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ORIGINAL ARTICLE

Thromboprophylaxis in COVID-19: Weight and severity adjusted intensified dosing

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Abstract

Background: Venous thromboembolism (VTE) frequently occurs in hospitalized patients with coronavirus disease 2019 (COVID-19). The optimal dose of anticoagulation for thromboprophylaxis in COVID-19 is unknown.

Aims: To report VTE incidence and bleeding before and after implementing a hospital-wide intensified thromboprophylactic protocol in patients with COVID-19.

Methods: On March 31, 2020, we implemented an intensified thromboprophylactic protocol consisting of 50 IU anti-Xa low molecular weight heparin (LMWH)/kg once daily at the ward, twice daily at the intensive care unit (ICU). We included all patients hospitalized in a tertiary care hospital with symptomatic COVID-19 between March 7 and July 1, 2020. The primary outcome was the incidence of symptomatic or

subclinical VTE and major bleeding during admission. Routine ultrasound screening for VTE was performed whenever logistically possible.

Results: We included 412 patients, of which 116 were admitted to the ICU. Of 219 patients with standard a prophylactic dose of LMWH, 16 (7.3%) had VTE, 10 of which were symptomatic (4.6%). Of 193 patients with intensified thromboprophylaxis, there were no symptomatic VTE cases, three incidental deep venous thrombosis cases (1.6%), and one incidental pulmonary embolism (0.5%). The major bleeding rate was 1.2% in patients with intensified thromboprophylaxis and 7.7% when therapeutic anticoagulation was needed.

Conclusion: In hospitalized patients with COVID-19, there were no additional symptomatic VTEs and a reduction in incidental deep vein thrombosis after implementing systematic thromboprophylaxis with weight-adjusted prophylactic (ward) to intermediate (ICU), but not therapeutic dosed anticoagulation. This intensified thromboprophylaxis was associated with a lower risk of major bleeding compared with therapeutic dosed anticoagulation.

KEYWORDS
anticoagulants, COVID-19, hemorrhage, heparin, low-molecular-weight, thrombosis

Essentials

- Blood clots frequently occur in hospitalized patients with COVID-19.
- The optimal dose of blood thinners to prevent these clots in COVID-19 is still debatable.
- After selectively increasing the dose for clot prevention, clots became rare in this center.
- When an even higher dose was required to treat established clots, the bleeding risk increased.

1 | INTRODUCTION

One and a half years after the first outbreak in Wuhan, China, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 305 million confirmed cases of infection and more than 5 million known deaths worldwide as of January 10, 2022.[1] Clinicians quickly learned that the coronavirus disease 2019 (COVID-19) is associated with a high incidence of symptomatic venous thromboembolism (VTE) in hospitalized patients, especially in patients on intensive care units (ICUs). Systematic screening for VTE in patients hospitalized with COVID-19 has also revealed a higher incidence of subclinical VTE, even in patients receiving prophylactic doses of low molecular weight heparin (LMWH).[2-12] Furthermore, more extensive activation of the coagulation system has been associated with worse clinical outcomes, and the use of LMWH in intermediate or therapeutic doses has been suggested to improve outcome in patients hospitalized with COVID-19.[13-18] Many studies have focused on identifying the optimal dose of LMWH for in-hospital thromboprophylaxis.[19-30] However, the results of these studies were not yet available to guide treatment in the large number of patients hospitalized early in the pandemic, resulting in high variability in institutional guidance for COVID-19 thromboprophylaxis.[31] Although the standard of care, fixed-dose use of LMWH seemed insufficient to prevent VTE in high-risk (ICU) patients, early reports warned for an increased risk of major bleeding with therapeutic doses of LMWH in the critically ill.[32,33] Therefore, the optimal thromboprophylactic scheme was unknown.

In March 2020, during the first peak of SARS-CoV-2 infections in Belgium, a hospital-wide thromboprophylactic protocol was implemented for hospitalized COVID-19 patients in an attempt to balance VTE prevention and bleeding risk in the absence of good evidence. In this "intensified prophylactic dose" protocol, typical prophylactic doses of LMWH were adjusted based on body weight and disease severity, with higher doses for ICU patients and weight-adjusted increases in LMWH dose. Full therapeutic doses (1 mg/kg twice daily) were not used for thromboprophylaxis but restricted to patients with prior indication for therapeutic anticoagulation with known VTE.

While awaiting randomized data, we analyzed the safety and efficacy of our center's protocol. These, meanwhile published, randomized trials provide some interesting data, but there are still open questions on the optimal thromboprophylactic dosing in clinical practice. We, therefore, report our single-center observation of the safety and efficacy of this "intensified prophylactic" dosing strategy.

2 | METHODS

This single tertiary-center retrospective study was performed at the University Hospitals Leuven in Belgium and was approved by the ethical committee (S64068). All adult patients (18 years or older) were included when hospitalized with symptomatic COVID-19 between March 7 and July 1, 2020. COVID-19 diagnosis was defined as a positive reverse transcription polymerase chain reaction (on a nasopharyngeal swab or bronchoalveolar lavage) and/or a compatible clinical history and pulmonary computed tomography. Patients with incidental SARS-CoV-2 infections admitted for other reasons were excluded.

