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Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)has led to a world-wide pandemic, and patients with the infection are referred to as having COVID-19. Although COVID-19 is commonly considered a respiratory disease, there is clearly a thrombotic potential that was not expected. The pathophysiology of the disease and subsequent coagulopathy produce an inflammatory, hypercoagulable, and hypofibrinolytic state. Several observational studies have demonstrated surprisingly high rates of venous thromboembolism (VTE) in both general ward and intensive care patients with COVID-19. Many of these observational studies demonstrate high rates of VTE despite patients being on standard, or even higher intensity, pharmacologic VTE prophylaxis. Fibrinolytic therapy has also been used in patients with acute respiratory distress syndrome. Unfortunately, high quality randomized controlled trials are lacking. A literature search was performed to provide the most up-to-date information on the pathophysiology, coagulopathy, risk of VTE, and prevention and treatment of VTE in patients with COVID-19. These topics are reviewed in detail, along with practical issues of anticoagulant selection and duration. Although a number of international organizations have produced guideline or consensus statements, they do not all cover the same issues regarding anticoagulant therapy for patients with COVID-19, and they do not all agree. These statements and the most recent literature are combined into a list of clinical considerations that clinicians can use for the prevention and treatment of VTE in patients with COVID-19.

Key words: COVID-19, SARS-CoV-2, thrombosis, anticoagulation, venous thromboembolism

Background

The first cases of a pneumonia of unknown cause were identified in the city of Wuhan in the Hubei province of China in 2019. By January 7, 2020, Chinese scientists had isolated and identified this novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The World Health Organization later designated the coronavirus disease of 2019 as COVID-19 and declared it a pandemic on March 11, 2020.[2]

Coronaviruses are enveloped positive-sense RNA viruses belonging to the *Coronaviridae* family. While most human coronavirus infections are mild, in the past 20 years there have been two coronavirus epidemics, the severe acute respiratory coronavirus (SARS-CoV or SARS) in 2003, and Middle East respiratory syndrome (MERS) in 2012.[3,4] These prior coronavirus infections had much higher mortality rates than SARS-CoV-2, with a 10% mortality for SARS and a 30% mortality for MERS.[5,6] Despite the lower case fatality rate for SARS-CoV-2, the virus has caused more overall deaths due to its rapid person-to-person transmission and potentially mild initial infection presentation.[7] Similar to these prior outbreaks, SARS-CoV-2 has been associated with a higher incidence of thrombotic events than would be expected in hospitalized infected or critically ill patients.[8] A detailed review of the mechanisms, coagulopathy, incidence, and potential management of thrombotic events is necessary for clinicians to appropriately care for patients with COVID-19.

Methods

A search of MEDLINE/PREMEDLINE (via EBSCOhost) and EMBASE (via embase.com) was performed using the following search strategy: (covid 19 OR coronavirus infection OR coronavirus OR corona virus OR sars coronavirus 2 OR severe acute respiratory syndrome cov 2) AND (hypercoagulability OR coagulopathy OR microthrombi OR immunothrombosis OR thrombosis OR thromboembolism OR cerebrovascular accident OR coronary artery thrombosis OR myocardial infarction OR acute coronary syndrome OR myocardial ischemia OR thromboprophylaxis OR anticoagulation OR thrombolytic OR alteplase OR antiplatelet OR antithrombotic OR apixaban OR betrixaban OR dabigatran OR dalteparin OR edoxaban OR enoxaparin OR factor Xa inhibitors OR fibrinolytic OR fondaparinux OR heparin OR LMWH OR nadroparin OR DOAC OR plasminogen activator OR rivaroxaban OR venous thromboembolism OR warfarin OR aspirin OR clopidogrel OR prasugrel OR ticagrelor OR anticoagulant agent OR anticoagulant therapy). The search was limited to English language papers only. Abstracts were screened individually to determine their eligibility for inclusion in this review if they addressed the pathophysiology, coagulopathy, risk of venous

thromboembolism (VTE), or antithrombotic therapy for patients infected with SARS-CoV-2. In addition, reference lists for publications included were also screened for suitability for inclusion in this narrative review.

Pathophysiology – Infection to Thrombosis

SARS-CoV-2 is a single stranded RNA virus that is characterized with club-shaped Spike (S) proteins projecting from the virion surface, giving it a corona shaped appearance on electron microscopic imaging.[9] The S protein consists of two subunits, S1 and S2, which are both necessary for infection of the host cell. Similar to SARS-CoV, the first step involves the S1 subunit binding to the host cell receptor, which is angiotensin converting enzyme 2 (ACE2).[10] Interestingly, the binding affinity of SARS-CoV-2 is considerably higher than that of SARS-CoV, consequentially potentially magnifying the virus's virulence and pathogenicity.[10] The next step requires cleavage of the S1-S2 subunits, which then allows the S2 subunit to fuse with the cell membrane to promote viral entry into the host cell.[9] While a number of proteases can cleave the S protein subunits, factor Xa is a major contributor to this reaction.[11]

One of the physiologic roles of ACE2 is the cleavage of angiotensin II (ATII) to angiotensin 1-7.[10] ACE2 is in found predominately on cell membranes in the lungs, which explains the primary, and sometimes severe, pulmonary symptoms of COVID-19. The receptor is also located in the kidney, heart, gastrointestinal tract, as well as on lymphocytes. Once ACE2 binds to the S1 subunit on SARS-CoV-2, the receptor is downregulated.[11-14] This produces an abundance of ATII, which can cause direct lung damage itself.[15]

SARS-CoV, and likely SARS-CoV-2, express proteins that inhibit type I interferon (INF-α and INF-β) production.[10] This INF inhibition delays the initial antiviral response and allows for rapid viral replication and extensive virus-induced cytopathic effects in the early phase of disease. The reduced INF response allows virus infected pneumocytes to recruit an excessive infiltration of monocytes/macrophages and neutrophils in the lung parenchyma.[10,12] These recruited mononucleated cells and neutrophils produce high levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, and chemokines, which potentially culminates in a hyperinflammatory response and "cytokine storm" that can be found in the most severe cases of

COVID-19.[14] Elevated IL-6 levels have been documented in intensive care unit (ICU) patients with COVID-19.[15-17]

Lymphopenia is also a common finding in patients with COVID-19.[7,15-20] CD4+ and CD8+ T-cells are reduced, which may be due to enhanced T-cell apoptosis from the dysregulated cytokine storm, as well as a direct cytopathic effect of the virus.[21] The reduction in CD4+ T-cells can worsen the inflammatory state due to their inability to downregulate the inflammatory process.[22] This in turn impairs the adaptive immune response through inadequate T-cell help to virus-specific CD8+ cytotoxic T-cells and β-cells.

The impaired INF defense, enhanced monocyte/macrophage and neutrophils response producing excessive cytokine and chemokine levels, along with the impaired lymphocyte response produces a hyperinflammatory state that consequentially produces alveolar tissue damage initiating multiple thrombotic processes. This connection between the immune response inflammation and thrombosis has been termed immunothrombosis or thromboinflammation.[23]

The clotting cascade is stimulated through both the extrinsic and intrinsic pathways. The extrinsic pathway is initiated by release of tissue factor from cytokine-damaged alveolar endothelial cells. In the setting of significant inflammation, monocytes and macrophages can also express circulating tissue factor.[23] The intrinsic cascade is activated through neutrophil release of neutrophil extracellular traps (NETs).[24] These NETs contain various bioactive molecules in a process called NETosis, which have the ability to stimulate activation of factor XII. NETs also contain proteases that are able to inactivate endogenous anticoagulants, and therefore worsen the procoagulant state. The dual activation of the extrinsic and intrinsic clotting cascade leads to significant thrombin generation and thrombosis.[23]

The immune function of platelets has been well documented over the last decade.[25] Platelets are attracted to the area of cytokine-induced endothelial injury and become activated. Through the process of platelet activation, molecules such as platelet factor 4 and neutrophil-activating peptide-2 are released from platelet α-granules, which are involved in the recruitment and activation of monocytes/macrophages and neutrophils.[25] Additional immune actions of activated platelets include being an important source of proinflammatory IL-1β, as well as the further recruitment of neutrophils

through interaction of platelet surface P-selectin. The impact of platelet on immune function and thrombosis has been specifically documented in patients with COVID-19.[26]

Patients with COVID-19 also have significant hypoxia, especially in severe disease. Hypoxemia triggers expression of hypoxia inducible factors.[27] Hypoxia inducible factors can promote thrombosis by directly activating coagulation proteins and platelets and increasing tissue factor expression, as well as inhibiting endogenous protective functions such as increasing plasminogen activator inhibitor-1 (PAI-1) and inhibiting anticoagulant protein S. Hypercoagulability is further induced by hypoxia inducible factors due to their ability to promote further inflammation and augmenting blood viscosity.[27]

