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Thromboprophylaxis strategies to improve the prognosis of COVID-19

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ABSTRACT

The outbreak of 2019 novel coronavirus disease (Covid-19) has deeply challenged the world population, but also our medical knowledge.

Special attention has been paid early to an activation of coagulation, then to an elevated rate of venous thromboembolism (VTE) in patients hospitalized with severe COVID-19. These data suggested that anticoagulant drugs should be evaluated in the treatment of patients with COVID-19. The publication of unexpected high rates of VTE in patients hospitalized with COVID-19, despite receiving thromboprophylaxis, open the way to dedicated trials, evaluating modified regimens of thromboprophylaxis. Moreover, the further improvement in our comprehension of the disease, particularly the pulmonary endothelial dysfunction increased the hope that anticoagulant drugs may also protect patients from pulmonary thrombosis.

In this comprehensive review, we cover the different situations where thromboprophylaxis standard may be modified (medically-ill inpatients, ICU inpatients, outpatients), and describe some of the current randomized controls trials evaluating new regimens of thromboprophylaxis in patients with COVID-19, including the preliminary available results. We also discuss the potential of anticoagulant drugs to target the thromboinflammation described in patients with severe COVID-19.

1. Introduction

The emergence of the new coronavirus [1–3] has profoundly changed our societies and challenged our medical knowledge. Recent advances in our understanding of the disease have clarified the key role of the endothelium [4,5], particularly the pulmonary vascular endothelium [6,7], in the physiopathology of COVID-19.

One of the main consequences of an acute damage of the vascular endothelium is the activation of coagulation [8]. This activation can lead to either venous thromboembolic disease or arterial thrombosis. Hence, the Chinese colleagues who took care of the first patients very quickly emphasized the frequency of an increased blood D-dimer rate [9], as well as its prognostic impact. The description of this COVID-associated coagulopathy [10] led clinicians to raise their awareness of thrombotic diseases in patients hospitalized for COVID-19 [11,12].

Early (mainly retrospective) epidemiological studies reported high rates of thrombotic vascular events [13,14], higher than those reported in trials validating thromboprophylaxis (mainly heparin and its derivates) in patients hospitalized for acute medical conditions, as sepsis or cardiac and/or respiratory failure [15]. Short-term prognosis was poor [16]. Several hypotheses have been proposed to explain these unexpectedly high rates [17–23]. Therefore, during the first phase of the pandemic, the COVID-associated coagulopathy, the associated endothelial damage and the oftentimes severe immobility in severely-ill inpatients were recognized to be key players in the COVID-19 prothrombotic profile. Clinically, this caused not only conventional

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venous thromboembolic events (pulmonary embolism, deep vein thrombosis), but also arterial macro-thromboses and local (immuno-) microthromboses, especially in the lung vasculature, which participate in the pathophysiology of the respiratory failure. These data led many clinicians, subsequently followed by several scientific societies, to empirically propose modifications to the usual thromboprophylaxis strategies, mainly increased doses of anticoagulant or extensions of thromboprophylaxis periods.

In this narrative review, we discuss the currently available data, which have challenged the traditional thromboprophylaxis strategies, in three specific situations: medical inpatients, critically-ill inpatients, and outpatients. Finally, we present the hypotheses which led to the hope that anticoagulants may modify the evolution of patients with COVID-19.

2. Thromboprophylaxis strategies for inpatients with COVID-19

2.1. Medically-ill inpatients

Since March 2020, various data and studies have demonstrated an important prothrombogenic effect of SARS-CoV-2 infection, including potentially fatal pulmonary embolism (PE) diagnosed in inpatients despite conventional thromboprophylaxis (TPX) [24–26].

Among medically-ill inpatients with COVID-19, there are currently limited data on VTE prevalence for patients hospitalized on the medical ward, as most studies have focused on critically-ill inpatients. VTE rates are significantly higher in patients requiring critical care compared with ward-level care [27–29]. Regarding the incidence of PE and DVT in patients on the ward, several meta-analyses identified a frequency ranging from 2.6% to 15% [27–29] and 4.6% to 12% [27] [29] [30] respectively. Furthermore, these studies confirmed a higher proportion of PE among all VTE COVID-19 patients in comparison with non-COVID-19 patients [27] and more segmental/sub-segmental PE compared to main/lobar arteries [28].

