

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up



JACC State-of-the-Art Review

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ABSTRACT

Coronavirus disease-2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), may predispose patients to thrombotic disease, both in the venous and arterial circulations, because of excessive inflammation, platelet activation, endothelial dysfunction, and stasis. In addition, many patients receiving antithrombotic therapy for thrombotic disease may develop COVID-19, which can have implications for choice, dosing, and laboratory monitoring of antithrombotic therapy. Moreover, during a time with much focus on COVID-19, it is critical to consider how to optimize the available technology to care for patients without COVID-19 who have thrombotic disease. Herein, the authors review the current understanding of the pathogenesis, epidemiology, management, and outcomes of patients with COVID-19 who develop venous or arterial thrombosis, of those with pre-existing thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic. (J Am Coll Cardiol 2020;75:2950-73) © 2020 by the American College of Cardiology Foundation.



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Coronavirus disease-2019 (COVID-19) is a viral illness caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and now has been deemed a pandemic by the World Health Organization (1-3). COVID-19 has a number of important cardiovascular implications (4-6). Patients with prior cardiovascular disease are at higher risk for adverse events from COVID-19. Individuals without a history of cardiovascular disease are at risk for incident cardiovascular complications (5).

There are several ways in which the COVID-19 pandemic may affect the prevention and management of thrombotic and thromboembolic disease (hereafter collectively referred to as thrombotic disease for brevity). First, the direct effects of COVID-19 or the indirect effects of infection, such as through severe illness and hypoxia, may predispose patients to thrombotic events. Preliminary reports suggest that hemostatic abnormalities, including disseminated intravascular coagulation (DIC), occur in patients affected by COVID-19 (7,8). Additionally, the severe inflammatory response, critical illness, and underlying traditional risk factors may all predispose

to thrombotic events, similar to prior virulent zoonotic coronavirus outbreaks (Table 1) (9,10). Second, investigational therapies for treating COVID-19 may have adverse drug-drug interactions with antiplatelet agents and anticoagulants. Third, the pandemic, because of resource allocations or social distancing recommendations, may adversely affect the care of patients without COVID-19 but who present with thrombotic events. For example, (mis)perception that antithrombotic agents confer increased risk for contracting COVID-19 may lead to untoward interruption of anticoagulation by some patients.

The current paper, authored by an international collaborative of clinicians and investigators, summarizes the pathogenesis, epidemiology, treatment, and available outcome data related to thrombotic disease in patients with COVID-19, as well as management of thrombotic events in patients without COVID-19 during this pandemic.

ABBREVIATIONS AND ACRONYMS

ACS	= acute coronary syndrome
COVID-19	= coronavirus disease-2019
DIC	= disseminated intravascular coagulation
DOAC	= direct oral anticoagulant
DVT	= deep vein thrombosis
ECMO	= extracorporeal membrane oxygenation
LMWH	= low-molecular-weight heparin
PE	= pulmonary embolism
SARS-CoV-2	= severe acute respiratory syndrome-coronavirus-2
STEMI	= ST-segment elevation myocardial infarction
UFH	= unfractionated heparin
VKA	= vitamin K antagonist
VTE	= venous thromboembolism

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Although the focus is on the prevention and management of venous thromboembolism (VTE) and antithrombotic therapy for acute coronary syndromes (ACS), many of the recommendations are relevant to

other conditions requiring antithrombotic therapy. We provide clinical guidance, when feasible, and also identify areas that require urgent attention for future research.

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Maddox, MD, MSc, served as Guest Editor-in-Chief for this paper. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [JACC author instructions page](#).

METHODOLOGICAL CONSIDERATIONS

Every effort was made to provide a comprehensive assessment of the published evidence (MEDLINE with PubMed interface; date of last search: April 12, 2020). To accommodate the rapidly evolving nature of information and concern for the delay between completion of studies and their publication, we also reviewed manuscripts on 2 preprint servers (medRxiv and SSRN; date of last search: April 12, 2020). We acknowledge that the manuscripts from the latter 2 sources are not peer-reviewed.

There is international variability in preventive measures and testing strategies by local authorities, diagnostic tests' availability, access to care, and treatment strategies, as well as variability in outcome reporting for COVID-19. These issues influence the reported diagnosed cases, casualties, and in turn, case-fatality rates. Moreover, to date, we lack large prospective cohorts. The existing evidence, including data on thrombotic complications, is derived primarily from small and retrospective analyses (Figure 1).

The current document represents an effort to provide general guidance for patient care related to thrombosis and antithrombotic therapy. Given the limitations of the evidence base, the steering committee (B.B., M.V.M., J.I.W., S.V.K., S.Z.G., A.J.T., M.M., H.M.K., G.Y.H.L.) chose several questions that seemed more challenging but relevant to patient care (11). These questions were sent to the entire group of authors twice. The Delphi method was implemented to provide consensus-based guidance. The questions included considerations for prophylactic or therapeutic anticoagulant regimens among various subgroups of patients with COVID-19, and antithrombotic therapy in the setting of suspected or confirmed DIC.

PATHOGENESIS AND TRANSMISSION

SARS-CoV-2 is a single-strand RNA coronavirus, which enters human cells mainly by binding the angiotensin-converting enzyme 2 (12), which is highly expressed in lung alveolar cells, cardiac myocytes, the vascular endothelium, and other cells (1,13). SARS-CoV-2 is transmitted primarily after viral particles are inhaled and enter the respiratory tract (1). In addition, the virus can survive for 24 to 72 h on surfaces, depending on the type of surface, which enables fomite transmission (14).

Initial symptoms of COVID-19 overlap with other viral syndromes, and include fever, fatigue, headache, cough, shortness of breath, diarrhea, headaches, and myalgias (15-17). As with other virulent

HIGHLIGHTS

- COVID-19 may predispose patients to arterial and venous thrombosis.
- Initial series suggest the common occurrence of venous thromboembolic disease in patients with severe COVID-19. The optimal preventive strategy warrants further investigation.
- Drug-drug interactions between antiplatelet agents and anticoagulants with investigational COVID-19 therapies should be considered.
- The available technology should be used optimally to care for patients without COVID-19 who have thrombotic disease during the pandemic.

zoonotic coronavirus infections such as SARS and Middle East respiratory syndrome, COVID-19 has the potential to result in severe illness including systemic inflammatory response syndrome (SIRS), acute respiratory disease syndrome (ARDS), multi-organ involvement, and shock (18). Although older age and comorbidities such as cardiovascular disease confer a higher risk for severe disease, young and otherwise healthy patients are also at risk for complications (19).

Common laboratory abnormalities found in patients with COVID-19 include lymphopenia (15) and elevation in lactate dehydrogenase and inflammatory markers such as C-reactive protein, D-dimer, ferritin, and interleukin-6 (IL-6) (20). IL-6 levels may correlate with disease severity and a procoagulant profile (21).

COVID-19 AND HEMOSTASIS PARAMETERS

The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia (22) and increased D-dimer levels (23), which are associated with a higher risk of requiring mechanical ventilation; intensive care unit (ICU) admission; or death (Table 2). Data related to other tests are less certain and often contradictory (24,25). Disease severity is variably associated with prolongation of the prothrombin time (PT) and international normalized ratio (INR) (1,20,26), and thrombin time (TT) (27), and variably by a trend toward shortened activated partial thromboplastin time (aPTT) (1,16,19,28). Recently, Tang et al. (7) assessed 183 patients with COVID-19, 21 (11.5%) of whom died. Among the notable differences between patients who died and those who survived were

TABLE 1 Select Summary of Thrombotic and Thromboembolic Events During Viral Outbreaks

