Debate: Should the dose or duration of anticoagulants for the prevention of venous thrombosis be increased in patients with COVID-19 while we are awaiting the results of clinical trials?

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Introduction

The World Health Organization declared COVID-19 a pandemic on 12th March 2020. Within a few weeks it became clear that venous thrombosis (VTE) is a frequent complication of COVID-19, particularly in the more severe cases.[1] Thrombotic events were occurring despite the use of prophylactic, low-molecular weight heparin (LMWH) at standard doses and significantly contributing to overall morbidity and mortality. Table I lists some of the largest published cohort studies (>75 patients) of thrombosis rates in COVID-19. There are some caveats to be considered when assessing the results. Thrombosis was not radiologically confirmed in all studies and screening with imaging was used in some, so that asymptomatic cases were included. Thrombosis prevention strategies differed with some later studies using intermediate or VTE treatment doses of LMWH alongside prophylactic doses. Because of the varying methodology, patient characteristics and thromboprophylaxis modifications, it is difficult to summate the results from these studies. We can surmise that in COVID-19 patients admitted to intensive care units (ICUs) on pharmacological thromboprophylaxis the VTE rate ranged from 18–47% and in patients on the general ward it was 3–7%. Two studies reported that these rates were much higher than those previously observed in their ICU patients with non-COVID infective acute respiratory distress syndrome (ARDS) of 6–8%.[2,3] However, the largest prospective study of septic patients on ICU prior to the COVID-19 pandemic showed a VTE rate of 37% in those on thromboprophylaxis.[4] A retrospective study of ICU patients with ARDS due to severe acute respiratory syndrome coronavirus (SARS-CoV) showed a VTE rate of 30% on thromboprophylaxis.[5] Similarly, a retrospective study of influenza H1N1 patients with ARDS found a VTE rate of 44% in patients on thromboprophylaxis with LMWH or unfractionated heparin.[6] It would seem that while there is undoubtedly a high rate of VTE associated with severe COVID-19, the rate is similar to other infective causes of ARDS.

Very few studies have reported on the haemorrhage rate and only one of the aforementioned studies has specifically considered this as a primary outcome measure alongside the thrombosis rate.[7] In this cohort, just over half the patients received VTE treatment doses of anticoagulation and the rate of significant haemorrhage was 21%. Although, there is currently no published clinical trial data that shows increased doses of anticoagulation to be effective at reducing the thrombosis rate, there is some retrospective data suggesting better survival rates with therapeutic anticoagulation.[8,9] Other studies have not found any benefit, and furthermore, it is not clear whether any benefit in reduction of thrombosis rates is not offset by an increased bleeding risk.[10] Several professional organisations have stated that clinical studies of therapeutic options for preventing VTE are of paramount importance in developing effective management strategies to combat COVID-19.[11]

While the results from clinical trials are awaited, clinicians have been looking for guidance on how to reduce the thrombosis risk. On 21st May 2020 the International Society on Thrombosis and Haemostasis (ISTH) published guidance statements that reflected the opinions of an expert panel.[12] The panel agreed that standard dose thromboprophylaxis should be offered to non-ICU hospitalized patients with COVID-19, but 30% felt that an intermediate dose could be considered. Presumably, the remaining 70% did not agree with this view. Half the panel felt that intermediate dose LMWH could be considered in high-risk ICU patients after weighing up the bleeding risk. A different expert panel convened by the American College of Chest Physicians (ACCP) published guidance on 2nd June that disagreed with this view, and suggested that standard dose thromboprophylaxis should

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Table I. Venous thrombosis rates in COVID-19 patients in studies with more than 75 patients.

Reference	Cohort, number studied	Anticoagulation type, (%)	Venous thrombosis rate (%)	Bleeding Rate (%)
Klok *et al*[35]	ICU, 184	Prophylactic	31	Not stated
Helms *et al*[2]	ICU with ARDS, 150	Prophylactic 70, Therapeutic 30	18	3
Maatman *et al*[46]	ICU with ARDS, 109	Prophylactic 94, Therapeutic 6	28	Not stated
Poissy *et al*[3]	ICU, 107	Prophylactic	21 (PE)	Not stated
Middeldorp *et al*[18]	ICU, 75	Prophylactic/ Intermediate	47	Not stated
	General ward, 123	(+ Antiplatelets in 21)	3	Not stated
Lodigiani *et al*[20]	ICU, 62	Prophylactic	28	Not stated
	General ward, 326	Prophylactic 75	7	Not stated
Fraissé *et al*[7]	ICU with ARDS, 92	Prophylactic 47, Therapeutic 53	34	21

