# COVID-19 Associated Thrombosis and Coagulopathy: Review of the Pathophysiology and Implications for Antithrombotic Management

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# COVID-19 Associated Thrombosis and Coagulopathy: Review of the Pathophysiology 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 (ACE2), highly expressed in the respiratory system, has been identified as a functional receptor for SARS-CoV-2. Notably, ACE2 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. Importantly, patients with COVID-19 may have thrombotic and coagulation abnormalities promoting a hypercoagulable state, resulting in an increased rate of thrombotic and thromboembolic events. This review will describe the pathophysiology of the cardiovascular involvement following infection by SARS-CoV-2, with a focus on thrombotic and thromboembolic manifestations and implications for antithrombotic management.

**Key words:** COVID-19; SARS-CoV-2; endothelium; platelets; thrombosis; myocardial infarction; anticoagulant therapy; antiplatelet therapy

**NON-STANDARD ABBREVIATIONS AND ACRONYMS**

ACT: Activated clotting time
APC: Activated protein C
ACS: Acute coronary syndrome
ALI: Acute lung injury
ARDS: Acute Respiratory Distress Syndrome
Ang: Angiotensin
ARBs: Angiotensin II receptor blockers
AT1: Angiotensin II receptor type 1
ACE2: Angiotensin-converting enzyme 2
ACE-I: Angiotensin-converting-enzyme inhibitors
CMR: Cardiac magnetic resonance
cTn: Cardiac troponin
cfDNA: Circulating cell-free DNA
CT: Computed tomography
CAS: Contact Activation System
COVID-19: Coronavirus disease 2019
CAHA: COVID-19-associated hemostatic abnormalities
DAMPs: Damage-associated molecular patterns
DVT: Deep vein thrombosis
DOAC: Direct oral anticoagulant
DIC: Disseminated intravascular coagulation
ELSO: Extracorporeal Life Support Organization
ECMO: Extracorporeal Membrane Oxygenation
GPI: Glycoprotein IIb-IIIa inhibitor
ICU: Intensive care unit
ISTH: International Society on Thrombosis and Haemostasis
LV: Left ventricle
LMWHs: Low-molecular weight heparin
MAS: Macrophage activation syndrome
MasR: Mas receptors

MOF: Multiple Organ Failure

MI: Myocardial infarction (MI)

NETs: Neutrophil extracellular traps

NLRP3: NLR family pyrin domain containing 3

NSTEMI: Non-ST-Segment Elevation Myocardial Infarction

ORF3a: Open reading frame 3a

ORF8b: Open Reading Frame-8b

PAMPS: Pathogen-associated molecular patterns

PCI: Percutaneous coronary intervention

PAI-1: Plasminogen activator inhibitor I

PT: Prothrombin time

PE: Pulmonary embolism

RCD: Regulated cell death

RAS: Renin-angiotensin system

RV: Right ventricle

sHLH: Secondary hemophagocytic lymphohistiocytosis

SOFA: Sequential organ failure assessment

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

STEMI: ST-Segment Elevation Myocardial Infarction

TriS: Synthesized trisulfated heparin

TEG: Thromboelastography

tPA: Tissue plasminogen activator

TRAF3: TNF Receptor Associated Factor 3

TLRs: Toll-like receptors

TMPRSS2: Transmembrane protease serine 2

UFH: Unfractionated heparin

UDMI: Universal Definition of Myocardial Infarction

VTE: Venous thromboembolism

VKA: Vitamin-K antagonists

WHO: World Health Organization

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.[1] 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, more than 48.7 million cases of COVID-19 have been reported in 190 countries or regions, resulting in over 1.23 million deaths.[2] 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.[3] Approximately 30-40% of infected individuals remain asymptomatic.[4] 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 has been associated with Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Failure (MOF). 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 pre-existing 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, resulting in an increased rate of thrombotic and thromboembolic events.[8] In patients who require hospitalization, the rate of any thrombotic event is approximately 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 pathophysiology 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 (WHO) named this virus SARS-CoV-2.

SARS-CoV-2 binds to the transmembrane ACE2 protein to enter type II pneumocytes, macrophages, and other cell types.[10] This process requires priming of the viral S protein by the transmembrane protease serine 2 (TMPRSS2) (**Figure 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 myocardiocytes.[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.[14] Pericytes are known for their important roles in vascular homeostasis and regulation of the inflammatory process.[14] Therefore, abnormalities or degeneration within pericytes may cause tissue injury that can lead to organ damage.[14] 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 (Ang) II into Ang (1-7). Ang II, an agonist of the Angiotensin II receptor type 1 (AT1) receptor, produces potent vasoconstrictor, pro-fibrotic, and pro-inflammatory effects. Conversely, Ang (1-7), which is an agonist of the Mas receptors (MasR), is a potent vasodilator, anti-apoptotic, and anti-proliferative agent (**Figure 1 and 2**). For these reasons, ACE2 is a negative regulator of classical ACE in the renin-angiotensin system (RAS).[15] In many patients with cardiovascular disease manifestations, there is an increase in the ACE/ACE2 ratio within organs. This ACE/ACE2 imbalance is often due to downregulation of ACE2, resulting in altered RAS homeostasis. This imbalance has been observed in animal models with high-salt and glucose diets, renal disease, and oxidative stress.[16] In humans, an ACE/ACE2 imbalance is associated with smoking, pulmonary arterial hypertension, and Alzheimer's disease.[17] Furthermore, the ACE/ACE2 ratio increase has been correlated with systolic blood pressure, serum creatinine level, fasting blood glucose level, and proteinuria.[18] It has been suggested that SARS-CoV-2 infection of the host cell can affect the ACE/ACE2 ratio leading to downregulation of ACE2.[19] This hypothesis is supported by the fact that ACE2

expression in the lung determines the primary SARS-CoV-2 entry method.[20] An important clinical observation is that patients with hypertension or preexisting cardiovascular disease, who have an increase ACE/ACE2 ratio, may be more susceptible to SARS-CoV-2 infection and impaired prognosis.[7] These observations have raised interest on the prognostic implications associated with the use of angiotensin-converting-enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) in patients with COVID-19 for which there are a number of ongoing investigations the description of which go beyond the scope of this manuscript.[21]

*Host cell death*

Most viral infections eventually lead to the death of host cells. Different types of regulated cell death (RCD) have distinct molecular mechanisms and signaling pathways.[22] Previously, with SARS-CoV, it was observed that SARS-Coronavirus membrane protein induces apoptosis through modulating the Akt survival pathway.[23] The most common mechanism of apoptosis is by activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome by SARS-CoV and the subsequent cell pyroptosis. Pyroptosis is a highly inflammatory form of RCD that occurs most frequently upon infection with intracellular pathogens.[24] In particular, the SARS-CoV E protein induces calcium leakage to the cytosol from Golgi storage, while open reading frame 3a (ORF3a) induces potassium efflux from the cytosol to the extracellular spaces.[25] This imbalance in the ionic concentration within the cells triggers NLRP3 inflammasome activation. Moreover, ORF3a promotes inflammasome assembly through TNF Receptor Associated Factor 3 (TRAF3)-mediated ubiquitination of an apoptosis-associated speck-like protein containing a caspase recruitment domain. The SARS-Coronavirus Open Reading Frame-8b (ORF8b) interacts directly with a leucine-rich repeat of NLRP3 to stimulate its activation. Inflammasome activation induces the formation of gasdermin-D pores on the cell membrane, causing IL-1b and IL-18 secretion and the influx of water leading to cell swelling and subsequent rupture.[25, 26] Ren et al., showed that SARS-CoV-2 ORF3a induces apoptosis.[25] Apoptosis, mainly pyroptosis, has been described in endothelial cells but can occur in any cell type. The RCD is the inception of a local an intense inflammatory response that may become systemic due to the release of potent pro-inflammatory cytokines such as IL-1b and IL-18 (**Figure 1 and 2**).[12]

*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 histology and electron microscopy.[13] 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.[27] 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.[27]

*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 to a cytokine storm or macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH).[28] 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.[29] However, some pivotal clinical characteristics differentiate sHLH or MAS from COVID-19. In sHLH or MAS, serum ferritin levels are extremely high, while these are only moderately elevated in COVID-19. Moreover, sHLH or MAS are associated with impaired liver function and thus coagulopathy. In contrast, these findings are not typically seen in patients with COVID-19.[30]

