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# Thromboprophylaxis in COVID-19 – Rationale and considerations

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ABSTRACT

The Corona Virus Disease-2019 (COVID-19) pandemic is associated with a very high incidence of thrombotic complications. The exact mechanisms for this excess risk for clots have not been elucidated although one of the often-quoted pathophysiological entity is immunothrombosis. Recognition of thrombotic complications early on in this pandemic led to an over-explosion of studies which looked at the benefits of anticoagulation to mitigate this risk. In this review, we examine the rationale for thromboprophylaxis in COVID-19 with particular reference to dosing and discuss what may guide the decision-making process to consider anticoagulation. In addition, we explore the rationale for thrombosis prevention measures in special populations including outpatient setting, pregnant females, children, those with high body mass index and those on extracorporeal membrane oxygenation.

## 1. Introduction

Nearly a year since the emergence of the new Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV-2), the Corona Virus Disease-2019 (COVID-19) pandemic is still carrying devastating implications for human health and socio-economic welfare. What has now become clear is rather than being an isolated respiratory infection, COVID-19 disease constitutes a syndrome of multi-system manifestations which mandates a multi-disciplinary approach (Gupta et al., 2020; Zuo et al., 2021). Coagulopathy has emerged as an integral component of the disease's pathogenesis and has been associated with poor prognosis (Tang et al., 2020). Thus, research has focused on elucidating the elements of haemostatic disturbance in this context, which has translated into clinical interventions to mitigate their effects. These interventions among others have contributed to a considerable improvement in morbidity and mortality (Boudourakis and Uppal, 2021).

### 1.1. The thrombotic risk in COVID-19 disease

Thrombosis has unequivocally been recognized as a frequent complication of COVID-19 disease with crucial prognostic implications. Both venous thromboembolic [ (ITU) IR:28%, 95% CI: 22–34%, $I^2$:89.5; (non-ITU) IR: 10%, 95% CI: 6–14%, $I^2$:96 ] and less commonly arterial events [ (ITU) IR:3%, 95% CI: 2–5%, $I^2$:4.1; (non-ITU) IR: 2%, 95% CI: 0–3%, $I^2$:0] (Boonyawat et al., 2020) have been reported at a much higher frequency than in similar viral infections (Freund et al., 2020; Goshua et al., 2020; Poissy et al., 2020).

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Incidence varies in relation to disease severity, the diagnostic approach used (routine asymptomatic screening versus on-demand investigation of symptoms), intensity of anticoagulation used and the definition of outcomes (e.g. Myocardial Infarction versus ST-elevation) (Table 1). Patients with COVID-19 disease who develop a thromboembolic event carry an increased risk of death of 74% (OR: 1.74; 95% CI: 1.01–2.98; p: 0.04) (Malas et al., 2020) (Table 1).

## 1.2. Pathophysiology of COVID-19 disease -related coagulopathy

Following inhalation, SARS-CoV-2 infects host type II pneumocytes provoking initially an innate and subsequently an adaptive immune response (Tay et al., 2020). The juxtaposed microvascular endothelial cells are also trans-infected by SARS-CoV-2 which compromises their homeostatic control of local inflammation and facilitates the entry of SARS-CoV-2 in the systemic circulation culminating in pyroptosis of other distant cells (Teuwen et al., 2020). For the majority of patients the immune system manages to control the infection through various cell-, humoral-, cytokine- and complement-mediated responses (Teuwen et al., 2020; Polykarpou, 2020).Nevertheless, some patients (Boechat et al., 2021) develop a maladaptive immune response triggered by cytokine over-production or macrophage activation syndrome (Tay et al., 2020). At the same time, inflammation and the related tissue injury activates the haemostatic mechanism through various means: a) apoptotic endothelial cells, (alveolar) epithelial cells, fibroblasts and innate immune cells release TF (Tissue Factor) which activates the extrinsic coagulation pathway (Xavier et al., 2020; Sriram and Insel, 2021); b) enhanced vascular permeability secondary to endothelial dysfunction facilitates the secretion of thrombin into pulmonary capillaries which can activate platelets and the coagulation cascade; c) microparticles secreted by neutrophils (e.g., Neutrophil Extracellular Traps; Cathelicidins) activate platelets and Factor XII resulting in the stimulation of the intrinsic coagulation pathway; d) endothelial cell damage results in the release of ultra-large vWF and exposure of the extracellular matrix proteins (e.g. P-selectin, collagen) but, also, diminishes the secretion of Thrombomodulin disturbing the haemostatic balance; e) cytokine-stimulated increased hepatic Thrombopoietin production increases the number of the circulating pro-thrombotic megakaryocytes; and f) complement stimulation catalyses further factor II,I and XIII activation (Sriram and Insel, 2021). As a consequence of haemostatic system activation, COVID-19 disease can be complicated at early stages by microvascular thrombosis (Nitsure et al., 2020) which aggravates hypoxia due to ventilation/perfusion mismatch. In turn, hypoxia can exacerbate tissue injury and inflammation (Garcia-Ortega et al., 2021; Marchadot et al., 2020) as can the triggered haemostatic system itself through several mechanisms (Sriram and Insel, 2021). In conclusion, the pathogenesis of COVID-19 disease-related coagulopathy encompasses activation of both the immune and the haemostatic systems with endothelial dysfunction playing a key role in this process (Pons et al., 2020) (Fig. 1).

