

Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research

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received
May 15, 2020
accepted
May 15, 2020

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Stuttgart · New York

DOI <https://doi.org/10.1055/s-0040-1713152>.
ISSN 0340-6245.

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Thromb Haemost 2020;120:1004–1024.

Abstract

Coronavirus disease 2019 (COVID-19), currently a worldwide pandemic, is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The suspected contribution of thrombotic events to morbidity and mortality in COVID-19 patients has prompted a search for novel potential options for preventing COVID-19-associated thrombotic disease. In this article by the Global COVID-19 Thrombosis Collaborative Group, we describe novel dosing approaches for commonly used antithrombotic agents (especially heparin-based regimens) and the potential use of less widely used antithrombotic drugs in the absence of confirmed thrombosis. Although these therapies may have direct antithrombotic effects, other mechanisms of action, including anti-inflammatory or antiviral effects, have been postulated. Based on survey results from this group of authors, we suggest research priorities for specific agents and subgroups of patients with COVID-19. Further, we review other agents, including immunomodulators, that may have antithrombotic properties. It is our hope that the present document will encourage and stimulate future prospective studies and randomized trials to study the safety, efficacy, and optimal use of these agents for prevention or management of thrombosis in COVID-19.

Keywords

- ▶ coronavirus disease 2019
- ▶ thrombosis
- ▶ inflammation
- ▶ fibrinolytic therapy
- ▶ anticoagulation
- ▶ immunomodulator
- ▶ antithrombin
- ▶ thrombomodulin

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic.^{1,2} SARS-CoV-2, which is responsible for coronavirus disease 2019 (COVID-19), can cause pneumonia and acute respiratory distress syndrome (ARDS) as well as several extrapulmonary manifestations. These include cardiovascular, hematologic, and thrombotic sequelae due to direct and indirect effects of the viral illness.^{3–5} Indeed, the limited data available on thrombotic complications in patients with COVID-19 suggest that rates of venous thromboembolic events may be as high as 25 to

30%, particularly in critically ill, mechanically ventilated patients.^{6–8} Thrombotic complications also include stroke, acute limb ischemia, and acute coronary syndromes.^{9–11}

Limited data are available to determine the antithrombotic therapy to improve outcomes in patients with COVID-19 who do not have confirmed evidence of thrombosis. The optimal dose and agent for thromboprophylaxis remain unknown. Conservative management has merit based on historical data pertaining to critically ill medical patients¹² as well as for COVID-19-specific escalation of treatment.¹³ For interim decision-making, consensus-based guidance has been provided by some groups,^{14–18} including the Global

COVID-19 Thrombosis Collaborative Group⁵ (►Table 1). However, unlike other extensively studied illnesses such as sepsis,¹⁹ a comprehensive assessment of potential options for prevention of thrombosis in various subgroups of patients with COVID-19 has not to date been proposed.

In this article, prepared by the Global COVID-19 Thrombosis Collaborative Group, we summarize potential therapeutic options for prevention of thrombosis in COVID-19 patients *in the absence of confirmed thrombotic events*. Our focus is on novel approaches to dosing commonly used antithrombotic agents (heparin-based regimens and direct oral anticoagulants [DOACs]), considerations for empiric use of less widely used antithrombotic drugs such as danaparoid, and the potential applications of antiplatelet agents. In addition to the direct antithrombotic effects, other mechanisms of action—including anti-inflammatory or antiviral effects—have been postulated.^{20,21} Finally, we discuss other therapies, such as immunomodulators, that may have antithrombotic properties. The goal is not to provide immediately actionable management recommendations (as high-quality data to reliably inform such guidance in patients with COVID-19 are lacking), but rather to summarize potential treatment options and their advantages and limitations for ongoing and future investigations. We outline research priorities for these agents across the relevant clinical subgroups.

Methodological Considerations

To provide a thorough assessment for the rationale and potential advantages and limitations of various antithrombotic agents, subcommittees from the collaborative drafted

the sections focused on specific agents, and these sections were then reviewed and revised by the entire group. The colead authors searched MEDLINE (with PubMed interface) to ensure that no other high-quality clinical study was missed (date of last search: May 5, 2020).

For research priority setting, a survey was sent to the group of coauthors who were asked to rate the overall priority for investigating each of the discussed agents and to identify the care setting wherein the investigation was most reasonable (outpatients with COVID-19, inpatients on the wards, critically ill patients in the intensive care unit [ICU], or patients posthospital discharge).

Investigational Strategies Targeting Thromboinflammation in COVID-19

In the subsequent sections, we describe various investigational strategies for anticoagulants, antiplatelet agents, hemostatic modulating agents, and immunomodulators that may have potential for further investigation for patients with COVID-19 (►Table 2; ►Fig. 1). In addition, a summary of the survey results for research priorities with these agents is provided in ►Table 3 and ►Figs. 2 and 3.

Anticoagulants

Unfractionated Heparin and Low-Molecular-Weight Heparins

Unfractionated heparin and low-molecular-weight heparins (LMWHs) are the most frequently administered parenteral anticoagulants.²² In addition to their antithrombotic activity, they have postulated anti-inflammatory and antiviral

Table 1 Suggested considerations for prevention and management of thrombosis among hospitalized patients with COVID-19^a

Risk stratification for VTE should be performed for all inpatients with COVID-19. In the absence of contraindications, the vast majority of inpatients, including all patients with severe COVID-19 who are critically ill should receive prophylactic anticoagulation
The optimal intensity of anticoagulation in patients with COVID-19 remains unknown. Although prophylactic dosing is most widely used, higher intensity of anticoagulation (including intermediate-dose and full-therapeutic anticoagulation) is being used by many clinicians/institutions. Additional studies are required to identify the optimal regimen in various patient groups with COVID-19
For hospitalized patients with COVID-19 who require therapeutic anticoagulation (for prior indications including AF, VTE, mechanical valves, or new incident events such as new VTE or type I myocardial infarction), presence or absence of DIC, and hepatic and renal function should be considered when determining the appropriate choice of anticoagulant agent and dose ^a
Hemostatic derangements, including elevated D-dimer levels, are common among inpatients with COVID-19. The majority of a consensus panel did not find sufficient evidence for routine screening for VTE (e.g., bilateral lower extremity ultrasound, or computed tomography pulmonary angiography) for hospitalized patients with COVID-19. However, a high clinical index of suspicion for VTE should be maintained and appropriate diagnostic tests should be pursued in case of signs or symptoms for DVT (including unexplained lower extremity pain or swelling) or PE (including unexplained chest pain, unexplained right ventricular dysfunction, or hypoxemia disproportionate to the pulmonary infiltrates)
Risk stratification for VTE should be done for hospitalized patients at the time of discharge. Extended pharmacological prophylaxis (up to 45 d) should be considered for patients at high risk of VTE who do not have a high risk of bleeding
Drug–drug interactions should be considered between investigational COVID-19 therapies and antithrombotic agents

Abbreviations: AF, atrial fibrillation; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

^aMore detailed recommendations are provided in a separate manuscript.⁵

Table 2 Empiric or investigational use of agents with antithrombotic properties in COVID-19

