Prevention, Diagnosis, and Treatment of VTE in Patients With COVID-19

CHEST Guideline and Expert Panel Report

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BACKGROUND: Emerging evidence shows that severe coronavirus disease 2019 (COVID-19) can be complicated by a significant coagulopathy, that likely manifests in the form of both microthrombosis and VTE. This recognition has led to the urgent need for practical guidance regarding prevention, diagnosis, and treatment of VTE.

METHODS: A group of approved panelists developed key clinical questions by using the PICO (Population, Intervention, Comparator, Outcome) format that addressed urgent clinical questions regarding the prevention, diagnosis, and treatment of VTE in patients with COVID-19. MEDLINE (via PubMed or Ovid), Embase, and Cochrane Controlled Register of Trials were systematically searched for relevant literature, and references were screened for inclusion. Validated evaluation tools were used to grade the level of evidence to support each recommendation. When evidence did not exist, guidance was developed based on consensus using the modified Delphi process.

RESULTS: The systematic review and critical analysis of the literature based on 13 Population, Intervention, Comparator, Outcome questions resulted in 22 statements. Very little evidence exists in the COVID-19 population. The panel thus used expert consensus and existing evidence-based guidelines to craft the guidance statements.

CONCLUSIONS: The evidence on the optimal strategies to prevent, diagnose, and treat VTE in patients with COVID-19 is sparse but rapidly evolving. CHEST 2020; ■(■):■-■

KEY WORDS: COVID-19; DIC; DVT; hypercoagulability; pulmonary embolism; VTE

ABBREVIATIONS: aPTT = acketivated partial thromboplastin time; COVID-19 = coronavirus disease 2019; DIC = disseminated intravascular coagulation; DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PICO = Population, Intervention, Comparator, Outcome; RR = relative risk; SIC = sepsis-induced coagulopathy; UFH = unfractionated heparin

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Summary of Recommendations

1. In the absence of a contraindication, in acutely ill hospitalized patients with COVID-19, we suggest anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis.

2. In the absence of a contraindication, in critically ill patients with COVID-19, we recommend anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis.

3. In acutely ill hospitalized patients with COVID-19, we suggest anticoagulant thromboprophylaxis with low-molecular-weight heparin (LMWH) or fondaparinux over anticoagulant thromboprophylaxis with unfractionated heparin (UFH); and we recommend anticoagulant thromboprophylaxis with LMWH, fondaparinux or UFH over anticoagulant thromboprophylaxis with a direct oral anticoagulant (DOAC).

Remarks: The panel favors LMWH and fondaparinux over UFH to limit staff exposure. The panel cautions against the use of DOACs in these patients secondary to the high risk of rapid clinical deterioration in these patients. In addition, it is likely that many of these patients will be receiving concomitant therapy (antiviral agents or other investigational treatments) that can significantly affect the pharmacodynamics of and thus bleeding risk associated with the DOACs.

4. In critically ill patients with COVID-19, we suggest anticoagulant thromboprophylaxis with LMWH over anticoagulant thromboprophylaxis with UFH; and we recommend anticoagulant thromboprophylaxis with LMWH or UFH over anticoagulant thromboprophylaxis with fondaparinux or a DOAC.

Remarks: The panel favors LMWH over UFH to limit staff exposure. The panel strongly cautions against the use of DOACs in critically ill patients secondary to their hemodynamic instability, the high likelihood of drug-drug interactions, and the high incidence of acute kidney injury in these patients. In addition, there is a lack of evidence for anticoagulant thromboprophylaxis even in non-COVID critically ill patients.

5. In critically ill or acutely ill hospitalized patients with COVID-19, we recommend against the use of antiplatelet agents for venous thromboembolism (VTE) prevention.

6. In acutely ill hospitalized patients with COVID-19, we recommend current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

Remarks: Although there has been some concern for increased risk of VTE in hospitalized COVID-19 patients, there is insufficient data to justify increased intensity anticoagulant thromboprophylaxis in the absence of randomized controlled trials.

7. In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

Remarks: Although there is anecdotal and observational data that suggest an increased VTE risk in critically ill patients with COVID-19, it is not clear if the most severely ill COVID-19 patients occupy a different level of risk for VTE than other severely ill nonsurgical, medical ICU patients. There is also insufficient data regarding bleeding risk in this population, and given severity of illness, it may be just as likely that critically ill COVID-19 patients are at high risk of adverse bleeding complications. Finally, it is not clear that this population has a higher risk of VTE when treated with standard doses of anticoagulant thromboprophylaxis per existing guidelines.

8. In patients with COVID-19, we recommend inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge.

Remarks: Extended thromboprophylaxis in patients with COVID-19 at low risk of bleeding should be considered, if emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis. See text for assumptions indicating net benefit.

9. In critically ill patients with COVID-19, we suggest against the addition of mechanical prophylaxis to pharmacological thromboprophylaxis.

Remarks: Although there is no evidence supporting the combination of mechanical and pharmacological thromboprophylaxis for patients with COVID-19 who are critically ill, it is not likely that adding mechanical prophylaxis in this population would cause major harm. We recommend that providers adhere to existing guidance regarding the use of mechanical thromboprophylaxis.

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

10. In critically ill patients with COVID-19 who have a contraindication to pharmacological thromboprophylaxis, we suggest the use of mechanical thromboprophylaxis.

11. In critically ill COVID-19 patients, we suggest against routine ultrasound screening for the detection of asymptomatic deep vein thrombosis (DVT).

Remarks: Although we suggest against a routine screening ultrasound for critically ill COVID-19 patients, we note that clinicians should have a low threshold for performing ultrasound in patients with a reasonable degree of clinical suspicion for VTE. Lower extremity ultrasound should also be part of point of care ultrasound (POCUS), particularly in situations like unexplained right ventricular dysfunction, unexplained/refractory hypoxemia or in patients with suspected PE who are unable to undergo a diagnostic study (ie, unstable for transport or advanced renal failure). It should be noted that even if clot is not visualized on lower extremity ultrasound, pulmonary embolism is not fully excluded.

12. For acutely ill hospitalized COVID-19 patients with proximal DVT or pulmonary embolism (PE), we suggest initial parenteral anticoagulation with therapeutic weight adjusted LMWH or intravenous UFH. The use of LWMH will limit staff exposure and avoid the potential for heparin pseudo-resistance. In patients without any drug-to-drug interactions, we suggest initial oral anticoagulation with apixaban or rivaroxaban. Dabigatran and edoxaban can be used after initial parenteral anticoagulation. Vitamin K antagonist therapy can be used after overlap with initial parenteral anticoagulation.

Remarks: The panel has downgraded the most recent ACCP recommendation regarding the use of oral anticoagulants in patients hospitalized with COVID-19 secondary to the high risk of rapid clinical deterioration in these patients. In addition, it is likely that many of these patients will be on concomitant therapy (antiviral agents or other investigational treatments) that can significantly affect the pharmacodynamics of and bleeding risk associated with the DOACs. Thus LMWH or UFH are favored over oral anticoagulants.

13. For outpatient COVID 19 patients with proximal DVT or PE and no drug-to-drug interactions, we recommend apixaban, dabigatran, rivaroxaban or edoxaban. Initial parenteral anticoagulation is needed before dabigatran and edoxaban. For patients who are not treated with a DOAC, we suggest vitamin K antagonists over LMWH (for patient convenience and comfort). Parenteral anticoagulation needs to be overlapped with vitamin K antagonists.

14. In critically ill COVID-19 patients with proximal DVT or PE, we suggest parenteral over oral anticoagulant therapy. In critically ill COVID-19 patients with proximal DVT or PE who are treated with parenteral anticoagulation, we suggest LMWH or fondaparinux over UFH.

Remarks: UFH might be preferred over LMWH or fondaparinux in patients at high bleeding risk (including those with severe renal failure), or in those with overt or imminent hemodynamic decompensation due to PE, in whom primary reperfusion treatment may be necessary. The decision to use UFH should be balanced with the risks associated with extra staff exposure and issues with heparin resistance as above.

15. For COVID 19 patients with proximal DVT or PE, we recommend anticoagulation therapy for a minimum duration of three months.

16. In most patients with COVID-19 and acute, objectively confirmed PE not associated with hypotension (systolic blood pressure < 90 mm Hg or blood pressure drop of ≥ 40 mm Hg lasting longer than 15 minutes), we recommend against systemic thrombolytic therapy.