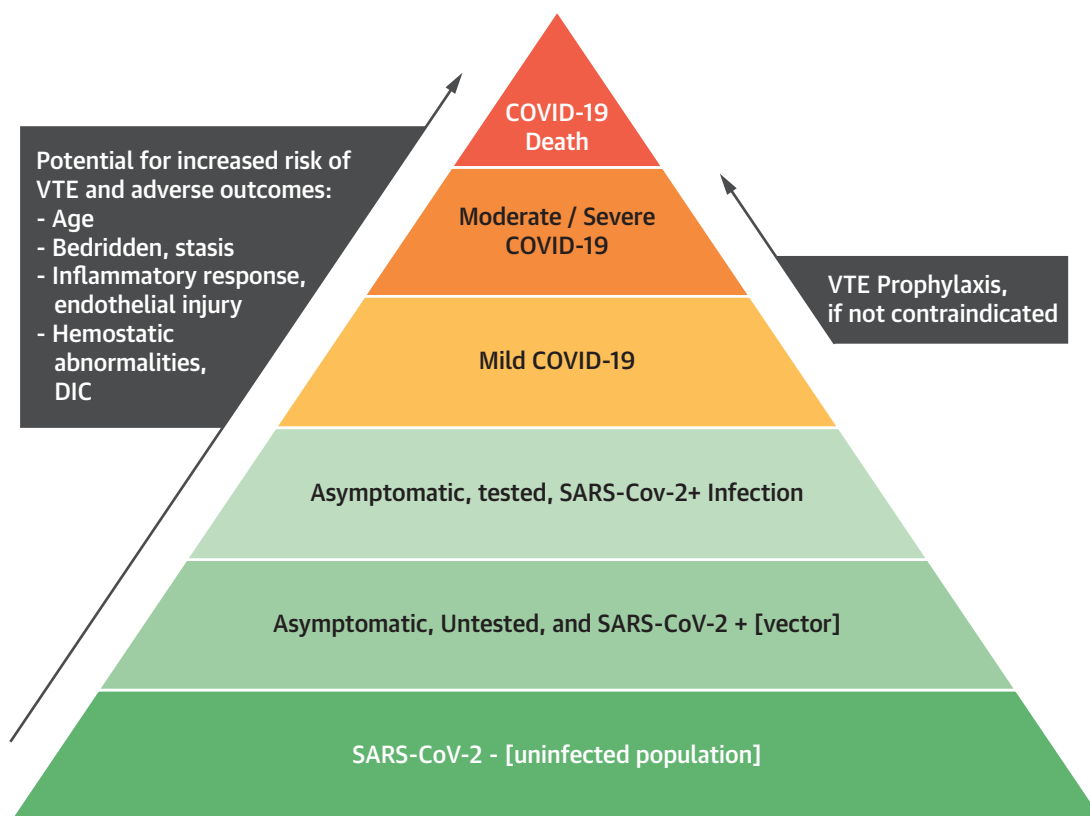
Proposed Mechanisms	Event Type	Epidemiological Data
SARS		
Inflammatory cytokine release	VTE	Retrospective analysis of 46 critically ill patients with SARS showed 11 DVT and 7 PE events (9). Case series of 8 SARS positive ICU patients. Autopsy identified PE in 4, and DVT in 3 individuals (138).
Critical illness	Arterial thrombotic events	In a prospective series of 75 patients, 2 patients died of acute myocardial infarction (within 3-week period) (139). Case report of an NSTEMI patient who received PCI but subsequently developed STEMI several hours later, concerning for immune-mediated plaque instability (140).
Traditional risk factors (138)	Other	In a case series of 206 patients with SARS, 5 developed large artery ischemic stroke with DIC present in 2 of 5 (141). In a retrospective analysis of 157 patients with SARS, isolated, subclinical elevations in aPTT were noted in 96 patients and DIC developed in 4 patients (142).
MERS		
Nonspecific mechanism; potentially similar to SARS. Models suggest elevated inflammatory cytokine levels (143) Transgenic murine models show evidence of microvascular thrombosis (144)	Other	In a series of 157 cases of MERS (confirmed and probable), at least 2 were reported to have a consumptive coagulopathy (145).
Influenza		
Possible de novo pulmonary emboli in certain cases (146) Acute inflammation and decreased mobility in hospitalized patients (147) Possible thrombosis owing to rupture of pre-existing high-risk plaques (98) Platelet aggregation over inflamed atherosclerotic plaques noted in animal models (148)	VTE Arterial thrombotic events	Retrospective study of 119 patients showed 4 VTE events in patients receiving prophylactic anticoagulation (147). Case series describes 7 PEs in patients with influenza pneumonia. In 6 of 7, there was no evidence of DVT (146). A multicenter, observational, case-control study (N = 1,454) suggested that lower VTE rates are associated with influenza vaccination (odds ratio: 0.74; 95% confidence interval: 0.57-0.97) (149). <i>This is a representative but not comprehensive list of associated studies.</i> A self-controlled study of 364 patients hospitalized with acute myocardial infarction found an increased incidence ratio (6.05; 95% confidence interval: 3.86-9.50) for myocardial infarction during periods after influenza compared with controls (97). Similar evidence exists in prior studies (150,151). A retrospective cohort study of 119 patients reports 3 arterial thrombotic events, 2 of which had STEMI (147). <i>This is a representative but not comprehensive list of associated studies.</i>
	Other	DIC has been described with influenza infection in a number of case reports and small case series (152-154).
COVID-19		
Mechanistic understanding continues to evolve	VTE	Two case series of acute pulmonary embolism were described in patients hospitalized with COVID-19 (83). In a study from 3 hospitals from the Netherlands, 31% of 184 critically ill patients with COVID-19 had thrombosis, with most events being VTE.
Factors may include inflammatory cytokine release and critical illness/underlying risk factors	Arterial thrombotic events	<i>Data are continuing to emerge regarding the risk of thrombotic events associated with COVID-19 infection, and an international registry for ACS is planned. Please see text for more detail.</i>
SARS-CoV-2 binds cells expressing angiotensin-converting enzyme 2 (155), and this may mediate further mechanisms of injury (3)	Other	Retrospective analysis of 183 patients found nonsurvivors had significantly higher D-dimer and PT values, compared with survivors. Further, 15 of 21 (71.4%) nonsurvivors met criteria for DIC vs. 1 of 162 (0.6%) survivors (7). Systematic review of literature published prior to February 24, 2020, suggests elevations in PT and D-dimer levels were associated with poor prognosis in patients with COVID-19 (25).
ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; COVID-19 = coronavirus disease-2019; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ICU = intensive care unit; MERS = Middle East respiratory syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PT = prothrombin time; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; STEMI = ST-segment elevation myocardial infarction; VTE = venous thromboembolism.		

increased levels of D-dimer and fibrin degradation products (~3.5- and ~1.9-fold, respectively) and PT prolongation (by 14%) ($p < 0.001$). Further, 71% of COVID-19 patients who died fulfilled the International Society on Thrombosis and Haemostasis (ISTH) criteria (29) for DIC, compared with only 0.6% among

survivors. Collectively, these hemostatic changes indicate some forms of coagulopathy that may predispose to thrombotic events (Central Illustration), although the cause is uncertain.

Nevertheless, it is yet unknown whether these hemostatic changes are a specific effect of

FIGURE 1 Variability in Resources and Testing Strategies, and in Contracting COVID-19 After Exposure to SARS-CoV-2



Such variability explains the dissimilar population rates of the infection, and the distinct case fatality rates, across various regions and countries. Inflammatory response, increased age, and bedridden status—which are more frequently observed in severe coronavirus disease-2019 (COVID-19)—may contribute to thrombosis and adverse outcomes. DIC = disseminated intravascular coagulation; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VTE = venous thromboembolism.

SARS-CoV-2 or are a consequence of cytokine storm that precipitates the onset of SIRS, as observed in other viral diseases (30-33). Another consideration that has not yet been investigated is that the hemostatic changes seen with COVID-19 infection are related to liver dysfunction (34). A recent study reported 3 cases with severe COVID-19 and cerebral infarction, with 1 associated with bilateral limb ischemia, in the setting of elevated antiphospholipid antibodies. Whether antiphospholipid antibodies play a major role in pathophysiology of thrombosis associated with COVID-19 requires further investigation (35).

COVID-19, MARKERS OF MYOCARDIAL INJURY, AND THROMBOTIC DISEASE. Elevated troponin levels are associated with poor outcomes in several studies of COVID-19 (36). However, the differential diagnosis for elevated troponin in COVID-19 is broad (37) and

includes nonspecific myocardial injury, impaired renal function (leading to troponin accumulation), myocarditis, pulmonary embolism (PE), and type 1 and 2 myocardial infarction (MI) (38,39). Similarly, elevation of natriuretic peptides is nonspecific (38), and consideration for thrombotic events (e.g., PE) should only be raised in the appropriate clinical context.

COVID-19 INVESTIGATIONAL THERAPIES AND CONSIDERATIONS FOR THROMBOTIC DISEASE

Several investigational agents are being tested in the management of COVID-19, especially for patients who develop severe disease. Some of these drugs have clinically important interactions with antiplatelet or anticoagulant agents (Tables 3 and 4).

Further, a few of these investigational agents have been associated with excess risk (or, in other cases,

TABLE 2 Association Between Coagulation Abnormalities or Markers of Thrombosis and Hemostasis and Clinical Outcomes in Patients With COVID-19

	Han et al., 2020 (24) (N = 94)	Huang et al., 2020 (1) (N = 41)	Yang et al., 2020 (26) (N = 52)	Zhou et al., 2020 (20) (N = 191)	Gao et al., 2020 (27) (N = 43)	Wang et al., 2020 (16) (N = 138)	Wu et al., 2020 (19) (N = 201)	Tang et al., 2020 (7) (N = 183)	Lippi et al., 2020 (22) (N = 1,779)	Lippi and Favaloro, 2020 (23) (N = 553)	Lippi et al., 2020 (36) (N = 341)
Platelet count											
Setting of comparison		ICU vs. non-ICU	Dead vs. alive	Dead vs. alive		ICU vs. non-ICU	Dead vs. alive		Dead vs. alive		
Outcome, per cubic millimeter		196 (165-263) vs. 149 (131-263)	191 (74) vs. 164 (63)	166 (107-229) vs. 220 (168-271)		142 (110-202) vs. 165 (125-188)	162 (111-231) vs. 204 (137-263)		-48 (-57 to -39)*†		
D-dimer											
Setting of comparison	Severe vs. nonsevere	ICU vs. non-ICU		Dead vs. alive	Severe vs. nonsevere	ICU vs. non-ICU	Dead vs. alive	Dead vs. alive		Severe vs. nonsevere	
Outcome, mg/l	19.1 vs. 2.1	2.4 (0.6-14.4) vs. 0.5 (0.3-0.8)		5.2 (1.5-21.1) vs. 0.6 (0.3-1.0)	0.5 (0.3-0.9) vs. 0.2 (0.2-0.3)	0.4 (0.2-13.2) vs. 0.2 (0.1-0.3)	4.0 (1.0-11.0) vs. 0.5 (0.3-1.2)	2.1 (0.8-5.3) vs. 0.6 (0.4-1.3)		3.0 (2.5-3.5)*	
Prothrombin time											
Setting of comparison	Severe vs. nonsevere	ICU vs. non-ICU	Dead vs. alive	Dead vs. alive	Severe vs. nonsevere	ICU vs. non-ICU	Dead vs. alive	Dead vs. alive			
Outcome, s	12.7 vs. 12.2	12.2 (11.2-13.4) vs. 10.7 (9.8-12.1)	12.9 (2.9) vs. 10.9 (2.7)	12.1 (11.2-13.7) vs. 11.4 (10.4-12.6)	11.3 (1.4) vs. 12.0 (1.2)	13.2 (12.3-14.5) vs. 12.9 (12.3-13.4)	11.6 (11.1-12.5) vs. 11.8 (11.0-12.5)	15.5 (14.4-16.3) vs. 13.6 (13.0-14.0)			
Troponin (hs-TnI)											
Setting of comparison		ICU vs. non-ICU		Dead vs. alive		ICU vs. non-ICU				Severe vs. nonsevere	
Outcome, pg/ml		3.3 (3.0-163.0) vs. 3.5 (0.7-5.4)		22.2 (5.6-83.1) vs. 3.0 (1.1-5.5)		11.0 (5.6-26.4) vs. 5.1 (2.1-9.8)				25.6 (6.8-44.5)*	

*Mean difference, results from meta-analysis data. †Subgroup analysis of 3 studies.