## 1.3. Guidelines for thromboprophylaxis in COVID-19 disease

Thromboprophylaxis has been associated with a statistically significant reduction in mortality (OR: 0.374; 95% CI: 0.154–0.901; p: 0.029) in patients with severe (SIC score≥ 4) COVID-19 disease as was noted early on in the pandemic (Tang et al., 2020). Nevertheless, the benefit remains for all hospitalised patients (Rentsch et al., 2021), although evidence is limited (Flumignan et al., 2020). Thus, considering at least the lack of harmful effect of prophylactic doses of anticoagulation (Ayerbe et al., 2020; Lu et al., 2020), guidelines suggest thromboprophylaxis for all (but only) hospitalised patients in the absence of any contraindications (e.g. active bleeding) (Coronavirus disease, 2019; Thachil et al., 2020; Baumann-Kreuziger et al., 2020; Lee et al., 2020; Moores et al., 2020; Spyropoulos et al., 2020; Barnes et al., 2020; Bikdeli et al., 2020a; Covid-19 rapid guid, 2021).Thromboembolic disease is associated with considerable morbidity that affects patients' quality of life (de Graaf et al., 2021)but rarely necessitates on its own hospital re-admission since the risk can be mitigated with anticoagulation (Tariq, 2020).Possible long sequelae of thromboembolic disease are pulmonary hypertension and pulmonary fibrosis secondary to chronic thromboembolic disease (Wang et al., 2020), neurological deficits and occasionally ischemic cardiomyopathy as well as chronic kidney injury (Nalbandian et al., 2021).

**Table 1**
*Cumulative incidence of Venous Thromboembolism and Arterial Thrombosis Events in patients with Covid-19 disease at different settings.* ITU: Intensive Treatment Unit; VTE: Venous ThromboEmbolism; PE: Pulmonary Embolism; DVT: Deep Venous Thrombosis; AT: Arterial Thrombosis; MI: Myocardial Infarction; Other: Acute limb ischemia, Upper extremity arterial thrombosis, Renal Infarcts, Splenic Infarcts, Portal Vein Thrombosis.

| Setting | Cumulative incidence |
|---|---|
| | **Venous thromboembolism** |
| **ITU** )ᶦ ()ᶦ ( (Klok, 2020; Middledorp et al., 2020; Hill, 2020; Bilaloglu, 2020; Moll, 2020; Nahum, 2020; Llitjos, 2020; Helms, 2020) | VTE: 9.3–50%; PE: 6.2–16.7%; DVT: 2–50% |
| **Non-ITU** (Middledorp et al., 2020; Hill, 2020; Bilaloglu, 2020; Fauvel, 2020; Santoliquido, 2020) | VTE: 0–10%; PE: 2.2–10%; DVT: 2–21% |
| **Outpatients** (Gervaise, 2020; Lodigiani, 2020)[a] | VTE: 3.8; PE: 2.5–18%; DVT: 1.3% |
| | **Arterial thrombosis** |
| **ITU** (Bilaloglu, 2020; Moll, 2020; Helms, 2020; Driggin, 2020) | AT: 2–5%; Stroke: 1.3–6.3%; MI: 0–22.2%; Other: 1.4–2.2% |
| **Non-ITU** (Middledorp et al., 2020) | AT: 0–3%; Stroke: 0.9%; MI: 7.3%; Other: 0.6% |
| **Outpatients** (Lodigiani, 2020)[a] | Stroke: 1.9%; MI: 1%; |