Remarks: Please see statement 18 for the select patients that may require systemic thrombolysis.

17. In patients with COVID-19 and both acute, objectively confirmed PE and hypotension (systolic blood pressure < 90 mm Hg) or signs of obstructive shock due to PE, and who are not at high risk of bleeding, we suggest systemically administered thrombolytics over no such therapy.

18. In patients with COVID-19 and acute PE with cardiopulmonary deterioration due to PE (progressive increase in heart rate, a decrease in systolic BP which remains >90 mm Hg, an increase in jugular venous pressure, worsening gas exchange, signs of shock (eg, cold sweaty skin, reduced urine output, confusion), progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers) after initiation of anticoagulant therapy who have not yet developed hypotension and who

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

have a low risk of bleeding, we suggest systemic thrombolytic therapy over no such therapy.

19. We recommend against the use of any advanced therapies (systemic thrombolysis, catheter-directed thrombolysis or thrombectomy) for most patients without objectively confirmed VTE.

Remarks: Thrombolysis may be considered in select patients when cardiac arrest is suspected to be caused by PE and imaging is not obtainable. We would suggest that providers consider the differential of RV strain (preexisting pulmonary hypertension, high PEEP, severe ARDS) before entertaining the use of empiric thrombolysis.

20. In those patients with COVID-19 receiving thrombolytic therapy, we suggest systemic thrombolysis using a peripheral vein over catheter directed thrombolysis.

21. In patients with COVID-19 and recurrent VTE despite anticoagulation with therapeutic weight adjusted LMWH (and documented compliance), we suggest increasing the dose of LMWH by 25% to 30%.

22. In patients with COVID-19 and recurrent VTE despite anticoagulation with apixaban, dabigatran, rivaroxaban or edoxaban (and documented compliance), or vitamin K antagonist therapy (in the therapeutic range) we suggest switching treatment to therapeutic weight-adjusted LMWH.

Background

In late December 2019, a novel beta coronavirus, the severe acute respiratory syndrome coronavirus 2, which causes coronavirus disease 2019 (COVID-19), was identified. It was officially declared a pandemic by the World Health Organization in March 2020.[1] Emerging evidence shows that severe COVID-19 can be complicated by coagulopathy. In the most severe cases, this manifests as disseminated intravascular coagulation (DIC), which is a pro-thrombotic condition with a high risk of VTE.[2]

The presence of DIC in these patients has been found to be a strong predictor of mortality. In a retrospective review of 183 consecutive patients with COVID-19 at a single institution, Tang et al[3] noted that 71.4% of nonsurvivors and 0.6% of survivors showed evidence of overt DIC (as defined by the validated International Society on Thrombosis and Haemostasis DIC score).

The literature also demonstrates that many patients with COVID-19 have highly abnormal D-dimer levels, which were also prognostic. The incidence of VTE in COVID-19 patients is not well defined, but early reports suggest it may be higher than in non-COVID hospitalized patients with similar degrees of illness, even in the presence of prophylactic anticoagulation.[4-15]

The mechanism for this is likely multifactorial. In fact, it could be argued that the lungs of patients with COVID-19 exhibit all components of Virchow's triad: hypercoagulable state, endothelial injury, and stasis of blood flow. High plasma levels of several proinflammatory cytokines (IL-2, IL-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A, and tumor necrosis factor-α) have been observed in COVID-19 patients admitted to the ICU.[2] As in other critical illnesses, this systemic cytokine storm triggers the coagulation system and a hypercoagulable state. There is also evidence of significant endothelial injury, as evidenced by reports of significantly elevated von Willebrand factor and Factor VIII levels.[16] Finally, severe COVID-19 is manifested as severe ARDS. Current evidence-based guidelines recommend positive-pressure ventilation with high levels of positive end-expiratory pressure and fluid restriction,[17] both of which may lead to decreases in pulmonary blood flow, leading to stasis and microthrombosis.

The recognition of the coagulopathy with COVID-19, and the early evidence that suggests that thrombosis in these patients is higher than that seen in similarly ill hospitalized patients with other respiratory infections, has led to the urgent need for practical guidance regarding prevention, diagnosis, and treatment of VTE. Current evidence in this specific population is lacking, but reports are emerging daily. The goal of this guidance statement is to review the current evidence that is available and, wherever possible, translate this into practical recommendations. Where this was not possible, the authors would like to remind readers that several well-done evidence-based guidelines regarding the management of patients with VTE and DIC in the non-COVID population exist and should direct patient care until robust trials can be completed in the COVID-19 population.[18-23] Given the rapidity with which new evidence is evolving, the authors consider this to be a living document with plans to update the guidance statements as appropriate.

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

Methods

The primary aim of this CHEST panel was to provide practical guidance on the most urgent questions regarding the prevention, diagnosis, and treatment of VTE in patients diagnosed with COVID-19. CHEST appointed a Chair for the panel (L. K. M.) who recruited panelists based upon their established expertise within the field of thromboembolism. The list of panelists was approved by CHEST leadership. All panel members were educated about the process and schedule. Formal conflict of interest review was not performed by the Professional Standards Committee given the timeline for the project, but all panelists were reminded that they would be required to disclose all relevant conflicts prior to voting and at the time of submission of the manuscript to the journal. The majority of panelists had no conflicts of interest to disclose. Two panelists (M. C. and G. L.) do not receive any personal honoraria and/or consulting fees but do receive funds that go directly to their institutional research fund. To reduce any perceived conflict, they abstained from voting on any statements that had overlap with their research or consulting relationships. Given the time-sensitive nature

TABLE 1] PICO Questions

Question	Population	Intervention	Comparator	Outcomes
Question 1	Patients with COVID-19	Standard dose UFH, LMWH, fondaparinux	Placebo	VTE, bleeding, mortality
Question 2	Patients with COVID-19	Intermediate dose anticoagulant thromboprophylaxis	Standard dose	VTE, bleeding, mortality
Question 3	Patients with COVID-19	Full (treatment dose) anticoagulant thromboprophylaxis	Standard or intermediate dose	VTE, bleeding, mortality
Question 4	Patients with COVID-19	Extended duration prophylaxis (45 days)	10 days (or duration of hospitalization)	VTE, bleeding, mortality
Question 5	Patients with COVID-19	Antiplatelet agent prophylaxis	No antiplatelet agent prophylaxis	VTE, bleeding, mortality
Question 6	Patients with COVID-19	Combined mechanical and chemical prophylaxis	Chemical prophylaxis	VTE, bleeding, mortality
Question 7	Patients with COVID-19 and objectively confirmed VTE	LMWH, fondaparinux, DOAC	UFH	Recurrent VTE, bleeding, mortality
Question 8	Patients with COVID-19 and objectively confirmed VTE	Thrombolytic therapy	Anticoagulation alone	Recurrent VTE, bleeding, mortality
Question 9	Patients with COVID-19 and objectively confirmed VTE while on standard or intermediate dose prophylaxis	125%-130% dose LMWH or UFH	Full dose UFH, LMWH, fondaparinux, DOAC	Recurrent VTE, bleeding, mortality
Question 10	Patients with COVID-19 and objectively confirmed VTE while on treatment dose anticoagulant	125%-130% dose LMWH or UFH	Full dose UFH, LMWH, fondaparinux, DOAC	Recurrent VTE, bleeding, mortality
Question 11	Patients with COVID-19	Routine screening ultrasound	No screening ultrasound	Symptomatic VTE
Question 12	Patients with COVID-19	Rapidly rising D-dimer	Standard elevated D-dimer	Sensitivity, specificity, false negative, false positive, efficiency
Question 13	Patients with COVID-19	Fibrinogen, PTT, PT, INR, TT, AT, FVIII, TEG, DIC score	D-dimer	Sensitivity, specificity, false negative, false positive, efficiency

COVID-19 = coronavirus disease 2019; DIC = disseminated intravascular coagulation; DOAC = direct oral anticoagulant; FVIII = Factor VIII; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PICO = Population, Intervention, Comparator, Outcome; PT = prothrombin time; PTT = partial thromboplastin time; TEG = thromboelastography; TT = thrombin time; UFH = unfractionated heparin.

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

of the topic amid the ongoing COVID-19 pandemic, the schedule spanned over a period of 3 weeks and included six conference calls to discuss topic and question development, literature evaluation using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology, discussion of suggested guidance statements, modified Delphi surveys, and manuscript development.

