Pharmacotherapy for Prevention and Management of Thrombosis in COVID-19

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Coronavirus disease-2019 (COVID-19) is an acute viral syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has resulted in a global pandemic.[1,2] The disease can affect a multitude of organ systems in the body.[3] Dysregulation of hemostatic pathways, evidenced by laboratory and clinical data, plays an important role in morbidity and mortality related to COVID-19. Various forms of thrombosis, from thrombotic microangiopathy to large-vessel thrombosis in the venous system (deep vein thrombosis, splanchnic vein thrombosis, pulmonary embolism) or the arterial system (including acute myocardial infarction, ischemic stroke, and acute limb ischemia), have been described.[4] However, existing epidemiological studies suggest that venous thromboembolism (VTE) is the predominant form of thrombotic events, with reported rates in the literature being variable between 7% up to more than 80% (upon routine screening of critically ill patients).[5–7]

In this setting, the optimal strategies for prevention of thrombotic events and choice of antithrombotic agents for management of pre-existing or new thrombotic events in patients with COVID-19 are of utmost importance. Herein, we provide a succinct summary of potential pharmacological options for the treatment and prevention of thrombosis in patients with COVID-19.

Principles of Pharmacotherapy for Known Thrombotic Disease

The main principles of pharmacotherapy for patients diagnosed with venous or arterial thrombotic disease are similar to the eras prior to COVID-19. Longstanding use of antithrombotic agents for guideline-recommended indications should be, in general, continued. Details about diagnostic challenges and optimal diagnosis of thrombosis in patients with COVID-19 have been previously described elsewhere.[4,8] Some important considerations for the choice and dose of antithrombotic agents are the urgency for need of invasive procedures (e.g., for patients in the intensive care unit [ICU]), considerations for management of acute impairment of renal and liver function, and drug–drug interactions between investigational COVID-19 therapies and antithrombotic agents.

The most prominent drug–drug interactions with investigational COVID-19 therapies and antiplatelet agents include those occurring between lopinavir/ritonavir and agents such as clopidogrel (may need dose increase) or ticagrelor (may need dose reduction). Replacing with prasugrel in patients without contraindications and alternatively utilizing $P2Y_{12}$ platelet function assay for dose adjustment are potential management alternatives.[4,7] Cilostazol, which can be used in the management of peripheral arterial disease, may also require dose reduction if coadministered with lopinavir/ritonavir.[7] For the most part, parenteral antiplatelet agents have a safe interaction profile.

For patients with indications for anticoagulation, rivaroxaban and edoxaban should not be coadministered with lopinavir/ritonavir. Additionally, dose adjustment would be necessary for agents such as vitamin K antagonists (VKAs), apixaban, and betrixaban.[4] VKAs potentially have major drug interactions when prescribed with investigatory agents such as ribavirin, interferon, methylprednisolone, and azithromycin, which often necessitates close international normalized ratio (INR) monitoring, dose adjustment, or using alternative options.[4,9] Parenteral anticoagulants have no established major drug interaction with investigational therapies for COVID-19 (►**Fig. 1**).