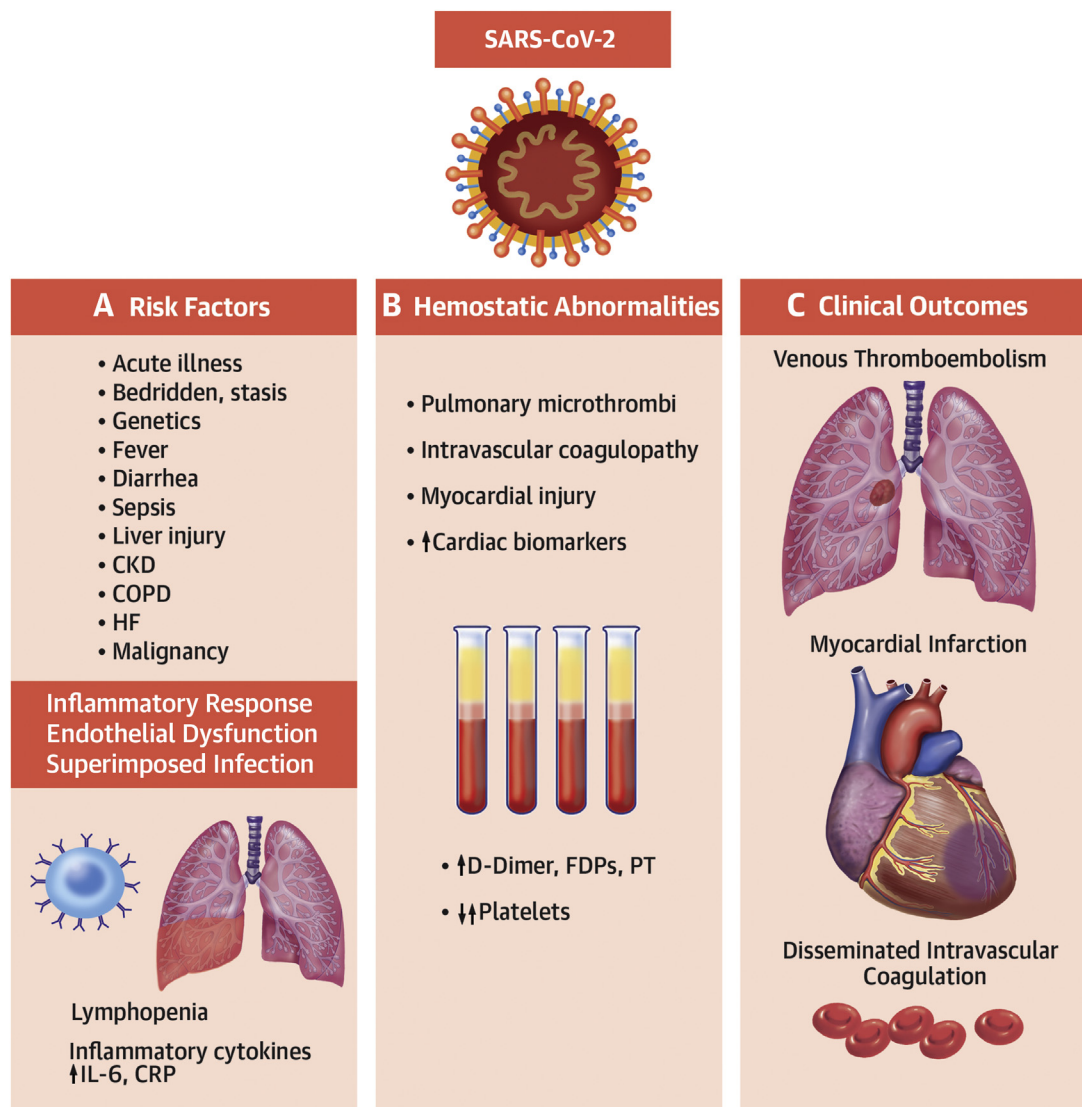
COVID-19 = coronavirus disease-2019; DIC = disseminated intravascular coagulation; hs-TnI = high-sensitivity troponin I; other abbreviations as in Table 1.

reduced risk) for thrombotic events, or for thrombocytopenia in prior studies of non-COVID-19 populations. For example, bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor, and is under investigational use for COVID-19, is associated with increased risk for adverse cardiovascular events, including MI, cerebrovascular accidents, and VTE (40,41). Alternatively, fingolimod, an immunomodulating agent being tried for COVID-19, may reduce reperfusion injury and improve outcomes in patients suffering from acute ischemic stroke (42). Hydroxychloroquine, recently receiving Emergency Use Authorization from the U.S. Food and Drug Administration for treatment of COVID-19, may potentially exert antithrombotic properties, especially against antiphospholipid antibodies (43).

COVID-19 INVESTIGATIONAL THERAPIES AND ANTIPLATELET AGENTS. Scientists are studying a number of agents for COVID-19 treatment that may have interactions with oral antiplatelet agents. Table 3 presents potential drug interactions between investigational drugs for COVID-19 and commonly

administered oral antiplatelet agents. Lopinavir/ritonavir is a protease inhibitor and inhibits CYP3A4 metabolism. Although the active metabolite for clopidogrel is mostly formed by CYP2C19, inhibition of CYP3A4 may also lead to reduction in effective dosage of clopidogrel. In contrast, inhibition of CYP3A4 may increase effects of ticagrelor. Therefore, the concomitant use of these agents along with lopinavir/ritonavir should be cautioned. Although limited clinical data exist, use of P2Y₁₂ platelet function testing to guide the use of clopidogrel or ticagrelor in this setting might be considered. An alternative, in the absence of contraindications, is to use prasugrel, which is not prone to these interactions (44-47). Remdesivir, a nucleotide-analog inhibitor of RNA-dependent RNA polymerase, is reportedly an inducer of CYP3A4; however, dose adjustments for oral antiplatelet agents are currently not recommended. Of note, there are no known major drug-drug interactions between investigational COVID-19 therapies and parenteral antiplatelet agents such as cangrelor and glycoprotein IIb/IIIa inhibitors.

CENTRAL ILLUSTRATION Postulated Mechanisms of Coagulopathy and Pathogenesis of Thrombosis in COVID-19



Bikdeli, B. et al. *J Am Coll Cardiol.* 2020;75(23):2950-73.

(A) Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection activates an inflammatory response, leading to release of inflammatory mediators. Endothelial and hemostatic activation ensues, with increase in von Willebrand factor and increased tissue factor. The inflammatory response to severe infection is marked by lymphopenia and thrombocytopenia. Liver injury may lead to decreased coagulation and antithrombin formation. **(B)** Coronavirus disease-2019 (COVID-19) may be associated with hemostatic derangement and elevated troponin levels. **(C)** Increased prothrombotic state results in venous thromboembolism, myocardial infarction, or in case of further hemostatic derangement, disseminated intravascular coagulation. CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FDP = fibrin degradation product; HF = heart failure; IL = interleukin; LDH = lactate dehydrogenase; PT = prothrombin time.

COVID-19 INVESTIGATIONAL THERAPIES AND ANTICOAGULANTS. Table 4 summarizes interactions between investigational drugs for COVID-19 and commonly administered oral anticoagulants. Lopinavir/ritonavir has the potential to also affect choice

and dosage of a number of anticoagulants. For example, vitamin K antagonists, apixaban, and betrixaban may all require dose adjustment, while edoxaban and rivaroxaban should not be coadministered with lopinavir/ritonavir. Tocilizumab, an IL-6

Investigational COVID-19 Therapy	Mechanism of Action of COVID-19 Therapy	P2Y ₁₂ Platelet Receptor Inhibitors			Phosphodiesterase III Inhibitor
		Clopidogrel	Prasugrel	Ticagrelor	Cilostazol
Lopinavir/ritonavir	Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A4 metabolism increasing lopinavir levels.	CYP 3A4 Inhibition (minor pathway): Reduction in clopidogrel active metabolite. Do not coadminister or if available utilize P2Y ₁₂ platelet function assays for monitoring.† With limited clinical data, prasugrel may be considered as alternative, if no contraindications.	CYP3A4 Inhibition: Decreased active metabolite but maintained platelet inhibition. Can administer with caution.	CYP3A4 Inhibition: Increased effects of ticagrelor. Do not coadminister or if available utilize P2Y ₁₂ monitoring or consider dose-reduced ticagrelor.*	CYP3A4 Inhibition: Recommend decreasing dose to maximum of 50 mg twice a day.
Remdesivir	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases.	Reported inducer of CYP3A4 (minor pathway): no dose adjustment recommended.	Reported inducer of CYP3A4 (major pathway): no dose adjustment recommended.	Reported inducer of CYP3A4 (major pathway): no dose adjustment recommended.	Reported inducer of CYP3A4 (major pathway): no dose adjustment recommended.
Tocilizumab	Inhibits IL-6 receptor: may potentially mitigate cytokine release syndrome symptoms in severely ill patients.	Reported increase in expression of 2C19 (major pathway) and 1A2, 2B6, and 3A4 (minor pathways): no dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway) and 2C9 and 2C19 (minor pathway): no dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): no dose adjustment recommended.
Sarilumab	Binds specifically to both soluble and membrane-bound IL-6Rs (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signaling: may potentially mitigate cytokine release syndrome symptoms in severely ill patients.	Reported increase in expression of 3A4 (minor pathways): no dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): no dose adjustment recommended.	Reported increase in expression of CYP3A4 (major pathway): no dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): no dose adjustment recommended.

