Coronavirus Disease 2019–Associated Thrombosis and Coagulopathy: Review of the Pathophysiological Characteristics and Implications for Antithrombotic Management

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ABSTRACT: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has posed a significant threat to global health. Although the infection is frequently asymptomatic or associated with mild symptoms, in a small proportion of patients it can produce an intense inflammatory and prothrombotic state that can lead to acute respiratory distress syndrome, multiple organ failure, and death. Angiotensin-converting enzyme 2, highly expressed in the respiratory system, has been identified as a functional receptor for severe acute respiratory syndrome coronavirus-2. Notably, angiotensin-converting enzyme 2 is also expressed in the cardiovascular system, and there are multiple cardiovascular implications of COVID-19. Cardiovascular risk factors and cardiovascular disease have been associated with severe manifestations and poor prognosis in patients with COVID-19. More important, patients with COVID-19 may have thrombotic and coagulation abnormalities, promoting a hypercoagulable state and resulting in an increased rate of thrombotic and thromboembolic events. This review will describe the pathophysiological characteristics of the cardiovascular involvement following infection by severe acute respiratory syndrome coronavirus-2, with a focus on thrombotic and thromboembolic manifestations and implications for antithrombotic management.

Key Words: anticoagulant therapy ■ antiplatelet therapy ■ coronavirus disease 2019 ■ endothelium ■ platelets ■ severe acute respiratory syndrome coronavirus-2 ■ thrombosis

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has posed a significant threat to global health. The outbreak was identified in Wuhan, China, in December 2019, declared a public health emergency of international concern on January 30, 2020, and recognized as a pandemic on March 11, 2020. By November 6, 2020, >48.7 million cases of COVID-19 have been reported in 190 countries or regions, resulting in >1.23 million deaths. Like with other respiratory viruses, respiratory tract symptoms are the most frequent. Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for coronaviruses. Infection by SARS-CoV-2 is mediated by binding of its spike protein to ACE2, which is highly expressed in type II pneumocytes in the respiratory system. Approximately 30% to 40% of infected individuals remain asymptomatic. Of those patients who develop symptoms, 81% are mild (no or mild pneumonia) and 14% are moderate (dyspnea and hypoxia). However, 5% of symptomatic patients develop intense endothelial activation with exuberant inflammatory response, similar to a cytokine release syndrome, which

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has been associated with acute respiratory distress syndrome (ARDS) and multiple organ failure. The overall case-fatality rate is estimated to be 2.3%.5

The ACE2 receptor is also widely expressed in the cardiovascular system.6 Therefore, there are multiple cardiovascular implications of COVID-19. Patients with preexisting cardiovascular disease are at increased risk for serious adverse events.5 Moreover, severe infections have been associated with myocardial injury, with a subsequent impact on mortality.7 Finally, individuals with COVID-19 may have thrombotic and coagulation abnormalities, promoting a hypercoagulable state and resulting in an increased rate of thrombotic and thromboembolic events.8 In patients who require hospitalization, the rate of any thrombotic event is ≈16%, varying between 11.5% in non–intensive care unit (ICU) to 29.4% in ICU settings.9 In this review, we provide insights on the current knowledge of the pathophysiological characteristics of COVID-19–related thrombosis and coagulopathy and the implications for antithrombotic management.

COVID-19: PATHOGENESIS OF VASCULAR INJURY AND HYPERCOAGULABILITY

Effects on the Endothelium
A novel betacoronavirus causes COVID-19, which probably originated from bats following gain-of-function mutations within the receptor-binding domain and acquiring a furin protease cleavage site. The World Health Organization named this virus SARS-CoV-2. SARS-CoV-2 binds to the transmembrane ACE2 protein to enter type I pneumocytes, macrophages, and other cell types.10 This process requires priming of the viral S protein by the transmembrane protease serine 2 (Figures 1 and 2).11 Because of the tropism of SARS-CoV-2 to type II pneumocytes, SARS-CoV-2 can interface with a large area of the pulmonary microvasculature. Furthermore, SARS-CoV-2 can infect the pericytes and perivascular cells present on the abluminal surface of microvessels, where they are embedded in the basement membrane. This phenomenon occurs mainly in the pulmonary alveolar tissue, but it has also been described in glomerular capillary loops, small intestine capillaries, and myocardocytes.12,13

In the endothelium, the gap junctions provide a portal of direct communication between endothelial cells and pericytes to promote autocrine and paracrine signaling and maintain vascular integrity.15 Pericytes are known for their important roles in vascular homeostasis and regulation of the inflammatory process.15 Therefore, abnormalities or degeneration within pericytes may cause tissue injury that can lead to organ damage.15 In humans, the abundant expression of ACE2 receptors on endothelial cells enhances their vulnerability to SARS-CoV-2 binding, membrane fusion, and viral entry, causing infection and resultant vascular injury, dysfunction, and endotheliitis.

Imbalance of ACE2 Regulation
ACE2 is an aminopeptidase that converts angiotensin II into angiotensin (1–7). Angiotensin II, an agonist of the angiotensin II receptor type 1 receptor, produces potent vasoconstrictor, profibrotic, and proinflammatory effects. Conversely, angiotensin (1–7), which is an agonist of the Mas receptors, is a potent vasodilator, antiapoptotic, and antiproliferative agent (Figures 1 and 2). For these reasons, ACE2 is a negative regulator of classic ACE in the renin-angiotensin system.16 In many patients with cardiovascular disease manifestations, there is an increase in the ACE/ACE2 ratio within organs. This ACE/ACE2 imbalance is often caused by downregulation of ACE2, resulting in altered renin-angiotensin system homeostasis. This imbalance has been observed in animal models with high-salt and glucose diets, renal disease, and oxidative stress.17 In humans, an ACE/ACE2 imbalance is associated with smoking, pulmonary arterial hypertension, and Alzheimer disease.18 Furthermore, the ACE/ACE2 ratio increase has been correlated with systolic blood pressure, serum creatinine level, fasting blood glucose level, and proteinuria.19 It has been suggested that SARS-CoV-2 infection of the host cell can affect the ACE/ACE2 ratio, leading to downregulation of ACE2.20 This hypothesis is supported by the fact that ACE2 expression in the lungs

| Nonstandard Abbreviations and Acronyms |
|----------------------------------------|
| APC             | activated protein C          |
| CAHA            | COVID-19–associated hemostatic abnormalities |
| COVID-19         | coronavirus disease 2019   |
| cTn             | cardiac troponin            |
| DIC             | disseminated intravascular coagulation |
| DOAC            | direct oral anticoagulant   |
| LMWHs           | low-molecular-weight heparin |
| MAS             | macrophage activation syndrome |
| NET             | neutrophil extracellular trap |
| SARS-CoV        | severe acute respiratory syndrome–associated coronavirus |
| SARS-CoV-2      | severe acute respiratory syndrome coronavirus-2 |
| UFH             | unfractionated heparin      |
determines the primary SARS-CoV-2 entry method.\textsuperscript{21} An important clinical observation is that patients with hypertension or preexisting cardiovascular disease, who have an increased ACE/ACE2 ratio, may be more susceptible to SARS-CoV-2 infection and impaired prognosis.\textsuperscript{7} These observations have raised interest on the prognostic implications associated with the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with COVID-19, for which there are several ongoing investigations, the description of which go beyond the scope of this article.\textsuperscript{22}

**Host Cell Death**

Most viral infections eventually lead to the death of host cells. Different types of regulated cell death have distinct molecular mechanisms and signaling pathways.\textsuperscript{23} Previously, with severe acute respiratory syndrome–associated coronavirus (SARS-CoV), it was
observed that SARS-coronavirus membrane protein induces apoptosis through modulating the Protein kinase B (also known as Akt) survival pathway. The most common mechanism of apoptosis is by activation of the NLR family pyrin domain containing 3 inflammasome by SARS-CoV and the subsequent cell pyroptosis. Pyroptosis is a highly inflammatory form of regulated cell death that occurs most frequently on infection with intracellular pathogens. In particular, the SARS-CoV E protein induces calcium leakage to the cytosol from Golgi storage, whereas open reading frame 3a induces potassium efflux from the cytosol to the extracellular spaces. This imbalance in the ionic concentration within the cells triggers NLR family pyrin domain containing 3 inflammasome activation. Moreover, open reading frame 3a promotes inflammasome assembly through tumor necrosis factor receptor–associated factor 3–mediated ubiquitination of an apoptosis-associated speck-like protein containing a caspase recruitment domain. The SARS-coronavirus open reading frame 8b interacts directly with a leucine-rich repeat of NLR family pyrin domain containing 3 to stimulate its activation. Inflammasome activation induces the formation of gasdermin-D pores on the cell membrane, causing interleukin-1β and interleukin-18 secretion and the influx of water, leading to cell swelling and subsequent rupture. Ren et al showed that SARS-CoV-2 open reading frame 3a induces apoptosis. Apoptosis, mainly pyroptosis, has been described in endothelial cells but can occur in any cell type. The regulated cell death is the inception of a local intense inflammatory response that may become systemic because of the release of potent proinflammatory cytokines, such as interleukin-1β and interleukin-18 (Figures 1 and 2).

