents. Using this approach, apixaban has been shown to be superior with respect to major bleeding compared with VKA, edoxaban and dabigatran but not rivaroxaban. By comparison, rivaroxaban has been shown to be superior to VKA only. However, the inclusion criteria for the apixaban and rivaroxaban trials were different and thought likely to favour the former treatment. Apixaban and rivaraoxaban were the most cost-effective options in the NMA economic analysis. As a consequence, both drugs were recommended as first-line options in the NICE guideline.[49]

The SIGN guideline development group also noted that patients with COVID-19 and acute VTE may be unstable and at risk of respiratory or renal failure, or alternatively may be vomiting and unable to take medications via the oral route.

Hospitalisation with COVID-19-related disease may increase medical instability in different ways, including poorer haemodynamic function, increased confusion or reduced level of consciousness or increased requirement for high-flow nasal oxygen, continuous positive airway pressure or intubation. In these scenarios, as in the case of haemodynamically unstable VTE for other reasons, a period of interim anticoagulation with heparin (preferably LMWH) is advisable until the patient's condition stabilises.

The International Society of Thrombosis and Haemostasis (ISTH) suggests that apixaban and rivaroxaban may be used to treat VTE in patients with obesity (body weight >120 kg or BMI >40 kg/m^2) without any adjustment for body weight and without the need for monitoring drug activity levels. The authors note that while "… plasma DOAC levels within published ranges may provide reassurance for the treating clinician, … in view of absent correlating clinical outcome data as to what constitutes therapeutic target values, they are currently insufficient to influence management."[50]

The evidence for these statements derives from phase 4 studies comparing DOACs with VKA. However, It is also suggested not to use dabigatran or edoxaban for treatment of VTE in patients with weight >120 kg or BMI >40 kg/m^2 because there is unconvincing data for dabigatran and a lack of clinical or pharmacokinetic and pharmacodynamic data for edoxaban.[50] **(EVIDENCE LEVEL 4)**

In patients with renal failure, the SPCs for apixaban and rivaroxaban should be followed. If creatinine clearance <15 mL/min, these medications should not be used and the patient should be anticoagulated with off-label dose-adjusted LMWH, or dose-adjusted UFH ± VKA according to local prescribing protocols.

R **Consider apixaban or rivaroxaban using the licensed dosing regimens as first-line anticoagulation for hospitalised patients with confirmed VTE and COVID-19.**

✓ If the patient is medically unstable or unable to take oral medication, use LMWH or UFH until their condition improves.

✓ If the patient is in end stage renal failure (creatinine clearance <15 mL/min), use dose-adjusted LMWH, or dose-adjusted UFH ± vitamin K antagonist.

5.2 Duration of anticoagulation

There is no published evidence to inform the duration of anticoagulation in patients with COVID-19-related disease. The optimal duration of anticoagulation depends on the relative balance of risk of VTE recurrence with risk of bleeding from anticoagulation. No evidence has yet emerged that there is a long-term thrombotic risk from COVID-19 itself and, in the absence of evidence to the contrary, it is assumed that risk of VTE recurrence returns to normal following recovery from the acute phase of the illness.

As COVID-19 probably represents a transient provoking factor for VTE, the period of therapeutic anticoagulation should be 3 months (as for provoked VTE from other causes) unless there are complications or other conditions requiring a shorter or longer duration. In cases of provoked VTE in active cancer, NICE recommends therapeutic anticoagulation for 3 to 6 months.[49] An alternative duration of anticoagulation should only be considered if there are other complications which alter the risk-benefit balance. These could include continued immobility or continued symptoms which raise the suspicion of significant chronic thromboembolic disease, both of which might lengthen the period of anticoagulation. Conversely, acute bleeding might shorten the period of anticoagulation that can be offered. **(EVIDENCE LEVEL 4)**

R **Offer anticoagulation for at least 3 months to hospitalised patients with confirmed VTE.**

✓ All patients should be reviewed at 3 months after discharge at which point the decision about continuation of anticoagulation should take into account:

- ongoing risk factors,
- bleeding risk, and
- patient preference.

✓ To ensure clear communication, the discharge summary should state how long anticoagulation should continue and how the patient's anticoagulation will be reviewed at 3 months after discharge. This should be shared with the patient and primary care team.

Table 2: Initial treatment of all VTE (pooled data of DVT, PE and unspecified VTE)

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Improvements compared to:							
VTE recurrence	UFH + VKA	-	-	UFH + VKA	-	UFH + VKA	UFH + VKA
Major bleeding	-	-	-	UFH + VKA LMWH + VKA Fond + VKA Dabigatran Edoxaban	-	-	UFH + VKA LMWH + VKA Fond + VKA
Clinically relevant non-major bleeding	-	-	-	UFH + VKA LMWH + VKA Fond + VKA Edoxaban Rivaroxaban	-	-	-
All-cause mortality	Fond + VKA	-	-	-	-	-	Fond + VKA
VTE-related mortality	-	-	-	-	-	-	-

Notes: data for VTE recurrence was of a low quality and total n=37,857, data for major bleeding was of moderate quality and total n=35,880, data for clinically relevant non-major bleeding was of low quality and total n=33,489, data for all-cause mortality was of moderate quality and total n=37,359

Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

6 Extended thromboprophylaxis in patients discharged from hospital after recovery from acute COVID-19

In medical patients with significant comorbidities, such as congestive heart failure or chronic obstructive pulmonary disease, the risk of venous thromboembolism while in hospital is increased.[10] There is also a recognition that the risk of VTE does not necessarily return to baseline at the point of discharge from hospital.[2] The role of extended thromboprophylaxis has been studied previously in these patients and although the risk of asymptomatic VTE is reduced overall, there is an increased rate of bleeding.[51] Therefore, extended thromboprophylaxis beyond discharge in medically unwell patients is not routinely recommended.

