Rapid Evidence Review

Clinical evidence for thromboprophylaxis in the management of COVID-19

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National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

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The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Note: *Much of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or "preprints". These are preliminary reports which have not been subjected to peer-review – the conventional model for judging the quality of research. In the interests of speed and open access, the international scientific community has recognised the advantage of preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is also a greater potential for dissemination of low-quality research. The ERG critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.*

Summary

Infection with COVID-19 is associated with the development of a procoagulant state that can lead to increased risk of thromboembolic events (TEs). Factors contributing to this risk are multifactorial including the SARs-CoV-2 infection itself and its pathology, and hospital-related factors including immobilisation, respiratory failure, mechanical ventilation and central venous catheter use. The evidence suggests that while there may be an underlying risk of TEs in all patients infected with SARs-CoV-2, the risk in hospitalised patients increases if the disease progresses from moderate to severe stages of the condition, when hyperinflammation may be a key clinical feature.

Several international guidelines recommend thromboprophylaxis for hospitalised patients admitted with COVID-19. There is accruing evidence available from randomised controlled trials on the appropriate anticoagulation strategy for patients with COVID-19. In the HEP-COVID trial, for patients with very high D-dimer levels, therapeutic anticoagulation reduced the incidence of the primary outcome (a composite of venous thromboembolism, arterial thromboembolism, and death) compared to prophylactic anticoagulation, and the benefit was more pronounced in a non-ICU population. These data were not supported by the results of the RAPID trial which included a number of patients in Ireland. No differences in the primary outcome of this trial, a composite of ICU admission, non-invasive or invasive mechanical ventilation or death up to 28 days, was shown for therapeutic anticoagulation over prophylactic anticoagulation. However, a potential benefit of the therapeutic regimen was noted with respect to all-cause mortality, although the events were limited to four in the follow-up period. The multiplatform randomised controlled trial involving collaboration between three international, adaptive clinical trials i.e. REMAP-CAP, ACTIV-4 and ATTACC was designed to assess the impact of full dose (therapeutic) anticoagulation, or prophylactic/intermediate dose anticoagulation in moderately ill or severely ill adults hospitalised for COVID-19. It also recruited participants in Ireland. The results indicate that in severely ill/critically ill COVID-19 patients requiring intensive care unit (ICU) support, therapeutic anticoagulation did not result in an improvement in the primary outcome of organ-support free days. Recruitment into this arm of the trial was discontinued following interim analysis review by the DSMB. In the moderately ill (non-critically ill) cohort, therapeutic doses of anticoagulants were associated with potential benefit. Further evidence around an appropriate anticoagulation regimen in critically ill patients were obtained from three trials. Two trials (Perepu et al, INSPIRATION trial) reported no benefit with intermediate dose (not therapeutic dose) anticoagulation regimens over prophylactic dose regimens. A benefit was demonstrated in the HESACOVID trial where therapeutic anticoagulation was included, although the primary outcome investigated was limited to a demonstration of variation in gas exchange. The ACTION trial was conducted in a non-critically ill cohort of patients and no difference with therapeutic anticoagulation for the primary outcome was observed.

A recent systematic review and meta-analysis of randomised controlled trials reported on the overall benefit of an escalated dose anticoagulation regimen as compared with a standard dose. Of note, the escalated dose included pooled data for both therapeutic dosage and intermediate doses of anticoagulants. Results were reported for the overall population of patients and according to clinical status i.e. critically ill vs non-critically ill. The primary efficacy end-point of the analysis was all-cause

mortality, and the primary safety end-point was major bleeding. In data extracted from the seven randomised controlled trials identified (all included in this rapid review), escalated-dose prophylactic anticoagulation was not associated with a reduction in all-cause death in the full population or when stratified according to clinical status, but was associated with an increase in major bleeding. The efficacy outcome analysed in this meta-analysis, all-cause death, was the primary outcome of one of the included trials. In all others, it was a component of composite outcome measures.

A systematic review and meta-analysis of observational studies supports the benefit of anticoagulation in hospitalised patients with COVID-19 infection compared to no anticoagulation. Many of the included studies are associated with limitations due to their retrospective design, and methodological challenges in relation to bias.

Conclusion

The evidence indicates that there is a risk of thromboembolic events in hospitalised COVID-19 patients and current consensus is that prophylactic anticoagulation is warranted in admitted patients with COVID-19 without an underlying bleeding risk. While one study suggested that treatment doses are of benefit in moderately ill patients, another evidence synthesis of multiple studies suggests the benefit is minimal and may be associated with an increase in bleeding risk.

Introduction

Infection with COVID-19 is associated with the development of a procoagulant state that can lead to increased risk of thromboembolic events. Increases in fibrin, fibrin degradation products, fibrinogen and D-dimers may indicate pro-thrombotic manifestations(McBane et al., 2020). The reported incidence and prevalence of thromboembolic events (TEs) among hospitalised patients varies depending on the setting (ICU vs non-ICU), and whether active screening is undertaken. In a meta-analysis of hospitalised patients, an overall venous thromboembolism (VTE) prevalence of 14.1% (95%CI, 11.6-16.9) was found, but was higher in studies where screening with ultrasound was performed(Nopp et al., 2020). A rate of 34% of thrombotic complications was reported in a systematic review of ICU patients(Jenner et al., 2021), and McBane *et al* reported a rate of between 2% and 69% of VTE in a pooled analysis of predominantly ICU patients(McBane et al., 2020). In addition to the pro-coagulant features of COVID-19, there are the usual additional baseline risks associated with hospitalisation. These include prolonged immobilisation, dehydration, an acute inflammatory state, presence of other cardiovascular risk factors, cardiovascular disease or conditions such as cancer, previous history of VTE and certain rare genetic and acquired conditions. The risks increase in the presence of pneumonia and escalate even further in patients who develop sepsis, which are also features of severe COVID-19. However, the venous thromboembolism event rates in COVID-19 are considerably higher than those previously reported in acutely ill surgical and non-surgical patients admitted to the ICU, and at least three times higher than in critically and non-critically ill patients admitted to hospital with other viral respiratory infections(Leentjens et al., 2021).