**Endotheliitis**

Endotheliitis is an immune response within the endothelium in blood vessels, in which they become inflamed. Several reports of patients who died of COVID-19 showed an accumulation of inflammatory cells and viral inclusions by histological analysis and electron microscopy. Furthermore, in autopsy and surgical tissue specimens, there was diffuse lymphocytic endotheliitis and apoptotic bodies. Of note, in endothelial cells, apoptosis is triggered by binding to the cell surface and subsequent apoptotic pathway signaling. The SARS-CoV-2 tropism for ACE2 receptors, along with the close anatomical juxtaposition of type II pneumocytes with the pulmonary vascular network,
can produce a severe inflammatory reaction, which can lead to a generalized pulmonary hypercoagulable state.\textsuperscript{28}

**Hyperinflammation**

The capacity of SARS-CoV-2 to infect the endothelial cells and produce an intense local inflammatory reaction is critical for the development of a systemic inflammatory response. The severity of systemic inflammation in response to SARS-CoV-2 has led some authors to compare its features with a cytokine storm or macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis.\textsuperscript{29}

Key features of a cytokine storm syndrome are the hemophagocytes and acute consumptive coagulopathy, leading to disseminated intravascular coagulation (DIC). DIC has also been observed in COVID-19 pneumonia, but usually in the context of critically ill patients.\textsuperscript{30} However, some pivotal clinical characteristics differentiate secondary hemophagocytic lymphohistiocytosis or MAS from COVID-19. In secondary hemophagocytic lymphohistiocytosis or MAS, serum ferritin levels are extremely high, whereas these are only moderately elevated in COVID-19. Moreover, secondary hemophagocytic lymphohistiocytosis or MAS is associated with impaired liver function and thus coagulopathy. In contrast, these findings are not typically seen in patients with COVID-19.\textsuperscript{31}

SARS-CoV-2 infection can result in diffuse lung inflammation that involves the extensive pulmonary vascular network. Some of the COVID-19 clinical and laboratory features resemble those of MAS-like syndrome. These clinical findings suggest that an initial pulmonary intravascular coagulopathy occurs in patients with COVID-19 pneumonia, distinct from conventional DIC.\textsuperscript{32} The extensive cytokine response in the pulmonary vasculature, resulting in intravascular coagulopathy, may lead to a more systemic inflammatory response in severe COVID-19 cases.

**Effects on Platelets**

Platelets represent the interplay between hemostasis and the immune system. Platelets play a role in protecting or promoting an immune-mediated response to different types of pathogens.\textsuperscript{33} Platelets can bind to different microbes, including viral pathogens, through direct interactions or indirectly. This pathogen-platelet interaction can trigger granule release, with subsequent platelet activation, promotion of platelet-leucocyte interaction, and recruitment and tissue infiltration necessary for pathogen clearance (Figures 1 and 2).\textsuperscript{34}

Most patients with mild to moderate COVID-19 symptoms may have normal or increased platelet count.\textsuperscript{35} However, in critically ill patients, platelet count may be decreased, and DIC may be found in almost 70% of nonsurvivors.\textsuperscript{30} The pathophysiological mechanisms of thrombocytopenia in patients with COVID-19 are not entirely understood but may be related to a reduction in primary platelet production, an increase in platelet destruction, or a decrease in circulating platelets.\textsuperscript{36} Platelet production can be impaired because of the bone marrow suppression induced by the cytokine storm or direct infection of the hematopoietic and bone marrow stromal cells; platelet destruction may be related to an increase in autoantibodies and immune complexes. Finally, a decrease in circulating platelets may be associated with the intense lung injury, producing a pulmonary intravascular coagulopathy.\textsuperscript{36}

In an autopsy case series of patients with COVID-19, Rapkiewicz et al described the presence of extramedullary megakaryocytes in the vascular beds of multiple organs with higher than usual numbers in the lungs and heart.\textsuperscript{37} Megakaryocyte numbers were increased compared with control patients who died of ARDS unrelated to COVID-19.\textsuperscript{37} This phenomenon appears to be a unique feature of COVID-19 and may play an important role in their increased thrombotic risk.\textsuperscript{38}

**Neutrophil Extracellular Traps**

Leukocyte activation, specifically neutrophils, through various vascular and platelet pathways, may promote neutrophil extracellular trap (NET) formation. NETs are large, extracellular, weiblike structures composed of cytosolic and granule proteins assembled on a scaffold of decondensed chromatin.\textsuperscript{39} NETs may have an essential role in the phenotypic expression and end-organ injury among patients with COVID-19.\textsuperscript{36} This hypothesis was proposed by Barnes et al, on the basis of findings of an autopsy series in which the authors observed neutrophil infiltration in pulmonary capillaries, acute capillaritis within fibrin deposition, extravasation of neutrophils into the alveolar space, and neutrophilic mucositis.\textsuperscript{40} NETs are an ideal foundation for binding activated platelets, erythrocytes and leukocytes, and activating factor XI, and generating thrombin for fibrin production.

In patients with COVID-19, Zuo et al reported higher circulating cell-free DNA and DNA-myeloperoxidase complexes compared with controls. Furthermore, levels correlated with disease severity, inflammatory response, and need for mechanical ventilation.\textsuperscript{41} At the tissue level, NETs cause platelet activation through toll-like receptors on platelets and other cells, activating the receptor integrin \(\alpha IIb\beta 3\), which promotes platelet aggregation, granule release, phosphatidyserine exposure, coagulation factor V (FV)/Activated FV (FVa) expression, and thrombin generation. For these reasons, NETs are recognized as linking inflammation, coagulation, and thrombosis, both locally (microvascular)
and systemically (macrovascular). In a case series of autopsies of patients with COVID-19, Nicolai et al. reported the presence of microvascular thrombi containing NETs in the lung, kidney, and heart tissues. Therefore, the authors suggest that an immunothrombotic dysregulation may explain the multiple organ failure and systemic hypercoagulability in patients with severe SARS-CoV-2 infection (Figures 1 and 2).

**EFFECTS ON THE COAGULATION AND FIBRINOLYTIC SYSTEM**

The predominant coagulation abnormalities in patients with COVID-19 suggest a hypercoagulable state, which has been termed thromboinflammation or COVID-19–associated hemostatic abnormalities (CAHA). The most consistent observation among patients with COVID-19, particularly those with severe illness, is D-dimer elevation. D-dimer is a degradation product of fibrin; its presence in the circulation signals the breakdown of fibrin polymers by plasmin and may correlate with the thrombus burden. However, it does not specify the site(s) of thrombus formation. Panigada et al. assessed several coagulation parameters in patients with COVID-19. Using whole blood thromboelastography, the authors identified hypercoagulability features, such as a decrease in time to fibrin formation, a decrease in time to clot formation, and an increase in clot strength. Using thromboelastography analysis, other authors found low lysis at 30 minutes, which is suggestive of fibrinolysis shutdown (Figures 1 and 2). Additional laboratory findings that are impaired in patients with COVID-19 are shown in Table 1.

The International Society on Thrombosis and Haemostasis has proposed assessing different parameters for the prompt recognition of coagulopathy in patients with COVID-19. These parameters, in decreasing order of importance, are D-dimer, prothrombin time, platelet count, and fibrinogen. Using these parameters may help decide which patients require hospital admission and close monitoring as well as specific antithrombotic treatment. The authors suggest that parameters, such as D-dimer raised 3 to 4 times fold, prolonged prothrombin time, platelet count <100×10^9/L, and fibrinogen <2.0 g/L, should be considered for hospital admission even in the absence of other conditions.