Question Development and Systematic search

The panel first proposed and shared questions of clinical interest via e-mail. The questions were then worded in the Population, Intervention, Comparator, Outcome (PICO) format, and each was discussed during the first conference call. Eighteen PICO questions were originally developed, but the panel chose to focus on 13 for this version of the guidance statement (Table 1). The panel was divided into pairs who each were assigned two or three PICO questions. The pairs then conducted comprehensive searches using MEDLINE via PubMed or Ovid, Embase, and Cochrane Controlled Register of Trials. Search strategy and the details of search results depicted in a PRISMA diagram for each PICO question are available in e-Appendix 1. Search strategies and inclusion criteria were broad given the anticipated low level of evidence at the time they were conducted.

Study Selection and Evidence Assessment

Screening and full text selection were performed in duplicate by the pairs. No meta-analyses or randomized controlled trials were available. Most of the evidence included retrospective cohorts and case series. Thus, none of the available direct and indirect literature provided sufficient evidence for the development of evidence tables or recommendations. The panel agreed that patients with COVID-19 appear to be a unique population with evolving evidence that their risk of thrombosis is higher than other hospitalized acutely ill medical or ICU patients. When this evidence was enough (albeit very low level) to adjust existing guideline statements, the panel made modifications to existing statements from CHEST guidelines.[19,20] When this was not possible, the panel simply applied existing guidance and adjusted the wording to this population. All of the statements in this document are thus expert opinion. When the perceived benefits outweighed perceived risks, the panel chose to "recommend" an intervention. When the balance of risk and benefit was less certain, the panel chose only to "suggest" an intervention.

Method for Achieving Consensus

Search results and suggestions written by the panel pairs for each PICO question were shared with all panel members. During a conference call, suggestions were reviewed and subsequently re-written based on panel input. This was followed by another conference call with 100% participation, soliciting additional comments and input. All panel members participated in the development of suggestions to be incorporated in the initial round of the modified Delphi survey. The modified Delphi technique is a widely accepted method for the development of consensus among experts.[24] To achieve consensus, an a priori decision was made to conduct up to three rounds of anonymous voting or until consensus was achieved (defined a priori as consensus agreement at $\geq$ 80% with a minimal response rate of 80%) for each draft recommendation, whichever came first. The survey incorporated the suggestions developed by all panelists and was developed and reviewed by the panel chair and sent to all panel members by a CHEST-designated project coordinator. The project coordinator tallied and reported the results of the survey to the group, and all votes were anonymous. The results of the survey were shared with all panel members and discussed via conference call. There was 100% survey participation from the members, and consensus was achieved on all statements. There were, however, several comments regarding clarification of wording and consistency. Following discussion and revision of statements, a second round of surveys was distributed, including 14 of the original 21 statements in which the panel clarified wording and remarks, and one new statement. There was 100% survey participation, and consensus was reached on all 22 statements in the second survey.

Results and Discussion

VTE Prevalence and Incidence in Hospitalized Patients With COVID-19

We found 11 studies that reported on VTE rates in patients diagnosed with COVID-19 (Table 2).[4-14,25] All 11 were observational reports at high risk for selection bias, and eight of 11 were retrospective. These studies included a total of 1,373 patients, the majority (800 [58.0%]) of whom were treated in an ICU. One other study reported 40% (407 of 1,099) of inpatients have a high risk for VTE by Padua risk score but did not report VTE rates.[26] This study, however, had major limitations (eg, 8% of patients had missing values for age, and missing values for other variables were not reported). Prevalence and incidence rates of TE are reported in Tables 3 and 4. Given the heterogeneity of the studies, we chose not to pursue a pooled analysis.

A qualitative review of the 11 studies reporting VTE prevalence and incidence is presented in Table 2. Patient selection procedures varied across studies and were often unclear. A detailed description of testing procedures was also lacking in most studies. Some studies reported only DVT.[4,12,14] Only five studies specified whether pulmonary embolism (PE) was subsegmental or more proximal,[5,6,9,10,13] and only three studies provided detailed information on DVT location.[6,9,10] Universal screening for events also varied across studies, and in many, outcomes were reported on patients still hospitalized. Average duration of hospitalization and/or the hospital day on which CT pulmonary angiography or lower extremity compression ultrasound was performed was variably reported. Lastly, thromboprophylaxis rates in Chinese hospitals are reported to be as low as 20% in some studies,[26,27] which affects interpretation of event rates in Chinese COVID-19 populations.

VTE Prevention

The panel first aimed to address the need for VTE prophylaxis in *acutely ill* hospitalized (general inpatient ward) and *critically ill* (ICU) patients with COVID-19.

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

TABLE 2] Characteristics of Studies Reporting on Prevalence or Incidence of VTE in Patients With COVID-19

Source	Study Design	Country	No. of Participating Centers	Peer-Review	Patient Selection	Thromboprophylaxis	Sample Size (ICU/Ward)	Age (y)	DVT Screening	Outcome Adjudication
Cui et al[4]	Retrospective cohort	China	1	Yes	Unclear	No	81/NA	Mean, 60	Yes	NR
Klok et al[6,7]	Retrospective cohort	The Netherlands	3	Yes	Consecutive ICU admissions	Nadroparin (weight-adjusted prophylactic dose)[a]	184/NA	Mean, 64	No	NR
Helms et al[5]	Prospective cohort	France	2	Yes	Consecutive ICU admissions	105/150 (70%) prophylactic heparin; 45/150 (30%) therapeutic heparin	150/NA	Median, 63	No	NR
Ranucci et al[25]	Prospective cohort	Italy	1	Yes	Unclear	Intermediate-dose nadroparin[b]	16/NA	Median, 61	NR	NR
Spiezia et al[12]	Prospective cohort	Italy	1	Yes	Consecutive ICU admissions	Anticoagulant prophylaxis	22/NA	Mean, 67	NR	NR
Llitjos et al[8]	Retrospective cohort	France	2	Yes	Consecutive ICU admissions	8/26 (31%) prophylactic heparin; 18/26 (69%) therapeutic heparin	26/NA	Median, 68	Yes	NR
Lodigiani et al[9]	Retrospective cohort	Italy	1	Yes	Consecutive hospital admissions	42/61(69%) prophylactic heparin; 17/61 (28%) weight-adjusted prophylactic heparin; 2/61 (3%) therapeutic heparin	61/327	Median, 66	No	NR
Poissy et al[11]	Retrospective cohort	France	1	Yes	Consecutive ICU admissions	NR[c]	107/NA	Median, 57	NR	NR
Thomas et al[13]	Retrospective cohort	United Kingdom	1	Yes	Consecutive ICU admissions	Weight-adjusted heparin at prophylactic dose	63/NA	Mean, 59	No	NR
Middeldorp et al[10]	Retrospective cohort	The Netherlands	1	Yes	Consecutive hospital admissions	Nadroparin (weight-adjusted prophylactic dose)[d,e]	75/123	Mean, 61	Partly[f]	Yes

(Continued)

TABLE 2] (Continued)

Source	Study Design	Country	No. of Participating Centers	Peer-Review	Patient Selection	Thromboprophylaxis	Sample Size (ICU/Ward)	Age (y)	DVT Screening	Outcome Adjudication
Xu et al[14]	Retrospective cohort	China	1	No	Unclear	Anticoagulant prophylaxis in at-risk population[g]	15/123	Mean, 52	Partly[h]	NR

NA = not applicable; NR = not reported. See Table 1 legend for expansion of other abbreviation.
[a]During the study period, the dose of thromboprophylaxis with nadroparin was doubled in 2 of 3 participating centers; 17 of 184 (7.2%) patients were on therapeutic anticoagulation at admission.
[b]Nadroparin 4,000 units twice daily, which was increased to nadroparin 6,000 units twice daily (or 8,000 units twice daily if BMI > 35 kg/m^2) in all patients after performance of coagulation and viscoelastic tests.
[c]Of the patients with pulmonary embolism, 20 received prophylactic heparin, 1 therapeutic heparin, and 1 vitamin K antagonist with therapeutic INR at time of diagnosis.
[d]Seven of 75 (9.3%) patients in the ICU and 12 of 123 (10%) patients on the ward continued therapeutic anticoagulation for an indication that was present at time of admission; none of those patients developed a VTE.
[e]During the study period, the dose of thromboprophylaxis with nadroparin was doubled for patients admitted to the ICU.
[f]Screening ultrasound for lower extremity DVT was performed in 38 of 75 (51%) critically ill patients and 17 of 123 (14%) patients on the ward.
[g]Patients with a Padua score ≥ 4 points were considered at risk for VTE; "routine thromboprophylaxis" was given to 15 of 15 (100%) ICU patients and 26 of 123 (21%) ward patients.
[h]Screening ultrasound for lower extremity DVT was performed in all critically ill patients; no screening was performed in patients on the ward.

