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Role of Acute Thrombosis in Coronavirus Disease 2019

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KEYWORDS

• COVID • Thrombosis • Coronary thrombus • Anticoagulation • NETs • D-dimer

KEY POINTS

- Patients infected with the SARS CoV-2 virus are at increased risk of thrombosis and coagulopathy.
- Patients with cardiovascular disease are predisposed to COVID-19 infection, and once infected, they are at elevated risk for cardiovascular complications.
- Most patients with COVID-19 who experienced strokes developed ischemic stroke.
- D-dimer is very commonly elevated during acute SARS-CoV-2 infection, particularly in hospitalized patients, rendering D-dimer alone of limited use in the assessment of VTE.
- Moderately ill patients with COVID-19 have a significant benefit from therapeutic-dose heparin compared with usual care-dose heparin in organ-free support days.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread across the world in late 2019 and early 2020 causing mild to severe multisystem disease. In addition to respiratory symptoms, coronavirus disease 2019 (COVID-19) causes coagulopathy, particularly in critically ill patients.[1–3] Thrombosis is crucial in infection to protect the host by limiting dissemination of viral and other pathogens, but when uncontrolled can cause tissue damage.[4,5] The pathogenesis of SARS-CoV-2 is exacerbated by microthrombi and macrothrombi that compromise circulation and threaten organ function.[6] In addition to limiting blood flow, the positive feedback loop of the immune response perpetuating clots further exacerbates inflammation and contributes to disease burden in COVID-19. Herein, the latest

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Abbreviations	
NETs	neutrophil extracellular traps
MPO	myeloperoxidase
NE	neutrophil elastase
IL	interleukin
COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CVA	cerebrovascular accident
VTE	venous thromboembolism
DVT	deep vein thrombosis

epidemiology, biologic mechanisms, organ-specific considerations, and therapeutic trials regarding thrombosis in COVID-19 are reviewed.

PATHOGENESIS OF CORONAVIRUS DISEASE 2019-INDUCED THROMBOSIS

The mechanisms by which SARS-CoV-2 infection promotes coagulopathy include host- and virus-related factors. Neutrophil extracellular traps (NETs) are weblike structures composed of DNA, histones, and immunomodulatory proteins that trap and kill microorganisms.[7,8] NETs have been implicated in thrombus formation via multiple mechanisms.[9–12] The SARS-CoV-2 virus and plasma from patients with COVID-19 can induce neutrophils to form NETs ex vivo.[13,14] NETs—detected by the presence of MPO-DNA and/or NE-DNA complexes—are increased in the blood of hospitalized patients with COVID-19 compared with healthy controls.[13,15,16] NET concentrations correlate with severity of SARS-CoV-2 disease.[14,16] Histologic analysis of autopsy tissue from patients who died of COVID-19 showed NETs within vascular thrombi, although whether NETs initiate clots or NET formation is activated by platelets at the site of preformed clots remains unclear.[15,17] The authors have demonstrated that NETs can cause human airway epithelia to increase secretion of interleukin IL-1 cytokines, another potential mechanism by which NETs could contribute to COVID-19 pathogenesis.[18] Drugs that affect NETs in COVID are currently being trialed. Endothelial, complement, and platelet activation also contribute to coagulopathy in COVID-19, the details of which are described in recent excellent reviews.[19,20]

EPIDEMIOLOGY OF VASCULAR THROMBI IN CORONAVIRUS DISEASE 2019

Patients infected with the SARS-CoV-2 virus are at increased risk of thrombosis and coagulopathy for reasons previously described, with coagulopathy itself predicting worse prognosis. In an early study of 184 Dutch patients in the intensive care unit (ICU), 27% of patients were found to have a venous thromboembolism (VTE)—most commonly due to pulmonary embolism (PE)—whereas 3.7% had an arterial thrombus. This study was evaluating symptomatic thrombotic events and did not include a universal screen; however, it demonstrated an overall thrombosis rate of 31%, which was higher than seen in other studies.[21] A study that included lower-extremity Dopplers on admission for 26 patients with COVID-19 in 2 French ICUs found an overall VTE rate of 69%. Moreover, high rates of PE and deep vein thrombosis (DVT) were observed on subsequent imaging, even in those treated with therapeutic anticoagulation.[22] Another small study using routine lower extremity Dopplers in a French ICU found DVTs in 22 (65%) patients on admission and 27 (79%) after 48 hours.[23] Of note, all 3 of these studies were limited to 1 to 2 centers and were performed early in the pandemic when treatment and anticoagulation protocols varied significantly across institutions.