ICU, intensive care unit; ARDS, acute respiratory distress syndrome; PE, pulmonary embolism.

be used in preference to intermediate or VTE treatment doses.[13] This document also suggested that LMWH was preferred over unfractionated heparin and direct oral anticoagulants for thromboprophylaxis because of the high likelihood of drug interactions and renal impairment in this group of patients. Both the ISTH and ACCP guidance reiterated the lack of evidence for the efficacy and safety of increased intensity anticoagulation and the urgent need for clinical trials.

Guidance published in the UK on the website of the Faculty of Intensive Care Medicine on 19th June 2020[14] stated that patients receiving ward-based care should receive standard thromboprophylaxis, but that those in critical care should receive intermediate doses. This document states that increased doses of LMWH may even be considered for general ward patients with two or more additional risk factors. While the lack of evidence for the role of anti-platelet therapy is pointed out, there is no mention of the lack of evidence for increased doses of anticoagulation nor discussion of the potential bleeding risks. The British Society of Haematology was asked to endorse this guideline but felt that in the absence of the necessary evidence, it could not support these recommendations nor produce consensus guidance of its own. The British Thoracic Society set out a 'possible approach to LMWH dosing' that suggested intermediate doses of LMWH for higher risk patients identified by parameters such as D-dimer thresholds.[15] In the absence of clear evidence that these approaches led to better clinical outcomes it was acknowledged that there is a need for clinical trials of higher doses of LMWH in COVID-19 patients. A summary of the statements and recommendations on anticoagulation dosing is given in Table II.

In the UK, two proposals for standalone studies of anticoagulation in COVID-19 were submitted to the National Institute for Health Research during March 2020, but were, unfortunately, rejected. Fortunately, many similar studies have been implemented globally. A search on the clinicaltrials.gov website of interventional studies of anticoagulation in COVID-19 on 19th September 2020 returned 23 studies. All of these studies are comparing VTE treatment or intermediate doses of anticoagulants [mostly LMWH, but also direct oral anticoagulants (DOACs)] with prophylactic anticoagulation (mostly LMWH but also unfractionated heparin). Some studies include other interventions such as antiplatelet therapy or fondaparinux. Those aiming to enrol 200 or more participants are listed in Table III. Several studies are aiming to complete recruitment by the end of 2020. Currently, the multi-intervention randomised, embedded, multifactorial, adaptive platform trial for community-acquired pneumonia (REMAP-CAP) study is the only open trial of different doses of anticoagulation in the UK. This is the largest COVID-19 study in terms of participant number, and although the trial as a whole is scheduled to close in 2023, outcome data for specific interventions will be released before this date.

In the UK, several institutions have introduced local protocols using intermediate or higher doses of LMWH for thromboprophylaxis in COVID-19. While we are awaiting the results of clinical trials, this article debates whether the dose or duration of anticoagulants given for the prevention of VTE should be increased in patients with COVID-19.

Yes - Mike Laffan

The spread of COVID-19 in Europe was rapidly followed by a realisation not only that the rate of thrombosis in critically ill COVID-19 patients was exceptionally high, but that thrombosis within the pulmonary vasculature itself was an important part of its pathophysiology. This prompted the question as to whether intensified thromboprophylaxis would be of benefit and several proposals to test this hypothesis in the UK were made but rejected. Faced with a new and important problem with no trial data and no trial available, the appropriate response is to utilise what is known about the disorder and about the available therapies, to formulate a logical therapeutic plan.

Many, but not all, of the guidelines published regarding thromboprophylaxis for COVID-19 adhere to existing guidelines for general medical or surgical admissions. The

Table II. Summary of published statements on treatment of thromboprophylaxis in COVID-19.