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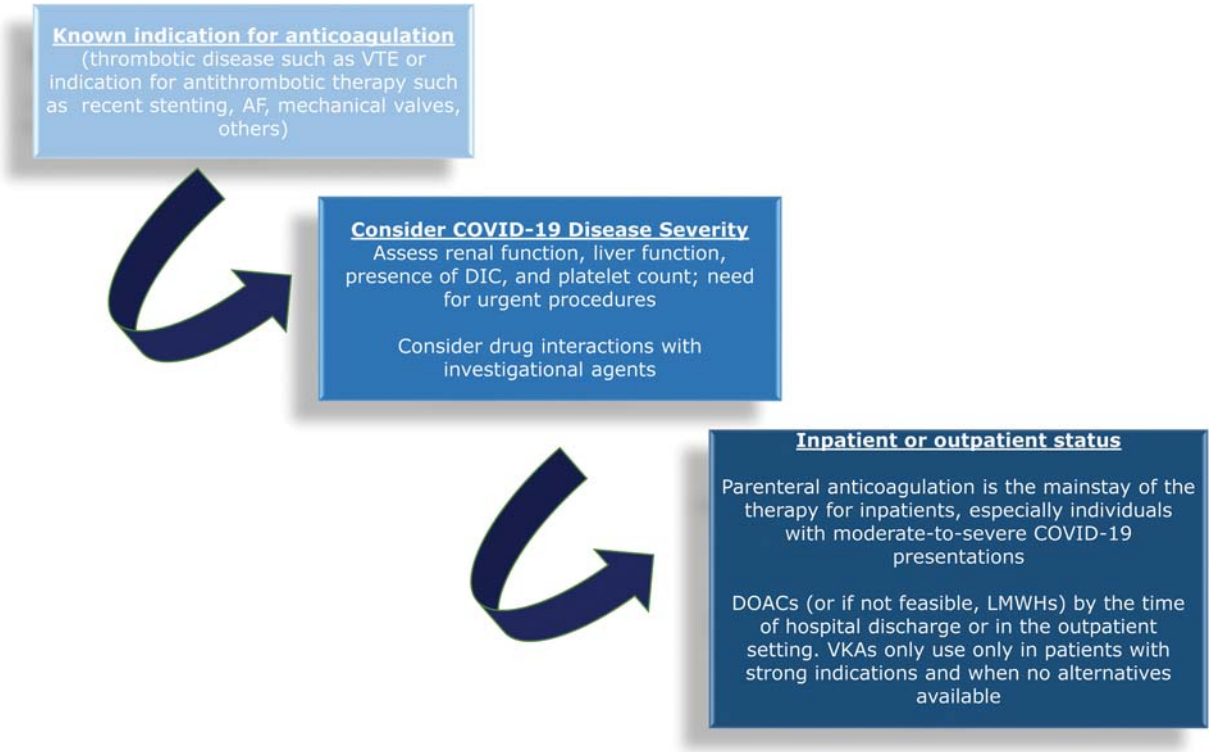

Fig. 1 Anticoagulation in patients with COVID-19 and an existing indication for anticoagulant drugs.

For fibrinolytic agents, which might need to be used for high-risk pulmonary embolism, ischemic stroke, and ST-elevation myocardial infarction (STEMI), there is no known risk of serious drug–drug interaction with the investigational therapies being studied in COVID-19. Although some institutions advocate for upfront use of fibrinolytic therapy to reduce the risk of health care worker exposure in patients presenting with features concerning for STEMI, such exercise must be practiced with caution given that many patients may present with STEMI-mimics and may not, in fact, have plaque-rupture-mediated acute coronary syndromes (ACS).[10] In addition, patients with COVID-19 may be at risk of excess bleeding events, including alveolar hemorrhage.

Empiric Use of Antithrombotic Agents in the Absence of Confirmed Thrombosis

Given the frequency of observed thrombotic events in patients with COVID-19, especially those with severe disease, a myriad of antithrombotic regimens are currently being administered as standard practice or are under investigation. Herein, we provide a brief summary about some of these regimens. Additional details are provided in ►**Table 1** and ►**Fig. 2**.

Parenteral Anticoagulants

Unfractionated heparin and low-molecular-weight heparin (LMWH) are the most common parenteral anticoagulant agents used for prophylaxis and treatment of thrombotic diseases. Besides antithrombotic roles, they have been shown to have anti-inflammatory and antiviral properties,[7,11] which possibly make them even more attractive in the management of COVID-19. LMWHs have the advantage of obviating the need for activated partial thromboplastin time (aPTT) monitoring, which may be difficult in COVID-19 due to considerable hemostatic derangement.[12]

Various dosing strategies, ranging from prophylactic to escalated dose (intermediate to full dose),[13] have been proposed. Consensus-based recommendations from the Global COVID-19 Thrombosis Collaborative Group as well as those from the National Institute of Health guidelines recommend prophylactic dosage of anticoagulation in the absence of known thrombosis or contraindication to anticoagulation.[4] Generally, high-risk individuals (comorbidities, respiratory failure, ICU admitted, bedridden, etc.) should receive in-hospital VTE prophylaxis unless contraindicated.[4] There are multiple ongoing studies in search of optimum dosage for thromboprophylaxis in COVID-19 (NCT04366960, NCT04367831, and others).

