Effectiveness of antithrombotic prophylaxis in hospitalised patients with SARS-CoV-2 infection

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ABSTRACT

Background Antithrombotic prophylaxis in hospitalised patients with SARS-CoV-2 acute infection has increased. Currently, most of the evidence relates to patients in intensive care units; however, there is little information on patients admitted to hospital wards and there is no consensus protocol on thromboprophylaxis during admission and after discharge.

Objective To assess the effectiveness of antithrombotic prophylaxis in patients admitted with COVID-19 and 30 days after discharge.

Method A prospective observational study was conducted of patients admitted with COVID-19 in which the hospital thromboprophylaxis protocol was applied, classifying the patients as having a standard or high risk of thrombosis. Pharmacists performed a daily follow-up and actively intervened during admission and at discharge. The main outcome measure was the global incidence of symptomatic venous thromboembolism (VTE) related to hospitalisation.

Results A total of 113 patients were included, 98.23% of whom were admitted to a hospital ward. The incidence of hospital-acquired VTE was 1.77%. In 75.22% of the subjects, thromboprophylaxis was adjusted to the protocol during admission. A total of 23 pharmaceutical interventions were conducted, with an adherence of 52.17%. At discharge, 94.28% of the patients who had no haemorrhage and ≥4 points on the Padua Prediction Score required thromboprophylaxis, aligning with the protocol. The global incidence of haemorrhagic events during the follow-up period was 0.88%.

Conclusion The incidence of hospital-acquired VTE was lower than that described in the literature. Although it cannot be certain that it is directly related to the instituted protocol, the data can show that the management of prevention of VTE is being optimally performed at the hospital. Long-term studies are needed to evaluate the incidence after discharge, as well as to agree on a specific protocol in the COVID-19 population for the prevention of these events during hospitalisation and post-discharge.

INTRODUCTION

Infection by coronavirus SARS-CoV-2, the causative organism of COVID-19, causes damage essentially in the respiratory system. In severely affected patients, the disease frequently progresses to an acute respiratory distress syndrome that can predispose the patients to a state of hypercoagulability, with thrombosis both at a venous and at an arterial level. These patients frequently have factors such as old age, obesity, cardiovascular disease, hypertension or diabetes which lead to a higher risk of thrombotic events, as well as COVID-19, which results in a state of hypercoagulability associated with the acute infection per se, excessive inflammation, hypoxaemia and immobilisation.[1] The risk of venous thromboembolism (VTE) in patients with COVID-19 is an emerging problem and several publications have addressed this matter in recent months. The Spanish Society of Thrombosis and Haemostasis confirmed in its published paper "Recomendaciones de tromboprofilaxis en pacientes con COVID-19"[2] that these patients have a higher risk of VTE; however, to date there is no approved outline on the dose and time of use of antithrombotic drugs in patients with SARS-CoV-2 infection.

The results of the recent scientific publications on the coagulopathy associated with COVID-19 and the risk of VTE have raised doubts and controversy about which is the best strategy of VTE prophylaxis, diagnosis and antithrombotic treatment; this can be seen in the variation in the published recommendations by the different scientific organisations and societies. The consensus papers most recently published relate thromboprophylaxis with a decrease in mortality and suggest an early use of low molecular weight heparin (LMWH) as the first option for thromboprophylaxis, in the absence of contraindications, in those patients who require hospital admission due to COVID-19.[3]

Several studies have assessed the incidence of VTE in COVID-19 patients, providing very heterogeneous results and focusing on subjects admitted to the intensive care unit (ICU), but with very little information on hospitalised patients as well as post-discharge.

This study aims to assess the effectiveness of antithrombotic prophylaxis in patients admitted with COVID-19 during the hospitalisation period and during a medium-term follow-up period after hospital discharge. The secondary objectives are to assess the degree of adaptation of the thromboprophylaxis prescribed during admission and post-discharge to the protocol instituted at the hospital, as well as the results of the pharmaceutical interventions conducted. The safety of the antithrombotic prophylaxis is also analysed.

