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Venous thrombosis epidemiology, pathophysiology, and anticoagulant therapies and trials in severe acute respiratory syndrome coronavirus 2 infection

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ABSTRACT

Objective: Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus confers a risk of significant coagulopathy, with the resulting development of venous thromboembolism (VTE), potentially contributing to the morbidity and mortality. The purpose of the present review was to evaluate the potential mechanisms that contribute to this increased risk of coagulopathy and the role of anticoagulants in treatment.

Methods: A literature review of coronavirus disease 2019 (COVID-19) and/or SARS-CoV-2 and cell-mediated inflammation, clinical coagulation abnormalities, hypercoagulability, pulmonary intravascular coagulopathy, and anticoagulation was performed. The National Clinical Trials database was queried for ongoing studies of anticoagulation and/or antithrombotic treatment or the incidence or prevalence of thrombotic events in patients with SARS-CoV-2 infection.

Results: The reported rate of VTE among critically ill patients infected with SARS-CoV-2 has been 21% to 69%. The phenomenon of breakthrough VTE, or the acute development of VTE despite adequate chemoprophylaxis or treatment dose anticoagulation, has been shown to occur with severe infection. The pathophysiology of overt hypercoagulability and the development of VTE is likely multifactorial, with evidence supporting the role of significant cell-mediated responses, including neutrophils and monocytes/macrophages, endothelialitis, cytokine release syndrome, and dysregulation of fibrinolysis. Collectively, this inflammatory process contributes to the severe pulmonary pathology experienced by patients with COVID-19. As the infection worsens, extreme D-dimer elevations, significant thrombocytopenia, decreasing fibrinogen, and prolongation of prothrombin time and partial thromboplastin time occur, often associated with deep vein thrombosis, in situ pulmonary thrombi, and/or pulmonary embolism. A new phenomenon, termed pulmonary intravascular coagulopathy, has been associated with morbidity in patients with severe infection. Heparin, both unfractionated heparin and low-molecular-weight heparin, have emerged as agents that can address the viral infection, inflammation, and thrombosis in this syndrome.

Conclusions: The overwhelming inflammatory response in patients with SARS-CoV-2 infection can lead to a hypercoagulable state, microthrombosis, large vessel thrombosis, and, ultimately, death. Early VTE prophylaxis should be provided to all admitted patients. Therapeutic anticoagulation therapy might be beneficial for critically ill patients and is the focus of 39 ongoing trials. Close monitoring for thrombotic complications is imperative, and, if confirmed, early transition from prophylactic to therapeutic anticoagulation should be instituted. The interplay between inflammation and thrombosis has been shown to be a hallmark of the SARS-CoV-2 viral infection. (J Vasc Surg: Venous and Lym Dis 2021;9:23-35.)

Keywords: Coagulopathy; Inflammation; SARS-CoV-2; Thrombosis; Venous thromboembolism; Virus

Impaired pulmonary function and coagulation abnormalities have been shown to be hallmarks of severe infections with coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The link among infection, inflammation, and hypercoagulability has been highlighted by the three clinical stages associated with COVID-19 infection recently described by Thachil et al[1] in primarily hospitalized patients: Stage 1: patients with nonsevere symptoms localized to the lungs and associated with a D-dimer level two to

three times greater than normal but normal prothrombin times (PTs) and partial thromboplastin times (PTTs) and normal or elevated platelet counts and fibrinogen levels. These patients can be treated in the hospital or at home.

Stage 2: patients with more severe symptoms requiring critical care associated with D-dimer levels three to six times greater than normal with a decreased platelet count and minor prolongation of the PT. These patients can develop deep vein thrombosis in the lower limbs and have filling defects on computed tomography imaging due to pulmonary thrombi or emboli.

Stage 3: patients with worsening clinical symptoms and requiring higher level critical care (eg. extracorporeal membrane oxygenation [ECMO] support). These patients can develop venous thromboembolism (VTE) and multisystem organ failure with ischemia in various organs. The D-dimer levels will be six times greater than normal or more, with significant thrombocytopenia, decreasing fibrinogen levels, and marked prolongation of the PT and PTT. Systemic thrombosis, including a disseminated intravascular coagulation (DIC)-like picture, and extensive pulmonary thrombi or emboli can develop. These changes can result in eventual mortality.[1]

Within the present review, we have examined the epidemiology of venous thrombosis in patients with COVID-19 infection, the role of the cellular and molecular mechanisms underlying coagulation abnormalities, and the data regarding anticoagulant use for these patients. We have highlighted the ongoing trials that could be of interest to vascular specialists.