[a] The data for Outpatients are extrapolated from Lodigiani (2020) and include events within 24 h of admission.
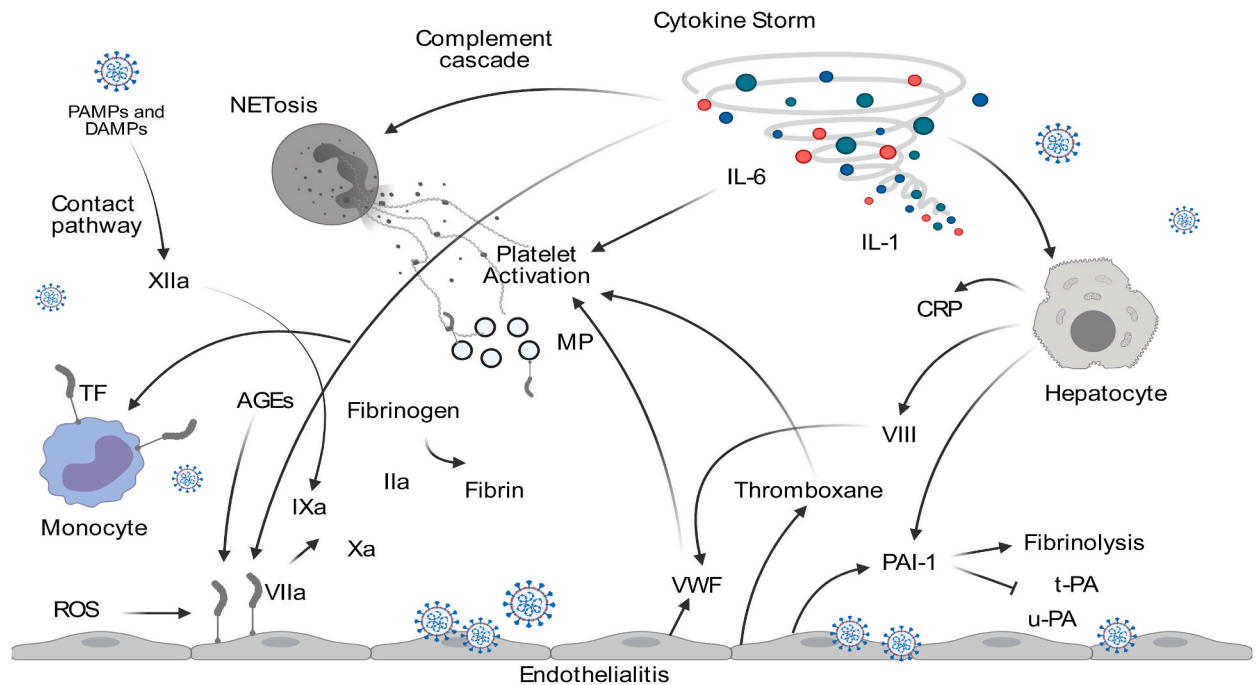
**Fig. 1.** *Pathophysiology of COVID-19 disease -related coagulopathy.* There is a bi-directional interaction of the immune system (including the complement cascade) and the haemostatic system in COVID-19 disease. Endothelial dysfunction facilitates the crosstalk between them and its role is pivotal in the development of thrombotic complications. NET-osis: Neutrophil Extracellular Traps formation; PAMPS: Pathogen-Associated Molecular Patterns; DAMPS: Damage-Associated Molecular Patterns; MP: MicroParticles; TF: Tissue Factor; ROS: Reactive Oxygen Species; AGEs: Advanced Glycosylated End products; VWF: Von Willebrand Factor; PAI-1: Plasminogen Activator Inhibitor-1; t-PA: tissue Plasminogen Activator; u-PA: urokinase Plasminogen Activator; CRP: C-Reactive Protein; IL-1/6: Interleukin 1/6. Permission for use of picture is granted from Dr. Dawn Swan.

### 1.4. Prophylactic anticoagulation-type of anticoagulant

Acknowledging the impact of thromboprophylaxis on the prognosis of COVID-19 disease, clinicians have trialled variable doses, types and periods of anticoagulation-indeed frequently adjusting their strategy according to patients' comorbidities as well as to clinical and/or laboratory evidence of disease severity.

Low molecular weight heparin has been the mainstay of prophylactic anticoagulation in COVID-19 disease in view of its predictable bioavailability and the ability to adjust dosing in critically ill patients, as well as its anti-inflammatory and immunomodulatory properties (Li and Ma, 2017; Brujsers et al., 2020; Tandon et al., 2021). Guidelines suggest the use of low molecular weight heparins (LMWHs) unless CrCl≤ 30 ml/min or there is a high risk of requiring rapid reversal of anticoagulant effect - when Unfractioned Heparin (UFH) can be used instead. UFH has been suggested in lieu of LMWHs in patients with severe COVID-19 disease who can exhibit heparin resistance (Barrett et al., 2020) due to Antithrombin deficiency (Lippi et al., 2021) and/or markedly raised acute phase reactants such as Fibrinogen (Asghar et al., 2020).Heparin resistance has, indeed, been documented occasionally in this subset of patients (Beun et al., 2020) (Dutt et al., 2020) but this cannot be bypassed by UFH(White et al., 2020) and actually the clinical outcomes are worse with UFH than with LMWHs even in this context (Pawloski et al., 2020a). Fondaparinux has been advocated as non-inferior to LMWHs in terms of thromboprophylaxis, bleeding complications and survival, but none of these outcomes have met the criteria of statistical significance (Russo et al., 2020; Viggiano et al., 2020).

Thrombin Inhibitors can, except from their known anti-thrombotic effect, exhibit invaluable anti-inflammatory,anti-viral and anti-apoptotic actions. Their anticoagulation effect is independent of Anti-Thrombin (AT), which distinguishes them as an appealing choice in patients with critical disease which can be complicated with AT deficiency. No interactions with standard of care medications for SARS-CoV-2 have been identified (Aiter and Al-Horani, 2021).Encouraging but limited data exist for the use of Argatroban as thromboprophylaxis in these patients (Arachchillage et al., 2020). Head-to-head randomized trials comparing Thrombin Inhibitors to Heparin are under way.

Acknowledging the key role of the endothelial glycocalyx destruction for the escalation of COVID-19 disease (Yamaoka-Tojo, 2020; Wadowski et al., 2021), a composite medication of heparin and dermatan sulphate called Sulodexide has been trialled in patients with early-stage disease. Thromboprophylaxis with Sulodexide reduced hospital admissions and the need for oxygen support but failed to show any statistically significant improvement in survival compared to placebo (Gonzalez-Ochoa, 2021).