Other parenteral anticoagulants include danaparoid, bivalirudin, fondaparinux, and argatroban. Danaparoid (primarily in Europe) and argatroban (particularly in some North American centers) have gained attention for use in patients with COVID-19, in part because of their favorable drug–drug interaction profile, but also because of anti-inflammatory properties, minor effects on platelets, and safe usage in heparin-induced thrombocytopenia. However, currently, there is no strong evidence to support their routine use for thromboprophylaxis for COVID-19. We are not aware of ongoing randomized trials for these agents in patients with COVID-19.

Table 1 Pharmacological agents used for thromboprophylaxis in patients with COVID-19

Agent	Background	Ongoing studies and current recommendations in COVID-19
Heparin-based products	• Antithrombotic, and potential anti-inflammatory and antiviral properties • No known drug–drug interactions with investigational COVID-19 therapies • Unfractionated heparin use may be difficult if monitoring required by aPTT (background hemostasis derangements in COVID-19)	• Several ongoing randomized trials to assess the optimal intensity of heparin-based prophylaxis • Currently, many experts including the Global COVID-19 Thrombosis Collaborative Group and the NIH Guidelines recommend prophylactic-dose anticoagulation, while others consider intermediate or fully therapeutic doses. If higher than prophylactic doses are considered, it may be best to administer in the setting of several ongoing clinical trials
Danaparoid	• Antithrombotic, and potential anti-inflammatory and antiviral properties. • No known drug–drug interactions with investigational COVID-19 therapies • Potential for management of DIC and safe in HIT	• No ongoing clinical trials for COVID-19 • Used as an empiric agent in some centers, although no current evidence for COVID-19
Vitamin K antagonists (VKAs)	• Risk of severe drug interactions with investigating agents such as lopinavir/ritonavir, tocilizumab, ribavirin, azithromycin, etc. • Requirement for INR monitoring (difficult with background hemostasis derangements in COVID-19)	• Currently no trial regarding VKA use in COVID-19 • Not advisable for empiric use in COVID-19. If used for other firm indications (e.g., mechanical valve), close monitoring is needed
DOACs	• Antithrombotic and possible anti-inflammatory properties • Drug–drug interaction especially with lopinavir/ritonavir and most DOACs, and between edoxaban and azithromycin	• Ongoing trial in patients with COVID-19 and suspected ACS assessing Rivaroxaban with DAPT, statins, and PPI (*NCT04333407*) • Particularly helpful for outpatients requiring oral anticoagulation and meeting eligibility criteria for DOACs. • Extended prophylaxis can be considered in carefully selected subgroups (rivaroxaban and betrixaban)
Fibrinolytic agents	• Lung protection properties in animal and a few nonclinical human trials of ARDS • Risk of bleeding, including ICH, DAH, and fatal bleeding	• Ongoing trial assessing role of TPA in respiratory function/oxygenation and mortality (*NCT0457730*), another study assessing safety and efficacy of inhaled fibrinolytic agents (*NCT04356833*) • Routine empiric use of fibrinolytic therapy in patients with COVID-19 is not currently advisable until further data emerge
Aspirin	• Antithrombotic and anti-inflammatory properties • Mixed evidence on whether it can mitigate the course of ARDS	• A trial assessing the role of early aspirin and vitamin D to reduce COVID-19 hospitalizations (*NCT04363840*), another trial assessing the protective effect of aspirin in patients with COVID-19 (*NCT04365309*) • Currently no evidence and no novel recommendations available for COVID-19
P2Y12 inhibitors	• Antithrombotic, and possible antiviral and anti-inflammatory properties (especially ticagrelor) • Risk of major drug interaction between lopinavir/ritonavir and clopidogrel (may need dose increase) and ticagrelor (may need dose reduction)	• Ongoing trial in patients with COVID-19 and suspected ACS assessing DAOCs with DAPT, statins, and PPI (*NCT04333407*) • Currently no evidence available for empiric use in COVID-19
Dipyridamole	• Antithrombotic, anti-inflammatory, and possible antiviral properties	• Higher cure and discharge rates in a small trial. An ongoing trial is assessing the utility of dipyridamole in preventing respiratory decompensation (*NCT04391179*) • Routine use is currently not advisable until additional data emerge
Antithrombin	• Potential antithrombotic and anti-inflammatory properties (including in the lung)	• Some ongoing studies assessing the prognostic impact of plasma antithrombin levels, but no ongoing randomized trials • Routine use is currently not advisable until additional data emerge
Thrombomodulin	• Potential antithrombotic and anti-inflammatory properties • Linked to improved sepsis-induced coagulopathy and survival in pre-COVID-19 studies	• Currently no evidence is available for COVID-19 • Routine use is currently not advisable until additional data emerge
Activated protein C (APC)	• Initially approved by the FDA for severe sepsis but discontinued due to concern for lack of efficacy and risk of bleeding • Data on ARDS modification in severe sepsis in non-COVID patients are contradictory	• Currently, limited evidence is available among patients with COVID-19 • Routine use is currently not advisable until additional data emerge