Currently, there is no consensus on the definition of the COVID-19 coagulopathy or CAHA. However, a group of experts proposed a classification of stages of CAHA, considering the lungs as the epicenter for the hemostatic abnormalities and using the available diagnostic biomarkers. A complete description of 3 stages of CAHA is shown in Figure 3. Stage 1 includes patients at home or hospitalized in non-ICU wards, frequently with mild symptoms. Pulmonary microthrombi are localized at the peripheral microvasculature and may not be detected by computed tomography. Stage 2 includes patients who may develop severe symptoms and may require ICU support. These patients may have lung ventilation/perfusion impairment caused by

Table 1. Distinguishing Laboratory Features of SIC, DIC, Thrombotic Microangiopathy, and CAHA

| Variable                  | SIC | DIC | Microangiopathy | CAHA |
|---------------------------|-----|-----|-----------------|------|
| Prothrombin time          | ↑   | ↑   | ↔              | ↑↑   |
| Activated partial thromboplastin time | ↑ | ↑ | ↔ ↔ ↑ | ↑ |
| Fibrinogen                | ↓   | ↓   | ↔              | ↑   |
| Fibrinogen degradation products | ↑ | ↑ | ↔      | ↑↑ |
| D-dimer                   | ↑   | ↑   | ↔              | ↑↑   |
| Platelet count            | ↓   | ↓   | ↓              | ↑ or ↑ |
| Peripheral blood smear + | +   | +   | ++             | + |
| von Willebrand factor     | ↑   | ↑   | ↔              | ↑    |
| ADAMTS13                  | ↔   | ↔   | ↓              | ↔   |
| Antithrombin              | ↓   | ↓   | ↓              | ↑   |
| Anticardiolipin antibodies| ↔   | ↔   | ↔              | +   |
| Protein C                 | ↓   | ↓   | ↔              | +   |
| Protein S                 | ↓   | ↓   | NA             | ↓   |
| Factor VIII               | ↑   | ↑   | NA             | ↑   |
| Plasminogen               | ↓   | ↓   | NA             | ↑   |

*Some laboratory features can change significantly, depending on the stage of the CAHA.
thrombi or emboli noted in the computed tomography scan and may have asymptomatic or symptomatic deep vein thrombosis (DVT). Stage 3 includes critically ill patients who need invasive mechanical ventilation or extracorporeal membrane oxygenation. These patients may exhibit venous thromboembolism (VTE) and extrapulmonary thrombosis involving several organs, such as intestine, limbs, and coronary or cerebral circulation. At this advanced stage, patients may develop a DIC with or without bleeding, which is often fatal. CAHA is a clinical entity different from DIC and other coagulopathies (Table 1). In the stages 1 and 2 of the disease, fibrinogen is usually increased, and patients exhibit a strong prothrombotic disorder with a marked increase of the D-dimer. However, patients in stage 3, who are critically ill and present pulmonary and extrapulmonary thrombotic manifestations, may advance to a consumptive coagulopathy with a prolongation of prothrombin time (>50%) and a decrease of platelet count and fibrinogen. Moreover, these patients may need blood product transfusion and may have an increase in bleeding events.

In normal lung physiology, the pulmonary alveolar space has been considered as a profibrinolytic environment. However, in patients with ARDS, the fibrinolytic system is often suppressed because of increased plasminogen activator inhibitor I in both plasma and the bronchoalveolar lavage fluid. Moreover, plasmin also cleaves numerous matrix proteins but, more important, also misfolded/necrotic proteins, which can be of significant importance in patients with COVID-19. At all CAHA stages, elevated D-dimer levels are a common feature, and this suggests that the endogenous fibrinolytic system is functional. However, in advanced stages (CAHA stage 3), the fibrinolytic system may fail to cope with the extent of fibrin and necrotic material needing to be removed. Thus, some authors have proposed the so-called “consumptive fibrinolysis” hypothesis. The authors claim that elevated levels of D-dimer are the consequence and not the cause of disease progression, but rather a failure of the host to clear the overwhelming levels of fibrin and misfolded proteins/necrotic tissue in the lung because of a decrease in plasmin-plasminogen activity. However, there are limited data on the effects of COVID-19 on the fibrinolytic system to support this hypothesis.

**Effects on the Myocardium**

Acute myocardial injury, defined by cardiac biomarkers’ elevation, mainly high-sensitivity cardiac troponin (cTn), is common in patients with COVID-19 infection.
Most studies have defined myocardial injury (acute or chronic) as cTn concentrations >99th percentile upper-reference limit, which is the definition according to the Fourth Universal Definition of Myocardial Infarction. Clinical registries have shown that patients with cardiovascular risk factors or cardiovascular disease have higher rates of myocardial affection and worse outcomes. In a meta-analysis of 26 observational studies, including 11,685 patients, the prevalence of acute myocardial injury was 20%. However, the prevalence of myocardial injury can vary significantly, depending on the definitions and protocols of each center.

In an autopsy case series of patients with COVID-19, Fox et al found notable cardiomegaly and right ventricular dilation. Coronary artery thrombosis was not seen on histologic examination. However, there was scattered individual myocyte necrosis with adjacent lymphocytes. These changes may be compatible with a pulmonary intravascular coagulopathy, promoting subacute pulmonary hypertension development, with elevations in cTn and other markers reflecting diffuse myocardial mechanical stressing and ischemia, especially in the right ventricle. In patients with COVID-19 who underwent echocardiographic assessment, the left ventricle diastolic and right ventricle function were impaired, and elevated cTn and poorer clinical grade are associated with worse right ventricle function. Moreover, myocardial involvement, assessed by cardiac magnetic resonance, was found in almost 80% of patients with recent COVID-19 infection. The most frequent abnormality was myocardial inflammation, found in 60% of patients, followed by regional scar and pericardial enhancement. Furthermore, there was a significant correlation between cardiac biomarkers and the degree of cardiac inflammation.

Although myocardial injury is common in patients with moderate to severe COVID-19, the pathophysiological mechanisms are not entirely understood. The clinical spectrum of myocardial involvement can vary from fulminant viral myocarditis to atherothrombotic myocardial infarction (MI). The mechanisms may vary according to the patient’s clinical characteristics: direct injury may be more frequent in younger patients, and MI may be more frequent in older patients with atherosclerotic disease (Figures 1 and 2).

**Direct Viral Myocardial Injury**

The presence of ACE2 receptors on myocardial and vascular endothelial cells supports the potential for direct viral infection of the heart with resultant myocarditis. Previously, with SARS-CoV, there were well-documented cases of viral myocarditis with detected viral RNA in autopsied hearts. Pirzada et al analyzed the reported cases of suspected myocarditis with SARS-CoV-2 among patients with COVID-19. Of the 9 reported cases, 2 had an endomyocardial biopsy, but the viral genome was not found in any cases. Nevertheless, as both viruses share the same cell entry receptor, the possibility of a direct viral myocardial entry may not be ruled out. A second plausible mechanism of direct viral injury can be through an infection-mediated vasculitis. Myocardial vasculitis has been previously reported with SARS-CoV. In COVID-19, either the direct effect of the virus or the indirect immunological response may trigger vasculitis.

**Microvascular Injury**

Thrombosis may occur in the myocardial microcirculation. In a case series of 18 patients with COVID-19 and ST-segment–elevation MI, 56% of patients had a nonobstructive disease, defined as either nonobstructive disease on coronary angiography or normal wall motion on echocardiogram. An autopsy report from Bergamo, Italy, reported a patient who presented with ST-segment–elevation MI and COVID-19; the patient underwent coronary angiography, which showed normal epicardial coronary vessels. An extensive heart pathologic examination observed microvascular thrombi, acute inflammatory infiltrates with contraction band necrosis, coinciding with the location of the ST-segment elevation on ECG. Therefore, in patients with ST-segment–elevation MI and COVID-19, if coronary angiography reveals nonobstructive disease, microvascular thrombi could represent a mechanism for myocardial injury.

**Systemic Hyperinflammatory Response With Resulting Myocardial Injury**

Patients with COVID-19 who develop a hyperinflammatory state may advance to severe manifestations with cytokine storm and multiple organ failure. The cytokine storm, which includes interleukin-1, interleukin-6, and tumor necrosis factor, can either affect preexisting atherosclerotic lesions or promote accelerated atherogenesis. At the site of preexisting atherosclerotic lesions, there can be a so-called “echo” phenomenon, in which circulating cytokines stimulate macrophages within the plaque to increase local cytokine production and tissue factor expression, and promote lesion thrombogenicity. Moreover, systemic cytokines can stimulate adhesion molecule expression and increase the recruitment of inflammatory cells. These alterations may enhance the vulnerability of preexisting plaques to rupture or promote accelerated atherogenesis.