Thromboprophylaxis with Vitamin K antagonists and Direct Oral Anticoagulants (DOACs) is generally discouraged due to the disease-related hepatic and/or renal dysfunction (Shutgens, 2021), unpredictable bioavailability secondary to potential drug

interactions with treatments for SARS-CoV-2 (Khiali and Entezari-Maleki, 2020), nutrition-related effects and absorption issues, and delayed onset but also long half-life of anticoagulation effect (Hardy et al., 2020; Testa, 2020).Interestingly, Vitamin K deficiency has also been associated with worse outcomes in COVID-19 disease, which may be due to an induced coagulation imbalance and/or reduction of the protective effect of Vitamin K against arterial calcification as well as lung fibrosis and/or the loss of its immuno-modulatory effect (Kudelko et al., 2021).In contrast, DOACs exhibit additional anti-inflammatory, endothelial protective effects (Esmon, 2014) and can even directly prevent the infection of host cells by SARS-CoV-2 (Du et al., 2007).Thromboprophylaxis with DOACs has shown improved efficacy without any statistically significant safety compromise compared to LMWH in medical inpatients without COVID-19 disease (Kow and Hasan, 2020). With regards to patients with COVID-19 disease, Billett et al. has shown equivalence of survival with prophylactic doses of either Apixaban or Enoxaparin (Billett et al., 2020) but more clinical trials (NCT0434377, NCT04416048, NCT04504032, NCT04508023, NCT04542408, NCT04505774, NCT04640181, NCT04736901) assessing DOACs, in various doses and settings, in comparison to LMWH are currently underway.

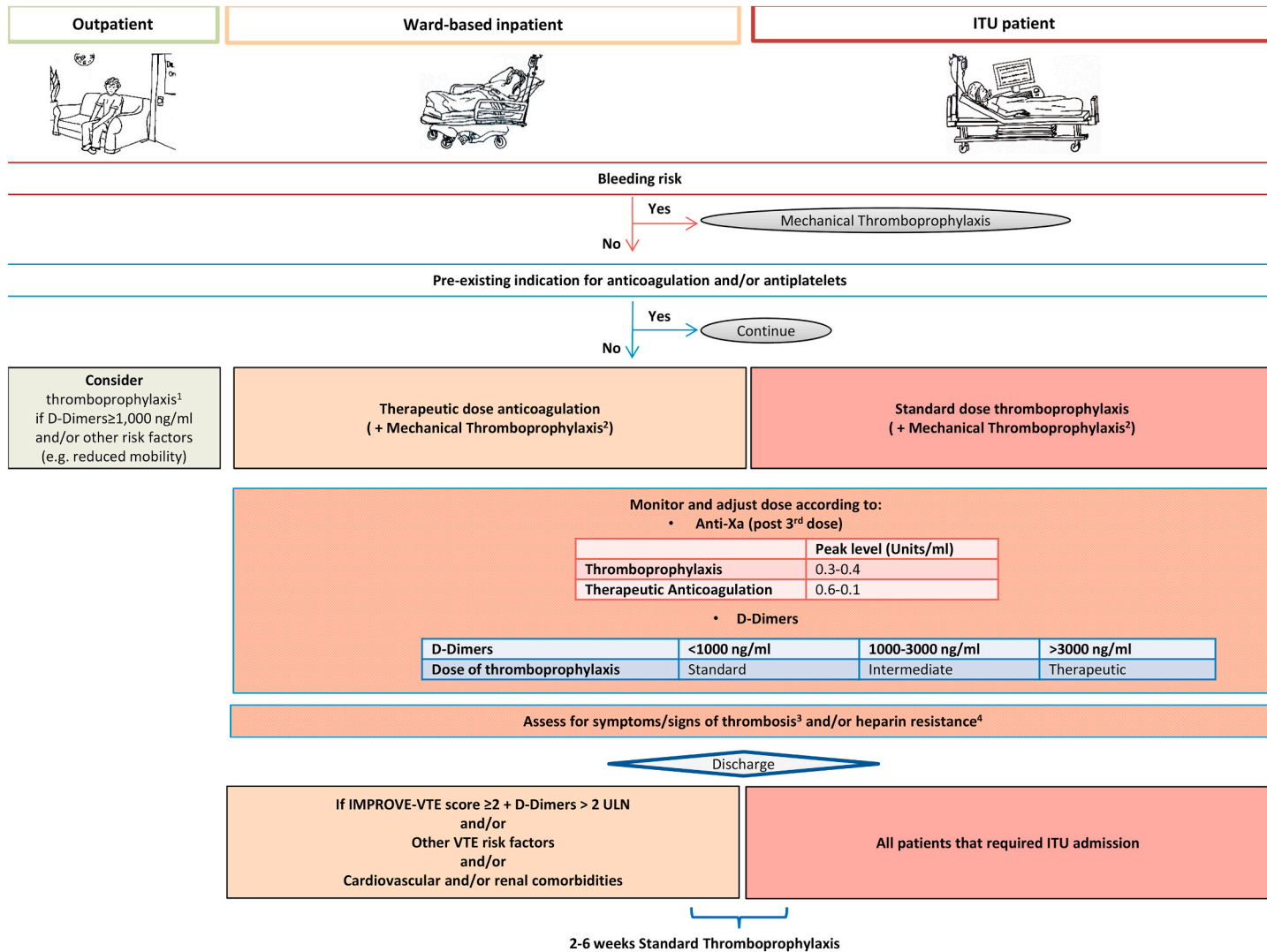### 1.5. Prophylactic anticoagulation-dose of anticoagulant