A large cohort study evaluated the incidence of VTE in greater than 3000 patients in the United States within 2 weeks of ICU admission. Only 3 of the 67 sites did routine

screening with imaging, for most patients radiographic evaluation was at the discretion of the treating team. The VTE incidence was found to be 6.3% in greater than 3000 patients.[24] This incidence is significantly lower than the initial studies of VTE in COVID-19; however, this US study did not include a universal screening protocol and excluded patients with confirmed or suspected DVT at the time of study enrollment.[24] Given the lack of a universal screening protocol, it is possible that many patients have thrombi that go undetected because they are asymptomatic or the contribution of microthrombi and macrothrombi were underrecognized. Furthermore, it is possible that if these studies were repeated now, rates of VTE may be further altered by our evolved standard-of-care treatments, for example, dexamethasone, for COVID-19.[71] Moreover, we agree with the National Institutes of Health (NIH) guidelines that recommend imaging for thrombi as part of the assessment of patients with COVID-19 with significant clinical deteriorations, if not contraindicated.[25]

CVA IN CORONAVIRUS DISEASE 2019

There have been varying reports on the risk of stroke in COVID-19 with rates ranging from 0.5% to 6%.[72,73] Initial reports from China suggested that the overall rate of strokes and vascular interventions for the general population was decreased during COVID-19.[74] However, this may have been due to external factors including reduced health care utilization and decreased use of vascular imaging during initial phases of the pandemic. A cross-sectional study using data from a New York health care system discharge and billing database of 24,808 patients (566 of whom were COVID-19 positive) showed an odds ratio (OR) of 0.25 of developing stroke compared with age- and comorbidity-matched COVID-19-negative patients.[26] More recent large meta-analyses suggest an incidence closer to 1.3% to 1.5%. When looking at the patients with COVID-19 who developed cerebrovascular events, they were approximately 4.5 to 6 years younger than their noninfected counterparts in the general population.[27,28] These patients often had the same cardiovascular risk factors such as coronary artery disease, hypertension, and diabetes. One important risk factor for development of stroke is COVID-19 disease severity.[28,29] In one meta-analysis, patients with severe COVID-19 had an incidence of 3.37%, whereas patients without severe disease had an incidence of 0.6%.[30] It is difficult to know the true incidence of stroke in COVID-19, in part due to critically ill patients—who are at the highest risk of stroke—often being intubated. We suspect that incidence of CVA in critically ill patients is underestimated because (1) patients are too sick to be transported for brain imaging, (2) neurologic examinations are limited in patients on sedation used for mechanical ventilation/proning leading to an underappreciation of potential deficits, and (3) patients die before imaging can occur or a meaningful neurologic examination can be completed.

Most patients with COVID-19 with strokes developed ischemic stroke (around 87%). In addition, 44.7% of strokes were cryptogenic and 21.9% were cardioembolic. The absence of atherosclerotic disease as a significant cause of stroke in this population is one possible explanation for the earlier age of onset. Compared with patients without COVID-19 infection, large vessel occlusion was seen around two and a half times more often.[28]

CORONARY THROMBOSIS IN CORONAVIRUS DISEASE 2019

Patients with cardiovascular disease are predisposed to COVID-19 infection, and once infected, they are at elevated risk for cardiovascular complications.[31] A significant source of COVID-19-related cardiac risk comes from myocardial injury related to coronary thrombosis. Case series from New York and Wuhan in early 2020 showed

patients presenting with ST elevation on electrocardiogram and elevated cardiac biomarkers of injury (troponin).[32,33] Troponin elevation as a sign of myocardial injury is an important marker of adverse prognosis in patients with COVID-19; patients with abnormally elevated troponin levels in the setting of COVID-19 are more likely to be admitted to the ICU and are more likely to die.[34] Case series have reported the incidence of acute myocardial injury (defined as both elevated levels of biomarkers and electrocardiographic abnormalities) in patients with COVID-19 ranging from 12% to 19.7%.[35,36] However, other than small case series, the true incidence of myocardial injury with COVID-19 is unclear because these series are mostly in hospitalized patients and we know that patients with comorbidities of coronary artery disease such as hypertension and diabetes are also more likely to be hospitalized with COVID-19. In addition, several case series only examined patients who had undergone coronary angiograms to define the incidence of coronary thrombosis. In many parts of the world, the COVID-19 pandemic changed practice patterns due to health care rationing such that patients who might have routinely undergone invasive cardiac testing were instead managed conservatively. For example, in Wuhan, one hospital system's published algorithm for patients with COVID-19 presenting with ST-elevation myocardial infarction articulated a delay in management of coronary thrombosis in patients with severe pneumonia and in those with less severe pulmonary disease, a fibrinolytic first strategy was recommended.[37]

