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

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

Running Head: COVID-19 and Thrombotic Disease

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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, due to 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, we review the current understanding of the pathogenesis, epidemiology, management and outcomes of patients with COVID-19 who develop venous or arterial thrombosis, and of those with preexisting thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic.

KEYWORDS: Coronavirus disease 2019, SARS-CoV-2, thrombosis, antithrombotic therapy, anticoagulant, antiplatelet

ABBREVIATIONS

ACS = acute coronary syndromes
COVID-19 = coronavirus disease 2019
DAPT = dual antiplatelet therapy
DIC = disseminated intravascular coagulation
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
ECMO = extracorporeal membrane oxygenation
LMWH = low-molecular-weight heparin
PE = pulmonary embolism
PERTs = pulmonary embolism response teams
SARS-CoV2 = severe acute respiratory syndrome coronavirus 2
STEMI = ST-segment elevation myocardial infarction
UFH = unfractionated heparin
VEGF = vascular endothelial growth factor
VKA = vitamin-K antagonist
VTE = venous thromboembolism

Introduction

The coronavirus disease of 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), now 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 manuscript, 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. 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.

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 two pre-print servers (https://www.medrxiv.org/ and https://www.ssrn.com/index.cfm/en/coronavirus/, date of last search April 12, 2020). We acknowledge that the manuscripts from the latter two 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 (BB, MVM, JIW, SK, SZG, AT, MM, HMK, GYHL) 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-CoV2 is a single-strand RNA coronavirus, which enters human cells mainly by binding the angiotensin converting enzyme 2 (ACE2) (12), which is highly expressed in lung alveolar cells, cardiac myocytes, the vascular endothelium, and other cells (1,13). SARS-CoV2 is transmitted primarily after viral particles are inhaled and enter the respiratory tract (1). In addition, the virus can survive for 24-72 hours 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 zoonotic coronavirus infections such as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS-CoV), COVID-19 has the potential to result in severe illness including systemic inflammatory response syndrome, 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. 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 of whom (11.5%) died. Among the notable differences between patients who died and those who survived were increased levels of D-dimer and fibrin degradation products ([FDPs], ~3.5- and ~1.9-fold increase, 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 SARS-CoV-2 or are a consequence of cytokine storm that precipitates the onset of systemic inflammatory response syndrome (SIRS), as observed in other viral disease (30-33). Another consideration which 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, one 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 non-specific myocardial injury, impaired renal function (leading to troponin accumulation), myocarditis, pulmonary embolism (PE), and Type I and II myocardial infarction (MI) (38,39). Similarly, elevation of natriuretic peptides is non-specific (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 4 and 5**).

Further, a few of these investigational agents have been associated with excess risk (or, in other cases, 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 (VEGF), 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). Hydroxychorloquine, 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 anti-phospholipid 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 $P2Y_{12}$ 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, reportedly an inducer of CYP3A4; however, dose adjustments for oral antiplatelet agents are currently not recommended. Of note, there are no major drug-drug interactions between investigational COVID-19 therapies and parenteral antiplatelet agents such as cangrelor and glycoprotein IIb/IIIa inhibitors.

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

co-administered with lopinavir/ritonavir. Tocilizumab, an IL-6 inhibitor, increases expression of CYP3A4; however, no anticoagulant dose adjustments are currently recommended with concomitant use of tocilizumab at this time. There are no 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, IMPROVE, and Padua models) (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 co-morbidities (e.g., active cancer, or 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-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 healthcare 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). While 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, co-morbidities such as active cancer,

and [according to some authors in the writing group], elevated D-dimer >2 times the upper normal limit) who have low risk of bleeding (74,77,78).

The role of thromboprophylaxis for quarantined patients with mild COVID-19 but significant co-morbidities, 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 at highest risk patients, including those with limited mobility and history of prior VTE or active malignancy.

Diagnosis of VTE in patients with COVID-19.

As described above, elevated D-dimer levels, is a common finding in patients with COVID-19 (23), and does 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 typical 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 healthcare 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. Deterioration of right ventricular function in this setting may be a critical finding, justifying the need for ways to diagnose and treat PE. 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 above and observations from prior viral illnesses (80), some clinicians use intermediate-dose 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, 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 >1,500ng/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 intermediate-dose or therapeutic dose to be reasonable.