	Postulated mechanism(s) or data from other ARDS series	Clinical evidence in patients with COVID-19	Comment
Anticoagulants			
Intermediate-dose heparin (UFH or LMWH)	<ul style="list-style-type: none"> ■ Heparin-based products have anti-inflammatory and antiviral properties ■ Meta-analysis of 9 trials including 465 patients suggested that adjunctive LMWH was associated with significantly lower rates of mortality at 28-d in patients with ARDS (RR 0.63, 95% CI 0.41–0.96).¹⁸² Subgroup analysis demonstrated greater effect on oxygenation in patients who received $\geq 5,000$ U/d of LMWH ■ In vitro data suggests heparin may prevent virus-induced cell death of human progenitor cells exposed to Zika virus¹⁸³ ■ In vitro data suggests heparin exposure may reduce infectivity of SARS-CoV¹⁸⁴ 	<ul style="list-style-type: none"> ■ Among a group of 449 patients admitted for COVID-19 in Wuhan, 99 (22%) received intermediate-dose UFH or LMWH¹⁸⁵ ■ No significant differences in 28-d mortality was noted in patients who received heparin-based products versus those that did not receive heparin (30.3% vs. 29.7%, $p = 0.91$), but anticoagulation in patients with Ddimer > 3 $\mu\text{g/mL}$ was associated with lower 28-d mortality (32.8% vs. 52.4%, $p = 0.017$) 	<ul style="list-style-type: none"> ■ There is limited evidence, suggesting that heparin may interact with the spike S1 protein receptor domain of SARS-CoV-2^{21,186}
Therapeutic heparin (UFH or LMWH)	<ul style="list-style-type: none"> ■ As above with intermediate-dose heparin ■ Empiric heparin reduced rates of thrombotic events without increased bleeding complications in H1N1 pneumonia²⁶ 	<ul style="list-style-type: none"> ■ In a retrospective analysis, use of therapeutic anticoagulation was associated with lower mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82–0.89, $p < 0.001$) without increased bleeding. The indication for anticoagulation, or the type of treatment were not described. Sufficient information was not provided about the comorbidity profile of the patients (e.g., contraindications to anticoagulation)¹⁸⁷ 	<ul style="list-style-type: none"> ■ As above
Danaparoid	<ul style="list-style-type: none"> ■ Danaparoid has been shown to reduce cytokine levels and attenuate thrombosis in animal models^{44,45} ■ It can be administered systemically or nebulized ■ Nebulized danaparoid can attenuate coagulation activity in the lungs and systemically as well as reduce levels of pulmonary inflammation. Animal models of lung injury suggest improved survival with its administration⁴⁶ 	<ul style="list-style-type: none"> ■ No current evidence for danaparoid in COVID-19 	<ul style="list-style-type: none"> ■ Heparan sulfate moiety in danaparoid may have antiviral actions and may restore heparan deficit on vascular endothelium ■ Given minimal effect on platelets⁴⁰ and ability to be used in patients with severe renal failure,¹⁸⁸ danaparoid may have the potential for use for thromboprophylaxis in patients with COVID-19
DOACs	<ul style="list-style-type: none"> ■ DOACs have demonstrated mixed results with regards to inpatient and postdischarge prophylaxis for VTE^{54,57} ■ In patients at high risk for VTE and low risk for bleeding (including those with severe infection), betrixaban and 	<ul style="list-style-type: none"> ■ No current evidence for DOACs in COVID-19 ■ There is an ongoing clinical trial assessing DOACs with DAPT, statins, and PPIs in patients with COVID-19 and suspected acute coronary syndrome (NCT04333407) 	<ul style="list-style-type: none"> ■ Considerations when administering DOACs in patients with COVID-19 include longer half-life, availability of reversal agents, renal clearance, and drug–drug interactions with

(Continued)

Table 2 (Continued)

	Postulated mechanism(s) or data from other ARDS series	Clinical evidence in patients with COVID-19	Comment
	rivaroxaban showed a net clinical benefit for inpatient thromboprophylaxis and for extended thromboprophylaxis posthospital discharge ^{54,56,58}		investigational therapies for COVID-19 ⁵
Fibrinolytic agents			
Fibrinolytic therapy (including tPA)	<ul style="list-style-type: none"> ■ There is some evidence to suggest microthrombi in the setting of ARDS and critically ill patients¹⁸⁹ ■ Urokinase and tissue-type plasminogen activator have been shown to be protective in murine models and to reduce the risk of ARDS in porcine models⁷⁶ 	<ul style="list-style-type: none"> ■ Systemic fibrinolytic therapy has been used off-label in ill patients with ARDS secondary to COVID-19 with transient improvement in oxygenation and ventilatory requirement.^{70,71} No long-term benefits have been established 	<ul style="list-style-type: none"> ■ Further evaluation of the role of fibrinolytics should be explored ■ Further prospectively collected data in this space is needed ■ Established risks include major bleeding events (including intracranial hemorrhage); however, further understanding of the risk for diffuse alveolar hemorrhage is needed
Antiplatelets			
Aspirin	<ul style="list-style-type: none"> ■ Aspirin is associated with diminished incidence of ARDS and improved survival in the setting of acute lung injury in animal models and observational human studies⁹⁴⁻⁹⁹ ■ While prospective analyses have suggested reduced mortality when used in the prehospital and ICU setting^{97,98}, these findings were not validated in a randomized trial which evaluated its use for preventing ARDS¹⁰⁰ 	<ul style="list-style-type: none"> ■ No current evidence for aspirin in COVID-19 ■ There is an ongoing clinical trial assessing DOACs with DAPT, statins, and PPIs in patients with COVID-19 and suspected acute coronary syndrome (NCT04333407) 	
P2Y12 receptor antagonists	<ul style="list-style-type: none"> ■ Ticagrelor administration within 48 h of pneumonia diagnosis was associated with reduced circulating platelet-leukocyte aggregates, interleukin-6 levels, and improved oxygen requirements and lung function in the randomized XANTHIPPE trial¹⁰⁵ 	<ul style="list-style-type: none"> ■ No current evidence for P2Y12 receptor inhibition in COVID-19 ■ There is an ongoing clinical trial assessing DOACs with DAPT, statins, and PPIs in patients with COVID-19 and suspected acute coronary syndrome (NCT04333407) 	<ul style="list-style-type: none"> ■ Ticagrelor-associated dyspnea should be considered
Dipyridamole	<ul style="list-style-type: none"> ■ The antithrombotic effect of dipyridamole is thought to be via phosphodiesterase inhibition ■ Animal models suggest potential antiviral activity in the setting of influenza¹¹³ 	<ul style="list-style-type: none"> ■ A small trial randomized 22 patients to dipyridamole (150 mg orally three times a day) vs. routine control in which the treatment group had higher hospitalization discharge rates compared with the control group (58.4% vs. 20.0%), increased platelet counts, stabilization of D-dimer levels, with trends to suggest faster recovery¹⁹⁰ 	

Table 2 (Continued)