Other drugs being studied to treat COVID-19 include azithromycin, bevacizumab, chloroquine/hydroxychloroquine, eculizumab, fingolimod, interferon, losartan, methylprednisolone, pirfenidone, and ribavirin. Drug-drug interactions between these medications and antiplatelet agents have yet to be identified. *Cangrelor, aspirin, dipyridamole, and glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, abciximab) are not known to interact with investigational therapies for COVID-19. †Monitoring of P2Y₁₂ levels can be assessed through the VerifyNow assay, or others. Evaluation of effect of protease inhibitors on P2Y₁₂ inhibitors has not been extensively studied. Dose reduction recommendations for P2Y₁₂ inhibitors or P2Y₁₂ platelet function assay monitoring is not commonly practiced.

IL = interleukin; other abbreviations as in [Table 1](#).

inhibitor, increases expression of CYP3A4; however, no anticoagulant dose adjustments are currently recommended with concomitant use of tocilizumab at this time. There are no known major drug-drug interactions between investigational COVID-19 therapies and parenteral anticoagulants. Although the focus of the current manuscript is primarily related to VTE and ACS, the guidance provided for antithrombotic considerations is broadly relevant across other clinical indications.

COVID-19 AND VTE

RISK STRATIFICATION AND IN-HOSPITAL PROPHYLAXIS. Hospitalized patients with acute medical illness, including infections such as pneumonia, are at increased risk of VTE (48,49). Prophylactic anticoagulation reduces the risk of VTE in acutely ill hospitalized medical patients (50–52), and appropriate use of VTE prophylaxis is covered in clinical practice guidelines (49,53,54). Multiple risk stratification tools are available for VTE risk assessment

in this setting (e.g., the Caprini score, IMPROVE [International Medical Prevention Registry on Venous Thromboembolism] model, and Padua model) (55–60).

The choice of specific risk assessment model may vary across health system. However, similar to other acutely ill medical patients, VTE risk stratification for hospitalized patients with COVID-19 should be undertaken. A recent study from China, using the Padua model, reported that 40% of hospitalized patients with COVID-19 were at high risk of VTE. The study did not provide data about the use of VTE prophylaxis, or the incident VTE events (61). Hospitalized patients with COVID-19 who have respiratory failure or comorbidities (e.g., active cancer, heart failure) (62), patients who are bedridden, and those requiring intensive care should receive pharmacological VTE prophylaxis, unless there are contraindications. The choice of agents and dosing should be based on available guideline recommendations (53,54,63). The World Health Organization interim guidance statement recommends prophylactic daily low-

TABLE 4 Potential Drug Interactions Between Anticoagulants* and Investigational Therapies for COVID-19

Investigational COVID-19 Therapies	Vitamin K Antagonists	Dabigatran	Apixaban	Betrixaban	Edoxaban	Rivaroxaban
Lopinavir/ritonavir	CYP2C9 induction: May decrease plasma concentration. Adjust dose based on INR.	P-gp inhibition: May increase plasma concentration. No dose adjustment recommended.	CYP3A4 and P-gp inhibition: Administer at 50% of dose (do not administer if initial dose is 2.5 mg twice daily).†	P-gp and ABCB1 inhibition: Decrease dose to 80 mg once followed by 40 mg once daily.	P-gp inhibition: Do not coadminister.	CYP3A4 and P-gp inhibition: Do not coadminister.
Tocilizumab	—	—	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.	—	—	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.
Interferon‡,	Unknown mechanism: Decreased dose may be needed.	—	—	—	—	—
Ribavirin	Mechanism not well known: Possibly decreased absorption of warfarin in the presence of ribavirin (156); increased dose may be needed.	—	—	—	—	—
Methylprednisolone	Unknown mechanism: Decreased dose may be needed.	—	—	—	—	—
Sarilumab§	—	—	Reported increase in expression of CYP3A4 (major pathway): No dose adjustment recommended.	—	—	Reported increase in expression of CYP3A4 (major pathway): No dose adjustment recommended.
Azithromycin	Unknown mechanism: Decreased dose may be needed.	P-gp inhibition: May increase plasma concentration. No dose adjustment recommended.	—	P-gp inhibition: Decrease dose to 80 mg once followed by 40 mg daily.	P-gp inhibition: VTE: Limit dose to 30 mg daily. Nonvalvular AF: No dose recommendation.	—
Hydroxychloroquine and chloroquine	—	—	—	—	—	—

Other drugs being studied to treat COVID-19 include bevacizumab, chloroquine/hydroxychloroquine, eculizumab, fingolimod, losartan, and pifeneidone. Drug-drug interactions between these medications and oral anticoagulants have yet to be identified. Bevacizumab has been reported to cause deep vein thrombosis (9%), arterial thrombosis (5%), and pulmonary embolism (1%). It is also reported to cause thrombocytopenia (58%). *Parenteral anticoagulants (including unfractionated or low-molecular-weight heparins, bivalirudin, argatroban, and fondaparinux) are non-CYP-metabolized and do not interact with any of the investigational agents. †These recommendations are based on the U.S. package insert. The Canadian package insert considers the combination of these agents to be contraindicated. ‡Interferon has been reported to cause pulmonary embolism (<5%), thrombosis (<5%), decreased platelet count (1%-15% with Alfa-2b formulation), and ischemic stroke (<5%). §Sarilumab has been reported to cause decreased platelet count, with decreases to <100,000 mm³ in 1% and 0.7% of patients on 200-mg and 150-mg doses, respectively. ||Reported with interferon alpha.

CYP = cytochrome P system; INR = international normalized ratio; P-gp = P-glycoprotein; other abbreviations as in Table 1.

molecular-weight heparins (LMWHs), or twice daily subcutaneous unfractionated heparin (UFH) (64). If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis (intermittent pneumatic compression) should be considered in immobilized patients (64,65). Missed doses of pharmacologic VTE prophylaxis are common and are likely associated with worse outcomes (66). Therefore, every effort should be made to ensure that patients receive all scheduled doses of pharmacologic VTE prophylaxis. In this regard, once daily dosing regimen of LMWHs may be advantageous over UFH to reduce personal protective equipment (PPE) use and exposure of health care workers.

Consideration for risk of VTE in pregnant patients with COVID-19 deserves further attention. The risk of VTE is increased during pregnancy and the postpartum period (67,68). Although limited data are available,

pregnant women admitted to hospital with COVID-19 infection are likely to be at an increased risk of VTE. It is reasonable to assess the risk of VTE and to consider pharmacological thromboprophylaxis, especially if they have other VTE risk factors. Weight-adjusted prophylactic dosing of anticoagulation is an interesting topic that requires additional investigation (69).

EXTENDED (POST-DISCHARGE) VTE PROPHYLAXIS. After hospital discharge from acute medical illness, extended prophylaxis with LMWH (70) or direct oral anticoagulants (DOACs) (71-74) can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding (75,76). Although no data specific to COVID-19 exist, it is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic risk, followed by consideration of extended prophylaxis (for up to 45 days) for patients

with elevated risk of VTE (e.g., reduced mobility, comorbidities such as active cancer, and [according to some authors in the writing group] elevated D-dimer >2 times the upper limit of normal) who have low risk of bleeding (74,77,78).

The role of thromboprophylaxis for quarantined patients with mild COVID-19 but significant comorbidities, or for patients without COVID-19 who are less active because of quarantine is uncertain. These patients should be advised to stay active at home. In the absence of high-quality data, pharmacological prophylaxis should be reserved for those patients at highest risk, including those with limited mobility and history of prior VTE or active malignancy.

DIAGNOSIS OF VTE IN PATIENTS WITH COVID-19. As described previously, elevated D-dimer levels represent a common finding in patients with COVID-19 (23), and do not currently warrant routine investigation for acute VTE in absence of clinical manifestations or other supporting information. However, the index of suspicion for VTE should be high in the case of typical deep vein thrombosis (DVT) symptoms, hypoxemia disproportionate to known respiratory pathologies, or acute unexplained right ventricular dysfunction.

A diagnostic challenge arises among patients with COVID-19, as imaging studies used to diagnose DVT or PE may not be pursued given risk of transmitting infection to other patients or health care workers and potentially due to patient instability. Moreover, imaging studies may be challenging in the setting of patients with severe ARDS who require prone positioning. Investigation for PE is not feasible due to critical illness and prone position. Lower extremity ultrasound is also limited due to patient positioning. However, it may be argued that the prognosis of patients with ARDS requiring prone position is so grave that investigation for underlying VTE may not alter the course. A potential option may be to consider echocardiography to assess for signs of potentially worsening right ventricular dysfunction and, in rare circumstances, clot in transit (79).

ROLE FOR EMPIRIC THERAPEUTIC ANTICOAGULATION WITHOUT A DIAGNOSIS OF VTE. In view of the hemostatic derangements discussed previously and observations from prior viral illnesses (80), some clinicians use intermediate- or full-dose (therapeutic) parenteral anticoagulation (rather than prophylactic dosing) for routine care of patients with COVID-19 (81), hypothesizing that it may confer benefit to prevent microvascular thrombosis. However, the existing data are very limited, and are primarily based on a subgroup analysis (n = 97) from

a single retrospective study with limited control for potential confounders (82). A single-center study from China suggested that D-dimer levels >1,500 ng/ml has a sensitivity of 85.0% and specificity of 88.5% for detecting VTE events. However, the study was limited by small sample size and lack of validation. At this moment, while practitioners use a variety of prophylactic, intermediate, or therapeutic doses of anticoagulants in patients, the optimal dosing in patients with severe COVID-19 remains unknown and warrants further prospective investigation. The majority of panel members consider prophylactic anticoagulation, although a minority consider an intermediate or therapeutic dose to be reasonable.

