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.

Summary

Please note that some of the articles included in this review are 'pre-prints' i.e. unpublished, non-peer-reviewed scientific manuscripts[1].

Emerging evidence indicates that alteration in the coagulation profile of people with COVID19 may contribute to an 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 and consensus statements recommend thromboprophylaxis for all hospitalised patients admitted with COVID-19. In severe presentations of the infection and the critically ill patients, the optimal dose is not currently known. Dose escalation strategies may be considered on a case-by-case basis, while evidence for post-discharge thromboprophylaxis is not available. A number of on-going clinical trials will provide more robust evidence as to whether thromboprophylaxis leads to enhanced outcomes, such as improved survival.

Conclusion

The evidence indicates that there is a risk of thromboembolic events in hospitalised COVID-19 patients and consensus is that thromboprophylaxis is warranted in admitted patients with COVID-19 without underlying bleeding risk. While the suggestion is that patients with hyperinflammation may be at increased risk of thromboembolic events, there are currently insufficient studies to identify which patients may be at greater risk and whether increasing thromboprophylaxis to intermediate or treatment doses alters outcomes.

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[1]*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.*

Introduction

While COVID-19 is primarily manifested as a respiratory tract infection, emerging data indicate that it should be regarded as a systemic disease involving multiple systems including cardiovascular, respiratory, gastrointestinal, neurological, haematopoietic and immune system(1,2). Evidence now indicates that changes in coagulation parameters are an important clinical manifestation of COVID-19 and may lead to an increased risk of thromboembolic events (TEs)(3–5). Factors contributing to this risk are multifactorial including the SARs-CoV-2 infection itself and its pathology, and the consequences of its clinical progression including 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 may be increased if the disease progresses from moderate to severe stages of the condition, when hyperinflammation may be a key clinical feature(2,6).

A number of proposed mechanisms of disease progression have recently been published(2,7,8). Saddiqi and Mehra propose that COVID-19 infection be classified into three stages i.e. Stage I – mild, Stage II – moderate without or with mild hypoxia (IIa) or with hypoxia (IIb), and Stage III – severe, each associated with distinct clinical findings, with features associated with coagulopathy emerging as the condition progresses(8). In this mild stage of early infection, there is little evidence to date of the occurrence of altered coagulation parameters although patients may reveal a lymphopenia and neutrophilia.

In the second stage of established pulmonary disease, viral replication is on-going and a viral pneumonia develops resulting in localised inflammation associated with increasing lymphopenia and transaminitis. Patients who have progressed to stage II are usually admitted for hospitalisation for observation and supportive care. Systemic hyperinflammation is the hallmark of Stage III severe COVID-19 infection with elevations in markers of systemic inflammation including IL-2, IL-6, Il-7, GCSF, macrophage inflammatory protein 1-α, TNFα, CRP and ferritin(8). This hyperinflammation shares features with macrophage activation syndrome (MAS)/systemic haemophagocytic lymphocystiocytosis (sHLH)(2). The key early laboratory observations in COVID-19 pneumonia include elevated D-dimer with elevated cardiac markers that may be associated with poor prognosis(6). Additional contributing factors to the extensive pulmonary inflammation and thrombosis pathology in COVID-19 include(9,10):

a) local pulmonary vasculature endothelial cell activation, which in turn leads to
b) activation of tissue factor leading to further amplification of the coagulation cascade activation

c) hypoxaemia itself may induce activation of the coagulation cascade
d) mechanical ventilation may further drive inflammation and,
e) the role of immunothrombosis itself.

Therefore, the pathology driving a pro-coagulant state in COVID-19 is multifactorial ranging from mild risks in early stages to profound risks in more severe infection.

In addition to the pro-coagulant features of COVID-19, there are the 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.

Incidence of thromboembolic events in COVID-19

Several studies have reported the incidence of thromboembolic events in patients with COVID-19 (Table 1)(3,11–18). Reported incident rates range from 16.7% to 69% based on single outcome assessment or composite outcome assessment, but the study designs are significantly different making naïve comparisons of rates difficult. The patient cohorts included in the studies were predominantly those with severe COVID-19 infection and/or critically ill patients. Rates of VTE seen in critically ill patients with other conditions range from 10-30%(19).

Table 1 Studies reporting incidence of thromboembolic events among patients with COVID-19

Study	Study design	No. of patients	Type of patients	Thromboprophylaxis at baseline	Primary outcome	Outcome
Klok *et al* (April 5th)(3)	Prospective cohort study	184	Critically ill with COVID-19	All patients. A proportion of patients were dose increased due to concerns regarding thrombosis during the course of the study	Incidence of composite outcome of symptomatic acute PE, DVT, ischaemic stroke, MI/systemic arterial embolism	Cumulative incidence of 31% with an overall rate for segmental PE, proximal DVT and catheter associated DVT of 11.4%

Cui *et al* 9th April(10)	Retrospective cohort study	81	Patients with severe novel coronavirus pneumonia (NCP)	No thromboprophylaxis	Incidence of VTE	25% of patients developed lower extremity venous thrombosis, of whom 8/20 (40%) died
Helms *et al* 18th April(11)	Prospective cohort study	150	Patients with ARDS due to COVID-19 in 4 ICU settings	All patients – 105 (70%) prophylactic dosing, 45 (30%) therapeutic dosing	Assessment of thrombotic risk in patients with and without COVID-19 ARDS	64 thrombotic complications in 150 patients, with 36 confirmed thromboembolic events
Lodigiani *et al* 20th April(12)	Retrospective cohort study	388	327 admitted to general wards; 61 to ICU	All patients admitted to ICU, 75% of patients admitted to general wards	Any thromboembolic complication (ischaemic stroke, ACS/MI)	TE events in 28 patients (7.7% of closed cases) corresponding to a cumulative rate of 21%
Llitjos *et al* 20th April(13)	Retrospective cohort study in 2 French ICUs	26	ICU patients with COVID-19	All patients (dose at discretion of treating physician) 8 (31%) patients treated with prophylactic anticoagulation, 19 (69%) treated with therapeutic anticoagulation	Systematic assessment of VTE rate using a planned complete duplex ultrasound (CDU) screening strategy at Days1-3 and again at Day7 in patients with persistent hypoxaemia or secondary deterioration	Overall rate of VTE 69%; proportion of VTE higher in patients on prophylactic regimen compared to those on full anticoagulation (100% vs 56% respectively, p=0.03)
Poissy *et al* 24th April(14)	Case series (with subsequent case-control analysis)	107	ICU patients with COVID-19	All patients	Incidence of pulmonary embolism	Estimated cumulative incidence of PE 20.4% (95%CI, 13.1 to 28.7%).

