COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year

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COVID-19 is associated with a high incidence of thrombotic complications, which can be explained by the complex and unique interplay between coronaviruses and endothelial cells, the local and systemic inflammatory response, and the coagulation system. Empirically, an intensified dose of thrombosis prophylaxis is being used in patients admitted to hospital with COVID-19 and several guidelines on this topic have been published, although the insufficiency of high quality and direct evidence has led to weak recommendations. In this Viewpoint we summarise the pathophysiology of COVID-19 coagulopathy in the context of patients who are ambulant, admitted to hospital, and critically ill or non-critically ill, and those post-discharge from hospital. We also review data from randomised controlled trials in the past year of antithrombotic therapy in patients who are critically ill. These data provide the first high-quality evidence on optimal use of antithrombotic therapy in patients with COVID-19. Pharmacological thromboprophylaxis is not routinely recommended for patients who are ambulant and post-discharge. A first ever trial in non-critically ill patients who were admitted to hospital has shown that a therapeutic dose of low-molecular-weight heparin might improve clinical outcomes in this population. In critically ill patients, this same treatment does not improve outcomes and prophylactic dose anticoagulant thromboprophylaxis is recommended. In the upcoming months we expect numerous data from the ongoing antithrombotic COVID-19 studies to guide clinicians at different stages of the disease.

Introduction

COVID-19 is caused by SARS-CoV-2, which is a highly transmissible and pathogenic coronavirus causing the current pandemic and affecting billions of people worldwide. SARS-CoV-2 infection is frequently asymptomatic, but 20% of patients require admission to hospital and the estimated infection fatality risk increases with age—up to 14% in those aged 75 years or older.[1] Besides respiratory failure, severe COVID-19 is characterised by high rates of thromboembolic complications and, even in the absence of clinically relevant macrothrombi, procoagulant markers such as D-dimers are often substantially increased.[2,3] Therefore, COVID-19-associated hypercoagulability has gained huge interest and a large number of clinical trials aimed at improving outcomes with antithrombotic therapies have started. In this Viewpoint we summarise what is currently known about COVID-19-associated hypercoagulability, with a focus on novel insights gained from randomised trials conducted last year, and we place these trials into perspective and integrate them with clinical guidelines. Additionally, we elaborate on antithrombotic knowledge gaps that still remain in relation to COVID-19 but will most likely be answered in the upcoming months by the ongoing randomised clinical trials.

Clinical features of COVID-19-associated coagulopathy

Aside from markedly increased mortality rates and the severe inflammatory response observed in critically ill patients with COVID-19, SARS-CoV-2 infections are characterised by a high prevalence of thrombotic complications.[4,5] A recent meta-analysis[6] identified 66 relevant studies in patients with COVID-19 and showed an estimated overall prevalence of venous thromboembolism of 14·1% (95% CI 11·6–16·9). Notably, studies which were included showed a high heterogeneity with regard to design, clinical setting, screening strategies for venous thromboembolism, and event rates. However, across all studies, patients in the intensive care unit (ICU) had a higher venous thromboembolism prevalence than those who were not in the ICU; around 45·6% (95% CI 31·0–66·2; I^2=91·0%) for patients in the ICU in studies that applied routine screening strategies compared with 23·0% (3·2–52·5; I^2=96·5%) in routinely screened patients who were not in the ICU. The venous thromboembolism event rates in COVID-19 are considerably higher than those previously reported in acutely ill surgical and non-surgical patients admitted to the ICU,[7–9] and at least three times higher than in critically and non-critically ill patients admitted to hospital with other viral respiratory infections.[4,10,11] In non-hospitalised patients with COVID-19—ie, those with mild disease—the incidence of venous thromboembolism is unknown. A recent study[12] found a venous thromboembolism incidence of 2·6% in the first 90 days after hospital discharge in patients who did not use anticoagulant therapy or prophylaxis, but another study[13] found a much lower incidence of 4·8 per 1000 discharged patients, which was similar to the incidence shown in patients who were discharged after admission for non-COVID-19 related disease. In addition to venous thromboembolism, increased prevalence of arterial thrombotic events such as myocardial and cerebral infarction (up to 3%, 95% CI 2–5% in an ICU setting) has been reported,[14] and remarkably high numbers of thrombosis in extracorporeal circuits (up to 8%) have been observed.[15] In accordance, autopsy studies showed high incidence of pulmonary macroemboli, but also revealed severe endothelial injury, increased angiogenesis, microemboli, and occlusion of alveolar capillaries in patients who died from COVID-19.[16,17] Notably, alveolar capillary microthrombi

were nine times as prevalent in patients with COVID-19 as in those who died of influenza.[17] These macrothrombi and microthrombi are caused by the strong procoagulant phenotype, which is also reflected by increased D-dimer, increased viscoelastic characteristics, and enhanced platelet activation in patients with COVID-19.[2,18–21]

Several studies[20,22] have reported an association between increased D-dimer concentration and poor prognosis. Other markers of coagulopathy such as platelet counts and prothrombin time are usually normal or slightly elevated in non-critically ill patients, with progressive aberrancies observed when the patient's clinical condition declines.

