Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated-dose thromboprophylaxis strategy

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As of September 19th, 2020, more than 30 million cases of novel coronavirus disease 2019 (COVID-19), the clinical syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, have been recorded, with more than 900,000 deaths worldwide and 200,000 in the United States, with a case fatality rate exceeding 3% [1].

Early studies from Wuhan, China identified a prothrombotic state associated with SARS-CoV-2 infection [2], characterized by pronounced elevations in D-dimer (≥0.5 mg/L fibrinogen equivalent units [FEU]) and associated with increased mortality [3]. Clinically, thromboembolic events (TEs) have been observed at alarming rates globally, with an early estimated venous thromboembolism (VTE) incidence of 30–69% [4–6] in COVID-19 intensive care unit (ICU) patients despite standard heparin thromboprophylaxis. In contrast, an increased propensity for bleeding among COVID-19 patients has not been demonstrated.

The increased prevalence of TEs in conjunction with a survival benefit observed with heparin use in severely ill COVID-19 patients [7] has led investigators to reconsider thromboprophylaxis regimens in this high-risk population, with an emphasis on more aggressive anticoagulation (AC) strategies. Our study aimed to investigate the rates of TE, hemorrhage, and mortality in the context of an escalated-dose thromboprophylaxis strategy in hospitalized patients with COVID-19.

We identified 192 consecutive patients with COVID-19 admitted across the three Duke University Health System (DUHS) hospitals between March 26th and May 8th, 2020. Hospitalized adults with positive SARS-CoV-2 RT-PCR were included. Patients were categorized as either ward or ICU patients based on a need for ICU level care at any point during hospitalization. Criteria for ICU admission included acute or impending respiratory failure requiring mechanical ventilation, hemodynamic instability, or multisystem organ failure.

An escalated-dose thromboprophylaxis protocol was implemented as part of a quality improvement initiative based on available literature and our initial experience with the COVID-19 population. Patients considered for escalated-dose thromboprophylaxis were those with severe disease, defined as requiring ICU level care or a D-dimer level > 2.5 mg/L FEU (Instrumentation Laboratory D-dimer HS500, ACL TOP750), and without indications for therapeutic AC. Escalated-dose thromboprophylaxis regimens included enoxaparin 0.5 mg/kg twice daily or a heparin infusion titrated to anti-factor Xa levels 0.3–0.5 U/mL in patients with renal failure (CrCl < 30 mL/min).

Patients without severe COVID-19 infection were started on standard-dose thromboprophylaxis with enoxaparin 40 mg daily if weight < 100 kg and 60 mg daily if weight > 100 kg, or 5000 U of unfractionated heparin three times daily in patients with renal failure.

Patients with a clinical indication for therapeutic dose AC on admission and those who developed TEs were treated with enoxaparin 1 mg/kg twice daily or a heparin infusion titrated to anti-factor Xa levels 0.5–0.7 U/mL in patients with renal failure.

Pharmacologic thromboprophylaxis was considered contraindicated in patients with severe thrombocytopenia (platelets < 25 × 10^9/L) or active bleeding. In such cases, mechanical thromboprophylaxis was recommended.

Pulmonary embolism (PE) was diagnosed using pulmonary CT angiography (CTA). Deep venous thrombosis (DVT) was diagnosed by compression ultrasonography. Ischemic stroke was documented by MRI, and acute limb ischemia was documented by CTA. Myocardial infarction was identified by characteristic symptoms and troponin elevation, leading to a change in AC. Notably, we followed a symptom-based imaging approach and did not screen asymptomatic patients.

Cases with high clinical suspicion for PE without radiographic confirmation due to clinical instability or imaging availability were included if an acute change in clinical status consistent with PE occurred, and therapeutic AC was initiated.

We included non-vessel thrombotic events in CVVHD circuits that resulted in inability to successfully perform CVVHD and up-titration to therapeutic AC.

Major bleeding was defined by ISTH criteria: fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin of ≥20 g/L, or leading to transfusion of ≥2 units of red cells [8].

A total of 192 consecutive COVID-19 patients admitted to DUHS

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Table 1
Patient demographics.

	No TE (*N* = 169)	TE (*N* = 23)	p-Value	Survived (N = 139)	Died (N = 53)	p-Value
Demographics						
Age (years)	64 (52–94)	59 (48–95)	0.52	61 (49–95)	76 (68–94)	0.000***
Female sex (%)	63 (37)	11 (48)	0.37	51 (37)	23 (43)	0.41
Non-white race (%)	120 (71)	17 (74)	1.00	104 (75)	3 (62)	0.11
Comorbidities						
Obese[a] (%)	87 (53)	15 (65)	0.37	77 (56)	25 (51)	0.62
CKD[b] (%)	42 (25)	4 (17)	0.60	28 (20)	18 (35)	0.06.
HTN (%)	115 (69)	19 (83)	0.23	92 (67)	42 (81)	0.07
Diabetes (%)	80 (48)	13 (57)	0.51	66 (48)	27 (52)	0.63
A. fibrillation (%)	29 (17)	4 (17)	1.00	14 (10)	19 (37)	0.000***
Active cancer (%)	17 (10)	0	0.23	8 (6)	9 (17)	0.02*
Prior VTE (%)	13 (8)	7 (30)	0.004**	15 (11)	5 (10)	1.00
Prior stroke (%)	27 (16)	6 (26)	0.25	19 (14)	14 (27)	0.05.
Clinical course						
Initial D-dimer (mg/L FEU)	1.0 (0.6–100.0)	1.64 (0.9–100.0)	0.007**	0.9 (0.5–100.0)	1.15 (0.8–12.0)	0.18
ICU stay (%)	74 (44)	20 (87)	0.000***	58 (42)	36 (68)	0.001**
Intubation (%)	40 (24)	16 (70)	0.000***	32 (23)	24 (45)	0.004**
Mortality (%)	44 (26)	9 (39)	0.19	0	53 (100)	0.000***