						Compared to a similar non-COVID control, 20.6% vs 6.1%
Thomas *et al* 25th April (15)	Retrospective case series	63	ICU patients with COVID-19	All patients on prophylactic dalteparin	Composite of PE, DVT and arterial thrombosis (MI, stroke or peripheral artery embolism)	Cumulative incidence of VTE 27%; arterial thrombosis 4%, and composite outcome 29% (95% CI 12-49%)
Klok *et al* 2 30th April(16)	Prospective cohort study (Follow-up study to Klok *et al* 1	184	Critically ill patients with COVID-19	All patients and dose increased according to clinical need	Incidence of composite outcome of symptomatic acute PE, DVT, ischaemic stroke, MI/systemic arterial embolism	Cumulative incidence of composite outcome adjusted for competing risk of death = 49% (95%CI, 41-57%)
Middeldorp *et al*(17)	Prospective cohort study	198	Hospitalised patients – both non-ICU and ICU	All patients on routine prophylaxis	Incidence of VTE	39 patients (20%) diagnosed with VTE of whom 25 (13%) had symptomatic VTE despite routine prophylaxis; cumulative incidence of VTE higher in ICU than on wards

ACS=Acute Coronary Syndromes; ARDS=Acute Respiratory Distress Syndrome; DVT=Deep Vein Thrombosis; MI=Myocardial Infarction; PE=Pulmonary Embolism; TE-thromboembolic events; VTE=Venous Thromboembolism

Of the 64 thrombotic events reported by Helms *et al*, while 36 (56%) were either PEs or DVTs, a significant number, n=28 (44%) were filter clotting episodes(12). When COVID-ARDS patients

were matched with non-COVID ARDS patients in this study, more thrombotic complications were diagnosed in COVID-19 ARDS patients than in patients with non-COVID-19 ARDS (9 patients (11.7%) versus 7 patients (4.8%), OR 2.6 [1.1 - 6.1], p=0.035), with significantly more pulmonary embolisms (9 patients (11.7%) versus 3 patients (2.1%), OR 6.2 [1.6 - 23.4], p=0.008)(12).

Elevated rates of thromboembolic events were associated with increased rates of mortality in patients with COVID-19 in two studies(11,18). Higher rates were found to occur among those on prophylactic anticoagulation compared to those on therapeutic anticoagulation in severe COVID-19 infection (100% v 56%, p=003)(14). In addition there is evidence that TEs occur more frequently in COVID-19 patients compared to matched historical control (not contemporary) non-COVID patients(12,15). Klok *et al* noted that in a competing risk model, chronic anticoagulation therapy at admission was associated with a lower risk of the composite outcome(17). One small study has reported a rate of 5% acute ischaemic stroke in a cohort of COVID-19 patients(20). Pathological findings from a limited number of studies support the concept of a hypercoagulative status and the presence of pulmonary microthrombi(21–23). Fogarty *et al* in a recent Irish study confirmed that severe COVID-19 infection is associated with a significant coagulopathy that correlates with disease severity(24).

Evidence of need for routine thromboprophylaxis for all hospitalised patients with COVID-19 infection

Although there is limited data to date to determine the impact of careful thromboprophylaxis management for patients with COVID-19 in terms of increased survival, there is a strong consensus that all confirmed or suspected COVID-19 patients admitted to hospital should be treated with pharmacological VTE prophylaxis unless contraindicated. The hypercoagulable status of patients based on baseline biomarkers of coagulopathy such as D-dimer and fibrinogen degradation products (FDP) have been reported in several studies(4–6,25–33) (Appendix 1). Therefore, based on this emerging evidence, hospitalised COVID-19 patients share the risks of VTE with all hospitalised or critically ill patients with the additional recognised risks of the pro-coagulant properties imposed by the virus.

A number of discipline specific guidelines(34–37), national guidelines(38–40), consensus statements(41–44) and local guidelines(45,46) relating to the management of thromboembolic events in patients with COVID-19 have been published recently. LMWH is the preferred thromboprophylactic agent of choice. If LMWH is contraindicated, mechanical thromboprophylaxis is recommended. Weight-based adjustment may be considered to ensure appropriate protection, as findings from Poissy *et al* noted that inadequate thromboprophylaxis

may have been a contributing factor in the increased risk of VTE in their patient cohort(15). Patients with impaired renal function should also have doses adjusted to prevent adverse bleed effects, similar to non-COVID patients. In suspected heparin-induced thrombocytopenia, a change to fondaparinux may be merited. On-treatment monitoring recommendations vary but generally, most recommend to monitor D-dimer, PT, platelets and fibrinogen (the latter to out-rule disseminated intravascular coagulopathy (DIC)). The importance of adhering to the LMWH dosing schedule is also emphasised in published guidelines. A summary of the recommendations from a number of discipline-specific guidelines is provided in Table 2(34–36,47), while details from additional guidelines are summarised in Appendix 2, and a useful algorithm to guide patient assessment from the ISTH is provided in Appendix 3.

Table 2: Summary of recommendations on management of thromboembolic events in COVID-19 patients from ISTH, ASH, ACC and BTS(34–36,47)

International Society of Thrombosis & Haemostasis (ISTH) ISTH interim guidance on recognition and management of coagulopathy in COVID-19(35) Version 1 (25th March 2020)	- Risk stratification: Based on D-dimer levels*** and less so PT and platelet count - For patients who have markedly raised D-dimer (~3-4 fold increases above normal) admission to hospital should be considered even in the absence of other severity symptoms as this is a clear indication of increased thrombin generation - Prophylactic dose LMWH should be considered in ALL patients (including non-critically ill) who require hospitalisation admission for COVID-19 infection, in the absence of any contraindications (active bleeding, platelet count <25 x 10^9/L) - LMWH or fondaparinux favoured over unfractionated heparin to reduce contact - If documented HIT, use fondaparinux - Monitoring is advised in severe renal impairment, abnormal PT or APTT is not a contraindication - Monitor D-dimer, PT, platelet count and fibrinogen (as a marker of potential DIC) - When anticoagulants contradicted or unavailable, use mechanical thromboprophylaxis - Seriously ill COVID-19 patients should not receive therapeutic intensity anticoagulation empirically (i.e. in the absence of confirmed venous thromboembolism) - Bleeding is rare in the setting of COVID-19
American Society of Haematology (ASH). Management of Patients with COVID-19 and VTE/Anticoagulation(36) Version 2.1 (17th April 2020)	- All hospitalised patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux (suggested over unfractionated heparin to reduce contact) unless the risk of bleeding is judged to exceed the risk of thrombosis - Dose adjustment for obesity may be used per institutional guidance. - In patients with a history of heparin-induced thrombocytopenia, use fondaparinux - In patients where anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices) - Combined pharmacologic and mechanical prophylaxis is not generally recommended Despite the lack of quality published evidence, many institutional protocols have adopted an intermediate-intensity (i.e., administering the usual daily LMWH dose twice daily) or even a therapeutic-intensity dose strategy for thromboprophylaxis based on local experience. We

