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Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines

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Summary

AIMS OF THE STUDY: Many centres have noticed a high number of venous thromboembolism (VTE) events among critically ill inpatients with COVID-19 pneumonia. The aims of this study were (1) to summarise the reported risk of VTE associated with COVID-19 infections and (2) to summarise guidance documents on thromboprophylaxis in COVID-19 patients, in a systematic review.

METHODS: We systematically searched for peer-reviewed evidence on the risk of VTE in patients with COVID-19, in PubMed, Embase and Twitter, and for guidelines or guidance documents for thromboprophylaxis, from international or national societies relevant to the field of thrombosis and haemostasis, up to April 30 2020.

RESULTS: We found 11 studies (1 clinical trial, 7 retrospective cohorts and 3 prospective cohorts), which included a range of 16 to 388 in patients with COVID-19 (total of 1369 inpatients). The diagnoses of COVID-19 and VTE were of high quality, but the follow-up was often unclear. Most studies reported universal in-hospital thromboprophylaxis. Among all inpatients and among intensive care unit (ICU) inpatients with COVID-19, reported risks of VTE were 4.4–8.2% (three studies) and 0–35.3% (six studies), respectively. Two studies at least partially screened for VTE in ICU inpatients with COVID-19, and found risks of 24.7–53.8%. We found 12 guidelines for thromboprophylaxis of COVID-19 patients. The majority suggested universal pharmacological thromboprophylaxis in all COVID-19 inpatients, but there was heterogeneity in the suggested intensity of thromboprophylaxis: seven advised considering intensified doses of heparin according to the clinical or biological severity of the disease, especially in the ICU setting.

CONCLUSIONS: Venous thromboembolism very commonly complicates the clinical course of inpatients with COVID-19, despite thromboprophylaxis. The risk appears highest among critically ill inpatients. We found no estimates of risks among outpatients. Many questions remain unresolved, as delineated by the heterogeneity of national and international guidelines. This situation calls for fast randomised clinical trials, comparing different schemes of thromboprophylaxis in COVID-19 inpatients.

Keywords: *COVID-19, SARS virus, venous thromboembolism, pulmonary embolism, heparin*

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Introduction

The SARS-Cov-2 is currently affecting millions of humans worldwide, creating the COVID-19 pandemic. As the epidemic hit Europe, we, like others, have observed a high number of venous thromboembolic (VTE) events in critically-ill COVID-19 inpatients. In parallel, elevated D-dimer levels have been recognised as a hallmark of severe COVID-19 infections and are strongly associated with the risks of developing adult respiratory distress syndrome (ARDS) [1], of intensive care unit (ICU) admission [2] and of death [1, 3]. Whether this is related to a COVID-19-specific prothrombotic state is possible but unclear at this stage. Nevertheless, several scientific societies have released guidelines based on expert opinions regarding thromboprophylaxis.

In order to inform urgently needed clinical decisions on thromboprophylaxis, our aim was to collect all published data reporting VTE rates in COVID-19 patients and to review available guidelines, in a systematic fashion.

Materials and methods

Systematic review of the reported rates of VTE in COVID-19 patients

The inclusion criteria were any peer-reviewed observational or interventional human studies reporting the risk (incidence, proportion or cumulative probability) of venous thromboembolism (pulmonary embolism [PE] and/or deep vein thrombosis [DVT]) in inpatients or outpatients suffering from symptomatic COVID-19 infections, from 1 January 2019 to 30 April 2020, without language restriction. Case reports were excluded. We searched PubMed and Embase, using combined keywords for VTE and COVID-19 in the search queries. In PubMed, we used "(COVID OR coronavirus OR SARS-Cov-2) AND (thrombosis OR thromboembolism OR pulmonary embolism)". In Embase, we used "(coronavirus OR covid)

AND ('thromboembolism'/exp OR 'lung embolism'/exp)". We also screened published COVID-19 observational cohorts of >100 COVID-19 patients and clinical trials, identified through PubMed. We identified recent relevant publications on Twitter, using the combinations of the keywords "COVID-19" or "SARS" and "thrombosis" or "thrombotic" (on 30 April 2020). Finally, we screened reference lists from evaluated full texts. Two authors (FG, MB) independently selected full texts for inclusion, with resolution of disagreement by discussion, and extracted the following data using standardised abstraction forms: study design, sample characteristics, assessment of VTE, use of thromboprophylaxis, screening for VTE, duration of follow-up, and presence of a control group. Quality of the non-comparative data was assessed through use of five important items, pre-identified by the authors: prospective vs retrospective data collection, single-centric vs multicentre hospitals, representativeness of participants, ascertainment of exposure (COVID-19) and of outcome (VTE) and adequacy of follow-up. Each item was provided a star based on criteria shown in table 2.

