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

Prepared by the COVID -19 Evidence Review Group with clinical contribution from Dr. Niamh O'Connell, Consultant Haematologist, National Coagulation Centre, St. James Hospital, Dublin and Dr. Fionnuala Ní Ainle, Consultant Haematologist, Rotunda Hospital and Mater Misericordiae University Hospital.

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Note: *Much of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or "preprints".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.

Evidence of the benefit conferred from thromboprophylaxis is limited to date, but several international guidelines recommend thromboprophylaxis for all hospitalised patients admitted with COVID-19. Data from a small number of randomised controlled trials are available. A robustly designed 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 dose anticoagulation in moderately ill or severely ill adults hospitalised for COVID-19. The results for the severely ill patients are available as a pre-print which reports that in severely 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. The peer-reviewed manuscript is pending. An interim analysis for the moderately ill cohort available in a press release, reports that therapeutic doses of anticoagulants are associated with potential benefit. The press release of trial results does not provide enough detail for full critique and peer reviewed publications are awaited. In the more recently published INSPIRATION open-label trial of patients admitted to ICU with COVID-19, intermediate-dose prophylactic anticoagulation did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. A small, open-label, phase II, randomised controlled trial (HESACOVID) investigated the impact of therapeutic enoxaparin or standard anticoagulant thromboprophylaxis in patients with COVID-19 requiring mechanical ventilation on variation in gas exchange over time as measured by the PaO_2/FiO_2 ratio. Therapeutic enoxaparin was associated with an improvement in gas exchange, but the study was limited to 20 patients and not powered to detect a difference in mortality.

A number of published observational studies support the benefit of anticoagulation in hospitalised patients with COVID-19 infection compared to no anticoagulation. Many of these 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 consensus is that prophylactic anticoagulation is warranted in admitted patients with COVID-19 without an underlying bleeding risk. Early evidence indicates that that escalated doses may benefit moderately ill, but not critically ill patients however the peer reviewed publications are awaited.

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(1). 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(2). A rate of 34% of thrombotic complications was reported in a systematic review of ICU patients(3), and McBane *et al* reported a rate of between 2% and 69% of VTE in a pooled analysis of predominantly ICU patients(1). 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 venous thromboembolism (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.

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

Multiplatform randomised controlled trial (mpRCT) – REMAP-CAP; ACTIV-4; ATTACC (Press release and pre-print)

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, therapeutic anticoagulation safely improves clinical outcomes (4–6). 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 (ICU) patients) or the control arm. Those randomised to the intervention arm received therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (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 low 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 OFSDs 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 patients (hospitalised but not initially requiring ICU therapies/level of care). Two Data and Safety Monitoring Board recommendations which have been accepted by all three platforms were published in December 2020 and January 2021 based on interim analyses of the combined data from each of the contributory trials(7). Enrollment was discontinued in the severe group on December 19th 2020 as the interim analysis demonstrated that statistical futility criteria were met.

A pre-print is available for the severe state cohort, but the moderate state cohort publication is awaited(8). Severe COVID-19 was defined as the provision of intensive care unit-level respiratory or cardiovascular organ support (high flow nasal oxygen ≥ 20 L/min, non-invasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes). Patients were ineligible if they were admitted to the ICU with COVID-19 for more than 48 hours (REMAP-CAP) or to hospital for more than 72 hours (ACTIV-4a, ATTACC) prior to 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.

For the severe cohort data, the primary analysis was based on 1,089 patients. The majority of patients in this cohort were enrolled via the REMAP-CAP study (84%). The usual care thromboprophylaxis dose was split between low dose (41%) and intermediate dose (51%). In those patients on the therapeutic dose anticoagulation (intervention arm) the median OFSDs was 3 (interquartile range (IQR) -1,16) compared to 5 (IQR -1,16) in the control arm. The median adjusted proportional OR for OFSDs was 0.87 (95% CrI 0.70 to 1.08). In-hospital survival was 64.3% in the intervention group and 65.3% in the control/usual care group (OR 0.88, 95% CrI 0.67 to 1.16). In severe state patients, therapeutic anticoagulation was associated with a mortality rate of 35.3% for therapeutic anticoagulation compared to 32.6% for usual

care thromboprophylaxis. The findings from this arm of the study therefore demonstrated that empiric administration of therapeutic anticoagulation in critically ill patients with COVID-19 did not improve hospital survival or days of organ support compared to usual care pharmacological thromboprophylaxis. Accordingly, recruitment into this arm was halted across the mpRCT(8). Major thrombotic events occurred in 5.7% and 10.3% in the therapeutic and standard LMWH groups respectively, although not powered for this outcome.