	recommend participation in well-designed clinical trials and/or epidemiologic studies when they become available.
American College of Cardiology (ACC) COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up(34) Version 2.1 (17th April 2020)	- The World Health Organisation interim guidance statement recommends prophylactic daily low-molecular weight heparins (LMWHs), or twice daily subcutaneous unfractionated heparin (UFH) - If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis (intermittent pneumatic compression) should be considered in immobilized patients - Missed doses of pharmacologic VTE prophylaxis are common and are likely associated with worse outcomes. Therefore, every effort should be made to ensure that patients receive all scheduled doses of pharmacologic VTE prophylaxis - In this regard, once daily dosing regimen of LMWHs may be advantageous over UFH to reduce personal protective equipment (PPE) use and exposure of healthcare workers
British Thoracic Society (BTS) Guidance on Venous Thromboembolic Disease in patients with COVID-19(47) Updated 4th May 2020	**Possible approach to LMWH dosing:** **Standard Risk Patient:** Standard weight-adjusted prophylactic dose LMWH (e.g. for a 70kg patient with CrCl>30mL/min dalteparin 5,000 units od, enoxaparin 40mg od) **High Risk Patient:** Intermediate dose LMWH (e.g. for a 70kg patient with CrCl>30mL/min: dalteparin 5,000 units twice daily, enoxaparin 40mg bd) **Proven or suspected acute VTE:** Therapeutic dose LMWH (bd dosing may be preferred in critical care patients who may require invasive procedures or if bleeding risk felt to be elevated). Duration of anticoagulation would generally be 3 months due to the strong provoking factor, but longer-term anticoagulation may be required if chronic thromboembolic pulmonary hypertension or significant chronic thromboembolic disease is subsequently suspected.

APTT=Activated Partial Thromboplastin Time; DIC=Disseminated intravascular Coagulopathy; HIT=Heparin-Induced Thrombocytopenia; LMWH=Low molecular weight heparin; PT=Prothrombin Time

Evidence supporting the role of anticoagulation in severe COVID-19 infection

In severe stages of COVID-19 infection when patients may be admitted to ICU, consideration must be given to both the VTE risks attributable to all critical care patients and the additional risks associated with the severe stage of COVID-19. However, there is uncertainty as to the optimal thromboprophylactic strategy both in critical care and furthermore in COVID-19 infection, and whether there is a role for thromboprophylaxis dose intensification or escalating to full therapeutic anticoagulation.

Previous data highlight the fact that critical care patients are a group at particularly high VTE risk, but for whom optimal thromboprophylaxis strategies remain uncertain. Sedation, mechanical ventilation and comorbidities contribute to the increase in VTE risk in critical care patients compared with non-critical care patients(48). A systematic review and recent data have demonstrated that PE is a leading cause of autopsy-confirmed potentially fatal misdiagnoses in intensive care unit (ICU) patients(49). Indeed, autopsy- detected PE is reported in 7 to 27 % of critically ill patients of whom only one-third were clinically suspected(50). ICU patients frequently have compromised cardiopulmonary function, such that PE consequences may be particularly severe but competing with this is an increased bleeding risk due to surgery, trauma, gastrointestinal bleeding, thrombocytopenia, and renal insufficiency(50). Older studies evaluating screening of asymptomatic patients report a prevalence of DVT in medical–surgical ICU patients not receiving thromboprophylaxis ranging from 13% to 31%(50). Therefore, appropriately addressing VTE risk in critical care may not just be a COVID-19 specific issue, but one that nevertheless represents an urgent knowledge gap**.** A recent single-centre prospective observational study including 281 patients addressing the cumulative incidence of ICU-acquired VTE demonstrated a high VTE rate (nearly 10% at 28 days) despite guideline-recommended thromboprophylaxis. Patients had an APACHE score of 17(51). Despite all patients receiving guideline-recommended thromboprophylaxis, the cumulative incidence of VTE at 7, 14, 21, and 28 days was 4.45% (95% CI 2.55–7.71), 7.14% (95% CI 4.61–10.97), 7.53% (95% CI 4.92–11.43), and 9.55% (95% CI 6.55–13.81) respectively(51).

The Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT) trial, which compared addition of intermittent pneumatic compression (IPC) to pharmacologic prophylaxis versus pharmacologic prophylaxis alone, revealed a 3.9% incidence of the primary outcome (new proximal lower-limb deep-vein thrombosis, as detected on twice-weekly lower-limb CUS) in the pneumatic compression group, and 4.2% in the control group (relative risk, 0.93; 95% confidence interval [CI], 0.60 to 1.44; P = 0.74). However, total VTE (PE or any lower limb DVT) was common in both groups, occurring in 10.4% and 9.4% of the pneumatic compression and control groups respectively (relative risk, 1.11; 95% CI, 0.85 to 1.44)(52).

In early 2020, a pre-planned sub-study of the PREVENT trial was published evaluating the impact of surveillance for deep vein thrombosis (DVT) among medical-surgical critically ill patients by twice-weekly ultrasonography. The surveillance group (n=1682 patients) included enrolled patients in the trial, while the non-surveillance group included eligible non-enrolled patients. Surveillance was associated with a decrease in 90-day mortality (adjusted HR 0.75; 95% CI 0.57, 0.98), earlier diagnosis of DVT and PE and an increase in diagnosis of DVT (adjusted HR 5.49; 95% CI 2.92, 13.02) with no change in frequency in diagnosis of PE (adjusted HR 0.56; 95% CI 0.19, 1.91)(53).

Of note, LMWH pharmacokinetics may be altered in critical care**,** as suggested by a study which reported that in 54 ICU patients who were given enoxaparin 30 mg SC twice a day, "low" 12-hour trough anti-FXa levels (defined as an anti-FXa level ≤ 0.1 IU/mL) were detected in 50% and were associated with an excess of three times the DVT rate (37% vs 11%; detected by planned CUS) compared with patients with higher peak levels(54). This and other studies, therefore, raises concerns about the appropriate LMWH dose in critically ill patients(50). No RCT has evaluated the optimal LMWH dose in critical care patients in an adequately powered RCT. ACCP guidelines recommend LMWH over LDUH for pharmacological thromboprophylaxis in critical care but do not make specific dosing recommendations in this population as distinct from general medical patients with VTE risk factors(55).