EPIDEMIOLOGY OF THROMBOSIS IN COVID-19

VTE is a common hospital-acquired condition, occurring in medical and surgical intensive care unit (ICU) patients at rates historically ranging from 6.6% to 30%.[2-5] Modern thromboprophylaxis has effectively reduced the risk of VTE development in the ICU patient population to 5% to 15%.[5-7] However, the initial reports of critically ill patients with COVID-19 in Wuhan, China, demonstrated a VTE rate of 25%, greater than expected in a population with a baseline low incidence of both VTE and thromboprophylaxis usage.[8,9] Similarities were quickly found across multiple other patient populations. The incidence of VTE in critically ill Dutch patients with COVID-19 was 31%[10] and was 32% in Swiss patients.[11] An autopsy study of 12 consecutive patients from Hamburg, Germany, found previously unsuspected deep vein thrombosis in 7 of the 12 patients (58%), with pulmonary embolism (PE) considered the direct cause of death for 4 patients.[12]

Pulmonary infection has been established as a risk factor for VTE in multiple studies.[13,14] A mild elevation in VTE risk continues for ≤1 year after recovery from the initial infection.[13] Data are lacking regarding the VTE risk from other coronavirus pneumonias. The SARS pandemic in 2003 was associated with a 23% to 33% risk of VTE in the critically ill; however, no findings of an association between VTE and Middle East respiratory syndrome were found in a review of the reported data.[15,16] In contrast, the exaggerated risk described in the early studies of patients with COVID-19 more closely approximated the severe coagulopathy associated with the 2009 H1N1 viral pneumonia pandemic. In that pandemic, the VTE incidence was estimated at 37% among ICU patients.[17] The remarkable similarities between the COVID-19 and 2009 H1N1 pandemics extend to a high incidence of breakthrough VTE, defined as the occurrence of VTE despite aggressive thromboprophylaxis or therapeutic anticoagulation.[3]

In 150 patients infected with SARS-CoV-2 who had developed adult respiratory distress syndrome (ARDS) in France, 64 (42.7%) thrombotic complications were reported. The thrombotic complications included PE in 16.7%, continuous renal replacement therapy circuit clotting in 28 of 29 patients, and ECMO circuit clotting in 3 of 12 patients receiving ECMO support, although all had receiving thromboprophylaxis (70% a prophylactic dose and 30% a therapeutic dose).[18] Another report of 107 ICU patients with COVID-19 pneumonia confirmed the presence of PE in 22 (21%) despite prophylactic dose anticoagulant therapy for 20 patients and a therapeutic dose for 2 patients.[19] In a cohort of French critically ill patients, the incidence of VTE was 100% for those treated with prophylactic anticoagulation and 56% for those who had received therapeutic anticoagulation.[20]

In a single-center study from Amsterdam of 198 hospitalized patients with COVID-19 (all of whom had received thromboprophylaxis), the cumulative VTE incidence at 7, 14, and 21 days was 16%, 33%, and 42%, respectively. The cumulative incidence of VTE was greater in the ICU patients (n = 75; 26%, 47%, and 59%) than in the non-ICU patients (n = 123; 5.8%, 9.2%, and 9.2%) at 7, 14, and 21 days, respectively. However, none of the 19 patients (0%) who had continued therapeutic anticoagulation therapy for other indications had developed VTE compared with 39 of 179 of the remaining patients (22%; Fisher's exact test, $P = .03$). VTE was associated with death (adjusted hazard ratio, 2.4; 95% confidence interval, 1.02-5.5).[21] In contrast, SARs-CoV-2—associated arterial thrombosis and thromboembolism has occurred at a lower frequency. In a study of three Dutch hospitals evaluating 184 ICU patients with proven COVID-19 pneumonia, arterial events, which included ischemic stroke, myocardial infarction, or systemic arterial embolism, occurred in 3.7%.[10] Of 829 ICU patients with a high prescription of chemical thromboprophylaxis, 18.6% had developed arterial thrombotic events, including myocardial infarction, ischemic stroke, and other systemic thromboembolism.[22]

Thus, patients infected with the novel coronavirus who develop severe pneumonia will exhibit higher than

expected rates of VTE compared with patients without such severe viral pneumonia. Hypercoagulability has been shown to be a manifestation of severe COVID-19 pneumonia.[23,24] Overt, pathological venous thrombosis might be an important contributor to the morbidity and mortality of critically ill patients with COVID-19, prompting multiple societies to recognize the importance of thromboprophylaxis for this patient population.[25-27] Further understanding of the cellular and molecular mechanisms responsible for this hypercoagulable state are necessary for the development of effective therapies.

CELL-MEDIATED INFLAMMATION

The usual cause of death and the need for ventilator-assisted hospitalization from COVID-19 has been the progression to ARDS. The hallmark of ARDS is the influx of neutrophils (polymorphonuclear [PMN] cell family) into the lungs after extravasation from the bloodstream. PMN degranulation releases a wide variety of inflammatory mediators, resulting in a positive feedback loop that results in a further influx of PMN cells, vascular leakage, a buildup of fluid in the lungs, and the inability to exchange oxygen. Alveolar neutrophil and platelet accumulation results in thromboinflammation. Platelets, in particular, have the ability to trigger deployment of neutrophil extracellular traps (NETs), which correlate with the alveolar—capillary and epithelial barrier disruption in ARDS.[28]