An inflammatory response and activation of thrombotic pathways occurs in a number of severe infections, and is not unique to SARS-CoV-2. Normal coagulation responses are often balanced with a fibrinolytic response to prevent fibrin deposition within alveolar tissues. This natural defense mechanism is initiated by the endogenous plasminogen activators, tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). These are responsible for the conversion of plasminogen to the proteolytic enzyme plasmin, which controls the breakdown of fibrinogen and fibrin deposits into the breakdown products D-dimer and other fibrin degradation products. The increased thrombotic potential in patients with COVID-19 is potentially a result of its interaction with ACE2.[12] The binding of SARS-CoV-2 to ACE2 produces a downregulation of the enzyme and consequentially an increase in AT II. Angiotensin II induces expression of PAI-1 in endothelial cells, which directly inhibits the actions of t-PA and u-PA.[28] Therefore, in patients with SARS and COVID-19, the balance between fibrinolysis with t-PA and u-PA is shifted to more hypofibrinolysis and thrombosis due to the excessive AT II and subsequent increase in PAI-1. The inability to breakdown and remove these fibrin deposits corresponds with poor clinical patient outcome as these deposits reduce normal gas exchange.[12]

Although most of the direct tissue damage and inflammation occurs in the lung, the impact of thromboinflammation can be systemic. Many institutions have reported an uncharacteristically high rate of VTE events in both medical ward and ICU COVID-19 patients.[29-44] Although there is a significant risk of deep vein thrombosis (DVT) in patients with COVID-19, some evaluations have identified a higher number of pulmonary emboli (PE) than DVT.[34.35.43,44] This discrepancy between

the frequencies of PE and DVT is unusual, since PE without DVT typically occurs in only about 20% of cases.[45] Therefore, in patients with COVID-19 many of the pulmonary thrombotic cases are likely pulmonary thrombi and not pulmonary embolism. This would be consistent with the pulmonary inflammation, alveolar tissue damage, and alveolar fibrin deposits found on autopsy in patients with COVID-19.[46-49]

Similar to autopsy findings from SARS and MERS, the primary finding associated with the cause of death is respiratory failure due to diffuse alveolar damage.[46-51] In contrast to patients with SARS and MERS, the morphological damage in the lungs and other organs is less severe in COVID-19, explaining the lower mortality rate. Whereas autopsies from cases of SARS and MERS did demonstrate fibrin deposits in the lungs, this seems to be amplified in cases of COVID-19. In a series of 10 autopsy cases of patients with severe COVID-19 from Brazil, 80% had a variable number of fibrinous thrombi in small pulmonary arterioles.[46] These thrombi were found in areas of both damaged and more preserved lung parenchyma. In a series of seven COVID-19 cases from Belgium, all had intraalveolar fibrin deposits and widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries.[47] Finally, a series of 11 COVID-19 autopsy cases from Austria reported that the most striking finding was obstruction of pulmonary arteries by thrombotic material found at both the microscopic and macroscopic level in all cases.[48] Interestingly, 10 of these 11 cases had received pharmacologic VTE prophylaxis, and VTE was not clinically suspected in any cases before autopsy as a contributor of death.

COVID-19 Thromboinflammation

The clinical spectrum of SARS-CoV-2 infection has broad presentation including asymptomatic infection, mild upper respiratory tract symptoms, up to severe viral pneumonia requiring mechanical ventilation, and even death (Table 1).[52] A number of studies have evaluated characteristics of patients with COVID-19, as well as those who progress to worse outcomes, such as ICU admission, acute respiratory distress syndrome (ARDS), or death (Table 2).[7,15-19,53-56] Although most patients have a favorable prognosis, patients with worse outcomes have a pronounced increase in inflammatory markers, referred to as a “cytokine storm”, approximately 7-14 days from the onset of initial symptoms.[57] This can coincide with the development of pulmonary thrombosis or PE, which may explain the rapid pulmonary collapse observed in patients suddenly progressing to ARDS. In general, patients progressing to worse outcome are about 10 to 15 years older and have more

comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease (Table 2). Laboratory findings demonstrate that patients with worse outcomes typically have more liver and renal dysfunction, and significantly lower lymphocyte counts. The sickest patients may also develop elevated procalcitonin and white blood cell counts, but these more likely represent acquired secondary bacterial infection versus caused by SARS-CoV-2 itself. Patients with COVID-19 often have elevated markers of inflammation.[20,58] One study in China reported that IL-6 was elevated in 52%, ferritin in 63%, erythrocyte sedimentation rate in 85%, and C-reactive protein (CRP) in 86% of patients.[20] These numbers are even higher in sicker patients (Table 2).

Markers of coagulopathy are also present in patients with COVID-19. Although the SARS-CoV-2 virus itself does not seem to have intrinsic procoagulant activity, the induced coagulopathy and thromboinflammation extend systemically and impact other organs, such as the kidney, and may eventually lead to multiorgan dysfunction and potentially death.[59] Patients with COVID-19 typically have elevated fibrinogen levels, but the extent of increase does not differ based on the severity of disease.[53] Antithrombin activity can also be decreased in patients with COVID-19, but as demonstrated in a study from China, the significantly lower activity (85% in COVID-19 vs. 99% in healthy volunteers; $p<0.001$) still falls within the normal range (>80%).[53] Prolongation of the prothrombin time (PT) or activated partial thromboplastin time (aPTT) has been demonstrated, but is not a common finding.[53-56] Tang N and colleagues found that in patients who died of COVID-19, their PT was prolonged by about 2 seconds compared to those who survived (Table 2).[56] A meta-analysis of 11 studies reported an average increase in the PT of about 14% in patients with COVID-19.[58] Although antiphospholipid antibodies have been reported in patients with COVID-19, and thought to promote the hypercoagulable state, these data should be interpreted with caution.[60-62] There is a high risk of false positive lupus anticoagulant testing in patients with COVID-19 due to the elevated levels of CRP. Many assays for lupus anticoagulant are sensitive to CRP and give a false positive finding.[63]

Although most patients with COVID-19 have normal platelet counts, thrombocytopenia has been reported in 20% to 35%, and is usually mild.[57,64] In a meta-analysis of nine studies, the platelet count was lower by about 31,000 x 10^9/L in severe cases compared to nonsevere cases, and about 48,000 x 10^9/L lower in nonsurvivors compared to survivors.[65] These lower platelet counts may not be enough to register as marked thrombocytopenia, but do likely represent platelet recruitment into pulmonary or systemic thrombi. Although not as common as other severe infectious diseases, the

occurrence and severity of thrombocytopenia is associated with higher mortality in patients with COVID-19.[17,66] In a study of 380 patients with COVID-19, platelet counts of less than 10 x 10^9/L occurred in 49% of patients with critical disease, 14% in severe disease, and 9% in those with moderate disease.[17] The odds of death in patients with thrombocytopenia was 8.33 (95% CI 2.56 – 27.15). Another study of 1476 patients with COVID-19 demonstrated increasing mortality in patients with thrombocytopenia, as well as increasing mortality with decreasing platelet counts.[66] Nonsurvivors (16%) were significantly more likely to have thrombocytopenia compared to survivors (72.7% vs. 10.7%; p<0.001), as well as lower nadir platelet counts (76 vs. 204 x 10^9/L; p<0.001), respectively. Patients with nadir platelet counts 150 x 10^9/L or more had a mortality rate of 4.7%, whereas mortality was 17.5% in those with 100-150 x 10^9/L, 61.2% in those with 50-100 x 10^9/L, and 92.1% in those with 0-50 x 10^9/L. The incidence of a nadir platelet count of 0-50 x 10^9/L was relatively rare (5%) compared to those with a platelet count of 150 x 10^9/L or more (68%).

Breakdown of fibrin or fibrinogen by u-PA or t-PA produces fibrin degradation products, one of which is D-dimer. An elevated D-dimer is typically a sign of excessive coagulation activation and hyperfibrinolysis. Therefore, D-dimer is often used to detect active thrombus with high sensitivity but low specificity.[67] The low specificity is due to other conditions, such as inflammation and infection that can also increase D-dimer in the absence of thrombosis, and are associated with COVID-19.

D-dimer is elevated in 36% to 43% of patients with COVID-19, but is commonly elevated in hospitalized patients.[62] Elevations of D-dimer are higher in ICU patients and those with worse outcomes by 2.5 to 9-fold (Table 2).[60,67] Han H and colleagues found that D-dimer levels were elevated with increasing severity of disease, with levels at 2140 ng/mL for patients classified with ordinary disease, 19,110 ng/mL in those with severe disease, and 20,040 ng/mL in those considered critical, compared to 260 ng/mL in healthy controls.[53] Since values are higher in patients with severe disease, D-dimer measurement may be associated with evolution toward worse clinical picture.