In order to homogenise study findings, which used a variety of measures to report risks (proportions, incidence, Kaplan-Meier estimates of cumulative probabilities, cumulative incidence functions), we summarised risks of VTE as simple proportions (number of patients with VTE / number of patients at risk), with 95% exact binomial confidence intervals (95% CIs). Data were not meta-analysed because of the heterogeneity and the limited number of studies. All abstractions were conducted with Microsoft Excel. Given the urgency of this analysis, no review protocol was published.

Review of major guidelines

We systematically searched for written guidance documents or guidelines from major international societies related to thrombosis and haemostasis, and from the national relevant societies of the top 10 countries with the largest numbers of confirmed COVID-19 cases (on 29 April 2020). Major societies were the International Society on Thrombosis and Hemostasis (ISTH), the European Society of Cardiology (ESC), the European Hematology Association (EHA), the American Society of Hematology (ASH), the American Heart Association (AHA) and the American College of Chest Physicians (ACCP). The top 10 countries according to ranks from the Johns Hopkins University web-based dashboard [4] (last accessed on 29 April 2020) were the United States, Spain, Italy, France, United Kingdom, Germany, Turkey, Russia, Iran and China. We also screened for position papers of national or international societies in the PubMed database using "COVID-19" and "thrombosis" as search keywords. Finally, we identified recent relevant publications on Twitter, using the combinations of the keywords "COVID-19" or "SARS" and "thrombosis" or "thrombotic" (on 29 April 2020). Relevant data were extracted by three different authors (PF, HRE and MR).

Results

Reported risk of VTE in COVID-19 patients

Our main search retrieved 104 published articles. We also evaluated 14 retrospective and 1 prospective cohorts of ≥100 COVID-19 patients, 4 clinical trials, 1 pre-print peer-reviewed study from Twitter and 2 studies found in citations of full-texts. Eleven studies met the inclusion criteria (fig. 1).

All studies included 1369 inpatients, with sample sizes ranging from 16 to 388 (median of 81 participants): 8/11 focused on ICU inpatients [5–13] and 3/11 included all hospitalised inpatients [14–16] (table 1). Most reports were observational studies from Europe. Most primarily aimed at evaluating thrombotic risks with COVID-19, two focused on COVID-19 coagulopathy [11, 12], and one was a single-arm trial of remdesivir [14].

When study quality was assessed, only four studies were prospective and four studies occurred in >1 hospital (table 2), but most included representative hospitalised ICU or general inpatients. COVID-19 was validly defined in 7/11 studies and it was likely the same in the other 4 studies, which did not report this specifically. Only objective diagnoses of VTE were included in 8/11 studies, with a VTE definition unreported in 3/11, and some studies focused on DVT [5, 14] or on PE [15]. Follow-up was seldom defined or provided.

Three studies included COVID-19 inpatients from acute and from critical wards [14–16] (fig. 2). Without systematic screening, the risks of VTE ranged from 4.4% to 8.2% (one study reporting only PE). One study provided stratified results by ward, and the risk of VTE was greater among ICU inpatients (8.3%) than among general ward inpatients (4.4%) [16].

Eight studies were restricted to ICU inpatients. Except for the study set in China [5], all ICU inpatients received pharmacological thromboprophylaxis, at a standard, augmented or therapeutic dose. Risks of VTE ranged from 0% to 53.8%. It was lowest (0%) in a small (n = 16) prospective cohort exploring COVID-19 coagulopathy, with 100% intensified thromboprophylaxis (enoxaparin 12–16,000 IU daily) [12]. It was greatest in a small (n = 26) retrospective cohort with systematic serial screening for DVT, which included distal DVT. Other estimates were 8.1–35.3%, and the study deemed of highest quality found a 16.7% risk of PE, despite universal thromboprophylaxis, including 30% of patients with therapeutic anticoagulation.

This highest quality study (5*, table 2) was the prospective ICU cohort [6]. Among the five studies with ≥4*, estimates of VTE risks ranged from 9.7 to −35.3% in ICU inpatients [6–8, 13] and from 4.4–5.7% in all inpatients [13, 14].