As regards the optimal dose of pharmacological thromboprophylaxis, this depends on the co-existing comorbidities and the individual bleeding risk of the patient and as well as the severity of the disease so that timely dose adjustments are made (Covid-19 rapid guid, 2021; Warrior et al., 2020; McBane et al., 2020a). Therefore, for patients that already receive anticoagulation for another indication on admission (e.g. previous thrombosis or atrial fibrillation), a switch to a similar intensity LMWH regimen should be considered since oral anticoagulants may run the risk of drug interactions (Covid-19 rapid guid, 2021; McBane et al., 2020b). Contrary to initial hopes (Harenberg et al., 2020), these patients are not protected from requiring intensive care for COVID-19 disease (Flam et al., 2020).Albeit rare and unrelated to intensity of anticoagulation (Al Raizah et al., 2021), the bleeding risk of patients should be considered in decisions about thromboprophylaxis. Although none of the widely used bleeding scores has been validated in COVID-19 patients (Mazzitelli, 2020), a HAS-BLED score $\geq$ 3 has been associated with a higher risk of major bleeding in this context (Yu et al., 2021). For these patients and those with active bleeding, severe thrombocytopaenia ($<25 \times 10^9$/L) and/or an underlying bleeding disorder, mechanical thromboprophylaxis should be applied (McBane et al., 2020a). Such patients should be given pharmacological thromboprophylaxis as soon as the contraindications are resolved.

Provided the patient has no other indications for anticoagulation and is not at high risk of bleeding, the dose of LMWH is determined currently by the severity of the disease. Relevant guidelines have recently been updated in response to the preliminary data published by the National Institutes of Health (NIH) multiplatform randomized controlled trial which incorporates three international studies (REMAP-CAP, ATTACC, and ACTIV-4A) (ATTACC, 2021; The Remap-CAP, 2021). For hospitalised patients that do not require HDU/ITU organ support (which includes high flow nasal oxygen and non-invasive mechanical ventilation) therapeutic dose of LMWH appears superior to non-therapeutic dose. In contrast, for patients requiring ITU-level organ support, therapeutic dose LMWH does not show a survival benefit compared with non-therapeutic dose, despite significantly reducing thrombotic events (Table 2). The latter comes as no surprise, as pulmonary embolism events do not seem to increase the risk of death in patients with COVID-19 disease at critical condition (Mir et al., 2020). Of note, retrospective studies in ITU patients have shown contradicting results regarding the effect of therapeutic anticoagulation on survival (Lynn et al., 2020; Jonmarker et al., 2020).Although preliminary results from the NIH trial show trends, none of the outcomes other than thrombotic events in the subset of patients with severe COVID-19 disease met criteria for statistical significance. Furthermore, the causes of increased mortality among patients receiving therapeutic dose of LMWH need to be elucidated, as the incidence of major bleeding is comparable between patients with moderate and severe disease and the severity of COVID-19 disease can be a confounding factor. One further limitation of NIH trial is that the comparator arm (non-therapeutic dose of LMWH) includes a mix of patients that have received either prophylactic or intermediate dose of LMWH. Thus, subgroup analysis is mandated in the comparator arm to further clarify the role of intermediate role thromboprophylaxis both in ITU and non-ITU patients.

Several other studies have shown a survival advantage of therapeutic to prophylactic anticoagulation compromised, though, by a

**Table 2**

*Odds of outcomes in patients with Covid-19 disease requiring intensive treatment that receive therapeutic versus prophylactic dose of Low Molecular Heparin (LMWH)* Odds ratios were calculated based on (ATTACC, 2021) data using IBM SPSS Statistics Software Version 26.

| | Therapeutic **vs** Non-therapeutic dose of LMWH |
|---|---|
| | Odds ratio |
| Mortality | 0.7250; 95% CI: 0.4749–1.1068; p = 0.1363 |
| Thrombotic events | 0.6589; 95% CI: 0.3469–1.2513; p = 0.2023 |
| Major Bleeding | 2.0204; 95% CI: 0.8105–5.0367; p = 0.1313 |
| | Therapeutic **vs** Non-therapeutic dose of LMWH |
| | Odds ratio |
| Mortality | 1.1301; 95% CI: 0.8567–1.4906; p = 0.3868 |
| Thrombotic events | 0.5385; 95% CI: 0.3387–0.8563; p = **0.0089** |
| Major Bleeding | 2.1106; 95% CI: 0.9015–4.9412; p = 0.0852 |

| Outpatient | Ward-based inpatient | ITU patient |
|---|---|---|

**Bleeding risk**

Yes → Mechanical Thromboprophylaxis

No ↓

**Pre-existing indication for anticoagulation and/or antiplatelets**

Yes → Continue

No ↓

| **Consider** thromboprophylaxis[1] if D-Dimers≥1,000 ng/ml and/or other risk factors (e.g. reduced mobility) | **Therapeutic dose anticoagulation** ( + Mechanical Thromboprophylaxis[2]) | **Standard dose thromboprophylaxis** ( + Mechanical Thromboprophylaxis[2]) |
|---|---|---|

