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

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) OR (SARS-CoV-2) 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 \[24, 25\] \(\text{(table 3)}\). 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 \[21, 24\] \(\text{(table 3)}\). 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

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**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

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**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/l) | PE | DVT |
| Cui [9] | 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] | Retrospective 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 unambiguous diagnosis for DVT | ICU stay (unknown median, but > 7 d) | 150 | 63 y | 81% | 100% (70% P, 30% T) | Median 2.27 (1.16–2.00) | 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) |
| Lilijs [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) | 28 | 68 y | 77% | 100% (31% P, 69% T) | Median 1.75 (1.13–2.85) | 6/26 | 14/26 |
| Lodigiani [16] | Prospective 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) | § | 10/3621 | 6/3622 |
| 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 |
|-----------|-------------------------------------|---------------------|-------------------------------------------|-------------------------------------|-----------------------------|-----------------------|
| 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 (*) |
| 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 14 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 5 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 | Pharmaco logical prophylaxis rec-ommended if no increased bleeding risk | Mechanical pro-phyllaxis | Type of antico-agulant | Adaptation to weight | Adaptation of dose to sever-ity of disease | Adaptation of dose to biologi-cal parameters | After discharge |
|-------------|-----------|------------------|-----------------------------------------------------------------|-------------------------|------------------------|----------------------|------------------------------------------|-----------------------------------------------|-----------------|
| ASH         | US        | April 17         | Yes, standard dose; in all hospitalised patients with COVID-19 | If pharmacologi-cal contraindicat-ed | LMWH or fon-daparinux over UFH to reduce contact | Dose adjust-ment for obe-sity may be used per institu-tional guid-ance | No | n/a | Consider extended thromboprophylaxis after discharge using a regulatory-ap-proved 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 pa-tients if pharma-co logical con-traindicat-ed | LMWH of UFH | Yes in severe-ly 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 pa-tients). | D-dimers may be part of the assessment of VTE risk and promote in-creasing the dose of antico-agulant | Yes if perceived to have persistent risk for VTE |
| CMDA        | China     | February 20      | Yes, standard dose, according to risk assessment | If pharmacologi-cal contraindicat-ed in severely ill patients | LMWH or UFH | n/a | No | No | Consider extended thromboprophylaxis after discharge ac-cording to VTE risk |
| GIHP/GFHT   | France    | April 3          | Yes, standard dose | Possible alterna-tive | LMWH or UFH or fondaparinux | Yes if BMI >30 kg/m², in-termediate dose: enoxa-parin 40 mg b.i.d. <120 kg and 60 mg b.i.d. >120 kg; therapeu-tic dose if ad-ditional risk factors (active cancer, past history of VTE in the last 2 years) and high-flow oxy-gen/ mechanical ventilation | Yes; if high flow oxygen therapy or me-chanical venti-lation, interme-di ate dose; therapeutic dose if addi-tional risk fac-tors (active cancer, past history of VTE in the last 2 years); therapeu-tic dose if ECMO | Yes (fibrinogen >8 g/l or D-di-mers >3000 ng/ml 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 pharmacologi-cal contraindicat-ed | LMWH | Yes, if BMI >30 kg/m², in-termediate dose | Yes, in ICU pa-tients; interme-di ate dose | Yes, if rapid in-crease of D-di-mers; interme-di ate dose | Yes, if persistent in-flammation or immo-bilisation or BMI >30 kg/m² or previous history of VTE or ac-tive 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); consid-ered for outpa-tients at high VTE risk | | LMWH or UFH | n/a | n/a | n/a | Yes, up to 45 days, for patients with elevated risk of VTE (re-duced mobility, ac-tive 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 | Consider thera-peutic anticoag-ulation if D-di-mers at admission >1000 ng/ml and increase during follow-up and imaging for VTE or PE not feasi-ble | n/a |
| SISET       | Italy      | April 7         | Yes, in inpa-tients and in ambu-latory patients with pre-existing risk factors (i.e. re-duced mobility), | If anticoagulation contraindicat-ed | LMWH or UFH or fondaparinux | Yes (BMI >30 kg/m²), inter-me diate 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., re-duced mobility, BMI >30 kg/m², previous |
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 dosages 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

| 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. | Switzerland | Yes, all hospitalised patients; standard dose | | | | | | | |
| | | | | | | | | | |
| SSC Spain April 22 Yes, in all hospitalised patients: standard dose | n/a | LMWH or UFH | Yes, if BMI >35 kg/m²: 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, lyso- | Yes, active cancer, etc., 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
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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References

1 Wu C, Chen X, Cai Y, Xia J, ZhouX, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020; (in press). doi: http://dx.doi.org/10.1001/jamainternmed.2020.0094. PubMed

2 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10232):497-506. doi: http://dx.doi.org/10.1016/S0140-6736(20)30183-5. PubMed