Incident venous thromboembolism.

Few published studies have commented on incident VTE in patients with COVID-19. 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 an preprint study of 25 patients with COVID-19 from Wuhan, who were suspected of having PE and underwent computed tomography angiography (CTA), 10 (40%) had evidence of acute PE on imaging (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3548771); however,

the study did not provide information related to use of VTE prophylaxis or the reason for performing CTA. In a study of 184 patients with severe COVID-19 from 3 academic medical centers in the Netherlands, the authors reported that 31% (95%CI 20-41) of patients developed incident VTE. All patients received pharmacological prophylaxis, although under-dosing 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. Concerns with UFH, however, include the time to achieve therapeutic aPTT, and increased healthcare worker exposure for frequent blood draws. Therefore, LMWHs may be preferred in patients unlikely to need procedures. The benefit of oral anticoagulation with DOACs include the lack of need for monitoring, facilitation of discharge planning, and outpatient management. The potential risk (especially in the setting or 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 healthcare services required for INR monitoring for VKAs.

***COVID-19 and interventional therapies for VTE*.**

Pulmonary embolism response teams (PERTs) allow for multidisciplinary care for patients intermediate and high-risk with VTE (49,88-90). During the COVID-19 pandemic, similar to other consultative services, PERTs 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 IVC 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 ESC classification, sub-massive 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 deep venous thrombosis (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 Acute Coronary Syndromes

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.[7] Furthermore, higher troponin levels are associated with severe COVID-19 (5,97). However, not all such events are due to thrombotic ACS. While anecdotal cases of patients with COVID-19 presenting with ACS due to plaque-rupture have been described (type I 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/plaque inflammation (10,98,99).

COVID-19 and antithrombotic therapy for ACS.

In presentations consistent with ACS due to plaque rupture (i.e. Type I MI) (39), dual antiplatelet therapy (DAPT) and full dose anticoagulation per American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC)

guidelines should be administered unless there are contraindications (100-103). 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, 5).

COVID-19 and interventional therapies for ACS.

The American College of Cardiology (ACC) and Society for Cardiovascular Angiography and Interventions (SCAI) recently provided guidance regarding catheterization laboratory procedures in the current climate (84,104). The recommendations note that it is reasonable to continue optimal medical therapy and defer non-urgent cardiac procedures, in order to preserve PPE, hospital resources including inpatient and ICU beds, and minimize exposure for patients and healthcare workers, alike.

Prior to intervention, efforts should be made to distinguish non-specific myocardial injury, myocarditis, and true plaque rupture presentations (104). A low threshold to use transthoracic echocardiography to identify wall motion abnormalities should be considered prior to catheterization laboratory activation. Even in case of STEMI, in which primary percutaneous coronary intervention (PCI) reduces mortality and reinfarction, risk of COVID-19 transmission from patients to healthcare 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 (105). Centers in which timely percutaneous coronary intervention 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, an systemic inflammatory state, mechanical ventilation and central venous catheters contribute to VTE risk within the ICU (106-108), Nutritional deficiencies and liver dysfunction may also interfere with the production of coagulation factors (109). Alterations in pharmacokinetics in critically ill patients may necessitate anticoagulation dose adjustment (110), due 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 (111). 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 (112). 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 out of 3 in another (113,114). There are currently insufficient data to recommend anticoagulation targets for COVID-19 patients requiring ECMO (115).

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 co-infection 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). Lastly, patients requiring targeted temperature management may exhibit prolongations of both PT and aPTT without evidence of bleeding diathesis (116). 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 (117), including those with COVID-19 (7,118). 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 (82,118). 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 ≥50,000, reduce to single antiplatelet therapy if 25,000≤platelet count<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 vs. 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 (119). In summary, the mainstay of blood products transfusion are as follows: platelet concentrate to maintain platelet count >50 × 10^9/L in DIC patients with active bleeding or >20 × 10^9/L in those with a high risk of bleeding or requiring invasive procedures., fresh frozen plasma (FFP) (15-25 mL/kg) in patients with active bleeding with either prolonged PT and/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 (PCC) if FFP transfusion is not possible. With the existing data, tranexamic acid should not be used routinely in COVID-19-associated DIC.