Attempts to try and define a population at higher thrombotic risk in the general medical population using risk stratification scores (including D-dimer levels and other VTE risk factors) have suggested that cohorts who may benefit from extended thromboprophylaxis could be identified and may benefit. However this has not yet been adopted into routine clinical practice.

With the COVID-19 pandemic, and the associated increases in VTE rates and thrombotic risk, attention has again returned to the possibility of giving patients thromboprophylaxis after discharge. It is increasingly recognised that there is an elevated risk of venous and arterial thrombosis in patients who are hospitalised with COVID-19 disease. However, whether this risk also applies to patients with COVID-19 who are managed in the community and who do not require hospitalisation *(see section 3)*, or indeed are discharged following a period of hospitalisation is unclear.

No systematic reviews or RCTs were identified that addressed the benefits or harms of extended thromboprophylaxis following discharge for patients hospitalised with COVID-19. Limited data exists from observational studies and guidelines based on expert consensus. At least one ongoing RCT considering the efficacy of anticoagulation compared with no intervention after hospital discharge in patients with COVID-19 was identified in international trial registries.

6.1 Benefits and harms of extended thromboprophylaxis in discharged patients

No evidence was identified to suggest that patients with COVID-19-related disease who do not require admission to hospital and who are managed in the community are at increased risk of VTE compared with the general population *(see section 3)*. There is also no evidence that they are at increased risk of VTE compared with those with COVID-19-related disease who are hospitalised. The same applies, in most cases, to those who have been discharged home following a stay in hospital, however there are anecdotal reports of patients recently discharged from hospital following COVID-19-related disease who return to hospital with a VTE. Medical inpatients are at increased risk of VTE for up to 6 weeks following discharge from hospital with the highest risk being in the first 3 weeks.[52] There is, however, no evidence that patients with COVID-19-related disease are at higher risk of VTE following discharge than other medical inpatients.

When first published in July 2020, this guideline included a rapid review of evidence based on expert opinion and identified 24 publications. Of these, two (the American College of Chest Physicians Guideline and Expert Panel (CHEST)[53] and the International Society on Thrombosis and Haemostasis (ISTH)[54]) provide guidance developed through international collaboration (with conflicts of interest recorded). Each provided a description of the methodology including some

form of systematic identification of the evidence, and an indication that a formal consensus method was used to develop the recommendations. Additional guidance based on consensus has been published by the British Thoracic Society (BTS)[55] and Global COVID-19 Thrombosis Collaborative Group.[56] The quality of these publications was not formally assessed. **(EVIDENCE LEVEL 4)**

6.1.1 Global COVID-19 Thrombosis Collaborative Group

The report published by the Global COVID-19 Thrombosis Collaborative Group provided a comprehensive assessment of the evidence at time of publication (June 2020) from which consensus-based guidance was developed using a Delphi method.[56] It notes that based on non-COVID-19 evidence, following hospital discharge from acute medical illness, extended prophylaxis with LMWH or DOACs can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding. The authors suggest that, in the absence of evidence for patients with COVID-19, it is reasonable to employ individualised risk stratification for risk of thrombosis and bleeding, followed by consideration of extended prophylaxis (for up to 45 days) for patients with elevated risk of VTE (eg those with reduced mobility, comorbidities such as active cancer, and, according to some authors in the writing group, elevated D-dimer >2 times the upper limit of normal) who have a low risk of bleeding. **(EVIDENCE LEVEL 4)**

6.1.2 International Society on Thrombosis and Haemostasis

Guidance published by the ISTH was developed collaboratively by a multidisciplinary panel of experts in thrombosis and haemostasis, and based on a narrative review of relevant literature, coupled with responses to a standardised and independently administered survey of preferred practices related to the diagnosis, prevention, and treatment of VTE in patients with COVID-19 using an independent, multi-institutional, and multidisciplinary panel of experts.[54] The survey of experts was done using a single cross-sectional assessment approach where panellists would select a prespecified management option or to indicate, through the “other option” category, that alternative management was preferred. The authors note that this was preferred to a Delphi approach based on the lack of relevant clinical evidence to guide consensus using the Delphi method.

The narrative review reports findings from non-COVID-19 evidence that in selected populations at high VTE risk and low risk of bleeding, extended-duration thromboprophylaxis for approximately 4 weeks with prophylactic-dose LMWH or a DOAC provides a net clinical benefit by reducing VTE risk without incurring a significant increase in the risk of major bleeding. This benefit appears more pronounced in patients whose index hospitalisation was due to infectious disease, particularly pneumonia.