	Postulated mechanism(s) or data from other ARDS series	Clinical evidence in patients with COVID-19	Comment
Anti-inflammatory			
Statins	<ul style="list-style-type: none"> ■ Anti-inflammatory effect: Regulation of MYD88 levels that mitigate NF-κB activation¹⁶⁷ ■ Anticoagulant and Anti-platelet effects: Downregulation of TF, upregulation of thrombomodulin, and inhibition of TXA₂¹⁷¹ 	<ul style="list-style-type: none"> ■ No current evidence for statin use in COVID-19 ■ Several ongoing studies evaluating the use of statins in COVID-19 (NCT04348695, NCT04333407, and NCT04343001) 	
Immunomodulators	<ul style="list-style-type: none"> ■ Murine models suggest that complement inhibition may reduce severity of SARS-CoV and MERS-CoV²⁰ 	<ul style="list-style-type: none"> ■ Complement inhibition and JAK inhibitors have been suggested as potential therapies for COVID-19²⁰ ■ JAK inhibitors have been shown to have in vitro activity against SARS-CoV-2¹⁷⁷ 	
Activated protein C	<ul style="list-style-type: none"> ■ Antithrombotic effect of activated protein C in early stage of sepsis-induced DIC ■ Activated protein C may reduce the damage caused by ischemia/reperfusion injury, gastrointestinal inflammation, sepsis, and Ebola virus infection¹³⁰ ■ Anti-inflammatory and cytoprotective effects through PAR1-mediated biased signaling¹⁹¹ ■ Recombinant-activated protein C may attenuate systemic coagulopathy and pulmonary coagulopathy,¹³³ but randomized controlled data of activated protein C for infectious or inflammatory ARDS did not improve alveolocapillary permeability nor clinical outcomes¹³⁴ 	<ul style="list-style-type: none"> ■ In critically ill COVID-19 patients, 4/11 individuals had a protein C level modestly lower than the average reference values¹¹⁹ 	<ul style="list-style-type: none"> ■ Further study needed to determine if low levels of protein C are common and whether activated protein C or 3K3A-APC have any benefit in patients with COVID-19
Corticosteroids	<ul style="list-style-type: none"> ■ Glucocorticoids modulate inflammatory response and coagulation factors (VWF, fibrinogen, plasminogen activator inhibitor-1)¹⁵¹ ■ Evidence in prior triggers for ARDS, including SARS-CoV and MERS-CoV, is inconclusive.¹⁴⁵⁻¹⁴⁷ 	<ul style="list-style-type: none"> ■ Retrospective analysis in COVID-19 patients with ARDS suggested reduced risk of death with methylprednisolone treatment (HR 0.38, 95% CI 0.20-0.72, $p < 0.001$)¹⁴⁴ ■ Data from a paper currently on a preprint server did not show any association between glucocorticoid use and 28-d mortality in critically ill patients¹⁹² 	
Hydroxychloroquine	<ul style="list-style-type: none"> ■ Prior studies suggesting mild antiplatelet effects and possible reversal of thrombogenic properties of antiphospholipid antibodies^{154,158} ■ No specific studies available in ARDS 	<ul style="list-style-type: none"> ■ No current evidence for the association between use of hydroxychloroquine and thrombosis in COVID-19 	<ul style="list-style-type: none"> ■ Data from a small case series suggests antiphospholipid antibodies may play a role in development of thrombosis in patients with COVID-19¹⁹³ Further data are needed to assess whether

(Continued)

Table 2 (Continued)

	Postulated mechanism(s) or data from other ARDS series	Clinical evidence in patients with COVID-19	Comment
			hydroxychloroquine may have a benefit in COVID-19
Other			
Antithrombin	<ul style="list-style-type: none"> ■ Reduced levels in SARS patients who developed osteonecrosis¹⁹⁴ ■ Inflammation and coagulopathy modulation in lung injury animal models^{122–124} ■ Increased bleeding in critically ill trial data¹²⁶ 	<ul style="list-style-type: none"> ■ When compared with 40 healthy controls, patients with COVID-19 had significantly lower antithrombin levels¹²¹ 	<ul style="list-style-type: none"> ■ Mechanisms for lower antithrombin in such patients is unclear, and this may potentially be mediated by consumption versus reduced synthesis by the liver
Thrombomodulin	<ul style="list-style-type: none"> ■ Anticoagulant and anti-inflammatory effects mediated through activated protein C-dependent and independent protein C mechanisms ■ A systematic review suggested that recombinant thrombomodulin in patients with sepsis-induced coagulopathy was associated with reduced rates of mortality¹²⁹ 	<ul style="list-style-type: none"> ■ No current evidence for thrombomodulin in COVID-19 	<ul style="list-style-type: none"> ■ Given that thrombocytopenia is not very common in COVID-19, it remains unclear if recombinant thrombomodulin would have benefit in this patient population
Contact activation system	<ul style="list-style-type: none"> ■ Nonhuman primate models of bacterial sepsis suggest that inhibition of the contact activation system can reduce levels of inflammatory cytokines, microvascular thrombosis, and potentially contribute to improved survival^{136–139} 	<ul style="list-style-type: none"> ■ No current evidence for modulation of contact activation system in COVID-19 	

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; HR, hazard ratio; ICU, intensive care unit; JAK, Janus kinase; LMWH, low-molecular-weight heparin; MERS-CoV, Middle Eastern respiratory syndrome coronavirus; NF- κ B, nuclear factor kappa B; PAR1, protease-activated receptor 1; PE, pulmonary embolism; RR, relative risk; SARS-CoV, severe acute respiratory syndrome coronavirus; STEMI, ST-segment elevation myocardial infarction; TF, tissue factor; tPA, tissue-type plasminogen activator; TXA₂, thromboxane A₂; UFH, unfractionated heparin; VTE, venous thromboembolism; vWF: von Willebrand factor.

properties. Their anti-inflammatory properties may occur through selectin blockade, inhibition of bradykinin and thrombin generation, and binding of inflammatory cytokines.^{23,24} Heparins may also possess antiviral properties. For example, heparin may attenuate viral interaction with the angiotensin-converting enzyme 2 (ACE2) receptor by binding SARS-CoV-2 spike protein.²⁵

The use of empiric heparin anticoagulation in patients with H1N1 ARDS was associated with reduced risk of thrombotic events without an increase in bleeding complications.²⁶ With this consideration and the concern for breakthrough rates of thrombotic events despite prophylactic anticoagulation,⁷ several randomized trials evaluating varying intensities of heparin-based anticoagulation, ranging from prophylactic, or weight-adjusted prophylactic dose treatment to intermediate to full-dose therapy are underway (NCT04345848, NCT04344756, NCT04373707, NCT04359277, NCT04367831, NCT04362085, NCT04377997). Additionally, several institutions have implemented protocols to initiate therapeutic anti-

coagulation empirically, utilizing risk stratification based on an individual's thrombotic and bleeding risk.^{27,28} Future prospective studies are needed to evaluate the use of these strategies on thrombotic and bleeding complications.

One potential challenge in the use of unfractionated heparin is the utility of the activated partial thromboplastin time (aPTT) for monitoring heparin. In patients with COVID-19, besides the intensity of heparin-based regimens, substantial heterogeneity in the aPTT response may be driven by high levels of factor VIII and fibrinogen, or the presence of a lupus anticoagulant.^{29,30} Consequently, anti-factor Xa levels may need to be measured to ensure that a therapeutic heparin level is achieved.³¹

Trials of inhaled heparin for treatment of COVID-19 are being planned to disrupt SARS-CoV-2 and its ACE2 receptor interaction. Docking of the virus to host cells is mediated by the interaction between the spike (S) protein and heparan sulfate chains of proteoglycans. This facilitates further binding of SARS-CoV-2 to its cell-surface