In terms of the benefit of thromboprophylaxis in COVID-19, Tang undertook a *post hoc* analysis on 449 patients with severe COVID-19 of whom 99 received heparin – 94 patients received LMWH (enoxaparin 40-60mg/day) and 5 patients unfractionated heparin (UFH) (10,000-5,000 units daily) for a minimum of 7 days(56). No difference in 28-day mortality was found between heparin users and non-users (30.3% vs 29.7%, p=0.910) but when the two groups were stratified into a Sepsis-induced Coagulopathy Score (SIC) of ≥4 or <4, the 28-day mortality of heparin users was 40% compared to 63.2% in non-users (p=0.029). Porfidia *et al*, however, noted that in the cohort described by Tang, that those not treated with heparin fitted the criteria for thromboprophylaxis, and may have had increased mortality due to the development of pulmonary emboli inferring an over estimation of the mortality difference between the two groups. Furthermore, it was suggested that risk stratification based on the PADUA score may have been merited, in addition to the SIC score used by Tang(57).

Disease severity in COVID-19 has been linked to markers of coagulation disturbances (Appendix 1), and higher levels of D-dimer and other coagulation disturbances have been independently associated with respiratory failure and death(28). In addition, the association between hyperinflammation that ultimately leads to activation of the coagulation cascade causing thrombotic phenomena has also been reported(2). Shi *et al* conducted a small comparative study on 42 patients hospitalised with severe COVID-19, of whom 21 were commenced while 21

patients did not receive LMWH, to determine the effect on blood counts, coagulation profile, inflammatory cytokines and serum biochemical indicators(58). This study (which has not been peer-reviewed), found beneficial effects of LMWH in the intervention group in terms of the percentage of lymphocytes, D-dimer and FDPs with no apparent difference in CRP. The authors report a significant reduction in the levels of the pro-inflammatory cytokine, IL-6, leading them to postulate that LMWH may have a role in mitigating the cytokine storm (hyperinflammation) that manifests in some patients with COVID-19. This study is based on findings of surrogate outcomes of benefit, not hard outcomes.

In severe COVID-19 accompanied by acute respiratory syndrome (ARDS), patients are clinically severely hypoxaemic albeit with near normal pulmonary compliance(7). Negri *et al* postulated that the normal compliance respiratory failure might be due to extensive pulmonary capillary obstruction with systemic disseminated intravascular coagulation contributing to the hypoxaemia(59). They therefore considered adding early heparin therapy to their standard of care in an effort to arrest the coagulation cascade. In their small case series involving 27 patients, 6 were given prophylactic heparin or enoxaparin, 3 were previously on enoxaparin 0.5mg/kg twice daily and maintained on that dose, and 18 patients were escalated to either full intravenous heparin or enoxaparin 1mg/kg twice daily. Of the 27 patients, 22 (81%) were discharged from hospital, one was transferred to another hospital and lost to follow-up. Following commencement of anticoagulation, PaO_2/FiO_2 ratios increased significantly over the following 72 hours. Nine patients were admitted to ICU of whom 6 were subsequently discharged to general wards. Eight patients required intubation and 5 patients were successfully weaned off after an average of 12.5 days. Of note, nineteen patients received methylprednisolone during the course of their disease. In this report, which has not been peer-reviewed, the authors postulate that anticoagulant therapy may have contributed to preventing the consequences of DIC, but the role of co-prescribed agents may confound this hypothesis(59).

Paranjpe *et al* recently reported the findings from 2,773 hospitalised COVID-19 patients, of whom 786 (28%) received systemic anticoagulation during their hospital course(60). In-hospital mortality for patients treated with anticoagulation was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients who did not receive anticoagulation. Patients who received anticoagulation were more likely to require invasive mechanical ventilation (29.8% vs 8.1%, $p<0.001$). In patients who required mechanical ventilation (n=395), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with anticoagulation as compared to 62.7% with a median survival of 9 days in patients who did not receive anticoagulation. Patients were not randomised to treatment groups, and the study had significant methodological limitations with potential sources of bias. In a multivariate proportional hazards model, longer duration of anticoagulation treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89,

p<0.001)(60), although potential immortal time bias was not adequately addressed. These findings may indicate that anticoagulation is associated with improved outcomes among hospitalised patients with COVID-19, albeit drawn from an observational study with a number of limitations. In terms of potential risks of anticoagulation, among those who did not receive anticoagulation, 38 (1.9%) had bleeding events, compared to 24 (3%) among those who received anticoagulation. Therefore, the potential benefits of systemic anticoagulation must be weighed against the risk of bleeding and undertaken on a case by case basis(60).

It is important to note that apart from the anticoagulant effect of heparin, there may be additional benefits associated with heparin use in COVID-19, i.e. dampening of the inflammatory response by blocking thrombin, mitigating the COVID-19 related pulmonary coagulopathy, protecting the endothelium, and, based on experimental models, inhibition of viral attachment(61).

The optimal anticoagulation dosing strategy for patients with severe COVID-19 or critically ill patients is currently not known, although evidence will emerge as data is accrued from further observational studies and on-going randomised controlled trials.

Recommendations from guidelines for increased dose of anticoagulation

The ISTH recommend dose escalation to prophylactic intensified doses or therapeutic doses in patients with COVID-19 only in the presence of documented VTE, while the American Society of Haematology currently recommend this strategy only within the context of clinical trials(35,36). The American College of Cardiology advise that the optimal dosing in patients with severe COVID-19 remains unknown and warrants further investigation, although a minority of guideline authors consider intermediate or therapeutic dosing to be reasonable(34).

In early April, the Italian Society of Thrombosis and Haemostasis published a position paper on COVID-19 and haemostasis(42), and made recommendations for escalation to intermediate-LMWH based on an individual basis for patients with multiple risk factors for VTE. However, they do caution that therapeutic anticoagulant use is currently not supported by evidence and cannot be recommended as standard of care. Their recommendations are similar to other guidelines but they also recommend that thromboprophylaxis, in addition to being administered for the entire duration of stay, should be maintained at home for 7-14 days after hospital discharge or in the pre-hospital phase, in case of pre-existing or persisting VTE risk factors. They recommend that monitoring of laboratory tests should always include haemostasis for hospitalised COVID-19 patients. They also highly recommend that standardised procedures be adopted to collect clinical and laboratory data on all hospitalised patients(42).