METHODS

An observational and prospective study of patients admitted with COVID-19 infection was conducted in a hospital in Madrid, which covers a population

of approximately 170 000 inhabitants. Patients aged ≥18 years who were hospitalised between 12 October and 9 November 2020 in a hospital ward and intensive care unit (ICU) were consecutively included. A diagnosis of acute COVID-19 was confirmed through reverse transcription-polymerase chain reaction (RT-PCR) or a positive SARS-CoV-2 antigen test.

The primary outcome was the global incidence of symptomatic VTE related to hospitalisation (hospital-acquired VTE), defined as new VTE events during admission and up to 30 days after hospital discharge. Deep venous thrombosis (DVT) in any location and pulmonary thromboembolism (PTE) confirmed by an imaging test were accepted as events, as well as probable PTE based on a high clinical suspicion when it could not be confirmed by CT angiography due to the patient's severe condition. The incidence of VTEs accumulated at 14 days of admission was estimated, as well as the incidence of VTEs after 30 days of discharge. Patients were excluded if they had an episode of VTE during the 3 months prior to admission or if they had an acute VTE diagnosed within the first 48 hours after their arrival at the emergency department.

The secondary outcomes were: (1) adequacy of the thromboprophylaxis protocol during admission, defined as the percentage of patients with a regimen of antithrombotic prophylaxis since the first day of admission, regulated depending on the thrombotic risk, weight and renal function (online supplemental table 1); (2) adequacy of the thromboprophylaxis protocol at discharge, defined as the percentage of patients receiving antithrombotic prophylaxis at discharge, using Padua Score modified[4] (only in the absence of haemorrhagic risk (online supplemental table 2); (3) safety of the thromboprophylaxis, defined as the incidence of major haemorrhage or non-major haemorrhage but clinically significant according to the definition of the International Society on Thrombosis and Haemostasis.[5]

Comorbidities related to a poorer prognosis of COVID-19 were reported: age, diabetes, hypertension, obesity (body mass index >30), active cancer, chronic kidney disease (established nephropathy during ≥3 months with or without renal function deterioration and/or glomerular filtration <60 mL/min/1.73 m^2), severe liver failure (Child–Pugh C) and immunosuppression (immunosuppressive disease or active therapy with immunosuppressant or doses of corticosteroids equivalent to ≥2 mg/kg/day prednisone for more than 14 days). A personal or family history related to a high risk of suffering a VTE and arterial ischaemic pathology (peripheral, cardiac or neurological) were also reported. The level of severity of the respiratory tract infection was defined following the classification of the Spanish Ministry of Health[6] as an uncomplicated illness, mild/severe pneumonia, respiratory distress or sepsis. Laboratory findings were reported at admission (platelets, fibrinogen, D-dimer, ferritin, C-reactive protein, interleukin-6 and lymphocytes), thromboprophylaxis during hospital admission, at discharge, and its duration.

The pharmacist intervened during the admission by prospectively reporting and informing about the discrepancies identified in relation to the indication for anticoagulation (treatment required or contraindication) and the dose regulated according to the weight and renal function (overdosage or underdosage). In case of discrepancy, the treating physician was contacted by telephone or through the tools available in the electronic medical record.

The follow-up after discharge was performed retrospectively for 30 days using the electronic medical record of Selene and the HORUS platform, which allows access to primary care clinical records, other public hospitals in the Region of Madrid and the electronic prescription.

The analysis was performed mainly using descriptive statistical methods. The quantitative variables were described using mean (SD) and median (IQR). The qualitative variables were described using absolute frequencies and percentages.

As a primary result, the global incidence of VTE episodes, the incidence of hospital-acquired VTE and the cumulative incidence rate at 14 days since admission were estimated, performing a survival analysis using the Kaplan–Meier method in the presence of competitive risks, considering death as a competitive event of VTE. The cumulative incidence rate of VTE 30 days after hospital discharge was also estimated. The 95% CI was estimated using the Wilson methodology.

The data were analysed using the statistical software STATA v.13 and SPSS v.17.