The guidance recommends that either LMWH (30% of respondents chose this management option) or a DOAC (30% of respondents) can be used for extended thromboprophylaxis. Extended thromboprophylaxis should be considered for all hospitalised patients with COVID-19 that meet high VTE risk criteria. The duration of postdischarge thromboprophylaxis can be approximately 14 days at least (50% of respondents), and up to 30 days (20% of respondents). **(EVIDENCE LEVEL 4)**

6.1.3 American College of Chest Physicians Guideline and Expert Panel

Based on studies in non-COVID-19 populations the CHEST Guideline and Expert Panel Report recommended inpatient thromboprophylaxis only on the basis that, “despite evidence suggesting a higher risk of VTE during hospitalisation in patients with COVID-19 than in patients without COVID-19 … postdischarge VTE and major bleeding rates in COVID-19 patients are currently unknown”. They also noted that “extended thromboprophylaxis … should be considered if emerging data … indicate a net benefit of such prophylaxis”.[53] **(EVIDENCE LEVEL 4)**

6.1.4 British Thoracic Society

The guidance on venous thromboembolic disease in patients with COVID-19 published by BTS identified the sources of evidence reported in sections 6.1.1 to 6.1.3, in addition to the original version of this SIGN guideline.[55] The authors note that there are no specific RCTs to guide the optimal duration of thromboprophylaxis in patients recovering from moderate or severe COVID-19. A number of observational studies have reported low incidences of acute VTE following hospital discharge of 0–0.6% which do not appear to be greater than in non-COVID-19 patients. They conclude that the role of extended thromboprophylaxis after discharge is not clear and that patients should be offered enrolment into clinical trials. **(EVIDENCE LEVEL 4)**

In summary, there is no high-quality primary evidence that can support the routine prescription of anticoagulation in patients who have been discharged after hospitalisation with COVID-19. International collaborative guidance based on expert consensus suggests consideration for eligibility based on individualised risk assessment. There are patients that will have ongoing clinical risk factors following discharge that may predispose them to a higher risk of VTE including prolonged immobility, comorbid disease or significant obesity. It is therefore good clinical practice that patients should have a formal assessment made for ongoing VTE prior to discharge. Thereafter, clinical judgement should be employed as to whether patients who have been discharged following a COVID-19 hospitalisation will benefit from ongoing thromboprophylaxis balanced with their risk of bleeding.

✓ All patients discharged from hospital after admission with COVID-19 disease should be assessed for ongoing risk of VTE.

✓ The use of extended thromboprophylaxis should be based on clinical judgement taking into account the balance between the patient's risks for venous thrombosis and bleeding.

6.2 Duration and choice of anticoagulation

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.

COVID-19 may yield unknown long-term effects on lung function and cases of pulmonary cavitation and fibrosis have been seen. It is, therefore, important to be aware of this when choosing the agent for extended anticoagulation.

Concerns about the use of DOACs in patients with COVID-19-related disease extends to their use for extended thromboprophylaxis. Reports have cautioned against their use due to the possibility of an increased DOAC-related bleeding risk when used with experimental antiviral treatments, and the potential for organ dysfunction.[54,57]

Although there is no clinical evidence to support the routine use of extended thromboprophylaxis in patients discharged from hospital following COVID-19-related disease, or clear evidence as to which agent or duration of treatment to use, 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/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 *(see section 6.1)*, the choice of agent and duration of treatment should be decided on a case by case basis after discussion between the patient and the clinician. Options for treatment include a LMWH or DOAC for 14 days following discharge in patients without contraindications, however, choice and duration of extended thromboprophylaxis will depend on clinical judgement.

It is important to note that none of the DOACs licensed for use in the UK have a licence for thromboprophylaxis in medical inpatients. If used, local unlicensed medication policies, including patient consent, should be followed.

7 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing thromboembolism with patients and carers and in guiding the production of locally-produced information materials.

7.1 Checklist for provision of information

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

People with COVID-19 and at risk of VTE in the community setting

- Explain to patients and their relatives/carers that patients with COVID-19 who require care only in the community may be at increased risk of VTE but that level of risk is unknown.
- Explain that there is no evidence that the use of anticoagulation in patients with COVID-19 who are managed in the community will reduce the risk of VTE.
- Explain that some patients with COVID-19 who are cared for in the community may already have risk factors for VTE and the GP may decide to obtain advice from specialists in thrombosis.
- Provide information to patients with COVID-19 who have risk factors for VTE and their family on the signs and symptoms of thrombosis and guidance on seeking medical investigation if they suspect they have developed a DVT or PE.

People hospitalised with COVID-19 and no confirmed VTE

- Explain to hospitalised patients and their relatives/carers that COVID-19 is associated with a high risk of VTE, and in patients with COVID-19, the VTE usually affects the lungs. Explain that the development of VTE while in hospital with COVID-19 could make the patient's condition worse.
- Explain that there is evidence that the use of anticoagulation can significantly reduce the risk of VTE in patients admitted to hospital with serious medical conditions and that this benefit is very likely to apply to patients in hospital with COVID-19.
- Provide written or online information to patients and their family about the benefits and risks of VTE prophylaxis.
- Offer patients the opportunity to be part of clinical research studies.