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 and healthcare workers and health systems. Outpatient

management or early discharge for acute VTE should be instituted when possible (120-122), and early discharge after medication stabilization for low-risk ACS or PCI for high-risk ACS should be considered (100-102). 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" (123), 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 due to 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 (124). 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 Healthcare Workers and Health Systems

Considerations for healthcare workers.

The CDC recommends contact and droplet personal PPE for healthcare 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 (5,104).

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 non-urgent appointments. For necessary in-person visits, visitor restrictions and staggering of appointments are important considerations (125). 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, healthcare 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 (126). In patients who require, emergent cardiac catheterization with unknown COVID-19 status, airborne PPE with an N95 respirator and/or Powered Air Purifying Respirator is recommended (127,128).

Considerations for health systems.

Active involvement of health systems with respect to the care of patients with thrombotic disease are critical to achieving good 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 (5,84,104), 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 SCAI 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, the American Heart Association (AHA), American Society of Hematology, ESC, the 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 WHO 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 (129). In the most affected areas, governments have enacted mandatory home quarantine for all non-essential personnel (130-132). 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 (133-137). 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 (138). 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. Providers and patients should be aware of these risks, and patients should be advised to maintain stable diet to the best of their ability. Third, the COVID-19 pandemic has produced damaging economic effects (139), with 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 (140,141). As the economic effects of COVID-19 continue to evolve, these communities may come under new and significant stress.

Future Directions and Conclusions

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 preexisting 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 Registro Informatizado Enfermedad TromboEmbólica [RIETE]) (142) 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, BWH Thrombosis Research Group; PI: G. Piazza). A multicenter multinational ACS registry is has begun and 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 healthcare 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) (143) 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 (PCORI) and the North American Thrombosis Forum (NATF) can ensure the voices and concerns of patients are at the forefront of research questions. Professional societies, including the AHA, ESC, ISTH, IUA, and others should promote knowledge generation and dissemination and advocacy in this challenging climate.

The current manuscript 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.

Bullet Points

- Coronavirus disease 2019 (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.

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Figure Legends

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 bed-ridden status –which are more frequently observed in severe COVID-19– may contribute to thrombosis and adverse outcomes. Coronavirus Disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), VTE indicates venous thromboembolism.

Figure 2. Risk stratification of acute coronary syndromes and venous thromboembolism with COVID-19. Proposed algorithm to risk stratify patients based on severity of 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, have evidence of right ventricular dysfunction or dilatation, or with worsening or 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/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 4 and 5**. ACS indicates acute coronary syndrome; GDMT, guideline-directed medical therapy; TTE, transthoracic echocardiogram; VTE, venous thromboembolism.

Figure 3. Considerations for Switching Vitamin-K Antagonists (VKAs) Due to Limitations with Access to Care or Healthcare Resources During 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 DOACs include mechanical heart valves, valvular AF, pregnancy or breastfeeding, APLS, and co-administration of medications including strong CYP3A and P-glycoprotein inhibitors (-azole medications, HIV protease inhibitors [dependent on DOAC, may just require dose reduction], CYP3A4 inducers (anti-epileptics), St. John's Wort, rifampin, etc. Patient education about stable dietary habits while receiving VKA is also important. If DOACs area not available or approved by insurance, LMWHs could be used in select cases. Abbreviations: AF: atrial fibrillation, APLS: anti-phospholipid syndrome, DOAC: direct oral anticoagulant, INR: international normalized ratio, LMWH: low-molecular weight heparin, VKA: vitamin-K antagonist.

Figure 4. Considerations for Thrombotic Disease for Patients, Healthcare Providers, and Health Systems and Professional Societies During the COVID-19 Pandemic. 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 2**). 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 healthcare 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 (see Figure 4). Healthcare workers should continue

existing precautions including use of 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, DOAC: direct oral anticoagulant, INR: international normalized ratio, PT: prothrombin time, PPE: personal protective equipment, VKA: vitamin-K antagonist, VTE: venous thromboembolism.