Our search identified three single-center studies reporting estimates for the incidence of VTE in acutely ill hospitalized patients (Tables 2 and 4).[9,10,14] None of the studies allows for comparison between anticoagulant thromboprophylaxis and placebo, or comparison between different drugs or doses. The majority of patients included in those studies received anticoagulant thromboprophylaxis at prophylactic or higher dose. Lodigiani et al[9] reported a cumulative incidence of venous and arterial thromboembolic events of 6.6% during hospital admission. A total of 2.4% of the patients developed a PE, and 0.9% of the patients were diagnosed with a symptomatic isolated proximal DVT of the lower extremities. As reported by Middeldorp et al, [10] the cumulative incidence of symptomatic VTE was 9.2% at 14 days, comprising one patient with proximal PE, one patient with subsegmental PE, and two patients with distal DVT. Xu et al[14] reported confirmation of DVT in one of 123 (0.8%) patients on the ward.

Noteworthy, most COVID-19 patients would have been eligible for at least one of the three landmark randomized controlled trials of anticoagulant thromboprophylaxis in acutely ill medical inpatients.[28-30] In these studies, the proportion of patients who developed symptomatic VTE or any VTE at 14 to 21 days was 0.3% to 1.0% and 2.8% to 5.6%, respectively.[28-30] Because the incidence of VTE in acutely ill medical inpatients is too low (below 1% without thromboprophylaxis) to justify anticoagulant thromboprophylaxis—and incurred risk of bleeding—in every patient,[19] several risk stratification scores have been developed to identify medical inpatients at higher risk of VTE. The Padua and IMPROVE risk scores are the most extensively validated scores[31,32] but both showed heterogeneous discriminatory performance in external validation studies[32-41] and they lack validation in an impact study. Considering that hospitalized patients with COVID-19 are confined to their room, immobilization, a major risk factor for VTE in medical inpatients,[42] affects many inpatients with COVID-19. Infectious disease is an additional risk factor for VTE,[42] which is present in all patients with COVID-19. Taking into account those risk factors and that the current estimates of the incidence of VTE in non-critically ill patients with COVID-19 is well above 1% even on anticoagulant thromboprophylaxis, the panel considers all hospitalized patients with COVID-19 at increased risk of VTE. We therefore suggest against individualized

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

TABLE 3] Prevalence or Incidence of VTE in Critically Ill Patients With COVID-19

Source	Follow-up Duration	Patients Still Admitted at Study End	Isolated Leg DVT	Isolated Proximal Leg DVT	PE ± DVT	Proximal PE ± DVT	Major Bleeding	Mortality
Cui et al[4]	NR	NR	20/81 (25%)	NR	NR	NR	NR	8/81 (10%)
Klok et al[6,7]	Median, 14 days	65/184 (35%)	1/184 (0.5%)	1/184 (0.5%)	65/184 (35%)	46/184 (25%)	NR	41/184 (22%)
Helms et al[5]	Mean, 9.6 days	100/150 (67%)	3/150 (2.0%)	NR	25/150 (17%)	22/150 (15%)	4/150 (2.7%)	13/150 (8.7%)
Ranucci et al[25]	NR	3/16 (19%)	0	0	0	0	NR	7/16 (44%)
Spiezia et al[12]	NR	NR	5/22 (23%)	NR	NR	NR	NR	NR
Llitjos et al[8]	NR	7/26 (27%)	14/26 (54%)[a]	NR	6/26 (23%)[b]	NR	NR	3/26 (12%)
Lodigiani et al[9]	Median, 18 days	13/61 (21%)	1/61 (1.6%)	Unclear[c]	2/61 (3.3%)	NR	NR	NR[d]
Poissy et al[11]	NR	22/107 (21%)	2/107 (1.9%)	NR	22/107 (21%)	Unclear	NR	15/107 (14%)
Thomas et al[13]	Median, 8 days	28/62 (45%)	0	0	5/62 (8.1%)	4/62 (6.5%)	NR	10/62 (16%)
Middeldorp et al[10]	Median, 15 days	NR[e]	23/75 (31%)	14/75 (19%)	11/75 (15%)	10/75 (13%)	NR	NR[f]
Xu et al[14]	NR	NR	3/15 (20%)	NR	NR	NR	NR	NR

PE = pulmonary embolism. See Table 1 and 2 legends for expansion of other abbreviations.
[a]Six patients on thromboprophylaxis at prophylactic doses; 7 on thromboprophylaxis at therapeutic doses, thromboprophylaxis dose for 1 patient not reported.
[b]Six of 14 patients on thromboprophylaxis at therapeutic doses.
[c]Inconsistent reporting of distal vs proximal DVT in published article.
[d]In the entire study population, 92 of 388 (24%) patients died.
[e]In the entire study population, 16 of 198 (8%) patients were still admitted at time of data analysis.
[f]In the entire study population, 38 of 198 (19%) patients died.

TABLE 4] Prevalence or Incidence of VTE in Acutely Ill Hospitalized Patients With COVID-19

Source	Follow-up Duration	Patients Still Admitted at Study End	Isolated Leg DVT	Isolated Proximal Leg DVT	PE ± DVT	Proximal PE ± DVT	Major Bleeding	Mortality
Lodigiani et al[9]	Median, 9 days	13/327 (4%)	4/327 (1.2%)	3/327 (0.9%)	8/327 (2.4%)	NR	NR	NR[a]
Middeldorp et al[10]	Median, 4 days	NR[b]	2/123 (1.6%)	0/124	2/123 (1.6%)	1/123 (0.8%)	NR	NR[c]
Xu et al[14]	NR	NR	1/123 (0.8%)	NR	NR	NR	NR	NR

See Table 1, 2, and 3 legends for expansion of abbreviations.
[a]In the entire study population, 92 of 388 (24%) patients died.
[b]In the entire study population, 16 of 198 (8%) patients were still admitted at time of data analysis.
[c]In the entire study population, 38 of 198 (19%) patients died.

VTE risk assessment and suggest anticoagulant thromboprophylaxis in all hospitalized patients with COVID-19 in the absence of contraindications.

1. In the absence of contraindications, in acutely ill hospitalized patients with COVID-19, we suggest anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis.

Our search identified 11 studies providing estimates for the incidence or prevalence of VTE in critically ill patients with COVID-19 (Table 2 and 3).[4-14,25] None of the studies allows for comparison between anticoagulant thromboprophylaxis and placebo, or comparison between different drugs. The proportion of critically ill patients with COVID-19 diagnosed with VTE on at least standard dose anticoagulant thromboprophylaxis ranged from 0% to 54%[5-14,25]; the reported cumulative incidence of VTE during hospital stay ranged from 20% to 59%.[7,10,11,13] One single-center retrospective cohort study of 449 patients hospitalized in the Tongji Hospital in Wuhan suggests that heparin at prophylactic dose is associated with an absolute mortality reduction of 24% in patients with sepsis-induced coagulopathy (SIC) compared with no anticoagulant thromboprophylaxis.[27] No mortality difference was shown in patients who were less sick. Considering that low-molecular-weight heparin (LMWH) at prophylactic doses did not reduce mortality in a randomized placebo-controlled trial in critically ill patients with COPD,[43] the mortality difference in sick patients with COVID-19 appears striking. However, the study has several major limitations. A total of only 22% of the patients received thromboprophylaxis; thromboprophylaxis was defined as the use of heparin $\geq$ 7 days, which may have introduced immortal time bias; and the analysis was not adjusted for other potential confounders.

In critically ill medical patients without COVID-19, the failure rate of anticoagulant thromboprophylaxis in randomized controlled trials ranged from 6% to 16%.[43-45] The incidence of VTE in cohort studies of critically ill medical patients varies depending on patient population.[19] Pooled risk estimates for benefits and harms of anticoagulant thromboprophylaxis in critically ill medical patients without COVID-19 differ across meta-analyses,[19,22,46] but practice guidelines consistently recommend anticoagulant thromboprophylaxis with LMWH (or unfractionated heparin [UFH]) over no such therapy.[19,22] We recommend anticoagulant thromboprophylaxis in all

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

critically ill patients with COVID-19, because current evidence suggests that the failure rate of thromboprophylaxis in critically ill patients with COVID-19 seems higher than in randomized controlled trials assessing anticoagulant thromboprophylaxis in critically ill medical patients without COVID-19 and at least as high as the failure rate in prospective cohort studies of critically ill patients with severe sepsis or septic shock.[47]

2. In the absence of contraindications, in critically ill patients with COVID-19, we recommend anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis.