**Monitor and adjust dose according to:**
- Anti-Xa (post 3rd dose)

| | Peak level (Units/ml) |
|---|---|
| Thromboprophylaxis | 0.3-0.4 |
| Therapeutic Anticoagulation | 0.6-0.1 |

- D-Dimers

| D-Dimers | <1000 ng/ml | 1000-3000 ng/ml | >3000 ng/ml |
|---|---|---|---|
| Dose of thromboprophylaxis | Standard | Intermediate | Therapeutic |

**Assess for symptoms/signs of thrombosis[3] and/or heparin resistance[4]**

Discharge

| If IMPROVE-VTE score ≥2 + D-Dimers > 2 ULN and/or Other VTE risk factors and/or Cardiovascular and/or renal comorbidities | All patients that required ITU admission |
|---|---|

**2-6 weeks Standard Thromboprophylaxis**

**Fig. 2.** *Suggested thromboprophylaxis in COVID-19 disease in relation with disease severity*. Heparin, either Low Molecular Weight Heparin or Unfractioned Heparin (if Creatinine Clearance < 30 ml/min) is the first-line anticoagulant due to drug interactions of alternative anticoagulants with treatments for COVID-19 disease. DOACS (Direct Oral Anticoagulants) or Warfarin can be used instead for post-discharge thromboprophylaxis. [1]Limited data exist to guide the need and the intensity of anticoagulation in these circumstances; [2] Level of Evidence: 5; [3] If diagnosed with thrombosis, consider the possibility of being pre-existing and undiagnosed, ensure optimal dosing (according to Anti-Xa levels), assess for Heparin-Induced Thrombocytopaenia (HIT) or Heparin Resistance and consider Thrombophilia screen. [3,4]If HIT/Heparin Resistance confirmed, change to Fondaparinux or Direct Thrombin Inhibitors. Please refer to (Goshua et al., 2020) for calculation of IMPROVE-VTE score. Permission for use of the picture granted from Dr. Sofia Zacharioudaki.

statistically significant increase in major bleeding complications (Ionescu et al., 2020; Trinh et al., 2020).Nevertheless, these studies lack adjustment of outcomes based on the severity of COVID-19 disease. Indeed, Paranjpe (Paranjpe et al., 2020) has shown similar survival in ITU patients regardless of the intensity of anticoagulation with exponential increase in the bleeding risk. Intermediate dose anticoagulation has, also, failed to exhibit any survival benefit (OR: 1.09; 95% CI: 0.78–1.53, p:0.5) (Investigators, 2021) or reduction in VTE incidence (Middledorp et al., 2020) in unselected patients admitted to ITU compared to prophylactic dose and was associated with increased rate of major bleeding (OR: 1.83; 95% CI: 0.53–5.93, p:0.33) (Investigators, 2021).Indeed, even the presence of cardiovascular risk factors cannot justify the escalation of thromboprophylaxis to an intermediate dose for ITU patients (Jonmarker et al., 2020).Another retrospective study has shown that intermediate dose anticoagulation confers a survival advantage in comparison to prophylactic dose but this study also included non-ITU in-patients in whom therapeutic anticoagulation has been advocated as more effective (Meizlish et al., 2021). Poulakou et al. has suggested that intermediate dose thromboprophylaxis provides survival benefit compared to therapeutic anticoagulation in non-ITU patients (OR: 0.0494; 95% CI: 0.0022–1.1086; p: 0.0581) (Poulakou et al., 2021). The added benefit of co-administered mechanical thromboprophylaxis has not been explored in clinical trials as yet, but their application is advocated in patients at critical condition by several guidelines (Spyropoulos et al., 2020; Bikdeli et al., 2020b; Zhai et al., 2020) and based on favourable outcomes in non- COVID-19 patients (Kakkos et al., 2016).

Should D-Dimers and anti-Xa levels guide anticoagulant therapy?

Adjustment of anticoagulation intensity has been suggested based on D-Dimer levels. Deepa et al. have trialled an escalation of thromboprophylaxis to intermediate dose if D-Dimers were between 1000 and 3000 ng/ml. The risk of VTE (OR: 0.2733; 95% CI: 0.114–0.6701; p:0.0046) and death (OR: 0.4804; 95% CI: 0.2044–1.1290; p:0.0926) was reduced in the group receiving the intermediate dose thromboprophylaxis compared to standard dose without any confounding factors (such as cardiovascular risk factors) apart from admission to ITU (but not Multi Organ Failure) identified (Arachchillage et al., 2021). Outcome sub-analysis based on the clinical condition of the patient would hopefully confirm the usefulness of D-Dimers to adjust thromboprophylaxis, which can facilitate evidence-based optimisation of the dose-especially for ITU patients. The latter is addressed in a study on ITU patients which has shown that adjustment of thromboprophylaxis based on D-Dimers (as Deepa et al. have suggested) reduced mortality compared to the group that received standard thromboprophylaxis (or therapeutic only when a VTE event was identified) (Tassiopoulos et al., 2021). As regards patients requiring no ITU support, REMAP-CAP, ATTACC, and ACTIV-4A multiplatform RCT interim results suggest that they benefit the most from therapeutic dose anticoagulation regardless of D-Dimers levels (ATTACC, 2021). Thus, D-dimer levels appear to have a role in guiding the escalation of thromboprophylaxis, but it is less clear whether they can safely mandate dose reductions in patients transferred to ITU and/or patients with long-admissions due to COVID-19 complications. Thromboprophylaxis dose adjustment based on Anti-Xa levels in patients with COVID-19 disease has, also, been investigated. Escalating the thromboprophylaxis dose in ITU patients, who frequently exhibit suboptimal anti-Xa levels, has been associated with improved survival (OR: 0.18; 95% CI: 0.033–0.95; p: 0.031) (Trunfio et al., 2020)but this may be beneficial for ward-level patients (Dutt et al., 2020) as well. In patients that are critically ill, D-Dimers-guided thromboprophylaxis should be monitored by anti-Xa levels (Quarterman and Cole, 2020).Nevertheless, concerns have been expressed about the reliability of anti-Xa monitoring in patients with severe COVID-19 disease (Adie and Farina, 2021).

