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LETTER TO THE EDITOR

POST-discharge thromboprophylaxis in patients with COVID-19: a single-center experience

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Dear Editor,

Several data demonstrated that the incidence of COVID-19 associated-venous thromboembolism (VTE) is high [1–4]. However, data regarding rates of VTE after discharge for patients hospitalized for COVID-19 are limited and extended out-of-hospital thromboprophylaxis is not routinely recommended, because the risk–benefit remains uncertain [5].

We aim to evaluate the rates of patients discharged after COVID-19 infection with or without prescribed thromboprophylaxis; type, dose, and timing of thromboprophylaxis; 30-day clinical outcomes in patients discharged with or without antithrombotic prophylaxis.

This was an observational, retrospective single-center cohort study. We enrolled all consecutive patients aged ≥ 18 years admitted to the General Internal Medicine Unit of the Padua University Hospital between November 2020 and May 2021 with a diagnosis of acute SARS-CoV2 infection. Exclusion criteria were: ongoing anticoagulant therapy before admission, starting of anticoagulant therapy during hospitalization, inter- or intra-hospital patient transfer before the discharge. Demographics, comorbidities, medications, risk factors for VTE (according to Padua Prediction Score [PPS] and IMPROVE-DD score), Sequential Organ Failure Assessment (SOFA) score, Sepsis-Induced Coagulopathy (SIC) score, and PaO_2/FIO_2ratio were collected. Both during hospitalization and at discharge, the antithrombotic regimen (i.e., no thromboprophylaxis, standard dose, or intermediate sub-therapeutic thromboprophylaxis) and its duration was selected by the attending physician. Any symptomatic VTE, bleeding event, re-hospitalization, and all causes of mortality within 30 days after the discharge were considered as outcomes. Symptomatic VTE was assessed by ultrasonography or computed tomography pulmonary angiography. The study was approved by the local institutional ethics committee (Ref: 5001/AO/21) and conducted in compliance with the principles of the Declaration of Helsinki.

The cumulative incidence and 95% CI for the outcomes was estimated by exact mid-p. The odds ratios (ORs) and 95% confidence interval (CI) were calculated by conditional maximum-likelihood estimate. Logistic univariate and multivariate regression analyses were performed to evaluate clinical characteristics associated with extended prophylaxis and with 30-day death (IBM SPSS Statistics 27.0 for Windows, Inc., Chicago, IL, USA).

Out of 388 eligible patients admitted, 202 (M:F = 111:91, age range 36–100 years) patients were included in the study (Fig. 1). The most frequent comorbidity was arterial hypertension ($n = 120$, 59.4%), followed by diabetes ($n = 43$, 21.3%) and chronic kidney disease ($n = 40$, 19.8%). At discharge, 177 (87.6%) received extended prophylaxis with enoxaparin 4000 IU subcutaneous daily or 6000 IU if body max index (BMI) ≥ 30 kg/m^2 (exposed), while 25 (12.4%) did not received thromboprophylaxis (unexposed) (Table 1). Exposed patients had median age 73 years [IQR 62–82], and 96 (54.2%) were male and had a median BMI of 27.1 kg/m^2 [23.8–31.1]; these characteristics were similar to unexposed patients. The prevalence of a PPS ≥ 4 and an SOFA score ≥ 2 were significantly higher in the exposed group compared to the unexposed (p 0.0405 and 0.0359, respectively). Moreover, a PaO_2/FIO_2 ratio < 300 was significantly more frequent in patients who received thromboprophylaxis at discharge ($n = 92$, 52.0% vs. $n = 7$, 28.0%; p 0.0422). The number of patients who received antiviral treatment ($n = 91$, 51.4%) and glucocorticoids ($n = 169$, 95.5%) was significantly

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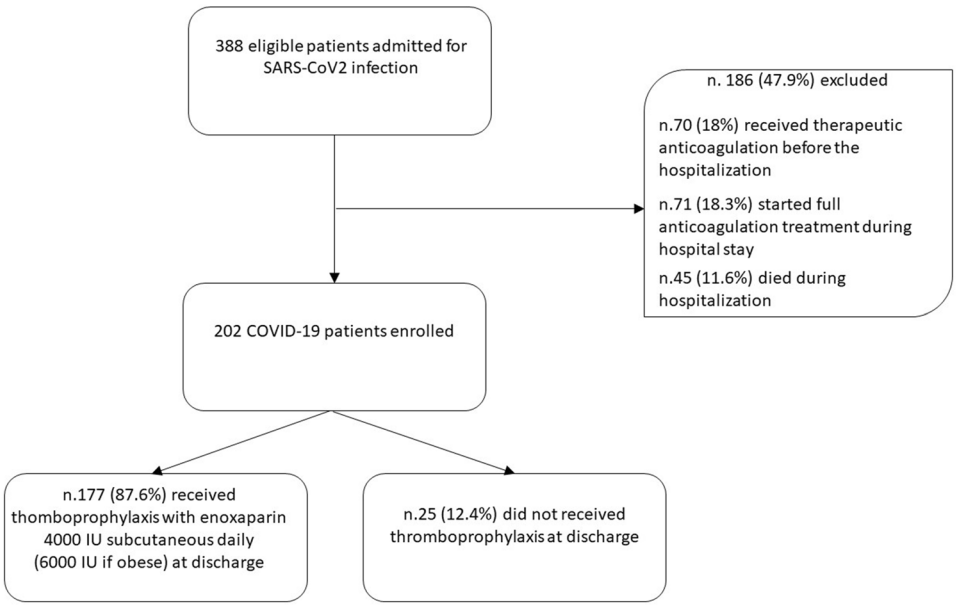