On the basis of clinical course and observed coagulation parameters, three stages of clinical COVID-19 coagulopathy have been proposed.[23] Stage 1 is characterised by mild symptoms without the need for oxygen supply or other respiratory support, mild systemic inflammation, and mildly systemic coagulopathy (figure). In stage 2, patients develop more severe symptoms and often require additional oxygen supply. This phase is characterised by progressive pulmonary inflammation and local coagulopathy with increased incidence of microthrombi (figure). In stage 3, the patient's condition deteriorates further and requires critical organ support such as high-flow oxygen therapy, mechanical ventilatory support, or circulatory support including extracorporeal membrane oxygenation. This stage is characterised by a strong proinflammatory reaction and development of overt local and systemic coagulopathy with high D-dimer and fibrinogen concentrations, prolonged prothrombin time, reduced platelet counts, and a very high incidence of pulmonary embolism and deep venous thrombosis.

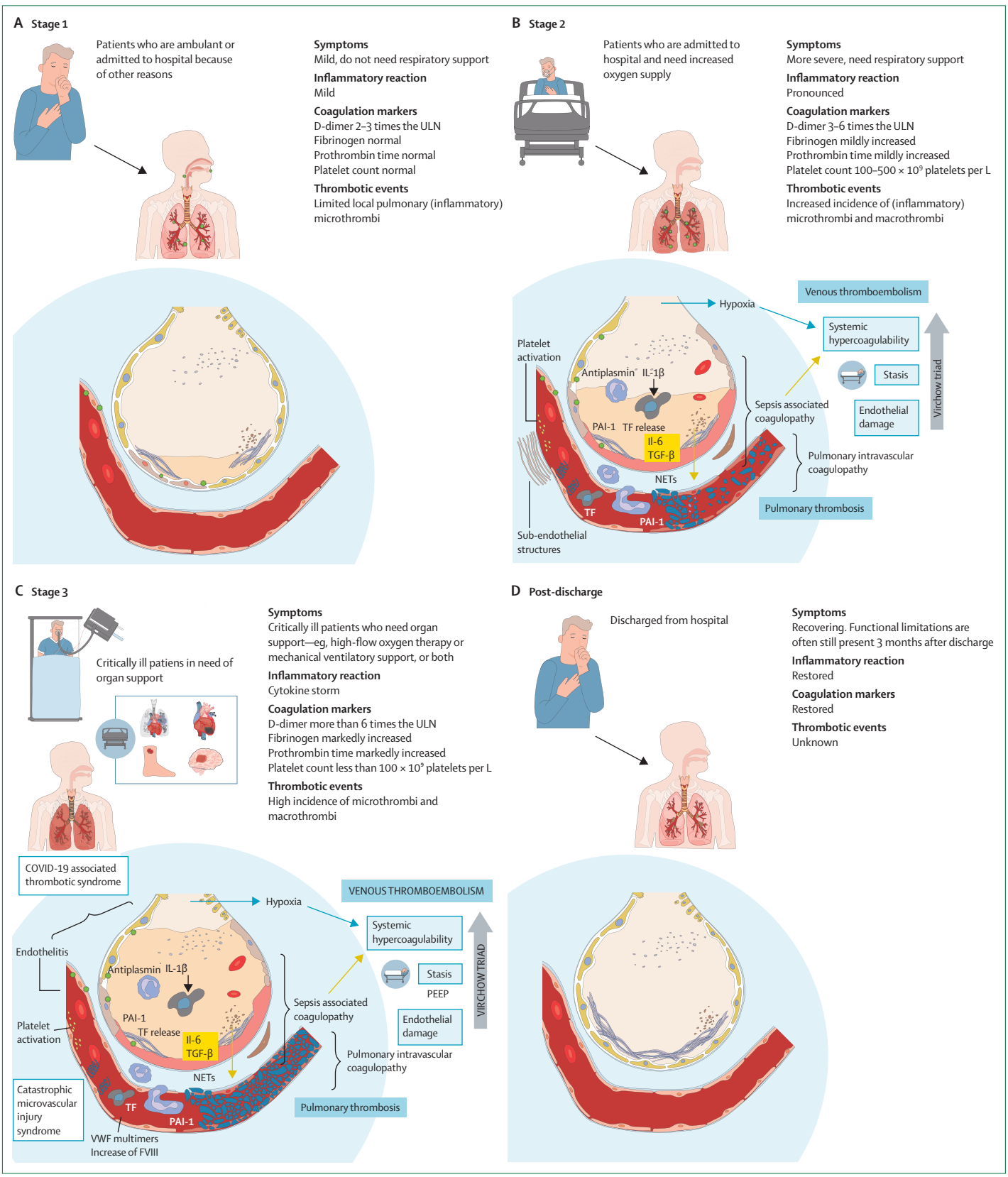
Pathophysiology of COVID-19-associated coagulopathy