Choice of Agent: We did not identify any studies allowing for comparisons between different anticoagulants for thromboprophylaxis in acutely ill hospitalized patients with COVID-19. LMWH, UFH, fondaparinux, and direct oral anticoagulants (DOACs) have each been assessed in randomized trials of thromboprophylaxis in acutely ill hospitalized patients without COVID-19.[22] Compared with placebo, parenteral anticoagulant thromboprophylaxis with LMWH or fondaparinux reduces the risk of symptomatic PE and any DVT.[22] Pooled results indicate no statistically significant difference in symptomatic DVT, major bleeding, or mortality.[22] No difference in critical outcomes have been shown in randomized trials comparing LMWH and UFH; no randomized study compared fondaparinux with LMWH/UFH.[22] Compared with LMWH, DOACs do not reduce the risk of PE or symptomatic DVT but are associated with an increased risk of major bleeding (relative risk [RR], 1.70; 95% CI, 1.02-2.82).[48] Therefore, the panel recommends using LMWH, fondaparinux, or UFH over the use of DOACs in acutely ill hospitalized patients with COVID-19. Considering the reduced nursing staff exposure with LMWH or fondaparinux due to the once-daily administration and the possibly lower risk of heparin-induced thrombocytopenia with LMWH or fondaparinux compared with UFH, we suggest LMWH or fondaparinux over UFH in acutely ill hospitalized patients with COVID-19.

3. In acutely ill hospitalized patients with COVID-19, we suggest anticoagulant thromboprophylaxis with LMWH or fondaparinux over anticoagulant thromboprophylaxis with UFH; and we recommend anticoagulant thromboprophylaxis with LMWH, fondaparinux or UFH over anticoagulant thromboprophylaxis with a DOAC.

Remarks: The panel favors LMWH and fondaparinux over UFH to limit staff exposure. The panel cautions against the use of DOACs in these patients secondary to the high risk of rapid clinical deterioration in these patients. In addition, it is likely that many of these patients will be receiving concomitant therapy (antiviral agents or other investigational treatments) that can significantly affect the pharmacodynamics of and thus bleeding risk associated with the DOACs.

We did not identify any studies allowing for comparisons between different anticoagulants for thromboprophylaxis in critically ill patients with COVID-19. LMWH and UFH are the only anticoagulants which have been assessed in randomized trials of thromboprophylaxis in critically ill patients without COVID-19. The panel therefore recommends using LMWH or UFH over other options such as fondaparinux or DOAC. Pooled results of three randomized controlled trials indicate no difference between LMWH and UFH in symptomatic DVT, major bleeding, or mortality.[19,22] The Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) of 3,746 critically ill patients showed a lower risk of symptomatic PE with dalteparin 5,000 units daily compared with UFH 5,000 units twice daily (hazard ratio, 0.51; 95% CI, 0.30-0.88).[44] Even though this difference was only driven by 19 events, the panel suggests LMWH over UFH for critically ill patients with COVID-19, because LMWH has the additional advantages over UFH that it has a potential lower risk of heparin-induced thrombocytopenia and that it requires fewer nursing staff contact given its once-daily administration regimen.

4. In critically ill patients with COVID-19, we suggest anticoagulant thromboprophylaxis with LMWH over anticoagulant thromboprophylaxis with UFH; and we recommend anticoagulant thromboprophylaxis with LMWH or UFH over anticoagulant thromboprophylaxis with fondaparinux or a DOAC.

Remarks: The panel favors LMWH over UFH to limit staff exposure. The panel strongly cautions against the use of DOACs in critically ill patients secondary to their hemodynamic instability, the high likelihood of drug-drug interactions, and the high incidence of acute kidney injury in these patients. In addition, there is a lack of evidence for anticoagulant thromboprophylaxis even in non-COVID critically ill patients.

Our literature search did not identify any randomized trials assessing the efficacy and safety of aspirin (or any

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

other antiplatelet agent) for VTE prophylaxis in COVID-19 patients requiring hospitalization. Due to the absence of direct evidence, the guideline panel decided to consider indirect evidence available from systematic reviews of randomized controlled trials conducted in non-COVID-19 patients. The Antiplatelet Trialists' Collaboration produced a detailed overview of randomized trials to determine the efficacy of antiplatelet therapy for VTE prophylaxis. They reported a modest reduction in the odds of having detectable DVT in high-risk medical patients.[49] In contrast, systematic reviews have shown that heparins reduce the risk for developing PE (RR, 0.59; 95% CI, 0.45-0.78), symptomatic proximal DVT (RR, 0.28; 95% CI, 0.06-1.37), and symptomatic distal DVT (RR, 0.75; 95% CI, 0.17-3.34).[22] Based on indirect comparisons, we expect the net benefit of anticoagulant thromboprophylaxis in COVID-19 patients requiring hospitalization to be substantially greater than the benefits of aspirin thromboprophylaxis. Consequently, we do not consider antiplatelet agents a reasonable alternative to anticoagulant prophylaxis in these patients for VTE events.

5. In critically ill or acutely ill hospitalized patients with COVID-19, we recommend against the use of antiplatelet agents for VTE prevention.

Dosing Regimen for Anticoagulant Thromboprophylaxis: We found no studies that reported a comparison of one specific anticoagulant thromboprophylaxis regimen to another. One retrospective study reported a reduction in mortality with heparin at prophylactic doses (most were on 40-60 mg enoxaparin per day) compared with no prophylaxis in a highly select group of ICU patients.[27] This study suffers from confounding by indication for prophylaxis and lack of adjustment for co-factors in the specific analysis that found a mortality difference with heparin. For all comers in this study, there was no mortality difference related to heparin prophylaxis. In a single-center retrospective study of 2,773 patients, of whom 786 (28%) received therapeutic anticoagulation, in-hospital mortality was similar between anticoagulated and non-anticoagulated patients (22.5% vs 22.8%).[50] Among patients who were mechanically ventilated, in-hospital mortality was lower in patients who received anticoagulation (29%, median survival of 21 days) than in those who did not receive anticoagulation (63%, median survival of 9 days). In a multivariable Cox proportional hazards model, longer duration of therapeutic anticoagulation was associated with a reduced risk of mortality. The risk of major bleeding was 3% and 1.9% in anticoagulated and non-anticoagulated patients, respectively. Of note, pulmonary hemorrhage was not part of the definition of major bleeding, and the incidence of VTE was not reported. While this study is hypothesis-generating and supports the rationale for randomized controlled trials evaluating thromboprophylaxis at therapeutic doses, it should not inform patient management due to its limitations. First, the authors did not specify anticoagulant agents, the indication for anticoagulation, and whether non-anticoagulated patients did receive anticoagulant thromboprophylaxis. Second, the results may be flawed by immortal time bias, confounding by indication, and other residual confounding. Finally, the median duration of anticoagulation was 3 days, which challenges the biological plausibility of the large mortality reduction observed among patients who were mechanically ventilated.

Several studies provide data that are indirectly relevant. A retrospective, observational report on 16 ICU patients (all mechanically ventilated and diagnosed with ARDS) reported no VTE events in patients who had VTE anticoagulant thromboprophylaxis titrated to serum coagulation studies and adjusted for BMI.[25] They used LMWH, anti-thrombin concentrate, and clopidogrel, and there is no report on bleeding rates. Several other studies report high VTE rates despite standard prophylaxis in critically ill COVID-19 patients.[6,12,14]

Because all identified studies of VTE rates and anticoagulant thromboprophylaxis regimens for hospitalized COVID-19 patients are observational with select populations, definitive interpretation is difficult. It seems that critically ill, intubated patients with COVID-19 can develop a profound coagulopathy and form clot at a high rate despite prophylaxis. While adjusting prophylaxis by coagulation studies seems reasonable, specific protocols have not been systematically studied nor bleeding rates reported. Of note, several studies have reported critically ill COVID-19 patients are at high risk for bleeding based on the IMPROVE bleeding risk score.[14,26] Until we have more data, an accurate risk-benefit assessment of VTE vs bleeding, particularly with increasing anticoagulant thromboprophylaxis above standard dosing, is not possible.