The data on the moderate state cohort is available as a press release only based on 1,398/1,772 patients for whom OFSD outcomes was known at the time of the interim analysis. The moderate state patients were stratified according to baseline D-dimer levels (high D-dimer (baseline ≥2 x local upper limit of normal (ULN), low D-dime (baseline D-dimer<2x ULN) and unknown (baseline D-dimer unknown). For the primary outcome, in this cohort of patients for both low and high D-dimer levels, therapeutic anticoagulation was associated with a proportional median odds ratio (OR) for OFSDs of 1.57 (95% CI, 1.14-2.19) (low D-dimer levels), and OR 1.53 (95%CI, 1.09-2.17) (high D-dimer levels) respectively. For the secondary outcomes, in moderate state patients, therapeutic anticoagulation was associated with a 5.7% mortality rate compared to 7.7% in usual care thromboprophylaxis (no statistical significance reported). This interim analyses of the collaborative mpRCT, indicated that in hospitalised moderate state patients, therapeutic AC dose was superior to usual care venous thromboprophylaxis with regard to OFSDs in each D-dimer subgroup, with a positive effect across morbidity and mortality components of the primary end-point(7). However, peer reviewed manuscripts are awaited.

INSPIRATION randomised controlled trial (Sadeghipour *et al* March 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(9). 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(10). 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(10).

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 generalizability 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.

HESA-COVID (Lemos et al. 2020)

One small Brazilian study comprising 20 patients was published in September 2020, HESA-COVID(11). 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 yrs, appropriate dose adjustments were also made. Prophylactic doses in the control arm included UFH 5,000IU tds or enoxaparin 40mg daily in those weighing ≤120kg, and UFH 7,500IU or enoxaparin 40mg bd 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 open label design.

Evidence from observational studies

Systematic reviews

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)(12). 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 intensive care units, 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.

In terms of the effect of any anticoagulant therapy vs no treatment, one study reported a reduction in all-cause mortality (adjusted odds ratio (OR) 0.42, 95%CI, 0.26-0.66; 2075 participants). One study reported a reduction in mortality only in a subgroup of 395 people who required mechanical ventilation (hazard ratio (HR) 0.86, 95%CI 0.82-0.89). Three studies reported no differences in mortality (adjusted OR 1.64, 95% CI 0.92-2.92; 449 participants; unadjusted OR 1.66, 95%CI, 0.76-3.64; 154 participants and adjusted risk ratio (RR) 1.15, 95%CI 0.29-2.57; 192 participants). One study reported no events in both intervention groups (42 participants). The overall risk of bias for all-cause mortality was regarded as critical (i.e. subject to extensive bias) and the certainty of the evidence was very low. One non-randomised study reported bleeding events in 3% of the intervention group and 1.9% of the control group (OR 1.62, 95%CI, 0.96 2.71; 2773 participants), but this was associated with low certainty of evidence.

Addressing the issue of therapeutic-dose anticoagulants versus prophylactic-dose anticoagulants, one study was retrieved involving 244 participants. The study reported a reduction in all-cause mortality (adjusted HR 0.21, 95%CI, 0.10-0.46) and a lower absolute rate of death in the therapeutic group (34.2% versus 53%). However, the overall risk of bias for all-cause mortality in this study was considered serious and the certainty of the evidence was rated as low. The study also reported bleeding events in 31.7% of the intervention group and 20.5% of the control group (OR 1.8, 95% CI 0.96 to 3.37), which again was rated as low-certainty evidence).

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.

A further systematic review and meta-analysis addressed the question as to whether the use of therapeutic or/and prophylactic AC was associated with decreased mortality and incidence of VTE in hospitalised adult COVID-19 patients, where mortality was defined as death during hospitalisation(13). 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 AC and reduced mortality (RR=0.56, 95%CI 0.36-0.92, p=0.02). Both therapeutic and prophylactic AC 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.