INCIDENT VTE. Few published studies have commented on incident VTE in patients with COVID-19 (83,84). In a retrospective study from China, among 81 patients with severe COVID-19 admitted to ICU, 20 (25%) developed incident VTE. Of note, none of the patients had received VTE prophylaxis (85). In a study of 184 patients with severe COVID-19 from 3 academic medical centers in the Netherlands, the authors reported that 31% (95% confidence interval: 20% to 41%) of patients developed incident VTE. All patients received pharmacological prophylaxis, although underdosing was observed in 2 of the 3 participating centers (81). These findings require validation in additional studies.

It is possible but unknown that VTE remains underdiagnosed in patients with severe COVID-19. This is important, as ARDS in patients with COVID-19 is itself a potential etiology for hypoxic pulmonary vasoconstriction, pulmonary hypertension, and right ventricular failure. Further insult from PE may be unrecoverable.

MEDICAL THERAPY FOR VTE. Therapeutic anticoagulation is the mainstay of VTE treatment (49,86,87). Selection of an agent requires consideration of comorbidities such as renal or hepatic dysfunction, thrombocytopenia, and gastrointestinal tract function, and the agent will likely change across the hospital course to the time of discharge. In many ill inpatients with VTE, parenteral anticoagulation (e.g., UFH) is preferred as it may be temporarily withheld and has no known drug-drug interactions with investigational COVID-19 therapies. However, concerns with UFH include the time to achieve therapeutic aPTT and increased health care worker exposure for frequent blood draws. Therefore, LMWHs may be preferred in patients unlikely to need procedures. The benefit of oral anticoagulation with DOACs includes the lack of need for monitoring,

FIGURE 2 Risk Stratification of ACS and Venous Thromboembolism With COVID-19

	LOW-RISK COVID-19	HIGH-RISK COVID-19 [†]
HIGH-RISK ACS OR VTE*	For ACS: • GDMT per ACS algorithm • Urgent/emergent angiography and intervention • Consider need and safety of hemodynamic support and monitoring For VTE: • Anticoagulant therapy • If recurrent symptoms or deterioration, consider systemic thrombolysis or potentially catheter-directed therapy as an alternative • Consider need and safety of hemodynamic support and monitoring[‡]	For ACS: • GDMT per ACS algorithm • Consider emergent TTE • Urgent/emergent angiography and intervention vs. systemic fibrinolysis • Consider need and safety of hemodynamic support and monitoring in select patients For VTE: • Anticoagulant therapy • Consider systemic fibrinolysis • Catheter-directed or surgical therapies in case not suitable for systemic fibrinolysis • Consider need and safety of hemodynamic support and monitoring
LOW/INTERMEDIATE RISK ACS OR VTE	For ACS: • GDMT per ACS algorithm • Angiography and intervention only if recurrent/persistent symptoms or decompensation For VTE: • Anticoagulant therapy • Catheter-directed or surgical therapies only if recurrent/persistent symptoms or decompensation	For ACS: • GDMT per ACS algorithm • Other therapies reserved for select cases such as those with significant recurrent/persistent symptoms or decompensation For VTE: • Anticoagulant therapy • Other therapies reserved for select cases such as those with significant recurrent/persistent symptoms or decompensation

Proposed algorithm to risk stratify patients based on severity of acute coronary syndromes (ACS), VTE, and COVID-19 presentations. *High-risk ACS refers to patients with hemodynamic instability, left ventricular dysfunction or focal wall motion abnormality, or worsening or refractory symptoms. High-risk VTE refers to patients with pulmonary embolism who are hemodynamically unstable, evidence of right ventricular dysfunction or dilatation, or worsening of refractory symptoms. [†]High-risk COVID-19 refers to patients with high suspicion for or confirmed COVID-19, including individuals with high viral load, symptomatic with coughing or sneezing or other respiratory symptoms, and at risk for requiring intubation and aerosolizing viral particles. [‡]Hemodynamic support includes intra-aortic balloon pump, percutaneous ventricular assist device, and extracorporeal membrane oxygenation. Hemodynamic monitoring refers to Swan-Ganz catheter for invasive hemodynamic assessment. For potential drug-drug interactions, please refer to [Tables 3 and 4](#). GDMT = guideline-directed medical therapy; TTE = transthoracic echocardiogram; other abbreviations as in [Figure 1](#).

facilitation of discharge planning, and outpatient management. The potential risk (especially in the setting of organ dysfunction) may include clinical deterioration and lack of timely availability of effective reversal agents at some centers. For patients who are ready for discharge, DOACs or LMWH would be preferred to limit contact of patients with health care

services required for INR monitoring for vitamin K antagonists (VKAs).

COVID-19 AND INTERVENTIONAL THERAPIES FOR VTE. PE response teams allow for multidisciplinary care for patients intermediate and high-risk with VTE ([49,88-90](#)). During the COVID-19 pandemic,

TABLE 5 Areas Requiring Further Investigation

Area	Comment
Patients with mild COVID-19 (outpatient)	
To determine the optimal method for risk assessment for outpatients with mild COVID-19 who are at risk of VTE	The options include the Caprini model, the IMPROVE model, and the Padua model, and others for assessment of the risk of VTE. These should be weighed against the risk of bleeding.
To determine the incidence ACS in population-based studies	
Patients with moderate or severe COVID-19 without DIC (hospitalized)	
To determine the incidence and predictors of VTE among patients with COVID-19 who present with respiratory insufficiency and/or hemodynamic instability; these include lower extremity DVTs, central line-associated DVT in upper or lower extremities, and also PE	Prospective multicenter cohort (observational) data are needed, and these protocols should not interfere, and could run in parallel with, interventional trials that are planned or already underway.
To develop an appropriate algorithm for the diagnosis of incident VTE in patients with COVID-19	D-dimer is elevated in many inpatients with COVID-19, although negative value may still be helpful. In some cases of COVID-19 with worsening hypoxemia, CTPA may be considered instead of noncontrast CT (which only assesses the pulmonary parenchyma). Unresolved issues include diagnostic tests for critically ill patients, including those in prone position, with limited options for CTPA or ultrasonography.
To determine the optimal total duration of prophylactic anticoagulation	Ultrasound screening in select patients may need to be studied.
To determine the optimal dose of prophylactic anticoagulation in specific populations (e.g., those with obesity or advanced kidney disease)	Weight-adjusted prophylactic dosing for patients with obesity, or dosing based on creatinine clearance in patients with kidney disease require further investigation.
To determine if LMWH constitutes the preferred method of pharmacological prophylaxis	
To determine the optimal method for risk stratification and VTE prophylaxis after hospital discharge	The options include the Caprini model, the IMPROVE model, and the Padua model, and others for assessment of the risk of VTE. These should be weighed against the risk of bleeding.
To determine if routine use of higher doses of anticoagulants (i.e., higher than prophylactic doses as described in the international guidelines) confer net benefit	An important question would be whether monitoring anti-Xa activity would be preferable over aPTT.
To determine the incidence and predictors of type 1 acute myocardial infarction in patients with COVID-19, and to compare their process measures and outcomes with noninfected patients	
To determine the potential role of agents including danaparoid, fondaparinux, and sulodexide in select patients with moderate/severe COVID-19	
Patients with moderate or severe COVID-19 and suspected or confirmed DIC (hospitalized)	
To determine if routine use of pharmacological VTE prophylaxis or low- or standard-dose anticoagulation with UFH or LMWH is warranted (if no overt bleeding)	A relevant question is whether prophylactic, or other, dose anticoagulation should be given to patients with DIC who do not have bleeding, even without immobility.
To determine if additional clinical characteristics and variables in the setting of DIC (e.g., lymphopenia) should be considered to help risk-stratify and assess prognosis	
To determine utility of other interventions including antithrombin concentrates	
Patients without COVID-19 but with comorbidities, and homebound during the pandemic	
To determine the optimal method of screening and risk stratification for consideration of VTE prophylaxis	The options include the Caprini model, the IMPROVE model, and the Padua model, and others for assessment of the risk of VTE. These should be weighed against the risk of bleeding.
To conduct population-level studies to determine the trends in incidence and outcomes of thrombotic disease in the period of reduced office visits	Although telemedicine is reasonable to control the COVID-19 pandemic, potential adverse consequences on noncommunicable disease, including thrombotic disease deserve investigation.

CTPA = computed tomography pulmonary angiography; IMPROVE = International Medical Prevention Registry on Venous Thromboembolism; LMWH = low-molecular weight heparin; UFH = unfractionated heparin; other abbreviations as in Table 1.

similar to other consultative services, PE response teams should transition from in-person inpatient evaluation to e-consults using phone calls or telemedicine systems whenever feasible. It is important to note that there are minimal available data demonstrating lower mortality from routine use of advanced VTE therapies (91,92). Therefore, the use of catheter-directed therapies during the current

outbreak should be limited to the most critical situations. Indiscriminate use of inferior vena cava filters should be avoided (93). Recurrent PE despite optimal anticoagulation, or clinically significant VTE in the setting of absolute contraindications to anticoagulation, would be among the few scenarios in which placement of an inferior vena cava filter may be considered (11). Even after inferior vena cava

filter placement, anticoagulation should be resumed as soon as feasible, and this is often done with gradually increasing doses and close observation for bleeding. With regard to reperfusion strategies for acute PE, current guideline recommendations should be followed. Intermediate-risk hemodynamically stable patients (intermediate-low risk, or intermediate-high risk PE according to European Society of Cardiology [ESC] classification, submassive PE according to prior classifications) (49,87,91,94) should be managed initially with anticoagulation and close monitoring. In case of further deterioration, rescue systemic fibrinolysis should be considered, with catheter-directed options as an alternative. For patients with overt hemodynamic instability (high-risk PE according to the ESC classification, massive PE according to prior classifications) (49,87,91,94) systemic fibrinolysis is indicated, with catheter-based therapies reserved for scenarios that are not suitable for systemic fibrinolysis. If infection control settings are equal, bedside initiation of extracorporeal membrane oxygenation (ECMO) is preferred in cases with known COVID-19 positivity or uncertain status, rather than support strategies requiring the use of a catheterization laboratory or an operating room (95). **Figure 2** presents a potential algorithm for treatments based on risk due to VTE and COVID-19 severity.