PATHOPHYSIOLOGY OF CARDIAC THROMBUS IN COVID-19

The burden of coronary thrombosis varies widely, ranging from nonobstructive thrombus to large thrombi burden in multiple vessels.[38] Patients with COVID-19 with myocardial infarction can have coronary thrombus in epicardial vessels that can be associated with coronary stenosis or plaque rupture, similar to patients without COVID-19. However, there are also numerous reports of patients with COVID-19 with epicardial thrombus without any evidence of coronary artery atherosclerotic plaque or stenosis and cases in which no epicardial vessel thrombus was seen during coronary angiogram.[39] In these cases, it is likely that microemboli or thrombosis in vessels that are not visible to the naked eye on coronary angiogram could still be causing significant myocardial injury. In a case series of postmortem examinations of 40 hearts from patients who died of COVID-19, 35% had evidence of myocardial necrosis.[40] Of these cases, only 2 (14.2%) had evidence of epicardial coronary artery thrombi, whereas the rest had evidence of microthrombi in myocardial capillaries, arterioles, and small muscular arteries.[40]

Timing of coronary thrombosis during a COVID-19 infection also needs further elucidation, but there is some evidence that this is an early phenomenon. In one case series from Lombardy, Italy, 85% of patients diagnosed with coronary thrombosis by coronary angiogram presented with chest pain and ST-segment elevations before diagnosis of COVID-19 and the remainder were diagnosed with ST-segment elevation myocardial infarction during the hospitalization.[41] Owing to the heterogeneous patient population (including many patients who are at high risk for coronary events due to many cardiac comorbidities), it is important to have myocardial ischemia as a differential diagnosis for new patients presenting with COVID-19 and for patients with COVID-19 who clinically decompensate during a hospitalization.

There are several potential mechanisms for why COVID-19 may cause coronary thrombosis. There are many similarities between the potential causes of coronary thrombosis and the postulated causative role of COVID-19 in thrombosis in other vascular distributions. Specifically, there are 4 proposed hypotheses, which are not mutually exclusive, to explain the large role that cardiovascular system plays in

morbidity and mortality in COVID-19. (1) Cardiac tissue is a substrate for SARS-CoV-2 binding. (2) The role of SARS-CoV-2-induced endothelial dysfunction causes acute thrombosis. (3) Proinflammatory immune responses to the virus cause acute thrombosis. (4) COVID-19 preferentially affects people with cardiovascular risk factors.

The SARS-CoV-2 virus has an affinity for the angiotensin-converting enzyme (ACE) receptor, which is highly concentrated in myocardial tissue, and this could explain the role of COVID-19 in causing coronary thrombosis, myocarditis, and arrhythmias. The ACE receptor is also found on vascular endothelium, and endothelial dysfunction could result in the inciting injury that is further propagated by the proinflammatory state of acute infection associated with severe COVID-19 infection. The proinflammatory cascade is known to interfere with the coagulation to form a prothrombotic milieu that can then proceed to acute myocardial infarction, as has been shown in other types of acute infection including other types of pneumonia.[42,43] Finally, all of this is occurring in a patient group with multiple coronary artery disease risk factors including preexisting coronary artery disease, older age, hypertension, and diabetes.[44] The combination of high affinity for myocardial tissue for SARS-CoV-2 binding, endothelial dysfunction, proinflammatory state, and the at-risk patient cohort contributes to the risk for coronary thrombosis in patients with COVID-19.