2.1 | Introduction of an intensified COVID-19 thromboprophylactic protocol

Before March 31, 2020, hospitalized patients without an indication for therapeutic anticoagulation received a prophylactic dose of 4000 anti-Xa units of LMWH as per standard of care; "standard thromboprophylactic protocol." From March 31 onwards, a hospital-wide COVID-19 thromboprophylactic protocol was introduced as described by our group in April 2020[34] and later recommended by the Belgian Society of Thrombosis and Hemostasis[35] (Table 1): "intensified COVID-19 thromboprophylactic protocol." In summary, patients admitted to the ward received a dose of 50 IU anti-Xa LMWH per kg body weight once daily, with a minimum of 4000 IU. To prevent early reduction of prophylactic dosed enoxaparin in patients hospitalized at the ward, there was no standing order on dose reduction in patients with or developing renal insufficiency. Instead, all cases eligible for dose reduction were discussed with our center's department of thrombosis and hemostasis. When creatine clearance was expected to drop below 15 ml/min, the case was first discussed with the department of thrombosis and hemostasis before administering a new dose. When admitted to the ICU, the dose increased to an intermediate dose of 50 IU anti-Xa LMWH per kg body weight twice daily (once daily when creatinine clearance was below 30 ml/min). Cases eligible for dose reduction were also discussed with the department of Thrombosis and Hemostasis. Full therapeutic anticoagulation was restricted to patients with a prior indication for therapeutic anticoagulation or patients with newly diagnosed VTE. Patients needing continuous veno-venous hemofiltration or extracorporeal membrane oxygenation (ECMO) were treated with unfractionated heparin, monitored by parallel activated partial thromboplastin time and anti-Xa levels. Case-based anticoagulation was provided when the treating physician assessed an increased bleeding risk. All patients who received at least one day of "standard prophylactic" treatment were analyzed in the standard prophylactic group.

2.2 | Screening for VTE

Given the preliminary reports on the high incidence of thrombotic complications in hospitalized COVID-19 patients,[6,7] clinicians were educated to be highly observant for signs of thrombotic complications and apply a low threshold for diagnostic imaging. Additionally, because of these alarming reports, clinicians started screening for deep venous thrombosis (DVT) in some ICU patients early on. Routine screening with venous duplex-ultrasound (CX 50 ad Sparq, Philips), aimed toward all ICU and ward patients, was initiated once logistically feasible given the challenging circumstances

TABLE 1 Hospital-wide intensified COVID-19 protocol

Anticoagulation regimen for thromboprophylaxis in hospitalized patients with COVID-19		
	ICU **Weight-adjusted intermediate dose**	**Non-ICU** **Weight-adjusted prophylactic dose**
CrCl > 30 ml/min	50 IU anti-Xa/kg BID	50 IU anti-Xa/kg OD
CrCl < 30 ml/min	50 IU anti-Xa/kg OD and case discussion	50 IU anti-Xa/kg OD and case discussion
CrCl < 15 ml/min	Case discussion[a]	Case discussion[a]
CVVH, ECMO	Unfractionated heparin	/
High bleeding risk[b]	Case discussion[a]	Case discussion[a]
Anticoagulation regimen for treatment of COVID-19-related venous thromboembolism		
	Weight-adjusted therapeutic dose	
CrCl > 30 ml/min	100 IU anti-Xa/kg BID	
CrCl < 30 ml/min	Dose-adjusted therapeutic LMWH or tinzaparin should be considered	
CrCl < 15 ml/min	Unfractionated heparin if feasible	

Abbreviations: BID, twice daily; CrCl, creatinine clearance; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OD, once daily.

[a]Risks and benefits of thromboprophylaxis are weighed on individual basis.

[b]Low platelet count/recent major bleeding/dialysis.

of availability of trained personnel and (protective) equipment in an overburdened health care system (i.e., April 28, 2020). Ultrasound screening was performed by radiologists, vascular ultrasound technicians, and trained residents internal medicine supervised by the latter.

2.3 | Outcome

The primary outcome of this study was the in-hospital incidence of VTE, including upper and lower limb DVT, catheter-related thrombosis, and pulmonary embolism (PE). Both computed tomography pulmonary angiogram and ventilation-perfusion scan are used to detect PE in this center. Subsegmental PE was differentiated from non-subsegmental PE. VTE was considered symptomatic when a clinical suspicion was confirmed with a technical investigation. Incidental VTE was any VTE found incidentally during a diagnostic examination not specifically aimed at detecting DVT or PE. The secondary endpoint was major bleeding as defined by the International Society on Thrombosis and Haemostasis.[36] Type and dose of anticoagulation at the time of bleeding were obtained, and major bleedings were subsequently reported as a percentage of all patients receiving the same type of anticoagulation and pooled by indication. Data on therapeutic, intermediate, and prophylactic dosages could therefore be reported. Further, markers of thromboinflammation were collected: D-dimers reported as fibrinogen equivalent units (ACL TOP 700 LAS, Werfen; HemosIL D-dimer HS 500, Werfen) and C-reactive protein (CRP; Cobas 8000, Roche; Cobas CRP4, Roche).