The vast majority of patients with symptomatic acute DVT, should be managed with anticoagulation, with home treatment whenever possible. The few that may require acute endovascular techniques (either local fibrinolysis or embolectomy) include those with phlegmasia, or truly refractory symptoms (96).

COVID-19 AND ACS

COVID-19 AND INCIDENT ACS. Myocardial injury in COVID-19, as evidenced by elevated cardiac troponin levels or electrocardiographic and echocardiographic abnormalities, is associated with severe disease (5,36). Furthermore, higher troponin levels are associated with severe COVID-19 (5,36). However, not all such events are due to thrombotic ACS. Although anecdotal cases of patients with COVID-19 presenting with ACS due to plaque rupture have been described (type 1 MI), currently no such cases have been published. Such cases have been also previously described with influenza or other viral illnesses, and have been attributed to a combination of SIRS as

well as localized vascular or plaque inflammation (10,97,98).

COVID-19 AND ANTITHROMBOTIC THERAPY FOR ACS. In presentations consistent with ACS due to plaque rupture (i.e., type 1 MI) (39), dual antiplatelet therapy and full-dose anticoagulation per the American College of Cardiology (ACC)/American Heart Association (AHA) and ESC guidelines should be administered, unless there are contraindications (99-102). In patients with perceived elevated bleeding risk, regimens with less potent antiplatelet agents, such as with clopidogrel, should be considered, given that hemorrhagic complications are not uncommon. Special attention should be also given to drug-drug interactions between antiplatelet agents or anticoagulants and COVID-19 investigational therapies. Parenteral antithrombotic agents, in general, do not have known major interactions with the COVID-19 investigational therapies (Tables 4 and 5).

COVID-19 AND INTERVENTIONAL THERAPIES FOR ACS. The ACC and Society for Cardiovascular Angiography and Interventions recently provided guidance regarding catheterization laboratory procedures in the current climate (84,103). The recommendations note that it is reasonable to continue optimal medical therapy and defer nonurgent cardiac procedures, in order to preserve PPE, as well as hospital resources including inpatient and ICU beds, and minimize exposure for patients and health care workers alike.

Prior to intervention, efforts should be made to distinguish nonspecific myocardial injury, myocarditis, and true plaque rupture presentations (103). A low threshold to use transthoracic echocardiography to identify wall motion abnormalities should be considered prior to catheterization laboratory activation. Even in case of ST-segment elevation MI (STEMI), in which primary percutaneous coronary intervention (PCI) reduces mortality and reinfarction, risk of COVID-19 transmission from patients to health care workers, or vice versa (asymptomatic vectors) must be considered. In light of this, individual centers in China and elsewhere have developed adjusted ACS protocols, which call for consideration of fibrinolytic therapy in selected patients with STEMI (104). Centers in which timely PCI is less feasible may be more likely to adopt such a strategy. However, given that presentations of COVID-19 can mimic ACS (e.g., in the setting of myocarditis), fibrinolytic therapy must be used with caution.

CRITICAL ILLNESS WITH SARS-CoV-2 AND MANAGEMENT OF ANTITHROMBOTIC AGENTS

The risk of VTE, which is increased in critically ill patients, is likely even higher in those with SARS-CoV-2 and critical illness. Aside from hemostatic derangements, immobility (a systemic inflammatory state), mechanical ventilation, and central venous catheters contribute to VTE risk within the ICU (105-107), nutritional deficiencies and liver dysfunction may also interfere with the production of coagulation factors (108). Alterations in pharmacokinetics in critically ill patients may necessitate anticoagulation dose adjustment (109), owing to factors relating to absorption, metabolism, and renal (or hepatic) elimination of these drugs in the setting of potential organ dysfunction.

Parenteral anticoagulation is recommended in most cases in which anticoagulant therapy is needed for known thrombotic disease. UFH can be used in the setting of anticipated procedures, or in patients with deteriorating renal function. If no urgent procedures are anticipated, LMWHs are a reasonable alternative (54). In patients requiring ECMO, anticoagulation is frequently required to maintain circuit patency, especially at lower flow settings. Rates of complications are unknown in patients with SARS-CoV-2, but rates of thrombosis and hemorrhage may be as high as 53% and 16%, respectively, in other populations with respiratory failure (110). The limited outcome data that are available for ECMO in patients with SARS-CoV-2 suggest poor outcomes, with 5 of 6 patients dying in one series and 3 of 3 in another (20,26). There are currently insufficient data to recommend anticoagulation targets for COVID-19 patients requiring ECMO (111).

ADDITIONAL CONSIDERATIONS. As previously mentioned, severe COVID-19 may predispose to DIC, with such patients experiencing particularly poor outcomes (7). Supportive care and addressing the underlying hypoxia or coinfection are appropriate (29). There are insufficient data to recommend transfusion thresholds that differ from those recommended for other critically ill patients. If invasive procedures are planned, prophylactic transfusion of platelets, fresh frozen plasma, fibrinogen, and prothrombin complex concentrate may be considered (29). Last, patients requiring targeted temperature management may exhibit prolongations of both PT and aPTT without evidence of bleeding diathesis (112). Therefore, correction of coagulopathy in

unselected patients without overt bleeding is not currently recommended.

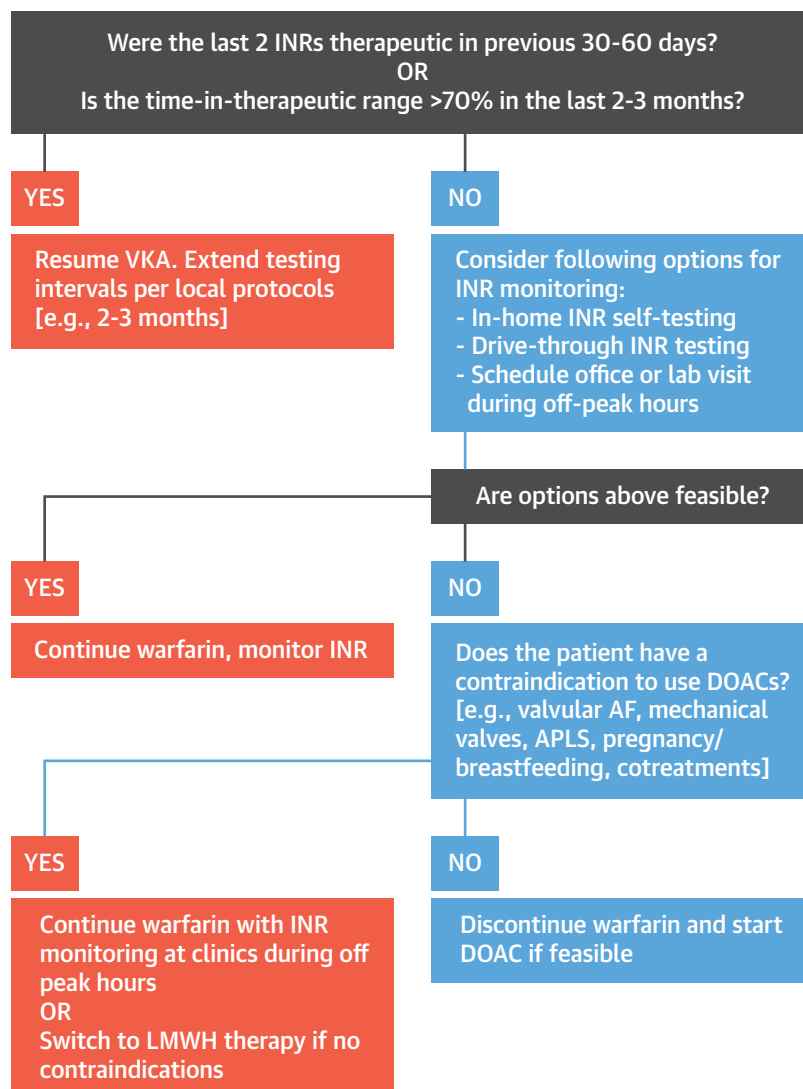
DIC AND CONSIDERATIONS FOR ANTITHROMBOTIC THERAPY

DIAGNOSIS AND MANAGEMENT. DIC is common in many patients with critical illness (113), including those with COVID-19 (7,114). It is uncertain whether COVID-19 has unique characteristics to cause direct activation of coagulation. The diagnosis of DIC is best established using the ISTH DIC score calculator (29). Regular laboratory monitoring of platelet count, PT, D-dimer, and fibrinogen in patients with COVID-19 is important to diagnose worsening coagulopathy. The first step in management of DIC is to identify and treat the underlying condition(s). Bacterial superinfections should be treated aggressively.