Two studies compared the risk of VTE with a non-COVID-19 cohort. The first found that COVID-19 ICU inpatients had more than twice the risk of PE than non-COVID-19 ICU patients in the same period in 2019 and in influenza ICU inpatients [10]. The second compared the COVID-19 ARDS cohort with a matched historical non-COVID-19 ARDS cohort, with a much greater risk of PE associated with COVID-19 (odds ratio [OR] 15.2, 95% CI 4.5–80.4) [6].

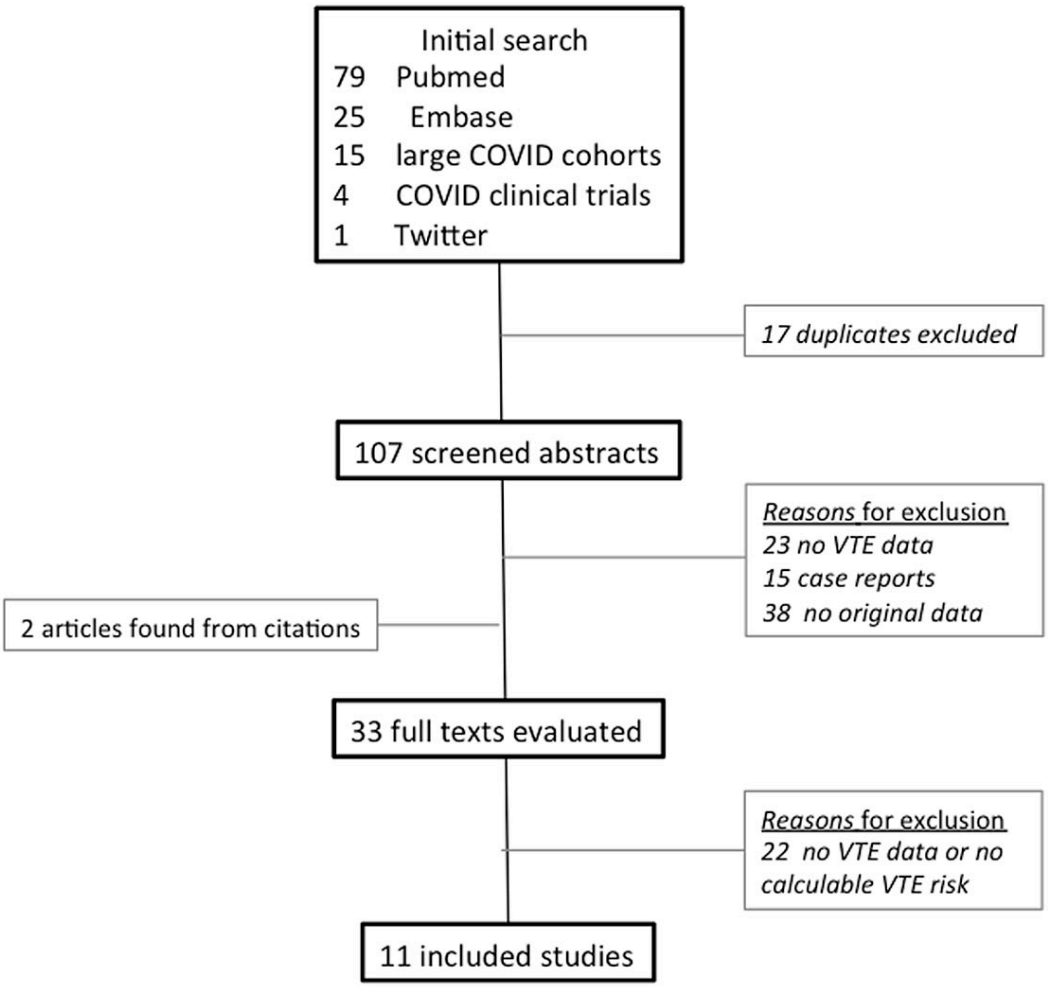
Further, the occurrence of disseminated intravascular coagulation was rarely reported, but appeared low: 0% (0/184 [7, 8]), 0% (0/150 [6]) and 2.1% (8/388 [16]).