2.4 | Data collection and statistics

The center's COVID-19 registry identified patients with confirmed COVID-19. Patient characteristics and data on VTE were obtained retrospectively by reviewing electronic medical records (J.V., M.M.E., C.M., and V.S.). Continuous variables are expressed as median (interquartile range [IQR]) and were compared with the nonparametric Kruskal-Wallis test. Categorical variables are represented as frequencies and proportions (%) and, when appropriate, compared by χ^2 or Fisher exact test. An adjusted multivariable model for predefined outcomes was fitted. The statistical analysis is performed using R-software (version 4.0.3) on a 0.05 significance level. Figures were created using GraphPad Prism (version 9.0.0).

3 | RESULTS

3.1 | Baseline characteristics

A total of 412 patients hospitalized from March 8 until July 1 were included (Figure 1). Of those, 219 patients (53%) were admitted before March 31, 2020, and received the standard prophylactic dose until March 31, 2020; 193 patients (47%) were admitted after implementing the intensified COVID-19 protocol. Of 116 patients (28%) admitted to the ICU, 34 (29%) were treated during their entire hospitalization with the intensified protocol and 82 (71%) were admitted before the implementation of this protocol.

The median age was 68 years (IQR 57–81), and 58% were male. Nine percent of patients had a history of VTE before hospitalization. The median hospital stay was 11 days (IQR 6–20); 28% of patients had been admitted to the ICU with a median ICU stay of 12 days (IQR 7–24). Of those critically ill patients, 62% needed invasive mechanical ventilation and 11% required ECMO. At admission, 17% of all patients were on therapeutic anticoagulation and 25% on antiplatelet therapy (Table 2).

Sequential groups ("standard" thromboprophylaxis, before March 31, and "intensified" thromboprophylaxis, after March 31) were comparable in terms of basic characteristics and in-hospital severity parameters (Table 2). At the ward, there was a higher percentage of male patients (58 vs. 45%, $p = 0.03$); platelet count was significantly lower on admission (199 vs. 215 $\times$ 10^9/L, $p = 0.04$) in the group hospitalized before the introduction of the intensified protocol. All other parameters, including length of hospital stay, baseline antithrombotic therapy, D-dimer and CRP levels, and respiratory support, were comparable. Except for maximal D-dimer values during hospitalization, ICU patients were comparable for both groups. The maximal rise in D-dimer levels was lower in ICU patients treated with the intensified protocol since admission (2086 vs. 4729 ng/ml, $p = 0.04$), whereas there was no difference in baseline D-dimer values, or any other severity parameters like ICU stay, respiratory support, and cardiopulmonary resuscitation.

3.2 | Incidence of VTE and major bleeding

Of the 219 patients who (initially) received standard-dosed thromboprophylaxis, 16 (7.3%) were diagnosed with VTE during hospitalization, 10 of whom were symptomatic (4.6%) (Figure 2). There were six patients with PE diagnosed and treated, two of which were subsegmental. In the 193 patients who were started on the intensified COVID-19 protocol from admission, there were no cases of symptomatic VTE. Four patients (2.1%) were diagnosed with VTE during hospitalization, none of whom were symptomatic. As such, all four VTE cases were incidental, of whom three incidental DVT and one incidental PE were diagnosed in the intensified group. As illustrated in Figure 2B, nine of 27 (33.3%) screened ICU patients were diagnosed with incidental DVT before implementing the intensified protocol. Afterward, only two of 17 (11.8%) screened ICU patients, and none of the 38 screened ward patients were diagnosed with incidental DVT. Before and after implementing the intensified protocol, 33% and 50% of ICU patients were screened.

Figure 3 shows the incidence of major bleeding by type and dose of anticoagulation. Most major bleeds occurred in patients treated with unfractionated heparin (46.2%) and all supported with ECMO. The incidence of major bleeding was significantly higher in patients

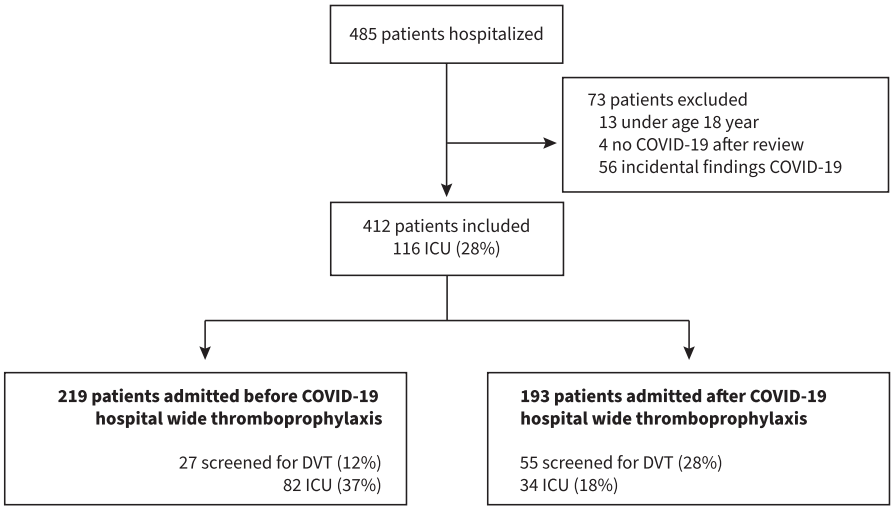

FIGURE 1 Patient selection. Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit

with an indication for therapeutic dosed anticoagulation compared with patients treated with intensified thromboprophylaxis (7.7% vs. 1.2%, $p = 0.003$). The difference in major bleeding between ICU (50 IU anti-Xa LMWH/kg, twice daily) and ward patients (50 IU anti-Xa LMWH/kg, twice daily) treated according to the intensified COVID-19 protocol was not statistically significant (1.7% vs. 1.1%, $p = 0.6$). There were no major bleedings registered in patients on standard thromboprophylaxis; given the low event rate, the difference with the intensified COVID-19 thromboprophylactic protocol was not significant ($p = 0.9$).

4 | DISCUSSION

Thrombotic complications are frequent in patients hospitalized with COVID-19. Several reports have shown a high incidence of VTE even despite the use of standard prophylactic doses of LMWH. In contrast, full therapeutic doses of LMWH increase the risk of bleeding in the critically ill. This study shows that using a hospital-wide protocol focused on intensified thromboprophylaxis was associated with a low VTE incidence and a low rate of major bleeding.

We shifted from a standard thromboprophylactic strategy with a fixed dose of 4000 anti-Xa units LMWH toward an intensified COVID-19 thromboprophylactic protocol (Table 1) in our center from March 31 onwards. Patients treated with—or started on—standard thromboprophylaxis had a relatively low incidence of VTE (4.7%) compared with other reports despite standard thromboprophylaxis.[4,7] After introducing the intensified protocol, there were no additional symptomatic VTEs reported in the patients treated with this protocol from admission onward. Additionally, the incidence of screening-detected DVT decreased from 33.3% to 11.8% in ICU patients. These results suggest that the intensified protocol effectively reduces the thrombotic risk in hospitalized COVID-19 patients. Despite intensifying thromboprophylaxis, the incidence of major bleedings remained low and did not significantly differ between intermediate and prophylactic dosed LMWH. Also, major bleedings were significantly lower in patients receiving (intensified) thromboprophylaxis compared with patients treated with therapeutic-dosed anticoagulation when indicated.

Patients in both the standard and intensified protocol show comparable basic characteristics, in-hospital severity parameters (hospital stay, ICU stay, respiratory support) and thrombo-inflammatory parameters (CRP and D-dimers). However, interestingly, in patients treated with the intensified scheme from admission onward, we noted a significantly lower maximal D-dimer value ($p = 0.04$), which may reflect a better suppression of the thrombotic response with higher intensity thromboprophylaxis and is in keeping with the possible lower risk on VTE in this group.

Several studies have investigated the use of therapeutic doses of LMWH. Just recently, the contrasting results from the multiplatform ATTACC, ACTIV-4a, and REMAP-CAP trials in critically and noncritically ill were published (REMAP-CAP, NCT02735707[21]; ACTIV-4, NCT04505774; ATTACC, NCT04372589[22]). The investigators report a potential benefit of therapeutic dosed LMWH in the noncritically ill but with an increased risk of major bleeding.[23] In contrast, there was no benefit of therapeutic-dosed LMWH in the critically ill, with a high probability of inferiority and higher risk of bleeding compared with standard thromboprophylaxis.[24,33,37] Although both multiplatform trials compare prophylactic with therapeutic doses, in practice, a large number of patients in both the control and the intervention arm actually received intermediate to subtherapeutic dosages of LMWH. Only 40.4% of critically ill patients in the control arm received a low dose of thromboprophylaxis; 51.7% received an intermediate dose. Additionally, in the intervention group, 22.4% of critically ill patients and 20.4% of noncritically ill patients did not receive a therapeutic dose. Indeed, the suboptimal dose adherence makes it difficult to draw definitive conclusions about the optimal antithrombotic strategy based on these trials. Hospitalized COVID-19 patients with elevated D-dimer levels treated with therapeutic anticoagulation (rivaroxaban) in the ACTION trial, also had increased bleeding without improved outcome.[25] In the RAPID COVID COAG trial, therapeutic dosages were not associated with an increased bleeding risk but did not improve the composite outcome (death, invasive mechanical