In patients with severe infection of SARS-CoV-2 viral pneumonia progressing to respiratory failure, serum cell-free DNA, myeloperoxidase (MPO)-DNA, and citrullinated histone H3 levels will be elevated; the latter are two highly specific markers for NETs. Cell-free DNA and MPO-DNA correlate strongly with the absolute neutrophil count.[29] Cell-free DNA and MPO-DNA were more elevated in hospitalized patients receiving mechanical ventilation compared with hospitalized patients breathing room air, suggesting that the severity of the illness is associated with the degree of neutrophil response.[29] Additionally, serum from individuals infected with SARS-CoV-2 triggered NET release from control neutrophils in experiments performed in vitro.[29] In addition, a recent retrospective case-control study of hospitalized patients with COVID-19 reported that the patients who had developed thrombosis had had significantly greater blood levels of NET remnants (cell-free DNA, MPO-DNA complexes, and citrullinated histone H3) and neutrophil activation (calprotectin) compared with those without thrombosis and were associated with increased D-dimer levels.[30]

Taken together, these data provide evidence that SARS-CoV-2 infection induces a pro-NETotic state in hospitalized patients. These NETs could be partially responsible for the thrombotic phenotype of severely ill patients with COVID-19 (Table I). Thirteen studies are

Table I. Cell-mediated molecular mechanisms of hypercoagulability

Neutrophils	NETs
Monocytes/macrophages	Type I interferons, IL-1β, IL-6, IL-8, TF
Endothelial cells	Increased TF, decreased TFPI, AT, protein C

AT, Antithrombin; *IL*, interleukin; *NETs*, neutrophil extracellular traps; *TF*, tissue factor; *TFPI*, tissue factor pathway inhibitor.

listed in ClinicalTrials.gov under COVID and NETs, pointing to the potentially important role of activated neutrophils in COVID-19 illness.

In addition to neutrophils, pathologic studies have demonstrated a low to moderate number of mononuclear cells in the lungs of patients who died of COVID-19.[31] The direct role they play is not entirely clear but is likely multifactorial because of the diverse roles monocytes and macrophages (Mo/MΦ) play in lung physiology. Broadly, Mo/MΦ are classified by their inflammatory or anti-inflammatory functions.[32-34] For example, interleukin (IL)-1 and IL-12 secretion and cell surface Ly6C^{hi}, CCR2^{++}, and CX3CR1^{+} antigen expression characterize classically activated proinflammatory Mo/MΦ. In contrast, IL-10 secretion, *Nr4a1* transcription factor dependency, and cell surface Ly6C^{lo}, CCR2^{-}, and CX$_3$CR1^{++} antigen expression characterize alternatively activated Mo/MΦ with prohealing and inflammation-resolving activities. It has been shown that the number of monocytes is the same in patients infected with COVID-19 and controls. However, in patients from China with COVID-19, significant morphologic and functional differences were seen in the monocytes, with the differences more pronounced in those who had required ICU admission and had a prolonged length of stay. These monocytes were larger on flow cytometry and were positive for CD11b, CD14, CD16, CD68, CD80, CD163, and CD206. They also secreted IL-6, IL-10, and tumor necrosis factor-α, an indication of both an inflammatory and anti-inflammatory phenotype.[35,36]

Humans can manifest a significant cytokine storm with severe COVID-19 pneumonia that can lead to death,[37,38] and many of the responsible mediators are derived from Mo/MΦ.[39-41] These include proinflammatory cytokines such as IL-1β, IL-8, IL-6, and interferon (IFN) type I. These cells then directly interact with the other major leukocytes that could be involved in the development of VTE.[42,43] The direct viral infection might promote the release of monocyte chemoattractants by alveolar epithelial cells, alveolar macrophages, and stromal cells and result in a sustained recruitment of monocytes into the lungs, creating a vicious circle.[44] These monocytes then differentiate into proinflammatory macrophages. Consistently, inflammatory Mo/MΦ have been shown to mediate the pathogenesis of experimental SARS-CoV-2 pneumonia in mice.[45]

Mo/MⱮ also activate and are activated by natural killer cells and T cells, further promoting the recruitment of these monocyte-derived macrophages through the production of granulocyte-macrophage colony-stimulating factor, tumor necrosis factor, and IFN-γ.[44,46] In the lungs, oxidized phospholipids can accumulate and can also activate these Mo/MⱮ through a number of pathways.[44] Virus-sensing pathways such as toll-like receptor 7, which senses single-stranded RNA recognition, and IFN type I can induce the expression of entry receptors, allowing the virus to enter into the cytoplasm of the macrophages, activating the NLRP3 inflammasome.[44] This can then lead to the secretion of mature IL-1β and IL-18, which then amplify the activation of the macrophages through paracrine or autocrine effects and might have procoagulant effects.[29] Oxidative stress, pathogen-associated molecular patterns, and damage-associated molecular patterns (DAMPs) also activate Mo/MⱮ via the TLR4-TRIF-TRAF6-NFκβ pathway, resulting in surface tissue factor expression.[44,47] Additionally, activated inflammatory cells (neutrophils and Mo/MⱮ) can directly bind to platelets, and these neutrophil—platelet and platelet—monocyte complexes and activated platelets can induce and amplify thrombosis.