Central Illustration. Postulated Mechanisms of Coagulopathy and Pathogenesis of Thrombosis in COVID-19. A) Sars-COV-2 infection activates an inflammatory response, leading to release of inflammatory mediators. Endothelial and hemostatic activation ensues, with decreased levels of TFPI 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) COVID-19 may be associated with hemostatic derangement and elevated troponin. C) Increased thromboembolic state results in venous thromboembolism, myocardial infarction, or in case of further hemostatic derangement; disseminated intravascular coagulation. COPD: chronic obstructive pulmonary disease; CRP: c-reactive protein; FDP: fibrin degradation product; HF: heart failure; TFPI: tissue factor pathway inhibitor; IL: interleukin; LDH: lactate dehydrogenase; PT: prothrombin time.

Table 1. Select Summary of Thrombotic and Thromboembolic Events During Viral Outbreaks		
Proposed Mechanisms	**Event Type**	**Epidemiological data**
Severe Acute Respiratory Syndrome (SARS)		
• Inflammatory cytokine release • Critical illness • Therapeutic risk factors.(144)	Venous Thromboembolism	• Retrospective analysis of 46 critically ill patients with SARS showed 11 DVT and 7 PE events.(145) • Case series of 8 SARS positive ICU patients. Autopsy identified PE in 4, and DVT in 3 individuals.(144)
	Arterial Thrombotic Events	• In a prospective series of 75 patients, 2 patients died of acute myocardial infarction (within 3-week period).(146) • Case report of an NSTEMI patient who received PCI but subsequently developed STEMI several hours later, concerning for immune-mediated plaque instability.(147)
	Other	• In a case series of 206 patients with SARS, 5 developed large artery ischemic stroke with DIC present in 2/5.(148) • 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.(149)
Middle East Respiratory Syndrome (MERS-CoV)		
• Nonspecific mechanism; potentially similar to SARS. Models suggest elevated inflammatory cytokine levels.(150) • Transgenic murine models show evidence of microvascular thrombosis.(151)	Other	• In a series of 161 cases of MERS (confirmed and probable), at least 2 were reported to have a consumptive coagulopathy.(152)
Influenza		
• Possible *de novo* pulmonary emboli in certain cases.(153) • Acute inflammation and decreased mobility in hospitalized patients.(154) • Possible thrombosis due to rupture of pre-existing high risk plaques.(99) • Platelet aggregation over inflamed atherosclerotic plaques noted in animal models.(155)	Venous Thromboembolism	• Retrospective study of 119 patients showed 4 VTE events in patients receiving prophylactic anticoagulation.(154) • Case series describes 7 PEs in patients with influenza pneumonia. In 6/7 there was no evidence of DVT.(153) • A multicenter, observational, case-control study (n=1454) suggests lower VTE rates are associated with influenza vaccination (odds ratio: 0.74; 95% CI: 0.57-0.97).(156) • *This is a representative but not comprehensive list of associated studies.*
	Arterial Thrombotic Events	• A self-controlled study of 364 patients hospitalized with acute myocardial infarction found an increased incidence ratio (IR=6.05, 95% confidence interval: 3.86 to 9.50) for myocardial infarction during periods after influenza compared with controls.(157) Similar evidence exists in prior studies.(158,159) • A retrospective cohort study of 119 patients reports 3 arterial thrombotic events, two of which had STEMI (154). • *This is a representative but not comprehensive list of associated studies.*
	Other	• DIC has been described with influenza infection in a number of case reports and small case series (160-162).
COVID-19		
• Mechanistic understanding continues to evolve. • Factors may include inflammatory cytokine release and critical illness/therapeutic risk factors. • SARS-CoV-2 binds cells expressing angiotensin converting enzyme 2 (163) and this may mediate further mechanisms of injury.(164)	Venous Thromboembolism	• In a preprint retrospective study, 10/25 patients who underwent computed tomography pulmonary angiography had acute PE (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3548771) • 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 VTE.
	Arterial Thrombotic Events	• Evidence regarding ACS with concurrent COVID-19 infection is limited to anecdotal reports. A pre-print single-center retrospective study reported 11 cases of acute ischemic stroke among 221 patients with COVID-19 (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3550025) • *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.*
	Other	Retrospective analysis of 183 patients found non-survivors had significantly higher D-dimer and PT values, compared with survivors. Further, 15/21 (71.4%) of non-survivors met criteria for DIC, versus 1/162 (0.6%) of 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.(165)
ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; COVID-19 = coronavirus disease of 2019; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ICU= intensive care unit; MERS = Middle East Respiratory Syndrome; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PT = prothrombin time; SARS = severe acute respiratory syndrome; STEMI = ST-elevation myocardial infarction; VTE = venous thromboembolism.		