TABLE 2 Baseline characteristics

	Ward			ICU		
	Before March 31, 2020 (*N* = 137)	After March 31, 2020 (*N* = 159)	*p* value	Before March 31, 2020 (*N* = 82)	After March 31, 2020 (*N* = 34)	*p* value
History						
Age, median, y (IQR)	69.0 [57.0;82.0]	72.0 [59.0;86.5]	0.055	65.0 [53.0;73.0]	60.0 [54.0;73.0]	0.504
Male sex, no. (%)	80 (58.4)	72 (45.3)	0.033	64 (78)	24 (70.6)	0.54
Caucasian ethnicity, no. (%)	134 (97.8)	155 (97.5)	1.000	80 (97.6)	33 (97.1)	1.000
Body weight, median, kg (IQR)	78.0 [69.0;89.6]	72.1 [62.9;84.0]	0.016	85.0 [74.2;96.9]	77.3 [69.0;89.3]	0.15
Body mass index, median (IQR)	26.3 [24.0;31.1]	26.2 [23.3;29.2]	0.326	27.8 [24.9;31.7]	25.6 [23.8;29.6]	0.1
Diabetes mellitus, no. (%)	37 (27.0)	50 (31.4)	0.479	28 (34.1)	17 (50.0)	0.17
HbA1c, median (IQR)	6.20 [5.90;6.50]	6.00 [5.60;6.50]	0.118	6.30 [6.00;6.80]	6.55 [6.00;7.10]	0.37
Smoking (ever), no. (%)	49 (44.1)	55 (43.3)	1.000	37 (50.0)	19 (65.5)	0.23
Hypertension, no. (%)	65 (47.4)	85 (53.5)	0.360	46 (56.1)	16 (47.1)	0.5
Chronic kidney disease						
eGFR <60 ml/min/1.73 m^2, no. (%)	51 (37.2)	59 (37.1)	1.000	27 (32.9)	10 (29.4)	0.9
eGFR <30 ml/ min/1.73 m^2, no. (%)	16 (11.7)	26 (16.4)	0.33	4 (4.88)	3 (8.82)	0.42
eGFR (ml/min/1.73 m^2), median (IQR)	74.5 [48.0;95.0]	70.0 [43.0;91.8]	0.42	75.0 [52.0;90.5]	76.0 [54.0;101]	0.41
History of VTE, no. (%)	15 (10.9)	13 (8.18)	0.539	5 (6.10)	4 (11.8)	0.45
Active cancer, no. (%)	12 (8.76)	17 (10.7)	0.718	11 (13.4)	3 (8.82)	0.76
Concomitant drugs, no. (%)						
Therapeutic anticoagulation	25 (18.2)	37 (23.3)	0.360	7 (8.54)	2 (5.88)	1.00
DOAC	20 (14.6)	24 (15.1)	1.000	3 (3.66)	2 (5.88)	0.63
LMWH	1 (0.73)	5 (3.14)	0.222	2 (2.44)	0 (0.00)	1.00
Vitamin K antagonists	4 (2.92)	8 (5.03)	0.533	2 (2.44)	0 (0.00)	1.00
Antiplatelet drugs	32 (23.4)	43 (27.0)	0.553	18 (22.0)	9 (26.5)	0.78
Aspirin	29 (21.2)	39 (24.5)	0.585	16 (19.5)	8 (23.5)	0.82
P2Y12 inhibitor	4 (2.92)	6 (3.77)	0.757	4 (4.88)	4 (11.8)	0.23
Statin therapy	49 (35.8)	57 (35.8)	1.000	29 (35.4)	13 (38.2)	0.94
Antihypertensive drugs	57 (41.6)	79 (50.0)	0.185	44 (53.7)	15 (44.1)	0.46
COVID-19 diagnosis						
PCR positive, no. (%)	115 (83.9)	137 (86.2)	0.710	74 (90.2)	31 (91.2)	1.00
Length of stay (days), median (IQR)						
Total hospital stay	8.00 [5.00;13.0]	9.00 [6.00;14.0]	0.350	25.5 [13.0;41.8]	25.0 [17.2;33.8]	0.55
ICU stay	N/A	N/A	N/A	15.5 [7.00;29.0]	12.0 [7.00;18.5]	0.18
Laboratory values, median (IQR)						
Hemoglobin, admission, g/dl	13.2 [11.7;14.6]	12.7 [11.1;14.3]	0.090	14.1 [13.0;15.7]	13.4 [12.1;14.3]	0.03
Platelet count, admission, $\times 10^9$/L	199 [152;256]	215 [169;294]	0.039	186 [146;238]	229 [172;259]	0.03
White blood cell count, admission, x10^9/L	5.85 [3.97;7.84]	6.35 [4.42;8.32]	0.170	7.07 [5.29;8.67]	7.32 [5.94;9.23]	0.62

TABLE 2 (Continued)

	Ward			ICU		
	Before March 31, 2020 (*N* = 137)	After March 31, 2020 (*N* = 159)	*p* value	Before March 31, 2020 (*N* = 82)	After March 31, 2020 (*N* = 34)	*p* value
D-dimer, ng/ml						
Admission	870 [609;1495]	838 [517;1388]	0.855	1135 [661;1402]	1173 [718;1640]	0.59
Maximum	1203 [674;1871]	1126 [662;1643]	0.412	4729 [2032;16855]	2086 [1382;5935]	0.04
C-reactive protein, mg/L						
Admission	64.3 [29.5;102]	50.4 [18.1;91.9]	0.076	112 [51.6;163]	109 [57.1;171]	0.57
Maximum	91.1 [50.8;153]	77.0 [39.0;150]	0.242	273 [180;343]	218 [121;333]	0.15
Respiratory support during hospitalization, no. (%)						
Oxygen	106 (77.4)	122 (76.7)	1.000	82 (100)	32 (94.1)	0.08
Mechanical ventilation	N/A	N/A	N/A	51 (62.2)	21 (61.8)	1.00
ECMO	N/A	N/A	N/A	8 (9.76)	5 (14.7)	0.52

Note: Baseline characteristics of all patients, by severity and timing of hospital admission.