Endothelial cell infection has been implicated as a cause of the multiple organ involvement associated with severe COVID-19 infection. The induction of endotheliitis occurs as a direct consequence of viral involvement (as noted by the presence of viral bodies) and the host inflammatory response.[48] Other proposed mechanisms of endothelial injury include the induction of apoptosis and pyropotosis.[48] Endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds (including the kidneys and lungs) and their clinical sequelae (ie, acute kidney injury, ARDS) in patients with COVID-19 infection. During inflammation, natural anticoagulants such as the tissue factor pathway inhibitor, antithrombin (AT), and protein C will also be downregulated on the endothelial cell surface, with tissue factor upregulated, contributing to thrombosis.[43,49] Thus, a therapy that targets the endothelial cells might play an important protective role in the treatment of COVID-19.[48] One potential candidate could be selectin inhibitors, because selectins are critical to the interactions among inflammatory cells, platelets, and the endothelium.

CLINICAL COAGULATION ABNORMALITIES AND HYPERCOAGULABILITY

The pathophysiology of COVID-19—associated hypercoagulability has many unique aspects (Table II). Severe COVID-19 hypercoagulopathy is associated with features of both DIC and thrombotic microangiopathy, conferring

Table II. Coagulation parameter abnormalities associated with severe coronavirus disease 2019 (COVID-19) infection

Increased
D-dimer
FDPs
Fibrinogen
vWF
Factor VIII
Soluble uPAR
Angle and MA (TEG)
Decreased
Antithrombin
R and K values (TEG)
Platelets

FDPs, Fibrin degradation products; *K,* kinetic; *MA,* maximum amplitude; *R,* reaction time; *TEG,* thromboelastography; *uPAR,* urokinase plasminogen activator receptor; *vWF,* von Willebrand factor.

a procoagulant state associated with VTE risk. This hypercoagulable state appears to be related to the severity of illness and resultant thromboinflammation and not to intrinsic viral activity. Systemic coagulopathy is a marker of adverse outcomes for these patients, and elevated D-dimer levels at admission and increasing D-dimer levels after admission have been associated with significantly increased mortality.[50]

Coagulation abnormalities have been shown to be the hallmark of severe COVID-19 infection, with more marked abnormalities developing as patients progress from stage 1 to 3.[1] A study that had prospectively collected blood coagulation values from 94 admitted patients and 40 healthy controls in Wuhan, China, reported the following results (patients vs controls): lower AT values, elevated D-dimer levels, elevated fibrin degradation products (FDPs), and elevated fibrinogen ($P < .001$ for all). Greater D-dimer elevations (not age adjusted) and FDP values correlated with more severe or critical disease.[51] In a retrospective study of 183 patients (Wuhan, China), elevated PT, D-dimer, and FDP values on hospitalization were associated with patient death.[52] The investigators had also analyzed the values for a period of 14 days. They noted that a further increase in D-dimer and FDP levels with a decrease in fibrinogen and AT activity was observed in the patients who had eventually died compared with the survivors after 7 to 10 days.[52] D-dimer elevation has been consistently associated with disease severity, mortality, and need for assisted ventilation.[53,54] These serologic and coagulation markers should be measured and monitored throughout the course of the infection. Whether a change in serologic markers, such as further increases in D-dimer and FDP levels and a decrease in fibrinogen and AT activity, can be used as a method to determine when to switch from prophylactic to therapeutic anticoagulation

remains to be determined. However, some experts have recommend transitioning to therapeutic anticoagulation at D-dimer levels of three to six times the upper limit of normal.[1]

Only approximately one third of 1099 patients with COVID-19 from 31 provinces in China developed clinical thrombocytopenia.[53] In 30 patients infected with SARS-CoV-2, the thromboelastography parameters were consistent with a state of hypercoagulability as shown by decreased reaction times and kinetic values, increased angle and maximum amplitude values, and a small decrease in Ly30. Other laboratory abnormalities included increased fibrinogen, D-dimer, C-reactive protein, factor VIII, protein C, and von Willebrand factor (n = 11), suggesting the presence of hypercoagulability with a severe inflammatory state.[55] These results differ from the hallmark characteristics often seen with acute DIC, which will typically include consumptive coagulopathy with significantly prolonged PT/activated PTT, thrombocytopenia, and low fibrinogen clotting activity.[55] It is only at the most severe stage of infection (stage 3) that the laboratory abnormalities in COVID-19 will appear more consistent with DIC, such as significant thrombocytopenia, marked prolongation in the PT and PTT, and decreasing fibrinogen levels.[1]

Recently, soluble urokinase has been identified as a predictor of the development of severe respiratory failure in the setting of SARS-CoV-2 infection.[56] Consistently, mice infected with murine-adapted related SARS-CoV-2 developed more severe lung pathology in the setting of a dysregulated urokinase pathway. Similar changes in the urokinase, coagulation, and fibrinolytic pathway expression signatures have been noted in those with highly pathogenic SARS-CoV-2 and influenza virus infections, arguing for a conserved role for these pathways in virus-induced end-stage lung disease, similar to that in acute lung injury and ARDS.[57]

A recent review has suggested that elevated plasmin or plasminogen might be a common risk factor for COVID-19 susceptibility. The rationale for this includes that elevated plasmin or plasminogen has been common in patients identified as having a high risk of COVID-19, that plasmin cleaves the SARS-CoV-2 spike protein, which might enhance the action of the virus, and that the very high D-dimer levels (which have been related to mortality and severity) might relate to increased fibrinolysis as mediated by plasmin.[58] Thus, another approach to treatment could be the use of antiprotease compounds.