On the other hand, the hyperinflammatory response may also be related to a nonobstructive disease, such as stress cardiomyopathy (Takotsubo), because of the intense release of potent inflammatory cytokine and sympathetic surge. However, stress cardiomyopathy
may also be related to microvascular injury. A small case series of stress cardiomyopathy in patients with COVID-19 suggests that the mechanism can be associated with a catecholamine-induced microvascular dysfunction secondary to the metabolic, inflammatory, and emotional distress related to COVID-19.67

### Acute Coronary Syndrome

Several infections have been associated with the risk of an acute coronary syndrome. Epidemiologic studies have shown that hospitalization for pneumonia is associated with a higher risk for acute coronary events.68 Influenza infection has been shown to have a temporal association with cardiovascular complications and acute coronary syndrome.69 Furthermore, in a meta-analysis of clinical trials, annual influenza vaccination was associated with a 36% lower rate of major adverse cardiovascular events.69 Therefore, although it is plausible that the COVID-19 pandemic can increase the rates of atherothrombotic events, a global increase in MI rates (ie, type 1 MI) has not been yet described. In the short-term phase, the entry of viral products into the systemic circulation,
| Variable | Recommendation* |
|----------|-----------------|
| **Venous thromboembolism** | |
| Risk assessment | - Risk assessment is recommended in all hospitalized patients with COVID-19 (eg, Padua, IMPROVE [International Medical Prevention Registry on Venous Thromboembolism], or Caprini model).<sup>5</sup> |
| Screening | - There are currently insufficient data to recommend for or against routine deep vein thrombosis screening in patients with COVID-19 without signs or symptoms of VTE, regardless of the status of their coagulation markers (NIH grade BIII).<sup>15</sup>  
- For hospitalized patients with COVID-19, the possibility of thromboembolic disease should be evaluated in the event of a rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion (NIH grade AII).<sup>92</sup> |
| Prophylaxis | - Hospitalized adults with COVID-19 should receive VTE prophylaxis, per the standard of care for other hospitalized adults (NIH grade AII).<sup>15</sup>  
- Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (NIH grade AIII).<sup>15</sup>  
- LMWHs or UFH may be preferred in hospitalized critically ill patients because of its shorter half-life, ability to be given intravenously or subcutaneously, and fewer known drug-drug interactions compared with oral anticoagulants (NIH grade AII).<sup>15</sup>  
- Prophylactic dosing should be adjusted on the basis of body weight extremes, severe thrombocytopenia (platelet count <50×10⁹/L or <25×10⁹/L), or impaired renal function. Of note, in case, thromboprophylaxis should be held only if the platelet count is <25×10⁹/L or fibrinogen level is <0.5 g/L.<sup>20</sup> |
| Treatment | - Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected of having a thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy, as per the standard of care for patients without COVID-19 (NIH grade AII).<sup>15</sup>  
- In patients taking treatment-dose DOACs or vitamin K antagonists, consider switching to LMWH, especially for those in critical care settings or taking relevant concomitant medications.<sup>6,93</sup>  
- The anticoagulation with LMWHs may be preferred in an inpatient setting, whereas DOACs may be preferred in an outpatient setting.<sup>20,25</sup>  
- In patients taking treatment-dose DOACs or vitamin K antagonists, consider switching to LMWH, especially for those in critical care settings or taking relevant concomitant medications.<sup>6,93</sup>  
- Duration of treatment is ≥3 mo.<sup>93</sup>  
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy, per the standard institutional protocols for those without COVID-19 (NIH grade AIII).<sup>92</sup> |
| Extended prophylaxis | - The routine discharge of patients on VTE prophylaxis is not generally recommended (NIH grade AII).<sup>20</sup>  
- In patients at high risk of VTE, if bleeding risk is low, extended prophylaxis can be considered with either LMWH or DOACs (rivaroxaban or betrixaban).<sup>75</sup>  
- The patients at risk for postdischarge VTE include those with reduced mobility and those with coexisting conditions, such as cancer, previous VTE event, D-dimer level >2 times the upper level of normal, older age (>75 years), ICU admission, or thrombophilia (NIH grade AII).<sup>92</sup>  
- The duration of postdischarge prophylaxis should be ≥14 d and up to 30 d.<sup>20</sup> |
| Previous indication of antithrombotic treatment (eg, CAD or NWAF) | - Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 (NIH grade AII).<sup>92</sup>  
- Drug-drug interactions should be considered between investigational COVID-19 therapies and antithrombotic agents.<sup>14</sup>  
- Patients who take low-dose aspirin should continue the treatment.<sup>14</sup>  
- In patients who take P2Y<sub>12</sub> inhibitors, clopidogrel and ticagrelor have a potentially dangerous drug-drug interaction and are contraindicated. Prasugrel can be used, taking into account its contraindications and precautions.<sup>24</sup>  
- In patients using anticoagulant therapy and who have the concomitant need for specific COVID-19 treatment, baseline anticoagulant therapy could be changed to LMWH. After COVID-19 treatment is completed, the baseline treatment can be reinitiated.<sup>8</sup> |
| Acute coronary syndromes | - Considerations for oral antithrombotic agents, mentioned in the section “Previous indication of antithrombotic treatment,” also apply to the ACS setting. |
| NSTEMI | - Parenteral antiplatelet, such as cangrelor, and anticoagulant therapies, such as UFH, bivalirudin, LMWH, or fondaparinux, do not have important drug-drug interactions with the COVID-19–specific treatment.<sup>24</sup> |
| STEMI | - If the patient’s clinical condition is not a contraindication, primary PCI is the standard care strategy.<sup>25</sup>  
- Parental antiplatelet therapies, such as GPI, have no significant drug-drug interaction with COVID-19 treatment.<sup>24</sup>  
- Tissue plasminogen activator or streptokinase has no relevant drug-drug interactions with COVID-19 treatment and can be used unless contraindicated.<sup>24</sup> |
| Arterial thrombosis events | |
| Acute ischemic stroke | - If COVID-19–associated coagulopathy is severe, it may contraindicate the use of intravenous thrombolytic. Even if intravenous thrombolysis is not contraindicated, increased inflammation and hypercoagulability may increase postthrombolysis mortality and morbidity.<sup>46</sup>  
- In patients treated with thrombolysis or endovascular therapy, antiplatelet therapy should be avoided until a complete risk assessment is well defined. In patients not treated with thrombolysis or endovascular treatment, SAPT or DAPT could be considered.<sup>26</sup> |
Table 3. Continued

| Variable                                      | Recommendation*                                                                                                                                 |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Acute limb ischemia                           | • In patients with COVID-19 who presented with acute limb ischemia, prolonged UFH might be warranted for both limb salvage and improved survival.77  |
| Coagulopathy                                  |                                                                                                                                                  |
| Diagnosis                                     | • In patients with significantly elevated D-dimer level (3- to 4-fold increase), prolonged PT, platelet count <100×10^9/L, or fibrinogen >2 g/L; consider hospital admission (regardless of other condition) and monitor once or twice a day. Patients with impaired renal function may require a closer follow-up.55  |
| Prophylaxis                                   | • Consider prophylaxis with LMWH in all patients, if not contraindicated (eg, active bleeding or platelet count <25×10^9/L).55  |
| Treatment                                     | • The management of DIC is focused on the treatment of the underlying condition.68  |
|                                             | • Without bleeding: blood products should be administered to maintain platelet count >25×10^9/L.45  |
|                                             | • With bleeding: blood products should be administered to maintain platelet count >50×10^9/L, fibrinogen >1.5 g/L, and PT ratio <1.5.46  |
|                                             | • In patients with DIC, antifibrinolytics are not recommended.28  |
|                                             | • Patients with COVID-19 who require ECMO with a hypercoagulable status may benefit from antiplatelet agents (eg, aspirin, clopidogrel, prasugrel, or ticagrelor), but there are few data to recommend or refute.29  |
| ECMO, renal replacement, or clotting of intravascular access devices | • Patients with COVID-19 who require ECMO or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated as per the standard institutional protocols for those without COVID-19 (NIH grade AII).92,99  |
|                                             | • With bleeding: blood products should be administered to maintain platelet count >50×10^9/L, fibrinogen >1.5 g/L, and PT ratio <1.5.46  |
|                                             | • In patients with DIC, antifibrinolytics are not recommended.28  |
|

ACS indicates acute coronary syndrome; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DAPT, dual antiplatelet therapy; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; GPI, glycoprotein IIb to IIIa inhibitor; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; LMWH, low-molecular-weight heparin; NIH, National Institutes of Health; NSTEMI, non-ST-segment–elevation myocardial infarction; NVAF, nonvalvular atrial fibrillation; PCI, percutaneous coronary intervention; PT, prothrombin time; SAPT, single antiplatelet therapy; STEMI, ST-segment–elevation myocardial infarction; UFH, unfractionated heparin; and VTE, venous thromboembolism.  