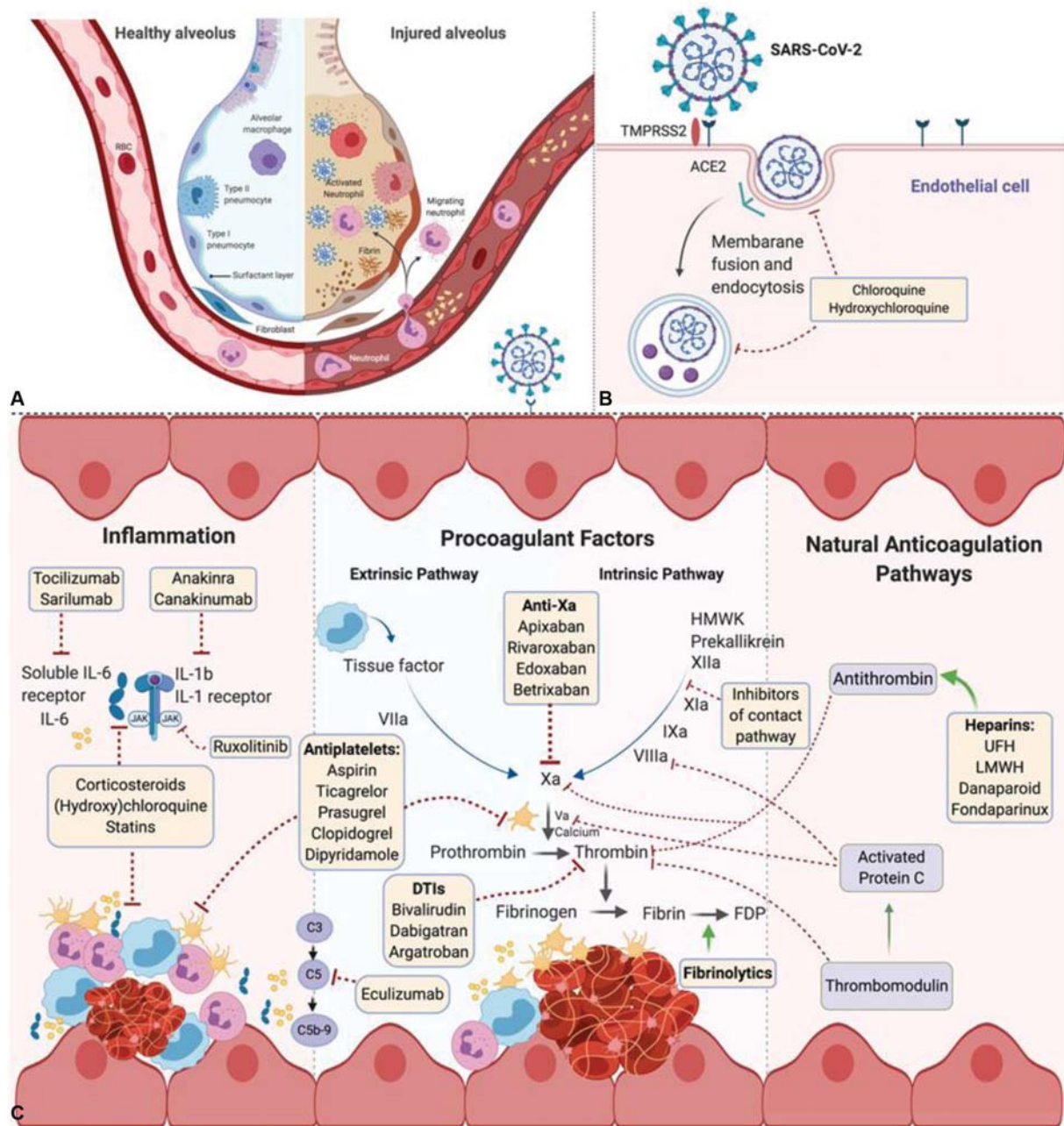


Fig. 1 Postulated mechanism of novel treatment options for management of thrombosis in COVID-19. (A) Viral alveolar injury and inflammation, including fibrin deposition. (B) Viral entry into the endothelial cells and the possible protective effect of hydroxychloroquine. (C) Potential mechanism of effect of various agents with antithrombotic properties for mitigating thrombotic complications in COVID-19. COVID-19, coronavirus disease 2019; tPA, tissue-type plasminogen activator.

receptor, ACE2, via the surface unit (S1) of its S protein.^{32–34} It is known that heparin can displace surface proteoglycans, and prevent SARS-CoV-2 entry into human cells.^{21,35} Drug–drug interactions between COVID-19 investigational therapies and antithrombotic agents should be also considered. ▶ **Fig. 3** provides a graphical summary of potential interactions.

Danaparoid

Danaparoid (a mixture of sulfated glycosaminoglycans including heparan sulfate, dermatan sulfate, and chondroitin

sulfate) attenuates thrombin generation by catalyzing the inhibition of factor Xa by antithrombin and by inhibition of thrombin by antithrombin and heparin cofactor II.³⁶ Currently, danaparoid is predominantly used in patients with heparin-induced thrombocytopenia in several countries other than the United States.

ARDS is associated with dysregulated inflammation and coagulation.^{5,20,37} Patients with ARDS have an increased risk of venous thromboembolism (VTE) as well as thrombocytopenia,³⁸ renal failure, and bleeding.³⁹ Because of its safety profile in patients with heparin-induced thrombocytopenia,

Table 3 Research priorities for use of antithrombotic agents in patients with COVID-19 without diagnosed thrombosis^a

Agent	Research priority, mean (SEM) ^b	Patient subgroups of highest relevance ^c
Intermediate dose heparin (unfractionated or LMWH)	7.82 (0.39)	Hospitalized ICU patients (62.5%) Hospitalized ward patients (47.5%)
Therapeutic dose heparin (unfractionated or LMWH)	7.53 (0.40)	Hospitalized ICU patients (82.5%)
Danaparoid	4.50 (0.40)	Hospitalized ward patients (51.3%) Hospitalized ICU patients (35.9%)
Other parenteral anticoagulants (bivalirudin, argatroban, fondaparinux)	4.89 (0.38)	Hospitalized ICU patients (56.4%) Hospitalized ward patients (38.5%)
Vitamin-K antagonists	3.08 (0.37)	Postdischarge patients (50.0%) Non-hospitalized patients (28.9%)
Direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban)	7.95 (0.29)	Postdischarge patients (80.0%) Nonhospitalized patients (20.0%)
Sulodexide	4.50 (0.46)	Hospitalized ward patients (35.3%) Postdischarge patients (23.5%)
Fibrinolytic therapy	6.20 (0.40)	Hospitalized ICU patients (86.8%)
Aspirin	5.87 (0.39)	Nonhospitalized patients (46.2%) Postdischarge patients (25.6%)
P2Y12 receptor antagonists	5.15 (0.40)	Nonhospitalized patients (34.2%) Hospitalized ward patients (34.2%)
Dipyridamole	4.00 (0.38)	Hospitalized ward patients (44.4%) Nonhospitalized patients (36.1%)
Dual-antiplatelet therapy	4.77 (0.44)	Hospitalized ward patients (35.3%) Postdischarge patients (24.3%)
Antithrombin	4.05 (0.42)	Hospitalized ICU patients (56.8%) Hospitalized ward patients (32.4%)
Thrombomodulin	4.43 (0.47)	Hospitalized ICU patients (60.6%) Hospitalized ward patients (30.3%)
Activated protein C	3.97 (0.41)	Hospitalized ICU patients (79.4%) Hospitalized ward patients (17.6%)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; LMWH, low-molecular-weight heparin; SEM, standard error of the mean.
^aBased on a survey of the Global COVID-19 Thrombosis Collaborative Group. For practical purposes, it was not possible to include all investigational agents.

^bFrom 1 to 10, 10 being the highest priority.