People hospitalised with COVID-19 and diagnosed VTE

- Explain to patients and their relatives/carers that if a patient develops a VTE while in hospital with COVID-19, they will need to receive anticoagulation to prevent the VTE affecting their health more severely.
- Explain that the anticoagulation that is used is the same that is used in any patient who develops a VTE, whether or not they have COVID-19-related disease.
- Explain that a VTE that develops as a result of COVID-19-related disease will require anticoagulation for a minimum of three months. At this point a decision will be made whether or not it is necessary to continue with anticoagulation and that decision will be discussed with the patient, taking into account their preferences.

People discharged after hospitalisation with COVID-19

- Explain to patients and their relatives/carers that a patient with COVID-19-related disease may remain at increased risk of VTE following discharge but that there is no evidence that routine continuation of anticoagulation after being discharged from hospital with COVID-19-related disease reduces the risk of VTE.
- Explain that in rare circumstances, a patient with COVID-19 may be considered to still be at very high risk of VTE even after they have left hospital. In these cases the medical team who have been caring for the patient may recommend that the anticoagulation continues for a period of time after the patient has left hospital.
- Provide written or online information to patients and their family about the benefits and risks of VTE prophylaxis.
- Provide information on the signs and symptoms of thrombosis and guidance on seeking medical investigation if they suspect they have developed a DVT or PE.

7.2 Sources of further information

NHS Inform - DVT

www.nhsinform.scot/illnesses-and-conditions/blood-and-lymph/deep-vein-thrombosis

NHS inform is Scotland's national health information service providing accurate and relevant information to help people make informed decisions about their own health and the health of the people they care for. It includes information for the public about the causes, treatment and prevention of DVT.

Think Clots

www.thinkclots.scot.nhs.uk

This NHSScotland website provides information about VTE risk.

Thrombosis UK

www.thrombosisuk.org

Thrombosis UK works to increase awareness, support research and extend understanding through education and the sharing of information to improve care for all those affected by thrombosis. The website provides information fact sheets and booklets for patients and a range of resources for healthcare professionals.

8 The evidence base

8.1 Systematic literature review

The evidence base for this guideline was synthesised in accordance with SIGN rapid guideline methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a Health Information Scientist from Healthcare Improvement Scotland. Databases searched include Medline, Embase, MedRxiv and BioRxiv. The date range covered was 1 January 2019 to 09 April 2021. Additional papers were identified by guideline development group members throughout the development period. Papers were selected by a Health Services Researcher from Healthcare Improvement Scotland. Each of the selected papers was evaluated by two Healthcare Improvement Scotland reviewers using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

The search strategies are available on the SIGN website, www.sign.ac.uk

8.2 Recommendations for research

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline *(see Annex 1)*. The following areas for further research have been identified:

- controlled studies investigating the association between VTE risk and clinical outcomes in individuals with VTE risk factors and COVID-19 in community settings
- RCTs of thromboprophylaxis in individuals with VTE risk factors and COVID-19 in community settings
- RCTs comparing the clinical efficacy of intermediate-dose with therapeutic-dose thromboprophylaxis in patients with COVID-19
- RCTs investigating the risks and benefits of anticoagulation options for patients with COVID-19 and diagnosed VTE
- RCTs investigating the benefits or harms of extended thromboprophlaxis following discharge for patients hospitalised with COVID-19.

8.3 Review and updating

This guideline was issued in December 2021 and will be considered for review based on the availability of relevant new evidence. The review history, and any updates to the guideline in the interim period, will be noted in the update report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: sign@sign.ac.uk).

9 Development of the guideline

9.1 Introduction

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals and patient representatives using a standard methodology based on a systematic review of the evidence. This guideline was developed according to version 1.0 of the SIGN rapid guideline methodology which is available at www.sign.ac.uk

9.2 The guideline development group

Professor Tom Evans (Chair)	Professor of Molecular Microbiology, Institute of Infection, Immunity & Inflammation, University of Glasgow and Consultant Infectious Disease Physician, Queen Elizabeth University Hospital, Glasgow
Dr Julia Anderson	Haematology Specialty Advisor to Scottish Government and Consultant Haematologist, Royal Infirmary of Edinburgh
Dr Catherine Bagot	Consultant Haematologist, NHS Greater Glasgow & Clyde
Dr Dan Beckett	Consultant Acute Physician, NHS Forth Valley and Chief Medical Officer Specialty Advisor for Acute Medicine
Dr Colin Church	Consultant in Respiratory and Pulmonary Vascular Medicine, Golden Jubilee National Hospital, Glasgow
Professor Mike Gillies	Consultant in Intensive Care Medicine, Royal Infirmary of Edinburgh
Ms Jo Jerrome	Patient representative, Thrombosis UK
Dr Martin Johnson	Director, Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow and Consultant Respiratory Physician, Queen Elizabeth University Hospital and Gartnavel General Hospitals, Glasgow
Mr Gordon Rushworth	Programme Director, Highland Pharmacy Education & Research Centre, NHS Highland
Mr Alan Timmins	Critical Care Pharmacist and Lead Clinical Pharmacist - Acute, Victoria Hospital, Kirkcaldy
Dr Michelle Watts	Associate Medical Director NHS Tayside and Primary Care Senior Medical Advisor, The Scottish Government