The underlying pathophysiology of COVID-19 is currently being unravelled, and the complex interplay between direct effects of SARS-CoV-2 on pneumocytes and the endothelium, the local and systemic inflammatory response, and interaction with the haemostatic system have been deemed as central and unprecedented. The possible mechanisms of COVID-19-associated coagulopathy are described extensively and in detail elsewhere.[24] To provide rational advice on thromboprophylaxis, including in situations that have not yet been studied, such as in patients who are ambulant or post-discharge, we summarised the core pathophysiological processes of COVID-19 in clinical stages (figure). In around 20% of infected patients, the initial immune response will not be sufficient to control viral replication because of aberrancies in the immune response[25] or a high initial viral load, or both.[26,27] These patients will develop more severe symptoms and proceed to stage 2, in which the uncontrolled viral replication will lead to apoptosis of pneumocytes and endothelial cells which in turn will activate platelets, induce coagulation factors, and lead to increased inflammation (figure). This cascade of events will result in further destruction of pneumocytes, pulmonary microangiopathy, and (inflammatory) microthrombi causing more severe symptoms and the need for additional oxygen supply; although, a relative balance between procoagulant and anticoagulant as well as proinflammatory and anti-inflammatory factors seems to be maintained. In approximately 5% of symptomatic patients, proinflammatory processes derail into a so-called cytokine storm. This cytokine storm will fuel proinflammatory and procoagulatory processes even further, which will result in systemic endotheliitis and capillary leakage, cellular dysfunction, organ dysfunction (including acute respiratory distress syndrome), and overt activation of the (systemic) coagulation cascade resulting in the need for critical organ support (stage 3; figure). Although thrombogenicity of COVID-19 differs considerably from other severe infectious and non-infectious diseases,[28] increased bleeding risk, especially in severely ill patients, remains a serious concern because bleeding complications are facilitated by thrombocytopenia, platelet dysfunction or coagulation factor deficiencies, or both,[29,30] which are often present in critically ill patients with COVID-19.

To date, little is known about the resolution of lung abnormalities after patients have been discharged from hospital (stage 4; figure). Most patients who were admitted to hospital have functional limitations until 3 months after discharge. Residual pulmonary parenchymal abnormalities were present in 91% of patients admitted to hospital, but only 7% of those patients had mild disease.[31] This finding is in accordance with another study[32] which found that patients who had more severe illness during the hospital stay also had more severely impaired pulmonary diffusion capacities and abnormal chest imaging manifestations 6 months after discharge.

Anticoagulation and clinical course of COVID-19: observational evidence

In response to the observed thrombotic complications, several retrospective studies[33–40] have provided observational evidence on the potential benefit of therapeutic anticoagulant treatment in patients with COVID-19. Inconsistent results on the association between use of chronic therapeutic anticoagulation and outcome in COVID-19 have been published, probably because of the dissimilar cohorts and improper correction of imbalances in baseline characteristics, including comorbidities.[33–35] In propensity score-matched comparisons,[36,37] there were no statistically significant differences in mortality, time to mechanical ventilation, or length of hospital stay in patients who received and those who did not receive chronic anticoagulatory therapy (some of these data have been published in a preprint and have not been peer reviewed).[37] Additionally, several small case series describe major bleeding complications in patients with COVID-19 who received intermediate dosed thromboprophylaxis.[38–40] These findings underpinned the need for


A Stage 1
Patients who are ambulant or admitted to hospital because of other reasons
Symptoms
Mild, do not need respiratory support
Inflammatory reaction
Mild
Coagulation markers
D-dimer 2–3 times the ULN
Fibrinogen normal
Prothrombin time normal
Platelet count normal
Thrombotic events
Limited local pulmonary (inflammatory) microthrombi
B Stage 2
Patients who are admitted to hospital and need increased oxygen supply
Symptoms
More severe, need respiratory support
Inflammatory reaction
Pronounced
Coagulation markers
D-dimer 3–6 times the ULN
Fibrinogen mildly increased
Prothrombin time mildly increased
Platelet count 100–500 × 10⁹ platelets per L
Thrombotic events
Increased incidence of (inflammatory) microthrombi and macrothrombi
Hypoxia
Venous thromboembolism
Systemic hypercoagulability
Platelet activation
Antiplasmin
IL-1β
Stasis
Endothelial damage
Virchow triad
PAI-1
TF release
Il-6
TGF-β
Sepsis associated coagulopathy
Pulmonary intravascular coagulopathy
NETs
TF
PAI-1
Pulmonary thrombosis
Sub-endothelial structures
C Stage 3
Critically ill patiens in need of organ support
Symptoms
Critically ill patients who need organ support—eg, high-flow oxygen therapy or mechanical ventilatory support, or both
Inflammatory reaction
Cytokine storm
Coagulation markers
D-dimer more than 6 times the ULN
Fibrinogen markedly increased
Prothrombin time markedly increased
Platelet count less than 100 × 10⁹ platelets per L
Thrombotic events
High incidence of microthrombi and macrothrombi
COVID-19 associated thrombotic syndrome
Endothelitis
Hypoxia
VENOUS THROMBOEMBOLISM
Systemic hypercoagulability
Antiplasmin
IL-1β
Stasis
PEEP
VIRCHOW TRIAD
Sepsis associated coagulopathy
Platelet activation
PAI-1
TF release
Il-6
TGF-β
Endothelial damage
Pulmonary intravascular coagulopathy
NETs
Catastrophic microvascular injury syndrome
TF
PAI-1
Pulmonary thrombosis
VWF multimers
Increase of FVIII
D Post-discharge
Discharged from hospital
Symptoms
Recovering. Functional limitations are often still present 3 months after discharge
Inflammatory reaction
Restored
Coagulation markers
Restored
Thrombotic events
Unknown