Alternative therapeutic strategies

Other interventions that have been postulated to be of benefit in severe cases of COVID-19 include the addition of antiplatelet therapy with escalation of LMWH dose and the use of systemic tissue plasminogen activator (tPA). The CHARTER trial protocol for nebulised heparin has recently been published in preprint form(62).

Ranucci *et al* published a case series of COVID-19 patients admitted to ICU with acute respiratory distress syndrome (ARDS) where extensive characterisation of their coagulation profile was undertaken i.e. aPTT, INR, platelet count, fibrinogen, D-dimer, and antithrombin (AT) activity(63). All patients were admitted to ICU on thromboprophylaxis of low molecular weight heparin (LMWH) 4,000 IU twice daily. Following the first round of standard coagulation and viscoelastic tests, patients were escalated to a higher dose of LMWH, given AT concentrate to correct values <70%, loaded with clopidogrel 300mg followed by 75 mg/day if platelet count was > 400 x 10^9/L. At baseline, median values of coagulation showed a prolongation of the aPTT, platelets within the normal range and one patient with thrombocytosis. Four patients had AT levels below the lower limit of the normal range and the median value of fibrinogen was higher than the upper limit of the normal range. D-dimer and IL-6 levels were higher than the upper limit of the normal range in all patients (consistent with a state of hyperinflammation). Following the introduction of the escalation protocol, the pro-coagulant profile of COVID-19 ARDS patients progressed to normalisation. The potential for the intensive regimen to increase the risk of bleed was not noted. No major thromboembolic events were observed in this case series.

It is postulated that enhancement of plasminogen activation or downregulation of fibrinolytic inhibition is required to address the clearing of fibrin clusters resulting from microthrombi formation in patients with COVID-associated ARDS. A small case series involving three patients with COVID-19 demonstrated a transient improvement in the P/F ratio in 2 cases and a 50% improvement in one case following the administration of a 25mg bolus of intravenous tPA while patients were concurrently maintained on intravenous heparin(64). Poor *et al* reported a further case series, published as a preprint, of four patients with refractory respiratory failure treated with systemic tPA who demonstrated immediate improvements in gas exchange and/or haemodynamics(65).

There are currently (5th May 2020) 12 interventional trials registered with www.clinicaltrials.gov investigating the impact of thromboprophylaxis with heparin or LMWH in COVID-19 infection and two studies investigating the role of tPA (Table 2). There are also 7 observational studies registered investigating aspects of haemostasis and coagulopathy in COVID-19 patients.

A number of trials have also been registered with the Chinese Clinical Trials Registry, and the following three trials are registered on the EUDRA-CT site (https://www.clinicaltrialsregister.eu/):

- The RAPID-COVID-COAG RCT, Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID COVID COAG) – No. 2020-002190-10 (clinical trials.gov NCT04362085; which will include Irish sites)
- Evaluation of the concentration-effect relationship of enoxaparin for thromboembolic prevention in COVID-19 resuscitation patients. COV-ENOX study (COV_ENOX study) – No. 2020-001823-15
- Effectiveness of low molecular weight heparin at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of venous thromboembolism in COVID-19 – No. 2020-001709-21
- Impact of the use of low molecular weight heparins (LMWH), at prophylactic versus intermediate doses, on SARS-CoV2 infection (COVID-19) – No. 2020-001891-4.

A number of sites in Ireland are participating in a number of interventional and observational clinical trials.

Table 3 Clinical trials involving thromboprophylaxis or anticoagulation strategies in COVID-19 registered with www.clinicaltrials.gov (6th May 2020)

	Trial No./Acronym	Title	Intervention	Location
Interventional studies				
1.	NCT04345848 COVID-HEP	Preventing COVID-19 Complications With Low- and High-dose Anticoagulation Study Documents Interventional study	Enoxaparin	Geneva, Switzerland
2.	NCT04362085 RAPID COVID COAG	Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care	Therapeutic anticoagulation	Canada
3.	NCT04344756 CORIMMUNO-COAG	Trial Evaluating Efficacy and Safety of Anticoagulation in Patients With COVID-19 Infection, Nested in the Corimmuno-19 Cohort	Tinzaparin or unfractionated heparin	Paris, France
4.	NCT04359277 No acronym	A Randomized Trial of Anticoagulation Strategies in COVID-19	Enoxaparin higher dose Lower dose prophylactic anticoagulation	New York, US
5.	NCT04360824 No acronym	Covid-19 Associated Coagulopathy	Intermediate dose thromboprophylaxis Standard of Care thromboprophylaxis	Not specified
6.	NCT04367831 IMPROVE	Immediate or Prophylactic-Dose Anticoagulation for venous or Arterial Thromboembolism in Severe COVID-19	Enoxaparin prophylactic dose Heparin infusion Heparin SC Enoxaparin Intermediate dose	Columbia Medical Centre, New York
7.	NCT4366960 X-COVID 19	Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients	Enoxaparin	Milan, Italy
8.	NCT04360824 No acronym	Covid-19 Associated Coagulopathy	Intermediate dose thromboprophylaxis Standard of Care thromboprophylaxis	Not specified
9.	NCT4354155 COVAC-TP	COVID-19 Anticoagulation in Children - Thromboprophylaxis (COVAC-TP) Trial	Enoxaparin	Johns Hopkins, Florida
10.	NCT4373703/NCT4373070 COVI-DOSE	Weight-Adjusted vs Fixed Low Doses of Low Molecular Weight Heparin For Venous Thromboembolism Prevention in COVID-19	Enoxaparin	Multicentre, France

11.	NCT04372589 ATTACC	Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)	Heparin	Canada
12.	NCT04359212 VTE-COVID	Increased Risk of VTE and Higher Hypercoagulability in Patients Recovered in ICU and in Medical Ward for COVID-19	Thromboprophylaxis with low-molecular-weight heparin or fondaparinux	Not specified
Interventions other that heparin or LMWH				
13.	NCT04356833 PACA	Nebulised Rt-PA for ARDS Due to COVID-19	Nebulised recombinant tissue-Plasminogen Activator (rt-PA)	Royal Free Hospital, London, UK
14.	NCT04357730 No acronym	Fibrinolytic Therapy to Treat ARDS in the Setting of COVID-19 Infection: A Phase 2a Clinical Trial	Alteplase 50mg vs alteplase 100mg	Not specified
Observational studies				
1.	NCT04377490 THROMBOCOVID-2	ThromboEmbolic Events in Hospitalized Patients With Covid-19 Serious Acute Pneumopathy	Observational – haemostasis	Amiens, France
2.	NCT04366752 THROMBOCOVID	Thrombo Embolic Events in Critical Care Patients With Covid-19 Serious Acute Pneumopathy	Observational - haemostasis	
3.	NCT04359992 THROMBOVID	Study of Haemostasis in Case of Severe COVID-19	Observational - haemostasis	Strasbourg, France
4.	NCT4327180 PREDICT	PREdiction of DIagnosed Covid-19 infecTion in IUC Patients	Observational - haemostasis	
5.	NCT04356950 COVID-TGT	Analysis of the Coagulopathy Developed by COVID-19 Infected Patients	Observational – coagulation profile	Multicentre, France
6.	NCT04367662 COVID'HEMOS	Study of the Vascular Compartment and Hypercoagulability During Coronavirus Infection COVID-19		
7.	NCT04343053 ATTAC-Co	Pro-thrombotic Status in Patients With SARS-Cov-2 Infection	No intervention – blood samples	Ferrara, Italy