Continuous variables reported as Median (Q1-Q3); categorical variables presented as n (% of total N, excluding missing variables).
Follow up duration was 28 days from original COVID-19 diagnosis or until death or last known alive.
Abbreviations: TE, thromboembolic event. CKD, chronic kidney disease. HTN, hypertension. VTE, venous thromboembolism. FEU, fibrinogen equivalent units. ICU, intensive care unit. BMI, body mass index. GFR, glomerular filtration rate.
[a] Obese defined as BMI > 30.
[b] CKD defined as GFR < 60 mL/min/1.73 m^2.
* p-Value < 0.05.
** p-Value < 0.01.
*** p-Value < 0.001.

Table 2
Clinical outcomes by anticoagulation management.

	Prophylactic AC only (*N* = 99; 51%)	Prophylactic ➔ escalated-dose AC (*N* = 25; 13%)	Prophylactic ➔ therapeutic AC (*N* = 28; 15%)	Therapeutic AC only (*N* = 27; 14%)	No AC (*N* = 13; 7%)
Outcomes					
Disposition					
Died (%)	24 (24)	4 (16)	11 (39)	10 (37)	4 (31)
Discharged (%)	70 (71)	14 (56)	8 (29)	15 (56)	8 (61)
Remained admitted (%)	5 (5)	7 (28)	9 (32)	2 (7)	1 (8)
Acute TE[a] (%)	0	1 (4)	16 (57)	6 (22)	0
Major hemorrhage[b] (%)	3 (3)	2 (8)	5 (18)	1 (4)	1 (8)

Categorical variables presented as n (% of total N). There were no missing variables.
Abbreviations: TE, thromboembolic event. AC, anticoagulation. P AC, prophylactic anticoagulation only. P➔E, prophylactic to escalated-dose anticoagulation. P➔T, prophylactic to therapeutic dose anticoagulation. T AC only, therapeutic anticoagulation only.
[a] At the time of acute TE: 1 patient in P➔E group was on no anticoagulation at the time of the event (stroke prior to admission); of the 16 patients P➔T AC group, 2 were on no AC, 7 were on prophylactic dose and 7 were on escalated dose AC at the time of their event; of the 6 patients T AC only, 4 patients were not on AC at the time of their event (PE prior to admission), 1 was on prophylactic dose and 1 was on escalated dose.
[b] At the time of major hemorrhage: all patients in the P AC only group were on prophylactic dose AC; both patients in the P➔E group were on escalated dose AC; of the 5 patients in the P➔T AC group, 4 were on therapeutic AC and 1 was off anticoagulation (bled prior to admission); 1 patient in the T AC only group was on therapeutic AC; the patient in the no AC group was not on anticoagulation at the time of hemorrhage.

hospitals during the study period were included. Baseline characteristics summarized in Table 1.

Outcomes by anticoagulation group to which patients were assigned are detailed in Table 2. Specific anticoagulation dose at time of event is detailed in Table 2 footnotes. Reasons for transitioning to escalated-dose thromboprophylaxis included elevated D-dimer > 2.5 mg/L FEU (n = 13), and clinical deterioration requiring ICU care (n = 12). The most common reasons for escalation to therapeutic AC included development of acute TE (n = 16) and resuming chronic AC (n = 8). Of note, 7% received mechanical thromboprophylaxis alone due to rapid deterioration resulting in death or transition to comfort care, brevity of admission (< 48 h), or clear contraindications to AC.

Seven (3.6%) patients had radiographically-confirmed PE. Five of these occurred in ambulatory patients off thromboprophylaxis. Concerning the two inpatient PEs, one occurred on standard thromboprophylaxis, and the other occurred post-operatively while off AC. Additionally, two (1.0%) line-associated DVTs occurred in patients on standard thromboprophylaxis. There were five (2.6%) clinically-diagnosed PEs in patients on standard or escalated dose thromboprophylaxis, all occurred in the ICU. Including clinically-diagnosed events, the overall VTE rate was 7.3% (n = 14).

One (0.5%) radiographically-confirmed ischemic stroke occurred pre-admission in a patient with atrial fibrillation off AC. There were no myocardial infarctions or acute limb ischemia events.