Abbreviations: DOAC, direct acting oral anticoagulant; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; ICU, intensive care unit; IQR, interquartile range; LMWH, low molecular weight heparin; N/A, not available; PCR, polymerase chain reaction; VTE, venous thromboembolism.

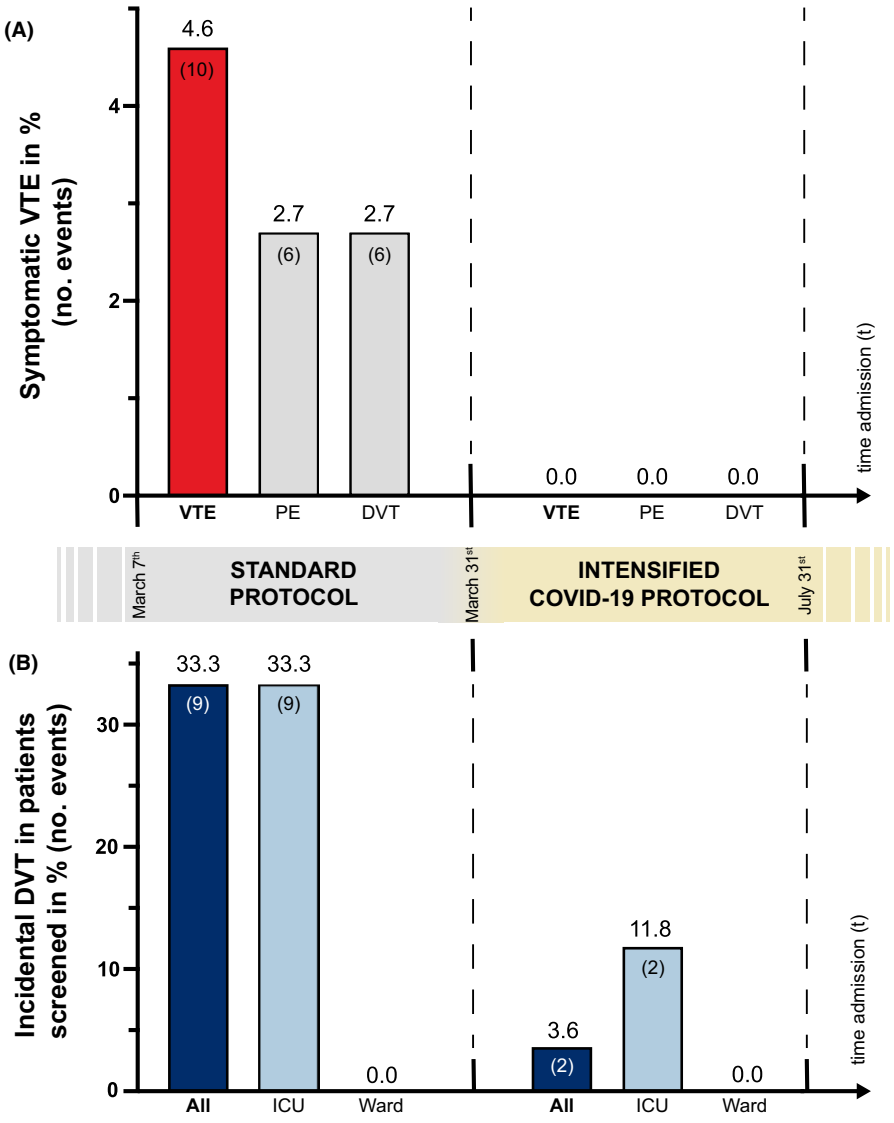

FIGURE 2 Incidence of venous thromboembolism. (a) Incidence of symptomatic venous thromboembolism (VTE) with the standard and the intensified protocol. (b) Incidence of incidental deep vein thrombosis (DVT) in patients screened with venous ultrasound (VUS). Abbreviations: ICU, intensive care unit; PE, pulmonary embolism