As would be expected, D-dimer is also elevated in patients with COVID-19 who develop VTE.[36,38,39,43-46] It has been suggested that D-dimer levels above a certain cut off could be used to predict those with VTE if appropriate diagnostic testing is not feasible.[29,30,36,38,39] Caution should be exercised in this myopic interpretation of elevated D-dimer levels. If elevated D-dimer is mainly due to coagulopathy and increased fibrinolysis of thrombi, this would suggest a consumption

coagulopathy. This is supported by a study conducted by Tang N and colleagues, where disseminated intravascular coagulation (DIC) was more common in nonsurvivors compared to survivors (71.4% vs. 0.6%).[56] DIC is considered a consumption coagulopathy, with elevated D-dimer levels due to significant fibrinolysis and breakdown of fibrin and fibrinogen. Most patients with COVID-19 have elevated fibrinogen levels that is inconsistent with a consumption coagulopathy. The lack of consistent moderate to severe thrombocytopenia and inconsistent prolongation of the PT also are not supportive of DIC being a common complication in patients with COVID-19. Therefore, most of the elevations of D-dimer are likely due to the excessive inflammatory state, similar to the elevations in erythrocyte sedimentation rate, CRP, and ferritin, and should not be considered to be solely from fibrinolysis.[68] This is supported by data demonstrating that a D-dimer 2-fold above the upper limit of normal has been used in patients without VTE to predict those at highest risk of development of VTE.[69] When DIC does occur, it is likely in the last stage of COVID pneumonia, when there may be increased systemic fibrinolysis and multiorgan failure.[70]

Hypercoagulability, but not a consumption coagulopathy, is also supported by findings in two thromboelastography studies that evaluated patients with COVID-19 compared to healthy volunteers.[54,55] Patients with COVID-19 had significantly higher D-dimer and fibrinogen levels compared to healthy controls (Table 2), but normal PT and aPTT. The first study demonstrated that patients with COVID-19 had significantly shorter clot formation time and higher maximum clot firmness.[54] The shorter clot formation time is reflective of the excessive thrombin generation and higher clot firmness reflects the increased fibrin and fibrinogen in these patients. The other study evaluated 24 intubated ICU patients with COVID-19, most of who were on VTE prophylaxis, compared to 40 health volunteers.[55] Similar to the previous findings, patients with COVID-19 had a shorter clotting times and firmer clots. All patients with COVID-19 also had reduced clot lysis at 30 minutes. The lack of clot lysis at 30 minutes does not support a hyperfibrinolytic state, which matches the pathophysiologic mechanism of impaired fibrinolysis from ACE2 binding of SARS-CoV-2.[9,10,12,13]

In summary, the coagulopathy associated with SARS-CoV-2 infection typically presents with elevated D-dimer and fibrinogen levels with normal to slightly lower platelet counts, and normal to slightly elevated PT and aPTT. With worsening disease severity, patients will have higher D-dimer levels, lower platelet counts, and eventually elevated PT and aPTT. These coincide with increased

markers of inflammation, such as IL-6 and CRP, as well as infection (lymphopenia and potentially leukocytosis), and organ dysfunction (renal and liver dysfunction).

Risk of VTE

Hospitalized patients with acute medical illness, such as infection, are at increased risk of VTE.[71] In general ward patients the rate of VTE without prophylaxis ranges from 5% to 15% depending on the method of assessment. The use of pharmacologic prophylaxis lowers the rate to 2.8% to 5%.[71] In ICU patients, the risk of VTE is higher. Rates from one meta-analysis ranged from 10% to 30%.[72] Another meta-analysis reported a rate of 12.7% for ICU patients mainly assessed by compression ultrasound (CUS).[73] Use of pharmacologic prophylaxis lowers this rate to 5.1% to 7.7%.[74,75]

A number of studies have reported a higher rate of VTE than would be expected in general ward and ICU patients with COVID-19 (Table 3).[29-44] Increased thromboembolic events were also documented with the SARS, MERS, and influenza A H1N1 viruses.[76-81] The true risk of VTE in patients with COVID-19 is difficult to determine since no placebo-controlled randomized trials have been conducted. Rates of VTE in general medical ward patients with COVID-19 have been reported to be around 4% in clinically evaluated patients and as high as almost 15% in patients screened with CUS (Table 3).[38-40]

In the early phase of the outbreak, before the thrombotic potential of COVID-19 was appreciated, patients in China did not commonly received VTE prophylaxis based on the assumption that they are a lower risk population. In this setting, Cui and colleagues screened 81 COVID-19 ICU patients for VTE with CUS, none of which were receiving VTE prophylaxis.[29] The rate of DVT was 25%, which is at the high end of the range for an ICU population. Another study from China in which only about one-third of screened ICU patients received VTE prophylaxis had a rate of DVT of 46%.[30] Other trials have evaluated VTE rates in CUS screened ICU patients with COVID-19 receiving pharmacologic prophylaxis with rates as high as 69% to 85%, which are higher than reported in typical ICU patients (Table 3).[31,32] Most institutions do not routinely screen patients for VTE, even in the ICU. Observational studies on the rates of VTE in ICU patients with COVID-19 when CUS is only done based on clinical suspicion has also been conducted. In patients receiving prophylaxis the rate of VTE ranges from 13% to 28%, which is 2- to 4-fold the rate demonstrated in typical ICU patients (Table 3).[34-37,40,42-44,74,75]

There have also been observational trials that have compared rates of VTE in COVID-19 patients to historical controls without COVID-19 (Table 3).[42-44] Marone and colleagues evaluated general ward patients all receiving CUS for clinical suspicion of DVT with COVID-19 to those without COVID-19 at the same time the previous year.[42] The rate of DVT was more than 2-fold higher in the patients with COVID-19. Poissy and colleagues conducted a similar time frame comparison, but only evaluated patients with clinical suspicion and all received prophylaxis.[43] The rate of PE was 3-fold higher in COVID-19 patients compared to those without, but was also more than 2-fold higher than influenza patients specifically during the same time frame. Finally, Helms and colleagues conduced a matched case control study of ARDS patients with COVID-19 compared to ARDS patients in the same ICU between 2014 and 2019.[44] Patients were evaluated based on clinical suspicion and the use of anticoagulation was similar between the groups. Patients with COVID-19 had over a 2-fold higher rate of thrombotic events and more than a 5-fold higher rate of PE, with no difference in DVT, compared to patients without COVID-19.

Prevention of VTE

Most hospitalized patients with COVID-19 are over age 40 years and have a number of risk factors for VTE, such as pneumonia, obesity, immobility, respiratory disease, elevated D-dimer levels, as well as potentially underlying heart failure, smoking, varicose veins, cancer, and previous VTE. Patients with COVID-19 in the ICU would have these risk factors, in addition to higher D-dimer levels, sedation, more significant immobility, respiratory failure, use of vasopressors, and central venous catheters. The multiple clinical risk factors and high D-dimer levels, along with the hypercoagulable and hypofibrinolytic condition created by SARS-CoV-2, help explain the thrombotic implications of this virus and the need to consider prophylactic anticoagulation in all hospitalized patients.

A number of questions about the appropriate level or intensity of anticoagulation exist, especially since most observational studies have demonstrated high rates of VTE despite the use of anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) for prophylaxis.[31-41,43,44] These data have led some clinicians to use an intensified prophylactic dose or intermediate dose, and even full therapeutic anticoagulant doses, instead of standard dose anticoagulant prophylaxis in ICU patients with COVID-19. There are also questions related to which anticoagulant (LMWH, UFH, or other) would be preferred. A tailored approach considering individual

patient characteristics leading to specific recommendations on anticoagulant agent and dose intensity may likely be the best approach. Ultimately the optimal approach will depend on the results from several ongoing randomized, controlled clinical trials that will serve to inform clinicians on the best approach (NCT04345848, NCT04359277, NCT04344756, NCT04360824, NCT04354155, NCT04359212, NCT04362085). Until results from these trials are available, clinicians must rely on currently available evidence to craft treatment approaches for both the individual patient, as well as over-arching institutional guidelines to help the bedside clinician.

Typically, hospitalized medically ill patients should be evaluated with a validated risk assessment tool to determine if pharmacologic VTE prophylaxis is needed (Table 4).[77,78] Hospitalized patients with COVID-19, whether on the medical ward or ICU, do not need to undergo the step of risk assessment. Both medical ward and ICU patients with COVID-19 have several VTE risk factors, known thromboinflammation, and unacceptable high rates of VTE despite some form of pharmacologic prophylaxis (Table 3).[31-41,43,44] Consequentially, all hospitalized patients with COVID-19 should receive pharmacologic VTE prophylaxis regardless of any risk assessment predictors unless the risk of bleeding is considered high. Risk assessment should be performed with symptomatic patients with COVID-19 treated at home, since a number of them may still have several VTE risk factors, including immobility, and are at risk of thromboembolic events.[52,79-81]

Support for the paradigm that a higher intensity of anticoagulation than standard prophylactic doses of heparin comes from previously published evidence from the H1N1 influenza pandemic in 2009.[82] An observational cohort study of critically ill patients with severe ARDS from H1N1 viral pneumonia demonstrated that empiric systemic heparinization titrated to a goal heparin level of 0.3 – 0.7 anti-Xa units/mL was significantly better at reducing VTE rates than standard prophylactic doses of either UFH or LMWH. Although these data were obtained only in critically ill patients with ARDS, they do support the idea that higher intensity anticoagulation may be needed in order to improve outcomes in patients with COVID-19.