There were eight (4.2%) clinically significant CVVHD circuit TEs. Three events occurred on standard thromboprophylaxis and five occurred on escalated-dose thromboprophylaxis.

Overall, 23 (12.0%) patients experienced TEs, with 20 requiring ICU level care during hospitalization. Fifteen (65.2%) were in the ICU at the time of their event. Among those with TEs, the mortality rate was

39.1% compared to 26.0% without (unadjusted OR = 1.8 [95% CI 0.72–4.5], p = 0.19).

Major bleeding occurred in 12 (6.3%) patients. Two (16.7%) were not on AC (bled before admission), three (25.0%) were on standard dose thromboprophylaxis, two (16.7%) were on escalated-dose thromboprophylaxis, and five (41.7%) were on therapeutic AC. Of these, one fatal CNS bleed occurred in a patient on therapeutic AC due to concern for heparin-induced thrombocytopenia.

In this mixed ward and ICU population, the overall mortality rate was 27.6%. TE rate was 17.0% in non-survivors compared to 10.1% in survivors. Further, the hemorrhage rate was 3.8% in non-survivors compared to 7.2% among survivors.

In this retrospective single-center study, we investigated the rate of TE, hemorrhage, and mortality in 192 consecutive patients hospitalized with COVID-19 managed with an escalated-dose thromboprophylaxis protocol. The incidence of VTE was 7.3% with a combined TE rate of 12%, lower than earlier reported rates [4–6] though consistent with more recent reports, with VTE rates of 5–15% [9,10].

The relatively low VTE and overall TE rate may be related to our early implementation of a more aggressive thromboprophylaxis strategy in patients with severe COVID-19 disease. This hypothesis is supported by a low rate of in-hospital VTE and the absence of radiographically-confirmed VTE in the escalated-dose thromboprophylaxis group. The benefit of escalated-dose thromboprophylaxis and/or therapeutic AC in high-risk COVID-19 patients is currently under investigation in prospective clinical trials (NCT04359277, NCT04406389, NCT04505774).

A notable finding of our investigations was that most radiographically-confirmed PEs occurred in ambulatory patients, suggesting thrombosis risk precedes admission. Phase 3 trials of anticoagulation and antiplatelets for primary thromboprophylaxis in ambulatory COVID-19 patients are currently underway (NCT04400799, NCT04498273).

Major bleeding occurred in twelve (6.3%) patients, including one fatal CNS bleed, consistent with existing data [9,10]. While most occurred in the presence of confounders, the rate of major hemorrhage is not negligible. Therefore, the risk of bleeding must be assessed on an individual and continual basis when using a more aggressive thromboprophylaxis strategy.

The overall mortality rate observed in our cohort was 27.6% and, importantly, was higher in patients with TE compared to those without. This has been previously reported and may be a result of endothelial injury and hypercoagulability induced by systemic inflammation [4,6]. However, it remains unknown if systemic AC prevents these immunothromboses [10].

This study is limited by its retrospective design, as well as several inherent biases. The evolution of COVID-19 therapies, particularly remdesivir and dexamethasone, coincided with the study period, but were utilized inconsistently. Additionally, those who elected early comfort care often did not receive pharmacologic thromboprophylaxis, thereby increasing their mortality rate. Since we did not evaluate clinically asymptomatic individuals, we may have underestimated subclinical VTE rates. Conversely, it was not possible to image all clinically symptomatic patients due to the incumbent challenges of transporting COVID-19 patients, potentially leading to an overestimation of the VTE rate.

Our study's strength is the intricate description of TE, hemorrhage and mortality rates in the context of an escalated-dose thromboprophylaxis protocol.

In conclusion, we observed a VTE rate of 7.3% and an overall TE rate of 12.0% in a mixed ward and ICU population of consecutive patients admitted with COVID-19 infection. Our use of an escalated-dose thromboprophylaxis regimen for patients with D-dimer > 2.5 mg/L FEU and critical illness was associated with a 6.3% rate of major hemorrhagic complications. However, two bleeds occurred before hospitalization while off AC, felt to be unrelated to COVID-19.

It remains speculative whether escalated-dose thromboprophylaxis improves outcomes in COVID-19 patients. Further investigation into this and the risks and benefits of thromboprophylaxis in the ambulatory patient is warranted.

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Molly M. Daughety[a], Andrew Morgan[b,c], Erin Frost[b,c], Chester Kao[c], Joyce Hwang[c], Rachel Tobin[c], Bhavik Patel[c], Matthew Fuller[d], Ian Welsby[d], Thomas L. Ortel[a,e,*]

[a] *Division of Hematology, Department of Medicine, Duke University Medical Center, Durham, NC, USA*

[b] *Department of Pediatrics, Duke University Medical Center, Durham, NC, USA*

[c] *Department of Medicine, Duke University Medical Center, Durham, NC, USA*

[d] *Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA*

[e] *Department of Pathology, Duke University Medical Center, Durham, NC, USA*

E-mail address: thomas.ortel@duke.edu (T.L. Ortel).

[*] Corresponding author at: Duke University Medical Center, Durham, NC 27710, USA.