well designed and large randomised controlled trials on the efficacy and safety of anticoagulant treatment in patients with COVID-19.

Randomised controlled trials

Early during the pandemic, an impressive number of randomised controlled trials investigating antithrombotic agents were designed, most of which are still in progress. In June, 2020, 6 months into the pandemic, 20 trials were already investigating increased dose anticoagulant interventions in patients admitted to hospital with COVID-19. These trials were succinctly summarised in a scoping review and call for international collaboration by the International Network of Venous Thromboembolism Clinical Research Networks.[41] In a preprint systematic review[42] that searched through trial registries up to December, 2020, and included any type of antithrombotic agent used at any stage of COVID-19 (ie, including non-hospitalised patients), 75 randomised controlled trials (some with multiple domains) were identified. All identified anticoagulant trials are summarised in the appendix (pp 1–4), according to clinical stage. All trials were open-label, most were multicentre, and study designs included adaptive design, multi-arm parallel group design, and factorial designs in flexible platform trials. Sample sizes ranged from 30 to 7000 participants and the pooled sample size of all trials included more than 50 000 participants. Importantly, most studies are not primarily designed to investigate thrombotic outcomes, and the primary endpoints included all-cause mortality and the need for organ support. Study results from trials investigating antithrombotic therapy are currently available from a few large collaborative, randomised controlled trials, in various clinical settings.[43] In table 1 and in this Viewpoint, we summarise and discuss the data from trials which have been communicated to the public domain either as preliminary results or as a full report, categorised by clinical setting.

Figure: **Clinical and pathophysiological staging in COVID-19**
(A) A good immune response will adequately control viral replication, resulting in mild symptoms in around 80% of infections. (B) Poorly controlled viral replication leads to apoptosis of pneumocytes and endothelial cells, which will activate platelets, induce coagulation factors such as TF, and release VWF multimers, and will lead to increased chemotaxis, cytokine and chemokine production, NET formation, and activation of the plasma kinin-kallikrein and complement system. Hypoxia contributes to the hypercoagulable state by increased expression of TF and PAI-1, decreased TF pathway inhibitor and protein S, and an increased inflammatory response and platelet activation. Further destruction of pneumocytes, pulmonary microangiopathy, and microthrombi cause more severe symptoms and need for additional oxygen supply. (C) The so-called cytokine storm fuels proinflammatory and procoagulatory processes further, resulting in systemic endotheliitis and capillary leakage, cellular dysfunction, organ dysfunction, and overt activation of the coagulation cascade, and leads to the need for organ support and a high prevalence of microthrombi and macrothrombi. (D) The timeframe of resolution of local inflammation and coagulation after discharge are still unknown. IL=interleukin. NETs=neutrophil extracellular traps. PAI-1=plasminogen activator inhibitor-1. PEEP=positive end-exploratory pressure. TF=tissue factor. TGF-β=transforming growth factor beta. ULN=upper limit of normal. VWF=von Willebrand factor.

ICU patients (stage 3)

Therapeutic dosed anticoagulation with heparin was studied in critically ill patients with COVID-19—ie, those admitted to the ICU, in three large international clinical trial platforms that decided to harmonise their study protocols and outcomes to acquire results as soon as possible. The collectively called multiplatform randomised controlled trials consist of the ACTIV-4 (NCT04505774), REMAP-CAP (NCT02735707), and the ATTACC (NCT04372589). The primary endpoint in these trials was organ support-free days up to day 21, which is an ordinal scale combination of in-hospital mortality and organ support-free days, with organ support defined as ICU level of care and receipt of mechanical ventilation, vasopressors, extracorporeal membrane oxygenation, or high flow nasal oxygen. On the basis of the data summarised in table 1, the multiplatform trial discontinued enrolment for ICU patients on Dec 19, 2020, after an interim analysis and advice from the data and safety monitoring board, because the prespecified futility boundary for the primary endpoint was reached and a potential for harm could not be excluded.[44] As shown in a preprint paper,[45] there were numerically fewer thrombotic events in patients assigned to therapeutic anticoagulation (27 [6%] of 471 *vs* 49 [10%] of 476 assigned to standard prophylaxis); however, the secondary efficacy outcome of major thrombotic events or death was similar between groups (200 [41%] of 483 *vs* 211 [43%] of 494, median adjusted odds ratio 1·05, 95% credible interval 0·79–1·41; posterior probability of futility 94·5%). Although the recommendation might be different if prevention of thrombosis was used as the primary outcome, the current outcome reflects morbidity and mortality, which in a pandemic are also more relevant from a health-care system and societal perspective. Notably, anticoagulation regimens were variable because in these pragmatic trials, therapeutic anticoagulation was used according to local treatment protocols in the participating centres, and the control group was heterogeneous because in many centres and countries intermediate dose thrombosis prophylaxis was adopted early in the pandemic.[51–54] However, subgroup analyses did not suggest a differential effect for sites using intermediate or low-dose thrombosis prophylaxis. In conclusion, therapeutic dose heparin does not improve clinical outcomes or mortality in critically ill patients with COVID-19 who require organ support and might even cause harm because there is a high probability of inferiority. Research on therapeutic anticoagulation in critically ill patients with COVID-19 is still ongoing (appendix p 1; preprint).[42]