(*Continued*)

Table 1 (*Continued*)

Agent	Background	Ongoing studies and current recommendations in COVID-19
Hydroxychloroquine	• Immunomodulatory and antithrombotic activity including against antiphospholipid antibodies • Risk of QTc prolongation and arrhythmias	• Results of ongoing studies are pending. Series and fatal arrhythmias have been reported in patient with COVID-19, dampening the interest in the drug. • No current guidelines for their use as an antithrombotic regimen in COVID-19
Statins	• Lipid-lowering, anti-inflammatory, and potential antithrombotic effects	• Multiple trials are investigating the possible role of statin therapy in COVID-19 such as *NCT0438040, NCT04343001*, and *NCT0433407* • Routine use in the absence of another indication is currently not advisable until additional data emerge

Abbreviations: ACS, acute coronary syndrome; aPTT activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; ASA, acetylsalicylic acid; COVID-19, coronavirus diseases of 2019; DAH, diffuse alveolar hemorrhage; DAPT, dual antiplatelet therapy; DIC, disseminated intravascular coagulation; DOAC, direct-acting oral anticoagulant; FDA, Food and Drug Administration; HIT, heparin-induced thrombocytopenia; ICH, intracerebral hemorrhage; INR, international normalized ratio ; LMWH, low-molecular-weight heparin; NIH, National Institutes of Health; TPA, tissue plasminogen activator; UFH, unfractionated heparin; VKA, vitamin K antagonist.