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.[31] 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.[32] 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-leucocytes interaction, and recruitment and tissue infiltration necessary for pathogen clearance (**Figure 1 and 2**).[33]

The majority of patients with mild to moderate COVID-19 symptoms may have normal or increased platelet count.[34] However, in critically ill patients, platelet count may be decreased, and DIC may be found in almost 70% of non-survivors.[29] The pathophysiological mechanisms of thrombocytopenia in COVID-19 patients are not entirely understood but may be related to a reduction in primary platelet production, increase in platelet destruction or a decrease in circulating platelets.[35] Platelet production can be impaired due to 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.[35]

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.[36] Megakaryocyte numbers were increased as compared with control patients who died of ARDS unrelated to COVID-19.[36] This phenomenon appears to be a unique feature of COVID-19 and may play an important role in their increased thrombotic risk.[37]

*Neutrophil extracellular traps*

Leucocyte activation, specifically neutrophils, through various vascular and platelet pathways, may promote neutrophil extracellular traps (NETs) formation. NETs are large, extracellular, web-like structures composed of cytosolic and granule proteins assembled on a scaffold of decondensed chromatin.[38] NETs may have an essential role in the phenotypic expression and end-organ injury among patients with COVID-19.[37] This hypothesis was proposed by Barnes et al., based on 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.[39] NETs are an ideal foundation for

binding activated platelets, erythrocytes and leukocytes, activating factor XI, and generating thrombin for fibrin production.

In patients with COVID-19, Zuo et al., reported higher circulating cell-free DNA (cfDNA) and DNA-myeloperoxidase complexes compared to controls. Furthermore, levels correlated with disease severity, inflammatory response, and need for mechanical ventilation.[40] At the tissue level, NETs cause platelet activation through toll-like receptors (TLRs) on platelets and other cells, activating the receptor integrin αIIbβ3, which promotes platelet aggregation, granule release, phosphatidylserine exposure, FV/Va expression, and thrombin generation. For these reasons, NETs are recognized as linking inflammation, coagulation, and thrombosis, both locally (microvascular) and systemically (macrovascular).[41] 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.[42] Therefore, the authors suggest that an immunothrombotic dysregulation may explain the MOF and systemic hypercoagulability in patients with severe SARS-CoV-2 infection (**Figure 1 and 2**).[42]

**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).[43-45] The most consistent observation among patients with COVID-19, particularly those with severe illness, is D-dimer elevation.[46] 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.[34] Employing whole blood thromboelastography (TEG), 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 TEG analysis, other authors found low lysis at 30 minutes, which is suggestive of fibrinolysis shutdown (**Figure 1 and 2**).[47] Additional laboratory findings that are impaired in patients with COVID-19 are shown in **Table 1**.[48]

The International Society on Thrombosis and Haemostasis (ISTH) 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.[44] The authors suggest that parameters such as D-dimer raised 3-4 times fold, prolonged prothrombin time (PT), platelet count $<100x10^9$/L, and fibrinogen <2.0 g/L, should be considered for hospital admission even in the absence of other conditions.[44]

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 employing the available diagnostic biomarkers.[45] A complete description of three 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 (CT). Stage 2 includes patients who may develop severe symptoms and may require ICU support. These patients may have lung ventilation/perfusion impairment due to thrombi or emboli noted in the CT 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 (ECMO). These patients may exhibit venous thromboembolism (VTE) and extrapulmonary thrombosis involving several organs such as intestine, limbs, 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 exhibited 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 manifestation may advance to a consumptive coagulopathy with a prolongation of PT (>50%), a decrease of platelet count and fibrinogen. Moreover, these patients may need blood product transfusion and an increase in bleeding events.

In normal lung physiology, the pulmonary alveolar space has been considered as a profibrinolytic environment.[49] However, in patients with ARDS, the fibrinolytic system is often suppressed due to increased plasminogen activator inhibitor I (PAI-1) in both plasma and the bronchoalveolar lavage fluid.[49] Moreover, plasmin also cleaves numerous matrix proteins but, importantly, also misfolded/necrotic proteins, which can be of significant importance in COVID-19 patients.[50] At all CAHA stages, elevated D-dimer levels are a common feature, and this

suggests that the endogenous fibrinolytic system is functional. However, in advance stages (CAHA stage 3) the fibrinolytic system may fail to cope with the extent of fibrin and necrotic material needing to be removed.[50] 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 due to a decrease in plasmin-plasminogen activity.[50] However, there is 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 >99$^{th}$ percentile upper-reference limit, which is the definition according to the Fourth Universal Definition of Myocardial Infarction.[51, 52] Clinical registries have shown that patients with cardiovascular risk factors or cardiovascular disease have higher rates of myocardial affection and worse outcomes.[7] In a meta-analysis of 26 observational studies, including 11685 patients, the prevalence of acute myocardial injury was 20%.[53] However, the prevalence of myocardial injury can vary significantly depending on the definitions and protocols of each center.

In an autopsy case series form COVID-19 patients, Fox et al., found notable cardiomegaly and right ventricular dilation.[54] 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 a subacute pulmonary hypertension development with elevations in cTn and other markers reflecting diffuse myocardial mechanical stressing and ischemia, especially in the right ventricle.[55] In patients with COVID-19 who underwent echocardiographic assessment, the left ventricle (LV) diastolic and right ventricle (RV) function were impaired, and elevated cTn and poorer clinical-grade are associated with worse RV function.[56] Moreover, myocardial involvement, assessed by cardiac magnetic resonance (CMR), was found in almost 80% of patients with recent COVID-19 infection.[57] The most frequent abnormality was myocardial inflammation found in 60% of patients, followed by regional scar and pericardial enhancement.[57]

Furthermore, there was a significant correlation between cardiac biomarkers and the degree of cardiac inflammation.[57]

Although myocardial injury is common in patients with moderate to severe COVID-19, the pathophysiologic 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 more frequent in older patients with atherosclerotic disease (**Figure 1 and 2**).[58, 59]

*Direct viral myocardial injury*

The presence of ACE2 receptors on myocardial and vascular endothelial cells support the potential for direct viral infection of the heart with resultant myocarditis.[60] Previously, with SARS-CoV, there were well-documented cases of viral myocarditis with detected viral RNA in autopsied hearts.[61] Pirzada et al., analyzed the reported cases of suspected myocarditis with SARS-CoV-2 among COVID-19 patients.[60] Of the nine reported cases, two had an endomyocardial biopsy, but in none, the viral genome was found. 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.[62] In COVID-19, either the direct effect of the virus or the indirect immunological response may trigger a vasculitis.[58]

*Microvascular injury*

Thrombosis may occur in the myocardial microcirculation. In a case series of 18 patients with COVID-19 and ST-Segment Elevation Myocardial Infarction (STEMI), 56% of patients had a nonobstructive disease, defined as either nonobstructive disease on coronary angiography or normal wall motion on echocardiogram.[63] An autopsy report from Bergamo, Italy, reported a patient who presented with STEMI and COVID-19, the patient underwent coronary angiography, which showed normal epicardial coronary vessels.[64] 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 electrocardiogram. Therefore, in patients with STEMI 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 MOF. The cytokine storm, which includes interleukin-1 and -6 and tumor necrosis factor, can either affect pre-existing atherosclerotic lesions or promote accelerated atherogenesis. At the site of pre-existing atherosclerotic lesions, there can be a so-called "echo" phenomenon, in which circulating cytokines stimulate macrophages within the plaque to increase local cytokine production, tissue factor expression, and promote lesion thrombogenicity.[65] Moreover, systemic cytokines can stimulate adhesion molecule expression and increase the recruitment of inflammatory cells. These alterations may enhance the vulnerability of pre-existing plaques to rupture or promote accelerated atherogenesis.[59]

On the other hand, the hyperinflammatory response may also be related to a non-obstructive disease such as stress cardiomyopathy (Takotsubo), due to 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 suggest that mechanism can be associated with a catecholamine-induced microvascular dysfunction secondary to the metabolic, inflammatory, and emotional distress related to COVID-19.[66]