Data from the INSPIRATION trial,[47] investigating the efficacy and safety of intermediate dose thrombosis prophylaxis with low-molecular-weight heparin (n=276 patients) versus the standard dose (n=286 patients),

See Online for appendix

	Design and methods	Intervention	Patients	Primary outcome (intervention *vs* control)	Key secondary outcomes (intervention *vs* control)
REMAP-CAP (NCT02735707), ATTACC (NCT04372589), and ACTIV-4 (NCT04505774)[44,45] (preprint)	Open-label, Bayesian, adaptive, multiplatform, randomised controlled trials	Therapeutic anticoagulation dose heparin (n=529) versus standard prophylaxis (n=545) as per hospital policy	Patients in the ICU	Organ support-free days up to day 21, including in-hospital mortality* (median 3 *vs* 5 days; adjusted OR 0·87, 95% CrI 0·70–1·08); posterior probability of futility 99·8%; posterior probability of inferiority 89·4%; posterior probability of superiority 10·6%	Hospital mortality (35·7% *vs* 34·7%; adjusted OR 0·88, 95% CrI 0·67–1·16); major haemorrhage as defined by the International Society on Thrombosis and Haemostasis[46] (3·1% *vs* 2·4%; 1·19, 0·57–2·49); major thrombotic events or death (41·4% *vs* 42·7%; 1·05, 0·79–1·41; posterior probability of futility 94·5%)
INSPIRATION trial (NCT04486508)[47]	Multicentre, randomised trial with a 2 × 2 factorial design	Intermediate dose heparin (n=276) versus standard prophylaxis (n=286)	Patients in the ICU (43% had low flow oxygen support at inclusion)	Primary endpoint (45·7% *vs* 44·1%; OR 1·06, 95% CI 0·76–1·48): a composite of adjudicated venous thromboembolism events (3·3% *vs* 3·5%; 0·93, 0·37–2·32) or acute arterial thrombosis events (ischaemic stroke 0·3% *vs* 0·4%), treatment with extracorporeal membrane oxygenation (none in both groups), or all-cause mortality within 30 days (43·1% *vs* 40·9%; 1·09, 0·78–1·53)	Length of stay in the ICU (6 days, 2–11 95% CI *vs* 6 days, 3–11); major bleeding according to Bleeding Academic Research Consortium[48] (type 3–5; 2·5% *vs* 1·4%; OR 1·83, 97·5% CI 0·00–5·93); clinically relevant non-major bleeds (4·3% *vs* 1·7%; 2·55, 0·92–7·04); severe thrombocytopenia (6 *vs* 0 patients)
ATTACC (NCT04372589), ACTIV-4a (NCT04505774), and REMAP-CAP (NCT02735707; unpublished interim analysis)[49]	Open-label, Bayesian, adaptive, multiplatform, randomised controlled trials	Therapeutic anticoagulation dose heparin (n=699) versus standard prophylaxis (n=699) as per hospital policy	Patients who are moderately ill (general ward)	Organ support-free days up to day 21, including in-hospital mortality: low D-dimer at baseline cohort (proportional median OR† 1·57, 95% CrI 1·14–2·19; posterior probability of superiority 99·7%); high D-dimer at baseline cohort (1·53, 1·09–2·17; posterior probability of superiority 99·1%)	Hospital mortality (5·7% *vs* 7·7%); major haemorrhage (1·6% *vs* 0·9%); thrombotic event rates (1·9% *vs* 3·2%)
Sulodexide trial (NCT04483830)[50]	Randomised placebo-controlled trial	Oral dose of sulodexide (500 lipoprotein lipase-releasing units twice a day; n=124) versus placebo for 21 days (n=119)	Ambulant patients who are at high-risk of complications	Need of hospitalisation (17·7% *vs* 29·4%; RR 0·6, 95% CI 0·37–0·96)	Need for supplemental oxygen (29·8% *vs* 42%; RR 0·71, 95% CI 0·5–1); mean length of hospital stay (mean 6·29 days [SD 4·1] *vs* 7·8 days [4·5]; p=0·21); thromboembolic events (2 *vs* 2); mortality rate (2% *vs* 6%; 0·41, 0·10–1·55); major haemorrhage (0 *vs* 1)

CrI=credible interval. ICU=intensive care unit. OR=odds ratio. RR=risk ratio. *Ordinal scale combination of in-hospital mortality and organ support-free days, with organ support defined as ICU level of care and receipt of mechanical ventilation, vasopressors, extracorporeal membrane oxygenation, or high flow nasal oxygen. †OR higher than 1 represents a benefit.