^cUp to two categories each with > 15% vote, not mutually exclusive.

its minor effects on platelet function⁴⁰ (particularly in sepsis), and potential for management of disseminated intravascular coagulation (DIC),^{36,41} danaparoid appears to be an attractive option for research in critically ill patients with COVID-19. Importantly, however, no reversal agent is available in the setting of bleeding complications.

Thrombi have been noted in the pulmonary arteries and vessels of other organs including the liver and kidneys in patients having died of COVID-19. The presence of these in situ thrombi raises the possibility that widespread endothelial activation in COVID-19 triggers thrombosis.^{42,43} In animal models of sepsis, danaparoid reduces cytokine levels and attenuates thrombosis.^{44,45} Intra-alveolar deposits of fibrin and activated leukocytes also contribute to the respiratory failure in patients with COVID-19 pneumonia. Danaparoid can be nebulized and has been shown to attenuate pulmonary coagulopathy, systemic coagulation, pulmonary inflammation, and improve survival in a lung injury model.⁴⁶

Nebulized danaparoid administration may concentrate its effect on the lungs and decrease the risk of systemic adverse reactions. Although danaparoid is being empirically used in some centers, no published report or registered clinical trials exist for its use in COVID-19.

Other Parenteral Anticoagulants

Parenteral anticoagulants such as bivalirudin, argatroban, and fondaparinux have been studied in management of patients with acute coronary syndromes, VTE, and heparin-induced thrombocytopenia.^{47,48} However, these agents are more expensive than unfractionated heparin or LMWH, and there are limited data about their use in COVID-19.

Vitamin-K Antagonists

Vitamin-K antagonists (VKAs), including warfarin, function by inhibiting vitamin K epoxide reductase, which results in

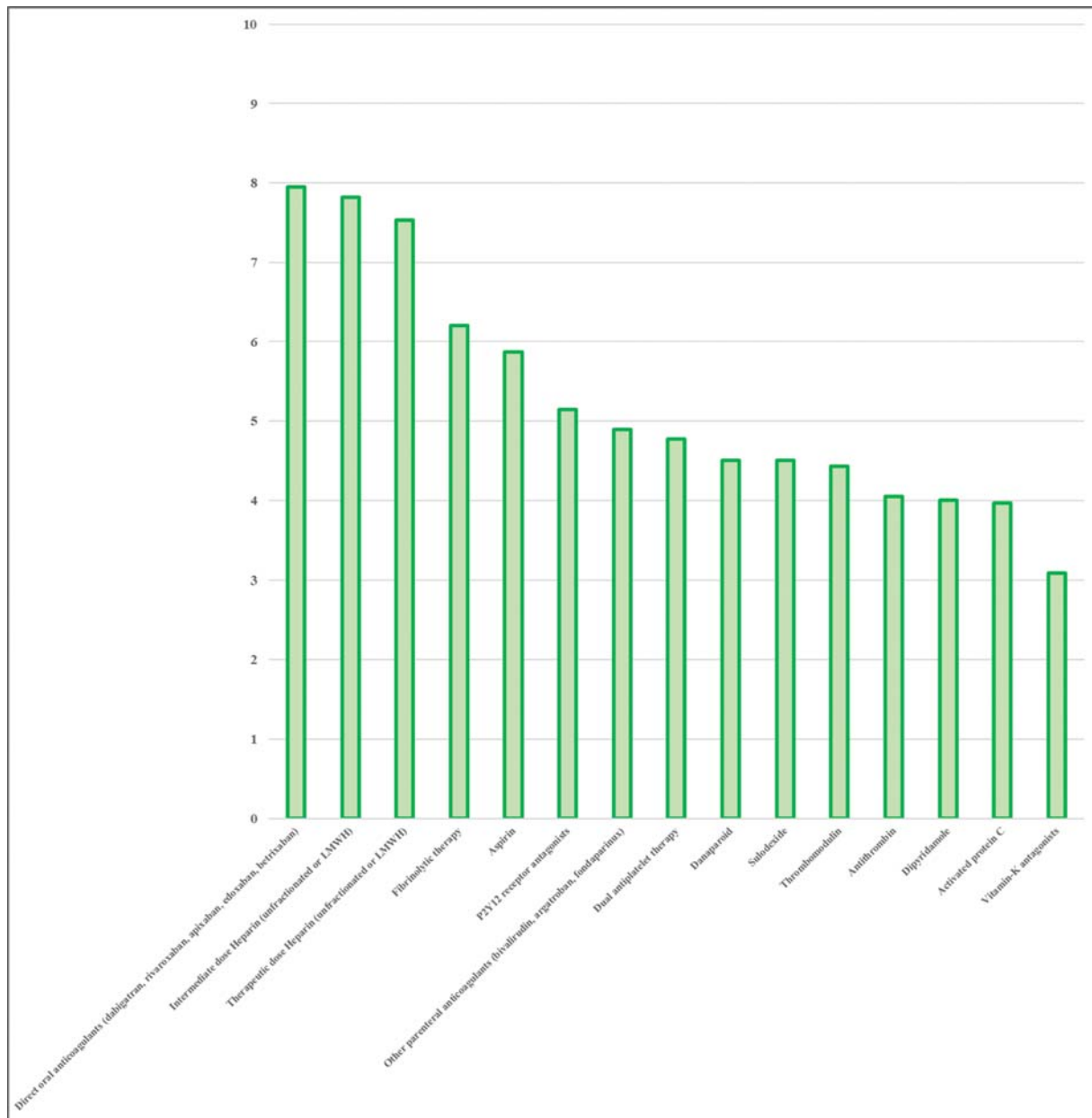


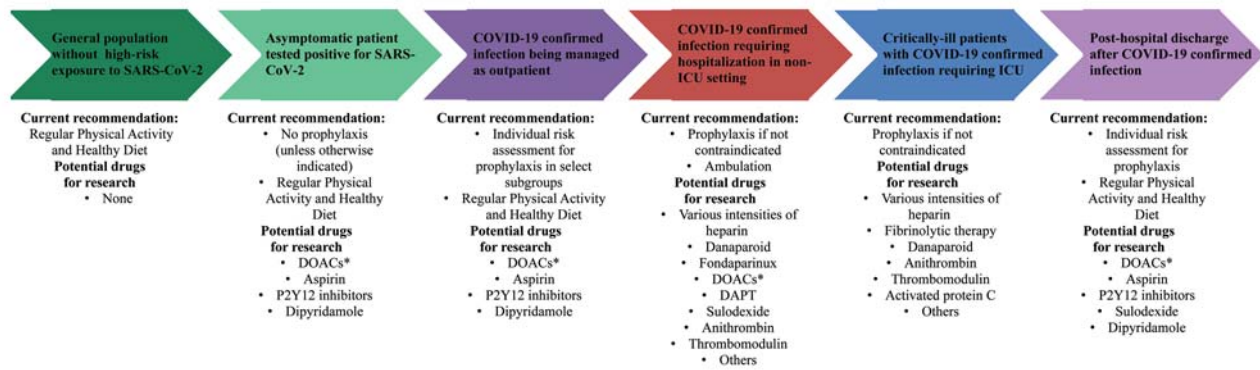
Fig. 2 Bar graph representing the research priorities as voted by the coauthors.

the prevention of the recycling of vitamin K epoxide back to its active form.⁴⁹ The active form of vitamin K is essential for synthesis of clotting factors in the coagulation cascade (e.g., II, VII, IX, and X) and anticoagulant factors (proteins C and S),⁴⁹ and so VKAs result in reduction of these factors. These drugs are used for treatment of established thrombotic events (e.g., deep venous thrombosis or pulmonary embolism) or for prophylaxis in patients with specific indications (e.g., atrial fibrillation and prosthetic mechanical heart valves). However, in the course of COVID-19 there are several challenges with use of VKAs, including drug-drug interactions, and need for international normalized ratio monitoring, as described previously.⁵ There are currently no active studies evaluating the use of VKAs in COVID-19.