Anticoagulation strategies in COVID-19 infection

Evidence that COVID-19 infection is associated with a procoagulant state and the development of TEs prompted a focus on the role of anticoagulation in the prevention of potential thromboembolic events in this patient cohort. During the first wave of the pandemic the optimum dosing regimen of anticoagulant therapy was based on extrapolation from similar at-risk groups in the hospitalised setting. To address the gap in knowledge around optimum dosing schedules i.e. standard prophylactic dosing vs escalated prophylactic dosing vs therapeutic dosing, a number of clinical trials were initiated. In addition, several observational studies have reported their findings following mainly retrospective analyses, a number of which have been included in evidence synthesis publications. The key question involves the most appropriate dose selection for specific hospitalised COVID-19 phenotypes (i.e. moderately ill, acutely ill, critically ill etc.) and balancing the potential benefits in the prevention of TEs with the potential increased risk of bleeding events.

Evidence from randomised controlled clinical trials

1. **Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high risk hospitalised patients with COVID-19 - HEP-COVID RCT**(Spyropoulos et al., 2021)

This randomised controlled clinical trial (RCT) was designed to evaluate the effects of two anticoagulant strategies in high-risk hospitalised patients with COVID-19 i.e. therapeutic-dose low molecular weight heparin (LMWH) vs institutional standard prophylaxis or intermediate-dose LMWH. High risk was defined as patients with D-dimer levels > 4 times the upper limit (ULN) or a sepsis-induced coagulopathy score of

4 or greater. The study setting was 12 centres in the US and patients were recruited over a year long period from May 8th 2020 to May 14th 2021. Patients randomised to the therapeutic dose arm were administered enoxaparin at a dose of 1mg/kg twice daily if CrCl was ≥ 30/mls/min or 0.5mg/kg if CrCl was 15-29mls/min. Patients in the standard-dose group received either prophylactic or intermediate dose heparin regimens as per local institutional standard. The primary outcome was a composite of VTE or arterial thrombotic event (ATE) or death from any cause within 30 ± 2 days from randomisation. Secondary outcomes included the composite primary outcome within 14 days after admission, progression to acute respiratory distress syndrome, new-onset atrial fibrillation, acute kidney injury, nonfatal cardiac arrest, endotracheal intubation, extracorporeal membrane oxygenation, and rehospitalisation within 30 ± 2 days. The principal safety outcome was major bleeding based on the International Society on Thrombosis and Haemostasis criteria within 30 ± 2 days after randomisation.

A total of 257 patients (of 11,649 screened) were randomised, and 253 patients were included in the modified intention-to-treat analysis, n=129 in the therapeutic arm and n=124 in the standard dose arm. Baseline characteristics were similar in both groups. The mean D-dimer level was 3,183 ng/mL in the standard-dose group and 3,837 ng/mL in the therapeutic dose group. Similarly, the mean sepsis-induced coagulopathy score was 2.31 and 2.35 in the standard-dose group and therapeutic dose groups respectively.

The incidence of the primary efficacy outcome was 41.9% (28.2% VTE, 3.2% ATE, 25.0% death) in the standard dose group vs 28.7% (11.7% VTE, 3.2% ATE, 19.4% death) in the therapeutic-dose group (Relative Risk (RR), 0.68; 95% CI, 0.49-0.96; p=0.03), driven by a reduction in thromboembolism (29.0% vs 10.9%; RR 0.37; 95%CI, 0.21-0.66; p<0.001). The majority of thromboembolic events consisted of symptomatic deep vein thrombosis and nonfatal pulmonary embolism. There was no significant difference in death between groups (25.0% vs 19.4%; RR,0.78; 95%CI,0.49-1.23; p=0.28). There were 8 major bleed events (3.2%), 2 (1.6%) in the standard-dose vs 6 (4.7%) in the therapeutic dose groups (RR, 2.88; 95% CI, 0.59-14.02; p=0.17). No major bleed events were fatal.

When the arms were stratified according to ICU vs non-ICU status, compared with standard-dose heparins, therapeutic dose LMWH reduced the incidence of the primary efficacy outcome among patients in the non-ICU stratum (36.1% vs 16.7%; RR, 0.46; 95%CI, 0.27-0.81; p=0.004), but not in the ICU stratum (55.3% vs 51.1%; RR,0.92; 95%CI,0.62-1.39; p=0.71). There was no significant difference in major bleeding between groups in either stratum, although there were numerically more major bleeds among patients in the ICU stratum in the therapeutic dose compared with the standard-dose group (4 [8.9%] vs 0; RR, 7.62; 95% CI, 0.42-137.03; p=0.12).

2. 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 RCT.(Sholzberg et al., 2021)

The aim of this adaptive, open-label RCT was to evaluate the effects of therapeutic heparin compared with prophylactic heparin among moderately ill patients with COVID-19 admitted to hospital. Moderately

ill patients were defined as patients who were admitted to hospital (not ICU) for COVID-19 infection and had increased D-dimer levels within the first 5 days of admission, were not mechanically ventilated and not imminently requiring mechanical ventilation or critical care. D-dimer levels were required to be above the ULN of the local hospital in the presence of an O_2 saturation of $\leq$93% on room air, or $\geq$ 2 times the ULN of normal, irrespective of oxygen saturation. Patients allocated to therapeutic heparin received therapeutic doses of LMWH or unfractionated heparin (UFH) as routinely used in the treatment of VTE. Patients allocated to the prophylactic arm received dose capped prophylactic subcutaneous heparin adjusted for body mass index and CrCl. The primary outcome was a composite of ICU admission, non-invasive or invasive mechanical ventilation, or death up to 28 days. Several secondary outcomes were also investigated. Between May 29th 2020 and April 12th 2021, a total of 3,975 patient were screened and 465 were included in the study with 228 patients randomly assigned to therapeutic heparin and 237 to prophylactic heparin.

The baseline characteristics of the patients in both arms were well balanced in terms of demographics, co-morbidities, concomitant medications and D-dimer levels. The primary outcome occurred in 37 patients (16.2%) in the therapeutic heparin arm and 52 (21.9%) in prophylactic group (Odds Ratio (OR) 0.69; 95%CI 0.43-1.1; p=0.12). This result indicates that in moderately ill patients with COVID-19 and increased D-dimer levels admitted to hospital, therapeutic heparin was not associated with a significantly lower incidence of the primary composite of death, mechanical ventilation, or ICU admission compared with prophylactic heparin.