PULMONARY INTRAVASCULAR COAGULOPATHY

Data are emerging that COVID-19 infection causes diffuse bilateral pulmonary inflammation associated with a novel pulmonary-specific vasculopathy, which has recently been termed pulmonary intravascular coagulopathy (PIC). PIC is distinct from DIC in its early stages.[59-61] Lung pathologic examinations from autopsy of patients with COVID-19 have confirmed significant microvascular thrombosis and hemorrhage, in addition to the extensive alveolar and interstitial inflammation causing diffuse alveolar damage. The common pulmonary vascular findings in these postmortem reports of patients with COVID-19 pneumonia included vascular thrombosis, fibrin thrombi, small vessel occlusion, blood vessel wall edema, immune cell infiltration, and pulmonary infarction.[31,62,63] Infection of the type II pneumocytes with COVID-19 virus induces pulmonary macrophage and neutrophil recruitment (similar to macrophage activation syndrome) triggering diffuse pulmonary inflammation and immunothrombosis. Pulmonary microthrombi formation will stimulate local fibrinolytic activity in the lung, which might not be adequate. Thus, ultimately, the local immunothrombosis induced by COVID-19 could result in pulmonary infarction and hemorrhage, with resultant PIC-induced pulmonary hypertension. A recent small study compared the lungs from patients who had died of COVID-19 and patients who had died of influenza A (H1N1) infection.[64] They reported three distinctive pulmonary vascular features of COVID-19 infections, including (1) severe endothelial injury associated with intracellular virus and disrupted cell membranes; (2) widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries; and (3) significant new vessel growth through a mechanism of intussusceptive angiogenesis. Also, the alveolar capillary microthrombi were nine times greater in the COVID-19 lungs compared with the influenza A lungs, and vascular angiogenesis was 2.7 times greater.[64]

MULTIFACETED ROLE OF HEPARIN AND DATA ON USE OF ANTICOAGULANTS IN SARS-CoV-2 INFECTION

Heparin serves a multifaceted role in the setting of acute infection. In addition to its function as an anticoagulant, it has a role as a negative regulatory factor for smooth muscle cell proliferation and migration and shifts the localization of urokinase-type plasminogen activator from the cell layer to the medium, depending on the mitogen used.[65] Heparin alters fibrinolysis by potentiating the effect of AT to inhibit the plasminogen system and plasmin.[66,67] Heparin has also exhibited significant anti-inflammatory effects by neutralizing DAMPs to protect the endothelial cells and reducing the toxicity of histones on endothelial tight junctions, resulting in decreased lung edema and vascular leakage.[68,69]

Cell-surface heparin sulfate has been implicated as a viral binding site.[70] Specifically, blocking this virus binding site with heparin inhibited viral infection in a cell-based assay.[71] A direct antiviral effect of heparin has been reported for SARS-CoV-2.[72] Binding of the viral spike protein to the cell surface heparin sulfate was

reduced in the presence of heparin, inhibiting viral infection into cells.[73] A mutation in the spike protein residue 614 from aspartic acid to glycine has recently been identified as a possible fitness advantage, increasing the transmission of the virus in Europe and the Americas.[74] Whether this mutation (or future mutations in the spike protein) will significantly affect heparin binding is an important translational question.

Anticoagulants, including unfractionated heparin and low-molecular-weight heparin, possess a number of general anti-inflammatory effects. These include (1) inhibition of the activation and function of neutrophils; (2) prevention of the expression of inflammatory mediators, which initiate and drive the activation of the innate immune system, reducing many cytokines; (3) inhibition of the proliferation of vascular smooth muscle cells; and (4) inhibition of thrombosis with a decrease in thrombin and a subsequent decrease in inflammation.[75] These effects appear independent of achieving therapeutic anticoagulation.[76] Heparin might serve a dual role in critically ill patients with severe COVID-19, inhibiting viral cell infection and decreasing the proinflammatory effects of the cytokine storm, including chemokines and danger signals (DAMPs). It might be possible to design heparin-like molecules to enhance the antiviral and anti-inflammatory effects and lessening the anticoagulant effect, which would decrease bleeding.[77]

Heparin administered at prophylactic doses[78] and at just less than therapeutic doses has shown beneficial effects on COVID-19 mortality and influenza A H1N1 mortality.[17] A recent Chinese study compared heparin prophylaxis in 99 patients with severe COVID-19 infection and 350 patients without heparin prophylaxis.[78] They reported that the 28-day mortality rate was significantly decreased from 64.2% to 40% with heparin prophylaxis ($P = .029$) in patients with increased sepsis-induced coagulopathy scores of ≥ 4 or D-dimer levels more than sixfold the upper limit of normal (mortality, 32.8% vs 52.4%; $P = .017$).[78] Additional studies are underway to validate these important findings.