Direct Oral Anticoagulants

Beyond their anticoagulant effects, DOACs, especially factor Xa inhibitors, may exert anti-inflammatory effects in COVID-19.⁵⁰ As has been demonstrated with rivaroxaban, DOACs can prevent arterial and venous thrombosis in patients with history of acute coronary syndrome,⁵¹ stable atherosclerotic vascular disease,⁵² or peripheral artery disease undergoing revascularization.⁵³ Rivaroxaban and betrixaban reduce the risk of VTE in medically ill patients.^{54–56} As such, there is interest in administering DOACs to patients with severe COVID-19. These benefits should be weighed against the increased risk of bleeding events.

DOACs offer the potential for in-hospital and posthospital VTE prophylaxis. Results of studies with DOACs for extended prophylaxis in medically ill patients without COVID-19 have



*Standard or low dose. COVID-19: coronavirus disease 2019. DAPT: dual antiplatelet therapy. DOAC: direct oral anticoagulant.

Fig. 3 Considerations for research investigations of pharmacotherapy for prevention of thrombosis or disease progression in patients with SARS-CoV-2 infection.

been mixed.^{54,57} However, recent investigations in patients who are at high risk for VTE and low risk for bleeding (including those with severe infection) have demonstrated a net clinical benefit, especially for extended thromboprophylaxis posthospital discharge with betrixaban or rivaroxaban.^{54,58} There is currently one registered clinical trial (C-19-ACS) assessing low-dose rivaroxaban along with dual-antiplatelet therapy, statins, and a proton-pump inhibitor in patients with COVID-19 and a suspected acute coronary syndrome (NCT04333407).

A few centers have integrated DOACs into VTE prophylaxis algorithms for both in-hospital and postdischarge care.²⁸ However, concerns remain about DOAC use in patients with COVID-19-associated complications, including its renal clearance and acute renal insufficiency, need for invasive procedures (e.g., dialysis access), extracorporeal membrane oxygenation, and difficulty in administering reversal agents.^{59,60} Finally, drug–drug interactions need to be considered when using DOACs with some investigational COVID-19 therapies (see ►Fig. 4).⁵ A recent small study showed increased absorption with high drug levels of DOACs in patients with COVID-19 who received antiviral agents.⁶¹ DOACs may offer an attractive option to prevent thromboembolic events in the prehospitalization period for high-risk patient groups with COVID-19, such as those with underlying cardiovascular disease or high VTE risk factors. There is at least one planned study with rivaroxaban underway in outpatients with COVID-19 (Prevent HD).

In patients with high suspicion for VTE, diagnosis should be sought when possible. For empiric treatment of select patients in whom presumed VTE events cannot be confirmed during the hospitalization period, for logistical reasons, use of DOACs upon hospital discharge offers additional convenience.⁶² Challenges with this approach include the uncertainty in the diagnosis of VTE, and that delayed VTE imaging may not have sufficiently high negative predictive value to exclude an earlier event. Some COVID-19 patients will not be candidates for DOACs, such as those with severe renal dysfunction, mechanical heart valves, and antiphospholipid syndrome, or those taking antiviral or immunomodulatory medications that may be

associated with drug–drug interactions, and poor medication adherence.

Sulodexide

Sulodexide is an orally administered purified glycosaminoglycan consisting of heparan sulfate (80%) and dermatan sulfate.⁶³ It exerts antithrombotic properties through reduction of fibrinogen^{64,65} and plasminogen activator inhibitor-1 (PAI-1)^{64,66} and is thought to have anti-inflammatory properties.^{65,67,68} In a recent systematic review of randomized trials across a variety of cardiovascular indications, use of sulodexide compared with control was associated with reduced risk of VTE, myocardial infarction, cardiovascular mortality, and all-cause mortality.⁶⁹ Despite the potential interest, limited data exist about the safety and efficacy of sulodexide in patients with COVID-19 and there are currently no registered trials for sulodexide in these patients.

Fibrinolytic (Thrombolytic) Agents

Systemic Fibrinolytic Therapy

Systemic fibrinolytic (thrombolytic) therapy is approved for management of ST-segment elevation myocardial infarction, ischemic stroke, and high-risk pulmonary embolism. Off-label use has been reported for the treatment of a small number of severely ill patients with ARDS secondary to COVID-19.^{70–72} While empiric use of fibrinolytic agents is not based on solid clinical evidence and confers significant bleeding risk, there is precedent for its use in ARDS. As with other causes of ARDS, fibrin-rich hyaline membranes have been reported in lung biopsy specimens from patients with COVID-19.⁷³ Additionally, D-dimer, prothrombin time, and fibrinogen levels may all be increased in COVID-19 patients with significant lung involvement,⁷⁴ suggesting derangement of coagulation. The presence of microthrombi in the pulmonary microcirculation has been implicated as a possible mechanism for clinical deterioration.⁷⁵

Fibrinolytic agents such as urokinase and tissue-type plasminogen activator have reduced the risk of ARDS in porcine models.⁷⁶ Similarly, lung-protective findings have

	Lopinavir/Ritonavir	Remdesivir	Tocilizumab	Hydroxychloroquine	Ribavirin	Methylprednisolone	Sarilumab	Anakinra	Azithromycin
FIBRINOLYTIC THERAPY									
Streptokinase									
Alteplase (rtPA)	-								
ANTICOAGULANTS									
Unfractionated heparin									
LMWH									
Danaparoid	-								
Bivalirudin	-								
Argatroban									
Fondaparinux									
Vitamin-K antagonists			ψ		†				‡
Dabigatran	*								€
Apixaban	†								∇
Rivaroxaban									∇
Edoxaban									∇
ANTIPLATELET AGENTS									
Aspirin									
Clopidogrel									
Prasugrel									
Ticagrelor									
Cangrelor									
Dipyridamole									
Cilostazol	‡								
HEMATOLOGICAL FACTORS									
Protein C	-								
Antithrombin	-								
Thrombomodulin	-		-				-	-	

*Avoid use if CrCl < 50 ml/min. †50% apixaban dose reduction in patients who would otherwise receive 5 or 10 mg twice daily, and avoid in patients who would otherwise receive 2.5 mg twice daily. The Canadian product monograph states that the combination is contraindicated. ‡Consider reducing the cilostazol dose to 50 mg twice daily. ψMay decrease serum concentration of CYP3A4 substrates. Monitor INR. †Decreases efficacy of warfarin. ‡May increase serum concentration, monitoring recommended. †P-glycoprotein inhibition: may increase serum concentration, monitoring recommended. ‡Dose adjustments necessary when used in combination with CYP3A4 inhibitors.