An early efficacy signal for the secondary outcome of death was reported. Death from any cause occurred in four patients (1.8%) in the therapeutic heparin group and 18 (7.6%) in the prophylactic heparin group (0.22, 0.07 to 0.65; P=0.006). These data indicate that the odds of all cause death in the group allocated to therapeutic heparin was significantly reduced, by 78% although interpretation of this benefit may be associated with uncertainty and results of larger trials are required. No fatal thromboembolic events occurred. Major bleeding events occurred in two patients (0.9%) in the therapeutic heparin group and four (1.7%) in the prophylactic heparin group (odds ratio 0.52, 95% confidence interval 0.09 to 2.85; P=0.69,). No fatal bleeding events or cases of intracranial haemorrhage occurred.

3. Multiplatform randomised controlled trial (mpRCT) – REMAP-CAP; ACTIV-4; ATTACC (peer reviewed)

A multi-platform randomised controlled trial (mpRCT) involving a collaboration between three independent, international clinical trials (the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial, the Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 (ACTIV-4) trial and the Antithrombotics Inpatient and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) trial), was initiated to investigate the hypothesis that in hospitalised patients with confirmed COVID-19, the benefits and risks of therapeutic-dose anticoagulation would vary according to disease severity. The trials had harmonised protocols and common primary, secondary and safety outcomes, and common combined prospective superiority and futility rules. The mpRCT was a randomised, open-label, adaptive Bayesian trial, that enrolled hospitalised patients with COVID-19 who were randomised within

72 hours of admission to the intervention arm (48 hours in REMAP-CAP for severe state (intensive care unit (ICU) patients) or the control arm. Those randomised to the intervention arm received therapeutic LMWH or UFH, where therapeutic dose was defined as per hospital policy for treatment of venous thrombotic events. Patients in the control arm received usual care pharmacological VTE prophylaxis, which included standard and intermediate dose thromboprophylaxis. Duration of therapy was 14 days or hospital discharge (or liberation from supplemental oxygen (ATTACC)), whichever occurred first. The primary outcome was organ support-free days (OSFDs), to day 21. This was defined as a combination of an ordinal scale of in-hospital mortality and OSFDs and a composite measuring clinically relevant morbidity and mortality. Participants who were discharged from hospital prior to 21 days were assumed to be alive and free of organ support through 21 days. The key secondary outcomes were safety (major haemorrhage and heparin-induced thrombocytopenia (HIT)), and efficacy (mortality, intubation, major thrombosis, PE, VTE, stroke, MI, length of stay (LoS) in ICU and hospital. *A priori* the mpRCT main analysis population was stratified into two cohorts i.e. a) severe state/critically ill patients (receiving organ support/ICU level care) and b) moderate state/noncritically ill patients (hospitalised but not initially requiring ICU therapies/level of care).

Critically ill cohort

The peer-reviewed publication for the critically ill cohort was published in August 2021(The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, 2021). Severe COVID-19 was defined as COVID-19 that led to receipt of ICU-level respiratory or cardiovascular organ support (high flow nasal oxygen ≥ 20 L/min, non-invasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes). Patients were ineligible if they were admitted to the ICU with COVID-19 for more than 48 hours (in REMAP-CAP) or longer (in ACTIV-4a and ATTACC) prior to randomisation, at imminent risk of death without an ongoing commitment to full organ support, at high risk of bleeding, receiving dual antiplatelet therapy, had a separate clinical indication for therapeutic anticoagulation, or had a history of heparin sensitivity including heparin-induced thrombocytopenia.

Enrolment commenced on November 20th, 2020 and was discontinued for this critically ill cohort on December 19th, 2020. The primary analysis is based on 1,098 patients of whom 536 received therapeutic-dose anticoagulation and 567 patients received usual-care thromboprophylaxis. The majority of patients in this cohort were enrolled via the REMAP-CAP study (84%). Among patients assigned to receive therapeutic anticoagulation, the median value for OSFDs was 1 (interquartile (IQR) range -1 to 16), while among the patients assigned to usual-care pharmacologic thromboprophylaxis, the median value was 4 (IQR, -1 to 16). The median adjusted proportional odds (apOR) for the effect of therapeutic-dose anticoagulation on OSFDs was 0.83 (95% credible interval (CrI), 0.67 to 1.03), yielding a posterior probability of futility of 99.9% and a posterior probability of inferiority of 95.0%. A total of 335 of 534 patients (62.7%) assigned to receive therapeutic-dose anticoagulation and 364 of 564 patients (64.5%) assigned to receive usual-care thromboprophylaxis survived to hospital discharge. The median apOR for survival to hospital discharge was 0.84 (95% CrI, 0.64 - 1.11; posterior probability of inferiority, 89.2%). The median adjusted absolute difference in the percentage of patients who survived to hospital discharge (therapeutic dose anticoagulation minus usual-care thromboprophylaxis) was –4.1 percentage points

(95% CrI –10.7 - 2.4). While major thrombotic events occurred in 6.4% and 10.4% in the therapeutic and standard LMWH groups respectively, the incidence of the secondary efficacy outcome of major thrombotic events or death was similar in both groups (40.1% and 41.1%, respectively). The findings from this study demonstrated that an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual care pharmacological thromboprophylaxis. Accordingly, recruitment into this arm was halted across the mpRCT (The REMAP-CAP et al., 2021).

Non-critically ill cohort

The peer-reviewed publication for the non-critically ill cohort was also published in August 2021(The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, 2021). Moderate disease severity (non-critically ill) was defined as hospitalisation for COVID-19 without the need for ICU-level care as previously described. This cohort were further stratified according to their baseline D-dimer levels (a high D-dimer (baseline $\geq$2 x local upper limit of normal (ULN), a low D-dimer level (baseline D-dimer$<$2x ULN) and an unknown (baseline D-dimer unknown). Patients were ineligible for enrolment in the ATTACC and ACTIV-4a platforms if 72 hours had elapsed since hospital admission for COVID-19 or since in-hospital confirmation of the presence of SARS-CoV-2; in the REMAP-CAP platform, patients were ineligible if 14 days had elapsed since admission. Patients were also excluded if hospital discharge was expected within 72 hours or if they had a clinical indication for therapeutic anticoagulation, a high risk of bleeding, receipt of dual antiplatelet therapy, or a known heparin allergy, including HIT. The primary outcome for the trial was the same as the critically ill arm. Enrolment commenced on April 21st, 2020 and was discontinued on January 22nd 2021 on the advice of the data and safety monitoring boards.