*The selected international guidelines and consensus documents are as follows: International Society on Thrombosis and Haemostasis Scientific and Standardization Committee Clinical Guidance on Diagnosis, Prevention, and Treatment of Venous Thromboembolism in Hospitalized Patients With COVID-19; International Society on Thrombosis and Haemostasis Interim Guidance on Recognition and Management of Coagulopathy in COVID-19; National Institutes of Health (NIH) COVID-19 Treatment Guideline; Global COVID-19 Thrombosis Collaborative Group COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up; The European Society for Cardiology ESC Guidance for the Diagnosis and Management of CV [Cardiovascular] Disease During the COVID-19 Pandemic; Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic; and Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report.100 Grade of recommendation is only provided for the NIH guidelines.

also known as pathogen-associated molecular patterns, can cause innate immune receptor activation, with subsequent activation of immune cells resident in preexisting atheroma plaques, and promote their rupture.70 Damage-associated molecular patterns are host biomolecules that can initiate and perpetuate a noninfectious inflammatory response, potentially leading to plaque rupture.70

**Myocardial Injury Secondary to Oxygen Supply and Demand Mismatch**
Cardinal signs of any infection include fever and tachycardia, physiological adaptations that increase the myocardium’s oxygen requirements. Furthermore, as COVID-19 pneumonia is associated with hypoxemia, oxygen supply can be significantly reduced. In critical patients, clinical scenarios, such as sepsis, septic shock, and coagulopathy with associated bleeding, can impair coronary perfusion. Moreover, sympathetic activation and biological stress caused by cytokine storm can produce coronary vasospasm. Collectively, these factors can affect the oxygen supply/demand balance and lead to myocardial injury with nonobstructive disease, consistent with the diagnosis of type 2 MI, according to the Fourth Universal Definition of Myocardial Infarction. Patients with preexisting coronary artery disease may be at higher risk of type 2 MI.71 Of note, patients who had a type 2 MI have a similar rate of major adverse cardiovascular events as those with type 1 MI.71 Given that patients with moderate or severe COVID-19 who require hospitalization are usually older and with more cardiovascular comorbidities, type 2 MI in this population is common and represents a marker of poor outcomes.72

**Cardiac Arrhythmias and Pericardial Effusion**
Most patients presenting with COVID-19 will not have symptoms or signs of arrhythmias or conduction system disease. However, in patients who are critically ill, cardiac arrhythmias are more common.73 Risk factors for arrhythmias are myocardial injury or ischemia, hypoxia, shock, and electrolyte disturbances; those receiving medications that prolong the QT interval are also at risk.73 In an observational study, the most frequent arrhythmias were atrial fibrillation (3.6%), nonsustained ventricular tachycardia (1.4%), cardiac arrest (1.3%), and bradyarrhythmias (1.3%).74 In a cardiac magnetic resonance series, pericardial effusion was found in 20% of the patients.86 It is hypothesized
that viruses cause pericardial inflammation via direct cytotoxic effects, systemic inflammation, or immune-mediated mechanisms.\textsuperscript{75}

**COVID-19: THROMBOTIC AND THROMBOEMBOLIC CLINICAL MANIFESTATIONS**

A variety of thrombotic and thromboembolic clinical manifestations characterize patients with COVID-19, underscoring the importance of antithrombotic therapy (Table 2).\textsuperscript{76–90}

Data on antithrombotic treatment regimens mostly derive from retrospective studies, many with a small sample size. Therefore, the level of evidence is low, and current recommendations on screening, diagnosis, and treatment of COVID-19–associated thrombosis and coagulopathy are mostly based on expert opinion consensus (Table 3).\textsuperscript{14,91–100}

**Venous Thromboembolism**

The prevalence of VTE, including DVT and pulmonary embolism (PE), varies according to the severity of COVID-19 and is common in critically ill patients. The main risk factors are immobilization, acute inflammatory state, hypoxia, and endothelial cell activation or damage.\textsuperscript{93} An accurate prevalence of VTE associated with COVID-19 is unknown because most studies did not include systematic and comprehensive investigation protocols. In a large cohort of patients with COVID-19, Wang et al reported that 40% of hospitalized patients with COVID-19 were at high risk of VTE.\textsuperscript{101} In patients with severe COVID-19 who required ICU admission, the prevalence of VTE, particularly PE, ranges from 17% to 47%. Many of the thromboembolic events occurred despite thromboprophylaxis.\textsuperscript{102,103} In a non-ICU setting, 6.4% of patients presented symptomatic VTE. However, half of the events were diagnosed during the first day of admission, suggesting that these occurred before thromboprophylaxis was initiated.\textsuperscript{102} Interestingly, PE can be found without associated DVT.\textsuperscript{102} Therefore, the absence of an embolic source has promoted the “in situ” pulmonary thrombosis hypothesis.\textsuperscript{101} Of note, in a retrospective study analyzing thrombotic events in patients who required hospitalization, of the 28 patients who had any thrombotic complication, 25% presented with isolated PE.\textsuperscript{102}

**Risk Assessment**

Previously developed VTE risk assessment tools can be applied in patients with COVID-19 (eg, the Padua, International Medical Prevention Registry on Venous Thromboembolism [IMPROVE], and Caprini models).\textsuperscript{8}

The choice of specific risk assessment model may vary according to the physician and healthcare system. All hospitalized patients with COVID-19 should undergo VTE risk stratification.\textsuperscript{8}

**Screening and Diagnosis**

There is currently insufficient data in favor of or against a routine DVT screening in patients with COVID-19, regardless of status of coagulation markers.\textsuperscript{92} The benefits of routine screening may be early diagnosis of DVT and PE prevention. Although DVT has been associated with worse prognosis,\textsuperscript{104} there are no trials supporting that routine screening may improve clinical outcomes. Routine screening may increase incidental findings, exposure of healthcare personnel, and costs. An interesting approach can be performed by screening only high-risk patients, such as those with CURB-65 (confusion status, urea, respiratory rate, and blood pressure) score 3 to 5, Padua prediction score \( \geq 4 \), and D-dimer >1.0 \( \mu \text{g/mL} \).\textsuperscript{104} However, in a prospective study of hospitalized patients with COVID-19, the strategy of using D-dimer levels of dimer >1.0 \( \mu \text{g/mL} \) did not prove to be useful for risk stratification in asymptomatic patients.\textsuperscript{105}

Ultimately, clinical judgment must prevail and the threshold for evaluation or diagnosis of DVT and PE should be low, given the high frequency of these events. In hospitalized patients with COVID-19, VTE clinical evaluation and the diagnostic test may be indicated in patients with rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion.\textsuperscript{92} On the other hand, in outpatients, the evaluation of abnormal symptoms or findings on examination is similar to inpatients.\textsuperscript{92}

**Prophylaxis**

Most scientific societies agree that in the absence of contraindications and careful evaluation of bleeding risk, hospitalized adults with COVID-19 should receive thromboprophylaxis.\textsuperscript{8,53,100} Current recommendations are based on expert consensus (Table 3). An essential unanswered question is whether all hospitalized patients will have a net clinical benefit from thromboprophylaxis or whether this would be limited to patients on the basis of their VTE risk score and D-dimer levels.

Most scientific societies recommend prophylaxis with daily low-molecular-weight heparins (LMWHs) or twice-daily subcutaneous unfractionated heparin (UFH). If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis (eg, intermittent pneumatic compression) should be considered in immobilized patients.\textsuperscript{8} LMWHs have several potential advantages for prophylaxis when compared with UFH.
or oral agents. First, basic research models have proposed that the SARS-CoV-2 Spike S1 protein receptor-binding domain interacts with LMWHs. Therefore, they can have antiviral properties by acting as an effective inhibitor of viral attachment. Second, LMWHs have anti-inflammatory and immunomodulatory effects. Third, LMWHs have reliable pharmacokinetic and pharmacodynamic response profiles. Of note, LWMH has higher availability than UFH (90% versus 30%). More important, with intense systemic inflammation, UFH has a higher degree of binding to plasma protein. Moreover, LMWHs have a longer half-life than UFH, which allows twice or once daily administration regimens and reduces healthcare workers’ exposure. However, LMWHs have a shorter half-life than oral therapies, which can be useful in patients who require procedures or need short time bleeding risk assessment.

An important clinical observation is the occurrence of thrombotic events despite thromboprophylaxis. In critically ill patients receiving anticoagulant treatment, 80% of patients had heparin resistance with UFH, and 50% had suboptimal anti-activated factor X (anti-FXa) effects with LMWH. In non-ICU patients, up to 30% of the patients had suboptimal anti-FXa effects. The use of higher dose of anticoagulation was beneficial in terms of mortality reduction and need for mechanical ventilation. The mechanism related to such “heparin resistance” phenomena is not completely understood, but may be attributed to high factor VIII and fibrinogen and low antithrombin levels. The use of high-dose thromboprophylaxis (4 times the conventional dose) in critically ill patients with COVID-19 was associated with on-target levels of anti-Xa activity. However, viscoelastic tests still demonstrated a procoagulant pattern. The optimal dosing regimen of anticoagulant therapy for prophylaxis is the subject of ongoing investigation. In the interim, a potential approach could be to apply anti–FXa-guided LMWH dosing. In non-ICU patients, predictors of a suboptimal anti-Xa peak with LMWH were D-dimer >3000 µg/L, current or previous cancer, and need of high-flow nasal oxygen therapy or noninvasive ventilation. In ICU patients, suboptimal anti-Xa levels were associated with hypoalbuminemia, higher sequential organ failure assessment score, and elevated D-dimer. Most recently, a phase 2 randomized clinical trial comparing prophylaxis with therapeutic regimens of enoxaparin found that the therapeutic regimen improves gas exchange and decreases the need for mechanical ventilation in severe COVID-19.

