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Thromboprophylaxis in COVID-19: Anti-FXa—the Missing Factor?

To the Editor:

Coronavirus disease (COVID-19) infection was declared a public health emergency of international concern in January 2020. The medical literature has since seen a succession of reports questioning a link between the disease in its severe form, a dynamic spectrum of coagulopathy, and a concerning incidence of thrombotic complications. As we accumulate observational data from around the globe and await well-designed prospective studies to inform best practice, clinical guidance on the management of thrombotic risk remains pragmatic.

We have read with interest initial reports from Wuhan, China, describing significant differences in D-dimer levels between survivors and nonsurvivors of COVID-19 and the overt presence of disseminated intravascular coagulation in over 70% of deaths (1). In light of the histological features of thrombotic occlusion of the pulmonary vasculature at autopsy (2), the Shanghai Clinical Treatment Group advised the early application of anticoagulation therapy in severe COVID-19. This led to a retrospective comparison of patients who had not received any heparin before the guidance with those who had, and, unsurprisingly, heparin treatment was associated with a reduced mortality. A prophylactic dose of low-molecular-weight heparin (LMWH) was mostly used; however, the authors proposed that a higher dose may be more beneficial for non-Asian patients (3).

With growing awareness of a distinct coagulopathy accompanying COVID-19 infection, the medical community has been keen to address the significant thrombotic risk for this patient group. Institutions have anecdotally reported what were perceived to be higher than expected rates of pulmonary embolus (PE), deep vein thrombosis, and occlusion of citrated circuits.

Klok and colleagues reported a 31% cumulative incidence of venous and arterial thrombosis, increasing to 49% after adjustment

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Table 1. Thromboprophylaxis Regimes from Studies Reporting the Incidence of VTE in Patients with COVID-19 Infection

Study	Heparin	Dose	Patient Cohort
Tang and colleagues (4)	Enoxaparin	40–60 mg once daily	ITU
	UFH	10–15,000 u once daily	
Klok and colleagues (5)	Nadroparin	2,850 IU once daily* increased in some to 5,700 IU twice daily later in study†	ITU
Helms and colleagues (6)	Not stated	Prophylactic/therapeutic	ITU
Middeldorp and colleagues (7)	Nadroparin	2,850 IU once daily increased to twice daily later in study*	ITU
	Nadroparin	2,850 IU once daily	Ward

Definition of abbreviations: COVID-19 = coronavirus disease; ITU = intensive therapy unit; UFH = unfractionated heparin; VTE = venous thromboembolism.
*5,700 IU once daily for patients weighing more than 100 kg.
†For patients weighing more than 100 kg, the dose was increased to 5,700 IU twice daily.

for competing risk of death, despite anticoagulant therapy in patients admitted to the intensive therapy unit (ITU). The authors suggested that ITU patients may warrant higher thromboprophylaxis dosing such as enoxaparin 40 mg twice daily versus 40 mg once daily (4).

Helms and colleagues compared a prospective cohort of ITU patients with COVID-19 with a historical cohort non–COVID-19 acute respiratory distress syndrome (ARDS). They also observed a high prevalence of clinically relevant thrombosis, most commonly PE (16.7%), despite prophylactic or therapeutic anticoagulation; this was usually diagnosed within a few days of ITU admission. The authors advised that anticoagulant treatment should be guided by anti–factor Xa (anti-FXa) activity and that higher targets would likely be required (5).

Interestingly, Middeldorp and colleagues compared ITU patients with ward patients and commented on a much lower rate of venous thromboembolism (VTE) in the latter (6).

The consensus from reports to date is that there appears to be a greater than expected VTE risk despite pharmacological thromboprophylaxis. Authors consistently acknowledge the current divergence in thromboprophylaxis dosing from what would usually be considered a standard dose (Table 1).

We reviewed anti-FXa activity in patients admitted to hospital with COVID-19 infection, all receiving pharmacological thromboprophylaxis with enoxaparin 40 mg once daily, creatinine clearance of >30 ml/min, and platelet count of $>30 \times 10^9$/L (7). We compared 4-hour after dose anti-FXa activity levels for 22 ward patients and 20 ITU patients (Table 2).

With a significantly lower mean anti-FXa activity of 0.1 IU/ml, 95% of ITU patients failed to achieve a target anti-FXa activity (0.2–0.4 IU/ml) compared with 27% ward patients. This difference appeared to relate to the degree of respiratory support required. Patients admitted with COVID-19 now receive weight-adjusted LMWH thromboprophylaxis with anti-FXa–guided dose escalation/reduction to achieve target anticoagulation levels.