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website www.sign.ac.uk

Juliet Brown	Health Information Scientist, Healthcare Improvement Scotland
Evan Campbell	Health Services Researcher, Healthcare Improvement Scotland
Molly Dobson-Hailey	Project Officer
Karen Graham	Patient and Public Involvement Advisor
Kirsty Littleallan	Project Officer
Charis Miller	Health Information Scientist, Healthcare Improvement Scotland
Moray Nairn	Programme Manager
Gaynor Rattray	Guideline Co-ordinator
Domenico Romano	Publications Designer
Carolyn Sleith	Health Information Scientist, Healthcare Improvement Scotland

9.3 Consultation and peer review

9.3.1 Specialist review

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are included in this report.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Gail Allsopp	Clinical Lead for Clinical Policy, on behalf of the Royal College of General Practitioners
Ms Laura Boyce	Professional Advisor for Midwifery and Perinatal Care, on behalf of The Scottish Government
Ms Anne Byrne	Lay Representative, Middlesex
Ms Sarah Connelly	Intensive Care Clinical Pharmacist, University Hospital Monklands, Airdrie
Dr Tom Craven	Consultant in Intensive Care, Royal Infirmary of Edinburgh
Ms Angela Cunningham	Midwifery Clinical Lead, Maternity and Children Quality Improvement Collaborative, Healthcare Improvement Scotland
Ms Diane Eaton	Lay Representative, Surrey
Mr Harry Hall	Lay Representative, Dumbartonshire
Mr Richard Hull	Honorary Secretary, on behalf of the Royal College of Physicians and Surgeons of Glasgow
Ms Joanna Hutchison	Respiratory Pharmacist, Royal Infirmary of Edinburgh

Dr Mohammed Khan	Consultant Haematologist, Aberdeen Royal Infirmary
Dr Catherine MacLean	Consultant in Acute Medicine, NHS Forth Valley
Mr Gordon McPherson	Lay Representative, Renfewshire
Dr Barbara Miles	Clinical Director of Critical Care, Glasgow Royal Infirmary
Dr Sue Pound	Vice President, on behalf of the Royal College of Physicians of Edinburgh
Ms Alison O'Prey	Intensive Care Clinical Pharmacist, Queen Elizabeth University Hospital, Glasgow
Dr Ryan Rodgers	Consultant Haematologist, Glasgow Royal Infirmary
Dr Jeyakumar Selwyn	Consultant Physician and Lead for VTE, Forth Valley Royal Hospital, Larbert Thrombosis Committee, NHS Greater Glasgow and Clyde
Dr James Tiernan	Consultant Physician in Acute Medicine, Royal Infirmary of Edinburgh
Dr Simon Watson	Medical Director, Healthcare Improvement Scotland
Ms Rosemary Wilkie	Lay Representative, Dumbartonshire
Professor David Wilson	Personal Chair of Paediatric Gastroenterology and Nutrition, Child Life and Health, Centre for Inflammation Research, University of Edinburgh

9.3.2 SIGN editorial group

As a final quality control check, the guideline is reviewed by an editorial group to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. All members made declarations of interest. A register of interests is available on request from the SIGN Executive. The editorial group for this guideline was as follows.

Dr Roberta James	SIGN Programme Lead; Co-Editor
Dr Oliver Koch	Consultant and Honorary Senior Clinical Lecturer in Infectious Diseases, NHS Lothian, Regional Infectious Diseases Unit, Western General Hospital, Edinburgh; Member of the Clinical Cell
Dr Safia Qureshi	Director of Evidence, Healthcare Improvement Scotland
Professor Angela Timoney	Chair of SIGN; Co-Editor

Abbreviations

ACTIV-4a	Accelerating COVID-19 Therapeutic interventions and Vaccines-4 Antithrombotics Inpatient platform trial
APTT	activated partial thromboplastin time
ATTACC	Antithrombotic Therapy to Ameliorate Complications of COVID-19 trial
BMI	body mass index
BTS	British Thoracic Society
CHEST	American College of Chest Physicians Guideline and Expert Panel
CI	confidence interval
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CrI	credible interval
CVD	cardiovascular disease
DOAC	direct oral anticoagulant
DSE	display screen equipment
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
GMC	General Medical Council
GP	general practitioner
HIS	Healthcare Improvement Scotland
HIT	heparin-induced thrombocytopaenia
HR	hazard ratio
ICU	intensive care unit
IMPROVE	International Medical Prevention Registry on Venous Thromboembolism
IRR	incidence rate ratio
ISTH	International Society on Thrombosis and Haemostasis
IV	intravenous
LMWH	low molecular weight heparin
MA	marketing authorisation
mpRCT	multiplatform randomised controlled trial
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
OSFD	organ support free days