Table 1: **Summary of results from randomised controlled trials available in the public domain**

are also summarised in table 1. The primary efficacy outcome (a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days) occurred in 126 (45·7%) patients in the intermediate dose group and in 126 (44·1%) in the standard dose prophylaxis group. Major bleeding occurred in seven (2·5%) patients in the intermediate dose and four (1·4%) in the standard dose prophylaxis groups. Hence, based on results from the INSPIRATION trial, there is no rationale for the current widely used intermediate dose of low-molecular-weight heparin as thrombosis prophylaxis in critically ill patients with COVID-19. Notably, this study was designed by an international committee and was done in ten centres in Iran, which might affect the generalisability to other countries and health-care systems. The INSPIRATION trial population was heterogeneous and might not be categorised as ICU patients because 43% only receive low-flow oxygen support at the time of randomisation. The mortality rate was around 40% in both study groups, which is similar to the population of critically ill patients in the multiplatform trials. Moreover, not only the intermediate low-molecular-weight heparin dose was weight adjusted, but the standard dose thromboprophylaxis was also doubled in patients who weighed more than 120 kg, which is not part of standard practice elsewhere. Notably, the higher bleeding rate in the intermediate prophylaxis group is not driven by the higher dose per kg in patients with a bodyweight higher than 120 kg, because only four of these patients were included.

Studies investigating intermediate dose heparin in ICU patients are still ongoing. The REMAP-CAP study has amended its anticoagulation domain for critically ill patients and will start randomly assigning these patients to the intermediate or low dose thrombosis prophylaxis groups shortly.

We expect that data on antiplatelet agents will become available soon, but to our knowledge, results from randomised controlled trials have not yet been published.

Non-ICU patients admitted to hospital (stage 2)

ACTIV-4, REMAP-CAP, and ATTACC multiplatform trials also studied therapeutic dose anticoagulation in patients with COVID-19 admitted to hospital wards, referred to as moderate state. Moderately ill patients were a priori stratified according to baseline D-dimer (high, low, or missing), with a high D-dimer defined as at least twice the local upper limit of normal at baseline. Otherwise, the study design was similar to that in critically ill patients, with the same primary endpoint of organ-free support days up to day 21. For the moderately ill population, on Jan 21, 2021, the data and safety monitoring board recommended to discontinue enrolling patients because the prespecified boundary for superiority—ie, more than 99% posterior probability on the primary outcome—had been reached. At that time, 1772 patients were randomly assigned, and unadjudicated preliminary data from 1398 patients with an evaluable primary outcome were available (unpublished; based on the ACTIV-4, REMAP-CAP, and ATTACC trials; table 1).[49] As a post-hoc analysis, investigators estimated the need for organ support—eg, transitioning from the ward to ICU or receiving high flow nasal oxygen. Therapeutic anticoagulation decreased the need for organ support from approximately 25% to 18% in patients with a high D-dimer at baseline and from 19% to 13% in those with a low D-dimer at baseline.[49] Full study results with adjudicated outcome data from all randomly assigned patients are eagerly awaited, but given the Bayesian approach of the trial, the overall conclusion will probably be similar to the results which are already available. The number needed-to-treat to prevent one patient from transitioning to organ support (including high nasal oxygen) would be approximately 14 patients in those with high D-dimer at baseline and 16 in those with low D-dimer at baseline, and the number needed to prevent one death would be approximately 50 patients.[49] These results are promising, but they are not comprehensively communicated into the public domain or peer reviewed. The question arises whether guidelines and treatment protocols should be changed to include therapeutic anticoagulation in all patients admitted to the wards with COVID-19. On March 25, 2021, NICE adapted the COVID-19 rapid guidelines[55] to consider a therapeutic dose of low-molecular-weight heparin in patients with COVID-19 who are likely to be in hospital for at least 2 days, need supplemental oxygen, and have not yet received high-flow oxygen or other organ support. However, we are reluctant to change our clinical practice on the basis of preliminary data, and the generalisability of this study population to all patients should be judged first from the full paper to assess the risk–benefit balance. Once the paper is published after peer-review, this hesitation will potentially change into adoption in guidelines and practice during this fast-changing pandemic landscape, especially if results from ongoing studies addressing the effect of therapeutic anticoagulation in this population, such as the RAPID trial,[56] confirm these observed findings. Again, we expect that data on antiplatelet agents will become available in the near future, but to our knowledge, data from randomised controlled trials have not yet been published.