A recent guideline reviewed the data on SIC and DIC in non COVID-19 patients.[23] The authors noted that SIC/DIC can lead to a pro-thrombotic coagulopathy. They concluded that adjustment to standard anticoagulant

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

thromboprophylaxis in the presence of SIC/DIC remains controversial but could be considered. Whether COVID-19 induces a different or more profound type of SIC/DIC remains unknown, but even if one assumes it is similar to non-COVID-19 SIC/DIC, the optimal approach to anticoagulant thromboprophylaxis is uncertain.

6. In acutely ill hospitalized patients with COVID-19, we recommend current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

Remarks: Although there has been some concern for increased risk of VTE in hospitalized COVID-19 patients, there is insufficient data to justify increased intensity anticoagulant thromboprophylaxis in the absence of randomized controlled trials.

7. In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

Remarks: Although there is anecdotal and observational data that suggest an increased VTE risk in critically ill patients with COVID-19, it is not clear if the most severely ill COVID-19 patients occupy a different level of risk for VTE than other severely ill nonsurgical, medical ICU patients. There are also insufficient data regarding bleeding risk in this population, and given severity of illness, it may be just as likely that critically ill COVID-19 patients are at high risk of adverse bleeding complications. Finally, it is not clear that this population has a higher risk of VTE when treated with standard doses of anticoagulant thromboprophylaxis per existing guidelines.

Duration of Thromboprophylaxis: Our search identified no study reporting incidence of VTE or major bleeding after hospital discharge in patients with COVID-19. In non-COVID patients, a significant proportion of VTE events associated with hospitalization occur after discharge.[28-30,51] Anticoagulant thromboprophylaxis up to 45 days after discharge reduces the risk of VTE following hospital admission (RR, 0.61; 95% CI, 0.44-0.83) but increases the risk of major bleeding (RR, 2.04; 95% CI, 1.42-2.91).[52] A post hoc analysis of the MAGELLAN trial suggests that extended thromboprophylaxis is associated with a net benefit in patients at high risk of VTE as per modified IMPROVE score and low risk of bleeding (ie, absence of active cancer, dual antiplatelet therapy, history of bronchiectasis or pulmonary cavitation, active gastroduodenal ulcer, or any bleeding in the previous 3 months).[53] However, in the MARINER trial of 12,069 patients at risk of VTE as per modified IMPROVE score, rivaroxaban 10 mg daily for 45 days after hospital discharge did not reduce symptomatic VTE.[54] The 2018 Q17 American Society of Hematology practice guideline recommends against the use of extended thromboprophylaxis, because they determined a net harm associated with extended thromboprophylaxis.[22] Many hospitalized patients with COVID-19 would likely have been eligible for randomized controlled trials assessing extended thromboprophylaxis, and it appears therefore justified to extrapolate relative treatment effects from those studies to hospitalized patients with COVID-19. Assuming that patients with COVID-19 incur the same risk of bleeding as patients without COVID-19 at high risk of VTE (ie, 0.7% at 35 days after discharge without extended thromboprophylaxis in patients at low risk of bleeding)[53] and that symptomatic VTE is associated with a similar burden to patients as major bleeding,[22] the panel suggests that extended thromboprophylaxis would result in a net benefit in patients with COVID-19 at low bleeding risk, if the risk of symptomatic VTE would be above 1.8% at 35 to 42 days after hospital discharge. Despite evidence suggesting a higher risk of VTE during hospitalization in patients with COVID-19 than in patients without COVID-19, the panel recommends only inpatient anticoagulant thromboprophylaxis, because post-discharge VTE and major bleeding rates in COVID-19 patients are currently unknown.

8. In patients with COVID-19, we recommend inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge.

Remarks: Extended thromboprophylaxis in patients with COVID-19 at low risk of bleeding should be considered, if emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis. See text for assumptions indicating net benefit.

Role of Mechanical Prophylaxis: We were unable to identify any studies that reported on mechanical methods for prophylaxis in COVID-19 patients. While it may seem reasonable to add mechanical to pharmacological prophylaxis in patients thought to be at high baseline risk for VTE, a recent randomized

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

controlled trial found no benefit to this approach.[55] Therefore, it seems unlikely that mechanical, in addition to pharmacological, prophylaxis will affect VTE rates in critically ill patients with COVID-19.

9. In critically ill patients with COVID-19, we suggest against the addition of mechanical thromboprophylaxis to pharmacological thromboprophylaxis.

Remarks: Although there is no evidence supporting the combination of mechanical and chemical thromboprophylaxis for patients with COVID-19 who are critically ill, it is not likely that adding mechanical prophylaxis in this population would cause major harm. We recommend that providers adhere to existing guidance regarding the use of mechanical thromboprophylaxis.

10. In critically ill patients with COVID-19 who have a contraindication to pharmacological thromboprophylaxis, we suggest the use of mechanical thromboprophylaxis.

Diagnosis of VTE

Role of Screening Ultrasound: Screening ultrasound for asymptomatic DVT is not routinely performed in critically ill patients. Lower extremity ultrasound is reserved for critically ill patients with a clinical suspicion for VTE. General screening ultrasound carries an increased risk of personnel exposure and resource utilization during the COVID-19 pandemic. As we have noted, there is growing evidence to suggest that patients with COVID-19 are at an increased risk of VTE events.[6,56] This risk is exacerbated in critically ill ICU patients compared with those on a general medical ward.[9,10] Middeldorp et al[10] reported an increased incidence of venous thrombosis in ICU (32%) vs non-ICU patients (1.6%). Lodigiani et al[9] reported similar venous thrombosis rates in ICU (4.16%) vs non-ICU patients (1.27%). Cui et al[4] suggested a 25% (20 of 81 ICU patients) rate of DVTs in their critically ill cohort, but none of the patients in the study were on pharmacological thromboprophylaxis. We found inconsistent methods of ultrasound screening in COVID-19 patients. In the study by Middeldorp et al,[10] ultrasound was performed every 5 days in ICU patients, and 10 days prior to data analysis in cross-sectional fashion for general ward patients. In a second study by Llitjos et al,[8] screening ultrasound was performed at the time of ICU admission (between day 1 and 3) and then at day 7. We therefore suggest against routine screening, but suggest a low threshold for performing lower extremity ultrasound or full body ultrasound in COVID-19 patients who experience abrupt hypoxemia or clinical deterioration. Tables 3 and 4 summarize the reported DVT incidence in the published literature.

11. In critically ill COVID-19 patients, we suggest against routine ultrasound screening for the detection of asymptomatic DVT.

Remarks: Although we suggest against a routine screening ultrasound for critically ill COVID-19 patients, we note that clinicians should have a low threshold for performing ultrasound in patients with a reasonable degree of clinical suspicion for VTE. Lower extremity ultrasound should also be part of point of care ultrasound (POCUS), particularly in situations like unexplained right ventricular dysfunction, unexplained/refractory hypoxemia or in patients with suspected PE who are unable to undergo a diagnostic study (ie, unstable for transport or advanced renal failure). It should be noted that even if clot is not visualized on lower extremity ultrasound, PE is not fully excluded.

Role of D-Dimer and Other Biomarkers in the Diagnosis of VTE: Currently, there are few studies that have evaluated either D-dimer levels, at a single cut point value or using dynamic change, or other laboratory values, to predict a diagnosis of VTE in patients with COVID-19. The lack of systematic surveillance for DVT and PE has severely limited the ability to establish a meaningful context for biomarkers.

Two studies described biomarkers, including D-dimer, in relationship to VTE diagnosis but did not describe systematic evaluation for suspected VTE which must be employed to understand sensitivity and specificity.[4,6] Cui et al[4] reported only DVT rather than DVT and PE, which further brings to question which diagnostic procedure was employed as venous ultrasound cannot be employed in isolation to diagnose PE. Furthermore, it was not clear what diagnostic imaging was employed and if imaging was triggered by clinical parameters or as screening as only DVTs were found. The study suggested a 94% negative predictive value for D-dimer cutoff of 1.0 μg/mL but did not compare vs other biomarkers which correlated with VTE.[4] They also reported that other laboratory markers correlated with increased risk of VTE, including the activated partial thromboplastin time (aPTT) and lymphocyte count, but did not evaluate single cut points or trending values. Klok et al[6] did not report on D-dimer levels but noted that prolongation of the prothrombin time > 3 seconds

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

or the aPTT > 5 seconds were independently predictors of VTE. Again, the VTE surveillance was not well described.

