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LETTER TO THE EDITOR

Bleeding prevalence in COVID-19 patients receiving intensive antithrombotic prophylaxis

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To the editor

In-hospital patients with severe acute respiratory syndrome coronavirus 2-induced disease (COVID-19) have a high risk of thrombosis [1–4]. Pharmacological thromboprophylaxis is strongly encouraged, and several experts even suggest the use of high-dose prophylaxis or full anticoagulation for patients with severe disease at low risk of bleeding, but up to now, data on safety of this approach are lacking [1, 5–8].

Here, we report observational single-center prevalence of major bleeding events (ISTH definition, Table S1) in patients with COVID-19 receiving intensive thromboprophylaxis [9]. We included all consecutive adult patients with laboratory-proven COVID-19 treated between April 1st and May 6th 2020 at the Hospital La Carità, Locarno, Switzerland. On April 1st 2020, we have implemented the following intensive thromboprophylaxis scheme: Patients with COVID-19 with an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2 received subcutaneous enoxaparin twice daily (BID) at a dose of 40 mg (< 80 kg), or 60 mg (≥ 80 kg) for a minimum of 14 days (dose level 1). Dose escalation to 60 mg BID (< 80 kg), or 80 mg BID (≥ 80 kg) was discussed if D-dimer levels increased during follow-up > 2.0 mg/L, irrespective of the presence of thromboembolic complications (dose level 2). Patients with COVID-19 with an eGFR < 30 ml/min/1.73 m^2 received subcutaneous UFH at a dose of 5000 IU three times a day in the regular ward, or continuous intravenous UFH in the intensive care unit (ICU) with a target anti-Xa activity of 0.3–0.5 U/ml. The study was approved by the Ethical Committee Ticino, Switzerland (2020-00838 RIF.CE 3621).

A total of 270 inpatients with confirmed COVID-19 were eligible for this analysis. 22 (8.2%) patients received regular thromboprophylaxis with once daily enoxaparin 40 mg or UFH 5000 IU two times a day, 183 (67.8%) patients received the intensified thromboprophylaxis, and 65 (24%) patients had full anticoagulation (Table 1). Of the 65 patients with therapeutic anticoagulation, 20

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Table 1 Characteristics of patients with COVID-19 with and without major bleedings

	COVID-19 patients without major bleedings n = 256 (94.8%)	COVID-19 patients with major bleedings n = 14 (5.2%)	*p*-value*
Age (years)[a]	70.28 (22–96)	73.89 (59–88)	0.17
Male sex (%)	157 (61.3)	9 (64.3)	0.83
Time from first symptoms to hospital admission (days)[a]	6 (0–43)	6.5 (0–18)	0.62
Comorbidities (%)	194 (75.8)	14 (100)	0.04
Cardiovascular disease (%)	102 (39.8)	7 (50)	
Diabetes mellitus (%)	55 (21)	4 (28.6)	
Arterial hypertension (%)	128 (50)	9 (64.3)	
Pulmonary disease (%)	55 (21.5)	5 (35.7)	
Chronic renal failure (%)	31 (12.6)	2 (14.3)	
Malignancy (%)	18 (7.1)	1 (7.1)	
Immunosuppression (%)	21 (8.2)	2 (14.3)	
COVID-19 clinical syndrome (%), WHO definition [15]			0.093
Mild illness	13 (5.1)	0.(0)	
Pneumonia	27 (10.5)	0 (0)	
Severe Pneumonia	114 (44.5)	4 (28.6)	
Mild ARDS	13 (5.1)	1 (7.1)	
Moderate ARDS	21 (8.2)	4 (28.6)	
Severe ARDS[b]	68 (26.6)	5 (35.7)	
COVID therapy protocol (%)			
Hydroxychloroquine	56 (21.9)	6 (42.9)	0.1
Lopinavir + ritonavir	40 (15.6)	6 (42.9)	0.02
Remdesivir	26 (10.2)	2 (14.6)	0.65
Antithrombotic drug (%)			0.26
UFH	39 (15.3)	5 (35.7)	
LMWH	201 (78.5)	9 (64.3)	
DOAC	8 (3.1)	0	
VKA	8 (3.1)	0	
Antithrombotic strategy[c]			< 0.01
Regular prophylaxis	22 (8.6)	0	
Intensive prophylaxis (dose level 1)	151 (59)	2 (14.3)	
Intensive prophylaxis (dose level 2)	29 (11.3)	1 (7.1)	
Full anticoagulation	54 (21.1)	11 (78.6)	
Dose intensification of the antithrombotic strategy during inpatient treatment (%)	65 (25.4)	8 (57.1)	0.03
ICU treatment (%)	65 (26.9)	11 (78.6)	< 0.01
Mortality (%)	40 (15.6)	6 (42.9)	0.02