RESULTS

During the selected dates a total of 113 patients with COVID-19 acute infection were hospitalised: 111 were admitted to a hospital ward and two to the ICU, for which follow-up was performed throughout the hospital admission and for 30 days after discharge, with a total of 112 days of study. The median age was 70 years (IQR 56–77) and 58.40% (n=66) of the subjects were men. At admission, 23.9% of the patients (n=27) did not have any comorbidities, 69% (n=78) had 1–3 comorbidities and 7.1% (n=8) had ≥4 associated comorbidities (online supplemental table 3). The median number of hospitalisation days was 7 (IQR 4–11). Of the total population, 8.8% (n=10) of the subjects required transfer to the ICU during their hospital stay. In-hospital mortality was 15.9% (n=18); no deaths were reported during the 30 days post-discharge.

The demographic data, comorbidities, clinical and analytical parameters on admission as well as anticoagulant therapy prior to admission are shown in online supplemental table 3.

During the follow-up period, including the hospitalisation period and the 30 days post-discharge, four patients suffered a VTE event, giving a global incidence of 3.53% (95% CI 0.14% to 8.75%). Of the four patients, two had acute VTE diagnosed within the first 48 hours after hospital admission, so the incidence of hospital-acquired VTE according to the definition previously provided was 1.77% (95% CI 0.49% to 6.22%). The cumulative incidence at 14 days was 0.88% (95% CI 0.16% to 4.84%), with a hospital survival rate without VTE, estimated by the Kaplan–Meier method at 14 days, of 94.8%. Of the 95 patients discharged, one developed VTE during the follow-up period after hospital discharge, giving a cumulative incidence at 30 days of 1.05% (95% CI 0.19% to 5.72%).

The two patients with acute VTE were men aged 80 and 72 years who both suffered a PTE on the first day of admission. The two patients had two and one life-threatening comorbidities, respectively (hypertension together with previous ischaemic pathology in the first case and obesity in the second case). The first patient had severe COVID-19 and both were categorised as being at high risk of thrombosis on the basis of their personal history and the analytical parameters on admission. The prescription for both patients was adjusted to the hospital's protocol, starting treatment with LMWH at effective doses during the admission and assigning a regimen of 20 mg rivaroxaban daily for 6 months from hospital discharge. The length of hospital stay was 10 and 5 days, respectively, and transfer to ICU was not required in any of the cases.

Regarding the two patients with hospital-acquired VTE, the first took place during admission and the second during discharge. The first case was a woman aged 50–60 years,

categorised as severe COVID-19 and with a high risk of thrombosis due to a personal history of previous ischaemic pathology and the following analytical parameters on admission: D-dimer 2.440 ng/mL, PCR 283 mg/L, ferritin 192 ng/mL and lymphocytes 300×10^9/L. On the first day of admission the patient was assigned a regimen of bemiparin at 2500 IU, which did not align with the protocol. After pharmaceutical intervention, the dose was increased to 3500 IU bemiparin. According to the protocol, the appropriate dosage would have been 60 mg enoxaparin; however, the patient had a recent history of subarachnoid haemorrhage. Ten days after hospital admission the patient died with a diagnosis of severe VTE without being able to confirm the event radiologically. The second case was a man aged >75 years with a personal history of hypertension, categorised as non-severe COVID-19 and standard risk of thrombosis. On the first day of admission the patient was assigned a regimen of 60 mg enoxaparin every 24 hours, which was in agreement with the hospital's protocol, and he was discharged after 12 days with no order to continue anthrombotic prophylaxis, which was not in alignment with the protocol. Thirteen days after discharge the patient was readmitted with clinically diagnosed PTE confirmed with an imaging test. He began anticoagulant therapy with LMWH at effective doses and 5 days later, after a favourable evolution, was discharged and began therapy with 5 mg apixaban every 12 hours, assigned for at least 6 months.

Regarding the secondary variables, in 85 patients (75.22%) the assigned regimen of prescription at admission was in agreement with the protocol instituted in the hospital. A total of 23 interventions (82.14%) were carried out by the Pharmacy Service, in 82.6% (n=19) of cases due to underdosage of thromboprophylaxis, in 8.69% (n=2) due to overdosage and in 8.69% (n=2) due to its omission on the first day of admission. Of the total, 52.17% (n=12) of the pharmaceutical interventions were accepted.