To counterbalance the risk of VTE, increased dose of TPX was used widely based on an empirical approach and clinical judgment, early in the pandemic. Such doses could be an therapeutic dosing or an "intermediate" dosing, somewhat ill-defined but greater than low-dose and lower than the therapeutic dose. This decision was often motivated by the following arguments.: a high incidence of venous thromboembolism despite the use of low-dose TPX [31]; an association between the use of TPX and a lower mortality in COVID-19 inpatients, compared with no TPX [24]; the fact that fixed low-dose TPX may be insufficient in severe obese patients. On the other hand, there remained many unresolved questions that were not supportive of the decision to augment TPX dosing: so far, no data had demonstrated that an increased dose of TPX was a safe and effective approach to prevent VTE, compared with low-dose TPX; trials assessing the role of anticoagulation in sepsis had been negative [32]; it was unknown whether pulmonary microthromboses diagnosed in COVID-19 patients (in comparison with traditional VTE) were sensitive to anticoagulation; increasing anticoagulation dose could expose patients to an increasing risk of bleeding that should not be neglected.

To address this controversy, an international consensus including major scientific societies found that 63% of responders would prescribe for patients on the ward a conventional low-dose TPX using low molecular weight heparin (LMWH) and 32% an intermediate dose [33]. Recently, American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 issued conditional recommendations in favor of prophylactic-intensity anticoagulation over intermediate-intensity or therapeutic-intensity anticoagulation for patients who do not have confirmed or suspected VTE [34]. However, this recommendation is based on a very-low evidence of a very limited number of observational studies comparing therapeutic-dose TPX to conventional-dose TPX.

This scarcity of data from observational retrospective studies on associations of increased-dosed TPX with prognosis in medically-ill inpatients is explained because a majority of studies performed in the ICU or because no subgroup analysis was done to separate ICU patients from patients in the general ward. Nevertheless, two comparative studies deserve to be mentioned. First, Martinelli et al. examined a retrospective monocentric cohort study of COVID-19 inpatients, who received standard low-dose TPX or an augmented TPX, depending on their time of admission and a severity risk stratification. There was no association between the dose of TPX and the risk of VTE in COVID-19 (OR = 0.76 [95% CI; 0.27–2.16], comparing intermediate dose with low dose) [35]. The ETHRA cohort study evaluated beneficial effects of an intermediate dose vs. therapeutic anticoagulation on the prognosis of COVID-19 patients. While the composite endpoint of intubation/VTE/death was reduced in patients treated vs. not treated, authors did not identify a difference of effect between the two intensities [36]. Conversely, Ionescu et al. compared in a large retrospective multicenter cohort different survival probabilities at 25 days post-admission in patients receiving therapeutic anticoagulation compared to those receiving only prophylactic anticoagulation (78.5% vs 65.7%). The greatest impact was seen primarily in patients with critical illness, but benefit was also observed in patients hospitalized in the general ward. However therapeutic anticoagulation was associated with a significant increased risk of major bleeding vs. standard prophylactic or no anticoagulation [37]. While encouraging, these observational data remain inconsistent, with a potential for well-known methodological biases (confounding, confounding by indication, immortal time bias) [38], and illustrate the need for proper interventional studies.

Regarding interventional data, to date, no randomized controlled trial has reported final findings of the impact of an increased thromboprophylaxis dose in the general ward population, but several are ongoing. In this setting, the COVI-DOSE trial (NCT04373707, INNOVTE F-CRIN research network), is a French multicenter randomized (1:1) open-label controlled trial that is randomizing +600 hospitalized adults with COVID-19 infection (both in the ICU and in the general ward) to weight-adjusted prophylactic dose vs. lower prophylactic dose of LMWH. Also, the multicentric Swiss COVID-HEP trial (NCT04345848) is randomizing 200 severe medical or critically-ill COVID-19 inpatients to low-dose TPX (intermediate-dose in the ICU) or therapeutic-dose TPX. The results of these trials are expected soon to help inform decision making for VTE prophylaxis of this important patient population. Interim analyses from three platform trials (ACTIV4, REMAP-CAP, and ATTACC) were recently released [39], and reported a lower risk of organ support and all-cause death with full-therapeutic heparin-based prophylaxis compared with standard-dose prophylaxis. However, the events are not adjudicated and full results will be awaited.