In addition to preventing VTE, LMWH prophylaxis may decrease thrombin generation and modify the course of DIC. Preliminary results, albeit with small number of events and limited adjustment, may suggest a favorable response from LMWH prophylaxis (82,114). Long-acting antiplatelet agents should be generally discontinued in most patients with DIC, unless required (e.g., recent ACS or stent implantation). For patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g., PCI within the past 3 months or recent MI) and with suspected or confirmed DIC without overt bleeding, in the absence of evidence decisions for antiplatelet therapy need to be individualized. In general, it is reasonable to continue dual antiplatelet therapy if platelet count is $\geq 50,000$, reduce to single antiplatelet therapy if platelet count is $\geq 25,000$ and $< 50,000$, and discontinue if platelets $< 25,000$. However, these guidelines may be revised upward or downward depending on the individualized relative risk of stent-related thrombotic complications versus bleeding. Recovery from DIC is dependent on endogenous fibrinolysis breaking down the disseminated thrombi.

MANAGEMENT OF BLEEDING. Clinically overt bleeding is uncommon in the setting of COVID-19. However, when bleeding occurs in COVID-19-associated DIC, blood products support should be considered as per septic coagulopathy (115). In summary, the mainstay of blood products transfusion are as follows: platelet concentrate to maintain platelet count $> 50 \times 10^9/l$ in DIC patients with active bleeding or $> 20 \times 10^9/l$ in those with a high risk of bleeding or

FIGURE 3 Considerations for Switching VKAs Because of Limitations With Access to Care or Health Care Resources During the COVID-19 Pandemic



If switching the anticoagulant agent is planned, care should be taken to be sure that the patient is able to afford and receive the alternative therapy. Contraindications to direct oral anticoagulant (DOACs) include mechanical heart valves, valvular atrial fibrillation (AF), pregnancy or breastfeeding, antiphospholipid syndrome (APLS), and coadministration of medications including strong CYP3A and P-glycoprotein inhibitors (-azole medications), HIV protease inhibitors (dependent on DOAC, may just require dose reduction), CYP3A4 inducers (antiepileptics), St. John's wort, rifampin, etc. Patient education about stable dietary habits while receiving VKAs is also important. If DOACs are not available or approved by insurance, low-molecular-weight heparin (LMWHs) could be used in select cases. COVID-19 = coronavirus disease-2019; INR = international normalized ratio; VKA= vitamin K antagonist.

requiring invasive procedures, fresh frozen plasma (15 to 25 ml/kg) in patients with active bleeding with either prolonged PT or aPTT ratios (>1.5 times normal) or decreased fibrinogen (<1.5 g/l), fibrinogen concentrate, or cryoprecipitate to patients with

persisting severe hypofibrinogenemia (<1.5 g/l), and prothrombin complex concentrate if fresh frozen plasma transfusion is not possible. With the existing data, tranexamic acid should not be used routinely in COVID-19-associated DIC.

TABLE 6 Summary of Consensus Recommendation on Antithrombotic Therapy During the COVID-19 Pandemic

Patients with mild COVID-19 (outpatient)

For outpatients with mild COVID-19, increased mobility should be encouraged. Although indiscriminate use of pharmacological VTE prophylaxis should not be pursued, assessment for the risk of VTE and of bleeding is reasonable. Pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk VTE, without high bleeding risk.*

There is no known risk of developing severe COVID-19 due to taking antithrombotic agents (i.e., antiplatelet agents or anticoagulants). If patients have been taking antithrombotic agents for prior known thrombotic disease, they should continue their antithrombotic agents as recommended.

For outpatients on vitamin K antagonists who do not have recent stable INRs, and are unable to undergo home or drive-through INR testing, it is reasonable to transition the treatment DOACs if there are no contraindications and no problems with drug availability and affordability. If DOACs are not approved or available, LMWH can be considered as alternative.*

Patients with moderate or severe COVID-19 without DIC (hospitalized)

Hospitalized patients with COVID-19 should undergo risk stratification for VTE prophylaxis.

For hospitalized patients with COVID-19 and not in DIC, prophylactic doses of anticoagulation should be administered to prevent VTE.*†‡ If pharmacological prophylaxis is contraindicated, it is reasonable to consider intermittent pneumatic compression.

For hospitalized patients with COVID-19 and not in DIC, there are insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*§

Routine screening for VTE (e.g., bilateral lower extremity ultrasound) for hospitalized patients with COVID-19 with elevated D-dimer (>1,500 ng/ml) cannot be recommended at this point.||

Patients with moderate or severe COVID-19 and suspected or confirmed DIC (hospitalized)

For patients with moderate or severe COVID-19 and in DIC but without overt bleeding, prophylactic anticoagulation should be administered.*†¶

For hospitalized patients with COVID-19 with suspected or confirmed DIC, but no overt bleeding, there are insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*

For patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation, who develop suspected or confirmed DIC without overt bleeding, it is reasonable to consider the indication for anticoagulation and weigh with risk of bleeding when making clinical decisions regarding dose adjustments or discontinuation. The majority of authors of this paper recommended reducing the intensity of anticoagulation in this clinical circumstance, unless the risk of thrombosis is considered to be exceedingly high.#

For patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g., percutaneous coronary intervention within the past 3 months or recent myocardial infarction) and with suspected or confirmed DIC without overt bleeding, in the absence of evidence, decisions for antiplatelet therapy need to be individualized. In general, it is reasonable to continue dual antiplatelet therapy if platelet count is >50,000, reduce to single antiplatelet therapy if platelet count is >25,000 and <50,000, and discontinue if platelet count is <25,000. However, these guidelines may be revised upward or downward depending on the individualized relative risk of thrombotic complications vs. bleeding.

For patients who were admitted and are now being discharged for COVID-19, routine screening for VTE risk is reasonable for consideration of pharmacological prophylaxis for up to 45 days post-discharge. Pharmacological prophylaxis should be considered if there is elevated risk for thrombotic events, without high bleeding risk.**

Ambulation and physical activity should be encouraged.

Patients with COVID-19 presenting with ACS

For presentations concerning for STEMI and COVID-19, clinicians should weigh the risks and severity of STEMI presentation with that of potential COVID-19 severity in the patient, as well as risk of COVID-19 to the individual clinicians and to the health care system at large. Decisions for primary percutaneous coronary intervention or fibrinolytic therapy should be informed by this assessment.*

Patients without COVID-19 who have previously known thrombotic disease

There is no known risk of developing severe COVID-19 due to taking antithrombotic agents. Patients should continue their antithrombotic agents as recommended.

To minimize risks associated with health care worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.

Patients without COVID-19 who develop new thrombotic disease

To minimize risks associated with health care worker and patient in-person interactions, in-home treatment or early discharge should be prioritized.

To minimize risks associated with health care worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.

Patients without COVID-19 but with comorbid conditions (e.g., prior VTE, active cancer, major cardiopulmonary disease), who are homebound during the pandemic

Recommendations include increased mobility, and risk assessment for the risk of VTE and risk of bleeding is reasonable. Administration of pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk for thrombotic events, without high bleeding risk.

*Indicates recommendations as reached by consensus of at least 66% of authors determined via the Delphi method. †Although high-quality data are lacking, some panel members (55%) considered it reasonable to use intermittent pneumatic compression in patients with severe COVID-19, in addition to pharmacological prophylaxis. Specific areas of concern included limited data on use in the prone position as well as potential high incidence of pre-existing asymptomatic DVT. ‡If VTE prophylaxis is considered, enoxaparin 40 mg daily or similar LMWH regimen (e.g., dalteparin 5,000 U daily) can be administered. Subcutaneous heparin (5,000 U twice to 3 times daily) can be considered for patients with renal dysfunction (i.e., creatinine clearance <30 ml/min). §Although the majority of the writing group did make this recommendation, 31.6% of the group were in favor of intermediate-dose anticoagulation (e.g., enoxaparin 1 mg/kg/day, or enoxaparin 40 mg twice daily, or UFH with target aPTT of 50-70 s) and 5.2% considered therapeutic anticoagulation. ¶The majority of the investigators recommended against routine VTE screening (68%); however, the remaining members of the group (32%) recommended to consider such testing. #The majority of the investigators recommended prophylactic anticoagulation (54%). A minority of investigators (29.7%) voted for intermediate-dose parenteral anticoagulation in this setting, and 16.2% considered therapeutic anticoagulation. #Although the majority of investigators voted to reduce the intensity of anticoagulation if the indication were not acute (62%), this survey question did not meet the prespecified cutoff of 66%. **The majority of the writing group recommended prophylaxis with DOACs (51%) and a minority (24%) recommended LMWH, if available and appropriate.

DOAC = direct oral anticoagulant; INR = international normalized ratio; other abbreviations as in Tables 1 and 5.