Figure guide			
Low risk of interaction	Risk for mild-or moderate interaction (see legend for details)	High risk of serious interaction. Need dose adjustment or do not co-administer	No data available

Fig. 4 Graphical summary of drug–drug interactions between coronavirus disease 2019 (COVID-19) investigational therapies and anti-thrombotic agents.

been noted in murine models.⁷⁷ A meta-analysis of preclinical studies corroborated these findings in various animal models.⁷⁸ Anecdotal reports have noted improvement in oxygenation and ventilation parameters.⁷⁹ A recent small study ($n = 60$) study found improvement in surrogate parameters of ventilation and a reduction in ICU mortality in patients with severe non-COVID-19-related ARDS treated with inhaled streptokinase.⁸⁰

The bleeding risks of fibrinolysis must be balanced against these preclinical data and small human series. Systemic fibrinolysis has been associated with a 1 to 3% rate of intracranial hemorrhage and notable risk of other forms of major bleeding across a wide span of acute diseases.^{81–83} Additionally, there is concern for diffuse alveolar hemorrhage after fibrinolysis, though reports of this complication have yet to be reported. Prior studies have suggested fibrinolytic agents such as alteplase can be associated with prolonged hypofibrinogenemia.⁸⁴

Based on the present evidence utilization of fibrinolysis for COVID-19-associated ARDS, even when severe, cannot uniformly be recommended given its unknown risk–benefit ratio. However, investigational use of fibrinolytic agents in carefully selected patients may be considered. A phase 2a randomized trial is underway to test the hypothesis whether systemic tissue-type plasminogen activator results in an improvement of respiratory function/oxygenation and reduction in mortality (NCT04357730). Further, inhaled fibrinolytic agents are an interesting option, potentially limiting systemic complications.⁸⁵ Assessment of their safety and efficacy requires further investigation (NCT04356833).

Antiplatelet Agents

Aspirin

Dysregulated immune response and abnormal coagulation are common occurrences in the pathophysiology of viral sepsis, ARDS, and organ failure in COVID-19.⁸⁶ Platelets play a key role in the pathogenesis of sepsis and thrombosis, and are a potential target for prevention of the complications.⁸⁷

In addition to thrombosis and hemostasis, platelets have immunomodulatory activity, including both inflammatory and anti-inflammatory responses, as well as an effect on antimicrobial host defense.^{88,89} There is evidence that the initial intrinsic defense against infections is mediated by platelet–neutrophil cross-communication that tightly regulates immune and complement responses.⁸⁸ These interactions can facilitate a variety of proinflammatory effects such as cytokine release, endothelial cell activation, platelet–leukocyte interaction, formation of neutrophil extracellular traps, and fibrin/microthrombus formation that while potentially harmful^{90,91} can also inhibit macrophage-dependent inflammation and thus may on balance be protective.^{87,92,93}

Acetylsalicylic acid (aspirin) has been extensively studied in ARDS. Aspirin has been associated with ARDS prevention and higher survival rates from acute lung injury in animal models and observational human studies.^{94–99} Aspirin has been associated with reduced mortality in the setting of both prehospital use and use in ICU.^{97,98} These findings, however, were not validated in a phase 2b randomized clinical trial.¹⁰⁰ Some investigators have hypothesized that higher maintenance doses of aspirin (325–650 mg/d) may be required to

achieve the desired anti-inflammatory effect in patients with an exuberant immune response.^{101,102}

P2Y₁₂ Receptor Antagonists

The role of P2Y₁₂ receptor inhibitors has also been described in ARDS and sepsis. Adenosine diphosphate-mediated activation of the P2Y₁₂ receptor may occur in many inflammatory and immune cell types including platelets, leukocytes, and dendritic cells. Among 224 consecutive patients admitted for community-acquired pneumonia, those receiving antiplatelet agents (aspirin and/or thienopyridines) for at least 6 months had lower use of the ICU and shorter stay in the hospital compared with age-matched controls.¹⁰³ In a post hoc analysis from the PLATO trial, patients with acute coronary syndromes treated with the potent P2Y₁₂ inhibitor ticagrelor and aspirin had fewer adverse pulmonary events and sepsis and lower mortality with those events compared with patients treated with the less potent P2Y₁₂ inhibitor clopidogrel and aspirin.¹⁰⁴

The XANTHIPPE trial (Examining the Effect of Ticagrelor on Platelet Activation, Platelet-Leukocyte Aggregates, and Acute Lung Injury in Pneumonia) was the first double-blind, placebo-controlled, randomized study to evaluate the effect of ticagrelor on inflammation, platelet activation, and lung function in patients with community- or hospital-acquired pneumonia.¹⁰⁵ Among 60 randomized patients, ticagrelor administration within 48 hours of pneumonia diagnosis was associated with an anti-inflammatory effect evidenced by reduced platelet-leukocyte aggregates in the circulation, lowered interleukin (IL)-6 levels, and improved lung function with a decrease in supplemental oxygen requirements. However, given the potential bleeding risks, in the absence of phase III trials demonstrating favorable clinical outcomes, these research findings have not translated into routine clinical practice.

With respect to COVID-19 and antiplatelet agents, there are many unknowns as regards their use and utility. First, it is not clear which phase of the disease might best respond. Second, the optimal agent and dose to maximize efficacy while minimizing bleeding risks are unknown. Due to its pleiotropic effects, ticagrelor may have more potent anti-inflammatory and even bactericidal characteristics than other agents.^{106,107} Randomized trials evaluating role of aspirin and clopidogrel in COVID-19 patients at increased cardiovascular risk are underway (NCT04333407). Third, antiplatelet therapies may have adverse drug-drug interactions with some investigational COVID-19 therapies such as lopinavir/ritonavir and remdesivir.^{5,108,109} Fourth, thrombocytopenia (immune-mediated or consumption-related) is associated with increased risk for worse clinical outcomes with COVID-19.^{110,111} Finally, the extent to which bleeding risks are increased, particularly in patients with DIC, is unknown.

Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor that inhibits platelet aggregation by increasing intracellular concentrations of cyclic adenosine monophosphate.¹¹² In addition to

its well-known antithrombotic properties, dipyridamole may have antiviral effects with proposed activity against influenza in animal models.¹¹³ In mouse models of viral pneumonia, dipyridamole administration promoted interferon response and prolonged survival in infected mice. Dipyridamole has antiviral effects in vitro, specifically confirming the affinity of dipyridamole for a SARS-CoV-2 main protease (M^{Pro}).¹¹⁴ To date, one study has examined dipyridamole in the treatment of COVID-19; 31 patients with COVID-19 were randomized to dipyridamole (150 mg three times a day for 7 days) versus control. In this small study, those treated with dipyridamole showed trends toward higher cure and hospital discharge rates. Increased platelet counts and decreased D-dimer levels were also noted with dipyridamole treatment, attributed to infection resolution.¹¹⁵ Further high-quality data are needed to evaluate the anti-SARS-CoV-2 therapeutic potential of dipyridamole.

Vorapaxar

Vorapaxar is an antiplatelet agent that exerts its antiplatelet activity through antagonism of the protease-activated receptor 1 (PAR-1) and inhibition of thrombin-induced platelet aggregation.¹¹⁶ In patients with history of myocardial infarction, or peripheral arterial disease, vorapaxar has been shown to reduce thrombotic cardiovascular events.¹¹⁷ The main concern associated with vorapaxar is its increased risk of bleeding events and reports of intracranial hemorrhage in patients with a previous history of stroke. PAR-1 is thought to have an important role in thrombin-induced platelet aggregation, and the link between coagulation, inflammation, and the fibrotic response. As such, investigating vorapaxar in patients with COVID-19 has received some attention.⁵⁰ However, its terminal half-life of 8 days renders it difficult to use in patients with severe COVID-19. To date, there are no registered randomized trials for use of vorapaxar in patients with COVID-19.