Summary of retrieved guidelines and position papers

There were no specific guideline documents on prophylaxis in the webpages of international societies, but we found information on prophylaxis included in a document on COVID-19-induced coagulopathy on the ISTH website [17]. The ASH provides guidance on a webpage dedicated to "frequently asked questions" in COVID-19 [18], whereas all other national societies address the issue of thromboprophylaxis in a dedicated document. Among the 10 countries screened, we found 8 national guidelines [18–23], including 2 from China [24, 25] (table 3). There were no specific guidelines in the websites of the Turkish Society of Thrombosis, Haemostasis and Angiology website, the Iranian Society of Thrombosis and Haemostasis, and the Russian National Association of Thrombosis, Clinical Hemostasiology and Hemorheology Specialists . An additional national position paper from the Swiss Society of Haematology (SSH) was also retrieved through the PubMed search [26]. Finally, a joint consensus statement endorsed by the ISTH, the North American Thrombosis Forum (NATF), the European Society of Vascular Medicine (ESVM), and the International Union of Angiology (IUA) [27] and a report of the National Institute for Public Health of the Netherlands (NIPHN) [28] were identified through Twitter.

All relevant documents were released between 25 March and 23 April 2020. The Chinese Medical Doctor Association (CMDA) [24], the ISTH [17] and Thrombosis-UK [21] recommendations were published first and suggest a standard approach to in-hospital thromboprophylaxis of COVID-19 patients, with standard dose and following a validated clinical score [21, 24] (table 3). In contrast, seven groups propose consideration of intensified doses of heparin as thromboprophylaxis, based on the severity of the clinical or biological disease: the Chinese Consensus Statement (CCS) [25], the joined guidelines of the French Working Group on Perioperative Hemostasis (GIHP) and the French Study Group on Thrombosis and Hemostasis (GFHT) [19], the NIPHN [23], the Society of Thrombosis and Haemostasis (GTH) [6], the Spanish Society of Cardiology (SSC) [28] and the Swiss Society of Haematology [26]. Of note, four guidelines suggest the use of full-dose anticoagulation according to inflammation-related biological parameters in all patients on oxygen therapy [19, 28] or in patients with an increase of D-dimers while on prophylaxis [23, 26]. Prophylaxis after hospital discharge is addressed in ASH guidelines [18], the CMDA [24], the

Figure 1: Flow-chart of the search for the risk of venous thromboembolism (VTE) among COVID-19 patients.



CCS [25] recommendations, the GTH [22], the Italian Society for Thrombosis and Haemostasis (SISET) [20], and the ISTH/NATF/ESVM/IUA position paper [27], with prolongations up to 45 days after discharge in case of a high risk of VTE with a low bleeding risk [20]. For outpatients with COVID-19, the SISET and the GTH suggest the use of standard-dose thromboprophylaxis in case of multiple VTE risk factors. The ISTH/NATF/ESVM/IUA consensus paper also recommends to consider thromboprophylaxis on an individual case basis for patients who have elevated risk of VTE without high bleeding risk [27].

Discussion

Among 11 studies reporting the risk of VTE, we found risks ranging from 4.4–8.2% in all hospitalised COVID-19 inpatients, and much greater risks in ICU COVID-19 inpatients, up to 53.8%. Strikingly, these numbers occurred despite universal thromboprophylaxis and without systematic screening for VTE in most studies. The risk of VTE in the ICU appeared greater than that of other ICU inpatients, although this may be partly explained by a greater propensity to look for PE with COVID-19 (detection bias). We did not find reports of risks of VTE among outpatients. Our results

Table 1: Characteristics and findings of the studies reporting the risk of venous thromboembolism in COVID-19 patients.