Organisation	Date published	ICU patients	General ward patients
British Thoracic Society	4th May 2020	• Standard thromboprophylaxis • Consider higher doses of LMWH in a proportion of patients • D-dimer may indicate risk	• Not specifically discussed
International Society on Thrombosis and Haemostasis	21st May 2020	• Standard thromboprophylaxis after considering the bleeding risk • Consider intermediate dose LMWH in high-risk patients (50% of panel)	• Standard thromboprophylaxis after considering the bleeding risk • Consider intermediate dose LMWH (30% of panel)
American College of Chest Physicians	2nd June 2020	• Standard dose LMWH preferred over intermediate or higher doses	• Standard dose LMWH during in-patient stay only
Global COVID-19 Thrombosis Collaborative Group	16th June 2020	• Standard thromboprophylaxis • Insufficient data to recommend intermediate or therapeutic doses	• Standard thromboprophylaxis • Insufficient data to recommend intermediate or therapeutic doses
Faculty of Intensive Care Medicine	19th June 2020	• Intermediate or higher doses of LMWH	• Standard dose LMWH • D-dimer levels alone should not be used to guide LMWH dosing

ICU, intensive care unit; LMWH, Low-molecular weight heparin.

limitation of this approach is that guidelines, like the studies on which they are based, apply to specific groups of patients, and so it is important to ask whether they apply to the patient(s) you are treating. Do hospitalised and critically ill patients with COVID-19 match the database?

The major quoted meta-analysis of thromboprophylaxis for critically ill patients contained 7226 patients but only 3000 were in studies comparing thromboprophylaxis with placebo and 1935 of these were from a trial comparing recombinant activated protein C with placebo. Nonetheless, the analysis reported an odds ratio (OR) (95% confidence interval) for deep vein thrombosis (DVT) of 0·51 (0·41–0·63) and pulmonary embolism (PE) of 0·52 (0·28–0·97).[16] Notably, it was not significant for symptomatic DVT: there was no increase in bleeding and the PE rates were only 1% in the heparin arm and 1·9% in the placebo arm. The thrombosis risk may be higher in critically ill sepsis patients. The series of 113 patients with sepsis reported by Kaplan *et al.* did report a high incidence of thrombosis at 37%, but 16 of42 thromboses were catheter-related and symptomatic PE occurred in only 3·5%,[4] this was despite receiving standard thromboprophylaxis. Are these figures comparable to COVID-19?

Multiple reports have documented very-high rates of thrombosis, particularly PE, in patients with COVID-19 admitted to ICU, despite, at least standard, thromboprophylaxis. Poissy *et al.* found that 21% of COVID-19 ICU patients had PE compared to 6·1% in the same period the previous year, despite similar severity scores. This was also higher than the incidence of PE in influenza patients admitted a month before (7·5%).[3] In a French, multicentre study of 150 consecutive patients admitted to ICU with COVID-19, all patients received some form of anticoagulation therapy (70% prophylactic dose and 30% at therapeutic dose) and yet relevant thrombotic complications occurred in 43% of patients, including 16·7% with PE.[2] Matching to non-COVID patients admitted to ICU revealed that thrombotic complications were much more frequent in the COVID patients: OR 2·6 91·1–6.1), ($P = 0·035$), with significantly more PE, OR 6·2 (1·6–23.4), ($P = 0·008$). In both these studies the PE were objectively diagnosed by computed tomography pulmonary angiography.

In their updated analysis of 184 patients, Klok *et al.* reported a cumulative incidence of 49% for all thrombotic events and 42% (or 87% of all VTE) were PE, despite all their patients receiving LMWH thromboprophylaxis.[17] Excluding subsegmental PE, the figure is still 27% of cases. Middeldorp *et al.* reported on 198 patients and found the cumulative risk of PE at 21 days to be 15% for ICU patients.[18] Once more, all patients had received LMWH and latterly at an increased dose. Several other studies have reported high rates of thrombosis.[19–22]

Certainly these data are at risk of bias from various factors including counting methods and incomplete follow-up and some thrombosis-in situ may have been mislabelled as embolic. But it seems clear that the frequency of thrombosis, and in particular of PE in patients with COVID-19, is much higher than in any previous reports of ICU patients, with or without sepsis and persists despite the use of standard thromboprophylactic regimens recommended in standard guidelines.

A natural response to these data is to conclude that the intensity of thromboprophylaxis should be increased. But when moving beyond trial data it is important to consider

Table III. Clinical trials of anticoagulation in COVID-19 with 200 or more participants listed on the clinicaltrials.gov website on 19th September 2020.