### 1.6. Thromboprophylaxis post discharge

Patients with COVID-19 infection may be at increased risk for VTE (30–42 days) post discharge although not statistically different to non- COVID-19 medical inpatients (Roberts et al., 2020). Patients with COVID-19 disease that required ITU support during their admission and/or patients with cardiovascular and/or renal comorbidities exhibit persistent endothelial activation, especially if there is sustained cytokine production (Chioh et al., 2021).Classical risk factors such as age, restricted mobility (which can be expected post prolonged/premature discharges) and underlying prothrombotic conditions (e.g. malignancy; thrombophilia)are also expected to increase the risk of post-discharge VTE(Giannis et al., 2021a).A score of ≥4 in the modified IMPROVE-VTE score or ≥2 plus D-Dimer level>2 ULN(Upper Limit of Normal) at discharge has been extrapolated from historical studies on medical inpatients and used alternatively to guide decisions about extended thromboprophylaxis. Prophylactic anticoagulation with either LMWH or a DOAC for this subset of patients has been variably advocated for 2–6 weeks post discharge provided the bleeding risk is low (British Thoracic Society, 2021)and has been shown to reduce the risk of VTE (OR: 0.54; 95% CI: 0.47–0.81) (Giannis et al., 2021a) (Fig. 2).

### 1.7. Thromboprophylaxis in special populations

Thromboprophylaxis in certain special populations with COVID-19 disease such as ambulatory patients, in pregnancy (antepartum and postpartum), in children, morbidly obese patients and patients on Extra Corporeal Membrane Oxygenation (ECMO) needs to take into consideration their particularities.

#### 1.7.1. Ambulatory patients

Although the heightened risk for thromboembolic events in patients with COVID-19 disease requiring hospital admission is well documented and thromboprophylaxis strategies have been extensively studied, the data for those who remain outpatients are scarce and the guidance is largely opinion-based. The incidence of thrombosis in this setting varies in relation to individual's underlying cardiovascular risk factors, level of mobility and severity of COVID-19 disease from 0 to 1.09% (Giannis et al., 2021b; Piazza et al., 2020).Thus, standard dose thromboprophylaxis for (at least) 14 days with heparin (LMWH or UFH) or even DOACS should be considered for patients with additional thrombotic risk factors (Bikdeli et al., 2020b; Zhai et al., 2020; Chacek-Saslavsky, 2021; Reis

and Lima, 2020; Anticoagulation managemen, 2021; Clinical guide for the pr, 2021).As peak D-Dimers levels that are above 6 times the upper limit of normal (Giannis et al., 2021c; Khan et al., 2020) can predict thromboembolic events in this context, it would be of interest to explore the potential benefit (Clinical guide for the pr, 2021) of repeating D-Dimers levels 10–12 days after diagnosis (Pawloski et al., 2020b) and initiating thromboprophylaxis if raised-even if these patients remain ambulatory (Paliogiannis, 2020). Some researchers have advocated the use of antiplatelet agents instead of anticoagulation in low risk ambulatory patients (Chacek-Saslavsky, 2021; Costa et al., 2020).Although we acknowledge the scientific basis (Rapkiewicz et al., 2020) of this recommendation and the survival benefit of people that acquire a COVID-19 disease while already being on antiplatelet agents (Osborne et al., 2021; Yuan et al., 2020; Merzon, 2021), we cannot support this practice in the absence of any randomized controlled trial evidence and in view of their inferior efficacy in preventing venous thromboembolism in similar settings (Diep and Garcia, 2020).