TREATMENT OF CORONARY THROMBUS IN CORONAVIRUS DISEASE 2019

In cases of suspected coronary thrombosis with ST-segment elevation myocardial infarction the recommendation of the American College of Cardiology is to proceed with primary percutaneous coronary intervention (PCI) unless there are limitations in local resources that might result in delayed care.[45] In situations that may result in delay to primary PCI, a fibrinolytic first strategy could be considered. This is similar to recommendations for the care of ST-segment elevation myocardial infarctions in the general population where geography, weather, or other systemic delays in care sometimes prevent a primary PCI strategy and fibrinolytics are still used. In cases of non-ST elevation myocardial infarction or in cases in which an ST elevation diagnosis is not clear, efforts should be made to differentiate between demand ischemia from occlusive coronary thrombosis. Tools that could help with such differentiation include trending biomarkers, serial electrocardiograms, and point-of-care echocardiography. If the patient is clinically stable and symptom free—depending on the local resources needed for the care of other patients—a deferred strategy can be considered with medical treatment with antiplatelet and antithrombotic agents. Of note, patients with COVID-19 frequently present with thrombocytopenia with one study showing 36% of patients diagnosed with COVID-19 presenting with a platelet count of less than 150,000/μL.[46] The risk/benefit for antiplatelet and antithrombotic therapy in these patients needs to be individualized, and careful monitoring for both bleeding and thrombotic complications is essential. Finally, in cases in which a patient undergoes a coronary angiogram and no occlusive epicardial disease is found, consideration should then turn toward other causes of elevated troponin levels including myocarditis, stress-induced cardiomyopathy (Takotsubo), and microvascular coronary ischemia.

CURRENT EVIDENCE FOR PREVENTION OF MICROTHROMBI AND MACROTHROMBI IN CORONAVIRUS DISEASE 2019

There has been a substantial amount of research on whether anticoagulation or antiplatelet therapy changes outcomes and rates of thrombosis in patients with COVID-19. Earlier studies primarily focused on an end point of thrombosis and mortality; however, when most of those were negative or showed no benefit to anticoagulation, later

studies began to focus on risk stratification with severity of illness, location of treatment (ICU vs floor), and laboratory evaluation. In addition, as described herein, the presence of PE or stroke significantly increases mortality. Because of this, there was significant interest in prevention of thrombosis with multicenter clinical trials testing full-dose versus prophylactic-dose anticoagulation as well as different antithrombotic agents.

Although most trials focused on anticoagulation on the inpatient side, there are several studies in progress to assess the use of prophylactic dose anticoagulation as an outpatient during SARS-CoV-2 infection. PREVENT-HD trial assessed the safety and efficacy of Xarelto 10 mg daily on an outpatient basis for 35 days.[47] Two trials, the OVID trial and the early thromboprophylaxis in covid-19 (ETHIC) trial, are comparing 40 mg subcutaneous lovenox daily versus placebo.[48,75] The accelerating covid-19 therapeutic interventions and vaccines (ACTIV-4b trial studied apixaban (2.5 or 5 mg twice daily) versus 81mg of aspirin daily versus placebo. This trial was stopped early at an interim evaluation due to lack of thrombotic events in all arms of the study.[49] At present, there are insufficient data to support routine use of prophylactic anticoagulation on an outpatient basis.

XARELTO

The anticoagulation coronavirus (ACTION) trial was one of the early trials, and it compared treatment-dose Xarelto (20 mg or 15mg daily) in stable patients and lovenox at 1 mg/kg twice a day or IV unfractionated heparin in unstable patients with prophylactic dosing anticoagulation in hospitalized patients followed by Xarelto, all totaling 30 days.[50] Clinically unstable patients had severe COVID-19, a life-threatening comorbidity and required mechanical ventilation or the ICU. It should be noted that in this trial, only 39 of the 615 patients were deemed clinically unstable. There was no difference in the primary outcome of mortality (11.3% in therapeutic arm, 7.6% in prophylactic), but there was a trend toward higher mortality in the treatment arm. There were nonsignificant trends toward lower VTE rate (3.5% in treatment arm, 5.9% in prophylactic arm). The only clinical end point to reach significance was ISTH-defined bleeding, which occurred in 8.3% of patients in the treatment group compared with 2.3% of the patients receiving prophylactic doses of anticoagulation.[50]