*Acute coronary syndrome*

Several infections have been associated with the risk of an acute coronary syndrome (ACS). Epidemiologic studies have shown that hospitalization for pneumonia is associated with a higher risk for acute coronary events.[67] Influenza infection has been shown to have a temporal association with cardiovascular complications and ACS.[68] Furthermore, in a meta-analysis of clinical trials, annual influenza vaccination was associated with a 36% lower rate of major adverse cardiovascular events.[68] Therefore, although it is plausible that the COVID-19 pandemic can increase the rates of atherothrombotic events, a global increase in MI rates (i.e., type 1 MI) has not been yet described. In the acute phase, the entry of viral products into the systemic circulation, also known as pathogen-associated molecular patterns (PAMPS), can cause innate immune receptor activation with subsequent activation of immune cells resident in pre-existing atheroma plaques and promote their rupture.[69] Damage-associated molecular patterns (DAMPs) are host biomolecules that can initiate and perpetuate a noninfectious inflammatory response, potentially leading to plaque rupture.[69]

*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 due to cytokine storm can produce coronary vasospasm. Collectively, these factors can affect the oxygen supply/demand balance and lead to myocardial injury with non-obstructive disease consistent with the diagnosis of type 2 MI according to the Fourth Universal Definition of Myocardial Infarction. Patients with pre-existing coronary artery disease may be at higher risk of type 2 MI.[70] Of note, patients who had a type 2 MI have a similar rate of major adverse cardiovascular events as those with type 1 MI.[70] 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.[71]

*Cardiac arrhythmias and pericardial effusion*

The majority of 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.[72] Risk factors for arrhythmias are myocardial injury or ischemia, hypoxia, shock, electrolyte disturbances, or those receiving medications that prolong the QT interval.[72] In an observational study, the most frequent arrhythmias were there were atrial fibrillation (3.6%), non-sustained ventricular tachycardia (1.4%), cardiac arrest (1.3%), and bradyarrhythmias (1.3%).[73] In a CMR series, pericardial effusion was found in 20% of the patients.[57] It is hypothesized that viruses cause pericardial inflammation via direct cytotoxic effects, systemic inflammation, or immune-mediated mechanisms.[74]

## 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**).[75-89]

It is important to note that data on antithrombotic treatment regimens most derive from retrospective studies, many of 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**).[90-100]

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**Venous thromboembolism**

The prevalence of VTE, including DVT and pulmonary embolism (PE), varies according to the severity of COVID-19 and is very common in critically ill patients. The main risk factors are immobilization, acute inflammatory state, hypoxia, and endothelial cell activation or damage.[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 COVID-19 patients, Wang et al., reported that 40% of hospitalized patients with COVID-19 were at high risk of VTE.[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.[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. [102]Interestingly, PE can be found without associated DVT.[102] Therefore, the absence of an embolic source has promoted the "in situ" pulmonary thrombosis hypothesis.[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.[102]

*Risk assessment*

Previously developed VTE risk assessment tools can be applied in COVID-19 patients (e.g., the Padua, IMPROVE, and Caprini models).[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.[8]

*Screening and diagnosis*

There is currently insufficient data in favor of or against a routine DVT screening in COVID-19 patients, regardless of status of coagulation markers.[92] The benefits of routine screening may be early diagnosis of DVT and PE prevention. Although DVT has been associated with worse prognosis,[104] there are no trials supporting that routine screening may improves clinical outcomes. Routine screening may increase incidental findings, exposure of healthcare

personnel, and costs. An interesting approach can be performed 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 ≥4, and D-dimer >1.0 μg/mL.[104] However, a prospective study of hospitalized patients with COVID-19, the strategy of using D-dimer levels of dimer >1.0 μg/mL did not prove to be useful for risk stratification in asymptomatic patients.[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.[92] On the other hand, in outpatients, the evaluation of abnormal symptoms or findings on examination is similar to inpatients.[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.[8, 93, 100] Current recommendations are based on expert consensus (**Tables 3**). An essential unanswered question is whether if all hospitalized patients will have a net clinical benefit from thromboprophylaxis or if this would be limited to patients based on their VTE risk score and D-dimer levels.

The majority of 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 (e.g., intermittent pneumatic compression) should be considered in immobilized patients.[8] LMWH have several potential advantages for prophylaxis when compared to 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.[106] Second, LMWH have anti-inflammatory and immunomodulatory effects.[86] Third, LMWHs have reliable pharmacokinetic and pharmacodynamic response profiles. Of note, LWMH has higher availability than UFH (90% vs. 30%).[107] Importantly, with intense systemic inflammation, UFH have a higher degree of binding to plasma protein.[108] Moreover, LMWHs have a longer half-life than UFH, which allows twice or once daily administration regimens and reduce healthcare workers' exposure. However, LMWHs have a shorter half-live than oral

therapies, which can be useful in patients who require procedures or need short time bleeding risk assessment.[107]

An important clinical observation is the occurrence of thrombotic events despite thromboprophylaxis.[109, 110] In critically ill patients receiving anticoagulant treatment, 80% of patients had heparin resistance with UFH, and 50% had a sub-optimal anti-Xa effects with LMWH.[111] In non-ICU patients, up to 30% of the patient had suboptimal anti-FXa effects.[112] The use of higher dose of anticoagulation was beneficial in terms of mortality reduction and need for mechanical ventilation.[87] 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.[111] The use of high-dose thromboprophylaxis (four times the conventional dose) in critically ill COVID-19 patients was associated with on-target levels of anti-Xa activity. However, viscoelastic tests still demonstrated a procoagulant pattern.[113] The optimal dosing regimen of anticoagulant therapy in for prophylaxis is subject of ongoing investigation. In the interim, a potential approach could be to apply an anti-FXa–guided LMWH dosing. In non-ICU patients, predictors of a sub-optimal anti-Xa peak with LMWH were D-dimer >3,000 μg/L, current or previous cancer, and need of high flow nasal oxygen therapy or non-invasive ventilation.[109] In ICU patients, sub-optimal anti-Xa levels were associated with hypoalbuminemia, higher sequential organ failure assessment (SOFA) score, and elevated D-dimer.[110] Most recently, a phase II randomized clinical trial comparing prophylaxis vs. therapeutic regimens of enoxaparin found that therapeutic regimen improves gas exchange and decreases the need for mechanical ventilation in severe COVID-19.[88]

Although direct oral anticoagulants (DOACs) are appealing for thromboprophylaxis, but 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.[91] **Table 3** provides details, taking into consideration to several parameters, prophylactic dosing, including adjustments as well as when it should be held. In non-hospitalized patients with COVID-19, anticoagulants should not be initiated for prevention of VTE unless there are other indications.[92]

*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 in function of the patient's clinical condition and clinical care setting. In the in-hospital setting, parental drugs are preferred based on their pharmacological advantages (**Table 3**). Patients taking therapeutic-dose DOACs or vitamin-K antagonists (VKA) should consider switching to LMWH. Use of LMWH may be preferred in an in-patient setting, while 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.[93]

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.[114] Guideline recommendations should be followed for reperfusion strategies in patients with acute PE.[115] 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 post-discharge prophylaxis in patients with COVID-19 post-discharge.[8] A post-discharge follow-up study did not find a higher risk of post-discharge VTE in COVID-19 patients when compared to other acute medical illness.[116] Therefore, a routine use of extended prophylaxis is not recommended. However, patients at high-risk of post-discharge VTE (**Table 3**) and low bleeding risk may consider extended prophylaxis (≥14 days and up to 30 days) with either LMWH or DOACs.[93]

**Arterial thrombotic events**

*Acute coronary syndromes*

COVID-19 patients 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 LV dysfunction.[51, 90] Some however support systematic cTn measurements.[117] Such approach can have advantages such as prompt diagnosis of myocardial injury, identification of

high-risk patients (ARDS or death) who required further evaluation, recognize patients who may require ICU care, and potential selection for COVID-19 experimental therapies.[51] 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.[51]

When incorporating cTn it is important to apply the Fourth Universal Definition of Myocardial Infarction (UDMI) and use of serial measurements to facilitate the understanding of results. Sandoval et al., have proposed an algorithm for assessing cardiac biomarker results.[51] The authors suggested that baseline cTn measurements can facilitate stage classification of the disease (early infection, pulmonary or hyperinflammatory)[118] 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 >99$^{th}$ percentile (delta change <20%) have a lower risk than those who have a significant increase of cTn measurements (delta change >20%) who are at high-risk.[51] There is not a specific consensus on the periodicity of cTn determinations. Still, some authors proposed that in patients with determinations of cTn >99$^{th}$ percentile, serial measurements every 24-48 hours may be reasonable. Moreover, the addition of natriuretic peptides could complement the cTn data and clarify the clinical scenario.[51]