A total of 2219 patients were included in the primary analysis of whom 1181 received therapeutic-dose anticoagulation and 1048, usual-care thromboprophylaxis. The posterior probability that therapeutic-dose anticoagulation increased OFSDs as compared with usual-care thromboprophylaxis was 98.6% (median aOR, 1.27; 95% CrI, 1.03 to 1.58). Of the 1048 patients in the usual-care thromboprophylaxis group, 801 (76.4%) survived until hospital discharge without receipt of organ support during the first 21 days, as compared with 939 of 1171 patients (80.2%) in the therapeutic-dose anticoagulation group. The median adjusted absolute difference in this value was 4.0 percentage points (95% CrI, 0.5 to 7.2), favouring the therapeutic dose anticoagulation group. In the primary adaptive analysis groups, the final posterior probability for superiority of therapeutic-dose anticoagulation as compared with usual-care thromboprophylaxis was 97.3% in the high D-dimer cohort, 92.9% in the low D-dimer cohort, and 97.3% in the cohort with an unknown D-dimer level. Among all the patients with non-critical disease, the treatment effect did not vary meaningfully according to age, level of respiratory support at enrolment, or dose of thromboprophylactic drugs (72% received low dose and 27% received intermediate dose).

In terms of secondary outcomes, in the overall cohort of patients with moderate disease, the posterior probability that therapeutic-dose anticoagulation increased survival until hospital discharge as compared with thromboprophylaxis was 87.1% (median aOR, 1.21; 95% CrI, 0.87 - 1.68), for a median adjusted

between-group difference of 1.3 percentage points (95% CrI, −1.1 - 3.2). The posterior probabilities that patients in the therapeutic-dose anticoagulation group were more likely to survive without organ support or survive without invasive mechanical ventilation at 28 days were 99.1% and 92.2%, respectively. In summary, in non-critically ill patients with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared to usual-care thromboprophylaxis.

4. 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 (Lopes et al Lancet June 2021)(Lopes et al., 2021)

This open-label multicentre, randomised controlled trial was conducted in 31 centres in Brazil. The aim of the study was to compare the efficacy and safety of therapeutic versus prophylactic anticoagulation in a population of patients admitted with COVID-19 infection. Patients were required to be aged ≥18 years, be hospitalised with COVID-19, have elevated D-dimer concentration, and have had COVID-19 symptoms for up to 14 days prior to randomisation. Patients were randomly assigned (1:1) to receive either therapeutic or prophylactic anticoagulation. Therapeutic anticoagulation was in-hospital oral rivaroxaban (20 mg or 15 mg daily) for stable patients, or initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0.3–0.7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30. Prophylactic anticoagulation was standard in-hospital enoxaparin or unfractionated heparin. The primary efficacy outcome was a hierarchical analysis of time to death, duration of hospitalisation, or duration of supplemental oxygen to day 30, analysed with the win ratio method (where a ratio >1 reflected a better outcome in the therapeutic anticoagulation group) in the intention-to-treat population. The primary safety outcome was major or clinically relevant non-major bleeding through 30 days.

Between June 24, 2020, and Feb 26, 2021, 615 patients were randomly allocated to the therapeutic anticoagulation group (n=311) and the prophylactic anticoagulation group (n=304). Of these, 576 (94%) were clinically stable and 39 (6%) clinically unstable. The primary efficacy outcome was not different between patients assigned therapeutic or prophylactic anticoagulation, with 28,899 (34.8%) wins in the therapeutic group and 34,288 (41.3%) in the prophylactic group (win ratio 0.86 [95% CI 0.59 - 1.22], p=0.40). Consistent results were seen in clinically stable and clinically unstable patients. The study concluded that in patients hospitalised with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation. The study authors concluded that the use of therapeutic-dose rivaroxaban, and other direct oral anticoagulants, should be avoided in these patients in the absence of an evidence-based indication for oral anticoagulation. The study findings are limited by the broad stratification of study participants as those hospitalised with COVID-19 and elevated D-dimer levels, and hence the results cannot be directly compared to the moderately ill cohort from the multiplatform trial, which had a stricter stratification criteria of critically and noncritically ill patients.

5. **Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19 – a multicentre, open-label randomised controlled trial (Perepu et al May 2021)**(Perepu et al., 2021)

In May 2021, Perepu *et al* reported the results of an open-label, randomised controlled trial comparing standard prophylactic versus intermediate dose enoxaparin in hospitalised adults with severe COVID-19, in three centres in the US. Adults aged 18 years or older with SARS-CoV-2 infection and requiring hospitalization were eligible if they were admitted to an ICU and/or had a modified ISTH Overt Disseminated Intravascular Coagulopathy (DIC) score ≥3. Patients were excluded if there was an indication for full therapeutic dose anticoagulation or they had active major bleeding, severe thrombocytopenia (platelet count <25,000/µL), current pregnancy, a history of acute venous or arterial thrombosis within the prior 3 months, or acute or chronic renal insufficiency with an estimated creatinine clearance <30 ml/min. Patients were randomly assigned in a 1:1 ratio to receive either a standard prophylactic dose or an intermediate dose of enoxaparin, with the standard and intermediate doses adjusted for obesity. The primary outcome of the trial was all-cause mortality at 30 days. Secondary outcome measures included acute kidney injury, defined as estimated creatinine clearance <30 ml/min, arterial or venous thrombosis confirmed with imaging, major bleeding, and minor bleeding. Major bleeding was defined according to ISTH criteria while minor bleeding was defined as a bleeding event that did not meet ISTH criteria for major bleeding.