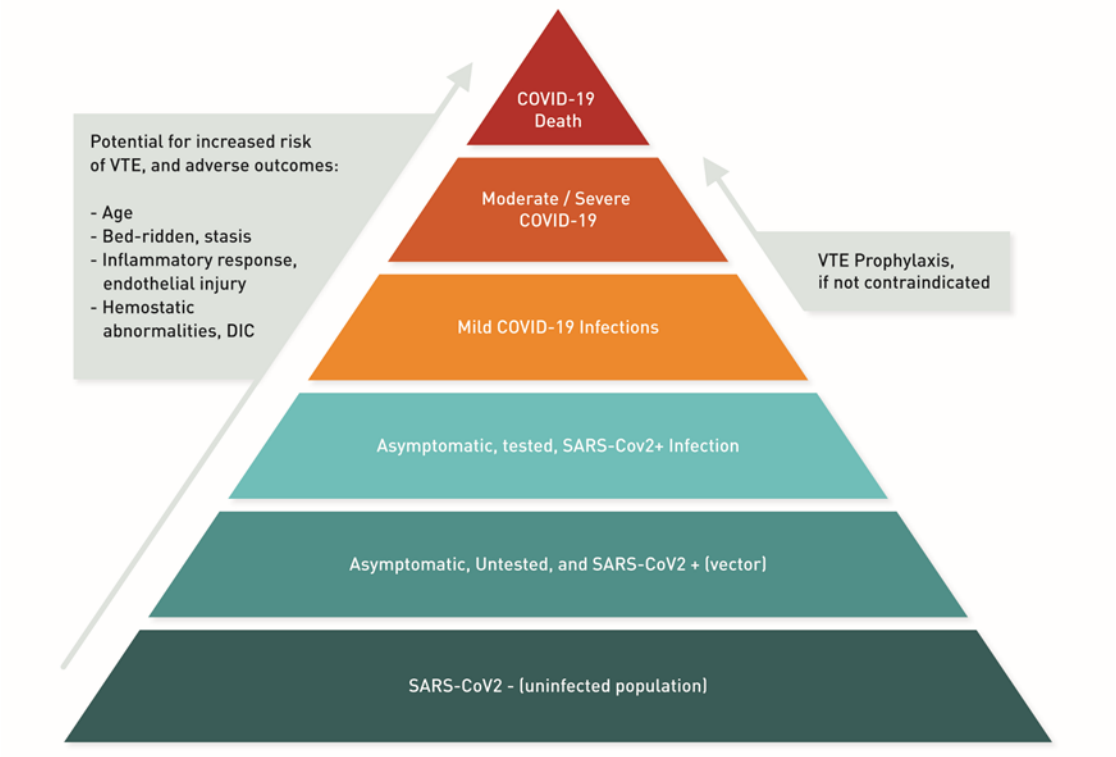
Table 2. Association Between Coagulation Abnormalities or Markers of Thrombosis and Hemostasis and Clinical Outcomes in Patients with COVID-19											
	Han 2020 (N=94)(24)	**Huang 2020 (N=41)(1)**	**Yang 2020 (N=52)(26)**	**Zhou et al (N=191)(20)**	**Gao 2020 (N=43)(27)**	**Wang 2020 (N=138)(16)**	**Wu 2020 (N=201)(19)**	**Tang 2020 (N=183)(7)**	**Lippi 2020 (N=1779)(22)**	**Lippi 2020 (N=553)(23)**	**Lippi 2020 (N=341)(36)**
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		
Platelet Count		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 - -39)*^		
D-dimer (mg/L)											
Setting of Comparison	Severe vs. non-severe	ICU vs. non-ICU		Dead vs. alive	Severe vs. non-severe	ICU vs. non-ICU	Dead vs. alive	Dead vs. alive		Severe vs. non-severe	
D-dimer (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 (s)											
Setting of Comparison	Severe vs. non-severe	ICU vs. non-ICU	Dead vs. alive	Dead vs. alive	Severe vs. non-severe	ICU vs. non-ICU	Dead vs. alive	Dead vs. alive			
Prothrombin time (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. non-severe
Troponin (hs-TnI)		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)*