Irrespective of the pathophysiological mechanism, any patient with a cTn increase >99$^{th}$ percentile, elevations should be classified as either: chronic myocardial injury, acute nonischemic myocardial injury, or acute MI (**Figure 4**).[51] Patients with chronic conditions and comorbidities, chronic 'stable' (<20% change) cTn increases, can be categorized as chronic myocardial injury.[52] These elevations indeed represent myocardial injury and are associated with an adverse prognosis even without concomitant disease.[119] Whereas, patients who are categorized as acute nonischemic myocardial injury (>20% change) exhibit an acute event without overt symptoms or signs of myocardial ischemia. Within this category cardiac and non-cardiac causes can be identified. From a cardiovascular perspective, the most worrisome condition is acute MI. Of note, patients in this category should have an acute event (>20% change) and present overt myocardial ischemia as defined in the UDMI.[52] 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.[51, 95]

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 in order to define management (i.e., invasive vs. non-invasive) as well antithrombotic treatment regimens. In patients with STEMI, primary percutaneous coronary intervention (PCI) should be performed.[120] If the clinical condition of the patient does not allow or if timeframes are not feasible for primary PCI, then fibrinolysis can be considered.[95] Patients with non-ST-Segment Elevation Myocardial Infarction (NSTEMI) with a high-risk criteria should be referred for invasive management and PCI if appropriate. In patients with low-risk NSTEMI, a SARS-CoV2 test is recommended and the decision on management (invasive vs. non-invasive) should be performed in line with practice guidelines. Medical management should be reserved for low risk patients (e.g. cardiac enzyme negative patients).

In MI patients, dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor is pivotal for the reduction of thrombotic complications, particularly among those undergoing coronary stenting.[121] Three oral $P2Y_{12}$ inhibitors are clinically available: clopidogrel prasugrel, and ticagrelor. Prasugrel and ticagrelor are preferred over clopidogrel in ACS patients in light of their enhanced efficacy.[121] The pro-thrombotic status which characterizes COVID-19 patients further underscores the need to use more potent $P2Y_{12}$ inhibitors. However, the potential drug-drug interactions between many antiviral agents with some of the oral $P2Y_{12}$ inhibitors (i.e., clopidogrel and ticagrelor) as described in more details below need to be taken into consideration when choosing a specific oral $P2Y_{12}$ inhibitor.[91, 122] In addition, the antithrombotic regimen to be used during percutaneous coronary revascularization should take into consideration that a considerable number of COVID-19 patients present with heparin resistance. Hence, it is pivotal to check that patients have achieved target activated clotting time (ACT). 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 profile, and thus represent reasonable treatment alternatives.[123] [120] Ultimately, the use of intravenous antiplatelet therapies (i.e., cangrelor, glycoprotein IIb/IIIa inhibitors) which are known to achieve potent platelet inhibitory effects are also reasonable treatment options to strongly consider in ACS patients undergoing percutaneous coronary revascularization.[123, 124]

*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.[96, 97, 125, 126] Furthermore, there has been reported atypical presentations of thrombotic events such as acute multivessel coronary occlusion.[127] Of note, a small case series of patients have reported stent thrombosis in COVID-19.[128] Clinicians should be aware and suspicions of these infrequent events and unusual clinical presentations.

**Coagulopathy**

*Severe coagulopathy without bleeding*

The recommendations for managing coagulopathy in COVID-19 patients 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 above $25x10^9$/L.[44]

*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 increase morbidity.[129] As in routine clinical practice, the management of DIC is focused on treating the underlying condition. There is limited data regarding 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**).[44] 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 (ECMO). Patients on ECMO patients require full dose anticoagulation to avoid circuit thrombosis.[99] Moreover, observational studies have found a higher rate of ECMO circuit thrombosis in patients with COVID-19.[130] The

Extracorporeal Life Support Organization (ELSO) 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 to 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.

## PATIENTS ON ANTITHROMBOTIC THERAPY PER STANDARD OF CARE

### Patients at risk or with mild presentation who do not require COVID-19 investigational therapies

There is a consensus among scientific societies that there is no known risk of contracting or developing severe COVD-19 due to taking antithrombotic agents.[8] Patients receiving antiplatelet or anticoagulant therapies for underlying conditions should continue these medications regimen without any change.[92] In patients with suspected or confirmed COVID-19 who are asymptomatic or with mild symptoms and do not require any COVID-19 investigational therapies, should continue the same standard of care antiplatelet or anticoagulant treatment regimen without any changes.[92]

### 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.[91] In patients requiring a $P2Y_{12}$ inhibitor, the drug of choice depends on the COVID-19 specific treatment. Some of the antiviral agents have drug-drug interactions with oral $P2Y_{12}$ inhibitors by sharing the same metabolic pathway (e.g.,

CYP3A4) (**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 (age> 75 years, weight <60 kg, or history of bleeding) also need to be carefully considered.[94] Cilostazol also has an interaction with antiviral therapy, especially with lopinavir/ritonavir. Whereas dipyridamole has no reported important interactions.[91] Regarding parenteral antiplatelet agents such as cangrelor or glycoprotein IIb-IIIa inhibitor (GPI), there are no reported important drug-drug interactions with COVID-19 investigational treatments.[91]

*Anticoagulant therapy*

Anticoagulant therapies exhibit several drug-drug interactions that warrant attention (**Figure 5**), and most include VKA and DOACs with antiviral agents (lopinavir/ritonavir) and monoclonal antibodies (tocilizumab and sarilumab).[91] 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.[8] 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.[94]

*Fibrinolytics*

Tissue plasminogen activator (tPA) 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.[91]

## COVID 19: ONGOING RESEARCH AND FUTURE DIRECTIONS

There are a number of 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**[131-134].

*VTE*

VTE, including DVT and PE, is among the most prevalent complications in COVID-19 patients. 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 vs. full therapeutic doses of anticoagulant therapies in hospitalized patients is being tested in more than 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 (TMPRSS2 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 COVID-19 patients is unknown. Although bleeding in COVID-19 patients is less frequent than thrombosis, there is very limited data regarding 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., myocardial infarction, 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, ACE-I/ARBs, statins, or DOACs, for preventing cardiovascular death, myocardial infarction (including myocardial injury), heart failure, or severe cardiac arrhythmias. Many of these studies are powered for differences in ischemic outcomes.

*Lung injury and Acute Respiratory Distress Syndrome*

Pulmonary intravascular coagulopathy in COVID-19 pneumonia is associated with acute lung injury (ALI) 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 phenomenon. 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 side 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.[89] However, most of these trials are still at proof of concept stages and evaluating surrogate endpoints.

*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.

- Danaparoid: anticoagulant which 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 ALI in rats.[135]
- Sulodexide: anticoagulant made of low molecular weight heparin and dermatan sulfate, which potentiates the antiprotease activities of antithrombin III and heparin cofactor II simultaneously.[136] In a recent meta-analysis, sulodexide has shown a reduction in bleeding while protecting from recurrent DVT risk when compared to placebo, VKA, or DOACs.[131]
- Antithrombin: a small glycoprotein that inactivates several enzymes of the coagulation system. Antithrombin was found to be slightly decreased in patients with COVID-19.[34] 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.[132]
- Thrombomodulin: an integral membrane protein expressed on endothelial cells' surface and serves as a cofactor for thrombin. Thrombomodulin has potent anticoagulant effects through the activated protein C (APC)-dependent and APC independent protein C

mechanisms. In a meta-analysis, in patients with sepsis-induced coagulopathy, thrombomodulin was associated with reduced mortality.[133]

- Activated Protein C (APC): recombinant human protein, which performed its anticoagulant function by inactivating proteins 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.[134]
- Contact Activation System (CAS): CAS links inflammation and coagulation by triggering thrombin and bradykinin production. In animal models, CAS inhibition was associated with reduced inflammatory cytokines and attenuated microvascular thrombosis.[137]
- Sulfated polysaccharides: non-anticoagulant low molecular weight heparin are glycosaminoglycans with non-coagulant properties. Specifically, the synthesized trisulfated heparin (TriS) have shown a high-affinity interaction with the SARS-CoV2 protein S. Therefore, in basic models, they can act as decoys to interfere with S-protein binding to the heparan sulfate co-receptor in host tissues inhibiting viral infection. Furthermore, TriS could be used in combination with current antiviral therapies to improve inhibition of SARS-CoV-2 replication.[138]

**CONCLUSIONS**

Thrombosis and coagulopathy are frequent complications in patients with COVID-19. The extent of these manifestations is correlated with the severity of 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 immunothrombotic 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 ALI and ARDS, all represent areas of unmet clinical need.