Between April 26th 2020 and January 6th 2021, a total of 1529 patients hospitalised were screened for enrolment, with more than 85% of those screened not enroled, primarily due to lack of eligibility. A total of 173 patients were randomised, 86 to the standard dose arm and 87 to the intermediate dose arm. A total of 31 of the 173 patients (18%) in the intention-to- treat population died within 30 days of enrolment. All-cause mortality at 30 days was 15% for those assigned to receive intermediate dose enoxaparin and 21% for those assigned to receive standard dose enoxaparin (p=0.31). In an unadjusted Cox proportional hazard model, the hazard ratio (HR) for mortality in the intermediate dose group compared to the standard dose group was 0.67 (95% confidence interval [CI], 0.33–1.37; p=0.28). After adjustment for age, gender, BMI, and ICU admission, the hazard ratio for mortality was 0.57 (95% CI, 0.28 - 1.17, p=0.12) in the intention-to-treat population and 0.53 (95% CI, 0.24–1.13, p=0.10) in the per-protocol population. This trial therefore concluded that among patients with severe COVID-19, prevention of death or thrombosis at 30 days did not differ significantly between standard prophylactic dose and intermediate dose enoxaparin in hospitalised adults with severe disease. The evidence from this trial is limited by small patient numbers and the absence of stratification of the patient cohort into severity of disease.

6. **INSPIRATION randomised controlled trial (Sadeghipour *et al* March 2021)**(INSPIRATION Investigators et al., 2021)

The INSPIRATION study was designed to evaluate the effects of intermediate-dose vs standard-dose prophylactic anticoagulation among patients with COVID-19 admitted to ICU(INSPIRATION Investigators et al., 2021). It was a multicentre randomised trial with a 2 x 2 factorial design performed in 10 academic centres in Iran. Recruitment took place between July 2020 and November 2020 and the primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or mortality within 30 days. Secondary efficacy outcomes included all-cause mortality, adjudicated VTE, and ventilator-free days. Pre-specified safety outcomes included major

bleeding and severe thrombocytopenia. The anticoagulant regimen was modified according to weight/body mass index, and creatinine clearance. Enoxaparin was the primary choice for anticoagulation, with unfractionated heparin reserved only for patients with creatinine clearance of ≤15 mL/min. Standard-dose prophylaxis was defined as enoxaparin 40 mg/day, adjusted for obesity or creatinine clearance, while intermediate-dosing regimens were carefully outlined in the trial protocol, also adjusted for obesity or creatinine clearance(Bikdeli et al., 2020). For example, in a patient with a CrCl >30mls/min and a weight of 61-70kg, the standard prophylactic dose was 40mg enoxaparin compared to 70mg in the intermediate dose arm. Intermediate-dosing was chosen over therapeutic-dosing as it was thought by the steering committee to have the potential to confer benefit while mitigating the high risk of bleeding associated with higher doses of therapeutic anticoagulation(Bikdeli et al., 2020).

A total of 562 patients were included in the primary analysis in which the primary outcome occurred in 126 (45.7%) in the intermediate-dose arm and 126 (44.1%) in the standard-dose prophylactic arm; absolute risk difference 1.5% [(95%CI, -6.6%-9.8%); OR 1.06(95%CI, 0.76-1.48), p=0.70], indicating no difference between the intermediate-dosing and standard dosing regimens. In terms of the secondary outcomes, during the 30-day follow-up, all-cause mortality occurred in 236 patients (42%) and was not significantly different in the intermediate-dose compared with the standard-dose prophylaxis group (119 [43.1%] vs 117 [40.9%]; risk difference, 2.2% [95%CI, -5.9-10.3]; OR, 1.09[95%CI, 0.78-1.53];p=0.5). VTE rates were quite low occurring in 19 patients (3.4%), including 12 episodes of deep vein thrombosis and 7 pulmonary embolism events. The risk of VTE was not significantly different between the intermediate-dose and standard-dose groups (3.3% vs 3.5%; risk difference, −0.2% [95%CI, −3.2% to 2.7%]; OR, 0.93 [95%CI, 0.37-2.32]; P = .94). The findings of this study may be limited by the open-label nature of the trial, the exclusion of the most severely ill patients which may contribute to lack of generalisability of the results, the low VTE event rate, the wide confidence interval around the primary outcome indicating that the possibility of a small benefit or a small and important harm cannot be excluded, the focus on hard clinical end-points due to resource limitations and the potential that the results may not be generalisable to patients weighing >120kg who were excluded from the study.

7. HESA-COVID (Lemos et al. 2020)(Lemos et al., 2020)

One small Brazilian study comprising 20 patients was published in September 2020, HESA-COVID(Lemos et al., 2020). This was a randomised, open-label, single centre phase III study which recruited patients with respiratory failure requiring mechanical ventilation and randomised them to therapeutic anticoagulation or standard thromboprophylaxis. At baseline patients were required to have D-dimer levels >1,000µg/L, a PT/INR <1.5, an APTT ratio <1.5 and platelets >100 x 109/L. In the therapeutic arm, patients <75 yrs, with CrCl >50ml/min were dosed with 1mg/kg twice daily, to 0.75mg/kg twice daily if CrCl was between 30-50ml/min and 1mg/kg daily if CrCl was between 10 and 30ml/min. In corresponding patients <75 years, appropriate dose adjustments were also made. Prophylactic doses in the control arm included UFH 5,000IU three times daily or enoxaparin 40mg daily in those weighing ≤120kg, and UFH 7,500IU or enoxaparin 40mg twice daily if weight >120kg. The primary outcome was variation in gas exchange over time i.e. PaO_2/FiO_2 at baseline, day 7 and day 14 after randomisation. Secondary outcomes included successful liberation from mechanical ventilation, ventilator-free days, variation in D-dimer

levels collected at baseline and repeated 72-96 h later, all cause 28-day mortality, in-hospital mortality, and the ICU-free days at 28 days. Ten patients were recruited into each arm and a statistically significant difference in the primary outcome at day 7 and Day 14 (p=0.0004) was obtained in the therapeutic dose arm as compared with the prophylactic dose arm. Higher rates of liberation from mechanical ventilation were also achieved (p=0.031) at 28 days and ventilator free days (p=0.028). In addition, there was a statistically significant difference in reduction in D-dimer levels in the therapeutic dose arm as compared to the prophylactic dose arm. There was no difference in all cause 28-day mortality, in-hospital mortality or ICU-free days. In terms of safety, no major bleeding was observed in patients on therapeutic doses. The study findings may be limited by the small sample size and the open label design.