Other observational studies (not included in the evidence syntheses)

A number of additional observational studies have been published which were not included in the published systematic reviews. Three retrospective studies have recently reported their findings on the use of anticoagulation versus no anticoagulation (n=3)(14–16) or compared the use of therapeutic vs prophylactic anticoagulation (n=1)(17), while one study analysed both(18) (Table 1). These studies included a ***broad population of hospitalised patients*** with numbers of patients ranging from 374 to 4,389, with all cohorts derived from patients hospitalised in the first wave of the pandemic in spring, early summer 2020. Patients were not stratified according to admission to ICU or otherwise. Findings from the three studies comparing any anticoagulation with none reported positive findings for the intervention arms, while the small study comparing therapeutic anticoagulation vs prophylactic anticoagulation reported a statistically significant increased risk of hospital mortality (Table 1). In the final study, among 4,389 patients, therapeutic AC and prophylactic AC was associated with decreased rates of in-house mortality compared to no AC(18). These studies are limited by the observational nature of their design and the retrospective retrieval of data, and the absence of randomisation.

Two studies reported their findings among ***patients admitted to ICU***. Helms *et al* undertook a retrospective before and after study (before prophylactic anticoagulation; after therapeutic anticoagulation)(19). The primary outcome was the occurrence of any thrombotic or ischaemic event in patients admitted to ICU with ARDS. A total of 179 patients were included: 108 in the prophylactic arm and 71 in the therapeutic arm. Fifty-seven patients (31.8%) developed at least one clinically relevant thrombotic event during their ICU stay, which were less frequent in the therapeutic group (adjusted OR at 0.38 [0.14–0.94], p = 0.04). Jonmaker *et al* undertook a retrospective analysis of critically ill patients admitted to ICU and stratified them according to the dose of anticoagulation received i.e. low, medium or high dose thromboprophylaxis(20). The primary outcome of the study was the hazard ratio of death within 28 days from ICU admission. For patients who received high-dose prophylaxis, mortality was lower (13.5%) compared to those who received medium dose (25.0%) or low dose (38.8%), p = 0.02. The

hazard ratio of death was 0.33 (95% confidence intervals 0.13–0.87) among those who received high dose, and 0.88 (95% confidence intervals 0.43–1.83) among those who received medium dose, as compared to those who received low-dose thromboprophylaxis. There were fewer thromboembolic events in the high (2.7%) vs medium (18.8%) and low-dose thromboprophylaxis (17.9%) groups, $p = 0.04$. The findings of this study must be interpreted in the light of the subsequent press release of the interim findings from REMAP-CAP, where the pooled analysis demonstrated futility of therapeutic anticoagulation in improving organ support, and a concern for safety.

Table 1 – Summary of observational studies

Study reference	Study design (data collection dates)	Study question	Study population	Study endpoints	Results	Summary
Rentsch *et al* (US) 1st February 2021(16)	Retrospective observational (01/03/2020-31/07/2020)	AC# vs no AC	Hospitalised patients with severe COVID-19 (N=4297)	1y: 30-day mortality 2y: In-patient mortality; initiation of therapeutic AC; bleeding requiring transfusion	Cumulative incidence of mortality at 30 days was 14.3% for prophylactic AC vs 18.7% for no AC (HR 0.73, 95%CI, 0.66-0.81)	Positive for AC vs no AC in terms of 30-day mortality
Helms *et al* January 2021(19)	Before (prophylactic AC) & after (therapeutic AC) (01/03/2020-30/05/2020)	Comparison of prophylactic dose of AC vs therapeutic AC	Patients admitted to ICU (n=179)	1y: Occurrence of any thrombotic/ischaemic event	Relevant thrombotic complications during ICU stay occurred less frequently in therapeutic group (aOR*0.38 [0.14–0.94], p = 0.04) compared the prophylactic group	Positive for therapeutic AC vs prophylactic AC in detection of thrombotic complications; therapeutic anticoagulation failed to improve prognosis of critically ill ARDS patients with COVID-19: no difference in mortality rate between groups
Di Castelnuovo *et al* (Italy) January 2021(15)	Retrospective observational (19/02/2020-05/06/2020	Heparin vs no heparin	Hospitalised patients (n=2,504)	1y: Time to event of in-patient death	Death rate 7.4/1000 person days in heparin arm vs 14/1000 person days; after adjustment for propensity scores lower risk of death in patients receiving heparin (HR 0.60; 95%CI, 0.49–0.74)	Positive for heparin vs no heparin for in-patient death
Motta *et al* (US) December 2020(17)	Retrospective observational (01/04/2020-12/06/2020)	Pre-emptive enoxaparin or heparin at therapeutic vs	Hospitalised patients with COVID-19 & treated with	1y: Dichotomous variable for in-hospital death	Increased risk of mortality for patients on therapeutic vs prophylactic AC using a	Negative for therapeutic AC – associated with