Fig. 1 Study enrollment flow-chart

higher in the exposed group vs unexposed ($n = 6$, 24.0% and $n = 16$, 64.0%, respectively; p 0.0186 and 0.0000, respectively).

In the exposed group, 25 patients (9.2%) received less than 7 days of prophylaxis, 99 (36.3%) up to 7–10 days, 4 (1.5%) up to 15–21 days, and 1 (0.4%) up to 30 days because of a recent hip fracture; for 48 subjects (17.6%), the duration of thromboprophylaxis was not specified (until complete mobilization/negativization/full recovery).

Among the 177 patients who received post-discharge prophylaxis, two (1.13%) VTE events occurred during the follow-up: a proximal DVT of the leg occurred soon after stopping a 7 day prophylaxis in a male patient, 56 years old, carrying heterozygous FV Leiden, with a past history of distal DVT, who had severe COVID-19; a stroke due to paradoxical embolism from proximal DVT in a female who received a 7 day-thromboprophylaxis occurred 32 days after the discharge, she did not recover full mobilization after COVID-19. No bleeding events occurred during the follow-up. On the other hand, among the 25 patients discharged without prophylaxis, neither VTE nor bleeding was recorded. No significant difference was detected in 30-day VTE occurrence between exposed and unexposed patients (OR 0.45 [95% CI 0.03–16.9]) (Table 2).

Only the above-mentioned patient with stroke was re-hospitalized within 32 days after the discharge, while no patient was re-admitted in the unexposed group (OR 0.23 [95% CI 0.04–11.2]. Finally, among the exposed group, 4 patients died within 16 days (1 sepsis and multiorgan failure, 1 worsening of general condition, 2 unknown reason) and 1 for cancer 32 days post-discharge (2.8% [95% CI 1.03–6.62]), while 2 patients from the unexposed group (8.0% [95% CI 1.08–26.1]) died within 15 days one for ab ingestis pneumonia and one for unknown reason (OR 0.33 [95% CI 0.06–2.63]) (Table 2). Interestingly, at the multivariate logistic regression analysis, the use of extended prophylaxis was significantly associated with a better outcome (OR for 30-day death 0.25 [95%CI 0.15–0.91]. The ORs remained statistically significant also after considering as covariates age, gender, BMI, and comorbidities (including cancer, hypertension, and diabetes).

Finally, at the multivariate logistic regression analysis, the use of extended prophylaxis was significantly associated with steroids (OR 8.91 [95%CI 2.87–27.7], therapy with remdesivir (OR 3.35 [95%CI 1.27–8.78] and P/F (= R 0.993 [95%CI 0.986–0.999). On the other hand, it was not associated with the presence of comorbidities, BMI, previous VTE, previous cardiovascular events, endotracheal intubation, non-invasive ventilation, age, immune plasma, antibiotics, and SIC/SOFA/IMPROVE-DD/PPS scores.

Anticoagulant therapy with heparin has become a cornerstone of COVID-19 pneumonia [6, 7]. It has also been shown that the hypercoagulable state associated with COVID-19 continues at least for 30 days after discharge [5]. A recent study by our group showed that circulating platelet and leukocyte extracellular vesicles remained