The results from two other studies have suggested potentially beneficial effects of treatment-dose heparin anticoagulation in patients with COVID-19. In a study from Brazil, 27 consecutive patients with COVID-19 had been treated with therapeutic heparin anticoagulation.[79] The investigators reported that the partial pressure of arterial oxygen/fractional inspired oxygen ratio had increased significantly during the 72 hours after the start of anticoagulation. Also, 81% of the patients could be discharged home within 11 days.[79] The patients who had required intubation and mechanical ventilation had been extubated within 12.5 days, and no bleeding complications had occurred.[79] Additionally, in a study from New York, from March 14 to April 11, 2020, 2773 patients had been hospitalized within the Mount Sinai Health System in New York City. These patients had been given treatment-dose systemic anticoagulation.[80] After adjustment for demographics and comorbid disease, mortality was assessed. For the patients who had required mechanical ventilation, the mortality in the hospital had decreased from 62.7% to 29.1%, with a median survival of 21 days compared with 9 days for those who had not received anticoagulation.[80] No survival benefit was seen for the non-ICU patients. This observational study had not accounted for immortal time bias, which could have contributed to the reported association between therapeutic anticoagulation and beneficial outcomes.[80]

At our institution, because of the high observed incidence of VTE events and previous clinical success with heparin infusion for severe influenza, we have endorsed heparin infusion for critically ill patients with SARs-CoV-2 infection (Fig). Duplex ultrasound scanning is performed only for patients considered at high risk of bleeding and thrombosis by the bedside clinician, with the aid of clinical prediction models.[81] Widespread duplex ultrasound screening is not feasible during

	Low Bleeding Risk	High Bleeding Risk
Low Thrombosis Risk	Thromboprophylaxis (Ward patients) Full dose anticoagulation (ICU patients)	Thromboprophylaxis
High Thrombosis Risk	Full dose anticoagulation	DVU Scan to determine therapy

Fig. Summary of Michigan Medicine venous thromboembolism thromboprophylaxis, empiric treatment, and duplex venous ultrasound (DVU) screening guidelines. Clinicians use clinical prediction models such as the Wells score, modified Wells score, and VTE-BLEED score in conjunction with bedside assessment to determine the best therapy. All patients treated with empiric therapeutic anticoagulants undergo deep vein thrombosis scanning once they have recovered from severe acute respiratory syndrome coronavirus 2 infection.

Table III. Ongoing trials evaluating anticoagulant/antithrombotic treatment or incidence/prevalence of thrombotic events in severe acute respiratory syndrome coronavirus 2 (*SARS-CoV2*) infection (as of June 4, 2020; N = 39)

Sponsor (ClinicalTrials.gov Identifier)	Study design	Patients, No.	Treatment group	Primary end point
Karolinska Institute (NCT04412304; completed)	Observational cohort	166	LMWH (prophylaxis and treatment dose)	Days alive from ICU admission of first 28 days
Quovadis Associazione (NCT04393805)	HETHICO; observational cohort	877	LMWH prophylaxis	Bleeding, thrombosis, mortality (28 days)
University of Iowa (NCT04360824)	Interventional clinical trial	170	LMWH (prophylaxis vs intermediate dose)	Risk of all-cause mortality in first 30 days
Northwell Health (NCT04401293)	Interventional clinical trial	308	LMWH (full dose vs prophylactic or intermediate dose) in high-risk COVID-19	Composite of arterial/venous thromboembolic and all-cause mortality at day 30
University of Manitoba (NCT04372589)	ATTACC; interventional clinical trial	3000	LMWH vs standard unfractionated heparin	Intubation and mortality over 30 days
University Hospital, Geneva (NCT04345848)	COVID-HEP; interventional clinical trial	200	Therapeutic LMWH or IV unfractionated heparin vs prophylactic LMWH or unfractionated heparin	Composite outcome of arterial or venous thrombosis, DIC and all-cause mortality over 30 days
Sociedad Espanola de Angiologia y Cirugia Vascular (NCT04361981)	Observational registry	50	No intervention	Deep venous disease in first 30 days
Uppsala University (NCT04390074)	Observational case control	9,905	No intervention	Chronic medications (including oral anticoagulants) as risk factor for intensive care for COVID-19 (within 6 months before inclusion); comorbidities as risk factor for intensive care for COVID-19 (5 years before inclusion)
University Hospital, Strasbourg, France (NCT04373486)	Observational	160	No intervention	Rate of positivity for acute PE
University Hospital, Strasbourg, France (NCT04359992)	Observational	50	Obtain extra blood sample	Platelet activation intensity with occurrence of clinical thrombotic complications (change in platelet activity from admission day in ICU to 2 days and 7 days)
Columbia University (NCT04367831)	IMPROVE; interventional clinical trial	100	Unfractionated heparin (SC vs infusion) and LMWH (enoxaparin [Lovenox] intermediate dose vs prophylactic dose)	Total patients with clinically relevant venous or arterial thrombotic events in ICU (discharge from ICU or 30 days)
Xijing Hospital (NCT04365309)	Interventional clinical trial	128	Low-dose aspirin added to standard of care	Clinical recovery time not >14 days and time of SARS-CoV-2 overcasting
Brazilian Clinical Research Institute (NCT04394377)	ACTION: Interventional clinical trial	600	LMWH (full vs prophylactic dose)	End point of mortality, no. of days alive, no. of days in hospital, and no. of days with oxygen therapy at end of 30 days

Table III. Continued.