		prophylactic doses	AC during hospital stay (n=374)	2y: Mortality in pts with peak CRP ≥200mg/L	multivariate logistic regression (RR 2.3 95%CI, 1.4.9, p=0.04)	increased risk of mortality
Jonmaker *et al* (Sweden) November 2020(20)	Retrospective observational (01/03/2020-30/04/2020)	Comparison of low, medium or high dose prophylactic AC	Critically ill patients admitted to ICU (n=152)	1y: HR of death within 28 days from ICU admission	For patients who received high-dose prophylaxis, mortality was lower (13.5%) compared to those who received medium dose (25.0%) or low dose (38.8%), *p* = 0.02; (HR 0.33 (95%CI, 0.13–0.87) for high dose & 0.88 (95%CI 0.43–1.83) for medium dose, compared to low-dose thromboprophylaxis	Positive for high or medium dose AC vs no AC in critically ill patients in terms of death within 28 days of ICU admission
Albani *et al* (Italy) September 2020(14)	Retrospective observational cohort (20/02/2020-10/07/2020)	AC (enoxaparin) vs no AC	Hospitalised patients (n=1403)	1y: In-hospital mortality	In an adjusted analysis enoxaparin was associated with lower in-hospital mortality (OR 0.53, 95%CI, 0.40-0.70) compared with no enoxaparin treatment	Positive for AC vs no AC for in-hospital mortality
Nadkarni *et al* (NYC, US) October 2020(18)	Retrospective observation cohort (01/03/2020-30/04/2020)	Therapeutic AC or prophylactic AC vs no AC	All hospitalised patients admitted to 5 hospitals (n=4389)	1y: in-hospital mortality 2y: Intubation; major bleeding	Overall, 1,703 in-patient deaths; proportion of deaths in no AC vs prophylactic AC vs therapeutic AC was 25.6%, 21.6% and 28.6% respectively. Reduced risk of in-house mortality in therapeutic AC vs no AC - aHR:0.53; 95%CI, 0.45-0.62; p<0.001; reduced risk of in-house mortality in prophylactic AC vs no AC – aHR: 0.5, 95%CI, 0.45-0.57, p<0.001	Positive for AC vs no AC; no statistically significant difference between therapeutic vs prophylactic

[#]AC=anticoagulation; *aOR=adjusted odds ratio; HR=hazard ratio;

Clinical guidelines

Several international clinical guidelines have included recommendations around coagulopathy and prevention and management of VTE in patients with COVID-19 (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. Dose escalation is only recommended in the specific groups in two different guidelines. NICE guidelines which include advice for patients having respiratory support, 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(21). In addition, the International Society on Thrombosis and Haemostasis also provide for dose escalation in obese patients(22).

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 February 2021)(23)	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 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).
National Institute for Health Antithrombotic Therapy in Patients with COVID-19 - Section 10 11th February 2021(24)	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)**.
Alkhazzani *et al* Surviving Sepsis campaign Guidelines on the Management of Coronavirus Disease 19 (COVID-19) in the ICU: First Update. March 2021(25)	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(21)	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 - Offer pharmacological VTE prophylaxis, unless contraindicated, with a standard prophylactic dose (for acutely ill medical patients) of low molecular weight heparin (LMWH)
WHO COVID-19 Clinical management - Living guidance 25 January 2021(26)	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).

Spyropoulos *et al*. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19 Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the Version 2 (21st May 2020)(22)	Non-ICU hospitalised patients and ICU hospitalised patients	**4.1 Guidance statement 2 - VTE prophylaxis in non-ICU hospitalized COVID-19 patients:** 1. A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. Intermediate dose LMWH may also be considered (30% of respondents). 2. VTE prophylaxis recommendations should be modified based on extremes of body weight, severe thrombocytopenia (i.e. platelet counts of $50{,}000 \times 10^9$/L or $25{,}000 \times 10^9$/L) or deteriorating renal function. **5.1 Guidance statement 3 - VTE prophylaxis in sick ICU hospitalized COVID-19 patients:** 1. Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH (50% of respondents) can also be considered in high risk patients. Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis. Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available. 2. Multi-modal thromboprophylaxis with mechanical methods (i.e. intermittent pneumonic compression devices) should be considered (60% of respondents)