Evidence on risk assessment for thromboembolic events

Consensus has not yet been reached on a definitive panel of biomarkers that can adequately predict the increased risk of TEs among patients with COVID-19 despite evidence synthesis by a number of groups(66–68). There is some evidence of the clinical significance of increased D-dimer for predicting VTE in COVID-19 cases, and it may also serve as a prognostic tool for risk stratification(32,69). The ISTH recommend very specific pre-treatment risk stratification for admission to hospital based on baseline D-dimer levels (although this has not been endorsed by other groups)(35). However, the clinical utility of D-dimer testing may be limited by a one-threshold-fits-all approach (particularly regarding age) and the D-dimer assay used across different laboratories, and therefore caution should be exercised in estimating its clinical significance until more robust data is obtained(70–72). Therefore, validation of its utility requires further evidence(70). The potential for bleed events and the potential for heparin-induced thrombocytopenia merit close monitoring of platelets and baseline assessment of bleed risk using validated instruments(5).

The identification or phenotypical profiling of patients that may benefit from thromboprophylaxis in the absence of overt signs of infection, or thromboprophylaxis dose intensification or therapeutic doses of anticoagulant therapy in the more advanced stages of the infection, is, as yet, definitively not known.

Clinical expert opinion (unpublished)

Clinical opinion supports routine thromboprophylaxis for hospitalised COVID-19 patients.

Caution should be exercised in the use of D-dimer as a prognostic tool in patients with COVID-19. At present elevated d-dimers on admission are a prognostic indicator for disease outcome and are not proven, as yet, as a predictor for thromboembolism. D-dimers are commonly raised in hospitalised patients and older patients. Therefore, dimers should not be used as marker of thrombosis, rather a negative result has utility as a negative predictor for thrombosis in settings outside of COVID19.

Clinical opinion suggests that for the majority of patients either low or intermediate dose LMWH may currently represent the optimal dosing strategy in critical care patients but that the optimal dose is not currently known. Either standard or intermediate intensity LMWH may be considered (e.g. the latter may be considered in selected centres in which on site specialist advice is available). If further cohort studies demonstrate a lower risk or a higher risk, it may be appropriate to downgrade or upgrade these recommendations.

There is considerable ongoing debate, which was reflected in the recent ACC/ISTH guideline footnote highlighting the split of the panel on recommendations for critical care patients. It should be remembered that in other circumstances, international guidelines provide nuanced, graded recommendations (rather than no recommendations) for scenarios in which large cohort/clinical management studies are available but where RCT data are lacking. For critical care patients, optimal thromboprophylactic strategies both in COVID and non-COVID affected patients are uncertain. Local audit data and specialist expertise should be considered, to guide individualised dosing strategies, informed by emerging data. Patients who have been cared for in a critical care environment should be considered for post-discharge thromboprophylaxis, if no contraindications exist**.**

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Appendix 1

Summary of case series reporting outcomes and data on baseline coagulation parameters in patients with COVID-19

Study Title (location)	Methodology	Population	Outcomes assessed	Outcome data	Reference
Peer-reviewed reports					
China (January 24th)(25)	Retrospective case series	41 patients admitted with a pneumonia up to January 2nd	Epidemiological, clinical, laboratory, and radiological characteristics Plus treatment and clinical outcomes of these patients stratified by ICU admission or not	ICU admissions accounted for 32% (13) of the cohort. D-dimer and PT levels were higher on admission among patients requiring ICU support (median D-dimer 2.4mg/L for ICU vs 0.5mg/L for non-ICU, p=0.0042; median PT12.2. sec for ICU vs 10.7 sec, p=0.012).	Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Feb;395(10223):497–506
China (January 30th) (26)	Retrospective case series	99 hospitalised patients	Epidemiological and clinical characteristics	Average age 55.5yrs, 51% had chronic diseases, 75% had bilateral pneumonia, 17% developed ARDS and 11% of these developed multi-organ failure and died Elevated D-dimers (≥1.5microg/L) detected in 36% of patients	Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019

					novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020 Feb;395(10223):507–13.
China (February 24th)(4)	Retrospective case series	138 hospitalised patients with novel coronavirus 2019 pneumonia from 1st – 28th January 2020	Epidemiological, demographic, clinical, laboratory, radiological & treatment data described Outcomes from critically ill & non-critically ill patients compared.	47 patients (34%) were discharged, 6 died (4.3%), remaining patients still hospitalised at time of reporting. Patients requiring ICU treatment had significantly higher D-dimer levels ($p<0.001$) compared with less severe cases.	Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061.
China (February 24th) (6)	Descriptive case series	183 patients with novel coronavirus pneumonia	Conventional coagulation on admission results, clinical outcomes and assessment of DIC criteria	Overall mortality was 11.5% Non-survivors had a significantly higher D-dimer ($p<0.05$) and fibrin degradation product (FDP) levels ($p<0.05$), longer PT ($p<0.05$) and longer APTT time ($p<0.05$) compared to survivors on admission; 71.4% of	Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel

				non-survivors and 0.6% of survivors met the criteria for DIC during hospital stay	coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844–7.
China (February 28th)(27)	Multicentre retrospective study	1099 patients with laboratory-confirmed COVID-19 from 552 hospitals	Composite end-point of admission to ICU, use of mechanical ventilation or death	Primary composite end-point occurred in 67 (6.1%) of patients – 5% admitted to ICU, 2.3% underwent invasive mechanical ventilation, and 1.4% died. 260/560 (46%) of patients had a D-dimer level ≥0.5mg/L with the increases more pronounced among severe (56%) vs non-severe (43.2%) patients	Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, *et al*. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28;NEJMoa2002032.
China (March 13th)(28)	Retrospective cohort study	201 patients	Development of ARDS and death. Clinical characteristics & outcomes in patients with COVID-19 pneumonia who developed ARDS or died.	ARDS developed in 84 (41.8%) patients of whom 44 (52.4%) died. Risk factors associated with the development of ARDS and progression of ARDS to death included older age, neutrophilia, and organ and coagulation dysfunction. Increased PT was associated with increased risk of ARDS ($p<0.001$) and increased levels of D-dimer were associated with an increased risk of ARDS ($p<0.001$) and death ($p=0.002$).	Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, *et al*. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.