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**Table 1. Distinguishing laboratory features of sepsis-induced coagulopathy, disseminated intravascular coagulation, thrombotic microangiopathy, and COVID-19-associated hemostatic abnormalities (CAHA).**

| | SIC[48] | DIC[37] | Microangiopathy[37] | CAHA[37*] |
|---|---|---|---|---|
| Prothrombin time | ↑ | ↑↑ | ↔ | ↑↑ |
| Activated partial thromboplastin time, | ↑↑ | ↑↑↔↑ | ↔ | ↑ |
| Fibrinogen | ↓ | ↓ | ↔ | ↑↑ |
| Fibrin(ogen) degradation products | ↑ | ↑↑ | ↔ | ↑↑ |
| D-dimer | ↑ | ↑↔ | ↔ | ↑↑ or ↑+ |
| Platelet count | ↓ | ↓↓ | ↓ | ↑ or ↔ |
| Peripheral blood Smear + + | + | + | ++ | + |
| von Willebrand Factor | ↑ | ↑↑ | ↔ | ↑↑ |
| ADAMTS 13 | ↔ | ↔ | ↓ | ↔ |
| Antithrombin | ↓ | ↓ | ↓ | ↑ |
| Anticardiolipin antibodies | ↔ | ↔ | ↔ | + |
| Protein C | ↓ | ↓ | ↔ | + |
| Protein S | ↓ | ↓ | NA | ↓ |
| Factor VIII | ↑ | ↑ | NA | ↑ |
| Plasminogen | ↓ | ↓ | NA | ↑ |

*Some laboratory features can change significantly depending of the stage on the COVID-19-associated hemostatic abnormalities. + ≥ 6 times the ULN, ++ peripheral blood smear containing fragmented red blood cells. ADAMTS-13: A disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13; NA: not available.

**Table 2. Potential mechanisms and current evidence on use of antithrombotic therapies in patients with COVID-19.**

| Treatment | Potential mechanisms | Clinical evidence |
|---|---|---|
| **Anticoagulants** | | |
| UFH or LMWH | • Heparin-based products have anti-inflammatory and antiviral properties. Besides, in vitro data suggest that heparin may interreact with the spike S1 protein of SARS-CoV-2.[86]<br>• In patients with ALI/ARDS, the treatment with LMWH may reduce short-term mortality.[75] | - Intermediate dose:<br>• Yin et al., report that the 28-day mortality of heparin users was lower than non-users In the COVID-19 group with D-dimer >3.0 μg/mL.[76]<br>- Therapeutic dose:<br>• Paranjpe et al., report that the use of therapeutic anticoagulation was associated with lower mortality without increased bleeding.[77]<br>• Nadkarni et al., reported a large cohort of 4,389 patients, in which anticoagulation was associated with lower mortality and intubation among hospitalized COVID-19 patients.[87]<br>• Lemos et al. reported a phase II randomized clinical trial (N=10) comparing prophylaxis vs. therapeutic regimens of enoxaparin, they found that therapeutic regimen improves gas exchange and decreases the need for mechanical ventilation in severe COVID-19.[88] |
| DOACs | • Rivaroxaban and betrixaban showed a net clinical benefit for inpatient thromboprophylaxis and posthospital discharge extended prophylaxis.[78] | • No available data. |
| **Fibrinolytic agents** | | |
| Fibrinolytic therapy | • Pulmonary microthrombi may | • Wang et al., reported a case series of three |

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| | play a role in ARDS pathophysiology.[79]<br>• In animal models, tissue-type plasminogen activator could be beneficial in ARDS.[80] | patients treated with off-label intravenous administration of tPA for patients with ARDS had transient improvement in oxygenation and ventilatory requirement.[81]<br>• Wu et al., reported a case series of 13 patients with severe pneumonia treated with inhaled plasmin, who have improvement in gas exchange.[89] |
| **Antiplatelets** | | |
| Aspirin | • Acetylsalicylic acid (aspirin) may have anti-inflammatory properties. Aspirin has been extensively studied in ARDS. However, its efficacy was not validated in clinical trials.[82] | • No available data. |
| $P2Y_{12}$ inhibitors | • Pulmonary intravascular coagulopathy may have an essential role in COVID-19 pathophysiology.[55] Therefore, platelet $P2Y_{12}$ receptor inhibition could be beneficial.<br>• Ticagrelor improved lung function and reduced the need for supplemental oxygen in patients with pneumonia.[83] Of note, ticagrelor has a high-risk drug-drug interaction with lopinavir/ritonavir.[8] | • No available data. |
| Dipyridamole | • Dipyridamole provides platelet inhibition via phosphodiesterase inhibition. Furthermore, an animal model has suggested an antiviral effect in influenza virus A.[84] | • Liu et al., reported a proof-of-concept randomized trial (n=31); there was a significant decrease in D-dimer in patients treated with dipyridamole.[85] |

UFH: unfractionated Heparin; LMWH: low-molecular-weight heparin; DOACs: direct oral anticoagulants; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; t-PA: tissue plasminogen activator; COVID-19: coronavirus disease 2019.

**Table 3. Summary of recommendations from international guidelines and consensus documents.**

| | Recommendation* |
|---|---|
| **Venous Thromboembolism** | |
| *Risk assessment* | • Risk assessment is recommended in all hospitalized patients with COVID-19. (e.g., Padua, IMPROVE, or Caprini models).[8] |
| *Screening* | • There are currently insufficient data to recommend for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers (NIH grade BIII).[92]<br>• For hospitalized COVID-19 patients, 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 AIII). [92] |
| *Prophylaxis* | • Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults (NIH grade AIII).[92]<br>• 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).[92]<br>• LMWHs or UFH may be preferred in hospitalized critically ill patients due to their shorter half-lives, ability to be given IV or subcutaneously, and fewer known drug-drug interactions compared to oral anticoagulants (NIH Grade AIII).[92]<br>• Prophylactic dosing should be adjusted based on body weight extremes, severe thrombocytopenia (platelet count $<50\times10^9$/L or $<25\times10^9$/L), or impaired renal function. Of note, in case thromboprophylaxis should be held only if the platelet count is $<25\times10^9$/L or fibrinogen level is <0.5 g/L.[93] |
| *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 AIII).[92]<br>• 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.[8, 93] |

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| | • The anticoagulation with LMWHs may be preferred in an in-patient setting, while DOACs may be preferred in an outpatient setting.[8, 93]<br>• 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.[8, 93]<br>• Duration of treatment is ≥3 months.[8, 93]<br>• Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or 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).[92] |
| *Extended prophylaxis* | • The routine discharge of patients on VTE prophylaxis is not generally recommended (NIH Grade AIII).[92]<br>• 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).[93]<br>• The patients at risk for post-discharge VTE include those with reduced mobility, with co-existing 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 AIII).[92]<br>• The duration of post-discharge prophylaxis should be ≥ 14 days and up to 30 days.[93] |
| **Previous indication of antithrombotic treatment (CAD, NVAF, etc.)** | • 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 AIII).[92]<br>• Drug-drug interactions should be considered between investigational COVID-19 therapies and antithrombotic agents.[91]<br>• In patients who take low-dose aspirin should continue the treatment.[91]<br>• In patients who take $P2Y_{12}$ inhibitors, clopidogrel and ticagrelor have potentially dangerous drug-drug interaction and are contraindicated. Prasugrel can be used, taking into account its contraindications and precautions.[94]<br>• In patients using anticoagulant therapy and the concomitant need for specific COVID-19 treatment, baseline anticoagulant therapy could be change to LMWH. After COVID-19 treatment is completed, the baseline treatment can be reinitiated.[8] |
| **Acute coronary syndromes** | Considerations regarding oral antiplatelet and anticoagulation therapies mentioned in the section "Previous indication of antithrombotic treatment" also applies to the |