Evidence from evidence syntheses

A. Systematic reviews limited to RCTs

1. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically ill and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomised controlled trials(Ortega-Paz et al., 2021)

Ortega-Paz *et al* conducted a systematic review of the published RCTs evaluating anticoagulation strategies in patients with COVID-19 where therapeutic or escalated anticoagulation regimens were compared to standard prophylactic regimens. Further analysis was undertaken stratifying the included population by the severity of their illness as critically ill or non-critically ill. The primary efficacy end-point was all-cause death at the longest follow-up available while the primary safety end-point was major bleeding. A total of seven RCTs were identified.

In the overall population of patients included in the synthesis, the incidence of all-cause death was 17.8% in the escalated-dose and 18.6% in the standard-dose prophylactic anticoagulation group (RR 0.96, 95%CI 0.78-1.18). Compared to standard-dose prophylactic anticoagulation, escalated-dose prophylactic anticoagulation was not associated with a reduction in all-cause death (RR 0.96, 95%CI 0.78-1.18, I^2=56%) but was associated with an increase in major bleeding (RR 1.73, 95%CI 1.15-2.60, I^2=0%). In terms of secondary outcomes analysed, an escalated dose regimen was associated with lower rates of VTE driven by a reduction in pulmonary embolic events, not arterial thrombotic events. When the overall population was stratified into critically ill and non-critically ill groups, these results were consistent with those found in the overall group. The results from this meta-analysis indicate no benefit to escalated doses of anticoagulation in hospitalised patients with COVID-19, in either critically ill or non-critically ill patients, but it may be associated with an increased risk of bleed. The primary efficacy outcome analysed in this meta-analysis, all-cause death, was the primary outcome of one of the included trials. In all others, it was a component of composite outcome measures. Of note, the authors classified the usual care comparator as standard-dose prophylactic anticoagulation group, when it was actually a mix of escalated intermediate dose AND standard anticoagulation dose. Given the weight (>50% total; >25% critically ill and >25% not

critically ill) given to the REMAP CAP trial in this metanalysis, interpretation of its conclusions must be guarded.

2. **Prophylactic anticoagulants for people hospitalised with COVID-19 - Cochrane review**(Flumignan et al., 2020)

The Cochrane Emergency and Critical Care Group conducted a systematic review aimed to assess the effects of prophylactic anticoagulants versus active comparator, placebo or no intervention, on mortality and the need for respiratory support in people hospitalised with COVID-19 (Art. No.: CD013739) (Flumignan et al., 2020). The protocol was registered with the Open Science Framework on August 7th, 2020. The original protocol specified that the primary analyses were to be conducted on comparative RCTS and quasi-RCTs, although cohort studies were included in the search strategy. However, following the literature search, other non-randomised studies were included. The protocol specified that the Core Outcome Measures in Effectiveness Trials Initiative for COVID-19 were the outcomes to be evaluated. It was planned that assessment of risk for RCTs was to be undertaken using the Risk of Bias 1.0 tool and for quasi-RCTs or prospective non-randomised studies, the Risk of Bias for Non-randomised Studies of Interventions (ROBINS-I) tool. Due to the limited number of studies retrieved in the literature search, a number of deviations from the protocol were undertaken, and a meta-analysis was not performed as had been planned. GRADE was used to assess the certainty of evidence. The review was published in September 2020 based on studies retrieved during the period up to June 20th, 2020. Seven non-randomised studies were included in the review, three of them available as preprints at that time. All of the studies included people hospitalised with COVID-19, in either ICUs, hospital wards or emergency departments. The mean age of participants (reported in 6 studies) ranged from 59 to 72 years. Only three included studies reported the follow-up period, which varied from 8 to 35 days. The studies did not report on most of the outcomes of interest: i.e. need for additional respiratory support, mortality related to COVID-19, DVT, pulmonary embolism, adverse events, and quality of life.

The findings from this Cochrane systematic review suggested that at that time, there was insufficient evidence to determine the risks and benefits of prophylactic anticoagulants for people hospitalised with COVID-19. However, it must be noted this was in Oct 2020, when only very limited data from trials was available, and data from more robust clinical trials is now available.

A. Systematic reviews of observational studies

1. **Different Anticoagulant Regimens, Mortality, and Bleeding in Hospitalized Patients with COVID-19: A Systematic Review and an Updated Meta-Analysis** (Parisi et al April 2021)

This systematic review and meta-analysis was designed to assess the association between anticoagulants and their dosage with in-hospital all-cause mortality in COVID-19 patients in published non-randomised, observational studies. The main outcome was all-cause mortality occurring during hospitalization. Data

were combined using the general variance-based method on the effect estimate for each study. Separate meta-analyses according to type of COVID-19 patients (hospitalized or in ICU patients), anticoagulants (mainly heparin), and regimens (therapeutic or prophylactic) were conducted. A total of 29 articles were selected, with 23 retrospective studies eligible for quantitative meta-analyses. A meta-analysis of 25,719 hospitalised COVID-19 patients showed that anticoagulant use was associated with a 50% reduction in in-hospital mortality risk (pooled RR: 0.50, 95%CI, 0.40–0.62). Both anticoagulant regimens (therapeutic and prophylactic) reduced in-hospital all-cause mortality, compared with no anticoagulation. Overall a pooled meta-analysis of 10 studies showed a risk reduction of 43% in-hospital all-cause mortality when the therapeutic dose was compared to the prophylactic dose (pooled RR: 0.57, 95%CI 0.38-0.86). This risk was found to reduce still further in a small, pooled analysis of 4 studies of ICU patients, where the anticoagulant therapeutic regimen was associated with a reduced in-hospital mortality risk (RR: 0.30, 95% CI: 0.15–0.60; I2: 58%) compared with the prophylactic one. However, the former was also associated with a higher risk of bleeding (RR: 2.53, 95% CI: 1.60–4.00; I2: 65%). The authors concluded that anticoagulant use, mainly heparin, reduced all-cause mortality in COVID-19 patients during hospitalization. However due to the higher risk of bleeding at therapeutic doses, the use of prophylactic dosages of anticoagulant is probably to be preferred in non-critically ill COVID-19 patients. While the authors concluded that many of the included studies scored well on the Newcastle-Ottawa Score system for quality of observational studies, they opined that many were associated with a number of limitations including small sample sizes, absence of clarity on dose and type of anticoagulant used, clarity on outcome assessment and absence of reporting of adjustments of analyses.