Study	Study characteristics		Results										
	Design	Inclusion criteria	Country	Systematic screening for VTE	Definition of VTE	Follow-up	N	Age (median or mean)	Men	Use of TPX	Basal D-dimer (mg/)	PE	DVT
Cui [5]	Retrospective hospital cohort	ICU inpatients with COVID-19	China	Non-systematic screening	Objective imaging of DVT; no PE	Hospital or ICU stay (duration unknown)	81	60 y	46%	0%	§	n/a	20/81
Grein [14]	Prospective single arm clinical trial of remdesivir	Inpatients treated for severe COVID-19 infections and hypoxaemia	International	None	DVT; no PE	Hospital stay, max 28 d (median 18 d)	53	64 y	75%	n/a	n/a	n/a	3/53
Grillet [15]	Retropective hospital cohort	Inpatients with COVID-19	France	None	PE on performed angio-CT; no DVT	Not stated (likely hospital stay)	280	n/a	n/a	n/a	n/a	23/280	n/a
Helms [6]	Prospective two-centre hospital cohort	ICU inpatients with COVID-19 ARDS	France	None	Objective imaging of PE and unclear diagnosis for DVT	ICU stay (unknown median, but >7 d)	150	63 y	81%	100% (70% P, 30% T)	Median 2.27 (1.16-20.0)	25/150	3/150
Klok [7, 8]	Retrospective three-centre hospital cohort	ICU inpatients with COVID-19	Netherlands	None	Objective imaging (PE and DVT)	ICU stay (median 14 d)	184	64 y	76%	100% (P or augmented P)	n/a	65/184	3/184 (2 line DVT)
Lllitjos [9]	Retrospective two-centre hospital cohort	ICU inpatients with COVID-19	France	Whole-leg CUS at d1–3 + d7	Objective imaging (+ TOE for PE)	Not stated (likely ICU stay)	26	68 y	77%	100% (31% P, 69% T)	Median 1.75 (1.13–2.85)	6/26	14/26
Lodigiani [16]	Retrospective single-centre cohort	Inpatients with COVID-19	Italy	None	Objective imaging (PE and DVT)	Hospital stay (median 10 d)	388	66 y	68%	79% (71% P, 29% T)*	§	10/362†	6/362‡
Poissy [10]	Retrospective single-centre cohort	ICU inpatients with COVID-19	France	None	Objective imaging of PE and DVT	ICU stay (duration unknown)	107	57 y	59%	100% (91% P, 9% T)	n/a	22/107	5/107
Spiezia [11]	Prospective single-centre cohort	ICU inpatients with COVID-19, without cancer	Italy	Not stated	DVT	Not stated	22	67 y	91%	100% (P)	5.34 (SD 2.10)	Not stated	5/22
Ranucci [12]	Prospective single-centre ICU cohort	ICU inpatients with COVID-19, with mechanical ventilation	Italy	Not stated	Not stated	Not stated (median ≥14 d)	16	61 y	94%	100% (augmented P)	Median 5.5 (2.5–6.5)	0/16	0/16
Thomas [13]	Retrospective single-centre ICU cohort	ICU inpatients with COVID-19	UK	None	Objective imaging of PE and/or DVT	hospital stay (median 8 d)	62‡	59	n/a	100% (P)	n/a	5/62	1/62 (line DVT)

CT =computed tomography; CUS = compression ultrasound of the legs; DVT = deep vein thrombosis; n/a = not available; P = prophylactic; PE = pulmonary embolism;SD = standard deviation; T = therapeutic; TOE = transoesophageal echocardiography; TPX = pharmacological thromboprophylaxis; VTE = venous thromboembolism * 100% for ICU patients and 75% for non-ICU patients; † data only provided for "closed cases" (excluding patients still in-hospital); ‡ excluding 1 patient with no objectively diagnosed PE ; § data only provided in strata of survivors vs non-survivors, or VTE vs no VTE

can mainly inform thromboprophylaxis strategies in acute and critically ill inpatients.

There are several plausible mechanisms for this observed prothrombotic state. First, critically-ill patients cumulate important VTE risk factors such as a profound immobility, a severe infectious and inflammatory state, hypoxia, and central venous lines. Second, COVID-19 patients exhibit a particular form of coagulopathy, with dramatically elevated fibrinolytic biomarkers but without severe thrombocytopenia or hypofibrinogenaemia [29]. Whether this reflects a true prothrombotic intravascular state is unclear but likely, but it could also be related to fibrin accumulation in the lung, a hallmark of ARDS. Third, endothelial lesions, which may enhance the production of clots, may also be involved,. The SARS-CoV-2 virus enters host cells through the ACE2 surface receptor, which can be found not only in lung alveolar cells but also in arterial and venous endothelial cells. Fourth, a high proportion of critically-ill COVID-19 patients were found to have positive lupus circulating anticoagulant (88%), but the clinical significance of this finding remains unknown [6].

Table 2: Quality assessment of the studies.