The first report evaluating the use of VTE prophylaxis (UFH or LMWH) and the impact on mortality came from a retrospective review of 449 patients from Wuhan, China.[83] Patients with severe COVID-19 in the ICU received VTE prophylaxis for at least seven days with UFH 5000 units two to three times daily (n=5), enoxaparin 40-60 mg daily (n=94), or no anticoagulation prophylaxis (n=350).

Overall, there was no difference in 28-day mortality between the 22% of patients that received either UFH or LMWH compared to patients who received no anticoagulation (30.3% vs. 29.7%; p=0.910, respectively). However, when looking at the subset of patients with significant hypercoagulability as defined by a D-dimer level of at least six-fold above the upper limit of normal (> 3.000 ng/mL), there was a significant decrease in mortality with the use of heparin compared with no anticoagulation (32.8% vs. 52.4%; p=0.017, respectively). When stratifying patients by a sepsis-induced coagulopathy score of > 4, there was also a significant reduction in mortality with the use of heparin versus no anticoagulation (40.0% vs. 64.2%; p=0.029, respectively). These same authors compared these 449 patients with COVID-19 in the ICU to 107 patients in the ICU with non-COVID-19 pneumonia, of which 21.2% received heparin prophylaxis.[84] Although there was still no overall reduction in mortality in patients receiving heparin prophylaxis compared with no anticoagulation (13.6% vs. 15.9%; p=0.798, respectively), mortality is half what was seen in the COVID-19 patients. Interestingly, there was no difference in mortality between heparin users and non-users even when stratified for D-dimer and sepsis-induced coagulopathy in patients without COVID-19. Although this report was the first to suggest that the use of UFH or LMWH could improve outcomes in severely ill patients with COVID-19, there are a number of limitations that should be considered. First, the benefit seen with prophylaxis was only demonstrated in a subgroup of the sickest patients evaluated. The observational nature of the study cannot account for potential confounding variables between the groups. In fact, the authors noted that during the time of the study medical resources were strained and mortality rates may have been higher than other parts of the world.[83] The decision of whether to give LMWH or UFH, as well as doses used, were at the discretion of the clinician and were not controlled in the study. There is no information of the impact of actual VTE events, as this is also an important endpoint.

A second observational study from New York sought to identify the value of full therapeutic anticoagulation in patients hospitalized with COVID-19.[85] This single center retrospective study evaluated 2773 patients with COVID-19, of which 786 (28%) received therapeutic anticoagulation. Overall, in-hospital mortality was not different between patients who received therapeutic anticoagulation vs those that did not (22.5% vs. 22.8%, respectively). Patients who received therapeutic anticoagulation were more likely to require invasive mechanical ventilation (29.8% therapeutic anticoagulation vs. 8.1% no therapeutic anticoagulation; p<0.001). Consequentially, patients who were receiving mechanical ventilation (n=395) had a reduction of in hospital mortality by

over 50% with the use of therapeutic anticoagulation compared with those who received no therapeutic anticoagulation (29% vs. 63%, median survival 21 days vs. 9 days; p<0.01, respectively). Interestingly, major bleeding was not significantly increased in patients receiving therapeutic anticoagulation (3% therapeutic anticoagulation vs. 1.9% no therapeutic anticoagulation; p=0.2). In a multi-variate Cox proportional hazards model, mortality risk was reduced with longer durations of anticoagulation. Similar to the previous study, this report suffers from several limitations such as unaccounted for confounding variables. Specific anticoagulant agents used for therapeutic anticoagulation were not specified, the indication for anticoagulation was not provided, and it is unclear if non-anticoagulated patients received prophylaxis dose anticoagulation or nothing. The median length of hospitalization was 5 days and the median duration of anticoagulation was only 3 days. Despite these limitations, this report provides at least some insight into the role of higher levels of anticoagulation in the most severe patients with COVID-19, and support evaluating various levels of anticoagulation intensity in ongoing randomized controlled trials.

A number of smaller reports also provide partial insight to the appropriate level of VTE prophylaxis needed in patients with COVID-19. A retrospective observational study of 16 ICU patients with COVID-19 evaluated coagulopathy parameters after a nadroparin dose of 4000 IU twice daily for VTE prophylaxis, and then again after a 6000 IU twice daily dose (8000 IU twice daily in patients with body mass index >35).[86] The increase in dose provided a significant reduction in fibrinogen and D-dimer levels and an increase in antithrombin activity. An additional report in 26 patients with severe COVID-19 admitted to the ICU reported a higher frequency of VTE in patients receiving prophylactic compared to therapeutic anticoagulation (100% prophylactic vs. 56% therapeutic; p=0.03), although all 6 patients (23%) with PE were receiving therapeutic anticoagulation.[32]

As discussed previously, a number of observational studies have reported higher than expected rates of VTE in critically ill patients with COVID-19, despite the use of standard dose anticoagulant prophylaxis.[31-36,40,41,44] An important consideration within this area may be augmented renal clearance. Augmented renal clearance is a process whereby renal clearance of medications is increased in the setting of critical illness. A report in 47 ICU patients with COVID-19 identified 18 patients (38.3%) with augmented renal clearance.[87] Patients with augmented renal clearance had numerically more DVT (44% vs. 31%; p=0.352) and significantly more PE (33% vs. 10%; p=0.025) compared to those without, respectively. These data, although from a small group of patients, speaks

to the potential need for higher doses of anticoagulant prophylaxis to address both significant hypercoagulability as well as augmented renal clearance. Lastly, there is emerging information that standard doses of prophylaxis may be adequate to prevent DVT and PE, but higher doses may be need to prevent primary pulmonary thrombosis.[45] This is consistent with a number of observations that demonstrated a higher rate of pulmonary events than DVT.[34,35,43,44] Ultimately data from larger randomized controlled trials will help clarify many of these clinical questions.

Risk of VTE in patients with COVID-19 is unlikely to disappear at the time of hospital discharge. Studies in medially ill non-COVID-19 patients have demonstrated a high rate of VTE in the 30 days immediately after discharge.[88] This is likely due to patients still recovering and continued immobility. Two agents, betrixaban and rivaroxaban, are approved by the United States Food and Drug Administration for extended VTE prophylaxis in medically ill patients although betrixaban has recently been removed from the market due to a company acquisition. Assuming the appropriate inclusion and exclusion criteria are met (Table 5), both agents provided a significant reduction in VTE events without significantly increasing major bleeding when used for approximately 30 days post discharge.[89-91] Despite the lack of ability to get betrixaban, applying the criteria from the trial still has merit in appropriate patient selection for extended prophylaxis. If these agents cannot be used due to significant drug interaction or other reason, enoxaparin 40 once daily can be used. Although enoxaparin has also demonstrated the ability to significantly reduce VTE events in the 30 days post discharge, there is significantly more major bleeding with this regimen.[92] Apixaban should not be used since the trial with this agent did not demonstrate efficacy over placebo for thromboprophylaxis in medically ill patients, and it also had significantly more major bleeding.[93] Although none of these trials included patients with COVID-19, VTE after hospital discharge has been reported in these patients.[94] Patients with COVID-19 have prolonged hospital stays with significant deconditioning, immobility during recovery, high D-dimer levels, and additional risk factors. It is likely that a number of hospitalized patients with COVID-19 would have met criteria to be included in the trials and should realize similar benefit from extended VTE prophylaxis (Table 5).

Fibrinolytic Therapy for Patients with ARDS

Regardless of the underlying cause, ARDS has been associated with fibrin deposition in the airspaces along with fibrin-platelet microthrombi at the level of the pulmonary vasculature. These observations have also been noted in the lung microvasculature of patient with COVID-19.[46-49] In

conjunction with these findings, patients with COVID-19 can demonstrate hypercoagulable and hypofibrinolysis findings on thrombelastography.[54,55] These findings have prompted the hypothesis that fibrinolytic therapy may have a role in managing patients with ARDS, and more specifically in patients with COVID-19 who develop ARDS in the setting of a hypofibrinolytic thrombotic coagulopathy. Data supporting the role of fibrinolytic therapy in the management of patients with COVID-19 are limited at best.