PE	pulmonary embolism
PI	prediction interval
RCT	randomised controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia trial
RT-PCR	reverse transcription polymerase chain reaction
SARS	severe adult respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
SPC	summary of product characteristics
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism

Annex 1

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Section	Key question
4.3–4.5	1 Should patients admitted to hospital with COVID-19 and no confirmed VTE receive therapeutic or prophylactic doses of anticoagulation? Population: • Patients admitted to hospital with critical or severe COVID-19 illness (requiring critical care level organ support) and no confirmed VTE • Patients admitted to hospital with moderate COVID-19 illness (no organ support or critical care) and no confirmed VTE Interventions: Prophylactic anticoagulation at therapeutic dose (low molecular weight heparin (LMWH) or unfractionated heparin (UFH)) Comparators: Standard low-dose or enhanced intermediate-dose thromboprophylaxis Outcomes: Inhospital mortality, organ-support free days, major thrombotic events, major bleeding, any adverse events
5.1–5.2	2 What is the appropriate duration, dose and choice of anticoagulant for patients who are hospitalised with COVID-19 and diagnosed with any venous or arterial thrombosis? Population: Patients admitted to hospital with COVID-19 who are diagnosed with venous or arterial thrombosis Interventions: Standard therapeutic dose of: • LMWH • UFH • Vitamin K antagonist • Synthetic pentasacharides • DOAC Duration of treatment: • 3 months • 6 months • 12 months • >12 months Comparators: Each other or no treatment Outcomes: Major thrombotic events, mortality, major bleeding, quality of life, any adverse events

6.1–6.2	3	Is extended thromboprophlaxis following discharge associated with net benefit or harm for patients hospitalised with COVID-19? Population: Patients discharged from hospital following admission for COVID-19 illness (including individuals at high VTE risk and low bleeding risk following risk assessment using validated tool) Interventions: Standard prophylactic dose of LMWH or direct oral anticoagulant (DOAC) Duration of intervention post discharge: • 0–14 days • 15–30 days • >30 days Comparators: Standard care (no thromboprophylaxis outside of hospital) Outcomes: Major thrombotic events, mortality, major bleeding, quality of life, any adverse events
3.2	4	Is thromboprophylaxis in community settings for individuals at risk of VTE who become infected with COVID-19 associated with net benefit or harm? Population: Individuals not receiving oral anticoagulation who are at increased risk of VTE with confirmed or clinically suspected COVID-19 illness. Risk factors may include (but are not limited to): • age >60 years • BMI >30 kg/m^2 • thrombophilias • a personal or family history of VTE • active cancer treatment • HRT use • use of oestrogen-containing contraception • significantly reduced mobility for 3 days or more • within 12 weeks of major surgery Interventions: Standard prophylactic dose of LMWH or DOAC Comparators: No prophylaxis Outcomes: Major thrombotic events, mortality, major bleeding, quality of life, any adverse events

Annex 2

The following tables which describe results of the initial treatment of VTE in subgroups are extracted from NICE guideline 158 - Venous thromboembolic diseases: diagnosis, management and thrombophilia testing.[49]

Table 3: Initial treatment of DVT

Table 4: Initial treatment of PE

Table 5: Initial treatment of VTE in older adults

Table 6: Initial treatment of VTE in people with obesity

Table 7: Initial treatment of VTE in people with cancer

Table 3: Initial treatment of DVT

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Improvements compared to:							
VTE recurrence	UFH + VKA	-	-	UFH + VKA	-	-	UFH + VKA
Major bleeding	UFH + VKA	-	-	UFH + VKA LMWH + VKA	-	-	UFH + VKA
Clinically relevant non-major bleeding	-	-	-	-	-	-	-
All-cause mortality	UFH + VKA	-	-	Not available	Not available	Not available	UFH + VKA Fond + VKA

Notes: data for VTE recurrence was of a moderate quality and total n=19,107, data for major bleeding was of a moderate quality and total n=11,862, data for, data for all-cause mortality was of a moderate quality and total n=8,492

Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

Table 4: Initial treatment of PE

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Improvements compared to:							
VTE recurrence	-	-	-	-	-	-	-
Major bleeding	-	-	-	UFH + VKA Rivaroxaban LMWH+VKA Fond + VKA	Not available	Not available	UFH + VKA LMWH+VKA Fond + VKA

Notes: data for major bleeding was of a low quality and total n=12,821

Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

Table 5: Initial treatment of VTE in older adults

Outcome	LMWH + VKA	Apixaban	Dabigatran	Rivaroxaban
Improvements compared to:				
VTE recurrence	-	-		-

Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

Table 6: Initial treatment of VTE in people with obesity

Outcome	LMWH + VKA	Apixaban	Dabigatran	Rivaroxaban
Improvements compared to:				
VTE recurrence	-	-		-

Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

Table 7: Initial treatment of VTE in people with cancer

Outcome	LMWH + VKA	LMWH (alone)	Rivaroxaban	Edoxaban	Dabigatran	UFH + VKA	Apixaban
Improvements compared to:							
VTE recurrence	-	LMWH+VKA	LMWH+VKA	LMWH+VKA	-	-	-
Major bleeding	-	Edoxaban	-	-	-	-	-
Clinically relevant non-major bleeding	-	LMWH+VKA Rivaroxaban Edoxaban Dabigatran	-	-	-	LMWH+VKA Rivaroxaban Dabigatran	-
All-cause mortality	-	-	-	-	-	-	-

Notes: data for VTE recurrence was of a moderate quality and total n=4,197, data for major bleeding was of a very low quality and total n=4,291, data for clinically relevant non-major bleeding was of a low quality and total n=3,385.

Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

References

1 Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine 2020;29:100639.

2 Ho FK, Man KKC, Toshner M, Church C, Celis-Morales C, Wong ICK, et al. Thromboembolic Risk in Hospitalized and Nonhospitalized COVID-19 Patients: A Self-Controlled Case Series Analysis of a Nationwide Cohort. Mayo Clin Proc 2021;96(10):2587-97.

3 Boonyawat K, Chantrathammachart P, Numthavaj P, Nanthatanti N, Phusanti S, Phuphuakrat A, et al. Incidence of thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Thromb J 2020;18(1):34.

4 Bristogiannis S, Swan D, Thachil J. Thromboprophylaxis in COVID-19 - Rationale and considerations. Adv Biol Regul 2021;81:100819.

5 Bunce PE, High SM, Nadjafi M, Stanley K, Liles WC, Christian MD. Pandemic H1N1 influenza infection and vascular thrombosis. Clin Infect Dis 2011;52(2):e14-7.

6 Chen YG, Lin TY, Huang WY, Lin CL, Dai MS, Kao CH. Association between pneumococcal pneumonia and venous thromboembolism in hospitalized patients: A nationwide population-based study. Respirology 2015;20(5):799-804.

7 Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol 2008;143(2):180-90.

8 Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020;383(2):120-8.

9 Hanff TC, Mohareb AM, Giri J, Cohen JB, Chirinos JA. Thrombosis in COVID-19. Am J Hematol 2020;95(12):1578-89.

10 Scottish Intercollegiate Guidelines Network (SIGN). Prevention and management of venous thromboembolism. Edinburgh: SIGN; 2014. (SIGN Publication no. 122). [cited 16 Aug 2021]. Available from url: https://www.sign.ac.uk/our-guidelines/prevention-and-management-of-venous-thromboembolism/

11 Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Royal College of Paediatrics and Child Health, Public Health England and Public Health Scotland. Coronavirus (COVID-19) Infection in Pregnancy. Version 14 (25 August 2021). RCOG. [cited 18 Oct 2021]. Available from url: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/

12 Scottish Intercollegiate Guidelines Network (SIGN). COVID-19 position statement: Maternal critical care provision. Version 2.0 (25 Nov 2020). 2021. [cited 18 Oct 2021]. Available from url: https://www.sign.ac.uk/media/1787/sg-maternal-critical-care-provision_v33.pdf

13 The Scottish Government. COVID-19 Clinical Advice: Maternity care (4 Feb 2021). [cited 18 Oct 2021]. Available from url: https://www.sign.ac.uk/media/1821/nesd1442-sg-clinical-advice-obstetrics_v11.pdf

14 British Society for Haematology. Guidance from the Expert Haematology Panel on COVID-19 Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT). Version 2.2. 31 August 2021. [cited 11 Oct 2021]. Available from url: https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt/

15 National Institute of Health and Care Excellence. COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT). NICE guideline [NG200]; 2021. [cited 18 Oct 2021]. Available from url: https://www.nice.org.uk/guidance/ng200

16 NHS Inform. Coronavirus (COVID-19): General advice. [cited 22 Oct 2021]. Available from url: https://www.nhsinform.scot/illnesses-and-conditions/infections-and-poisoning/coronavirus-covid-19/coronavirus-covid-19-general-advice

17 Joint Formulary Committee. British National Formulary (online) London BMJ Group and Pharmaceutical Press. [cited 23 Jul 2021]. Available from url: https://about.medicinescomplete.com/publication/british-national-formulary/

18 General Medical Council (GMC). Good practice in prescribing and managing medicines and devices. London: General Medical Council; 2013. [cited 23 Jul 2021]. Available from url: http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf

19 Medicines and Healthcare products Regulatory Agency. Off label use or unlicensed medicines: prescribers' responsibilities. Drug Safety Update 2009;2(9):6.

20 Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. BMJ 2011;343:d4656.

21 Health and Safety Executive. The health and safety toolbox: How to control risks at work / Your workers / Homeworkers. [cited July 21]. Available from url: https://www.hse.gov.uk/toolbox/workers/home.htm

22 UK Government. Physical activity guidelines: UK Chief Medical Officers' report. 2019. [cited 21 July 2021]. Available from url: https://www.gov.uk/government/publications/physical-activity-guidelines-uk-chief-medical-officers-report

23 Hotoleanu C. Association between obesity and venous thromboembolism. Med Pharm Rep 2020;93(2):162-8.

24 Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020;324(8):799-801.