Sponsor (ClinicalTrials.gov Identifier)	Study design	Patients, No.	Treatment group	Primary end point
University Hospital, Linkoeping (NCT04400877)	Observational	12,000	No intervention	VTE in regional healthcare system
Niguarda Hospital (NCT04366960)	X-Covid 19; interventional clinical trial	2712	LMWH prophylaxis (enoxaparin 40 mg QD vs BID)	VTE incidence by imaging
NYU Langone Health (NCT04359277)	Interventional clinical trial	1000	LMWH or heparin (higher dose) vs LMWH or Heparin (prophylactic dose)	All-cause mortality over 30 days and many other outcomes (eg, DVT, MI) over 21 days
Assistance Publique-Hôpitaux de Paris (NCT04344756)	CORIMMUNO-COAG; interventional clinical trial	808	Unfractionated heparin or tinzaparin LMWH	Survival without ventilation in mild disease; ventilator-free survival over 14-28 days in respiratory failure ICU patients
Chimerix (NCT04389840)	Interventional clinical trial	524	Dociparstat sodium vs placebo	Alive and free of invasive mechanical ventilation through day 28
Azienda Ospedaliero-Universitaria di Modena (NCT04408235)	Interventional clinical trial	300	LMWH (low dose vs high dose)	Clinical worsening ≤30 days; death, MI, VTE, arterial thromboembolism, need for ventilation
Massachusetts General Hospital (NCT04377997)	Interventional clinical trial	300	LMWH or heparin therapeutic dose	Composite end point of death, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, MI, or hemodynamic shock, and major bleeding over 12 weeks
Frederick Health (NCT04397510)	Interventional clinical trial	50	Nebulized heparin vs placebo	Mean daily PaO_2/FiO_2 ratio over 10 days
Central Hospital, Nancy, France (NCT04373707)	Interventional clinical trial	602	LMWH (weight adjusted vs fixed prophylactic dosing)	VTE over 28 days
University of Zurich (NCT04400799)	Interventional clinical trial	1000	LMWH prophylaxis (enoxaparin 40 mg daily) for 14 days	Hospitalizations and all-cause death over 30 days
Neil Goldenberg, John Hopkins All Children's Hospital (NCT04354155)	Interventional clinical trial	38	LMWH prophylaxis adjusted by antifactor Xa	Safety of in-hospital thromboprophylaxis over 30 days
Tasly Pharmaceuticals, Inc (NCT04285190)	Interventional clinical trial	120	T89	Time to oxygen saturation recovery to normal level (≥97%) and proportion of patients with normal oxygen saturation (≥97%) over 10 days
Weill Medical College of Cornell University (NCT04406389)	Interventional clinical trial	186	Enoxaparin sodium, unfractionated heparin, fondaparinux, argatroban (therapeutic dose vs intermediate dose)	Mortality over 30 days
Imperial College London (NCT04333407)	Interventional clinical trial	3170	Aspirin 75 mg, clopidogrel 75 mg, rivaroxaban 2.5 mg, atorvastatin 40 mg, omeprazole 20 mg	Mortality after 30 days

Table III. Continued.

Sponsor (ClinicalTrials.gov Identifier)	Study design	Patients, No.	Treatment group	Primary end point
Assistance Publique-Hôpitaux de Paris (NCT04402892)	Interventional clinical trial	60	Lithium heparinate (hospitalized patients) and lithium heparinate (cured patients)	Immunologic memory: resolution of COVID-19 after SARS-CoV-2 infection over 5 years
University Hospital Padova (NCT04352400)	Interventional clinical trial	256	Nafamostat mesilate vs placebo	Time to clinical improvement (day 1 to day 28)
Medical University of Vienna (NCT04351724)	Interventional clinical trial	500	Chloroquine or hydroxychloroquine, lopinavir/ritonavir vs best standard of care; rivaroxaban vs thromboprophylaxis; candesartan vs non-RAS blocking antihypertensives; clazakizumab vs placebo for clazakizumab	Sustained improvement (>48 hours) of one point on WHO scale (inclusion to day 29; daily evaluation)
Quovadis Associazione (NCT04359212)	Observational	90	Thromboprophylaxis with LMWH or fondaparinux for medical nonsevere or intensive care patients	Incidence of DVT or symptomatic PE over 28 days
TIMI Study Group (NCT04409834)	Interventional clinical trial	750	Full-dose anticoagulation + antiplatelet therapy vs full dose anticoagulation and no antiplatelet therapy; Prophylactic anticoagulation + antiplatelet therapy vs prophylactic anticoagulation and no antiplatelet therapy	Death from venous or arterial thrombosis, PE, clinically evident DVT, type 1 MI, ischemic stroke, systemic embolism or acute limb ischemia, or clinically silent DVT over 28 days
Grupo de Investigación Clínica en Oncología Radioterapia (NCT04380818)	Interventional clinical trial	106	Low-dose radiotherapy; hydroxychloroquine sulfate; ritonavir/lopinavir; tocilizumab injection (Actemra); azithromycin; corticosteroid; LMWH; oxygen supply	Change in PaO_2/FiO_2 ratio by 20%, 2 days after interventional radiotherapy
Fundacion GenesisCare (NCT04394182)	Interventional clinical trial	15	Radiation: ultra-low-dose RT with ventilatory support with oxygen therapy; lopinavir/ritonavir, hydroxychloroquine, azithromycin, piperacillin/tazobactam, LMWH, corticosteroid injection, tocilizumab	Oxygen therapy status at day 2 after RT
University of Milan (NCT04368377)	Interventional clinical trial	5	Tirofiban injection + clopidogrel, ASA, and fondaparinux	PaO_2/FiO_2 ratio at baseline and 24, 48, and 168 hours after treatment initiation