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| | ACS setting. |
| *NSTEMI* | • Parenteral antiplatelet such as cangrelor and anticoagulant therapies such as UFH, bivalirudin, LMWH, or fondaparinux does not have important drug-drug interaction with the COVID-19 specific treatment.[94] |
| *STEMI* | • If the patient's clinical condition is not a counterindication, primary PCI is the standard care strategy.[95]<br>• Parental antiplatelet therapies such as GPI have no significant drug-drug interaction with COVID-19 treatment.[94]<br>• Tissue plasminogen activator or streptokinase has no relevant drug-drug interactions with COVID-19 treatment and can be used unless contraindication.[94] |
| **Arterial thrombosis events** | |
| *Acute ischemic stroke* | • If COVID-19 associated coagulopathy is severe may contraindicate the use of IV thrombolysis. Even if IV thrombolysis is not contraindicated, increased inflammation and hypercoagulability may increase post-thrombolysis mortality and morbidity.[96]<br>• 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.[96] |
| *Acute limb ischemia* | • In COVID-19 patients who presented acute limb ischemia, prolonged UFH might be warranted for both limb salvage and improved survival.[97] |
| **Coagulopathy** | |
| *Diagnosis* | • In patients with significantly elevated D-dimer level (3- to 4-fold increase), prolonged PT, platelet count $<100\times10^9$/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.[44] |
| *Prophylaxis* | • Consider prophylaxis with LMWH in all patients, if not contraindicated (for example, active bleeding, platelet count $<25\times10^9$/L).[44] |
| Treatment | • The management of DIC is focused on the treatment of the underlying condition.[98]<br>• Without bleeding: blood products should be administered to maintain platelet count $>25\times10^9$/L.[44]<br>• With bleeding: blood products should be administered to maintain platelet count |

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| | > $50\times10^9$/L, fibrinogen >1.5 g/L, and PT ratio <1.5.[44]<br>• In patients with DIC antifibrinolytics are not recommended.[98] |
| **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 AIII).[92, 99]<br>• Patients with COVID-19 who require ECMO with a hypercoagulable status may benefit from antiplatelet agents (such as aspirin, clopidogrel, prasugrel, ticagrelor), but there is little data to recommend or refute.[99] |

*The selected international guidelines and consensus documents are: International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH/SSC) clinical guidance on diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19.[93] International Society on Thrombosis and Haemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19.[44] National Institutes of Health (NIH) COVID-19 treatment guideline.[92] Global COVID-19 Thrombosis Collaborative Group. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up.[8] The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic.[90] Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic.[7] 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. COVID-19: coronavirus disease 2019; VTE: venous thromboembolism; NIH: National Institutes of Health; CAD: coronary artery disease; NVAF: non-valvular atrial fibrillation; LMWH: low-molecular-weight heparin; UFH: unfractionated Heparin; IV: Intravenous therapy; DOACs: direct oral anticoagulants; PCI: percutaneous cardiac intervention; GPI: glycoprotein IIb-IIIa inhibitor; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SAPT: single antiplatelet therapy; DAPT: dual antiplatelet therapy; PT: prothrombin time; DIC: disseminated intravascular coagulation; ECMO: extracorporeal membrane oxygenation

**Table 4. Evidence gaps and ongoing clinical trials.**

| | 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 sub-study testing the role of rivaroxaban for sustained clinical improvement. |
| | • Optimal time duration | | |
| | • Need for prophylaxis in ambulatory patients. | NCT04400799[†]<br>NCT04498273[†a] | Trial testing the role of thromboprophylaxis with enoxaparin in outpatients.<br><br>[a]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.<br>• Net clinical benefit in terms of arteriovenous | - Prophylaxis vs. Intermediate dose: NCT04366960[†] | The majority of the trials are focusing on determining the role |

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| | thrombotic events reduction without a significant increase in bleeding events. | NCT04360824<br>NCT04367831<br><br>- Prophylaxis vs. therapeutic dose:<br>NCT04372589[b†]<br>NCT04359277[†]<br>NCT04344756<br>NCT04373707<br>NCT04394377<br>NCT04362085<br>NCT04444700<br>NCT04377997<br>NCT04408235<br>NCT04345848<br>NCT04345848<br>NCT04420299<br><br>- Intermediate vs. therapeutic dose:<br>NCT04401293[§]<br>NCT04406389 | of different regimens of anticoagulant therapies (LMWH or UFH) for the prevention of arteriovenous thrombotic events or COVID-19 severity.<br><br>[b]Trial powered for assessing relevant clinical endpoints (need for ventilation or death). |
| | • Optimal dose in specific populations such as obesity and impaired renal function. | | |
| *Extended prophylaxis* | • Optimal method for risk stratification.<br>• Optimal time duration. | | |
| **Arterial thrombosis** | • Prevalence and predictors of arterial thrombosis events (stroke, coronary, and limbs) according to the disease severity. | | |
| *Treatment* | • Prevention of | NCT04409834 | Trial testing the role |

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| | arteriovenous thrombotic events. | | of anticoagulation (enoxaparin or UFH) ± 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[c†]<br>NCT04324463[c†]<br>NCT04333407[c†]<br>NCT04416048 | Trials that combine cardiovascular medications such as aspirin, ACE-I, statins, clopidogrel, or DOACs; to prevent adverse cardiac events.<br><br>[c]Trials statistically powered to assess meaningful clinical outcomes (death or MACE). |
| *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[d†] | [d]Trial design for low-risk patients assessing aspirin and vitamin D's role in |

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| | | | preventing the developing of COVID-19-associated coagulopathy and reducing the need for hospitalization. |
| *Moderate to severe patients (inpatient)* | • Optimal treatment to decrease the fibrin formation, deposition, and improve the prothrombotic state. | NCT04435015[e]<br>NCT04424901[f]<br>NCT04391179[g]<br>NCT04419610 | Trials designed for preventing fibrinogen generation by blocking several therapeutic targets related in the thromboinflamatory process.<br><br>[e]Trial testing the role of camostat mesylate (TMPRSS2 blocker).<br><br>[f]Trials assessing the role of dipyridamole.<br><br>[g]Trial exploring the efficacy of TRV027 (selective Angiotensin II receptor type 1 agonist) |
| *DIC* | • Prevalence and predictors of DIC. | | |
| | • Routine use of prophylaxis in patients without overt bleeding. | | |

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| | • Role of antithrombin concentrates as a potential treatment. | | |
| *Bleeding* | • Prevalence and predictors of severe bleeding events. | | |
| | • Specific treatment strategies for patients with COVID-19. | | |
| **ALI and ARDS** | | | Several trials are testing different drugs for thrombolysis, anticoagulation or platelet inhibition, and preventing pulmonary thrombosis. |
| *Treatment* | • Role of tissue-type plasminogen activator on pulmonary gas exchange. | NCT04357730<br>NCT04453371 | Trial testing different intravenous alteplase regimens. |
| | • Role of antiplatelet therapies pulmonary on gas exchange. | NCT04445623 | Trial studying the role of oral prasugrel. |
| | • Role of anticoagulant therapies on pulmonary gas exchange. | NCT04389840[h]<br>NCT04445935 | [h]Trial exploring the efficacy of intravenous bivalirudin. |
| | • Role of nebulized/ aerosolized therapies on pulmonary gas exchange. | NCT04396067[i]<br>NCT04355364[i]<br>NCT04397510<br>NCT04359654[i]<br>NCT04356833 | Nebulized therapies are compelling due to its local effect.<br><br>[i]Trials that are testing dornase alfa for NETs clearance. |

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| *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 VTE treatment or in sepsis-induced coagulopathy.<br>- Sulodexide,<br>- Antithrombin,<br>- Thrombomodulin,<br>- Activated Protein C. | None have RCT in COVID-19 patients. | • Sulodexide showed a reduction in recurrent VTE events.[131]<br>• Antithrombin, Thrombomodulin, and activated Protein C have been studied in the context of sepsis-induced coagulopathy. However, none of them were associated with a reduction in mortally.[132-134] |

*Only randomized clinical trials registered in clinicaltrials.gov were included. †Trials that aim to enrolled at least one thousand patients. The trials are listed in descendent order of target sample size. ‡Several trials included in VTE dose section also assess arterial thrombosis endpoints. §Patients with prophylactic anticoagulant regimens can also be included. VTE: venous thromboembolism; COVID-19: coronavirus disease 2019; LMWH: low-molecular-weight heparin; UFH: unfractionated Heparin; ACE-I: Angiotensin-converting-enzyme inhibitors; DOACs: direct oral anticoagulants; MACE: major adverse cardiovascular events; TMPRSS2: Transmembrane protease serine 2; DIC: disseminated intravascular coagulation; NETs: neutrophil extracellular traps.