Ambulant (stage 1) and post-discharge patients

Ambulant and post-discharge patients are under-represented in the ongoing studies and high quality guidance on routine thromboprophylaxis use is not expected in the short term. A randomised controlled trial[50] on the use of sulodexide in 243 ambulant patients with COVID-19 who were at high risk of severe clinical progression due to chronic comorbidities was recently published. Sulodexide, a natural glycosaminoglycan with antithrombotic and profibrinolytic activities, affects haemostasis to a lower extent than heparin with a very low risk of bleeding. The SURVET study[57] showed that sulodexide can be used as an alternative treatment option for extended anticoagulation in patients with unprovoked venous thromboembolism, but it has not yet been approved for this indication. In the current COVID-19 study (NCT04483830), 22 of 124 patients required admission to hospital at 21 days follow-up in the sulodexide group compared with 35 of 119 in the placebo group (relative risk 0·6, 95% CI 0·37–0·96). The number of venous thrombotic events was low and similar in both groups, and no statistically significant difference in mortality or length of hospital stay was observed. Therefore, these results require further large-scale investigation.

Clinical guidelines

Table 2 provides an overview of several published guidelines on thromboprophylaxis in COVID-19, according to clinical stage. Various recommendations, particularly in terms of risk assessment and dosing of anticoagulant drugs (mainly low-molecular-weight heparin), have been issued. Clearly, the absence of high quality, randomised trials precluded firm conclusions and these recommendations were weak with limited evidence. Because of the high thrombogenicity of COVID-19 in more severe stages, all guidelines agree that low-molecular-weight heparin thromboprophylaxis should be administered to all patients admitted to hospital with COVID-19. However, the appropriate thromboprophylaxis approach in ambulant patients and the right dose for hospitalised patients remains a topic of debate. The only preprint paper[45] to date in ICU patients suggests that a therapeutic dose of low-molecular-weight heparin or unfractionated heparin does not improve clinical outcome and might be associated with increased risk of bleeding complications. Thromboprophylaxis with intermediate dose low-molecular-weight heparin is advised in some guidelines for critically ill or non-ICU patients with additional thrombotic risk factors. However, this approach has not

	Outpatient	In hospital	Intensive care unit	Post-discharge
National Institutes of Health (February, 2021)[58]	Not advised unless clear (other) indication	Routine dosed thromboprophylaxis; no routine antiplatelet therapy	Routine dosed thromboprophylaxis; no routine antiplatelet therapy	Extended thromboprophylaxis considered in patients at low risk for bleeding and high risk for venous thromboembolism, as per protocol for patients without COVID-19
International Society on Thrombosis and Haemostasis (May, 2020)[51,52]	Not mentioned	Routine dosed thromboprophylaxis in the absence of contraindications	Routine dosed thromboprophylaxis; increased dose considered in high-risk patients	No routine prophylaxis; anticoagulant thromboprophylaxis (low-molecular-weight heparin or direct oral anticoagulants) considered in high-risk patients* with low risk of bleeding
Anticoagulation forum interim clinical guidance (July, 2020)[53]	Not mentioned	Routine dosed thromboprophylaxis in the absence of contraindications	Increased intensity thromboprophylaxis	No routine prophylaxis; anticoagulant thromboprophylaxis considered in high-risk patients with low risk of bleeding
The American College of Chest Physicians (CHEST) guideline and expert panel report (June, 2020)[59]	Not mentioned	Routine dosed thromboprophylaxis in the absence of contraindications	Routine dosed thromboprophylaxis	No routine prophylaxis; anticoagulant thromboprophylaxis considered in high-risk patients with low risk of bleeding
International Society on Thrombosis and Haemostasis (August, 2020)[54]	All patients should be evaluated regularly, D-dimers should be measured and if >1500 ng/mL, low-molecular-weight heparin prophylaxis should be considered	Routine dosed thromboprophylaxis; increased intensity thromboprophylaxis should be considered in patients with additional risk factors†	Increased intensity thromboprophylaxis should be considered	Thromboprophylaxis is reasonable in patients with persistent immobility, high inflammatory activity or additional risk-factors, or both†
American Society of Hematology guidelines (February, 2021)[60]	Not mentioned	Routine dosed thromboprophylaxis in the absence of contraindications	Routine dosed thromboprophylaxis; increased intensity thromboprophylaxis considered in high-risk patients with low bleeding risk	Not mentioned
National Institute for Health and Care Excellence guidelines (November, 2020)[61]	Assess the risk of venous thromboembolism and bleeding; consider pharmacological prophylaxis if the risk of venous thromboembolism outweighs the risk of bleeding	Routine dosed thromboprophylaxis in the absence of contraindications	Increased intensity thromboprophylaxis should be considered	Assess the risk of venous thromboembolism and bleeding; consider pharmacological prophylaxis if the risk of venous thromboembolism outweighs the risk of bleeding
WHO guidance (January, 2021)[62]	No routine thromboprophylaxis	Routine dosed thromboprophylaxis	Routine dosed thromboprophylaxis	No routine thromboprophylaxis
National Institute for Health and Care Excellence guideline (March, 2021)[55]	Not mentioned	Therapeutic dose thromboprophylaxis should be considered unless contraindications	Increased intensity thromboprophylaxis should be considered	Not mentioned