Table 3. Potential Drug Interactions Between Antiplatelet Agents* and Investigational Therapies for COVID-19					
		$P2Y_{12}$ Platelet Receptor Inhibitors			**Phosphodiesterase III Inhibitor**
Investigational COVID-19 Therapies	**Mechanism of Action of COVID-19 Therapy**	Clopidogrel [1,2]	Prasugrel [2]	Ticagrelor [3,4]	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 co-administer 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 co-administer or if available utilize $P2Y_{12}$ monitoring or consider dose-reduced ticagrelor*	**CYP3A4 Inhibition:** Recommend decreasing dose to maximum of 50 mg BID**.**
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 $P2Y_{12}$ inhibitors or P2Y12 platelet function assay monitoring is not commonly practiced.					

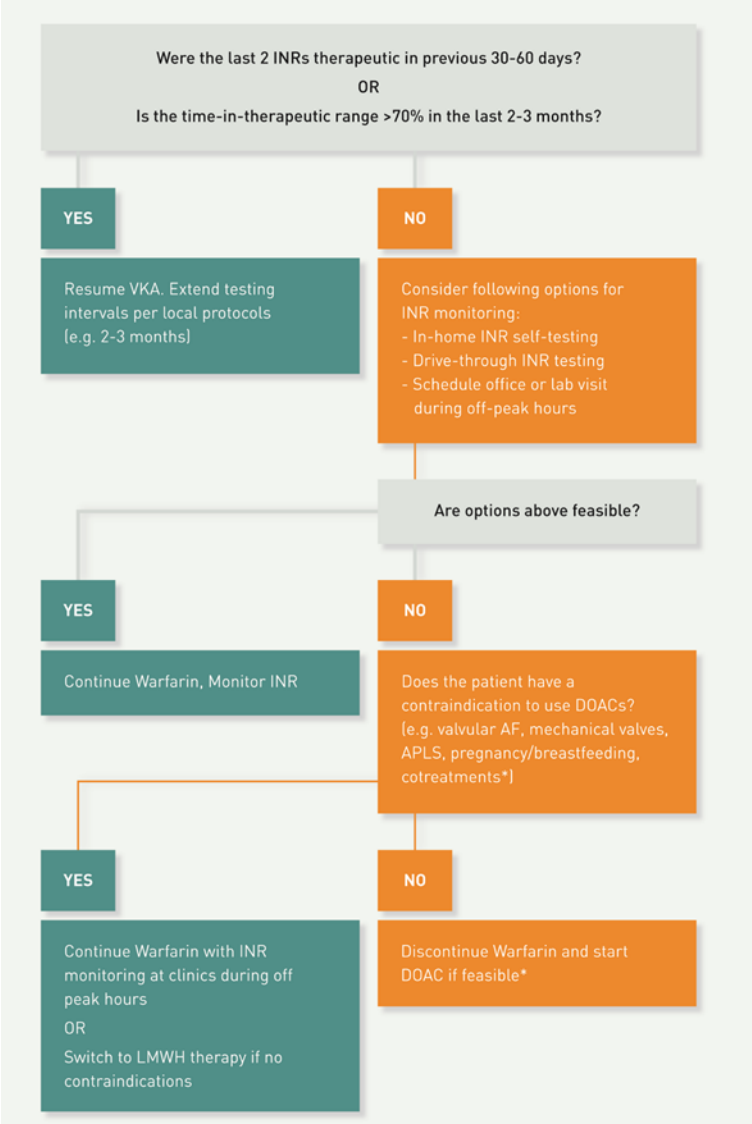
Table 4. Potential Drug Interactions Between Anticoagulants* and Investigational Therapies for COVID-19						
	Oral Anticoagulants					
Investigational COVID-19 Therapies	Vitamin K antagonists	Dabigatran	Apixaban	Betrixaban	Edoxaban	Rivaroxaban
Lopinavir/Ritonavir	**CYP2C9 induction:** May decrease plasma 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 co-administer	**CYP3A4 and P-gp inhibition:** Do not co-administer
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.(166) 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. Non-valvular AF: No dose recommendation	
Hydroxychloroquine and Chloroquine	-	-	-	-	-	-
Other drugs being studied to treat COVID-19 include bevacizumab, chloroquine/hydroxychloroquine, eculizumab, fingolimod, losartan, and pirfenidone. 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 don't interact with any of the investigational agents #Reported with interferon alpha. †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 less than 100,000 mm^3 in 1% an 0.7% of patients on 200 mg and 150 mg doses, respectively. CYP: Cytochrome P system. |						