Study and trial Number	Location	Expected participant number	Enrolment start	Estimated end
RAPID COVID-COAG NCT04362085	Canada	462	May 2020	December 2020
A Randomized Trial of Anticoagulation Strategies in COVID-19 NCT04359277	USA	1000	April 2020	April 2021
INSPIRATION NCT04486508	Iran	600	July 2020	December 2020
COVID-HEP NCT04345848	Switzerland	200	April 2020	November 2020
RAPID-BRAZIL NCT04444700	Brazil	462	July 2020	December 2020
ACTION NCT04394377	Brazil	600	June 2020	December 2020
HEP-COVID NCT04487990	USA	308	April 2020	April 2021
Antithrombotic Strategies in Hospitalized Adults With COVID-19 NCT04505774	USA	2000	September 2020	December 2021
COVID-PACT NCT04409834	USA	750	August 2020	May 2021
REMAP-CAP NCT02735707	Global	7100	April 2020	December 2023
ATTACC NCT04372589	North, Central and South America	3000	May 2020	January 2021
CORIMMUNO-COAG NCT04344756	France	808	April 2020	September 2020
COVI-DOSE NCT04373707	France	602	May 2020	October 2020
X-COVID-19	Italy	2712	May 2020	November 2020

what mechanistic and observational data are available to guide such an alternative strategy. It is not necessarily true that more anticoagulation will reduce the rate of thrombosis, some of which may be driven by a variety of inflammatory mechanisms, and secondly, such a move may result in an unacceptable rate of bleeding.

However, there is a logical argument for increasing the intensity of heparin. One of the most striking characteristics of COVID-19 has been the remarkably high levels of D-dimer. This been shown to be a powerful (possibly the most powerful) predictor of thrombosis and mortality[23] and results from thrombin production; other indicators including prothrombin fragment 1 + 2 and thrombin-antithrombin complexes are also elevated. Heparin is a potent, albeit indirect, inhibitor of thrombin and increased doses have been shown to reduce the progressive rise in D-dimer in these patients.[24] As already noted, heparin at standard doses is effective in reducing the rate of thrombosis in acutely unwell patients.

Preventing VTE would be a good reason for intensifying thromboprophylaxis, but there is also extensive evidence that small vessel thrombosis in COVID-19 is part of the pathophysiology leading to vascular shunting and hypoxemia. Imaging and postmortem studies have confirmed the presence of widespread, small and large vessel thrombotic occlusions. In keeping with this, we found that tissue plasminogen activator thrombolysis can be successful in restoring oxygenation.[25] Although the composition of these thrombi may be complex, including neutrophil extracellular traps, von Willebrand factor and platelets as well as fibrin, inhibition of thrombin is likely to reduce their formation.

Intensified anticoagulation may, therefore, reduce thrombosis, improve lung function and improve prognosis; a hypothesis supported by empirical data. Obi *et al*. recorded a 37% rate of thromboembolic events (29% PE) among patients with H1N1 compared to 6·2% for all other ICU patients over the preceding 5 years.[6] They instituted a programme of therapeutic heparinisation to deal with this, and

in multivariate analysis, adjusting for H1N1 status, non-anticoagulated patients were 33 times more likely to have any VTE compared with those treated with empirical therapeutic anticoagulation ($P = 0.01$). More recently, data from Mount Sinai Hospital showed an improved outcome in patients admitted to ICU who received therapeutic anticoagulation.[8] A subsequent paper from the same group showed lower (but not significant) mortality on therapeutic compared to prophylactic anticoagulation.[26] Our own data using graded thromboprophylaxis are in keeping with this.[27]

Increasing prophylaxis intensity runs the risk of increasing bleeding problems but not necessarily so, given the highly prothrombotic nature of this infection. The meta-analysis of thromboprophylaxis by Alhazzani *et al.* found no difference in the risk of major bleeding between heparin prophylaxis and placebo.[16] Historical data suggest a moderate or severe bleeding rate of 3·5% in patients receiving therapeutic heparin in hospital.[28] These compare well with the thrombosis rates reported above for COVID-19. Moreover, in the studies by Obi *et al.*,[6] Hsu *et al.*,[24] and Paranjpe *et al.*,[8] there was no increase in bleeding events associated with increased anticoagulation intensity.

Increasing intensity of thromboprophylaxis, therefore, represents a reasonable approach to a pressing clinical problem and is supported by logic, mechanistic evidence and observational clinical data, without evidence of increased bleeding or other detriment. Establishment of such an approach in guidelines will require randomised clinical trials, which are now under way and should be supported; however, for centres not participating in a relevant trial and for many patients who are ineligible for a trial, intensified thromboprophylaxis may be justified.