Table III. Continued.

Sponsor (ClinicalTrials.gov Identifier)	Study design	Patients, No.	Treatment group	Primary end point
University of Michigan (NCT04391179)	DICER; randomized clinical trial	80	Dipyridamole 100 mg 4 times daily for 14 days in hospital vs placebo	Change in D-dimer compared with baseline at enrollment
Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia (NCT04348383)	DEFACOVID; Interventional clinical trial	120	Defibrotide 25 mg/kg 24 hours continuous infusion for 15 days vs placebo	All-cause mortality
Charite University, Berlin, Germany (NCT04416048)	COVID-PREVENT; Interventional clinical trial	400	Rivaroxaban 20 mg daily for ≥7 days vs standard of care	Composite end point of VTE (DVT and/or fatal or nonfatal PE), arterial thromboembolism, new MI, nonhemorrhagic stroke, all-cause mortality, or progression to intubation and invasive ventilation 35 days after randomization
University Hospital, Strasbourg, France (NCT04412473)	CRASH; observational retrospective study	1000	No intervention	Respiratory distress and antithrombolytic therapy in COVID-19 patients over 1 month

aPTT, Activated partial thromboplastin time; *BID,* twice daily; *COVID-19,* coronavirus disease 2019; *DIC,* disseminated intravascular coagulation; *DVT,* deep vein thrombosis; *ICU,* intensive care unit; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *MI,* myocardial infarction; *PaO$_2$/FiO$_2$,* partial pressure of arterial oxygen/fractional inspired oxygen; *PE,* pulmonary embolism; *PO,* oral; *q12 h,* every 12 hours; *QD,* once daily; *RT,* radiotherapy; *SC,* subcutaneous; *VTE,* venous thromboembolism; *WHO,* World Health Organization.

pandemic circumstances owing to sheer number of patients, amount of time required for disinfection of the ultrasound machine, COVID-19 risk to the technician, and often prone positioning of the patients. At our institution, patients with a contraindication to anticoagulation and clinical imaging of acute VTE and those with thrombus found in ECMO cannulas will undergo inferior vena cava filter placement. The relative success or failure of this protocol compared with others remains to be seen. In particular, a pressing need exists for additional data regarding the risks of major bleeding for patients treated with full-dose anticoagulants. In a recent study, the development of major hemorrhage occurred in 4.8% of severely ill patients with COVID-19. Of these 21 patients, 7 had been receiving therapeutic full-dose anticoagulation at the occurrence of hemorrhage.[82]

Anticoagulation has been the genesis of many studies around the world in the treatment paradigm of COVID-19. We found 37 studies listed under COVID-19 and anticoagulation in the *ClinicalTrials.gov* website as of June 2, 2020. These studies are investigating heparin and low-molecular-weight heparin at various doses, alone and combined with other agents, such as direct oral anticoagulation agents and platelet inhibitors. A portion of these studies, plus others, are listed in Table III.

CONCLUSIONS: THE INFLAMMATORY–COAGULATION INTERACTION

Infection with COVID-19 clearly induces overlapping pathways that link the inflammatory response to the coagulation response. The overwhelming inflammatory response in patients with COVID-19 infection can lead to a hypercoagulable state, microthrombosis, large vessel thrombosis, and, ultimately, death. Thus, early VTE prophylaxis should be provided to all admitted patients, along with other agents that will interrupt the hyperimmune response that occurs with infection with the virus.[83] Close monitoring for thrombotic complications is imperative, and, if confirmed, early transition from prophylactic to therapeutic anticoagulation should be instituted. Therapeutic anticoagulation could be required in certain clinical situations, and the transition from prophylactic to therapeutic anticoagulation for many patients could be required when diagnostic imaging studies are not available.[81] Further guidelines will depend on the results of clinical trials.[84] We have no better example of the close interaction between inflammation and thrombosis, suggesting that inflammation augments thrombosis and that thrombosis augments inflammation. In such situations, it is likely that a combination of anticoagulation agents, anti-inflammatory agents, and antiviral agents will be necessary to treat this deadly disease. The specific anticoagulant and its formulation, dosage, and timing and the specific anti-inflammatory agent and antiviral agent to be used are important topics for further timely research.

AUTHOR CONTRIBUTIONS

Conception and design: AO, PH, TW
Analysis and interpretation: AO, GB, LN, PH, TW

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