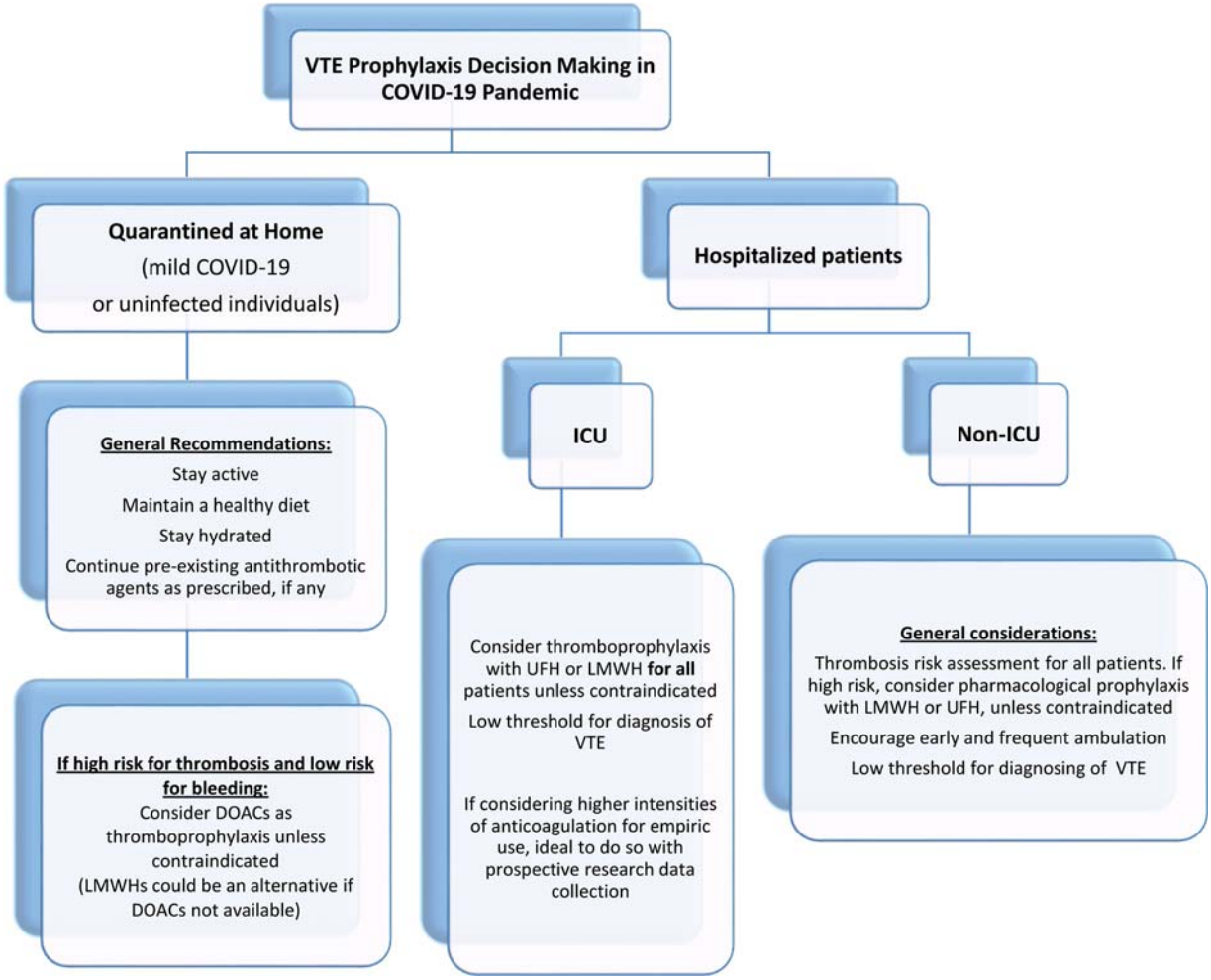

Fig. 2 VTE prophylaxis considerations during the COVID-19 pandemic. VTE, venous thromboembolism.

Oral Anticoagulants

While VKAs are readily available and inexpensive, the possibility of food–drug interactions, serious drug–drug interactions with investigational COVID-19 treatments, and the requirement for frequent INR check represent serious challenges.[7] Again, any drug monitoring using routine coagulation tests, including INR, is difficult due to COVID-19-associated hemostatic derangement.[12] Hence, the empiric use of VKAs is not advisable during the COVID-19 pandemic.