Tang et al[3] did not report on VTE incidence but noted derangement in coagulation and clotting markers (prothrombin time, aPTT, D-dimer, and fibrin degradation products) were higher in non-survivors. Dramatic increase of D-dimer also correlated with increase in all-cause mortality. It may follow that thrombosis is a major contributor to increase in all-cause mortality, as survival improved when patients received parenteral anticoagulation.[27] In conclusion, there is insufficient data to guide clinical practice for VTE diagnosis based on laboratory values. We suggest as in other inpatient populations biomarkers not be employed in the diagnostic evaluation for suspected DVT or PE.

VTE Treatment

Our literature search did not identify any randomized trials assessing the efficacy and safety of anticoagulants for the treatment of acute VTE in hospitalized or critically ill COVID-19 patients.

Although clinical practice guidelines recommend the use of DOACs for the vast majority of patients with acute symptomatic VTE,[20,21] there are reasons to make different suggestions for the preferred anticoagulant in patients with COVID-19, particularly for the critically ill: 1) many of these patients require administration of inhibitors or inducers of P-glycoprotein or strong inhibitors or inducers of cytochrome P450 enzymes. Treatment with potent P-glycoprotein inhibitors (eg, antiretrovirals, azithromycin, others) was an exclusion criterion in most landmark randomized trials that assessed the efficacy and safety of DOACs in patients with acute VTE.[57-60] A recent study enrolled 12 consecutive patients on DOACs who were hospitalized with severe COVID-19.[61] For each patient, C-trough DOAC level was compared with the one measured before hospitalization. On average, C-trough levels were six times higher during hospitalization than in the pre-hospitalization period; 2) GI dysfunction is a common problem in the critically ill patient, and can significantly affect the pharmacokinetics of oral drugs; and 3) acute renal failure is also common in the setting of critical illness, and DOACs are contraindicated in patients with severe (eg, creatinine clearance < 30 mL/min) renal failure. For these reasons, the panel endorsed that in critically ill COVID-19 patients with proximal DVT or PE, parenteral anticoagulation might be preferred to oral anticoagulant therapy.

Unfractionated heparin has an unpredictable dose response and a narrow therapeutic window; therefore, monitoring is essential to ensure optimal efficacy and safety. Alternatively, LMWHs and fondaparinux have more predictable pharmacokinetics and a greater bioavailability than UFH. Due to these pharmacologic features, body weight-adjusted doses of LMWH or fondaparinux can be administered subcutaneously without laboratory monitoring in the majority of these patients. UFH, not LMWH, can be affected by the phenomenon of heparin resistance which can "pseudo," in which the aPTT does not reflect the anti-Xa effect (best managed by avoiding the aPTT and monitoring by anti-Xa levels), and true resistance in which case acute phase reactants common in inflammatory states increase UFH clearance and can greatly increase the doses required. The former situation is common with elevated Factor VIII levels, common in COVID-19 patients. The latter situation may delay attainment of therapeutic levels of anticoagulation, which is highly undesirable in an acute VTE situation.[62,63] Based on this, and to avoid risk of exposure for staff, we suggest that LMWH or fondaparinux be used over UFH in critically ill COVID-19 patients with proximal DVT or PE. UFH might be preferred over LMWH or fondaparinux in patients at high bleeding risk (including those with severe renal failure [creatinine clearance < 30 mL/min]), or in those with overt or imminent hemodynamic decompensation due to PE, in whom primary reperfusion treatment may be necessary). Outpatients with COVID-19 and acute PE have not been described, but the approach to these patients can follow existing guidelines. Patients with VTE in the setting of COVID-19 are considered to have a provoking factor, and thus initial treatment should be for at least 3 months.

12. For acutely ill hospitalized COVID-19 patients with proximal DVT or PE, we suggest initial parenteral anticoagulation with therapeutic weight adjusted LMWH or intravenous UFH. The use of LWMH will limit staff exposure and avoid the potential for heparin pseudo-resistance. In patients without any drug-to-drug interactions, we suggest initial oral anticoagulation with apixaban or rivaroxaban. Dabigatran and edoxaban can be used after initial parenteral anticoagulation. Vitamin K antagonist therapy can be used after overlap with initial parenteral anticoagulation.

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

Remarks: The panel has downgraded the most recent ACCP recommendation regarding the use of oral anticoagulants in patients hospitalized with COVID-19 secondary to the high risk of rapid clinical deterioration in these patients. In addition, it is likely that many of these patients will be on concomitant therapy (antiviral agents or other investigational treatments) that can significantly affect the pharmacodynamics of and bleeding risk associated with the DOACs. Thus, LMWH or UFH are favored over oral anticoagulants.

13. For outpatient COVID 19 patients with proximal DVT or PE and no drug-to-drug interactions, we recommend apixaban, dabigatran, rivaroxaban or edoxaban. Initial parenteral anticoagulation is needed before dabigatran and edoxaban. For patients who are not treated with a direct oral anticoagulant, we suggest vitamin K antagonists over LWMH (for patient convenience and comfort). Parenteral anticoagulation needs to be overlapped with vitamin K antagonists.

14. In critically ill COVID-19 patients with proximal DVT or PE, we suggest parenteral over oral anticoagulant therapy. In critically ill COVID-19 patients with proximal DVT or PE who are treated with parenteral anticoagulation, we suggest LMWH or fondaparinux over UFH.

Remarks: UFH might be preferred over LMWH or fondaparinux in patients at high bleeding risk (including those with severe renal failure), or in those with overt or imminent hemodynamic decompensation due to PE, in whom primary reperfusion treatment may be necessary. The decision to use UFH should be balanced with the risks associated with extra staff exposure and issues with heparin resistance as above.

15. For COVID 19 patients with proximal DVT or PE, we recommend anticoagulation therapy for a minimum duration of three months.

Thrombolytic Therapy: Our literature search did not identify any randomized trials or prospective cohort studies assessing the efficacy or safety of any thrombolytic therapies for the management of critically ill patients with COVID-19 without objective evidence of VTE and VTE-associated hypotension. This includes either systemic delivery or catheter-directed thrombolysis.

Due to the absence of direct evidence, the guideline panel decided to consider indirect evidence from another population of patients receiving thrombolysis. In a randomized trial of normotensive patients without COVID-19 but with objectively confirmed PE and right heart strain, systemic thrombolysis was associated with major bleeding in 11.5% of patients.[64] The risk of major bleeding has not been systematically assessed during COVID-19. Diffuse alveolar damage[15] and frank alveolar hemorrhage have been identified in autopsy specimens from COVID-19 patients,[65] suggesting that bleeding risk could be high. Therefore, we recommend against thrombolytic therapy in COVID-19 patients without objectively confirmed PE and PE-induced hypotension (systolic BP $<$ 90 mm Hg or BP drop $\geq$ 40 mm Hg lasting for longer than 15 minutes).[20,21]

Patients with objectively confirmed PE who are normotensive represent a wide spectrum of disease. Some are very low risk of adverse outcome. Others are at the more severe end of the spectrum and may present with signs, imaging, or laboratory markers that suggest the presence of right ventricular dysfunction. As we have stated in earlier CHEST Guidelines,[20] these patients should be monitored closely for signs of deterioration. Clearly patients who develop hypotension meet criteria for thrombolytic therapy. Deterioration that has not resulted in frank hypotension may also prompt the use of thrombolytic therapy (progressive increase in heart rate, progressive decrease in systolic BP, an increase in jugular venous pressure, worsening gas exchange, signs of shock, progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers). This recommendation was based on the trial by Meyer et al,[64] in which almost 90% of patients with intermediate risk PE who received rescue thrombolysis survived.

None of the existing scores for assessing bleeding risk in patients with VTE have been studied or validated in patients with COVID-19. Until recently, we lacked any scores that were derived specifically from patients being treated with anticoagulants for VTE. Thus, we cannot recommend a specific risk score in patients with COVID-19. Several risk scores have been suggested, and many of the variables overlap between scores. We suggest that providers rely on institutional methods for assessing bleeding risk and would refer the reader to items noted to be associated with increased risk of bleeding as outlined in the most recent CHEST Guidelines[20] (age, previous bleeding, cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, poor anticoagulant control, comorbidities, recent surgery,

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

frequent falls, alcohol abuse, non-steroidal antiinflammatory use).