Table 1 Main demographic and clinical characteristics of the study population

	Extended thromboprophylaxis at discharge *n*. 177	No thromboprophylaxis at discharge *n*. 25	*p* value
Age, years	73 [62–82]	73 [54–79]	Ns
Gender male, *n* (%)	96 (54.2)	15 (60.0)	Ns
Body mass index, kg/m^2	27.1 [23.8–31.1]	25.8 [23.0–27.5]	Ns
Blood group, *n* (%)			
0	50 (41.3)	5 (31.2)	Ns
A	45 (37.2)	6 (37.5)	Ns
B	17 (14.1)	2 (12.5)	Ns
AB	9 (7.4)	3 (18.8)	Ns
Comorbidities, *n* (%)			
Arterial hypertension	104 (58.8)	16 (64.0)	Ns
Diabetes	35 (19.8)	8 (32.0)	Ns
Coronary heart disease	21 (11.9)	4 (16.0)	Ns
Cerebrovascular disease	12 (6.8)	2 (8.0)	Ns
Previous venous thrombotic event	7 (3.9)	1 (4.0)	Ns
Active cancer	10 (5.6)	1 (4.0)	Ns
Chronic kidney disease	34 (19.2)	6 (24.0)	Ns
Baseline medications, *n* (%)			
Antiplatelet agents	50 (28.2)	11 (44.0)	Ns
Statins	50 (28.2)	6 (24.0)	Ns
Padua prediction score, median [IQR]	3 [3–5]	3 [2–4]	Ns
≥4 *n* (%)	96 (54.2)	8 (32.0)	0.0405
IMPROVE-DD, median [IQR]	3 [2–4]	3 [1–4]	Ns
≥2 *n* (%)	92 (52.0)	14 (56.0)	
SOFA score, median [IQR]	2 [1–3]	1 [1–3]	Ns
≥2 *n* (%)	107 (60.5)	9 (36.0)	0.0359
SIC score, median [IQR]	2 [2, 3]	2 [1–3]	Ns
≥4 *n* (%)	19 (10.7)	4 (16.0)	Ns
PaO_2/FIO_2, median [IQR]	275 [246–321]	316 [275–382]	Ns
<300 *n* (%)	92 (52.0)	7 (28.0)	0.0422
Medications for SARS- CoV2 infection, *n* (%)			
Remdesivir	91 (51.4)	6 (24.0)	0.0186
Glucocorticoids	169 (95.5)	16 (64.0)	0.0000
Antibiotics	168 (94.9)	23 (92.0)	Ns
Convalescent plasma	83 (46.9)	8 (32.0)	Ns
Respiratory support, *n* (%)			
HFNC	82 (46.3)	8 (32.0)	Ns
NIV	43 (24.3)	4 (16.0)	Ns
IMV	24 (13.6)	5 (20.0)	Ns
Post-discharge thromboprophylaxis duration, *n* (%)			
3–6 days	25 (9.2)	–	
7–10 days	99 (36.3)		
15–21 days	4 (1.5)		
30 days	1 (0.4)		
not specified/until full recovery or mobilization or negativization	48 (17.6)		

Variables are expressed as median and interquartile range or number (%)

FIO_2 fraction of inspired oxygen, *HFNC* high flow nasal cannula, *IQR* interquartile range, *IMV* invasive mechanical ventilation, *NIV* non-invasive ventilation, *Ns* non-significant, *PaO_2* partial pressure of oxygen, *SIC* sepsis-induced coagulopathy, *SOFA* Sequential Organ Failure Assessment

Table 2 Clinical outcomes in relation to thromboprophylaxis administration at discharge

	Exposed *n*. 177	Unexposed *n*. 25	OR [95% CI]
30-day VTE, *n* (%, 95%CI)	2 (1.13% [0.04–4.29])	0	0.45 [0.03–16.9]
30-day bleeding, *n* (%, 95%CI)	0	0	–
30-day re-hospitalization, *n* (%, 95%CI)	1 (0.56% [0.0–3.45])	0	0.23 [0.04–11.2]
30-d all-cause mortality, *n* (%, 95%CI)	5 (2.8% [1.03–6.62])	2 (8% [1.08–26.1])	0.33 [0.06–2.63]

CI confidence interval, *d* day, *VTE* venous thromboembolism

increased 30 days after the discharge and were associated with persistent symptoms [8]. Given the lack of indications about extended thromboprophylaxis, we reported data on a single-center experience on VTE events after discharge according to thromboprophylaxis in a COVID-19 cohort of inpatients hospitalized in a medical Unit.

In our study, only 12.4% of patients was discharged without thromboprophylaxis, while extended prophylaxis was prescribed in 87.6%. The characteristics significantly associated with extended prophylaxis were intra-hospital use of steroids, remdesivir therapy, and a reduced P/F during hospitalization. These characteristics fostered physicians to prescribe a prolonged antithrombotic regimen after the discharge. Anticoagulant therapy was prescribed up to 7–10 days in 49% of cases, while 12.4% of patients received less than 7 days. Interestingly, the 2 VTE detected during the 30-day follow-up occurred 15 and 32 days after the discharge in patients who were prescribed 7–10 day prophylaxis. No bleeding events occurred in patients discharged with extended prophylaxis. Importantly, post-discharge prophylaxis was significantly associated with reduced 30-day mortality.

Current evidence is against the routine use of extended thromboprophylaxis for all discharged COVID-19 patients [9–11]. The ISTH guidelines suggest that in selected patients who have been hospitalized for COVID-19, post-discharge treatment with prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce the risk of VTE [10]. The NIH guidelines suggest prophylaxis after hospital discharge for patients who are at high risk for VTE and at low risk of bleeding [11].