					JAMA Intern Med [Internet]. 2020 Mar 13 [cited 2020 Apr 24]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184
China (March 16th)(29)	Case-control study	94 cases (confirmed SARs-CoV-2) vs 40 controls	Comparison of blood coagulation function of cases compared to controls	D-dimer (10.36 vs. 0.26 ng/L; p < 0.001) and FDP (33.83 vs.1.55 mg/L; p < 0.001), FIB (5.02 vs. 2.90 g/L; p < 0.001) were higher in cases compared to controls When SARS-CoV-2 patients were divided into 3 phenotypes of severity i.e. ordinary (n=49), severe (n=35) and critical (n=10), D-dimer and FIB levels were higher across all case phenotypes compared to controls. Note: No analysis on hard outcomes e,g, mortality	Han H, Yang L, Liu R, Liu F, Wu K-L, Li J, *et al*. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;
China (March 17th)(30)	Retrospective case series	113 patients admitted up to February 28th	Clinical characteristics and laboratory findings	Deceased patients (n=113) were more likely to be older, male, have comorbidities such as hypertension and other cardiovascular comorbidities than recovered patients (n=161)	Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, *et al*. Clinical characteristics of

				Concentrations of ALT, AST< creatinine, CK, LDH, cardiac troponin I, nBNP & D-dimer were markedly higher in deceased patients than in recovered patients.	113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;
China (March 28th)(31)	Retrospective cohort study	191 patients	Clinical course and risk factors for mortality	137 patients were discharged, 54 died in hospital Increased D-dimer levels (≥1microg/ml) were significantly associated with in-hospital death in a multivariate analysis (p<0.003)	Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020 Mar;395(10229):1054–62
China (April 4th)(5)	Descriptive case series	1026 admitted to hospital with COVID-19 infection	Odds of VTE using Padua Prediction Score stratified by a score ≥4 or less than 4	In patients with Padua Prediction Score ≥4 compared to <4, OR 8.51 (95% CI, 3.74-19.35), p<0.0001 40% considered at high risk of VTE on the basis of PPS score ≥44,	Wang T, Chen R, Liu C, Liang W, Guan W, Tang R, *et al*. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet

					Haematol. 2020 Apr;S2352302620301095.
China (April 19th)(32)	Retrospective case series	343 patients admitted between Jan 12th & March 15th with COVID-19	To determine the optimum cut-off value of D-dimer to predict hospital mortality	Optimum cut-off value was ≥2.0microg/ml with a sensitivity of 92.3% and a specificity of 83.3%. Patients with D-dimer levels ≥2.0microg/ml had a higher incidence of mortality compared to those with D-dimer levels <2.0microg/ml (12/g7 vs 1/267, p<0.001, HR 51.5, 95%CI, 12.9-206.7)	Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, *et al*. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020 Apr 19;jth.14859.
US (April 22nd)(33)	Retrospective case series	5,700 patients admitted to 12 hospitals in New York from March 1st to April 4th	Description of presenting characteristics, comorbidities, and outcomes	Mean D-dimer on admission – 438ng.ml (range 262-872) among 3,169 patients for whom data was available. Also raised troponin, BNP, Procalcitonin, ferritin, CRP were also raised on admission to hospital	Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al*. Presenting Characteristics, Comorbidities, and Outcomes Among

					5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA [Internet]. 2020 Apr 22 [cited 2020 Apr 24]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2765184

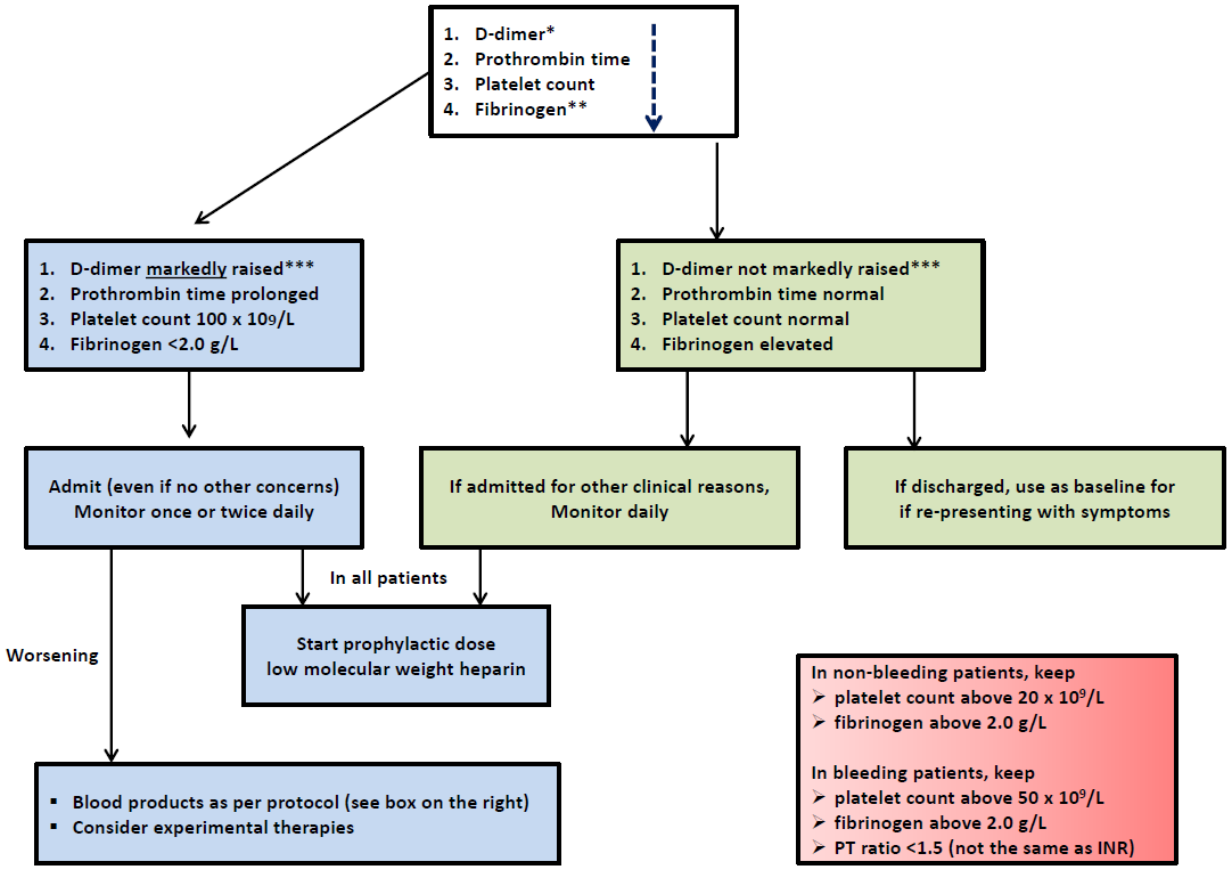
Appendix 2 – Summary of additional guidelines on anticoagulation in patients with COVID-19