However, both as an interim measure and in trials it would be a mistake to replace one blanket recommendation with another. It is now clear that the spectrum of COVID-19 disease is much wider than was apparent in March 2020. Many patients have a mild disease not requiring admission and not all those admitted will require ICU support. The focus of the case for intensified anticoagulation is on those patients with a severe and potentially fatal disease who develop or are developing respiratory failure. A graded response is required to identify patients at risk and most likely to benefit. The obvious candidate for this measure is D-dimer, which shows exactly this relationship.[23] An alternative marker for intensification may be C-reactive protein.[29]

Similarly, we should be more sophisticated in the amount of heparin given to the selected patients and some authors have recognised this instituting 'intensified' thromboprophylaxis as an intermediate between standard prophylaxis and 'therapeutic' anticoagulation. We should also consider additional modifiers. For example, there is evidence that larger patients require larger doses of LMWH to achieve the same level of anti-factor Xa activity[30] and that the inflammatory response reduces the expected anti-factor Xa level.[31]

This is not a suggestion to formulate an alternative guideline; there are insufficient data to do so. Rather, in the absence of applicable trial data, we should assess the individual risk, using available data and understanding to provide an individual therapy balancing thrombotic and haemorrhagic risks. In critically ill patients with COVID-19, a reasonable conclusion will often be that higher than usual doses of anticoagulants are warranted.[27]

No - Charlotte Bradbury and Keith Gomez

Changing clinical practice before there is adequate data to support a new approach, is contradictory to evidence-based medicine.[32] There have been many examples throughout medical history where what has been considered the correct approach based on theory or preconceived beliefs, has in fact subsequently been proven to be harmful. For example, resting in bed used to be recommended for many conditions such as pulmonary embolism and myocardial infarction, but it is now known that this can be harmful and early mobilisation is beneficial (CG172).[33] Closer to the subject of this debate, is the use of aspirin as primary prophylaxis against myocardial infarction. Early small studies suggested that it was of benefit and because doctors and patients believed in 'doing something', aspirin was widely prescribed. However, large randomised clinical trials subsequently showed no benefit and possibly harm.[34]

The COVID-19 pandemic has generated a sense of urgency to react, with rapid publications, guidelines and changing practice before there has been solid evidence to support any changes. While there is no doubting the need for rapid dissemination of data, many of these publications have not been through the peer review process and are of a lower quality than would normally be acceptable for scientific literature. The guidelines and local protocols that have been written were based largely on expert opinion rather than solid evidence, resulting in recommendations that often contradict each other. This sows confusion and variation in clinical practice, defeating the very purpose of guideline writing. There is much disagreement in recommended dosing of anticoagulation for VTE prevention, whether D-dimer results should inform dosing, whether critical care patients should routinely receive higher doses and whether and how post-discharge thromboprophylaxis should be given.

Early publications on COVID-19 indicated that disseminated intravascular coagulation (DIC) was common and many UK hospitals routinely implemented DIC scoring for COVID-19 patients.[9] In fact, although D-dimers are raised, fibrinogen is usually high with normal platelet counts and clotting screens. In addition, although a high rate of thrombosis has been consistently reported,[35] most of the early studies did not report data on rates of bleeding. One guideline recommended replacement of fibrinogen in non-bleeding patients with COVID-19 and levels < 2.0 g/l, but this was not based on evidence and would be counter to what is

recommended in other acquired coagulopathies (e.g. DIC or liver dysfunction).[36]

Many protocols and guidelines recommended prolonged post-discharge thromboprophylaxis with LMWH or DOAC for patients admitted to hospital for COVID-19, as post-discharge VTE rates were predicted to be high. However, when rates of post-discharge VTE were reported, these were far lower than expected at approximately 0·5% of admissions.[37] This does not justify routine prophylactic anticoagulation, particularly when there is a bleeding rate of 3·7% after discharge.[38] Some guidelines also recommend escalated heparin doses based on D-dimer results.[15] The rationale for this has been that D-dimer is associated with worse outcome in COVID-19 and is a test used in the diagnostic algorithm for VTE diagnosis as well as a predictor of secondary VTE recurrence. However, there is no evidence that in patients with high D-dimer results, the poorer outcomes are because of thrombosis, let alone that escalated anticoagulation can improve the outcome. Indeed, we are all aware that D-dimer rises with inflammation and patients with severe COVID-19 have markers of profound inflammation. Although some retrospective data has shown an association of higher D-dimer levels in patients with VTE and COVID-19, importantly this does not equate to D-dimer levels predicting VTE as raised D-dimer may follow rather than precede the VTE event. For these reasons, other guidelines that also promoted higher intensity anticoagulation have specifically recommended not using D-dimer to guide anticoagulation dosing.[13,14]