These preliminary data suggest that patients admitted to ITU with COVID-19 may warrant a higher starting dose of pharmacological thromboprophylaxis, an approach that has already been adopted in some institutions. Furthermore, anti-FXa–guided LMWH dosing may have a role in ward patients because almost 30% of these patients demonstrate suboptimal anti-FXa target levels with standard dosing and merit early dose escalation.

LMWH is broadly used in hospital patients for the prevention and treatment of VTE owing to a relatively predictable pharmacokinetic profile and ease of monitoring. The anticoagulant effect is measured using the anti-FXa activity. Monitoring for prophylaxis is not routinely used; however, on the basis of studies published, a reasonable target range for prophylaxis has been suggested as between 0.2 and 0.4/0.5 IU/ml (8). There are recognized situations, such as in pregnancy, renal impairment, and obesity, in which standard doses may not achieve optimal

Table 2. Comparison of Ward Patients and ITU Patients Receiving Standard-Dose LMWH Thromboprophylaxis

	ITU ($n = 20$)	Ward ($n = 22$)	Significance
Mean anti-FXa, IU/ml	0.10	0.25	$P < 0.001$*
Range (SD)	0.01–0.22 (0.06)	0.01–0.45 (0.12)	
Number of patients with anti-FXa 0.2–0.4 IU/ml	1	16	
Mean age, yr	50.6	61.1	$P = 0.049$*
Range (SD)	26–66 (11.8)	21–91 (20.2)	
Mean weight, kg	88.5	82.6	$P = 0.3$*
Range (SD)	60–120 (14.9)	57–133 (20.6)	
Respiratory support	19 intubated; 1 CPAP	22 wall-oxygen; max FI_{O_2} 0.35	

Definition of abbreviations: anti-FXa = anti–factor Xa; CPAP = continuous positive airway pressure; ITU = intensive therapy unit; LMWH = low-molecular-weight heparin.
*Independent *t* test.

thromboprophylaxis. Uncertainty remains, however, regarding the value of anti-FXa monitoring in such groups. The consideration of patient-specific risk factors for thrombosis and hemorrhage, together with the relationship between anti-FXa activity and clinical outcome, may be more important (9). This is of particular relevance in COVID-19, in which there is a recognized spectrum of thrombosis and bleeding risk in later stages of the infection (7). Furthermore, the growing autopsy histology literature demonstrates a heterogeneity of thrombotic disease manifestations, including mutually exclusive deep vein thrombosis and PE, often despite anticoagulant therapy (10). For pulmonary vascular occlusion that is more thrombotic than embolic, higher LMWH doses may not necessarily be more effective, and therefore the mechanism and relative contribution of the thrombotic burden to death and the best anticoagulation approach remain critical questions.

Potential mechanisms for the development of what appears to be an acquired heparin resistance include reduced antithrombin levels, as seen in patients with sepsis requiring ITU care. The coagulopathy of COVID-19, however, appears to differ (1). As a result of a disrupted equilibrium and the well-recognized battle between inflammation and coagulation at the endothelial surface, more heparin is required to counteract excess thrombin generation in patients with severe disease (11). We also know that significantly raised plasma concentrations of tissue factor and PAI-1 (plasminogen activator inhibitor-1) occur on approximately day 7 in patients with ARDS, which could in turn lead to increased alveolar fibrinolysis from an increase in local PAI-1 (12). Taken in the clinical context, patients who require higher levels of ventilation or develop ARDS may warrant increased doses of LMWH thromboprophylaxis, resulting in discordant anti-FXa activity. Interestingly, ARDS has also been identified as a risk factor for VTE prophylaxis failure in critically ill patients with sepsis (13).

Clinical thrombotic endpoints will undoubtedly form an important component of upcoming randomized controlled trials designed to define the relationship between optimal anticoagulation and thrombosis outcomes in COVID-19. Until then, the optimization of the anticoagulation strategy remains paramount. Amid consistent concerns for more effective prophylactic LMWH dosing, our data provide missing information regarding anti-FXa activity, confirming lower than expected activity, particularly in patients managed in the ITU. This informs the move by many institutions to start with higher thromboprophylaxis dosing pending the results of randomized controlled trials and provides additional clues as to the nature of the COVID-19–associated coagulopathy. ■

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