Study	Prospective vs. retrospective design	Number of hospitals	Representativeness of the studied patients	Ascertainment of exposure (COVID-19)	Assessment of outcome (VTE)	Adequacy of follow-up
	(*) if prospective	(*) if multiple centres	(*) if consecutive inpatients without exclusion criteria	(*) if PCR diagnosis	(*) if objective diagnoses of both PE and DVT	(*) if follow-up is stated and ≥7 days
Cui [5]	Retrospective	1 hospital	ICU COVID-19 patients*	PCR diagnosis (*)	Objective diagnosis of DVT; no PE	Unclear
Grein [14]	Prospective (*)	Multiple hospitals (*)	Participants in drug trial	PCR diagnosis (*)	Not stated	Hospital stay or 28 d, median 18 d (*)
Grillet [15]	Retrospective	1 hospital	All COVID-19 inpatients (*)	RT-PCR diagnosis or strong clinical suspicion (with exposure to COVID-19 case)	Objective diagnosis of PE; no DVT	Unclear
Helms [6]	Prospective (*)	2 hospitals (*)	All ICU COVID-19 patients (*)	PCR diagnosis (*)	Objective diagnosis of PE; unclear for DVT	ICU stay, median ≥7 d (*)
Klok [7, 8]	Retrospective	3 hospitals (*)	All ICU COVID-19 patients (*)	"Proven" COVID-pneumonia†	Objective diagnosis of PE and DVT (*)	ICU stay, median 14 d (*)
Lilitjos [9]	Retrospective	2 hospitals (*)	All ICU COVID-19 patients (*)	Not stated	Objective diagnosis of PE and DVT (*)	Unclear
Lodigiani [16]	Retrospective	1 hospital	All COVID/19 inpatients (*)	PCR diagnosis (*)	Objective diagnosis of PE and DVT (*)	Hospital stay, median 10 d (*)
Poissy [10]	Retrospective	1 hospital	All ICU COVID-19 patients (*)	Not stated	Objective diagnosis of PE and DVT (*)	Unclear
Spiezia [11]	Prospective (*)	1 hospital	Selection of ICU patients	Not stated	Not stated	Unclear
Ranucci [12]	Prospective (*)	1 hospital	Selection of ICU patients	Not stated	Not stated	Unclear
Thomas [13]	Retrospective	1 hospital	All ICU COVID-19 patients (*)	PCR diagnosis (*)	Objective diagnosis of PE and DVT (*)	Hospital stay, median 8 d (*)

DVT = deep vein thrombosis; ICU = intensive care unit; PCR = polymerase chain reaction; PE = pulmonary embolism; RT-PCR = real-time PCR * Unclear if all ICU inpatients were included; † diagnosis of infection not further detailed

Figure 2: Risks of venous thromboembolism (VTE) in individual studies, obtained from simple proportions (n VTE / n at risk). Error bars represent 95% confidence intervals. ICU = intensive care unit

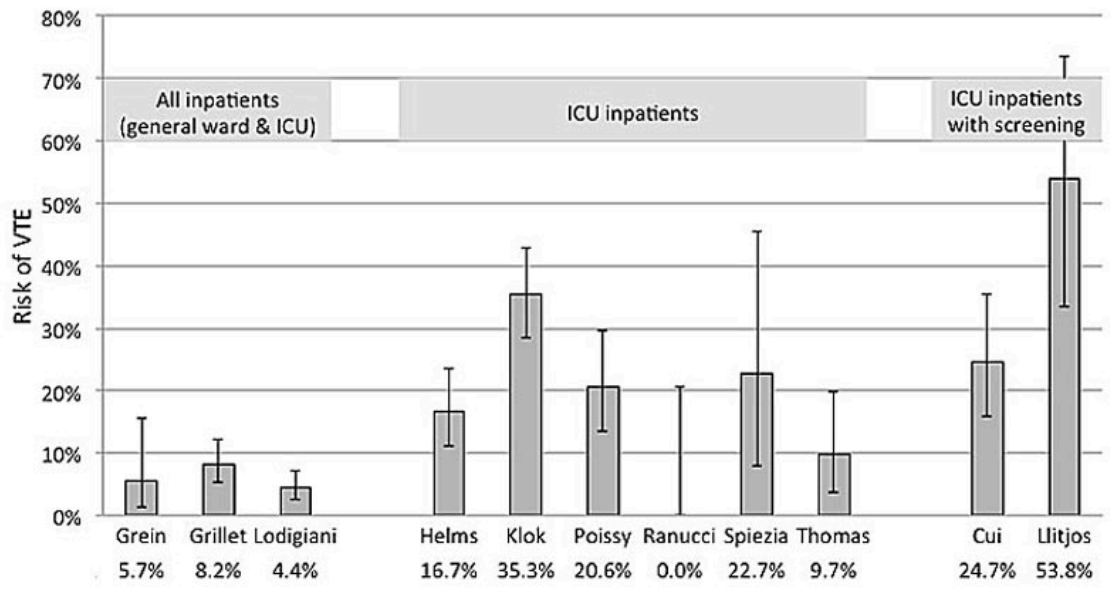


Table 3: Summary of thromboprophylaxis policies for COVID-19 patients.