### 1.7.2. Pregnancy

COVID-19 infection in pregnancy is associated with a substantially increased risk of complications including maternal VTE (OR: 3.43; 95% CI: 2.01–5.82), ITU admission and death (Coronavirus, 2021)but also possible placental insufficiency (Shanes, 2020). Also, the reference ranges of coagulation parameters differ to those of the normal population and vary according to the trimester so that the usefulness of D-Dimers to adjust thromboprophylaxis is limited (Servante et al., 2021).Society guidelines for thromboprophylaxis in pregnancy with COVID-19 disease vary. Provided the bleeding risk is low and labour is not due within 12 h, thromboprophylaxis with LMWH is generally advocated for all hospitalised antepartum and postpartum patients and patients discharged home who have increased (≥3) VTE risk score at booking. In view of the lack of randomized controlled trials, there is lack of expert consensus whether the intensity of thromboprophylaxis should be escalated to intermediate dosing in patients with moderate-severe disease and/or thromboembolic risk factors. Thromboprophylaxis should be continued for 10–42 days post-discharge with more prolonged duration favoured for patients with a severe presentation (D'Souza et al., 2020).The use of low-dose aspirin for the prevention of pre-eclampsia in high-risk pregnant women after the 12 weeks of gestation is controversial and should take into consideration the risk of bleeding and possibility of an emergency caesarean section if indicated by maternal condition (Kwiatkowski et al., 2020; Gavillet et al., 2020).

### 1.7.3. Paediatrics

Children and adolescents generally (74.1% of the cases) experience a mild course of COVID-19 disease (Saleh et al., 2021). Nevertheless, depending on the severity of the presentation (and the development of multisystem inflammatory syndrome) children risk developing VTE in 1.25%–26% of cases (Feldstein et al., 2020; Mitchell et al., 2021).Thromboprophylaxis in this subgroup is guided by expert opinion until further data becomes available through clinical trials (NCT04354155).Provided there is low bleeding risk, standard dose thromboprophylaxis with LMWH and a target 4-h post dose anti-Xa activity of 0.2–0.5 U/ml (or UFH with a target anti-Xa activity of 0.1–0.35 U/ml in patients with CrCl<30 ml/min) along with mechanical thromboprophylaxis has been suggested for hospitalised children with underlying prothrombotic risk factors or markedly elevated (≥5 times the upper normal limit) D-Dimers (Goldenberg et al., 2020).Escalation to intermediate dose thromboprophylaxis has been advocated in critically ill children and/or if D-Dimers>500 ng/ml along with Ferritin>500 ng/ml and to treatment dose if D-Dimers>2500 ng/ml, Platelets>450 × 10$^9$ and C-reactive protein (CRP) > 100 mg/dL (Karimi et al., 2020).Extended (30 days) post-discharge thromboprophylaxis should be considered for children with COVID-19 disease with markedly elevated (≥2 times the upper normal limit) D-Dimer levels on discharge or pre-existing prothrombotic risk factors (Goldenberg et al., 2020).Should children develop multisystem inflammatory syndrome in the context of COVID-19 disease, antiplatelet agents and/or therapeutic anticoagulation should be instituted as well (McCrindle et al., 2017).

### 1.7.4. Patients with high body mass index

Obesity (BMI ≥ 30 kg/m$^2$) has been recognized as an independent (to metabolic syndrome comorbidities) risk factor of VTE and death for patients with COVID-19 disease (Tartof et al., 2020; Hendrem et al., 2021).As in non- COVID-19 patients (Brenner et al., 2019), LMWH (or UFH) is the anticoagulant of choice but there is no consensus regarding the need to dose-adjust based on either the weight or the BMI of the patient (Spyropoulos et al., 2020; Wijaya and AndhikaHuang, 2020).Weight-based thromboprophylaxis has been shown to be superior to standard dose thromboprophylaxis in preventing VTE events and (possibly, though not statistically significantly) death (Arachchillage et al., 2021).Anti-Xa monitoring of anticoagulation effect might also be useful in this subgroup of patients (Dutt et al., 2020).

### 1.7.5. Patients on ECMO

ECMO, which has been used as life-rescue therapy in patients with severe COVID-19 disease, can significantly influence the haemostatic balance. To further complicate matters, patients on ECMO are frequently (20%) thrombocytopaenic, require anticoagulation to avoid clotting of the extracorporeal circuits and may develop Heparin-Induced Thrombocytopaenia (HIT) (Kowaleski et al., 2020).UFH is usually used but strict monitoring with either aPTT ratio (target range: 1.5–2.5) or anti-Xa (target range: 0.3–0.7 IU/ml) (Streng et al., 2020) is essential to limit the increased risk of bleeding (Major haemorrhage in 42% of the patients) (Schmidt et al., 2020).Should patients develop recurrent clotting within extracorporeal circuits (or any other VTE), the possibility of HIT must be considered and the intensity of anticoagulation can be increased acknowledging the bleeding risk of the patient (Lee et al., 2020).

## 2. Conclusion

COVID-19 disease-related coagulopathy is the aftermath of a complex interaction between SARS-CoV-2, the immune system and

the endothelium of the host. Without doubt, thromboprophylaxis has substantially improved outcomes of patients, but further improvements could perhaps be achieved by specifically targeting the underlying pathogenic processes underpinning coagulopathy in COVID-19. Thankfully, markers of haemostasis can safely be used to stage the disease, adjust treatment accordingly and to determine patients' prognosis.

## Conflicts of interest

None.

## CRediT authorship contribution statement

**Sotirios Bristogiannis:** Conceptualization, Methodology, Investigation, Resources, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Dawn Swan:** Validation, Writing – review & editing, Visualization. **Jecko Thachil:** Validation, Writing – review & editing, Supervision, Project administration.

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