The characteristics of the subjects are described according to the Padua Prediction Scores (PPS) of risk of VTE in online supplemental table 4.

At the end of admission the evaluation of the risk of thrombosis using the PPS estimated that 35 patients had no haemorrhagic risk and a score of ≥4, of which 94.28% (n=33) were discharged after a median of 6.5 days (IQR 4–11.5) with antithrombotic treatment, as indicated by the protocol. Of the remaining 60 patients, a subgroup of 20 subjects (21.05%) were discharged with treatment with LMWH with a score of <4 after a median of 5.5 days (IQR 3–9). It was concluded that, of the total patients, the protocol at discharge was aligned in 76.84% of the prescriptions (n=73).

With regard to the safety of the antithrombotic treatment, the incidence of haemorrhagic events was 0.88% (n=1). There was also one patient who developed temporary mild thrombocytopenia (125×10^3/µL) without haemorrhage.

DISCUSSION

Several studies have assessed the incidence of VTE in patients with COVID-19 both with and without a regimen of antithrombotic prophylaxis. Results in patients admitted to the ICU show very variable proportions (7.7–54%) as well as a cumulative incidence at 7–14 days of 20.4–37%.[3 7–18]

The study by Cui *et al*,[18] which included only those patients in the ICU who did not receive pharmacological thromboprophylaxis, estimated an incidence of VTE of 25%. The study by Llitjos *et al*[11] reported the highest incidence of VTE (54%), even though up to 69% of the patients had received full doses of anticoagulation. The severity of the cohort studied, the state of hypercoagulability and the performance of systemic screening to detect DVT by a scan of the lower limbs could partially explain these results. However, thus far, there is very little information available on the incidence of VTE in hospitalised patients, as well as post-discharge.

A recent meta-analysis has shown that the average percentage of VTE in COVID-19 hospitalised patients is 4.9% (95% CI 3.7% to 6.5%) if the studies that include a number of ICU patients lower than 75% of the total[19] are taken into account—a context similar to that of the present study. Assuming the methodological heterogeneity and the screening of VTE that can exist between both studies, the incidence rate identified is slightly lower than that of the abovementioned meta-analysis.

In the case of follow-up studies after hospital discharge, to date there is very little information on the incidence of thrombotic events. However, two studies should be highlighted; the study by Patell *et al*[20] reported a cumulative incidence of VTE after 30 days of 0.6% and, in the study by Eswaran *et al*,[21] 2% of individuals experienced VTE within 30 days of hospital discharge. In both cases the result is in line with the incidence rate of VTE within 30 days since hospital discharge estimated in the present study.

The Pharmacy Service actively cooperated in the compliance with thromboprophylaxis in the hospitalised patients with COVID-19, both in the hospital ward and in the ICU, performing interventions for discrepancies in relation to the protocol with a high percentage of approval by the medical staff. The underdosage of LMWH was the most frequently identified discrepancy. Concerning the adaptation at discharge, almost 20% of patients received post-discharge thromboprophylaxis without meeting the criteria according to the hospital protocol. It has to be taken into account that, currently, an approved scale for prophylaxis at discharge in the general population (both COVID-19 and non-COVID-19 patients) does not exist and that the Padua Prediction Score recommended by the American College of Chest Physicians[22] assesses the risk of VTE in hospitalised patients with acute medical illness but under no circumstance is it specific for outpatient care. Additionally, in order to simplify the management, the hospital's protocol contemplated a modified Padua score without taking into account criteria such as recent surgery (≤1 month) or acute myocardial infarction/stroke; as such, the medical staff could indirectly evaluate these items, focusing on a higher rate of LMWH prescription. Certain risk factors might also have raised controversy, such as reduced mobility. This item could have caused discrepancies, especially in patients who, with an acceptable state of mobility, required home isolation after hospital discharge. Bearing in mind that this subgroup of patients had a shorter hospital stay than the global stay which, together with a benefit-risk assessment of antithrombotic prophylaxis, could account for the regimen at discharge without strictly complying with the previously mentioned criteria.