An early systematic review and meta-analysis addressed the question as to whether the use of therapeutic or/and prophylactic anticoagulation was associated with decreased mortality and incidence of VTE in hospitalised adult COVID-19 patients, where mortality was defined as death during hospitalisation(Kamel et al., 2020). The review included case-control and cohort studies and 16 studies were retrieved in the literature search on June 22nd, 2020 and were included in the random-effects model. Results showed a statistically significant association between anticoagulation and reduced mortality (RR 0.56, 95%CI 0.36-0.92, p=0.02). Both therapeutic and prophylactic anticoagulation were associated with a lower risk of mortality. However, the overall quality of the included studies (observational, retrospective, non-randomised) introduces significant uncertainty into the outcomes of the synthesised evidence.

Clinical guidelines

Several international clinical guidelines have included recommendations on the prevention and management of VTE in patients with COVID-19, four of which are summarised in Table 2. Some confine their recommendations to critically ill patients while others encompass guidance for all hospitalised patients and additional subgroups of patients (Table 2). There is consensus that hospitalised acutely or critically ill patients with COVID-19 infection should receive appropriate thromboprophylaxis with prophylactic doses. Dose adjustment may be required in specific subgroups i.e. patients at extremes of body weight or with impaired renal function. Both the American Society of Haematology (ASH) and the National Institute for Health and Care Excellence updated their guidance based on the findings of the multiplatform RCT (Cuker et al., 2021a; National Institute for Health and Care Excellence, 2021). NICE

guidelines, which include advice for patients having respiratory support, recommend to consider increasing pharmacological VTE prophylaxis to an intermediate dose taking into account body weight, renal function and basing the decision on multidisciplinary or senior opinion, or locally agreed protocols.

Table 2: Summary of recommendations on management of thromboembolic events in COVID-19 hospitalised patients

Source of guideline	**Population**	**Recommendation**
American Society of Haematology (ASH). Cuker *et al*. American Society of Haematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 Version 2.1 (9th September 2021)(Cuker et al., 2021b)	Patients critically or acutely ill with COVID-19 infection	**Recommendation 1.** The American Society of Haematology (ASH) guideline panel suggests **using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation** for patients with coronavirus disease 2019 (COVID-19)-related ***critical illness*** who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects). **Recommendation 1a** The ASH guideline panel *suggests* using **prophylactic-intensity over intermediate-intensity anticoagulation** in patients with COVID-19 related **critical illness** who do not have suspected or confirmed VTE (conditional recommendation based on low certainty in the evidence about effects. (Updated May 2021). **Recommendation 2.** The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related ***acute illness*** who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects). *Of note the ASH guidelines do not include a recommendation for non-critically ill patients.*
National Institute for Health Antithrombotic Therapy in Patients with COVID-19 - Section 10 11th February 2021(National Institute of Health, 2021a)	Hospitalised patients, and subgroups of patients with COVID-19 infection	- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation **(AIII).** Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**. - There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the

		prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial. - There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers. - For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated **(AIII)**. *Of note, the NIH guidelines for this section have not been updated since February 2021 and therefore do not consider the results of the newer clinical trials, including the multiplatform trials.*
Alkhazzani *et al* Surviving Sepsis campaign Guidelines on the Management of Coronavirus Disease 19 (COVID-19) in the ICU: First Update. March 2021(Alhazzani et al., 2021)	Severely or critically ill patients with COVID-19 infection	**Recommendation 8** - For adults with severe or critical COVID-19, we recommend using pharmacologic venous thromboembolism (VTE) prophylaxis over not using prophylaxis (strong recommendation, moderate-quality evidence). **Recommendation 9** - For adults with severe or critical COVID-19 and no evidence of VTE, we suggest against the routine use of therapeutic anticoagulation outside of clinical trials (weak recommendation, very low quality evidence).
National Institute for Health and Clinical Care Excellence COVID-19 rapid guideline: reducing the risk of venous thromboembolism in over 16s with COVID-19 November 2020(National Institute for Health and Care	Acutely ill medical patients and subgroups of patients	For patients with COVID-19 pneumonia managed in hospital: - assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review (consensus recommendations) **Recommendation (New September 2021)** Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or

Excellence, 2021) (updated September 2nd 2021)		high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk. Treatment should be continued for a minimum of 7 days, including after discharge. **Conditional recommendation (New September 2021)** Consider a treatment dose of a LMWH for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk. Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances. Remark: For people with COVID-19 who do not need low-flow oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s. In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. **Only in research settings (New September 2021)** Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial. **Consensus recommendation** Do not base prophylactic dosing of heparin on levels of D-dimer. **Consensus recommendation** For people at extremes of body weight or with impaired renal function, consider adjusting the

		dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols. **Consensus recommendation** For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH). **Remark:** In August 2021, LMWHs and fondaparinux sodium were off label for people under 18 years.
WHO COVID-19 Clinical management - Living guidance 25 January 2021(World Health Organization, 2021)	Hospitalised patients	- Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways. - In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing (conditional recommendation, very low certainty).

LMWH=Low molecular weight heparin; VTE= venous thromboembolism

BMJ living review summary

Management guidance from the Coronavirus BMJ living review provides the following detailed guidance for venous thromboembolism prophylaxis as of October 14th 2021 which is a useful guide for hospitals. It includes the updated guidance from NICE and does not stratify patients according to their clinical status(BMJ, 2021):

- Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.
- Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised adults and adolescents provided there are no contraindications
    - The National Institute for Health and Care Excellence in the UK recommends starting as soon as possible (within 14 hours of admission) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk, and continuing for a minimum of 7 days including after discharge.
    - For hospitalised children, indications for VTE prophylaxis should be the same as those for children without COVID-19
- Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis
    - Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.
    - Avoid direct oral anticoagulants in the absence of an evidence-based indication for oral anticoagulation.
- The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended across most guidelines over intermediate- or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation. However, this recommendation varies and you should consult your local guidelines.
    - Dose adjustments may be required in patients with extremes of body weight or renal impairment.
- Evidence to support the best dose regimen is limited.
- For patients who are already on an anticoagulant for another condition, continue the patient's current therapeutic dose unless contraindicated by a change in clinical circumstances. Consider switching to low molecular weight heparin if the patient's clinical condition is deteriorating and the patient is not currently on low molecular weight heparin
- Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected. pathways if clinically suspected. If the patient's clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.
- Continue until hospital discharge. Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients. Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them

- There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalised patients with COVID-19.