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 March 19th 2021:(27)

- 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 with COVID-19 as per the standard of care for other hospitalised patients without COVID-19, provided there are no contraindications
    - Start as soon as possible and within 14 hours of admission, and continue for the duration of the hospital stay or 7 days, whichever is longer

- 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. Direct oral anticoagulants are not recommended
    - Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available
- The optimal dose is unknown
    - Standard prophylaxis doses are recommended over intermediate or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation
    - There are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial
    - However, some guidelines recommend that escalated doses can be considered in critically ill patients
        - The National Institute for Health and Care Excellence in the UK only recommends considering intermediate doses in patients who are having advanced respiratory support, and the decision should be based on multidisciplinary or senior opinion, or locally agreed protocols.[645] Reassess VTE and bleeding risks daily in these patients
        - NHS England recommends that therapeutic doses should not be offered unless there is a standard indication for therapeutic anticoagulation, as trials show that therapeutic doses do not improve clinical outcome of severe disease in the critical care setting
    - Dose adjustments may be required in patients with extremes of body weight or renal impairment
- 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
    - 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(29). However, results from robust clinical trials evaluating

the need for extended thromboprophylaxis are required(30). Guidelines for thromboprophylaxis for pregnant women with COVID-19 are available from the RCOG in the UK(31).

A recent 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(32). 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(33).

Safety considerations

The potential risk of bleeding, minor or major, must be considered in the context of AC recommendations. Preliminary analysis from the three platform pivotal trials did not indicate any increased risk of bleeds in those with moderately severe COVID-19 infection (7). In the mpRCT for the moderate cohort, major bleeding rates were <2% on therapeutic anticoagulation. In those with severe infection there was a numeric increase in major bleeding events and mortality, but the rate of major bleeding was within the predicted range for critically ill patients (3.7%).

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, 0.00-0.53).

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.

In a recently published systematic review and meta-analysis which included 42 observational studies, the pooled incidence of major bleeding was 3.9%. The highest pooled incidence estimate of any bleeding was reported for patients receiving intermediate- or full-dose anticoagulation (21.4%) and the lowest was in the only prospective study that assessed bleeding events (2.7%)(34).

In the observational studies, there were mixed results. In Helms *et al*, the occurrence of severe bleeding complications was not significantly different between the two groups, with 2 bleeding complications in the prophylactic group (1 haemorrhage on ECMO canulae and 1 gastro-intestinal bleeding) and 1 in therapeutic group (1 gastro-intestinal)(19). In the Rentsch study, receipt of prophylactic anticoagulation was not associated with increased risk of bleeding that required transfusion (HR 0.87, 0.71 to 1.05)(16). No increased risk of bleed was observed in the Jonmaker study(20). Therapeutic AC may have contributed to a small but significant increase in bleed risk in the Motta study(17), while Nadkarni *et al* reported that the proportion of patients with bleeding events after initiation of AC treatment was highest in patients on therapeutic AC (27 of 900; 3.0%) compared with patients on prophylactic AC (33 of 1,959; 1.7%) and no AC (29 of 1,530; 1.9%)(18).

Heparin-induced thrombocytopenia (HIT) II is a relatively rare complication of heparin therapy. A number of case reports have linked COVID-19 with the possible development of HIT, hence there may be a need for a vigilance in patients on thromboprophylaxis for this potential adverse effect(35,36).

On-going clinical trials

There are currently several interventional randomised controlled trials investigating a variety of antithrombotic agents, dosing and duration of therapy focusing on outpatients, hospitalised patients and critically ill patients(37). A number of these are still recruiting patients, while some are completed. The results from the pivotal platform trials will be of particular importance in providing evidence around optimal dosing schedules for hospitalised patients.

Clinical expert opinion

Clinical opinion supports routine standard-intensity thromboprophylaxis for hospitalised COVID-19 patients at this time. Interim analyses from the multiplatform ATTAC/ACTIV4a and REMAP-CAP suggest superiority for therapeutic LMWH in the pre-ICU population (over standard-intensity), but the full (adjudicated) data/manuscript is pending.

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Thromboprophylaxis search strategy March 6th 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