2.2. Critically-ill inpatients

Since last year, the observation of increased venous and arterial thrombotic events in patients with COVID-19, has made drawn the attention of clinicians and investigators. The risk is perceived to correlate with endothelial injury [5], a hypercoagulable state, and stasis [33], and is more pronounced among critically-ill patients admitted to the intensive care unit (ICU). A recent systematic review by Jimenez et al. estimated that as many as 28% of critically-ill patients with COVID-19 suffer from venous thromboembolism (VTE) [40]. Such notions have led some experts to consider empiric use of antithrombotic pharmacoprophylaxis, beyond standard-dose prophylactic anticoagulation [41–43]. However, there is much heterogeneity in the reported VTE event rates, with some multicenter studies reporting markedly lower rates of VTE than these pooled estimates. Further, even in the study by Jimenez et al., the majority of VTE events included sub-segmental pulmonary embolism (SSPE) and isolated distal DVT (IDDVT), of uncertain clinical significance [40]. In another large registry, three quarter of thrombotic events were catheter-associated [44]; again a form of VTE thought to be less ominous. Considering these concerns, understudied

bleeding rates, and with the absence of high-quality data to prove the benefit of escalated prophylactic antithrombotic regimens, other experts argue that standard prophylactic anticoagulation should be the norm, unless for patients enrolled in randomized controlled trials (RCTs) [33,45].

To address the equipoise related to the optimal thromboprophylactic regimens in the ICU setting, multiple RCTs have been designed and are ongoing [46,47]. These RCTs are investigating the use of intermediate-dose or fully-therapeutic systemic heparin-based regimens, nebulized heparin, antiplatelet agents (including aspirin and P2Y12 inhibitors) and even fibrinolytic therapy. The only published randomized trial among critically-ill patients with COVID-19 are pilot study (HESACOVID), and the INSPIRATION trial. In HESACOVID, among mechanically-ventilated patients with COVID-19 who received therapeutic (but not standard prophylactic) anticoagulation, showed improvement in PaO2/FiO2 [48]. However, the study had serious limitations, including small sample size ($N = 20$), use of a surrogate endpoint, and others [49].

Recently three large platform trials (ACTIV4a, REMAP CAP, and ATTACC) halted enrollment of critically-ill patients to therapeutic vs. standard prophylactic anticoagulation due to futility identified in an interim analysis, and we await further clarifications [50].

In turn, INSPIRATION was a multicenter randomized trial testing intermediate-dose (enoxaparin 1 mg/kg/day) vs. standard-dose prophylactic anticoagulation in among 600 patients admitted to the ICU in Iran. [51] [52]. Among 562 (93.7%) patients included in the primary analysis, intermediate-dose compared with standard-dose anticoagulation, did not reduce a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or death (45.7% vs. 44.1%; odds ratio, 1.06 [95% CI, 0.76–1.48]; $P = .70$). Major bleeding occurred in 7 patients (2.5%) of the intervention group, vs 4 patients (1.4%) of the control group (odds ratio, 1.83 [1-sided 97.5% CI, 0.00–5.93]). Similar findings were observed at 90-d of follow-up [53]. Results from several additional ongoing studies [47] will complement the findings from HESACOVID and INSPIRATION.

Specific attention has been paid to obese patients, who are at higher risk of severe respiratory form of COVID-19, and also at higher risk of thrombosis [54]. The potential of anti-Xa monitoring to improve low-molecular-weight heparin effectiveness remains unknown, with little evidence to support its therapeutic range but some observational evidence in ICU patients with SARS-CoV-2 supporting further research [55,56].

3. Thromboprophylaxis strategies for outpatients with COVID-19

Given the high burden of VTE among hospitalized COVID-19 inpatients, one may wonder if VTE prevention is useful in the outpatient setting. Outside of COVID-19, thromboprophylaxis (TPX) is mostly prescribed in-hospital, but there are situations where heparins or direct oral anticoagulants may be beneficial. Such situations include post-surgical extended TPX, in particular after major orthopedic or oncological interventions, primary VTE prevention among high-risk cancer patients and post-medical hospitalizations in high-risk patients.