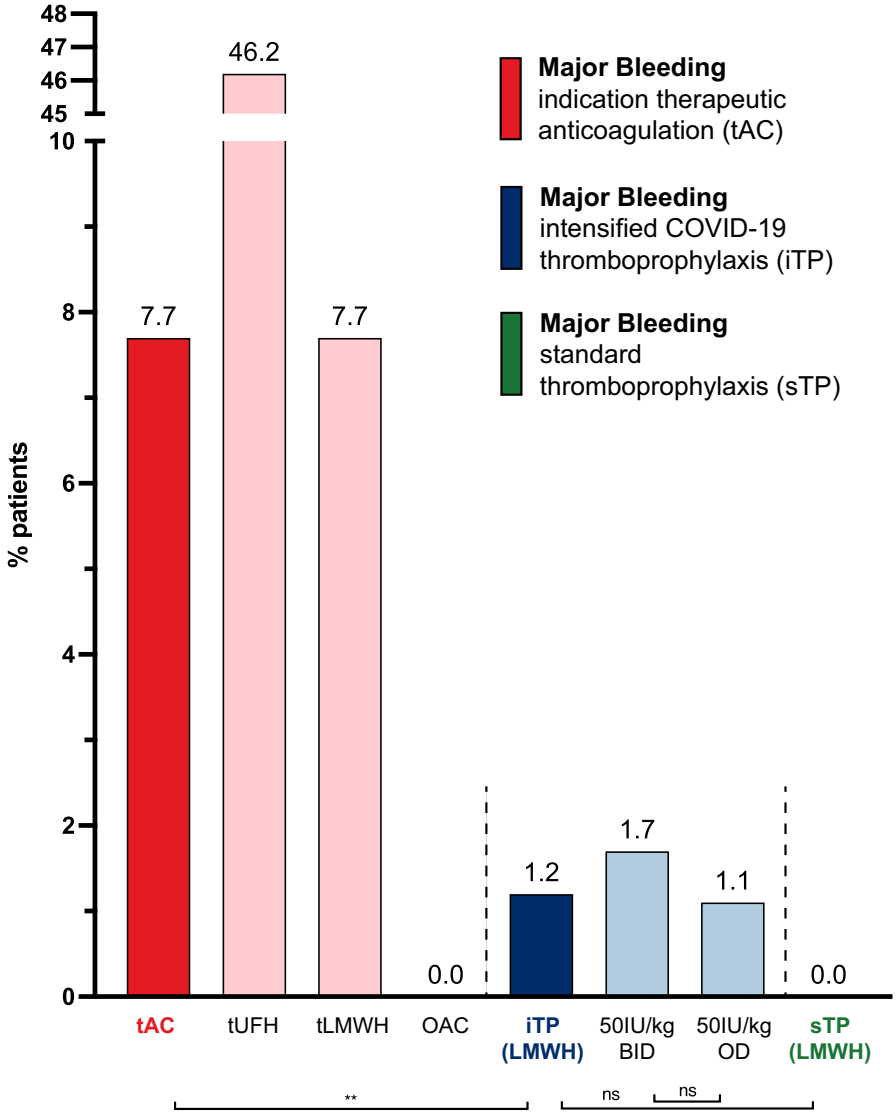

FIGURE 3 Incidence of major bleeding. The incidence of major bleeding was significantly higher in patients in need for therapeutic doses of anticoagulation compared with patients treated with nontherapeutic thromboprophylaxis. Abbreviations: BID, twice daily; LMWH, low molecular weight heparin; ns, not significant; OAC (vitamin K antagonists and direct oral anticoagulation), oral anticoagulation; OD, once daily; tLMWH, therapeutic dose of LMWH; tUFH, therapeutic dose of unfractionated heparin; **, $p = 0.003$

ventilation, noninvasive mechanical ventilation, or ICU admission) compared with prophylactic dosages in moderately ill ward patients (D-dimers two times upper limit of normal).[26] These results are in line with an early pooled analysis of observational data from Patell et al. and suggest that there may be little to no additive benefit beyond intermediate dosed LMWH.[27] In contrast, the HEP-COVID trial showed advantages of therapeutic dosages compared with institutional prophylactic or intermediate dosed heparins in ward, but not ICU, patients with elevated D-dimers (four times the upper limit of normal). In these therapeutically treated patients, there was no significant increase in major bleeding incidence.[30] The open-label INSPIRATION trial compared intermediate- with prophylactic-dosed heparin in ICU patients with a composite primary endpoint of adjudicated venous or arterial thrombosis, treatment with ECMO, or mortality within 30 days.[28] There was no statistical difference in the composite endpoint between the two strategies. However, the most critically ill patients were excluded, and the studied population was not as critically ill as can be expected from an ICU population. For example, the incidence of mechanical ventilation was around 20% in both groups compared with more than 60% in our ICU population. Recently, a meta-analysis comparing therapeutic dosages of heparin with lower dosages concluded that therapeutic heparin is beneficial in moderately—but not critically—ill patients.[29] However, one should be careful drawing definite conclusions because studies included in the meta-analysis have their limitations. The most weighted study in the moderately ill meta-analysis is the multiplatform trial discussed earlier, with only 79% of patients in the therapeutic group receiving full-dose anticoagulation. Additionally, the patients in the HEP-COVID trial represent a subset of patients with high D-dimer levels (four times the upper limit of normal). Furthermore, when looking at D-dimer subgroups in the multiplatform trial, only the overall cohort showed a significant risk difference and odds ratio confidence interval with "a high probability of superiority" for therapeutic dose anticoagulation; this was not the case in patients with low levels of D-dimers (less than two times upper limit of normal). Additionally, patients with a substantial bleeding risk or absolute indication for anticoagulation were excluded in these studies.[38]

Our data suggest that striving to monitored weight-adjusted intermediate doses in the critically ill and weight-adjusted prophylactic

doses at the wards may represent a good balance between thromboprophylaxis and bleeding. This is further supported by the higher major bleeding rate we report in those patients who received therapeutic-dosed LMWH compared with lower-than-therapeutic-dosed LMWH in our population, considering that our intensified but nontherapeutic COVID-19 protocol seems to prevent VTE effectively. These results could still be in line with randomized data because one-half of the ICU patients in the control group of the multiplatform trial received intermediate dosages. Therapeutic concentrations in ward patients seemed beneficial primarily in high-risk patients with elevated D-dimer levels (two to four times the upper limit of normal), which was not the case in most of our ward population. Bleeding risk in ward patients treated with therapeutic dosages was not significantly higher in most studies, but we need to be careful to extrapolate these findings to the general ward population because patients with a substantial bleeding risk or an absolute indication for anticoagulation were excluded from the randomized trials.