Association	Country	Date/last update	Pharmacological prophylaxis recommended if no increased bleeding risk	Mechanical prophylaxis	Type of anticoagulant	Adaptation to weight	Adaptation of dose to severity of disease	Adaptation of dose to biological parameters	After discharge
ASH	US	April 17	Yes, standard dose; in all hospitalised patients with COVID-19	If pharmacological contraindicated	LMWH or fondaparinux over UFH to reduce contact	Dose adjustment for obesity may be used per institutional guidance	No	n/a	Consider extended thromboprophylaxis after discharge using a regulatory-approved regimen
CCS	China	April 21	Yes, standard dose in severe or critically ill patients and according to RAM for mild or moderate patients; yes in ambulatory patients according to RAM for medical inpatients	Yes in severe or critically ill patients if pharmacological contraindicated	LMWH of UFH	Yes in severely or critically ill patients only; enoxaparin 6000 IU o.d. for weight 90–130 kg and 4000 IU bid if >130 kg	No (except in obese patients).	D-dimers may be part of the assessment of VTE risk and promote increasing the dose of anticoagulant	Yes if perceived to have persistent risk for VTE
CMDA	China	February 20	Yes, standard dose, according to risk assessment	If pharmacological contraindicated in severely ill patients	LMWH or UFH	n/a	No	No	Consider extended thromboprophylaxis after discharge according to VTE risk
GIHP/GFHT	France	April 3	Yes, standard dose	Possible alternative	LMWH or UFH or fondaparinux	Yes if BMI >30 kg/m^2, intermediate dose: enoxaparin 40 mg b.i.d. <120 kg and 60 mg b.i.d. >120 kg; therapeutic dose if additional risk factors (active cancer, past history of VTE in the last 2 years) and high-flow oxygen/ mechanical ventilation	Yes; if high flow oxygen therapy or mechanical ventilation, intermediate dose; therapeutic dose if additional risk factors (active cancer, past history of VTE in the last 2 years); therapeutic dose if ECMO	Yes (fibrinogen >8 g/l or D-dimers >3000 ng/m or rapidly increasing D-dimer levels), therapeutic dose	n/a
GTH	Germany Austria Switzerland	April 21	Yes, in all hospitalised patients and in ambulatory patients with D-dimer ≥1.5–2.0 mg/l; standard dose	If pharmacological contraindicated	LMWH	Yes, if BMI >30 kg/m^2, intermediate dose	Yes, in ICU patients; intermediate dose	Yes, if rapid increase of D-dimers; intermediate dose	Yes, if persistent inflammation or immobilisation or BMI >30 kg/m^2 or previous history of VTE or active cancer
ISTH	International	March 25	Yes, no particular dose mentioned; in all inpatients	n/a	LMWH	n/a	n/a	No	n/a
ISTH-NATF-ESVM-IUA	International	April 15	Yes, following a risk stratification rule for inpatients, standard dose (majority of panel members); considered for outpatients at high VTE risk	If anticoagulation contraindicated	LMWH or UFH	n/a	n/a	n/a	Yes, up to 45 days, for patients with elevated risk of VTE (reduced mobility, active cancer, ± elevated D-dimers) and with low risk of bleeding
NIPHN	Netherlands	April 23	Yes, in all hospitalised patients, standard dose	n/a	n/a	n/a	n/a	Consider therapeutic anticoagulation if D-dimers at admission >1000 ng/ml and increase during follow-up and imaging for VTE or PE not feasible	n/a
SISET	Italy	April 7	Yes, in all inpatients and in ambulatory patients with pre-existing risk factors (i.e. reduced mobility,	If anticoagulation contraindicated	LMWH or UFH or fondaparinux	Yes (BMI >30 kg/m^2), intermediate dose (enoxaparin 40 mg b.i.d.)	n/a	No	Yes, 7–14 days in cases of pre-existing or persisting VTE risk factors (i.e., reduced mobility, BMI >30 kg/m^2, previous