The safety of the thrombotic treatment in our study was considered acceptable, as only one event reported was classified as clinically significant minor haemorrhage and which was not directly related to the treatment with LMWH as the patient had had previous episodes of melaena due to inflammatory bowel disease. The patient in which thrombocytopenia was reported was mild and transient, without being able to relate it to the beginning of thromboprophylaxis with LMWH.

In conclusion, in patients admitted to the hospital ward, the incidence of hospital-acquired VTE was slightly lower than that described in the literature cited. Although it cannot be certain that it is directly related to the institutional protocol, the data can show that the management of preventing PTE and DVT

is being optimally performed at the hospital. The incidence of events after 30 days from discharge is not significant, and studies with a longer follow-up need to be performed to be able to establish if the consequences of COVID-19 have a thromboembolic consequence apart from short-term hospital discharge. It is necessary to have approved scales in the COVID-19 population that allow assessment of the need to use thromboprophylaxis after hospital discharge and to clarify appropriate and specific strategies for the management of VTE.

What is already known on this subject

⇒ In severe patients infected by SARS-COV-2, the disease can progress to a state of hypercoagulability with a risk of thrombosis that can be prevented with a specific regimen of thromboprophylaxis.
⇒ There is much heterogeneity in the recommendations for the prevention of thromboembolic events in patients with SARS-CoV-2 infection.
⇒ Most of the literature refers to patients admitted to intensive care units.
⇒ What this study adds:
⇒ Our study provides evidence on the management of thromboprophylaxis during hospitalization as well as the management of patients at hospital discharge.

Contributors HQA and PC-R: study conception, design and material preparation. HQA, PC-R, IP-S and JJMS: data collection. HQA, PC-R, EPF: analysis of data. HQA, PC-R, KAJ, MPE: writing of first draft of manuscript. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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Supplemental Material- Tables

Supplemental table 1. Thromboprophylaxis protocol in COVID-19 admitted patients.

Characteristics of anticoagulation prior to admission and thrombotic risk	**Recommendation**	
Patients chronically anticoagulated:		
VKA	Continue treatment. If absolute diet and/or general deterioration, change to LMWH.	
DOAC	Maintain the same if no outstanding interactions.	
Patients not previously anticoagulated, depending on the risk:		
Standard thrombotic risk (those that do not have a high risk).	Weight and/or clearance:	Dose:
	<50 kg or elderly with clearance <15-30 ml	2.500 IU sc/day of bemiparine or 20 mg sc/day of enoxaparin.
	51-80 kg	40 mg sc/day of enoxaparin or 3 500 IU sc/day of bemiparine.
	81-100 kg	60 mg sc/day of enoxaparin
	>100 kg	80 mg sc/day of enoxaparin
High thrombotic risk*	Weight and/or clearance:	Dose:
	<50 kg or elderly with clearance <15-30 ml	3.500 IU sc/day of bemiparine or 40 mg/sc/day of enoxaparin
	51-80 kg	60 mg/day/sc of enoxaparin

	81-100 kg	80 mg/day/sc of enoxaparin
	>100 kg	100 mg/day/sc of enoxaparin
High suspicion of PTE	1 mg/kg/12h of enoxaparin	

VKA: vitamin K antagonist. DOAC: direct oral anticoagulant. LMWH: low-molecular-weight heparin. PTE: pulmonary thromboembolism. *High thrombotic risk (any of the following criteria: severe COVID-19**, D-dimer >2.000 ng/mL, first-line personal or family history of VTD, and personal history of arterial ischemic pathology [peripheral, cardiological, or neurological]). **Severe COVID-19 (at least two of the following criteria: PCR >200 mg/L, D-dimer >1.000 ng/mL, IL-6 >40 pg/mL, ferritin >1.000 ng/mL, lymphocytes $<0.8x10^9$/L).

Supplemental table 2. Thromboprophylaxis protocol in COVID-19 patients at hospital discharge.