Published data on extended prophylaxis showed that post-discharge anticoagulation significantly reduced the risk of major thromboembolic events and all-cause death by 46% (OR 0.54 [95%CI, 0.47–0.81]) [12] (Table 3). Advanced age, cardiovascular risk factors, chronic kidney disease, IMPROVE-DD VTE score ≥ 4, and ICU stay increased the risk of post-discharge major events. Additionally, major bleeding events were not affected by extended prophylaxis [12]. The randomized controlled trial MICHELLE [13] reported a significant decrease of venous, arterial thrombosis and cardiovascular death in patients prescribed with rivaroxaban 10 mg for 35 days after discharge vs. placebo (RR 0.33 [95%CI 0.12–0.90]). Additionally, no difference in all-cause bleeding was observed (RR 1.33 [95%CI 0.30–5.86]). Finally, a recent retrospective study reported data on 1171 patients discharged, of whom 11.3% were prescribed extended anticoagulation for 28 days [14]. None of the 132 patients who received extended prophylaxis had a thromboembolic event compared to 13 of 1039 who did not receive extended prophylaxis ($P = 0.383$). The incidence of bleeding was higher among patients who received extended prophylaxis ($P = 0.019$) [12] (Table 3). Comparing our findings with these studies, we can observe that in the majority of our cohort, physicians decided to prescribe extended prophylaxis; enoxaparin was the only prescribed medication; the prophylaxis duration was shorter than that reported in other studies (Table 3). Extended thromboprophylaxis was mainly decided for patients treated during hospitalization with steroids and anti-retroviral drugs. Importantly, as in other studies [12, 13], post-discharge prophylaxis was associated with reduced mortality and appeared to be safe [12, 13] (Table 3).

According to our findings, extended thromboprophylaxis was significantly associated with reduced 30-day mortality and appears to be safe in patients with COVID-19. A longer course of prophylaxis up to 15–30 days may be more effective in preventing any VTE. The use of more intensive "anti-COVID" medical therapy during hospitalization was associated with the choice of extended prophylaxis. Wider studies are required to solve this issue.

Table 3 Published studies and main results on extended prophylaxis

Authors and date of publication [ref]	Study design	Population	Number of patients enrolled	Type of thromboprophylaxis at discharge	Thromboprophylaxis duration	Clinical outcomes	Results
Giannis D. et al. May 2021 [12]	Prospective registry	Consecutive discharged adult patients with COVID-19	4906 patients Post-discharge thromboprophylaxis prescribed in 12.7% (patients with IMPROVE VTE score ≥ 4 or D-dimer ≥ 2 ULN or higher)	Rivaroxaban 10 mg (6.9%) Apixaban 2.5 mg × 2 (3.7%) Enoxaparin 40 mg sc daily (1.3%)	30 days	VTE Arterial thrombosis Major bleeding All-cause mortality 90-day re-hospitalization	Post-discharge anticoagulation reduced major thromboembolic events and death by 46% (OR, 0.54; 95% CI, 0.47- 0.81) Of the 85 patients with major bleeding, only 17.6% were prescribed post-discharge anticoagulants
Ramacciotti E. et al. January 2022 [13]	Open-label, multicentre, randomized controlled trial	Patients discharged after a ≥ 3-day hospitalization for COVID-19	320 patients, randomly assigned to receive rivaroxaban (n = 160 [50%]) or no anticoagulation (n = 160 [50%])	Rivaroxaban 10 mg	35 days	VTE Arterial thrombosis Major bleeding All-cause bleeding Cardiovascular death	Post-discharge anticoagulation reduced VTE, arterial thrombosis and cardiovascular death by 67% (RR 0.33; 95% CI, 0.12–0.90) No major bleeding occurred in either study group No difference in all-cause bleeding (RR 1.33; 95% CI, 0.30–5.86)
Courtney L.A. et al. September 2022 [14]	Retrospective analysis	Patients discharged after hospitalization for symptomatic COVID-19	1171 patients 1039 did not receive extended prophylaxis 132 (11.3%) patients received extended prophylaxis	Rivaroxaban (86.3%) Enoxaparin (12.9%) Apixaban (0.8%)	28 days	VTE and bleeding events within 35 days post-discharge	0/132 patients who received extended prophylaxis had thromboembolic events vs. 13/1039 (1.3%) who did not receive ($P = 0.383$). Incidence of bleeding higher among patients who received extended prophylaxis (3.0% vs 0.6%, $P = 0.019$)

CI confidence interval, *OR* odds ratio, *RR* relative risk, *VTE* venous thromboembolism, *ULN* upper limit of normal

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Availability of data and materials Research data can be shared after request to the study team.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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