**Figure Legend:**

**Figure 1. Pathophysiological mechanism related to COVID-19 associated thrombosis and coagulopathy. *A*:** The interaction of the SARS-CoV2 with endothelial cells (type II pneumocytes, glomerular capillary loops, small intestine capillaries, etc.) ACE2 imbalance may promote susceptibility to the SARS-CoV2 infection of these cell types. Furthermore, cell infection and induced inflammation in pericytes and endothelial cells may promote local apoptosis and potent inflammatory cytokines. ***B*:** Inflammatory process in the pulmonary alveoli leading to pulmonary tissue edema and intravascular coagulopathy. ***C*:** Selection of thrombotic complications in COVID-19 and their approximate frequency. ***D*:** Proposed intravascular thrombosis pathways leading to micro and macrovascular thrombosis complications. Due to the potent local and systemic cytokines production, the platelet platelets are activated and interact with neutrophils. The NETosis process may also stimulate thrombin production and fibrin deposition. The excess of fibrin deposition and fibrinolysis shutdown leads to intravascular thrombosis, and finally, to clinical thromboembolic complications. The pointed black and continued black lines denote pathway connections, pointed red lines denote inhibition, and green arrows denote agonism. SARS-CoV2: severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus Disease 2019; IL: interleukin; TriS: synthesized trisulfated heparin; TMPRSS2: transmembrane protease serine 2; AT1: angiotensin II receptor type 1; ACE2: angiotensin-converting enzyme 2; ACE-I: angiotensin-converting-enzyme inhibitors; NETs: neutrophil extracellular traps; Anti-Xa: anti-factor Xa; UFH: unfractionated Heparin; LMWH: low-molecular weight heparin; PAI-1: plasminogen activator inhibitor I; tPA: tissue plasminogen activator; r-tPA: recombinant-tissue plasminogen activator; DTIs: direct thrombin inhibitors; PDFs: fibrin degradation products; D-D: D-dimer; CAHA: COVID-19-associated hemostatic abnormalities. Data derived and visual presentation modeled from Bikdeli et al.[91]

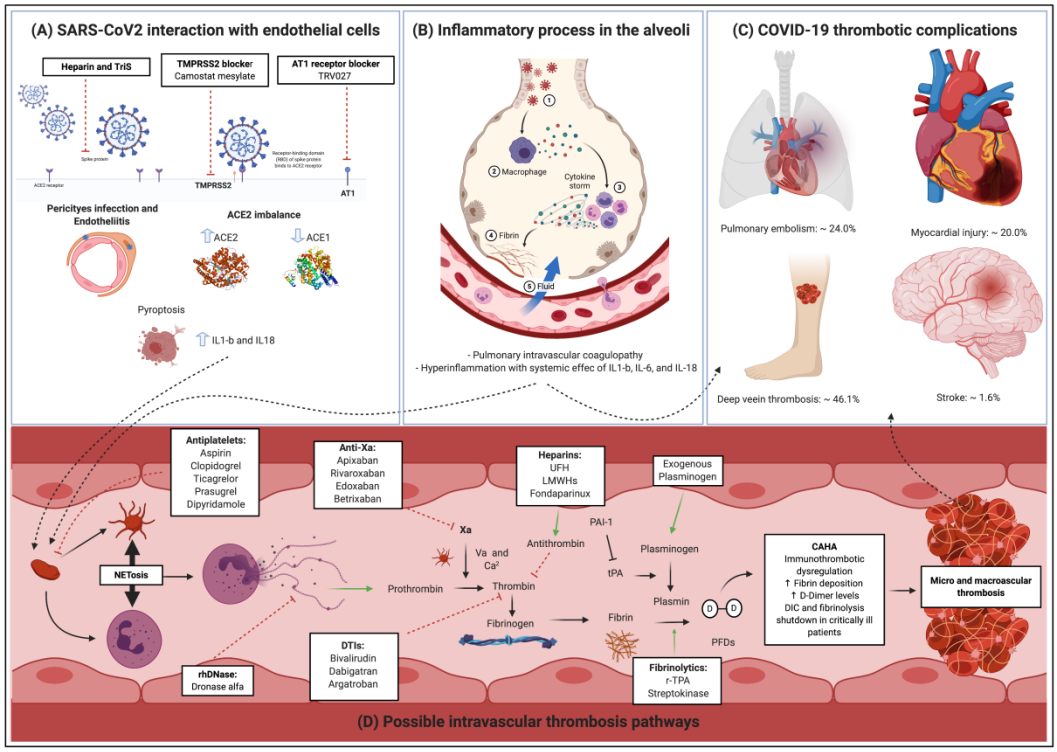
**Figure 2. Effects of COVID-19 on the cardiovascular and coagulation system.** COVID-19: coronavirus disease 2019; ACE2: Angiotensin-converting enzyme 2; ACE1: Angiotensin-converting enzyme 1; IL: interleukin.

**Figure 3. Stages of COVID-19-associated hemostatic abnormalities (CAHA).** *Laboratories parameters included in the COVID-19-associated hemostatic abnormalities stages described by

Thachil et al.[45] COVID-19: coronavirus disease 2019; URL: upper reference level; PT: prothrombin time; aPTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulation; LWMH: low-molecular weight heparin; HDU: high-dependency unit; ICU: intensive care unit; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation.

**Figure 4. Proposed algorithm for diagnosis and treatment of myocardial injury and acute myocardial infarction in patients with confirmed COVID-19.** *Signs of myocardial ischemia are needed to meet the criteria for this category. †The complete list of very-high and high-risk criteria are those defined in the corresponding clinical guidelines.[123] Immediate transfer for invasive stagey should be done regardless of the COVID-19 status. ‡If the COVID-19 diagnosis is unknown, the management decision can be delay until the COVID-19 status is confirmed or rule-out. URL: upper reference level; COVID-19: coronavirus disease 2019; UDMI: universal definition of myocardial infarction; CKD: chronic kidney disease; ESRD: end-stage renal disease; cTn: cardiac troponin; ARDS: acute respiratory distress syndrome; PE: pulmonary embolism; ECG; electrocardiogram; MI: myocardial infarction; pPCI: primary percutaneous cardiac intervention; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

**Figure 5. Summary of drug–drug interactions between COVD-19 investigational treatments and antithrombotic therapies.** UFH: unfractionated heparin; LWMH: low-molecular weight heparin; VKA: vitamin K antagonist; GPI: glycoprotein IIb-IIIa inhibitor; rTPA: recombinant tissue plasminogen activator; NA: not available. Data derived and visual presentation modeled from Bikdeli et al.[91]