MANAGEMENT OF PATIENTS WITH THROMBOEMBOLIC DISEASE WITHOUT COVID-19

The main goal of management for patients with known or new onset thrombotic disease but without

COVID-19 is to provide sufficient antithrombotic protection, while minimizing physical contact between patients, health care workers, and health systems. Outpatient management or early discharge for acute VTE should be instituted when possible (116-118), and early discharge after medication

FIGURE 4 Considerations for Thrombotic Disease for Patients, Health Care Providers, and Health Systems and Professional Societies During the COVID-19 Pandemic



PATIENTS HOSPITALIZED WITH COVID-19

- Pharmacological VTE prophylaxis, unless contraindicated
- Careful assessment for incident thrombotic events
- Follow PT/INR, APTT, D-dimer, fibrinogen
- Continuation of precedent antithrombotic therapy based on clinical condition and assessment for drug-drug interaction [see Tables 3 and 4]



PATIENTS WITHOUT COVID-19 OR MILD COVID-19 / POST-DISCHARGE

- Continue therapy, unless otherwise specified by practitioners
- Extend VTE prophylaxis in appropriately selected cases
- Home INR checks or drive-through INR check for patients on VKAs who need testing
- Encourage home exercise
- Home treatment for low-risk acute VTE
- Early, safe discharge after VTE or ACS



HEALTH CARE WORKERS

- Proper use and conservation of PPE
- Outpatient tele-visits
- Minimal team structure to reduce contact with COVID-19
- Deferring elective procedures, or those of less certain benefit
- Age/comorbidity restriction for patient visits



PROFESSIONAL SOCIETIES, FUNDING AGENCIES

- Research priority setting and knowledge generation
- Advocacy and improved public knowledge
- Expedited funding for research in thrombotic disease
- Updated evidence-based guidelines



HOSPITALS AND HEALTH SYSTEMS

- Provide tele-health infrastructure
- Drive-through INR checks
- In appropriate cases, consider switching VKAs to DOACs
- Frequent disinfection of patient room
- Negative pressure procedure rooms when possible
- Cancel or postpone elective procedures and visits
- Improve knowledge generation and dissemination

The approach to safe evaluation and management of thrombotic disease in patients with COVID-19 has several levels of involvement. Hospitalized patients with existing VTE should continue on anticoagulation with consideration of drug-drug interactions, especially with antiviral medications (Table 4). Hospitalized patients with reduced mobility should be started on VTE prophylaxis. Patients who are discharged or not hospitalized should continue recommended anticoagulation therapy. Telemedicine and drive-through or home INR checks can reduce the risk of exposure of both patients and health care providers to COVID-19 while assuring proper management of anticoagulation. In appropriate cases, consider switching VKAs to DOACs to diminish the need for frequent INR checks. Health care workers should continue existing precautions including use of personal protective equipment (PPE) and minimizing individual contact with COVID-19 patients. If emergent procedures for thrombotic disease (e.g., cardiac catheterization, pulmonary thrombectomy) are needed, procedure rooms should be disinfected, and the use of negative pressure operating rooms should be implemented as available. Expedited funding for observational and randomized control trials in management of thrombotic disease is encouraged. APTT = activated partial thromboplastin time; PT = prothrombin time; other abbreviations as in Figures 1 and 3.

stabilization for low-risk ACS or PCI for high-risk ACS should be considered (99-101). Telemedicine should be the preferred method of follow-up, and in-person visits should be reserved only for scenarios that cannot be addressed by telemedicine, or that may potentially warrant hospitalization.

In general, pharmacotherapy in patients with known thrombotic disease and without COVID-19 should be followed similar to the period prior to the pandemic. Although a recent document from the CDC indicated an increased risk of severe COVID-19 in patients receiving “blood thinners” (119), there is no evidence that antiplatelet agents or anticoagulants, increase the risk of contracting COVID-19, or of developing severe COVID-19. Sufficient education should be provided to patients for self-monitoring of symptoms, and to avoid unnecessary emergency department visits for nuisance bleeding.

For patients receiving VKAs, frequent INR monitoring may pose logistical challenges because of lockdowns and may unnecessarily increase the risk of being exposed to SARS-CoV-2. Therefore, thoughtful considerations should be given to potential alternatives, including using extended INR testing intervals if prior INRs have been stable (120). Other alternatives include home-based INR checks, if this can be set up promptly, drive-through INR testing, or switching to a DOAC or LMWHs when clinically appropriate (Figure 3). A summary of key recommendations is presented in Table 6.

IMPACT OF COVID-19 ON HEALTH CARE WORKERS AND HEALTH SYSTEMS

CONSIDERATIONS FOR HEALTH CARE WORKERS. The Centers for Disease Control and Prevention recommends contact and droplet personal PPE for health care workers in their routine care of patients with COVID-19. If an aerosol-generating procedure is being performed (e.g., intubation, extubation, cardiopulmonary resuscitation), additional airborne PPE with an N95 respirator is recommended. Use of telemedicine in place of in-person office visits is a strategy to minimize physical exposure. Further details have been discussed elsewhere (5,103).

The following considerations specific to the care of patients with thrombotic disease may be useful. Over-the-phone and telemedicine approaches should be considered for all nonurgent appointments. For necessary in-person visits, visitor restrictions and staggering of appointments are important considerations (20). For patients with COVID-19 who

require urgent procedures, such as interventions for ACS, high-risk PE, or critical limb ischemia, the fewest number of staff necessary should be involved. For patients without known infection, health care workers should screen patients for COVID-19 exposures or infectivity, consider appropriate PPE during the procedure, and apply disinfection techniques post-procedure, as outlined previously (103). In patients who require emergent cardiac catheterization with unknown COVID-19 status, airborne PPE with an N95 respirator or powered air-purifying respirator is recommended (121,122).

CONSIDERATIONS FOR HEALTH SYSTEMS. Active involvement of health systems with respect to the care of patients with thrombotic disease are critical to achieving optimal outcomes for both COVID-19-infected and uninfected patients. If feasible, resources should be allocated to enable at-home or drive-through INR checks. Further, system-based considerations should be made to monitor and make necessary adjustments to algorithms for management of suspected STEMI or severe PE requiring PERT teams. If procedures are deemed necessary for COVID-19-infected patients, specific protocols should be put into place regarding PPE use and room disinfection.

ROLE OF PROFESSIONAL SOCIETIES

Professional societies, along with other partners, have an important role in knowledge generation and dissemination for various aspects of COVID-19 (5,84,103), as well as leading by example. Illustrative examples include the responsible and wise decisions by the ACC to cancel the 2020 Annual Scientific Sessions, the Society for Cardiovascular Angiography and Interventions to cancel the 2020 Annual Scientific Sessions, and the ISTH to cancel the XXVIII Congress of the ISTH to promote social distancing and to avoid further spread of the disease. Enabling meetings to continue virtually, as with the recent ACC scientific sessions (in this case at no charge) further promotes knowledge dissemination and sense of community, allowing a semblance or normality in challenging times. Many professional societies, including the ACC, AHA, American Society of Hematology, ESC, ISTH, and others, are compiling COVID-related resources in dedicated websites. Professional societies can further foster collaborative knowledge generation by supporting multicenter multinational original research studies to address the pressing clinical or laboratory questions (Figure 4).

PUBLIC HEALTH CONSIDERATIONS RELATED TO CARE FOR THROMBOTIC DISEASE

The World Health Organization and government agencies have recognized the critical importance of public health interventions at the societal level (including social distancing and self-isolation) to decrease transmission rates and alleviate the burden on health systems (123). In the most affected areas, governments have enacted mandatory home quarantine for all nonessential personnel (124-126). There are several important issues to consider as these interventions relate to thrombotic disease.

First, given the recommendations to stay at home, with decreased daily activity and sedentary lifestyles, patients may be at increased risk for VTE (127-131). Clinicians should be aware of this (especially in older adults and higher-risk patients) and provide education on the importance of home activities to mitigate this risk (132). Second, as daily routines are disrupted, dietary changes (especially in daily intake of green vegetables, which are the major source of vitamin K in the Western diet) may affect patients who receive VKAs. As quarantine measures become more severe, changes in diet and vitamin K intake may impact INR values. Practitioners and patients should be aware of these risks, and patients should be advised to maintain a stable diet to the best of their ability. Third, the COVID-19 pandemic has produced damaging economic effects (133), with the United Nations estimating that COVID-19 is likely to cost the world economy more than \$2 trillion in 2020. These losses may adversely affect patients' treatment for thrombotic diseases. Socioeconomic disadvantage has been linked to higher rates of VTE and adverse outcomes (134,135). As the economic effects of COVID-19 continue to evolve, these communities may come under new and significant stress.

CONCLUSIONS AND FUTURE DIRECTIONS

More data and higher-quality data are required to learn how COVID-19 and thrombotic disease interact. Such data, ideally derived from prospective, multicenter, multinational studies, could help to elucidate the similarities and distinctions in disease presentation and outcomes of patients with COVID-19 and pre-existing and incident thromboembolic disease, and help to identify management strategies to optimize outcomes in these patients. Currently, one large international registry of patients with venous thromboembolism (the RIETE [Registro Informatizado Enfermedad TromboEmbólica] registry) (136) is

incorporating data elements for COVID-19, and a dedicated adjudicated prospective registry to study COVID-19 and other cardiovascular outcomes is being initiated (CORONA-VTE registry; BWH Thrombosis Research Group; principal investigator: G.P.). A multicenter, multinational ACS registry has been initiated, as well as a new AHA registry for cardiovascular care and outcomes of these patients. Special attention should also be given to patients with pre-existing thromboembolic disease who have limited access to care in the face of the COVID-19 pandemic, which has hindered transportation and limited the resources of the health care system.

Funding agencies, professional societies, and organizations with active patient participation will all play an important role when it comes to future research in this area. Funding agencies, including the National Institutes of Health (which has already responded swiftly) (137), should continue to pay specific attention to this pandemic. Coordination and cooperation are necessary to quickly address research priorities including those related to thrombotic disease (Table 5). Organizations such as the Patient-Centered Outcomes Research Institute and the North American Thrombosis Forum can ensure the voices and concerns of patients are at the forefront of research questions. Professional societies, including the AHA, ESC, ISTH, International Union of Angiology, and others, should promote knowledge generation and dissemination and advocacy in this challenging climate.

The current paper has provided an interim summary and guidance for considerations related to thrombotic disease and antithrombotic therapy during the COVID-19 pandemic. Such guidance should supplement, rather than supplant, clinical decision making. Nuances of conversations between patients and practitioners should be considered for appropriate patient-centered decisions.

In conclusion, thrombotic disease may be precedent factors or incident complications in patients with COVID-19. Important considerations for the preventive and therapeutic use of antithrombotic agents should be kept in mind to mitigate the thrombotic and hemorrhagic events in these high-risk patients. Funding agencies, professional societies, patients, clinicians, and investigators should work collaboratively to effectively and efficiently address numerous critical areas of knowledge gap.

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