This study's strengths include a large number of well-characterized patients treated at a tertiary center for COVID-19. We were able to treat 193 patients according to the intensified protocol from admission onward and add a supplemental sensitivity analysis for the observed symptomatic VTE rate through a systematic ultrasound screening in up to 50% of the critically ill in this group. The low incidence of incidental VTE in patients receiving the intensified COVID-19 protocol strengthens the idea that the underestimation of VTE in this group is negligible. Anti-Xa assays are integrated into the routine hospital laboratory, making monitoring of ICU patients and challenging cases readily available. This level of monitoring provides insights into the accumulation of LMWH, for example, in patients with progressive renal failure, or underdosing, typically, in obese patients. As a safety recommendation, physicians were encouraged to measure anti-Xa levels in critically ill patients. Dose adjustment based on these levels was left to the clinician's discretion, with support of the department of thrombosis and hemostasis, considering the clinical context. Therefore, it is unclear to which extent anti-Xa measurements have contributed to the efficacy and safety of our protocol.

Because of its retrospective and sequential nature, this study also has several limitations. Importantly, due to the lack of randomization and the sequential design during an emergency state during the pandemic with a rapidly changing clinical practice, it is not possible to confirm a causal relation between the intensified thromboprophylaxis strategy and the lower rates of VTE. As discussed in the Methods, this emergency state also prohibited routine venous ultrasound screening in all hospitalized patients at a predefined time point in the early phase of the pandemic. As resources became more readily available, we eventually screened up to 50% of the critically ill patients receiving the intensified protocol during hospitalization. This lack of systematic imaging does not affect the diagnosis of symptomatic VTE but is a major limitation when assessing asymptomatic DVT. However, this limitation was inherent to the timing of the study early in the pandemic and the limited resources at that time. As screening became more frequent after adopting the intensified thromboprophylaxis protocol, a higher proportion of patients was screened during the second part of the study. Thus, there is less potential for underestimating the true VTE incidence in patients receiving intensified versus standard thromboprophylaxis. Therefore, it is unlikely that more systematic screening would have affected our main findings. Last, given the relatively few events in the outcomes of interest—VTE and major bleeding—an adjusted multivariate model could not be adequately performed. Consequently, the reported findings should be interpreted cautiously.

Our retrospective analysis seems in line with available randomized data that strictly prophylactic doses of heparin may not be sufficiently effective to prevent venous thromboembolism in patients hospitalized with severe COVID-19.

Randomized trials have shown that systematically using therapeutic doses of heparin was associated with an increased bleeding risk in several subgroups of patients, most importantly in critically ill patients. Our data show that a patient-tailored approach to anticoagulation with intensified prophylactic, but not therapeutic doses of heparin, was associated with high efficacy to prevent thromboembolism and a low bleeding risk in our population.

Together with the results of randomized trials, this study stresses the importance of (1) a hospital-wide protocol and (2) higher than prophylactic-dosed anticoagulation in selected patients.

5 | CONCLUSION

In hospitalized patients with COVID-19, we report no symptomatic VTE and a decrease in screening-detected incidental DVT after implementing systematic thromboprophylaxis with weight-adjusted prophylactic (ward) to intermediate (ICU), but not therapeutic doses of LMWH. This strategy was associated with a low risk of major bleeding in patients receiving intensified but non-therapeutic dosed thromboprophylaxis.

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RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest for the submitted work.

AUTHOR CONTRIBUTIONS

All authors have read the manuscript and approved submission. Christophe Vandenbriele, Peter Verhamme, and Thomas Vanassche outlined the study protocol. Natalie Lorent, Paul De Munter, Rik Willems, Joost Wauters, Alexander Wilmer, Dieter Dauwe, Jan Gunst, and Stefan Janssens were directly involved

in COVID-19 patient care. Matthias M. Engelen, Christophe Vandenbriele, Pieter Sinonquel, and Griet Pieters performed additional venous ultrasound screenings, supervised by Griet Pieters. Matthias M. Engelen, Valérie Spalart, and Caroline P. Martens collected patient data. Matthias M. Engelen, Christophe Vandenbriele, Peter Verhamme, and Thomas Vanassche drafted the manuscript. Matthias M. Engelen created figures and tables. Ipek Guler performed statistics. Valérie Spalart, Caroline P. Martens, Bert Vandenberk, Pieter Sinonquel, Natalie Lorent, Paul De Munter, Rik Willems, Joost Wauters, Alexander Wilmer, Dieter Dauwe, Jan Gunst, Stefan Janssens, Kimberly Martinod, and Kathelijne Peerlinck reviewed and commented on the draft. Matthias M. Engelen, Christophe Vandenbriele, and Thomas Vanassche finalized the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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