Potential agents for thromboprophylaxis in an in-hospital setting include low-molecular-weight heparin and unfractionated heparin; intermediate dosing is commonly interpreted as twice the standard thromboprophylaxis dose. *Includes advanced age, stay in the ICU, cancer, previous history of venous thromboembolism, thrombophilia, severe immobility, an elevated D-dimer (>2 times the upper normal limit). †Body-mass index of more than 30 kg/m², history of venous thromboembolism, known thrombophilia, active cancer, or rapidly increasing D-dimer concentrations.

Table 2: **Recommendations on thromboprophylaxis in international guidelines**

Search strategy and selection criteria

We searched PubMed for articles published from database inception to March 10, 2021, using the keywords "COVID-19", "SARS-CoV-2", and "anticoagulation", "thromboprophylaxis", "thrombosis", or "embolism". Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the broad scope of this Viewpoint.

been confirmed by preliminary data from the first randomised trial,[63] and small observational studies[38,39] report increased bleeding rates. Thrombocytopenia, platelet dysfunction or coagulation factor deficiencies, or both, which are more pronounced in critically ill patients compared with moderately ill patients, might possibly cause the balance to shift towards an unacceptably high risk of bleeding, despite the high risk of thrombosis in these patients. Another explanation for the difference observed in the effect of therapeutic anticoagulation on moderately ill versus critically ill patients might be that the overwhelming inflammatory reaction and accompanying thrombotic complications in critically ill patients are too pronounced to be restored; whereas in non-ICU patients, therapeutic anticoagulation might still help to maintain an adequate balance. Nevertheless, the results of therapeutic anticoagulant trials in critically ill patients with COVID-19 emphasise that the delicate balance between anticoagulation strategy and thrombotic and bleeding complications should be carefully considered. On the basis of the current knowledge, we agree with the more conservative guidelines to

recommend routine dose thromboprophylaxis over intermediate dose for all patients admitted to hospital (ICU and non-ICU patients). Although, we also need to consider the preliminary, but possibly beneficial, data on therapeutic anticoagulation in hospitalised non-ICU and moderately ill patients. In ambulatory patients with COVID-19, or those post-discharge, routine administration of thromboprophylaxis is not recommended. Given the markedly increased thrombogenicity in patients with clinical deterioration, and because in clinical practice different aspects of proposed COVID-19 stages might overlap, conservative measures such as sufficient mobilisation and prevention of dehydration should be emphasised. However, in ambulant patients who are more severely ill, have elevated D-dimers and inflammatory parameters, or both, and seem to progress to stage 2, a prophylactic dose of low-molecular-weight heparin thromboprophylaxis could be considered (but only in those without risk factors for bleeding). The same holds true for patients that are severely ill but are for some reason not admitted to hospital. In patients who recovered from COVID-19 and can be discharged from hospital, extended out-of-hospital thromboprophylaxis is not routinely recommended. Nevertheless, in those with persistent immobility or high inflammatory activity, or both, anticoagulant thromboprophylaxis could be considered in absence of increased bleeding risk. Notably, until the benefit of routine monitoring of D-dimer concentrations is prospectively validated, most guidelines recommend that this measure should only be assessed within the overall clinical context, and markedly increased concentrations of D-dimers or sudden clinical deterioration might trigger screening for venous thromboembolism.

Conclusion

The balance between anticoagulation strategy and thrombotic and bleeding complications in patients with COVID-19 is complex. The unique international collaboration in large platform trials has yielded the first high quality data that guide clinicians to optimise anticoagulant prophylaxis and to treat COVID-associated coagulopathy. In the upcoming months we expect numerous data from the ongoing antithrombotic COVID-19 studies to guide clinicians further in different disease stages.

Contributors

SM designed the study. SM, JL, TFvH, and REGS did the literature search. PFW drew the figure. JL and SM drafted the manuscript. All authors revised the final draft of the manuscript and approved the final version.

Declaration of interests

JL and TFvH declare no competing interests. PFW reports personal fees from Sanofi, Bayer, Boehringer Ingelheim, Pfizer, and Sandoz. REGS reports grants from CSL Behring, Pfizer, Sanquin, and Sobi; grants and personal fees from Bayer and Novonordisk; and is a member of the scientific advisory board of Freeline, Boehringer Ingelheim, Roche, and Sobi. SM reports grants and personal fees from Daiichi Sankyo, Bayer, Pfizer, and Boehringer Ingelheim; and personal fees from Portola, Abbvie, and Bristol-Myers Squibb-Pfizer. SM is a steering committee member of the RAPID COVID COAG trial. SM and REGS are members of the anticoagulation domain of the REMAP-CAP trial.

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