25 Hill JB, Garcia D, Crowther M, Savage B, Peress S, Chang K, et al. Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. Blood Adv 2020;4(21):5373-7.

26 Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7.

27 Moll M, Zon RL, Sylvester KW, Chen EC, Cheng V, Connell NT, et al. VTE in ICU Patients With COVID-19. Chest 2020;158(5):2130-5.

28 Jimenez D, Garcia-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest 2021;159:1182-96.

29 Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: Systematic review and meta-analysis. Thromb Res 2020;196:67-74.

30 Zhang R, Ni L, Di X, Wang X, Ma B, Niu S, et al. Systematic review and meta-analysis of the prevalence of venous thromboembolic events in novel coronavirus disease-2019 patients. J Vasc Surg Venous Lymphat Disord 2021;9(2):289-98 e5.

31 Mansory EM, Srigunapalan S, Lazo-Langner A. Venous Thromboembolism in Hospitalized Critical and Noncritical COVID-19 Patients: A Systematic Review and Meta-analysis. TH Open 2021;5(3):e286-e94.

32 Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332(7537):325-9.

33 Turpie AG. Thrombosis prophylaxis in the acutely ill medical patient: insights from the prophylaxis in MEDical patients with ENOXaparin (MEDENOX) trial. Am J Cardiol 2000;86(12B):48-52.

34 World Health Organization. COVID-19 Clinical management: living guidance. WHO; 2021. (WHO/2019-nCoV/clinical/2021.1). [cited 20 July 2021]. Available from url: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1

35 COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health; 2021. [cited 20 July 2021]. Available from url: https://www.covid19treatmentguidelines.nih.gov/

36 Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med 2021.

37 Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet 2021;397(10291):2253-63.

38 Lemos ACB, do Espirito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thrombosis Research 2020;196:359-66.

39 Flumignan RLG, Tinoco JDDSa, Pascoal PIF, Areias LL, Cossi MS, Fernandes MICD, et al. Prophylactic anticoagulants for people hospitalised with COVID-19. Cochrane Database of Systematic Reviews 2020;2020.

40 Wijaya I, Andhika R, Huang I. The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review. Clinical and Applied Thrombosis/Hemostasis 2020;26.

41 RECOVERY Collaborative Group, Horby P, Pessoa-Amorim G, Staplin N, Emberson JR, Campbell M, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. 2021. Available from url: https://www.medrxiv.org/content/10.1101/2021.06.08.21258132v1

42 Nutescu EA, Spinier SA, Wittkowsky A, Dager WE. Anticoagulation: Low-Molecular-Weight Heparins in Renal Impairment and Obesity: Available Evidence and Clinical Practice Recommendations Across Medical and Surgical Settings. Annals of Pharmacotherapy 2009;43(6):1064-83.

43 Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med 2021.

44 Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ 2021;375:n2400.

45 Albuquerque A, Santolia C, Brophy J. BMJ Rapid Reposnse "There is high probability of clinically important benefit in the primary composite outcome" (Published online 16 Oct 2021). [cited 19 Nov 2021]. Available from url: https://www.bmj.com/content/375/bmj.n2400/rr

46 Ramirez P. BMJ Rapid Response "Differentiating between effects on composite outcome and death of therapeutic heparin in COVID-19 patients." Published online 6 November 2021. [cited 19 Nov 2021]. Available from url: https://www.bmj.com/content/375/bmj.n2400/rr-0

47 Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA 2021;325(16):1620-30.

48 McBane RD, 2nd, Torres Roldan VD, Niven AS, Pruthi RK, Franco PM, Linderbaum JA, et al. Anticoagulation in COVID-19: A Systematic Review, Meta-analysis, and Rapid Guidance From Mayo Clinic. Mayo Clin Proc 2020;95(11):2467-86.

49 National Institute of Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Evidence reviews for pharmacological treatment in people with suspected or confirmed deep vein thrombosis and/or pulmonary embolism. 2020. [cited 28 April 2021]. Available from url: https://www.nice.org.uk/guidance/ng158/evidence

50 Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost 2021.

51 Zayed Y, Kheiri B, Barbarawi M, Banifadel M, Abdalla A, Chahine A, et al. Extended duration of thromboprophylaxis for medically ill patients: a systematic review and meta-analysis of randomised controlled trials. Intern Med J 2020;50(2):192-9.

52 MacDougall K, Spyropoulos AC. New Paradigms of Extended Thromboprophylaxis in Medically Ill Patients. J Clin Med 2020;9(4).

53 Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. Chest 2020;158(3):1143-63.

54 Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18(8):1859-65.

55 British Thoracic Society. BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19 Updated 31 August 2021. [cited Available from url: https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-guidance-on-venous-thromboembolic-disease-in-patients-with-covid-19/

56 Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75(23):2950-73.

57 Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. Thromb Haemost 2020;120(6):937-48.

978-1-909103-88-7

SIGN 163

Healthcare Improvement Scotland

Edinburgh Office
Gyle Square
1 South Gyle Crescent
Edinburgh
EH12 9EB
0131 623 4300

Glasgow Office
Delta House
50 West Nile Street
Glasgow
G1 2NP
0141 225 6999