Although direct oral anticoagulants (DOACs) are appealing for thromboprophylaxis, their use is significantly limited by the multiple drug-to-drug interactions with several of the experimental therapies being used for COVID-19. However, in patients not on concomitant therapies associated with drug interactions, DOACs may be considered. Table 3 provides details, taking into consideration several parameters, prophylactic dosing, adjustments, and when it should be held. In nonhospitalized patients with COVID-19, anticoagulants should not be initiated for prevention of VTE unless there are other indications.

### Treatment
Therapeutic anticoagulation is the cornerstone of VTE treatment. Drug selection requires specific considerations, such as renal or hepatic dysfunction, thrombocytopenia, and gastrointestinal tract function. The choice of drug may change by function of the patient’s clinical condition and clinical care setting. In the in-hospital setting, parental drugs are preferred on the basis of their pharmacological advantages (Table 3). Patients taking therapeutic-dose DOACs or vitamin K antagonists should consider switching to LMWH. Use of LMWH may be preferred in an in-patient setting, whereas DOACs may be preferred in an outpatient setting. However, in patients who may need invasive procedures, UFH may be an optimal option because of the shorter half-life. Finally, the complete duration of treatment of the VTE event should be ≥3 months.

In patients with severe PE, the routine use of inferior vena cava filters is not recommended, although their placement may be considered in selected cases, such as recurrent PE, despite optimal anticoagulation, or clinically significant VTE in the setting of absolute contraindications to anticoagulation. Guideline recommendations should be followed for reperfusion strategies in patients with acute PE. Hemodynamically stable patients should be given anticoagulation. However, patients with hemodynamic instability should be managed with systemic fibrinolysis or with catheter-directed options as an alternative if not suited for systemic fibrinolysis. Most patients with DVT can be managed with anticoagulation. However, only patients with phlegmasia or with truly refractory symptoms may benefit from endovascular techniques.

### Extended Prophylaxis
There are no specific data on extended postdischarge prophylaxis in patients with COVID-19 postdischarge. A postdischarge follow-up study did not find a higher risk of postdischarge VTE in patients with COVID-19 when compared with patients with other acute medical illness. Therefore, routine use of extended prophylaxis is not recommended. However, patients at high risk of postdischarge VTE (Table 3) and low bleeding risk may consider extended prophylaxis (≥14 days and up to 30 days) with either LMWH or DOACs.
Arterial Thrombotic Events

Acute Coronary Syndromes

Patients with COVID-19 are commonly characterized by an increase in cardiac biomarkers. However, there is no consensus on how these should be used in clinical practice. Major scientific societies recommend measuring cTn T or I concentrations only if type 1 MI is suspected, or in new-onset left ventricle dysfunction. Some, however, support systematic cTn measurements. Such an approach can have advantages, such as prompt diagnosis of myocardial injury, identification of high-risk patients (ARDS or death) who required further evaluation, recognition of patients who may require ICU care, and potential selection for COVID-19 experimental therapies. Nonetheless, a systematic approach may also have disadvantages given the lack of a clear actionable therapy for the identified patients, increased exposure of healthcare professionals, and risk derived from unnecessary invasive procedures.

When incorporating cTn, it is important to apply the Fourth Universal Definition of Myocardial Infarction and use of serial measurements to facilitate the understanding of results. Sandoval et al have proposed an algorithm for assessing cardiac biomarker results. The authors suggested that baseline cTn measurements can facilitate stage classification of the disease (early infection, pulmonary or inflammatory) and determine the patient’s risk profile (low, intermediate, or high risk). Serial measurements of cTn can help determine short- and long-term likelihood for survival or adverse outcomes. Of note, patients with plateau determinations of cTn >99th percentile (Δ change, <20%) have a lower risk than those who have a significant increase of cTn measurements (Δ change, >20%) who are at high risk. There is not a specific consensus on the periodicity of cTn determinations. Still, some authors proposed that, in patients with determinations of cTn >99th percentile, serial measurements every 24 to 48 hours may be reasonable. Moreover, the addition of natriuretic peptides could complement the cTn data and clarify the clinical scenario.

Irrespective of the pathophysiological mechanism, in any patient with a cTn increase >99th percentile,
elevations should be classified as chronic myocardial injury, acute nonischemic myocardial injury, or acute MI (Figure 4). Patients with chronic conditions and comorbidities, and long-term “stable” (<20% change) cTn increases, can be categorized as having chronic myocardial injury. These elevations represent myocardial injury and are associated with an adverse prognosis, even without concomitant disease. However, patients who are categorized as having acute nonischemic myocardial injury (>20% change) exhibit a short-term event without overt symptoms or signs of myocardial ischemia. Within this category, cardiac and noncardiac causes can be identified. From a cardiovascular perspective, the most worrisome condition is acute MI. Of note, patients in this category should have a short-term event (>20% change) and present overt myocardial ischemia, as defined in the Fourth Universal Definition of Myocardial Infarction. It is essential to differentiate between type 1 MI and type 2 MI, as the management differs. The use of cardiac imaging could be useful to differentiate between type 1 MI and type 2 MI.

Patients with type 2 MI are a heterogeneous group of patients in whom the treatment of the underlying disease needs to be prioritized. Meanwhile, recognizing patients with type 1 MI is critical to define management (ie, invasive versus noninvasive) as well antithrombotic treatment regimens. In patients with ST-segment–elevation MI, primary percutaneous coronary intervention should be performed. If the clinical condition of the patient does not allow or if time frames are not feasible for primary percutaneous coronary intervention, then fibrinolysis can be considered. Patients with non–ST-segment–elevation MI with high-risk criteria should be referred for invasive management and percutaneous coronary intervention, if appropriate. In patients with low-risk non–ST-segment–elevation MI, a SARS-CoV-2 test is recommended, and the decision on management (invasive versus noninvasive) should be performed in line with practice guidelines. Medical management should be reserved for low-risk patients (eg, cardiac enzyme–negative patients).

In patients with MI, dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is pivotal for the reduction of thrombotic complications, particularly among those undergoing coronary stenting. Three oral P2Y12 inhibitors are clinically available: clopidogrel, prasugrel, and ticagrelor. Prasugrel and ticagrelor are preferred over clopidogrel in patients with acute coronary syndrome in light of their enhanced efficacy. The prothrombotic status that characterizes patients with COVID-19 further underscores the need to use more potent P2Y12 inhibitors. However, the potential drug-drug interactions between many antiviral agents with some of the oral P2Y12 inhibitors (ie, clopidogrel and ticagrelor), as described in more detail below, need to be taken into consideration when choosing a specific oral P2Y12 inhibitor. In addition, the antithrombotic regimen to be used during percutaneous coronary revascularization should take into consideration because a considerable number of patients with COVID-19 present with heparin resistance. Hence, it is pivotal to check that patients have achieved target activated clotting time. Although unfractionated heparin is the most common anticoagulant used during coronary interventions, it is well established that enoxaparin and bivalirudin have more favorable pharmacokinetic and pharmacodynamic profiles, and thus represent reasonable treatment alternatives. Ultimately, the use of intravenous antiplatelet therapies (ie, cangrelor and glycoprotein IIb/IIIa inhibitors), which are known to achieve potent platelet inhibitory effects, are also reasonable treatment options to strongly consider in patients with acute coronary syndrome undergoing percutaneous coronary revascularization.

Other Arterial Complications

There are also several reports of less frequent arterial thrombosis complications, such as acute ischemic stroke, acute limb ischemia, aortic thrombosis, or splenic infarcts. Furthermore, atypical presentations of thrombotic events, such as acute multivessel coronary occlusion, have been reported. Of note, a small case series of patients has reported stent thrombosis in COVID-19. Clinicians should be aware and suspicous of these infrequent events and unusual clinical presentations.

Coagulopathy

Severe Coagulopathy Without Bleeding

The recommendations for managing coagulopathy in patients with COVID-19 without bleeding are the same as in patients with VTE. The administration of blood products is recommended as in patients without COVID-19, to keep platelet count >25×10⁹/L.

Severe Coagulopathy With Bleeding

Bleeding is less common than thrombosis in patients with COVID-19, but it may occur, with the use of anticoagulation. Moreover, in critically ill patients who develop DIC, clinically relevant thrombocytopenia and reduced fibrinogen levels are rare but associated with significant bleeding manifestations and increased morbidity. As in routine clinical practice, the management of DIC is focused on treating the underlying condition. There are limited data on the
specific coagulopathy treatment in patients with COVID-19, and most of the recommendations are the same as in patients without COVID-19.98 The need for administration of blood products depends on the worsening of the coagulopathy and presence of bleeding (Table 3).45 If bleeding is present, initially, fresh frozen plasma and platelet transfusion may be considered. If bleeding is not controlled and fibrinogen levels are low, cryoprecipitate or fibrinogen concentrate may also be considered.