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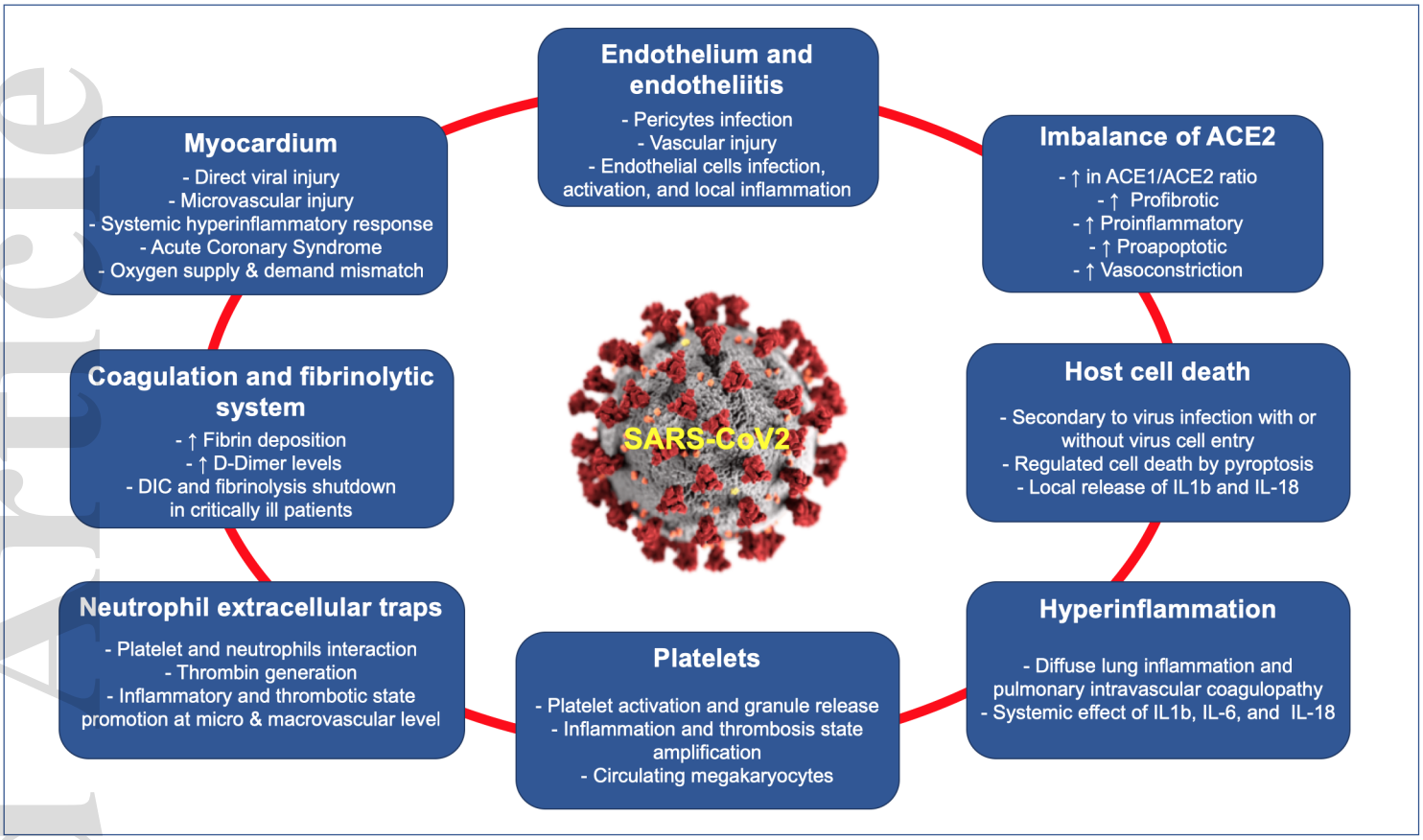


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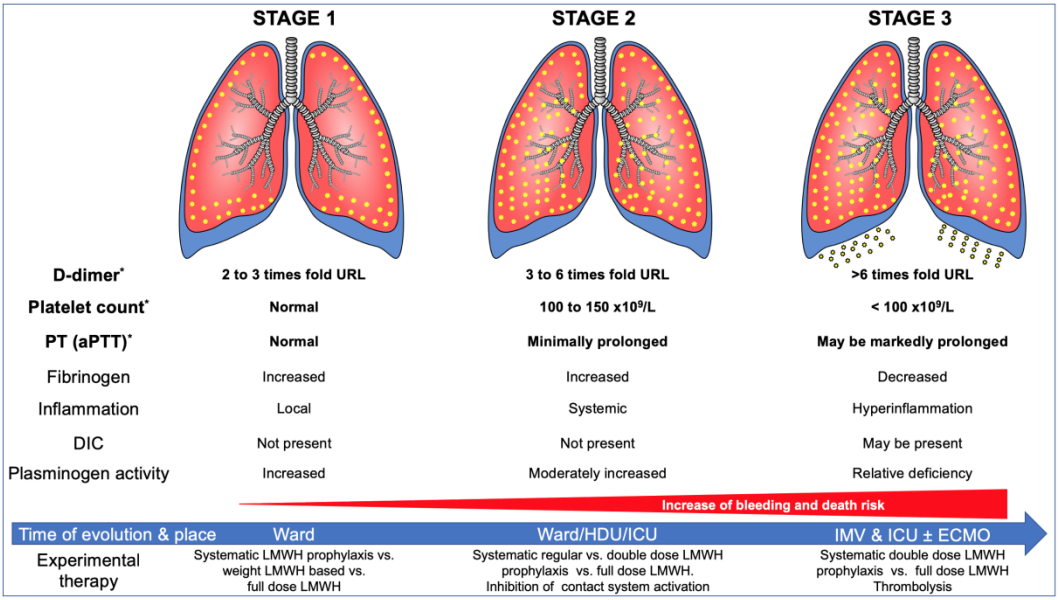


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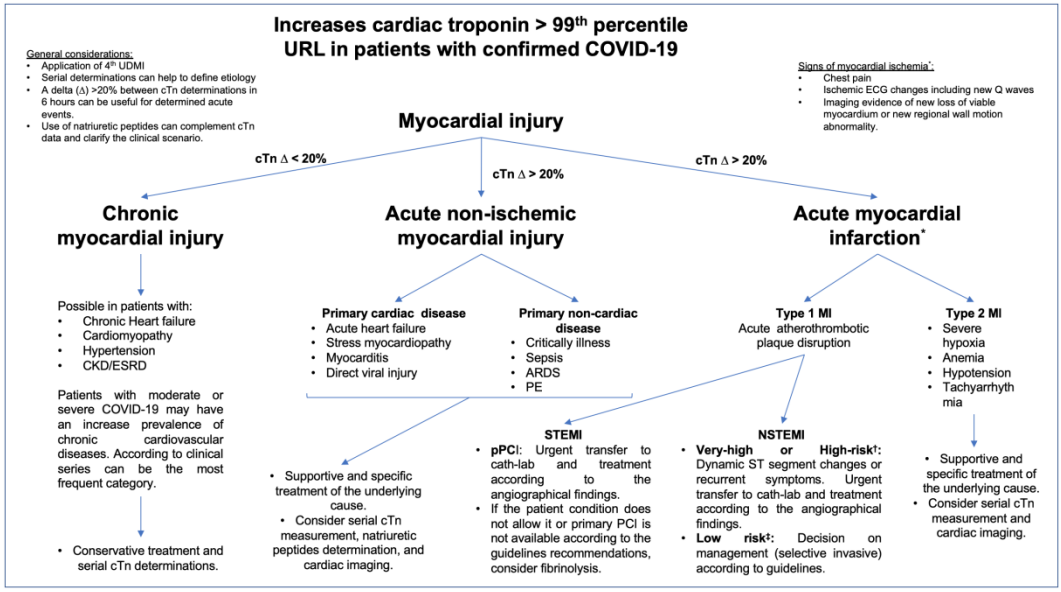


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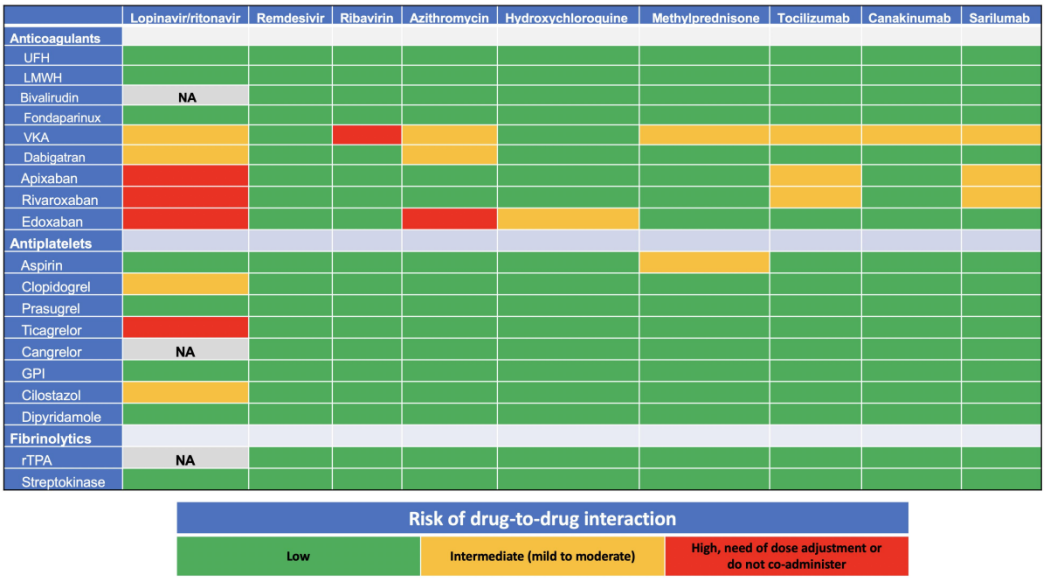


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