The vast majority of studies on COVID-19 and VTE have focused on inpatients, and our knowledge of VTE in ambulatory COVID-19 remains surprisingly vague. Several small case series have reported PE among COVID-19 outpatients, however without an available denominator to compute an incidence [57,58]. One retrospective cohort studied cardiovascular outcomes among 715 COVID-19 outpatients from a large health care network in the Greater Boston area [44]. These participants were on average young and healthy: they had a mean age of 45 years, low prevalences of previous CAD (3%), VTE (3%), but moderate prevalences of hypertension (25%) and diabetes (10%). Only 1 participant received thromboprophylaxis with LMWH, and although 6% were lost to follow up, there were no symptomatic PE or DVT at 30 days in this large cohort. A second retrospective cohort set in a large health management organization in California evaluated 24,746 patients with a positive SARS-CoV2 test in the outpatient setting or the emergency department, of whom 117 had a VTE after 30 days (risk of 0.5%) [59]. When restricting to those who were not admitted to hospital during the 30 days, the risk was even lower (0.1%). Such risk estimates are too low to promote the routine use of thromboprophylaxis in COVID-19 outpatients.

However, a proportion of COVID-19 patients may develop VTE before hospital admission, and perhaps VTE causes the need for hospitalization. In a retrospective cohort examined COVID-19 inpatients in an academic hospital in Milan [60], among 362 inpatients with complete hospital follow-up, 50% of the VTE events (2.2% out of 4.4%) occurred within 24 h of admission. Also, autopsy findings from the first epidemic phase in Paris have shown both a greater rate of unexplained death with COVID-19 and a greater prevalence of proximal PE in such deaths (23%) [61], similarly to other autopsy studies [62].

Overall, at this stage, these data are not convincing enough to promote the general use of thromboprophylaxis among COVID-19 outpatients. There may be exceptions, in subgroups of patients deemed a high risk of VTE, in relation to a personal history of VTE, a recent surgery, an active cancer, a prolonged immobilization, or particularly a combination of such risk factors. The actual benefit-risk of thromboprophylaxis with a 14-day course of LMWH (enoxaparin 40 mg) is being tested in the Swiss OVID trial of COVID-19 outpatients aged >50 years [63].

Another important clinical question is the usefulness of post-discharge TPX. Several large phase III randomized trials have shown some benefits of prolonging TPX in high-risk medical inpatients after hospital discharge, although this is not widely accepted in Europe [64]. Several guidelines have advocated for an extension of thromboprophylaxis regiments after discharge from a COVID-19 hospitalization [65], at the start of the pandemic. However, five studies have evaluated post-discharge VTE risks among >5800 COVID-19 inpatients (Table 1). They found very low risks of VTE within 15–90 days post-discharge, ranging from 0 to 0.6%. In the large study by Roberts et al. [66], the risk of post-discharge VTE was not greater in COVID-19 inpatients than in non-COVID-19 medical inpatients from 2019, and the risk was similar between ICU inpatients and medical inpatients (0.48% and 0.48%, respectively). These data conflict with guidance suggesting the use of post-discharge TPX, as its benefit-risk is doubtful given such low VTE risks, even in ICU inpatients. Similarly to ambulatory TPX, we suggest to avoid the use of post-discharge TPX, while recognizing that some patients may still benefit from post-discharge TPX in case of a presumed high-risk of VTE (persisting immobility or a personal history of VTE, for example).

4. Is there a benefit of anticoagulants beyond that of prevention of VTE?

Autopsy data revealed direct invasion of the pulmonary vascular endothelium by the coronavirus, inducing endothelial dysfunction [7]. This endothelial dysfunction leads to the activation of coagulation but also intervenes on the specific inflammatory mechanisms [8], which have been demonstrated in patients with severe forms of the disease. Further, local coagulation is also triggered by the presentation of tissue factor by circulating monocytes, once virally activated [71]. These elements have led to the concept of thromboinflammation [10] being put forward to explain part of the clinico-biological expression of the disease [8]. This thromboinflammation could explain the development of small thrombosis lesions in situ in the pulmonary circulation (in combination with infection of the endothelial cells by the virus), in addition to alveolo-interstitial damage [8]. These combined elements could explain the alteration in pulmonary diffusion, described in patients with respiratory sequels of COVID [72,73]. Whether increasing doses of anticoagulants modulate the occurrence of these immunothromboses remains however largely unknown.

Table 1
Risks of VTE after COVID-19 hospitalizations.