In a case series of three patients on mechanical ventilation, systemic t-PA at a dose of 25 mg over 2 hours followed by another 25 mg administered over the subsequent 22 hours has been evaluated.[95] All three patients were experiencing ARDS related respiratory failure, and had improvements in their ventilatory parameters and oxygenation following t-PA therapy, however the effects were transient. A second case series of three patients with significantly worsening ventilatory parameters and oxygenation were administered t-PA. One patient received 30 mg over 15 hours (2 mg/hr), while the over two received 50 mg over 3 hours[96]. All patients experienced improvement in ventilatory parameters and oxygenation and were discharged alive.[97] A final case series assessed the effects or aerosolized freeze-dried plasminogen in hospitalized patients with COVID-19.[97] Oxygenation and ventilatory parameters were also improved, but only transiently. A report using a Markov decision analysis approach to evaluate whether t-PA may improve outcomes in patients with COVID-19 demonstrated the use of fibrinolytic therapy in ARDS patients was associated with a mortality benefit, although this can be considered hypothesis generating only.[98] Given that systemic administration of fibrinolytics in the setting of PE is associated with a 10% risk of major bleeding and a 1-2% risk of intracranial hemorrhage, additional information from randomized clinical trials is needed to validate whether t-PA has any role in the management of patients with COVID-19 and ARDS.[99] Several trials are underway to address this clinical question (NCT04356833, NCT04357730). Based on the level of evidence currently available, routine fibrinolytic administration to patients with COVID-19 ARDS cannot be recommended at this time.

Clinical Considerations

Several clinical guidance and consensus statements have been developed and disseminated by international organizations to help guide clinicians in the management of the thromboembolic risks associated with COVID-19 (Table 6).[52,79,100-103] These guidance statements have been developed in the absence of randomized controlled trials in patients with COVID-19, and hence are largely based

on knowledge regarding the prophylaxis and treatment of VTE in patients without COVID-19, as well as the initial observational publications. As such, some of the recommendations should be considered expert consensus. Although these guidance statements attempt to include the most up-to-date information, data regarding VTE risk, prevention, and treatment in patients with COVID-19 is rapidly evolving. At the time of this writing, data presented in this manuscript cannot be found in many of these guidance documents. Also, each of the guidance documents do not address all the clinical issues, and not all of these organizations agree. Therefore, a table of clinical considerations has been provided that considers these different guidance documents together, as well as incorporates the most recent published data (Table 7). Clinicians wanting to keep up with the most current information can find information from the International Society of Thrombosis and Haemostasis (www.isth.org), Society of Critical Care Medicine (www.sccm.org/Home), Anticoagulation Forum (www.acforum.org/web/), and the American Society of Hematology (www.hematology.org)

Highlights from these clinical considerations include risk assessment in patients with COVID-19 who are not hospitalized, as some of them may have significant immobility at home with additional risk factors and VTE prophylaxis can be considered. In hospital VTE prophylaxis should be provided to all patients without a contraindication (currently bleeding, platelet count < 50 $x10^9$), regardless of any predictive risk scoring. Although standard dose anticoagulant prophylaxis should be used for general ward patients, mounting evidence supports higher doses in many hospitalized patients with COVID-19. Critically ill patients in the ICU, especially those on mechanical ventilation or with ARDS, should receive intermediate-doses of anticoagulant prophylaxis.This recommendation is based on higher failure rates for standard doses of VTE prophylaxis demonstrated in patients with COVID-19 (Table 3) in the ICU setting. For example, a study using standard doses of LMWH prophylaxis in ICU patients with COVID-19 reported a failure rate of 27%, which is 3-fold higher than prior reports in ICU patients without COVID-19 that documented a failure rate of 7.7%.[34,75] Evidence is also beginning to emerge that escalating the dose of VTE prophylaxis in patients who have evidence of thromboinflammation due to a heightened inflammatory state (increased IL-6, D-dimer, fibrinogen, or TEG findings) results in a significant decrease in inflammation and hypercoagulability.[86]

In-hospital VTE prophylaxis and treatment should be provided with LMWH or UFH instead of a direct oral anticoagulant (DOAC). Both LMWH and UFH have potential anti-inflammatory properties that

may make them beneficial in patients with COVID-19.[104-106] These agents also may prevent splitting of the S proteins of SARS-CoV-2, which is necessary for incorporation into the host via ACE2. The impact of DOACs on these properties is unknown.[13] Besides patients requiring dialysis, the use of a LMWH is preferred to UFH for both prevention and treatment of VTE. Prophylaxis with LMWH requires fewer injections per day compared to UFH, and treatment with LMWH can be give once or twice daily, with no need for the frequent monitoring and dose adjustments as is necessary with UFH. Use of LMWH instead of UFH will reduce exposure of health care professionals to patients with COVID-19, as well as preserving personal protective equipment. The preference for LMWH over UFH for prophylaxis is also based on benefit of LMWH over UFH in other high risk patients, such as those with trauma, cancer, and high risk medically ill patients.[107-112]

Patients receiving LMWH for VTE prophylaxis should have dose adjustments for obesity and renal function.[113] In patients with a BMI of 30 to 40 kg/m^2 or greater, or weighing more than 100 to 120 kg, increased doses of LMWH, such as enoxaparin 40 mg twice daily, 60 mg once daily, or 0.5 mg/kg have demonstrated improved efficacy and similar safety to standard doses.[114,115] Date also is available in patients undergoing bariatric surgery, as well as pregnancy, supporting the notion that doses of prophylaxis should be adjusted upwards based on the presence of elevated body weight.[116,117]

If UFH is used for VTE treatment, monitoring must be done with an anti-Xa assay instead of the aPTT.[62] The aPTT can be elevated or become elevated in patients with COVID-19, and therefore is unreliable for monitoring UFH. Even though bleeding is rare in patients with COVID-19, the current evidence does not support the use of therapeutic LMWH or UFH for prevention of VTE. The use of fibrinolysis outside of patients with hemodynamically compromised PE should also be avoided.

The use of DOACs in hospitalized patients, especially ICU patients with COVID-19, can be problematic if invasive procedures are needed, requiring longer hold times that may delay procedures. The use of DOACs may also be limited by drug interactions with certain antiviral therapies, such as lopinavir/ritonavir. If the perceived need for invasive procedures is low, and no drug interactions exist, DOACs could be considered as initial therapy for treatment of VTE in non-ICU patients. After discharge, patients initiated on injectable therapy in the hospital should be considered for transition to a DOAC if possible, or warfarin.

As all hospitalized patients with COIVD-19 should receive VTE prophylaxis, thrombocytopenia presents a conundrum. Platelet count drops to less than 100 x 10^9/L may represent the transition of the patient into a consumption coagulopathy, where withdrawal of anticoagulant therapy may worsen the patient's thrombotic potential. It is not uncommon to continue VTE prophylaxis until platelet counts get below 50 x 10^9/L or even 20 x 10^9/L. With the high use of anticoagulation in patients with COVID-19, heparin-induced thrombocytopenia must also be considered, especially in patients receiving UFH. Special attention to the timing and rate of platelet drop needs be considered. Since a consumption coagulopathy occurs fairly late in the course of SARS-CoV-2 infection in the most severe cases, it is relatively rare, but also difficult to distinguish from the timing of heparin-induced thrombocytopenia. In these cases, switching to an alternative agent such as argatroban or fondaparinux seems prudent.

Conclusion

Patients with COVID-19 should not only be considered to have a respiratory illness, but a thrombotic condition as well. SARS-CoV-2 not only produces an inflammatory and hypercoagulable state, but also a hypofibrinolytic state not seen with most other types of coagulopathy. The rate of VTE observed is higher than expected for general ward and ICU patients, especially for those receiving prophylaxis. All hospitalized patients with COVID-19 should be considered high risk and receive anticoagulants for VTE prophylaxis. Although a number of approaches have been observed in the literature, there is unfortunately no high-quality data to help make more definitive recommendations at this time. Although guideline statements differ on a number of the clinical issues, such as the best dose of anticoagulant for VTE prophylaxis, duration of prophylaxis, and use of fibrinolytics in patients with ARDS, a number of randomized controlled trials are ongoing to answer these questions. Until these randomized controlled trials become available, an understanding of the pathophysiology, coagulopathy, current guideline and consensus statements, and these clinical considerations (Table 7) are key resources to help clinicians care for patients with COVID-19.

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Table 1. Clinical classification of coronavirus 2019 infection[52]

Mild	mild clinical symptoms, no signs of pneumonia on imaging
Moderate	fever and respiratory symptoms, etc, with pneumonia signs on imaging
Severe	patients with any of the following conditions: • respiratory distress with respiratory rate 30 breaths per minute or higher • SPO_2 93% or less at rest • PaO_2/FiO_2 300 mm Hg or less
Critically ill	patients with any of the following conditions: • respiratory failure requiring mechanical ventilation • shock • other organ failure requiring admission to the ICU.

SPO_2=oxygen saturation; PaO_2=partial pressure of oxygen; FiO_2=fraction of inspired oxygen; ICU=intensive care unit

Table 2. Characteristics of disease severity in patients with COVID-19.