APIXABAN

A trial of prophylactic apixaban versus subcutaneous low-molecular-weight heparin (LMWH) demonstrated a significant decrease in mortality with prophylactic-dose apixaban or prophylactic-dose enoxaparin when compared with no anticoagulation at all. The investigators also saw a decrease in mortality in the therapeutic-dose anticoagulation arms; however, there was no significant difference between therapeutic and prophylactic. A subgroup analysis revealed that patients with COVID-19 with a normal D-dimer level less than 1.0 did not benefit from anticoagulation, whereas patients with very high levels of D-dimers (>10) did.[51]

ASPIRIN

The randomized evaluation of covid-19 therapy (RECOVERY) trial was a large multicenter trial in the United Kingdom looking at treatment of patients with COVID-19 admitted in a hospital with moderate-dose 150 mg aspirin daily to see if the anti-inflammatory effects had any significant decrease in hospitalization stay, progression to ventilator support, or mortality. In total, 14,892 patients were randomized. There was no difference in 28-day mortality or progression to invasive mechanical ventilation between those who did and did not receive aspirin. There was a small but significant

increase in discharge from hospital alive at 28 days (OR 1.06) and shorter duration of hospital stay in patients in the aspirin arm. For every 1000 patients treated with aspirin, there were 6 major bleeding episodes and 6 fewer thromboembolic events. Overall, aspirin did not show evidence of improving mortality or reducing progression of disease.[52] Trials of additional antiplatelet agents are currently ongoing in patients with moderate and severe COVID-19, for example, NCT04505774.

HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARINS

Most data regarding anticoagulation tested heparin, the historical agent of choice in VTE prophylaxis. There are multiple factors that make heparin more attractive than some other agents, such as avoiding drug interactions with tocilizumab that are seen with Xarelto or apixaban and the potential to reduce inflammation. Three multicenter, international, platform trials assessed the use of heparin: randomized, embedded multifactorial adaptive platform trial for community acquired pneumona (REMAP-CAP), ACTIV-4A, and antithrombotic therapy to ameliorate complications of covid-19 (ATTACC).[53,54] All these studies included a group of patients with critical COVID-19-related illness (severe) and a group of patients with moderate COVID-19. The definition of critically ill varied slightly between these trials. REMAP-CAP included patients admitted to the ICU, and ACTIV-4A enrolled severe patients on greater than 20L NC O2, regardless of their physical location (taking into accounting that many hospitals were having to expand ICU care beyond the ICU). In an effort to maximize enrollment and rapidly answer urgent clinical questions, these groups combined their data and analyzed the results together.[53,54]

The enrollment of critically ill patients was stopped early in December 2020 when no significant difference was seen in the primary outcome of organ support-free days for those who received therapeutic-dose heparin versus usual care dosing (prophylactic- or intermediate-dose subcutaneous (SQ) heparin). Sixty-two percent of 534 patients in the therapeutic heparin arm compared with 64.5% of the 564 patients in the usual care arm survived to hospital discharge. There were fewer thrombotic events noted with full-dose anticoagulation (7.2% vs 11.1%), and rates of major bleeding episodes (3.8% vs 2.3%) were similar between groups. It is important to note that the standard-of-care/prophylactic-dose anticoagulation arm used an intermediate-dose strategy in 51% of the patients.[54]

In contrast to the critically ill group, the moderately ill patients with COVID-19 had a significant benefit from therapeutic-dose heparin compared with usual care-dose heparin. After enrolling 2219 across the 3 platforms of hospitalized patients, there was a 98.6% probability of increasing organ support-free days with an OR of 1.27. When stratifying by patients with high and low levels of D-dimers the results were unchanged. Major bleeding did occur slightly more frequently in the therapeutic-dose group at 1.9% versus 0.9% prophylaxis group, although this did not reach statistical significance. Many of the secondary outcomes in this trial were promising. The rate of major thrombotic event (8.0% vs 9.9%; OR, 0.72; 95% confidence interval [CI], 0.53–0.90) were lower, and the rate of survival without organ support at 28 days (79.3% vs 75.4%; OR, 1.3; 95% CI, 1.05–1.61) was higher in the treatment-dose group. Patients on full-dose heparin had an 80.2% of survival to hospital discharge, compared with 76.4% in the usual care group, which did not reach statistical significance. As occurred in the severe group, there were moderate patients in the standard-of-care arm treated with an intermediate dose of heparin or LMWH; however, it was only about a quarter of patients. In addition, 20% of patients in the experimental group received lower than full therapeutic dose of heparin in the first 2 days after randomization.[53]