Direct oral anticoagulants (DOACs) have been tried as thromboprophylactic agents in patients with ACS, stable coronary artery disease, or peripheral artery disease.[7]

Anti-inflammatory effects of some DOACs such as rivaroxaban[14] and their favorable utility profile for outpatient management make them an attractive option for COVID-19. The main challenges associated with such agents include drug interactions (as noted above) and risk of bleeding. Use of DOACs should be limited in certain conditions such as renal failure, while their use should be avoided in patients with mechanical heart valves, atrial fibrillation in the setting of mitral stenosis, and antiphospholipid syndrome.[7] Clinicians may also consider switching from VKAs to DOACs in quarantined homebound non-COVID-19 patients under thrombosis prophylaxis, as they do not need frequent hospital visits or blood sampling for INR and/or aPTT.[4]

Post-Discharge Prophylaxis

Among patients with COVID-19 who are hospitalized, it seems reasonable to individually assess the risk of VTE prior to hospital discharge. High thrombosis risk individuals (including those with heart failure, active cancer, or D-dimer levels higher than two times the upper normal reference limit) with low bleeding tendencies may be considered for post-discharge VTE prophylaxis regimen unless contraindicated.[4] Based on studies prior to the COVID-19 era, rivaroxaban and betrixaban would be reasonable agents for this purpose.[15,16] LMWHs are also an alternative for this indication.

Fibrinolytic Agents

Fibrinolytic agents have been proposed as a theoretical option for selected number of patients with COVID-19, hypothesizing that they might alleviate the deranged intravascular and pulmonary parenchymal fibrinolytic mechanisms.[17] Animal studies and small preclinical human trials have shown that fibrinolytic agents may prevent or modify the course of acute respiratory distress syndrome (ARDS),[18] confer parenchymal lung protection,[19] or improve ventilatory parameters.[20] Nevertheless, there are significant concerns regarding empiric use of fibrinolytic agents in COVID-19. Most important is the risk of bleeding, including intracranial hemorrhage and diffuse alveolar hemorrhage. Overall, based on the current evidence, these agents should not be administrated empirically in COVID-19 patients. Ongoing studies, including a trial which is assessing the safety and efficacy of inhaled fibrinolytic agents, can better define the role of fibrinolytic therapy in the course of COVID-19.[4,21]

Antiplatelet Agents

Dysregulation in immune and coagulation systems, in both of which platelets play a key role, are among the most prominent features of the pathophysiology of COVID-19.[22] The antiplatelet and anti-inflammatory effects of acetyl salicylic acid (aspirin) are well known. Some,[23] but not all,[24] studies propose that aspirin might mitigate the severity of ARDS.[7]

P2Y12 inhibitors may also have anti-inflammatory properties in addition to antiplatelet effects. Particularly, prior studies have suggested a beneficiary response with ticagrelor with the potential to mitigate lung injury[25] seen in pneumonia,[26] although the findings are not conclusive. A recent prospective open-label nonrandomized study compared five patients receiving heparin-based regimens versus five patients who received a combination of aspirin, clopidogrel, tirofiban bolus and infusion, and fondaparinux. This small hypothesis-generating study suggested that the more intense antithrombotic regimen was associated with an improved ventilation/perfusion ratio, which deserves further assessment for efficacy and safety in larger studies.[27] There is at least one ongoing randomized trial where patients are randomized to dual-antiplatelet therapy with aspirin, clopidogrel, and low-dose rivaroxaban (in addition to statin and omeprazole) versus control (NCT 04333407).

Dipyridamole, a phosphodiesterase-3 inhibitor, is a parenteral antithrombotic agent which has no major drug–drug interaction with investigatory COVID-19 agents. On the background of its antiviral effects shown in animal models of influenza[28] as well as the in vitro activity against SARS-CoV-2,[29] a small study in COVID-19 has shown tendencies toward better clinical outcomes, including reduction in length of hospital stay and higher cure rate, with dipyridamole.[30] Additional studies are required before concrete recommendations could be made.