It may seem logical to escalate anticoagulation thromboprophylaxis for patients with COVID-19 in the same way that our predecessors considered it logical to confine patients with pulmonary embolism to bed rest. However, the mechanism of thrombosis in COVID-19 is complex and includes direct infection and damage to the endothelium, with vascular inflammation and immunothrombosis.[39] Therefore, it cannot be assumed that inhibition of thrombin generation by anticoagulation will be an effective strategy. In some other circumstances where thrombosis complicates vascular inflammation, such as Beçhet disease, therapeutic anticoagulation has very limited efficacy in the absence of immunomodulation.[40] The other key concern is that escalated anticoagulation will increase major bleeding to an extent that outweighs any benefit in thrombosis-risk reduction. This has turned out to be the case when extending thromboprophylaxis beyond discharge in medical patients. There is a reduction in VTE, but also an increase in major bleeding, so that overall, there is no net benefit.[41] Major bleeding in patients with COVID-19 is not rare, especially in the ICU ventilated cohort.[7,42] Another issue is that routinely escalating anticoagulation to therapeutic doses for VTE prevention will sometimes result in the assumption that there is no need to diagnose VTE as 'that base is covered'. That is, of course, not true as the duration of anticoagulation would be longer if VTE is diagnosed and if VTE occurs in an anticoagulated patient, a change in anticoagulation management is indicated.

It could be argued that changing protocols and writing guidance without the necessary supporting evidence is worse than no change, as this undermines subsequent efforts to gather reliable data in a trial setting. When clinical trials are available, some clinicians may not feel comfortable recruiting patients because of a belief that the correct approach is known and there is no longer the clinical equipoise needed to randomise patients. As an example, for the REMAP-CAP anticoagulation domain there were two reasons investigators gave for declining this study. The first was that clinicians believed all patients should be on therapeutic anticoagulation and the second was concern that therapeutic anticoagulation was an unsafe, high-risk strategy for ICU patients. Clearly both of these opposite points of clinical equipoise could not be correct. Interestingly, when corticosteroids were initially being trialled in COVID-19, some clinical investigators refused to take part due to concerns that this would cause harm by immunosuppressing patients who have active viral infection. Subsequently, randomised trials and meta-analysis have shown survival benefit with modest doses of corticosteroid.[43]

All data that is neither prospective nor randomised is subject to publication bias and only limited conclusions can be drawn. Although there are retrospective reports of hospitalised patients with COVID-19 receiving therapeutic anticoagulation, the results are conflicting with many likely confounders. Prospective data, particularly randomised controlled trials, are the best way to assess the safety and efficacy of a new approach. Using treatments without good evidence of efficacy and safety raises ethical concerns. Within a clinical trial the potential risks and benefits are explained so that patients can make an informed choice as to whether they wish to receive an unproven treatment or not. No such safety net is afforded to patients receiving off-license treatments through local protocols. Additionally, this practice undermines the national effort to answer questions about the role of anticoagulation as soon as possible. This concern was highlighted in a joint letter sent by the Chief Medical Officers to all NHS trusts in April 2020.[44] This stated: '*We strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible. Use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others*'.

In conclusion, it is far preferable to participate in randomised trials than alter standard care or write guidelines based on anecdote, theory and limited, poor-quality evidence.[45] We encourage the use of non-standard anticoagulation, but only within the setting of a clinical trial as this is the approach that will identify the best management strategies. There are many trials open and actively recruiting that will be able to properly assess the efficacy and safety of escalated anticoagulation protocols in hospitalised patients with COVID-19 as well as whether D-dimer results should influence intervention. These trials include Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC),

REMAP-CAP, REMAP-CAP COVID-19 and Accelerating COVID-19 Therapeutic Interventions (ACTIV)-4 with a combined current recruitment to anticoagulation randomisation of > 750 and an agreement for data sharing to enable a meaningful result as soon as possible. Our duty as doctors is to support these studies as opposed to adopting local protocols advocating off-license use that undermines them.

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