**Extracorporeal Membrane Oxygenation and Clotting of Intravascular Access Devices**

**Extracorporeal Membrane Oxygenation**

Critically ill patients with severe COVID-19 pneumonia and refractory ARDS may need respiratory support with extracorporeal membrane oxygenation. Patients on extracorporeal membrane oxygenation require full-dose anticoagulation to avoid circuit thrombosis.99 Moreover, observational studies have found a higher rate of extracorporeal membrane oxygenation circuit thrombosis in patients with COVID-19.130 The Extracorporeal Life Support Organization recommends that centers should follow existing anticoagulation guidelines and institutional protocols with appropriate monitoring and dose adjustments.99 Most protocols use continuous intravenous UFH infusion and target an activated partial thromboplastin time of at least 1.5 times the control value, although higher targets (2.0–2.5 times) are often used.99

**Clotting of Intravascular Access Devices**

Patients with COVID-19 who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy, per standard of care.92 Furthermore, in cases of recurrent clotting of access devices, the intensity of anticoagulation intensity can be increased, or the type of anticoagulant administered could be switched.
## Table 4. Evidence Gaps and Ongoing Clinical Trials

| Variable                  | Evidence Gap                                                                 | Ongoing Research*                                                                 | Comments                                                                                                    |
|---------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| VTE                       |                                                                              |                                                                                  |                                                                                                             |
| Risk assessment and prevalence | • Prevalence of VTE in the outpatient setting.                               |                                                                                  |                                                                                                             |
|                           | • Specific COVID-19 predictors of VTE.                                       |                                                                                  |                                                                                                             |
|                           | • Specific COVID-19 risk assessment tool and diagnostic algorithm.           |                                                                                  |                                                                                                             |
| Prophylaxis               | Optimal agents besides LMWHs.                                               | NCT04351724                                                                      | A multiple drug trial, with substudy testing the role of rivaroxaban for sustained clinical improvement. |
|                           | Optimal time duration.                                                       |                                                                                  |                                                                                                             |
|                           | Need for prophylaxis in ambulatory patients.                                | NCT04400799† NCT04498273††                                                         | Trial testing the role of thromboprophylaxis with enoxaparin in outpatients.†† Trial testing the role of low or full dose of apixaban for thromboprophylaxis. |
| Treatment                 | Optional drugs besides LMWHs.                                               |                                                                                  |                                                                                                             |
|                           | Need to treat incident VTE.                                                  |                                                                                  |                                                                                                             |
| Dose‡                     | Optimal dose.                                                               |                                                                                  | Most of the trials are focusing on determining the role of different regimens of anticoagulant therapies (LMWH or UFH) for the prevention of arteriovenous thrombotic events or COVID-19 severity. |
|                           | Net clinical benefit in terms of arteriovenous thrombotic event reduction without a significant increase in bleeding events. |                                                                                  |                                                                                                             |
|                           | Prophylaxis vs intermediate dose: NCT04366960† NCT04360824 NCT04367831     |                                                                                  |                                                                                                             |
|                           | Prophylaxis vs therapeutic dose: NCT04372589† NCT04359277†                  |                                                                                  |                                                                                                             |
|                           | Intermediate vs therapeutic dose:NCT04401293‡                              |                                                                                  |                                                                                                             |
| Extended prophylaxis      | Optimal method for risk stratification.                                      |                                                                                  |                                                                                                             |
| Arterial thrombosis       | Prevalence and predictors of arterial thrombosis events (stroke, coronary, and limbs), according to the disease severity. |                                                                                  |                                                                                                             |
| Treatment                 | Prevention of arteriovenous thrombotic events.                              | NCT04409834                                                                      | Trial testing the role of anticoagulation (enoxaparin or UFH) with or without clopidogrel for preventing arteriovenous thrombotic events. |
| Cardiac complications     |                                                                              |                                                                                  |                                                                                                             |
| Risk assessment and prevalence | Prevalence and predictors of cardiac complications, according to the disease severity. |                                                                                  |                                                                                                             |
| Treatment                 | Optimal treatment to prevent cardiac complications, such as cardiovascular death, myocardial infarction (including myocardial injury), heart failure, or severe cardiac arrhythmias. | NCT04343001‡ NCT04324463‡ NCT04333407‡ NCT04416048 | Trials that combine cardiovascular medications, such as aspirin, ACE-Is, statins, clopidogrel, or DOACs, to prevent adverse cardiac events. ‡Trials statistically powered to assess meaningful clinical outcomes (death or MACE). |

(Continued)
Table 4. Continued

| Variable                  | Evidence Gap                                                                 | Ongoing Research* | Comments                                                                                           |
|---------------------------|------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------------|
| **Long-term prognosis**   | • Long-term outcomes of patients who have severe cardiac complications are unknown. |                   |                                                                                                   |
| **Coagulopathy**          |                                                                               |                   |                                                                                                   |
| Low-risk patients (outpatient) | • Optimal treatment to prevent the development of COVID-19–associated coagulopathy. | NCT04363840**†   | Trial design for low-risk patients, assessing aspirin and vitamin D’s role in preventing the development of COVID-19–associated coagulopathy and reducing the need for hospitalization. |
| Moderate to severe patients (inpatient) | • Optimal treatment to decrease the fibrin formation and deposition, and improve the prothrombotic state. | NCT04435015†† NCT04424901†† NCT04391179§§ NCT04419610 | Trials designed for preventing fibrinogen generation by blocking several therapeutic targets related in the thromboinflammatory process. ††Trial testing the role of camostat mesylate (TMPRSS2 blocker). †‡Trials assessing the role of dipyridamole. §§Trial exploring the efficacy of TPV027 (selective angiotensin II receptor type 1 agonist) |
| **DIC**                   | • Prevalence and predictors of DIC.                                           |                   |                                                                                                   |
| **Bleeding**              | • Prevalence and predictors of severe bleeding events.                        |                   |                                                                                                   |
| **ALI and ARDS**          |                                                                               | Several trials are testing different drugs for thrombolysis, anticoagulation, or platelet inhibition, and preventing pulmonary thrombosis. |                                                                                                   |
| **Treatment**             | • Role of tPA on pulmonary gas exchange.                                      | NCT04357730 NCT04453371 | Trial testing different intravenous alteplase regimens.                                          |
|                           | • Role of antithrombotic therapies on pulmonary gas exchange.                | NCT04445623       | Trial studying the role of oral prasugrel.                                                       |
|                           | • Role of anticoagulant therapies on pulmonary gas exchange.                 | NCT04398984**†† NCT04445935 | ††Trial exploring the efficacy of intravenous bivalirudin.                                       |
|                           | • Role of nebulized/ aerosolized therapies on pulmonary gas exchange.       | NCT04396067**†† NCT04355364**†† NCT04397510 NCT04356954**†† NCT04356833 | Nebulized therapies are compelling because of their local effect. ††Trials that are testing dornase alfa for NET clearance. |
| **Long-term prognosis**   | • Long-term outcomes of patients who have severe pulmonary complications are unknown. |                   |                                                                                                   |
| **ECMO**                  | • Optimal anticoagulation targets.                                          | NCT04341285       | Trial assessing the role of early or delayed ECMO (including coagulation parameters) in critically ill patients. |
| **Potential therapies**   | • Determine the efficacy and safety of drugs previously tested for VTE treatment or in sepsis-induced coagulopathy. | None have RCT in patients with COVID-19. | Sulodexide showed a reduction in recurrent VTE events. §§ | Sulodexide, Antithrombin, Thrombomodulin, APC. | Antithrombin, thrombomodulin, and APC have been studied in the context of sepsis-induced coagulopathy. However, none of them was associated with a reduction in mortality. 132–134 |

ACE-I indicates angiotensin-converting enzyme inhibitor; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; APC, activated protein C; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; LMWH, low-molecular-weight heparin; MACE, major adverse cardiovascular event; NET, neutrophil extracellular trap; RCT, randomized controlled trial; TMPRSS2, transmembrane protease serine 2; tPA, tissue-type plasminogen activator; UFH, unfractionated heparin; and VTE, venous thromboembolism.

*Only RCTs registered in clinicaltrials.gov were included.
†Trials that aim to enroll at least 1000 patients. The trials are listed in descending order of target sample size.
‡Several trials included in VTE dose section also assess arterial thrombosis end points.
§Patients with prophylactic anticoagulant regimens can also be included. 5, 8, 13, 11, 52, 55, 44 indicates NCT number and corresponding comment.
severe COVID-19 attributable to taking antithrombotic agents. Patients receiving antithrombotic therapies for underlying conditions should continue these medications without any change. Patients with suspected or confirmed COVID-19, who are asymptomatic or who have mild symptoms and who do not require any COVID-19 investigational therapies, should continue the same standard of care antithrombotic or anticoagulant treatment regimen without any changes.

Patients With Moderate-Severe Presentation Who Require COVID-19 Investigational Therapies

In patients with suspected or confirmed COVID-19 who require any COVID-19 investigational therapy and concomitant antithrombotic therapy, it is essential to assess potential drug interaction (Figure 5).