Hemostatic Modulating Agents

Antithrombin, thrombomodulin, and recombinant activated protein C are among hemostatic modulating agents that have been proposed for COVID-19, regarding their role in modifying immune responses and thrombosis formation.[7] Some studies suggest lower plasma levels or less functional activity for inherent immunomodulators such as antithrombin and thrombomodulin in severe viral sepsis, including COVID-19.[4,7,31] Nevertheless, there is no strong evidence yet to make a conclusive recommendation for the use of these agents and further studies are needed to assess their safety and efficacy.[7] The *Thrombo Embolic Events in Hospitalized Patients with Covid-19 Serious Acute Pneumopathy (*THROMBCOVID2*)* study, currently recruiting, is a prospective observational study that plans to assess multiple laboratory coagulation tests including antithrombin in COVID-19 (NCT04377490). Currently, there are no registered randomized trials to test antithrombin, thrombomodulin, or recombinant activated protein C in patients with COVID-19.

The inflammation–coagulation paradigm of COVID-19 has been described earlier.[7] The contact activation system, which includes high-molecular-weight kininogen, prekallikrein, and factors XI and XII, links coagulation and inflammatory pathways. As demonstrated in animal models, modifications in the system may control the inflammatory–coagulation vicious cycle seen in conditions such as sepsis. Further studies are needed to test if modulating this pathway could confer benefit in COVID-19.[7]

Anti-inflammatory Agents

Glucocorticoids, by modulating inflammatory response and coagulation factors, can potentially be beneficial in COVID-19. Similar to prior studies in non-COVID ARDS, recent trials on COVID-19–related ARDS have shown conflicting results. The potential benefits must be weighed against well-established adverse effects (e.g., hyperglycemia, risk for infection,

poor wound healing, etc.) and possible drug interaction between agents such as methylprednisolone and VKAs.[7] Currently there is no specific recommendation for their use as an antithrombosis medication. Results from ongoing randomized trials will provide relevant data for clinical practice.

Hydroxychloroquine, with its known immunomodulatory and antithrombotic activity, including targeting antiphospholipid antibodies,[32] has been proposed for use in COVID-19.[7] However, hydroxychloroquine is associated with increased risk of arrhythmias, and its widespread use as an antithrombotic agent is not advisable.

Statins have anti-inflammatory, anticoagulant, and antiplatelet activities, all of which can potentially make them a fascinating treatment option for COVID19.[33] Results from several ongoing trials (such as NCT0438040, NCT04343001, NCT04348695, and NCT04333407) can be informative regarding their use in this circumstance (►**Table 1**).

Targeted immunomodulatory therapies have been also proposed to manage COVID-19 and associated thrombotic events. For instance, complement inhibitors might be beneficial for treatment of complement-mediated thrombotic microangiopathy, as thought to occur in some patients.[33,34] Tocilizumab, an interleukin-6 receptor inhibitor, has been shown to cause a reduction in rates of death or life support interventions on moderate to severe COVID-19 pneumonia and has been included in the Chinese National Health Commission guidelines for treating COVID-19.[35] Tocilizumab is thought to have potential antithrombotic properties, as well. Future studies are required to determine whether use of these agents confer net benefit to reduce the rate of thrombotic events in patients with COVID-19.

Conclusion

The existing body of evidence, consisting of pathophysiological, epidemiologic, and postmortem studies, indicates a prothrombotic state in COVID-19, and suggests there may be a close association between inflammatory and thrombotic pathways. Antithrombotic therapy for known (or incident) thrombotic disease in patients with COVID-19 will be largely similar to pre-COVID-19 era, with specific attention to the risk of pulmonary hemorrhages, acute deterioration of hepatic and renal function, need for invasive procedures, and drug–drug interactions with investigational COVID-19 therapies. However, optimal prevention of thrombotic events in this prothrombotic condition faces multiple unknowns with regards to the right regimen and dose. Additional epidemiological studies and comparative effectiveness studies are required to help identify the highest risk subgroups, and optimal preventive strategies to safely mitigate the risk of thrombotic events.

Conflicts of Interest

Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to a specific type of inferior vena cava filters. Dr. Madhavan reports being supported by an institutional grant by the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854).

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