Study	Patients Evaluated	Findings
Han H, et al.[53]	Patients with COVID-19 (n=94) vs. healthy volunteers (n=40)	Patients with COVID-19 Higher D-dimer (10,360 vs. 260 ng/mL; p<0.001) Higher fibrinogen (5.0 vs. 2.9 g/L; p<0.001)
Spiezia L, et al.[54]	Patients with COVID-19 (n=22) vs. health volunteers (44)	Patients with COVID-19 Higher D-dimer (5343 vs. 225 ng/mL; p<0.001) Higher fibrinogen (5.2 vs. 3.0 g/L; p<0.001)
Panigada M, et al.[55]	ICU patients with COVID-19 (n=24) vs. health volunteers (n=40)	Patients with COVID-19 High D-dimer (4877 ng/mL) High fibrinogen (6.8 g/L)
Guan W, et al.[7]	Patients with severe COVID-19 (n=173) vs. those in nonsevere COVID-19 (n=926)	Patients with severe COVID-19 Older by 7 years (52 vs. 45 years) More likely to have comorbidities (39% vs. 21%)
Wang D, et al.[18]	ICU patients (n=36) vs. ward patients (n=102)	ICU patients: Older by 15 years (66 vs. 51 years; p<0.001) Double the incidence of HTN, DM, and CVD Higher D-dimer (4140 vs. 1660 ng/mL; p<0.001) Higher LDH (435 vs. 212 IU/L; p<0.001)
Huang C, et al.[19]	ICU patients (n=13) vs. ward patients (n=28)	ICU patients: Higher PT (12.2 vs. 10.7 seconds; p=0.012) Higher D-dimer (2400 vs. 500 ng/mL; p<0.001)
Wu C, et al.[15]	Patients with (n=84) vs. patients without ARDS (n=117) and	ARDS patients: Older by 10 years (58 vs. 48 years; p<0.001)

	patients with ARDS who died (n=44) vs. those with ARDS who survived (n=40)	More liver and renal dysfunction More preexisting HTN and DM Higher IL-6 (7.4 vs. 6.3 pg/mL; p=0.03) Higher D-dimer (1160 vs. 520 ng/mL; p<0.001) Lower lymphocytes (0.67 vs. 1.08 x 10^9/L; p<0.001) ARDS patients who died: Older by 18 years (50 vs. 68 years; p<0.001) More liver and renal dysfunction Higher IL-6 (10.07 vs. 6.05 pg/mL; p<0.001) Higher D-dimer (3950 vs. 490 ng/mL; p=0.001 Lower lymphocytes (0.59 vs. 0.80 x 10^9/L; p=0.004)
Zhou F, et al.[16]	Patients who died (n=45) vs. those who were discharged (n=137)	Patients who died: Older by 17 years (69 vs. 52 years; p<0.001) Higher SOFA scores (4.5 vs. 1.0; p<0.001) Lower lymphocytes (0.6 vs. 1.1 x 10^9/L; p<0.001) Higher IL-6 (11.0 vs. 6.3 pg/mL; p<0.001) Higher LDH (521 vs. 234 IU/L; p<0.001) Higher troponin (22 vs. 3 pg/mL; p<0.001) Higher D-dimer (5200 vs. 600 ng/mL; p<0.001) More with D-dimer > 1000 ng/mL (81% vs. 24%; p<0.001)
Liao D, et al.[17]	Patients with moderate (n=149) vs. severe (n=145) vs. critical COVID-19 (n=86)	Moderate vs. severe vs. critical Thrombocytopenia (6% vs. 14% vs. 49%) D-dimer (420 vs. 1360 vs. 7240 ng/mL) IL-6 (14.1 vs. 23.8 vs. 37.4 pg/mL)

		Lymphocytes (0.95 vs. 1.2 vs. 0.89 x 10^9/L) CRP (10.2 vs. 40.6 vs. 92.8 mg/dL)
Tang N, et al.[56]	Patients who died (n=21) vs. those who survived (n=162)	Patients who died: Older by 12 years (64 vs. 52 years; p<0.001) Prolonged PT (15.5 vs. 13.6 seconds; p<0.001) Higher D-dimer (2120 vs. 610 ng/mL; p<0.001)

COVID-19=coronavirus 2019 infection; ICU=intensive care unit; IL=interleukin; CRP=C reactive protein; HTN=hypertension; DM=diabetes mellitus; CVD=cardiovascular disease; LDH=lactate dehydrogenase; PT=prothrombin time; ARDS=acute respiratory distress syndrome; SOFA=sequential organ failure assessment.

Table 3. Incidence of VTE in patients with COVID-19.

Authors	Patients	Evaluation Methods	Prophylaxis	Thrombosis Rates	Comments
Cui S, et al.[29]	81 ICU patients	Screened with CUS	None	25% (n=20) DVT	Patients with VTE where older, had lower lymphocyte counts, longer aPTT, and higher D-dimer level Suggest using D-dimer of > 1500 ng/mL as predictor of VTE
Zhang L, et al.[30]	143 hospitalized patients	Screened with CUS	37.1% received LMWH prophylaxis	46.1% (n=66) DVT 16.1% (n=23) proximal DVT 30.0% (n=43) distal DVT	Patients with DVT had higher D-dimer (6600 vs. 900 ng/mL; p<0.001)
Ren B, et al.[31]	48 ICU patients	Screened with CUS	Enoxaparin 30-40 mg QD	85% (n=41) DVT 10% (n=5) proximal DVT 75% (n=36) distal DVT	Median D-dimer level (p=0.09) No DVT=900 ng/mL Distal DVT=5310 ng/mL Proximal DVT=3530 ng/mL
Llitjos J-F, et al.[32]	26 ICU patients	Screened with CUS	LMWH or UFH prophylaxis in 31% and therapeutic doses in 69%	69% (n=18) DVT 23% (n=6) PE	VTE occurred more often in patients receiving prophylactic vs. therapeutic anticoagulation (100% vs. 56%; p=0.03). All PE occurred

					with therapeutic doses.
Trigonis RA, et al.[33]	45 ICU patients on ventilator	Screened with CUS	Enoxaparin 40 mg QD (16%), 30 mg BID (35%), 40 mg BID (13%), UFH (26%), and other (9%)	42% (n=19) DVT	Patients with DVT had higher D-dimer (6911 vs. 3148 ng/mL; p<0.01) No differences between prophylaxis regimens (p=0.35), but numbers too small to make comparisons
Klok FA, et al.[34]	184 ICU patients	Clinical suspicion evaluation	Nadroparin 2850 IU QD and 5700 IU QD if > 100 kg, or 5700 IU QD and BID if > 100 kg	31% (n=57) thrombosis 27% (n=50) VTE 3.8% (n=7) arterial	81% of VTE were PE (n=25) Predictors of thrombosis were age, prolonged PT > 3 sec, or aPTT > 5 sec
Beun R, et al.[35]	75 ICU patients	Clinical suspicion evaluation	LMWH or UFH	33.3% (n=25) thrombosis 26.7% (n=20) PE 4.0% (n=3) DVT 2.7% (n=2) ischemic stroke	
Maatman TK, et al.[36]	109 ICU patients	Clinical suspicion evaluation	56% UFH 5000 IU TID, 24% enoxaparin 40 mg QD, or 13% enoxaparin 30 mg BID. 6%	28% (n=31) VTE	Patients with VTE had higher D-dimer (4046 vs. 1934 ng/mL; p<0.001)

			received therapeutic anticoagulation		
Hippensteel JA, et al.[37]	91 ICU patients	Clinical suspicion evaluation	LMWH or UFH prophylaxis in 46% and therapeutic doses in 54%	26% (n=24) VTE 5.5% (n=5) lower-extremity DVT 6.6% (n=6) upper-extremity DVT 8.8% (n=8) jugular thrombosis 5.5% (n=5) PE	Patients with VTE had more days on the ventilator (15 vs. 11 days; p=0.02) and longer length of stay (26 vs.16 days; p=0.001) 73% of patients requiring ECMO developed VTE
Demelo-Rodriguez P, et al.[38]	156 ward patients	Screened with CUS if D-dimer >1000 ng/mL	98% received LMWH	14.7% (n=23) DVT 0.6% (n=1) proximal DVT 14.1% (n=22) distal DVT 4.5% (n=7) bilateral DVT	Patients with DVT had higher D-dimer (4527 vs. 2050 ng/mL)
Santoliquido A, et al.[39]	84 ward patients	Screened with CUS	97.6% received enoxaparin 40 mg QD and 2.4% received fondaparinux 2.5 mg QD	11.9% (n=10) DVT 2.4% (n=2) proximal DVT 9.5% (n=8) distal DVT 4.7% (n=4) bilateral DVT	Mean PADUA score of 5.1 Patients with DVT were more likely to have a D-dimer > 3000 ng/mL (60% vs. 23%; p<0.05)
Criel M, et al.[40]	82 patients = 52 ward	Clinical suspicion	Enoxaparin 40 mg QD or 60 QD if >100 kg in	7.3 % (n=6) VTE	Rate of VTE was higher in ICU patients (13% vs. 4%)