16. In most patients with COVID-19 and acute, objectively confirmed PE not associated with hypotension (systolic blood pressure < 90 mm Hg or blood pressure drop of ≥ 40 mm Hg lasting longer than 15 minutes), we recommend against systemic thrombolytic therapy.

Remarks: Please see statement 18 for the select patients that may require systemic thrombolysis.

17. In patients with COVID-19 and both acute, objectively confirmed PE and hypotension (systolic BP < 90 mm Hg) or signs of obstructive shock due to PE, and who are not at high risk of bleeding, we suggest systemically administered thrombolytics over no such therapy.

18. In patients with COVID-19 and acute PE with cardiopulmonary deterioration due to PE (progressive increase in heart rate, a decrease in systolic BP which remains > 90 mm Hg, an increase in jugular venous pressure, worsening gas exchange, signs of shock (eg, cold sweaty skin, reduced urine output, confusion), progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers) after initiation of anticoagulant therapy who have not yet developed hypotension and who have a low risk of bleeding, we suggest systemic thrombolytic therapy over no such therapy.

19. We recommend against the use of any advanced therapies (systemic thrombolysis, catheter-directed thrombolysis or thrombectomy) for most patients without objectively confirmed VTE.

Remarks: Thrombolysis may be considered in select patients when cardiac arrest is suspected to be caused by PE and imaging is not obtainable. We would suggest that providers consider the differential of right ventricular strain (preexisting pulmonary hypertension, high positive end-expiratory pressure, severe ARDS) before entertaining the use of empiric thrombolysis.

20. In those patients with COVID-19 receiving thrombolytic therapy, we suggest systemic thrombolysis using a peripheral vein over catheter directed thrombolysis.

Recurrent VTE: Our literature search did not identify any randomized trials assessing the efficacy and safety of different anticoagulation regimens for the management of recurrent VTE despite anticoagulation in patients with COVID-19. There are no randomized trials or prospective cohort studies that have evaluated management of patients with recurrent VTE despite anticoagulation. Important factors to consider include compliance, adequate absorption of DOACs, and absence of potential drug-to-drug interactions.

Due to the absence of direct evidence, the guideline panel decided to consider indirect evidence (low-quality) available from other another population at high risk of recurrent VTE, patients with cancer-associated thrombosis. There are no studies assessing the treatment of recurrent VTE despite anticoagulation with DOACs. One retrospective study reported reasonable outcomes (recurrent VTE of 9% [95% CI, 2 to 25]) when using therapeutic weight-adjusted LMWH in patients with recurrent VTE despite oral anticoagulation with vitamin K antagonists.[66] Two small retrospective cohort studies have also reported reasonable outcome by increasing the dose of LMWH to 125% and 130% in patients with recurrent events despite therapeutic weight-adjusted LMWH.[67,68] The rate of recurrent VTE and major bleeding was 8.6% (6 of 70; 95% CI, 4.0-17.5) and 4.3% (3 of 70; 95% CI, 1.5-11.9), respectively, among patients receiving increased dose (125% to 130%) of LMWH.[67] Finally, an International Society on Thrombosis and Haemostasis registry showed comparable findings to the aforementioned studies.[69] Based on indirect comparisons, we expect the net benefit of increasing the dose of LMWH by 25% to 30% in patients with COVID-19 and recurrent VTE despite therapeutic anticoagulation with LMWH and switching to LMWH in patients failing oral anticoagulation with a DOAC or vitamin K antagonist.

21. In patients with COVID-19 and recurrent VTE despite anticoagulation with therapeutic weight adjusted LMWH (and documented compliance), we suggest increasing the dose of LMWH by 25% to 30%.

22. In patients with COVID-19 and VTE despite anticoagulation with apixaban, dabigatran, rivaroxaban or edoxaban (and documented compliance), or vitamin K antagonist therapy (in the therapeutic range) we suggest switching treatment to therapeutic weight-adjusted LMWH.

Summary/Conclusions

The guidance statements in this document were specifically created to address what were felt to be common, urgent clinical questions that frontline

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

providers are likely to face regarding VTE and hypercoagulability in patients with COVID-19.

There are important limitations with this guidance. First is the lack of direct evidence to inform the guidance. Clearly more is being shared on a daily basis, but this emphasizes the importance of enrolling patients in clinical trials wherever possible and the need for international collaboration in collecting and rapidly disseminating relevant clinical experience, gaps in knowledge, and the research agenda. Second, due to the urgency of the situation, the panel was unable to address all of the likely questions that have arisen. As we consider this a living document that will be updated, we will incorporate additional questions to these updates as needed. Finally, and perhaps most importantly, the current body of evidence does not allow us to delineate between macro (DVT/PE) and microthrombosis, and the approach to these may differ. It is possible that studies looking for the prevalence of DVT and PE fail to represent the microthrombosis which could drive at least a portion of mortality in these patients.

The strengths of this document are the multidisciplinary panel that was composed of experienced clinicians and researchers in the field, many with extensive experience in the development of evidence-based guidelines. In addition, despite the lack of a robust evidence base, the panel followed a robust methodologic approach to formulate specific questions, evaluate the literature, and seek consensus.

We must acknowledge that there are > 10 other international guidelines, guidance statements, or online references that address this topic (although most focus on prevention, not diagnosis or treatment).[70-80] While this can seem overwhelming, the authors would like to emphasize the relative consistency in these statements. Most of these guidelines recommend VTE prevention in all hospitalized patients with COVID-19,[70,71,73,75-77] while some do recommend risk assessment to guide the decision.[72,74,79] As we discussed earlier, given the underlying risk factors present in these patients and that the current estimates of the incidence of VTE in non-critically ill patients with COVID-19 is well above 1% even on anticoagulant thromboprophylaxis, the panel considers all hospitalized patients with COVID-19 at increased risk of VTE. We therefore suggest against individualized VTE risk assessment and suggest anticoagulant thromboprophylaxis in all hospitalized patients with COVID-19 in the absence of contraindications. Almost all of these documents recommend standard dosing for anticoagulant thromboprophylaxis. One mentions escalating the dose, stating that it can be considered in patients with a large increase in the D-dimer level or severe respiratory failure.[73] Another suggests increased dosing in the critically ill patient with COVID-19, but recognizes that this was based largely on expert opinion.[80] The statements are consistent in the recommendation for the use of LMWH or UFH in COVID-19 patients. Those that address the use of mechanical prophylaxis note that it should be used in patients with a contraindication,[70,71,75,79,80] or can be added to anticoagulant thromboprophylaxis in patients who are completely immobilized.[74,80] Finally, only a few of these statements address the issue of extended duration prophylaxis. Bikdeli et al[72] note that there are no data in this population, although they state that it would be reasonable to take an individualized approach in each patient after risk stratifying for both thrombosis and bleeding risk. The Italian Society on Thrombosis and Haemostasis recommends prophylaxis throughout the hospitalization and for an additional 7 to 10 days' post-discharge.[75] The American Society of Hematology recommends following current guidelines, which recommend against extended duration prophylaxis in hospitalized medical patients.[22,71] As we noted earlier, we endorse this approach because the post-discharge VTE and major bleeding rates in COVID-19 patients are currently unknown.

It is our hope that clinicians caring for patients with COVID-19 will find this document helpful. Clearly, we still need well-designed randomized trials to answer many of our pressing questions. These include optimal dosing of prophylactic anticoagulant therapy, patients who might benefit from full-dose anticoagulant treatment, and the unique role of macro- and microthrombosis in COVID-19. We hope that this version of guidance will serve as a call to enroll patients in clinical trials wherever possible. We would also like to use this document as a call to reason. We are in a time of unprecedented economic, social, and medical uncertainty. We have been trained to accept uncertainty, and to be wary of undesirable consequences of acting too quickly on new observations that may not affect our usual care. As physicians, we are trained to practice evidence-based medicine. We need to always remember that any intervention can cause harm. In a time when our decisions may be driven by emotion, we risk the tendency to rely on anecdotes and early, small case series or cohorts. As recently stated by Zagury-Orly and

PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199

Schwartzstein, "We must reason critically and reflect on the biases that may influence our thinking processes, critically appraise evidence in deciding how to treat patients, and use anecdotal observations only to generate hypotheses for trials that can be conducted with clinical equipoise. We must act swiftly but carefully, with caution and reason."[81] We look forward to updating this guidance when well-designed trials have been completed.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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PGL 5.6.0 DTD ■ CHEST3241_proof ■ 23 June 2020 ■ 9:40 am ■ EO: CHEST-20-2199