	Country	Sample size	Use of hospital TPX	Use of post-discharge TPX	Risk of post-discharge VTE (period post-discharge)
Doyle et al. [67]	UK	129 ICU inpatients	Recommended	None	0% (90d)
Roberts et al. [66]	UK	1699 medical +208 ICU inpatients	Recommended	None	0.48% (42d)
Patell et al. [68]	USA	121 medical +42 ICU inpatients	96%	None	0.6% (30d)
Hill et al. [69]	USA	2075 inpatients	According to Padua risk score	Not routinely	0.14% (15d)
Rashidi et al. [70]	Iran	1410 medical +119 ICU inpatients	97%	4.6% anticoagulation	0.2% (45d)

Several other beneficial effects of heparins on the inflammatory response or the virus itself have been proposed, and are reviewed in details elsewhere [74,75]. Briefly, a possibly important player lies in the glycocalyx, the thick layer of negatively charged glycosaminoglycans on the surface of endothelial cells. Heparan sulfate, which is part of this glycocalyx, appears to function as a co-receptor to the ACE2 receptor for viral entry. Circulating heparins may compete with this co-receptor and decrease the potential for viral intracellular entry. Further, circulating heparins may bind to cytokines/chemokines (IL-8 for example) and perhaps inhibits the synthesis of TFN-alpha and IL-6. They may also decrease the possibility of margination, rolling, adhesion and migration of monocytes through the endothelium, through binding to P-selectin and L-selectin. They may also protect from cytotoxic histones from NETS. Such mechanisms, of uncertain clinical relevance yet, nevertheless underline a possible benefit from increasing doses of heparins in COVID-19 patients.

Perfusion sequels can be found in almost a third of patients monitored after pulmonary embolism [76], exposing the patients to the risk of chronic thromboembolic pulmonary hypertension. Inflammation seems to play a role in the genesis of chronic thromboembolic pulmonary hypertension [77–79], by favoring the appearance of inflammatory remodeling preventing pulmonary vascular recanalization of physiological fibrinolysis, after pulmonary embolism.

In addition to their effect on coagulation, some antithrombotic drugs have an immunomodulatory effect. For example, heparin and danaparoid have been tested by nebulization in animal models of lung injury [80,81]. Then, the potential place of anticoagulants in the control of thromboinflammation has been extensively reviewed [46]. The effect of anticoagulant strategies on the risk of long-term sequels remains unknown.

5. Conclusion

Although the epidemic is still ongoing, it is of crucial importance to draw some conclusions from the boom of recent months. The health crisis has profoundly challenged the dissemination of medical information, in order to maximize its clinical and public health benefit. This comes also with some drawbacks, promoting the implementation of low-quality evidence that sometimes shortcut a proper and thorough peer-review examination. The cacophony experienced during the health crisis calls for a more integrated health action plan [82]. Demonstrating the ability of teams to work together to set up innovative therapeutic trials, as quickly as possible, but without abandoning the scientific rigor necessary to evaluate each of the hypotheses raised [49], must remain a constant objective.

Anticoagulant treatments are a major part of the therapeutic arsenal against COVID-19. Low molecular weight heparins (at to a minor extend fondaparinux, or unfractionated heparin in cases of severe renal failure) are proposed for VTE thromboprophylaxis in patients hospitalized with COVID-19, by extrapolation from trials that have demonstrated their efficacy in patients hospitalized for sepsis and/or acute respiratory failure. The use of therapeutic-dose LMWH in COVID-19 inpatients without another indication should be limited to participants of research projects, while waiting for definite results of such trials. In patients with objectively confirmed VTE, therapeutic-dosed anticoagulants are the basis of management, for a minimum of 3 months. Management of recurrent VTE despite anticoagulant therapy is a clinical challenge that needs an individual-based analysis, and may include one of the available antithrombotic efficient on thromboinflammation [46].

Ongoing studies will make it possible to clarify the possible place of increased doses of LMWH in hospitalized patients and thromboprophylaxis in ambulatory patients, with definite results awaited in Spring 2021. This may challenge the paradigm of low-dose heparins to reduced hospital-associated VTE, if these studies show a benefit in some groups of COVID-19 patients, which may go beyond that of VTE prevention. The potential of anticoagulant therapy to decrease the risk of long-term sequelae will need further research.

While waiting for the results of these studies, clinicians should continue to propose the best-evidence-based care for their patients.

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Declaration of Competing Interest

None.

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