	patients and 30 ICU patients	evaluation	ward patients. Enoxaparin 40 mg BID or 60 mg BID if >100 kg in ICU patients		All patients with VTE in the ICU were on mechanical ventilation
Middeldorp S, et al.[41]	198 patients = 123 ward patients and 75 ICU patients	Screening with CUS	84% nadroparin 2850 IU QD and 5700 QD if > 100kg and ICU patients BID 9.6% therapeutic AC	20% (n=39) VTE 13% (n=25) symptomatic VTE 6.6% (n=13) PE 7.1% (n=14) proximal DVT 5.6% (n=11) distal DVT 0.5% (n=1) upper extremity	13% COVID-19 diagnosis not confirmed. D-dimer higher in ICU patients (2000 vs. 1100 mg/mL; p=0.006) VTE higher in ICU patients (47% vs. 3.3%; HR 7.9, 95% CI 2.8 – 23) Symptomatic VTE higher in ICU patients (28% vs. 3.3%; HR 3.9, 95% CI 1.3 – 12)
Marone EM, et al.[42]	30 ward patients with COVID-19 and 24 ward patients in 2019	All received CUS for clinical suspicion	Not mentioned	53% (n=16) DVT in COVID-19 patients 20.8% (n=5) DVT in 2019	
Poissy J, et	303 patients	Clinical	All patients received	Higher PE rate in COVID-19	91% of COVID-19 patients with PE

al.[43]	= 107 with COVID-19 and 196 during same time in 2019 (40 with influenza)	suspicion evaluation	guideline appropriate thromboprophylaxis	patients compared to 2019 (20.7% vs. 6.1%). Higher PE rate in COVID-19 patients compared to 2019 influenza (20.7% vs. 7.5%)	received some type of anticoagulation prior to diagnosis Report “low number of associated DVT” but number not provided.
Helms J, et al.[44]	222 matched patients = 77 ICU COVID-19 ARDS patients and 145 non-COVID-19 ARDS patients from 2014-2019	Clinical suspicion evaluation	LMWH or UFH COVID-19 patients 78% prophylaxis 22% treatment dose Non-COVID-19 patients 76% prophylaxis 24% treatment dose	COVID-19 vs. non-COVID-19 Thrombotic events (11.7% vs. 4.8%; p=0.04) PE (11.7 vs. 2.1%; p=0.01) DVT (0% vs. 2%; p=NS)	

VTE=venous thromboembolism; COVID-19=coronavirus 2019 infection; ICU=intensive care unit; CUS=compression ultrasound; DVT=deep vein thrombosis; aPTT=activated partial thromboplastin time; LMWH=low molecular weight heparin; QD=once daily; UFH=unfractionated heparin;

PE=pulmonary embolism; BID=twice daily; PT=prothrombin time; TID=three times daily; ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome.

AC=anticoagulation

Table 4. VTE risk assessment models[77,78]

Baseline features	Score
Active cancer‡	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility§	3
Already known thrombophilic condition¶	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30)	1
Ongoing hormone therapy	1

Padua Score†

VTE=venous thromboembolism; BMI=body mass index

† A score of 4 or higher demonstrates high risk of VTE and pharmacologic prophylaxis should be used.

‡ Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months.

§ Anticipated bed rest with bathroom privileges (either because of patient's limitations or on physician's order) for at least 3 days.

¶ Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

IMPROVE VTE Risk Score†

VTE Risk Factor	VTE Risk Score
Previous VTE	3
Known thrombophilia ‡	2
Current lower limb paralysis or paresis	2
History of cancer §	2
ICU/CCU stay	1
Complete immobilization ≥1 day¶	1
Age ≥60 years	1

† A score of 4 or higher demonstrates high risk of VTE and pharmacologic prophylaxis should be used.

‡ Congenital or acquired condition leading to excess risk of thrombosis

§ Cancer present at any time in the last 5 years

¶ Confined to bed or chair with or without bathroom privileges

IMPROVE=International Medical Prevention Registry on Venous Thromboembolism; VTE=venous thromboembolism; ICU=intensive care unit; CCU=cardiac care unit

Table 5. Patient criteria for use of extended VTE prophylaxis with betrixaban and rivaroxaban.[89-91]

	APEX Trial[89] (betrixaban trial)	**MAGELLEN Trial[90,91] (rivaroxaban trial)**
Inclusion criteria (on admission)	Age 40 years or older Hospitalized for acute medical illness Reduced mobility for at least 3 days Risk factors for VTE	Age 40 years or older Hospitalized for acute medical illness Reduced mobility for at least 4 days Risk factors for VTE
Acute medical illness	Acute decompensated heart failure Acute respiratory failure Acute infectious disease Acute ischemic stroke Acute rheumatic disease	NYHA class III or IV heart failure Acute respiratory insufficiency Acute infectious or inflammatory disease Acute ischemic stroke Active cancer
Additional risk factors	Age 75 years or greater, or Age 60 to 74 years with two additional risk factors or D-dimer at least 2-times the upper limit of normal, or Age 40 to 59 years with either a history of VTE or history of cancer, plus 1 additional risk factor or D-dimer at least 2-times the upper limit of normal Additional risk factors include: Previous VTE of superficial vein thrombosis History of NYHA class III or IV heart failure	History of cancer History of VTE History of NYHA class III or IV heart failure Major surgery or trauma in last 6-12 weeks Age 75 years or older BMI 35 or greater Acute infectious disease contributing to hospitalization Thrombophilia Chronic venous insufficiency

	Concomitant acute infection BMI 35 or greater History of cancer Inherited or acquired thrombophilia Current use of erythropoiesis stimulating agent Hormone therapy	Severe varicosities Hormone replacement therapy
Key exclusions	CrCl less than 15 mL/min Anticipated need for prolonged anticoagulation Receiving therapeutic anticoagulation for another indication Increased risk of bleeding History of bronchiectasis or active lung cancer History of intracranial bleeding History of head trauma or trauma in last 3 months Patients in shock syndrome Pregnancy or breastfeeding	CrCl less than 15 mL/min Receiving therapeutic anticoagulation for another indication Increased risk of bleeding History of intracranial bleeding History of head trauma in last 30 days Use of strong inhibitors or inducers of cytochrome P450 3A4 Patients with active cancer as their reason for admission Use of dual antiplatelet therapy History of bronchiectasis/pulmonary cavitation Active gastrointestinal bleeding Any bleeding within the previous 3 months Pregnancy or breast feeding

VTE=venous thromboembolism; NYHA=New York Heart Association; BMI=body mass index; CrCl=creatinine clearance

Table 6. Guideline or consensus statement recommendations for prevention and treatment of VTE in COVID-19.[52, 29, 100-103]

Guideline	Professional Organizations from China[52]	Bikdeli B, et al.[79] †	ACCP Guideline and Expert Panel[100]	AC Forum[101]	ISTH SSC[102]	SISET[103]
VTE prophylaxis may be considered in patients with COVID-19 treated at home if risk is considered high based on risk assessment models (IMPROVE or PADUA)	X	X				
Acutely ill hospitalized patients with COVID-19 should receive anticoagulant thromboprophylaxis.	X	X	X	X	X	X
Critically ill patients with COVID-19 should receive anticoagulant thromboprophylaxis	X	X	X	X	X	X
In acutely ill hospitalized patients with COVID-19, anticoagulant thromboprophylaxis with LMWH or fondaparinux is recommended over UFH. LMWH, fondaparinux, or UFH is recommended over a DOAC.	X		X			
In critically ill hospitalized patients with COVID-19, anticoagulant thromboprophylaxis with LMWH or fondaparinux is recommended over UFH. LMWH, fondaparinux, or UFH is recommended over a DOAC.	X		X			

In acutely ill hospitalized patients with COVID-19, standard dose anticoagulant thromboprophylaxis is recommended over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing.			X	X		X
In critically ill hospitalized patients with COVID-19, standard dose anticoagulant thromboprophylaxis is recommended over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing.			X			X
Critically ill patients with confirmed or highly suspected COVID-19, increased doses of VTE prophylaxis are recommended or can be considered (enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, UFH 7500 units TID)				X	X	X
Biomarker thresholds for inflammatory markers are not recommended as the sole reason to escalate anticoagulant dosing		X		X	X	
In patients with COVID-19 extended thromboprophylaxis after hospital discharge is not routinely recommended for all patients.			X	X		
Extended VTE prophylaxis after hospital discharge is reasonable to consider after a multidisciplinary discussion	X			X	X	X

and the patient has ongoing risk factors for VTE						
In critically ill patients with COVID-19 the addition of mechanical prophylaxis to pharmacological thromboprophylaxis is not recommended			X			
In critically ill patients, it is reasonable to employ both pharmacologic and mechanical VTE prophylaxis provided no contraindication to either exists				X	X	
In critically ill patients with COVID-19 who have a contraindication to pharmacological thromboprophylaxis, mechanical thromboprophylaxis is recommended.	X		X	X		
For acutely ill hospitalized COVID-19 patients with proximal DVT or PE, initial parenteral anticoagulation with therapeutic weight adjusted LMWH or intravenous UFH is recommended.			X	X	X	
In patients without any drug-to-drug interactions, initial oral anticoagulation with apixaban or rivaroxaban is suggested. Dabigatran and edoxaban can be used after initial parenteral anticoagulation. Vitamin K antagonist therapy can be used after overlap with initial parenteral anticoagulation.			X		X	