Antiplatelet Therapy

Patients who take low-dose aspirin should continue therapy. Confirmation or suspicion of COVID-19 is not considered an indication to stop aspirin. In patients requiring a P2Y12 inhibitor, the drug of choice depends on the COVID-19 specific treatment. Some of the antiviral agents have drug-drug interactions with oral P2Y12 inhibitors by sharing the same metabolic pathway (eg, Cytochrome P450 3A4) (Figure 5). These include lopinavir/ritonavir and darunavir/cobicistat with clopidogrel (reduces its efficacy) and ticagrelor (increases its efficacy). Hence, these drug combinations are contraindicated. For these reasons, at least during antiviral treatment, prasugrel is the drug of choice. Indeed, its contraindications (previous stroke) and precautions (aged >75 years, weight <60 kg, or history of bleeding) also need to be carefully considered. Cilostazol also has an interaction with antiviral therapy, especially with lopinavir/ritonavir. However, dipyridamole has no reported important interactions. For parenteral antiplatelet agents, such as cargrelor or glycoprotein IIb to IIa inhibitor, there are no reported important drug-drug interactions with COVID-19 investigational treatments.

Anticoagulant Therapy

Anticoagulant therapies exhibit several drug-drug interactions that warrant attention (Figure 5), and most include vitamin K antagonists and DOACs with antiviral agents (lopinavir/ritonavir) and monoclonal antibodies (tocilizumab and sarilumab). In case of clinical instability or significant drug-drug interaction, baseline anticoagulant therapy could be changed to LMWH at a dosing regimen that can minimize thromboembolic and hemorrhagic events. This switch must also be made when the antiviral therapy ends, and oral anticoagulation can be restarted. Parenteral anticoagulants, such as UFH, bivalirudin, LMWH, or fondaparinux, do not have important drug-drug interactions with COVID-19–specific treatment.

Fibrinolytics

tPA (tissue-type plasminogen activator) is appropriate for usual indications, unless there is a contraindication, as there are no important drug-drug interactions with COVID-19 investigational therapy (Figure 5). Moreover, there are no reported interactions between streptokinase and COVID-19 investigational treatments.

COVID 19: ONGOING RESEARCH AND FUTURE DIRECTIONS

There are several gaps in our knowledge on the optimal antithrombotic management of patients with COVID-19, for which there are several ongoing clinical studies. These are described in the section below and summarized in Table 4.

Venous Thromboembolism

VTE, including DVT and PE, is among the most prevalent complications in patients with COVID-19. Therefore, most antithrombotic research is related to this topic, with ongoing randomized clinical trials focusing on determining the efficacy and safety of different regimens of anticoagulant therapies for the prevention of venous thrombotic events (Table 4). In particular, the comparison of thromboprophylaxis regimens versus full therapeutic doses of anticoagulant therapies in hospitalized patients is being tested in >10 trials. Thromboprophylaxis in the outpatient setting with a variety of agents, including DOACs, is also being tested.

Coagulopathy

Several trials are assessing different drugs to decrease fibrin formation and the prothrombotic state. These drugs include aspirin, vitamin D, dipyridamole, camostat mesylate (transmembrane protease serine 2 blocker), and TRV027 (selective angiotensin II receptor type 1 agonist) (Table 4). These drugs or their combination may potentially block pathways of fibrin formation at different levels, therefore preventing the perpetuation of the thromboinflammatory state in COVID-19. One specific topic that deserves careful attention is DIC. Currently, the prevalence, predictors, and specific treatment of
DIC in patients with COVID-19 are unknown. Although bleeding in patients with COVID-19 is less frequent than thrombosis, there are limited data on its prevalence, clinical impact, and specific management.

Cardiovascular Complications
The pathophysiological mechanisms by which COVID-19 affects the cardiovascular system are not fully understood, and data on the prevalence and predictors of various cardiovascular complications (e.g., MI, stroke, or acute limb ischemia) are still limited. Moreover, the long-term effects of COVID-19 on the cardiovascular system are unknown. There are several randomized clinical trials assessing the efficacy of different combinations of cardiovascular drugs (Table 4). These include studies of aspirin, clopidogrel, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, or DOACs, for preventing cardiovascular death, MI (including myocardial injury), heart failure, or severe cardiac arrhythmias. Many of these studies are powered for differences in ischemic outcomes.

Lung Injury and ARDS
Pulmonary intravascular coagulopathy in COVID-19 pneumonia is associated with acute lung injury and ARDS. The long-term outcomes of patients who present with severe pulmonary manifestation are unknown. Several trials are currently testing different antithrombotic drugs for thrombolysis, anticoagulation, or platelet inhibition to treat such pulmonary thrombosis phenomena. Interestingly, some of these trials are using conventional intravenous administration of fibrinolytic or anticoagulant drugs. In contrast, others use nebulized or aerosolized formulations, which can deliver local therapy and reduce the adverse effects (Table 4). Moreover, some studies target NETs by promoting their clearance using nebulized dornase alfa (recombinant human deoxyribonuclease I). Other authors have tested the role of nebulized plasminogen in a small case series of patients with severe/critical COVID-19 pneumonia. The use of plasmin was associated with restored lung fibrinolytic activity and improvement in gas exchange. However, most of these trials are still at proof-of-concept stages and evaluating surrogate end points.

Potential Therapies
There are several drugs already studied in the setting of sepsis-induced coagulopathy and critically ill patients that may have a potential role in the treatment of the thrombotic state of COVID-19.

1. Danaparoid: anticoagulant that attenuates thrombin generation by indirect inactivation of factor Xa and direct inhibition of thrombin activation of factor IX. In basic animal models, danaparoid inhibits systemic inflammation and prevents endotoxin-induced acute lung injury in rats. In animal models, nebulized antithrombin was associated with decreased coagulopathy and improved thrombotic state of COVID-19. In randomized clinical trials, it did not reduce the short-term mortality and increased bleeding.

2. Sulodexide: anticoagulant made of LMWH and dermatan sulfate, which potentiates the antiprotease activities of antithrombin III and heparin cofactor II simultaneously. In a recent meta-analysis, sulodexide has shown a reduction in bleeding while protecting from recurrent DVT risk when compared with placebo, vitamin K antagonists, or DOACs.

3. Antithrombin: a small glycoprotein that inactivates several enzymes of the coagulation system. Antithrombin was slightly decreased in patients with COVID-19. In animal models, nebulized antithrombin was associated with decreased coagulopathy and inflammation. However, there was no benefit in terms of mortality, with an increase in bleeding events in a randomized clinical trial.

4. Thrombomodulin: an integral membrane protein expressed on endothelial cells’ surface, which serves as a cofactor for thrombin. Thrombomodulin has potent anticoagulant effects through the APC (activated protein C)-dependent and APC-independent protein C mechanisms. In a meta-analysis, in patients with sepsis-induced coagulopathy, thrombomodulin was associated with reduced mortality.

5. APC: recombinant human protein, which performed its anticoagulant function by inactivating protein factor Va and factor VIIIa. A systematic review of the randomized clinical trials showed that it did not reduce the short-term mortality and increased bleeding.

6. Contact activation system: the contact activation system links inflammation and coagulation by triggering thrombin and bradykinin production. In animal models, contact activation system inhibition was associated with reduced inflammatory cytokines and attenuated microvascular thrombosis.

7. Sulfated polysaccharides: nonanticoagulant LMWHs are glycosaminoglycans with noncoagulant properties. Specifically, the synthesized trisulfated heparins have shown a high-affinity interaction with the SARS-CoV-2 protein S. Therefore, in basic models, they can act as decoys to interfere with S-protein binding to the heparan sulfate coreceptor in host tissues, inhibiting viral infection. Furthermore, synthesized trisulfated heparins could be used in combination with current antiviral therapies to improve inhibition of SARS-CoV-2 replication.
COVID-19. The interaction of SARS-CoV-2 with the ACE2 receptor and subsequent endothelial activation and inflammation can trigger an intense thromboinflammatory state. Furthermore, the interaction between activated platelets and neutrophils may promote the formation of NETs and lead to immunothrombosis dysregulation. These pathological phenomena have a deleterious effect on hemostasis, leading to different clinical manifestations affecting the cardiovascular system. A better understanding of these pathophysiological mechanisms is essential for the development of safe and efficient treatment strategies. Most management recommendations are currently based on expert opinion because the scientific evidence supporting the used therapies is rather limited. There has been extraordinary development of several research lines evaluating antithrombotic therapies at a worldwide level. However, to date, most available data derive from observational studies, and results of randomized clinical trials are still eagerly expected. In particular, studies addressing not only the prevention and treatment of thrombotic complications, but also management of coagulopathy with or without DIC, bleeding events, and acute lung injury and ARDS, all represent areas of unmet clinical need.

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