3 Zhou F, Yu T, Du R, Fan G, Li Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi: http://dx.doi.org/10.1016/S0140-6736(20)30566-3. PubMed

4 Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-4. doi: http://dx.doi.org/10.1016/S1473-3099(20)30086-0. PubMed

5 Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1241-4. doi: http://dx.doi.org/10.1111/jth.14830. PubMed

6 Helms J, Taccaud G, Severez F, Leonard-Lorant J, Ohana M, Delabranche X, et al.; CRIS TRIGGERSEPS Group (Clinical Research in Intensive Care and Sepis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98. doi: http://dx.doi.org/10.1007/s00134-020-06060-x. PubMed

7 Klok FA, Kruij M, van der Meer NJM, Arbous MS, Gomers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–7. doi: http://dx.doi.org/10.1016/j.thromres.2020.04.013. PubMed

8 Klok FA, Kruij MJHA, van der Meer NJM, Arbous MS, Gomers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020;191:148–50. doi: http://dx.doi.org/10.1016/j.thromres.2020.04.041. PubMed

9 Litijos JF, Leecle M, Choochoi C, Monsairi JM, Ramakers M, Avra M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18:14869. doi: http://dx.doi.org/10.1111/jth.14869. PubMed

10 Pouta J, Goutay J, Caplan M, Parmentier E, Dubuqu T, Lassalle F, et al.; Lille ICU Haemostasis COVID-19 group. Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. Circulation. 2020. Epub ahead of print. doi: http://dx.doi.org/10.1161/CIRCULATION-A-104730. PubMed

11 Spiezia L, Boschiola A, Pollet F, Curnett L, Tiberio I, Campello E, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb Haemost. 2020;120:699-1000. doi: http://dx.doi.org/10.1055/s-0040-1710018. PubMed

12 Ranucci M, Ballowa A, Di Dedda U, Bayshnikova E, Dei Poli M, Rista M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020;18:14854. doi: http://dx.doi.org/10.1111/jth.14854. PubMed

13 Thomas W, Varley J, Johnston A, Symington E, Robinson M, Sheares K, et al. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. Thromb Res. 2020;191:176-7. doi: http://dx.doi.org/10.1016/j.thromres.2020.03.028. PubMed

14 Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe COVID-19. N Engl J Med. 2020;382(24):2327-36. doi: http://dx.doi.org/10.1056/NEJ- Moa2007016. PubMed

15 Griller F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT Angiography. Radiology. 2020;201544. doi: http://dx.doi.org/10.1148/radiol.2020201544. PubMed

16 Lodigiani C, Iapichino G, Caremolo L, Cecconni M, Ferrarini P, Sebastian T, et al.; Humansit COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14. doi: http://dx.doi.org/10.1016/j.thromres.2020.04.024. PubMed

17 Thachil J, Tang N, Gundo S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-6. doi: http://dx.doi.org/10.1111/jth.14810. PubMed

18 COVID-19 and VTE/ Anticoagulation: Frequently Asked Questions. https://www.hematology.org/covid-19/covid-19 and-vte-anticoagulation. 2020 March 27. Accessed 2020 April 29

19 GHF-GHGP Proposals: Prevention and treatment of new coronavirus pneumonia associated venous thromboembolism, a Consensus statement (Preliminary Protocol). Chinese Medical Journals Net- work. 2020.E007-E.

20 Zhi L, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J, et al.; Prevention Treatment of VTE Associated with COVID-19 Infection Consensus Statement Group. Prevention and treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. Thromb Haemost. 2020;124(6):937–48. doi: http://dx.doi.org/10.1111/jth.14768. PubMed

21 Casini A, Alberio L, Angelillo-Scherrer A, Fontana P, Gerber B, Graf L, et al. Thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19 - a Swiss consensus statement by the Working Party Hemostasis. Swiss Med Wkly. 2020;150:w20247. doi: http://dx.doi.org/10.4414/smw.2020.20247. PubMed

22 Bickel I, Madhavan MV, Jimenez D, Chuih T, Dreyfus I, Draggin E, et al.; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NAIF, ESM, and the IUA, Supported by the ESC. Working Group on Pulmonary Circulation and Right Ventricular Function in COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(23):2950-73. doi: http://dx.doi.org/10.1016/j.jacc.2020.04.031. PubMed

23 Oudkerk M, Builer RR, Kuipers D, van Es N, Oudkerk SF, McLoed TC, et al. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. Radiology. 2020;300:201629. doi: http://dx.doi.org/10.1148/radiol.2020300201629. PubMed

24 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7. doi: http://dx.doi.org/10.1111/jth.14708. PubMed

25 Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020;18(3):1020-2. doi: http://dx.doi.org/10.1111/jth.14821. PubMed

26 Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines
for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv. 2018;2(22):3198–225. doi: http://dx.doi.org/10.1182/bloodadvances.2018022954. PubMed.