Subgroups of patients

In general, the initiation of anticoagulants and antiplatelet therapy in non-hospitalised patients is not recommended for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial(National Institute of Health, 2021). Similarly, routine thromboprophylaxis on discharge is also not recommended, as the risk of thrombotic events in discharged patients appears to be very low(Berkman, 2021). However, results from robust clinical trials evaluating the need for extended thromboprophylaxis are required(Hunt et al., 2021). Guidelines for thromboprophylaxis for pregnant women with COVID-19 are available from the Royal College of Obstetrics and Gynaecology (RCOG) in the UK(RCOG, 2021).

A rapid evidence synthesis did not find any studies assessing the effectiveness and safety of thromboprophylaxis with LMWH for long-term care residents with COVID-19(Ontario RAEB Evidence to Action, 2021). The British Geriatrics Society guidance recommends the consideration of tailored thromboprophylaxis for residents of care homes, however this guideline has not been updated since November 2020(British Geriatric Society, 2020).

Safety considerations

The potential risk of bleeding must be considered in the context of anticoagulant recommendations. Overall, the clinical trial results indicate that there is no significant increased risk of major bleed associated with therapeutic or dose-intensified thromboprophylaxis, although the evidence synthesis of published RCTS did indicate an increased risk of major bleeding(Ortega-Paz et al., 2021).

In the HEP-COVID trial, There were 8 major bleed events (3.2%), 2 (1.6%) in the standard-dose vs 6 (4.7%) in the therapeutic dose groups (RR, 2.88; 95% CI, 0.59-14.02; p=0.17). No major bleed events were fatal. There was no significant difference in major bleeding between groups stratified according to ICU status, although there were numerically more major bleeds among patients in the ICU stratum in the therapeutic dose compared with the standard-dose group (4 [8.9%] vs 0; RR, 7.62; 95% CI, 0.42-137.03; p= 0.12).

In the RAPID trial, major bleeding events occurred in two patients (0.9%) in the therapeutic heparin group and four (1.7%) in the prophylactic heparin group (odds ratio 0.52, 95%CI 0.09 - 2.85; p=0.69)(Sholzberg et al., 2021). No fatal bleeding events or cases of intracranial haemorrhage occurred. Overall it was concluded that the risk of major bleeding appeared low in the trial.

In the critically ill cohort of patients in the multiplatform trial, a major bleed event occurred during the treatment period in 3.8% of the patients assigned to receive therapeutic-dose anticoagulation and in 2.3% of those assigned to receive usual-care thromboprophylaxis, but this was not statistically significant (adjusted OR 1.48, 95%crI 0.78-3.94)(The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, 2021). Similarly, in non-critically ill patients, therapeutic anticoagulation was not associated with a statistically significant difference in bleed risk (adjusted OR, 1.9 (95%crI 1.8(0.9-3.74) (The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, 2021). Further in this trial, fatal bleeding occurred in 3 patients in the

anticoagulation group and in 1 patient in the thromboprophylaxis group. There were no episodes of intracranial bleeding or confirmed HIT.

The Brazilian trial did report a statistically significant difference i.e. the primary safety outcome of major or clinically relevant non-major bleeding occurred in 26 (8%) patients assigned therapeutic anticoagulation and seven (2%) assigned prophylactic anticoagulation (relative risk 3.64 [95% CI 1.6-1.27], p=0.0010)(Lopes et al., 2021), while Parepu *et al* reported no difference in terms of major bleeding in patients treated with standard prophylaxis as compared to intermediate dose enoxaparin(Perepu et al., 2021). In the INSPIRATION trial, major bleeding occurred in 7 patients (2.5%) in the intermediate-dose arm and 4 patients (1.45%) in the standard-dose prophylaxis arm, representing an absolute risk difference of 1.1% [1 sided 97.5% CI, -∞-3.4%]; OR 1.83(1-sided 97.5%CI, 0.00-5.93) which did not meet the criteria for non-inferiority. In the HESACOVID trial, no major bleeding was observed in either the prophylactic dose arm or the therapeutic dose arm. Two patients (of 10) in the therapeutic enoxaparin arm experienced minor bleeding, and bleed events requiring medical intervention was observed for 4/10 patients in the therapeutic arm and 2/10 patients in the prophylactic enoxaparin group. No haemorrhages were recorded in either arm.

Heparin-induced thrombocytopenia (HIT) II is a relatively rare complication of heparin therapy. However, although this adverse effect with the use of heparin can occur in COVID-19 patients in addition to non-COVID-19 patients, HIT incidence has been suggested to be higher than in the non-critically ill COVID-19 patients(Daviet et al., 2020; Thachil J, 2021). The aetiology of this complication in the context of COVID-19 requires further research as a recent study by Nazy *et al* demonstrated the absence of anti-PF4/heparin antibodies in 10 critically ill COVID-19 patients(Nazy et al., 2021).

On-going clinical trials

A number of interventional randomised controlled trials investigating a variety of antithrombotic agents, dosing and duration of therapy focusing on outpatients, hospitalised patients and critically ill patients are on-going(Talasaz et al., 2021).

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Thromboprophylaxis search strategy October 14th, 2021

Source	Search
Pubmed	Search ((("coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19"))) AND/OR thromboembolism, venous thromboembolism, pulmonary embolism, thromboprophylaxis, anticoagulant, anticoagulation, enoxaparin, heparin, LMWH, UFH
MedRxiv/ BioRxiv	“COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19"))) AND/OR thromboembolism, venous thromboembolism, pulmonary embolism, thromboprophylaxis, anticoagulant/anticoagulation, enoxaparin, heparin, LMWH, UFH
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) and anticoagulation, heparin, enoxaparin, LMWH, UFH
EudraCT	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) AND anticoagulant, anticoagulation, enoxaparin, heparin, LMWH, UFH