RAPID was a randomized controlled trial evaluating treatment of hospitalized non-ICU patients with either treatment dose or prophylactic dose anticoagulation.[55] This study enrolled 465 patients and at interim analysis was found to be underpowered to reach their primary end point, which was a composite of ICU admission, noninvasive or invasive ventilation, or mortality at 28 days. There was, however, a significant decrease in the individual secondary outcomes of all-cause mortality (1.8% vs 7.6%) and an increase in mean ventilator-free days. There was no significant difference in need for ICU admission, venous or arterial thromboembolism, or international society on thrombosis and haemostasis (ISTH)-defined major bleeding. In addition, unlike the results of the pooled multiplatform trials, only 1.7% of the prophylactic-dose patients received an "intermediate" dose for standard of care (SOC) and 2.6% of the treatment-dose-arm patients received a reduced "therapeutic" dose.[55]

In addition to therapeutic- versus prophylactic-dose anticoagulation, a trial designed specifically to test the intermediate-dose strategy was proposed to minimize bleeding risk in severely ill patients. The INSPIRATION trial enrolled 562 patients in an ICU setting randomized to prophylactic-dose enoxaparin 40 mg daily (with adjustments for renal function) versus an intermediate-dose regimen of 1 mg/kg daily. In this study, there was no significant difference in the rate of venous or arterial thrombosis, organ support on extracorporeal membrane oxygenation, or mortality at 30 days.[56]

Utilization of D-Dimer in Coronavirus Disease 2019

Many clinical laboratories have been proposed to prognosticate risk of thrombosis in COVID-19, with D-dimer receiving considerable attention. D-dimer is a degradation product of fibrin formation and, before COVID-19, was used to rule out PE in patients with a low pretest probability.[57] In COVID-19, many studies have demonstrated that elevated D-dimer levels are associated with an increased risk of disease progression and/or mortality.[44,58–60] In one study, only 24% of survivors of COVID-19 were found to have a D-dimer level greater than 1 μg/mL, whereas 81% of nonsurvivors had a D-dimer level greater than 1 μg/mL.[35] A similar study found that 85% of patients with a D-dimer level greater than 3 μg/mL did not survive, suggesting prognostic value to the test.[2]

D-dimer level is very commonly elevated during acute SARS-CoV-2 infection, particularly in hospitalized patients, rendering D-dimer of limited use in the assessment of VTE.[54,61] In a study of people with suspected PEs with COVID-19, 91% of patients without PEs had an elevated D-dimer level (0.05 μg/mL or greater). The same D-dimer cutoff yielded a 100% negative predictive value but only a 14% positive predictive value.[62] Another study evaluating patients with COVID-19 with D-dimer levels greater than 1000 ng/mL found that only 14.7% had asymptomatic DVT.[63] Although higher cutoff values were more likely to be associated with DVT, there is currently no consensus on the D-dimer cutoff that should prompt further imaging.

D-dimer elevations may be due to microthrombotic events and disseminated intravascular coagulation, which are not assessed by imaging modalities. Specifically, at high risk is microthrombosis within the pulmonary vasculature due to regional inflammatory response. Owing to this concern, researchers began looking at whether anticoagulation would affect outcomes in patients with COVID-19 with elevated D-dimer levels. Notably, treatment effects stratified by D-dimer yielded inconsistent results. One study of ~450 patients, which found no overall difference in 28-day mortality with anticoagulation in hospitalized patients with COVID-19, demonstrated a significant reduction in mortality in patients with sepsis-induced coagulopathy (SIC) score greater than 4 or a D-dimer level greater than 6 times upper limit of normal.[64] A subsequent study in which there was a prespecified analysis of patients stratified by D-dimer, reported no significant differences in treatment effect in critically ill patients with high

versus low D-dimer levels.[54] In noncritically ill patients with COVID-19, the probability of superiority for therapeutic anticoagulation was slightly more in the high D-dimer group (97.3%) compared with the low D-dimer group (92.9%), but regardless of the D-dimer value, therapeutic anticoagulation was superior to prophylactic dosing.[53]