Table 5. Areas Requiring Further Investigation		
	Patients with Mild COVID-19 (outpatient)	**Comment**
	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 acute coronary syndromes 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 needed, these protocols should not interfere and could run in parallel with interventional trials which 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 non-contrast 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 I acute myocardial infarction in patients with COVID-19, and to compare their process measures and outcomes with non-infected 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 co-morbidities, 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 non-communicable disease, including thrombotic disease deserve investigation.
aPTT: activated partial thromboplastin time, COVID-19: Coronavirus disease 2019; CTPA: computed tomography pulmonary angiography; LMWH: low-molecular weight heparin; PE: pulmonary embolism; VTE: Venous thromboembolism		

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 COVD-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, low-molecular weight heparin 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 can 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 is 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 is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*β
	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 manuscript recommended reducing the intensity of anticoagulation in this clinical circumstance, unless the risk of thrombosis 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 >50,000, reduce to single antiplatelet therapy if 25,000<platelet count<50,000; and discontinue if platelets <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 healthcare 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 COVD-19 due to taking antithrombotic agents. Patients should continue their antithrombotic agents as recommended.
	To minimize risks associated with healthcare 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 healthcare worker and patient in-person interactions, in-home treatment or early discharge should be prioritized.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
	Patients without COVID-19 but with co-morbid 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 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 preexisting asymptomatic DVT. †If VTE prophylaxis is considered, enoxaparin 40mg daily or similar LMWH regimen (e.g. dalteparin 5000U daily) can be administered. Subcutaneous heparin (5000U twice to three times per day) can be considered for patients with renal dysfunction (i.e. creatinine clearance <30 mL/min). ‡While 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 1mg/kg/day, or enoxaparin 40mg BID, or UFH with target aPTT of 50-70] 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. ‖While the majority of investigators voted to reduce the intensity of anticoagulation if the indication were not acute (62%), this survey question did not meet prespecified cut-off of 66%. #The majority of the writing group recommended prophylaxis with DOACs (51%) and minority (24%) recommended LMWH, if available and appropriate. ACS: acute coronary syndrome; DOAC: direct oral anticoagulant, LMWH, low-molecular weight heparin; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin; VTE, venous thromboembolism.	




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/INTERMEIDATE 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


Were the last 2 INRs therapeutic in previous 30-60 days?
OR
Is the time-in-therapeutic range >70% in the last 2-3 months?
YES
NO
Resume VKA. Extend testing intervals per local protocols (e.g. 2-3 months)
Consider following options for INR monitoring:
- In-home INR self-testing
- Drive-through INR testing
- Schedule office or lab visit during off-peak hours
Are options above feasible?
YES
NO
Continue Warfarin, Monitor INR
Does the patient have a contraindication to use DOACs? (e.g. valvular AF, mechanical valves, APLS, pregnancy/breastfeeding, cotreatments*)
YES
NO
Continue Warfarin with INR monitoring at clinics during off peak hours
OR
Switch to LMWH therapy if no contraindications
Discontinue Warfarin and start DOAC if feasible*


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 Table 2)
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 excercice
- Home treatment for low-risk acute VTE
- Early, safe discharge after VTE or ACS
HEALTHCARE 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