Belgian Task Force Group Interim Clinical Guidance for adults with suspected of confirmed COVID-19 in Belgium(40) Version 7 (7th April 2020)	- In COVID-19 hospitalised patients, oral anticoagulant treatment (prior to admission) is to be replaced by curative LMWH therapy, due to multiple potential drug interactions and difficulties to monitor oral anticoagulation - Prophylactic LMWH is indicated in most (if not all) COVID-19 patients who require hospitalisation, according to the local institutional protocols, with standard weight adjusted and renal failure dose adjustments - Higher LMWH doses (enhanced prophylactic or therapeutic) are to be considered on a careful case by case analysis balancing potential risks and benefits - Usual precautions with regards to LMWH safety are applicable
Swiss Society of Haematology. Working Party on Haemostasis. Suggestions for thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19(38) (11th April 2020)	- All in-hospital COVID-19 patients should receive pharmacological thromboprophylaxis according to a risk stratification score, unless contraindicated. - In patients with CrCl >30 ml/min, LMWH should be administered according to the prescribing information - an increased dose should be considered in overweight patients (>100 kg) - In patients with CrCl <30 ml/min, unfractionated heparin (UHF) subcutaneously twice or three times daily or intravenously should be administered according to the prescribing information. An increased dose should be considered in overweight patients (>100 kg) - Anti-Xa activity should be monitored when indicated (e.g., evidence of renal dysfunction) - Antithrombin need not be monitored but could be considered on an individual basis in cases of disseminated intravascular coagulation or sepsis-induced coagulopathy or heparin resistance

	- Suggest regularly monitoring of prothrombin time, D-dimers, fibrinogen, platelet count, lactate dehydrogenase (LDH), creatinine and alanine aminotransferase (ALT) (daily or at least 2−3 times per week) - In patients in intensive care with a large increase in D-dimers, severe inflammation, or signs of hepatic or renal dysfunction or imminent respiratory failure, intermediate or therapeutic dosing of LMWH or UHF should be considered, according to the bleeding risk - Heparin-induced thrombocytopenia (HIT) should be considered in patients with fluctuations in platelet counts or signs of heparin resistance - In patients undergoing extracorporeal membrane oxygenation (ECMO) treatment we suggest maintaining UFH at doses bringing anti-Xa activity into the therapeutic range.
NHS Greater Glasgow & Clyde(45) (16th April 2020)	**Prescribe enoxaparin SC <u>40mg twice daily*</u>** for every COVID +ve inpatient on Critical Care who has no contraindications. **Dose adjustments:** - Reduce enoxaparin dose to SC 20mg twice daily if CrCl 15-29ml/min or weight <50kg - Increase enoxaparin dose to SC 60mg twice daily if weight >120kg (see below for additional monitoring if CrCl <30 ml/min) - Change to unfractionated heparin (UFH) SC 5000 units twice daily if CrCl <15ml/min *[recommended preparation: heparin sodium 5000 units in 0.2mL ampoules]* - For pregnant women weighing >90kg, specialist advice should be sought from obstetrics/haematology **Monitoring requirements** AntiXa monitoring is recommended in the following patient groups: - **CrCl <30 ml/min:** check antiXa 4 hours post dose after 10 doses - **Weight <50kg:** check antiXa 4 hours post dose after 10 doses - **Weight >120kg:** check antiXa 4 hours post dose after 3 doses, repeat after 10 doses if CrCl <30ml/min

	Target antiXa: 0.1-0.4 units/ml. If out with target, please seek advice from consultant haematologist. **Contraindications against thromboprophylaxis with UFH or LMWH** - Platelet count ≤ 50 x10^9/l - Receiving anticoagulation for another reason - Patient considered to be at high bleeding risk e.g. recent intracranial haemorrhage, untreated inherited/acquired bleeding disorders - Trauma with high bleeding risk - Active bleeding - Heparin induced thrombocytopaenia - Acute stroke (use IPC if immobile & contact stroke team for guidance) - Within 12 hours of procedures e.g. surgery, lumbar puncture - Acute bacterial endocarditis - Persistent hypertension (BP ≥230/120) - Liver failure and INR>2 - Patients with contraindication for thromboprophylaxis should be considered for mechanical thromboprophylaxis with intermittent pneumatic compression (IPC). When clinical condition improves and patient is moved to a downstream ward, standard prophylactic LMWH should be prescribed until discharge

Appendix 3: Algorithm for the management of coagulopathy in COVID-19 from the ISTH (2020)



Appendix 4: Thromboprophylaxis search strategy May 5th 2020

Source	Search
Pubmed 20th April	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, pro-coagulant, pro-thrombotic, hypercoaguable, venous thromboembolism, pulmonary embolism, coagulopathy, disseminated intravascular coagulopathy, pulmonary intravascular coagulopathy, venous thromboembolism, immunothrombosis, thromboprophylaxis, anticoagulant/anticoagulation, enoxaparin, heparin, alteplase
LitCovid	COVID-19, coronavirus, AND/OR thromboembolism, pro-coagulant, pro-thrombotic, hypercoaguable, venous thromboembolism, pulmonary embolism, coagulopathy, disseminated intravascular coagulopathy, pulmonary intravascular coagulopathy, venous thromboembolism, immunothrombosis, thromboprophylaxis, anticoagulant/anticoagulation, enoxaparin, heparin, alteplase
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, pro-coagulant, pro-thrombotic, hypercoaguable, venous thromboembolism, pulmonary embolism, coagulopathy, disseminated intravascular coagulopathy, pulmonary intravascular coagulopathy, venous thromboembolism, immunothrombosis, thromboprophylaxis, anticoagulant/anticoagulation, enoxaparin, heparin, alteplase
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) and anticoagulation, hypercoaguable, heparin, enoxaparin, alteplase
EudraCT	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) AND anticoagulation, hypercoaguable, heparin, enoxaparin, alteplase