For outpatient COVID 19 patients with proximal DVT or PE and no drug-to-drug interactions, apixaban, dabigatran, rivaroxaban, or edoxaban are recommended. Initial parenteral anticoagulation is needed before dabigatran and edoxaban. For patients who are not treated with a DOAC, vitamin K antagonists are recommended over LMWH (for patient convenience and comfort).			X		X	
In critically ill COVID-19 patients with proximal DVT or PE, parenteral over oral anticoagulant therapy is recommended. In critically ill COVID-19 patients with proximal DVT or PE who are treated with parenteral anticoagulation, LMWH or fondaparinux is recommended over UFH.	X		X		X	
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), systemic fibrinolytic therapy is not recommended			X	X		
In patients with COVID-19 and both acute, objectively	X		X	X		

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, systemically administered fibrinolytics are recommended						

VTE=venous thromboembolism; COVID-19=2019 coronavirus infection; ACCP=American College of CHEST Physicians; AC=Anticoagulation; ISTH SSC=International Society of Thrombosis and Haemostasis Scientific Standards Committee; SISET=Italian Society on Thrombosis and Haemostasis; IMPROVE=International Medical Prevention Registry on Venous Thromboembolism; LMWH=low molecular weight heparin; UFH=unfractionated heparin; DOAC=direct oral anticoagulant; BID=twice daily; TID=three times daily; DVT=deep vein thrombosis; PE=pulmonary embolism

† Global COVID-19 Thrombosis Collaborative Group, Endorsed by the International Society of Thrombosis and Haemostasis, North American Thrombosis Forum, European Society of Vascular Medicine, and International Union of Angiology; and supported by the European Society of Cardiology Working Group on the Pulmonary Circulation and Right Ventricular

Table 7. Clinical considerations for the prevention and treatment of VTE in patient with COVID-19.

Clinical Consideration	Comment
Coagulopathy monitoring should include a PT, aPTT, platelets, D-dimer, and fibrinogen	D-dimer should be used as a measure of disease severity, but should not be used as a marker to increase VTE prophylaxis intensity or use therapeutic anticoagulation. Fibrinogen will typically be elevated, and a decrease in severely ill patients, along with elevations in PT, can be an indicator of the patient transitioning to DIC.
Symptomatic patients treated at home with an elevated IMPROVE or Padua score should be considered for VTE prophylaxis	Significant fatigue and myalgia are common symptoms of COVID-19 leading patients to have immobility. With the addition of additional risk factors, especially previous VTE, and hypercoagulability of infection, VTE prophylaxis can be considered.
All general ward and ICU patients should receive VTE pharmacologic prophylaxis without risk assessment	Observational studies have demonstrated a higher rate of VTE than expected in both general ward and ICU patients. Due to the coagulopathy in patients with COVID-19, VTE prophylaxis without risk assessment is recommended in all guideline and consensus documents that address the issue.
Patients with contraindications to pharmacologic prophylaxis (current bleeding, platelet count < 50 x 10^9) should receive mechanical prophylaxis with pneumatic compression.	This is consistent with recommendations in patients without COVID-19
VTE prophylaxis in general ward patients should be provided with standard dose LMWH (enoxaparin† 40 mg QD) or UFH	Use of standard dose LMWH or UFH in general ward patients is consistent with most guideline and consensus documents. Both agents may provide an anti-inflammatory

(5000 units TID), with preference to the use of LMWH.	effect that may be beneficial in patients with COVID-19, but this is not proven. LMWH is preferred to UFH due to the need for less injections per day, which decreases health care professional exposure to infected patients and preserves personal protective equipment.
Increased doses of enoxaparin† should be provided in patients with obesity (60 mg QD if BMI > 30 kg/m^2, 40 mg BID if BMI > 40 kg/m^2, or 0.5 mg/kg). If UFH is used, consider 7500 units TID.	Data suggests that higher doses of enoxaparin provide better anti-Xa response and/or a reduction of VTE events.
Decreased doses of enoxaparin† of 30 mg QD should be used in patients with a CrCl 15-30 mL/min. If UFH is used, consider BID dosing. Patients with a CrCl < 15 mL/min should receive UFH.	This dose of enoxaparin is consistent with the labeling for the drug. Use of enoxaparin in this setting still allows for less doses per day compared to UFH. Data with anticoagulants with renal failure is limited and UFH is preferred.
Intermediate-dose enoxaparin† (60 mg QD, 40 mg BID, or 0.5 mg/kg) should be used in ICU patients, especially in patients on mechanical ventilation or with ARDS.	Observational studies have demonstrated a higher risk of VTE than would be expected in ICU patients. Most of these studies demonstrated these high rates of VTE while patients were receiving standard dose VTE prophylaxis.
The use of therapeutic doses of enoxaparin† or UFH should not be used for VTE prophylaxis.	Although a few reports suggest benefit of this approach, these data have significant limitations. Although bleeding is rare in patients with COVID-19, this approach requires evaluation in randomized controlled trials, which are currently underway.
At the time of discharge, patients should be evaluated as potential candidates for extended VTE prophylaxis using the trial	Although not specifically evaluated in the clinical trials, some patients with COVID-19 would have met the trial entry criteria and should recognize similar benefits. Rivaroxaban is

criteria, rivaroxaban is preferred over enoxaparin. Apixaban, dabigatran, and edoxaban should be avoided.	preferred due to benefit without an increase in major bleeding. Enoxaparin demonstrated benefit, but with more major bleeding. Apixaban demonstrated no benefit and more major bleeding. Dabigatran and edoxaban have not been evaluated for extended VTE prophylaxis.
Patients with VTE should receive therapeutic doses of enoxaparin† (1 mg/kg BID or 1.5 mg/kg QD) or UFH (80 unit/kg bolus followed by 18 units/kg/hr), with preference given to use of LMWH.	Monitoring of UFH requires frequent monitoring and dose adjustments, especially early in therapy. LMWH allows for QD or BID dosing and decreases health care professional exposure to infected patients and preserves personal protective equipment. This is also consistent with the preference of LMWH over UFH for treatment of VTE in patients without COVID-19.
If UFH is selected for VTE treatment, and the aPTT immediately before initiating UFH is prolonged, monitoring with an aPTT should be avoided and anti-Xa should be used.	If the aPTT in patients with COVID-19 is prolonged due to the coagulopathy, the aPTT is unreliable and should not be used to monitor UFH. Anti-Xa is not impacted by COVID-19 coagulopathy and is an appropriated substitution for the aPTT.
A DOAC may be considered for VTE treatment in general ward patients without need for invasive procedures or drug interactions.	The use of DOACs in hospitalized patients can be problematic if invasive procedures are needed, requiring longer hold times that may delay procedures. The use of DOACs may also be limited by drug interactions with certain antiviral therapies, such as lopinavir/ritonavir. If the perceived need for invasive procedures is low, and no drug interactions exist, DOACs could be considered as initial therapy for treatment of VTE in non-ICU patients. These conditions are unlikely to exist in ICU patients.
Fibrinolytic therapy should be not be used for patients with COVID-19 and ARDS,	Only case series have demonstrated a potential benefit in treating patients with COVID-19 and ARDS. Due to the

unless the patient has hemodynamically compromised PE.	significant bleeding risk of systemic fibrinolytic therapy, the results of ongoing randomized controlled trials are needed. Use in patients with hemodynamically compromised PE is consistent with use in patients without COVID-19.

VTE=venous thromboembolism; COVID-19=coronavirus 2019 infection; PT=prothrombin time; aPTT=activated partial thromboplastin time; DIC=disseminated intravascular coagulopathy; IMPROVE= International Medical Prevention Registry on Venous Thromboembolism; ICU=intensive care unit; LMWH=low molecular weight heparin; QD=once daily; UFH=unfractionated heparin; TID=three times daily; BMI=body mass index; CrCl=creatinine clearance; BID=twice daily; DOAC=direct oral anticoagulant; ARDS=acute respiratory distress syndrome; PE=pulmonary embolism.

† Dosing is recommended and doses provided specifically since it is the most common LMWH used in the United States. Other LMWHs, such as dalteparin or nadroparin, can also be used. Escalation from 5000 IU once daily to 5000 IU BID or 7500 IU (or even 10,000 IU QD in obese patients) can be considered if dalteparin is the formulary LMWH. Adjust doses based on clinical trial data and equal potent anti-Xa units.