There are several caveats when assessing the use of D-dimer in COVID-19. D-dimer can be measured using numerous assays, protocols vary across clinical laboratories, and the results are reported in many different units, collectively, making comparison across institutions challenging.[65] Before COVID-19, studies using age-adjusted values for D-dimer were better able to exclude PE in patients.[66] Age adjustment of D-dimer was done in few studies described herein, despite older patients being well represented in clinical trials of COVID-19.[62] D-dimer elevations can persist in 25% of people for at least 4 months after acute SARS-CoV-2 infection.[62,67] In addition, many factors can elevate a D-dimer level including age, liver disease, malignancy, pregnancy, and sepsis, rendering interpretation in patients with COVID-19 with other conditions less straightforward.[65]

In summary, an elevated D-dimer level is common in COVID-19, particularly in critically ill patients. If a patient with COVID-19 has a low D-dimer level, VTE is unlikely. Multiple studies demonstrate that the higher the D-dimer level, the greater the likelihood of VTE and poor clinical outcomes, but there is no consensus across studies regarding the cutoff value for D-dimer level to prompt imaging for VTE in COVID-19. Further study is needed before an isolated elevation in a D-dimer is sufficient to justify empiric full-dose anticoagulation or trigger evaluations for PE or DVTs in the setting of SARS-CoV-2 infection.

SUMMARY OF CURRENT GUIDELINES

The American Society of Hematology (ASH) suggests the use of prophylactic- over intermediate-dose (recommendation 1A) and prophylactic- over therapeutic-dose anticoagulation (recommendation 1B) in critically ill patients with COVID-19. These suggestions apply to patients who should be admitted to an ICU due to "an immediate life-threatening condition" and do not have suspected or confirmed VTE. ASH suggests the use of therapeutic-dose over prophylactic-dose anticoagulation (recommendation 1B) in patients with acute illness due to COVID-19. This recommendation applies to patients who are not critically ill, do not have suspected or confirmed VTE, or do not have another condition requiring treatment-dose anticoagulation.[68]

The NIH recommends therapeutic heparin dosing for hospitalized patients on low-flow oxygen with elevated D-dimer levels who are not in the ICU and without known contraindications (CIIa); it recommends prophylactic heparin dosing in patients in the ICU with COVID-19 (AI). For patients transferred from the floor to the ICU the NIH recommends switching from therapeutic- to prophylactic-dose heparin (BIII). The NIH does not recommend prophylactic anticoagulation or antiplatelet therapy in outpatients with COVID-19 (AIIa). The aforementioned recommendations apply to patients with COVID-19 without confirmed or suspected VTE. The NIH reports insufficient evidence to recommend routine screening for VTE in all patients with COVID-19, irrespective of their coagulation values; however, in hospitalized patients with sudden clinical deteriorations they recommend assessment for VTE (AIII). The NIH recommends patients on chronic anticoagulation or antiplatelet treatments at home continue those during their acute COVID-19 illness (AIII).[25]

MANAGEMENT SUMMARY

Given the aforementioned reduction in organ support-free days shown in ACTIV-4A, the authors recommend use of full-dose intravenous heparin to treat moderately ill

patients (those on < 20 L NC O_2) admitted to the hospital with COVID-19;. This effect may reflect the impact of heparin beyond ATIII inhibition including degradation of NETs and mitigation of the SARS-CoV-2 spike protein binding, but further mechanistic studies are needed.[15,69,70]

SUMMARY

Patients with COVID-19 are prone to venous, cerebrovascular, and coronary thrombi, particularly those with severe disease. The pathogenesis is multifactorial involving proinflammatory cascades and development of coagulopathy, but further investigations are needed to elucidate the mechanisms by which host-viral interactions promote thrombus formation. Elevated D-dimer levels are common in patients with COVID-19 and cannot be used in isolation to predict VTE in people with SARS-CoV-2. If given early in hospital admission, therapeutic-dose heparin improves clinical outcomes in patients with moderate COVID-19. To date antithrombotics have not improved outcomes in patients with severe COVID-19, possibly because significant tissue damage has already occurred. Finally, prompt recognition of extrapulmonary thrombi—particularly in the brain and heart—may be beneficial, but additional studies are needed and interventional response times may be limited by local resources.

CLINICS CARE POINTS

- The pathogenesis of SARS-CoV-2 is exacerbated by microthrombi and macrothrombi that compromise circulation and threaten organ function.
- Imaging for thrombi should be included as part of the assessment of patients with COVID-19 with significant sudden clinical deteriorations.
- To date, severely ill patients with COVID-19 do not significantly benefit from full-dose antithrombotic therapy.

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