Association	Country	Date/last update	Pharmacological prophylaxis recommended if no increased bleeding risk	Mechanical prophylaxis	Type of anticoagulant	Adaptation to weight	Adaptation of dose to severity of disease	Adaptation of dose to biological parameters	After discharge
			BMI >30, previous VTE, active cancer, etc.), standard dose						VTE, active cancer, etc.).
SSC	Spain	April 22	Yes, in all hospitalised patients; standard dose	n/a	LMWH or UFH	Yes, if BMI >35 kg/m^2: "increase dosage"	Yes, if severe respiratory insufficiency; intermediate dose (enoxaparin 1 mg/kg o.d.). Therapeutic dose if additional biological risk factors	Yes, if D-dimers >6 × "normal" or >2 of the following: CRP >15, D-dimers >3 × "normal", IL-6 >40, ferritin >1000, lymphopenia <800; intermediate dose. Therapeutic dose if associated severe respiratory insufficiency	Yes, standard dose 7–10 days
Thrombosis-UK	UK	March 25	Yes, in high risk patients (according to NICE/ASH stratification guidelines), standard dose	Yes, in addition to pharmacological prophylaxis if completely immobilised; and alone if platelets <30 G/l or bleeding.	LMWH or UFH or fondaparinux	n/a	n/a	n/a	n/a
SSH	Switzerland	April 11	Yes, in all hospitalised patients; standard dose	n/a	LMWH or UFH	Yes (>100 kg), no details	Yes (signs of hepatic or renal dysfunction or imminent respiratory failure), intermediate or therapeutic dose; therapeutic dose if ECMO.	Yes (large increase in D-dimers, severe inflammation), intermediate or therapeutic dose.	n/a

BMI = body mass index; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IL = interleukin; n/a = not available; RAM = risk assessment models; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism

This signal of an important venous thrombotic risk with COVID-19 infections requires much more data to shed light on the incidence and risk factors of thrombotic events in these patients, as well as the best prophylaxis strategy. Observational cohorts and registries are needed for non-critically ill inpatients, with a follow-up after hospital discharge. In the ICU, the incidence of asymptomatic DVT should be evaluated in research settings, with the hypothesis of a reduction of PE. Finally, the anti-thrombotic, anti-inflammatory and perhaps anti-viral effects of heparins call for interventional trials of intensified doses of thromboprophylaxis in COVID-19 inpatients. The pleiotropic effect of heparin and potential benefits on COVID-19 infections have been reviewed recently [30]. We have started the COVID-HEP randomised trial (NCT04345848) to assess the benefit-risk of therapeutic anticoagulation in severely-ill COVID-19 inpatients.

With regards to the published recommendations, the majority recommends universal thromboprophylaxis while in hospital. We found a large heterogeneity in the dosing of heparins, with several groups suggesting intensified doses based on the clinical and/or biological severity of the COVID-19 infection. For instance, for a non-obese acutely ill inpatient, the ASH and Thrombosis-UK guidelines suggest standard-dose thromboprophylaxis, but the French and the Swiss guidelines suggest a high-dose thromboprophylaxis, providing that the patient meets specific biological criteria [31]. There is a clear area of uncertainty here, highlighting the need for interventional studies for this topic.

Although our search was systematic, we acknowledge that the capture of rapidly evolving medical literature, through PubMed, Embase and Twitter is likely subpar, especially in China, and that the number of reports on COVID-19 and VTE will likely grow in the coming weeks and months. Second, a few studies reported the risk of VTE based on Kaplan-Meier estimates or cumulative incidence functions from competing risk modelling, but we chose not to use such numbers, as the assumption of non-informative censoring is likely untrue at the time of ICU discharge. Third, our findings on risks of VTE may underestimate the true risks, as some studies only reported PE or DVT, some used intensified thromboprophylactic regimens and most did not systematically screen for VTE. This variability, also in sample sizes, does not allow for meaningful pooling of the data and strong conclusions on precise risks of VTE. Fourth, we did not use a validated tool to assess the quality of studies, but a priori identified key quality factors. Fifth, we did not appraise the guidance documents we have summarised, acknowledge that their quality may be variable, as they mainly represent experts' opinions and should not be read as strong recommendations.

In conclusion, the reported risk of VTE appears high among inpatients and very high among critically ill patients suffering from COVID-19. This has led to the suggestion of thromboprophylaxis with intensified dosages of

heparin, which will be examined in randomised clinical trials. We are awaiting further data on the risk of VTE outside of the ICU to better understand the prothrombotic state associated with this infection and to adapt thromboprophylaxis efforts.

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