WHO World Health Organization, *ARDS* acute respiratory distress syndrome, *UFH* unfractionated heparin, *LMWH* low molecular weight heparin, *DOAC* direct oral anticoagulant, *VKA* vitamin K antagonist, *OD* once daily, *BID* two times per day, *TID* three times per day, *INR* international normalized ratio, *anti-Xa* anti-activated coagulation factor X activity, *ICU* intensive care unit

*Groups were compared by Chi^2, Fisher's exact test or ANOVA, as appropriate

[a]Median (range)

[b]Severe ARDS includes deaths attributed to not otherwise specified ARDS

[c]Regular prophylaxis = enoxaparin 40 mg OD or subcutaneous UFH 5000 UI BID if eGFR < 30 ml/min/1.73 m^2, Intensive prophylaxis (dose level 1) = subcutaneous enoxaparin 40 mg BID (< 80 kg), or 60 mg BID (≥ 80 kg), if eGFR < 30 ml/min/1.73 m^2 subcutaneous UFH 5000 IU TID in the regular ward, and continuous intravenous UFH in the ICU (target anti-Xa ≤ 0.4 U/ml), Intensive prophylaxis (dose level 2) = subcutaneous enoxaparin 60 mg BID (< 80 kg), or 80 mg BID (≥ 80 kg), if eGFR < 30 ml/min/1.73 m^2 continuous intravenous UFH (target anti-Xa 0.3–0.5 U/ml), Full anticoagulation = weight adapted enoxaparin, continuous intravenous UFH (anti-Xa 0.3–0.7 U/ml), standard dose DOAC, or VKA with a target INR of 2.5 (±0.5)

(30.7%) patients had prior anticoagulation for atrial fibrillation (Afib) (n = 17, 26.2%) and for venous thromboembolism (VTE) (n = 3, 4.6%) unrelated to COVID-19. During follow-up, 73 (27%) patients underwent dose escalation from regular prophylaxis or dose level 1 to dose level 2, or to full anticoagulation. Reasons for dose escalation were increasing D-dimer levels (n = 31, 11.5%), acute VTE (n = 36, 13.3%), and newly diagnosed Afib (n = 6, 2.2%).

Four (2.2%) bleedings, all retroperitoneal, were observed in the 183 patients receiving intensified prophylaxis (Table S2). Three out of these four patients had concomitant anti-platelet therapy. 10 (16.6%) bleedings occurred in patients receiving full anticoagulation because of Afib, catheter-associated thrombosis or pulmonary embolism (Table S2). No patient had overt disseminated intravascular coagulation or heparin-induced thrombocytopenia. Fatal bleeding occurred in none of the 183 patients receiving intensive thromboprophylaxis, and in three (4.6%) of the 65 patients with full anticoagulation.

The observed bleeding prevalence in patients with COVID-19 receiving high-dose thromboprophylaxis is two-fold higher when compared to medically ill patients receiving standard dose thromboprophylaxis, but lower than the 5.5% major bleeding rate in critically ill medical patients receiving standard dose thromboprophylaxis [10, 11]. Patients with COVID-19 who receive full-dose anticoagulation are at higher risk of major bleeding. Preventing the need for therapeutic anticoagulation is therefore a major goal of thromboprophylaxis. The predominance of intramuscular hemorrhage with two thirds of the bleedings localized in the retroperitoneum, the gluteal and the thigh muscles warrants further investigation (Table S2). SARS-CoV-2 induced muscle necrosis, and vasculopathy might contribute to this bleeding phenotype [12–14].

In conclusion, our data are reassuring and supportive of intensive thromboprophylaxis for hospitalized patients with COVID-19. Most major bleedings occurred after two weeks of hospitalization, and dose de-escalation after the first 10 to 14 days might be considered in patients with a favorable clinical course. Prospective trials are required to optimize patient selection, dosing and treatment duration for patients with COVID-19.

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Authors contribution BG, CK, MP, and HS designed the study; CK, MP, and BG collected and analyzed the data; GS performed the statistical analysis; CK, BG, and MP wrote the first draft of the manuscript; all authors collected patient data, and critically read, discussed and corrected the manuscript.

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Data availability Original data can be requested by contacting the corresponding author.

Compliance with ethical standards

Conflict of interest D. Rossi reports grants and personal fees from Abbvie, grants and personal fees from Janssen, grants and personal fees from Gilead, grants and personal fees from AstraZeneca, personal fees from Verastem, personal fees from Loxo, grants from Cellestia, during the conduct of the study; B. Gerber reports grants and personal fees from Pfizer; personal fees and funding for accredited continuing medical education from Sanofi and Alnylam, during the conduct of the study, funding for accredited continuing medical education program from Axonlab, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Janssen, Mitsubishi Tanabe Pharma, NovoNordisk, Octapharma, Takeda, Sanofi, SOBI; non-financial support from Axonlab and Thermo Fisher from outside the submitted work; All other authors report no conflict of interest related to this study.

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