Characteristics	**Recommendation**	
If absence of haemorrhagic risk* and score ≥4 in Padua**		
LMWH regimen	Weight and/or clearance:	Dose:
	≤50 kg or elderly with ACR <30 ml/min	2.500 IU sc/day of bemiparine or 20 mg sc/day of enoxaparin
	51-80 kg	40 mg sc/day of enoxaparin or 3 500 IU sc/day of bemiparine
	81-100 kg	60 mg sc/day of enoxaparin
	>100 kg	80 mg sc/day of enoxaparin
Duration	Two weeks. Four weeks if high thrombotic risk.	
If there is haemorrhagic risk and/or score of ≤4 in Padua	No treatment with LMWH.	

LMWH: low-molecular-weight heparin. *Absence of high haemorrhagic risk: absence of active significant haemorrhage or thrombopenia <50 000/µl, double anti-aggregation, or active peptic ulcer in the last three months. **Modified Padua score [5] (history of VTE: 3 points; thrombophilia: 3 points; active cancer: 3 points; BMI ≥30: 1 point; chronic pulmonary disease: 1 point; acute heart failure or respiratory failure: 1 point; life-threatening rheumatological disease: 1 point; reduced mobility: 3 points; hormone therapy with oral contraceptives: 1 point, and age ≥70 years: 1 point).

Supplemental table 3. Basal characteristics of the subjects.

Variable	N=113	
Sex, n (%)		66 (58.4) males
Age, median (IQR)		70 (56-77)
Weight, median (IQR)		76.5 (68.5-84.5)
Hypertension, n (%)		62 (54.9)
Obesity, n (%)		43 (38.1)
Diabetes, n (%)		28 (24.8)
Chronic pulmonary disease, n (%)		18 (15.9)
Chronic kidney disease, n (%)		10 (8.8)
Immunosuppression, n (%)		4 (3.5)
Severe liver failure, n (%)		1 (0.9)
Active cancer, n (%)		8 (7.1)
Previous VTE, n (%)		
	If previous VTE	9 (8)
	First-degree relative with VTE	1 (0.9)

History of arterial ischemic pathology (peripheral, cardiological, and neurological), n (%)		18 (15.9)
Analytical parameters at admission, median (IQR)		
D-dimer (ng/mL)		792 (479-1.622)
C-reactive protein (mg/L)		65 (26-142)
Ferritin (ng/mL)		402 (240-865)
Lymphocytes (10^9/L)		0.9 (0.6-1.2)
Clinical characteristics at admission, n (%)		
Level of severity of pneumonia		
	Uncomplicated illness	7 (6.2)
	Mild pneumonia	72 (63.7)
	Severe pneumonia	32 (28.3)
	Sepsis	2 (1.8)
Level of severity of COVID-19		
	Severe COVID-19	46 (40.7)
	Non-severe COVID-19	66 (58.4)
Thrombotic risk		
	Standard thrombotic risk	50 (44.2)
	High thrombotic risk	62 (54.9)

Anticoagulation prior to admission, n (%)		18 (15.9)
Anticoagulant therapy prior to admission, n (%)		
	DOAC	6 (5.3)
	VKA	8 (7.1)
	LMWH	4 (3.5)

IQR: interquartile range; VTE: venous thromboembolic events; DOAC: direct oral anticoagulant; VKA: vitamin K antagonist; LMWH: low-molecular-weight heparin.

Supplemental table 4. Characteristics of the subjects according to the Padua Predictive Scores.

Risk factors according to the adjusted Padua Prediction Scores	N=113
VTE history, n (%) (3 points)	18 (15.92)
Thrombophilia, n (%) (3 points)	2 (1.76)
Active cancer, n (%) (3 points)	5 (4.42)
BMI >30, n (%) (1 point)	40 (35.39)
Acute heart/respiratory failure, n (%) (1 point)	9 (7.96)
Chronic pulmonary disease, n (%) (1 point) (1 point)	17 (0.44)
Life-threatening rheumatological disease, n (%), n (%) (1 point)	4 (3.53)
Therapy with oral contraceptives, n (%), n (%)	0
Reduced mobility, n (%) (3 points)	26 (23)
Age >70 years, n (%)	42 (37.16)