Hemostatic Modulating Agents

Antithrombin

The single-chain glycosaminoglycan antithrombin, which is produced in the liver, is modestly decreased in patients hospitalized with COVID-19.^{118,119} Thus, reduced antithrombin may be a potential therapeutic target for patients with COVID-19. Furthermore, the β -isoform of antithrombin binds preferentially to vascular heparin sulfate proteoglycans and initiates prostacyclin production and inhibition of nuclear factor kappa B (NF- κ B), resulting in anti-inflammatory effects, which might be further pronounced by the binding of β -antithrombin to receptors on monocytes.¹²⁰ Limited supporting data exist from patients with severe acute respiratory syndrome (SARS). Compared with healthy individuals such patients had lower levels of the natural inhibitors of coagulation and higher levels of PAI-1.

Blood coagulation parameters were investigated in 94 patients with COVID-19 pneumonia, of whom 49 had "ordinary," 35 had severe, and 10 had critical forms of COVID-19.¹²¹ When compared with 40 healthy controls, patients in

all three categories of COVID-19 had significantly lower levels of antithrombin, and the three subsets of patients had similar levels (86.0, 85.6, and 82.4%). Nebulized antithrombin has resulted in decreased coagulopathy and inflammation in animal models of lung injury.^{122–124} Despite these promising findings, there is to date no clinical evidence to support antithrombin provision to critically ill patients or in those with DIC and COVID-19. In a randomized controlled trial of 2,314 patients with severe sepsis, there was no effect of antithrombin therapy on 28-day mortality.¹²⁵ Moreover, in a meta-analysis of 3,019 patients included in 11 trials, antithrombin administration in critically ill patients was associated with more bleeding events (relative risk [RR]: 1.58; 95% confidence interval [CI] 1.35–1.84).¹²⁶

Thrombomodulin

Thrombomodulin is an endothelial cell glycoprotein with potent anticoagulant and anti-inflammatory effects mediated through activated protein C (APC)-dependent and APC-independent protein C mechanisms. In inflammatory states, thrombomodulin production is downregulated and surface thrombomodulin is cleaved so that there is reduced activation of protein C.¹²⁷ The role of recombinant thrombomodulin as a potential modifier of clinical outcomes in patients with sepsis has been evaluated in clinical trials.

The SCARLET study (Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin) was a randomized placebo-controlled double-blind study of recombinant human soluble thrombomodulin in 800 patients with objective evidence of bacterial infection, sepsis-induced systemic inflammatory response syndrome, and concurrent cardiovascular and/or respiratory dysfunction.¹²⁸ There was no significant between-group differences in the 28-day primary mortality outcome or other secondary endpoints. A post hoc subgroup analysis in patients with coagulopathy reported a trend for reduced mortality compared with placebo (risk difference –5.40%; 95% CI –1.68% to 12.48%). A subsequent systematic review and meta-analysis suggested lower mortality among patients with (but not in those without) sepsis-induced coagulopathy treated with thrombomodulin (RR: 0.80; 95% CI, 0.65–0.98).¹²⁹ Currently, there is insufficient evidence to recommend the routine use of thrombomodulin in patients with severe COVID-19. However, investigational use is warranted in selected subgroups with evidence of coagulopathy.

Activated Protein C

APC can play a key role in reducing the damage caused by wide variety of triggers, including ischemia/reperfusion injury, gastrointestinal inflammation, sepsis, and Ebola virus infection.¹³⁰ In 2002, recombinant human protein C was approved by the U.S. Food and Drug Administration (FDA) for the clinical treatment of severe sepsis and ARDS. Protein C concentrates reduced the risk of mortality in early studies of sepsis and septic shock. However, subsequent clinical trials have reported neutral results.¹⁹ Specifically, a randomized trial of 1,697 patients did not demonstrate a reduction in mortality at 28 or 90 days after APC was administered in the

setting of septic shock,¹³¹ and subsequent concerns emerged regarding the risk of serious bleeding and death in individuals with bleeding precautions.¹³² A possible explanation is that APC may only benefit septic patients complicated by DIC, which was a minority of patients in these trials.

In a study of 27 patients with ARDS (16 treated with recombinant APC and 11 with placebo), the infusion of recombinant APC increased APC levels in the pulmonary compartment and attenuated systemic coagulopathy and pulmonary coagulopathy, providing faster resolution of pulmonary dysfunction without bleeding complications.¹³³ However, in a subsequent randomized controlled trial of 71 patients, infusion of recombinant APC for infectious or inflammatory ARDS did not improve alveolocapillary permeability nor the clinical course of ARDS patients.¹³⁴

It is intuitive that protein C concentrates may be more beneficial in patients with significant protein C reduction. However, in a small study of 11 critically ill COVID-19 patients, protein C levels were overall increased, with only 4 patients having a protein C level lower than normal.¹¹⁹ The protein C mutant, 3K3A-APC, being developed for acute stroke treatment, was engineered to have low anticoagulant activity (so low bleeding risk) while retaining APCs' anti-inflammatory and cytoprotective cell signaling properties that may be important in pneumonia. The potential utility of recombinant APC or 3K3A-APC in patients with COVID-19, including those with DIC, is worthy of prospective investigation.¹³⁵

Contact Activation System

Dysregulation of inflammation and coagulation are hallmarks of COVID-19. The contact activation system, which includes factor XII, factor XI, high-molecular-weight kininogen, and prekallikrein, links inflammation and coagulation by triggering the generation of thrombin and bradykinin. Thrombin promotes clot formation and platelet activation, whereas bradykinin induces the release of proinflammatory cytokines.

In nonhuman primate models of bacterial sepsis, inhibition of factor XIIa or blockade of reciprocal factor XI and factor XII activation reduced the levels of inflammatory cytokines, attenuated microvascular thrombosis, and improved survival.^{136–139} Likewise, in murine models of bacterial sepsis, inflammation and coagulation were attenuated, and survival was enhanced in factor XI-deficient mice compared with their wild-type counterparts.^{140,141} Several inhibitors of factor XII and factor XI are currently under investigation. Studies evaluating the efficacy and safety of these agents in COVID-19 are warranted.¹⁴²

Anti-Inflammatory Agents

Corticosteroids

There is conflicting evidence for the use of corticosteroids in COVID-19-related ARDS.¹⁴³ Postulated benefits, including reduction in inflammation and lung injury, must be weighed against the potential risks of delayed viral clearance and increased susceptibility to secondary infections.^{144–147}

Mechanisms as to whether corticosteroids may modulate thrombotic risk in this patient population are not well-established. As the microvascular and macrovascular thrombotic complications observed in COVID-19 may in part be attributable to the inflammatory environment precipitated by the infection, corticosteroids may reduce thrombotic risk through anti-inflammatory activity. Studies of inflammatory states, particularly rheumatologic conditions, have shown a proportional relationship between inflammatory activity, coagulability, and the risk of VTE. Results regarding frequency of thrombosis with disease-modifying therapies, including corticosteroids, are mixed.^{148,149} Possible beneficial¹⁵⁰ mechanisms include reductions in levels of procoagulant factors, including fibrinogen and von Willebrand factor.¹⁵¹ However, experimental studies have also linked steroid use to increased levels of various clotting factors, and several large-scale studies have shown exogenous glucocorticoids to be a risk factor for thrombosis.^{150–152} Prior studies of corticosteroids in patients with non-COVID-19-related ARDS have shown mixed results with potential benefit limited to only certain subgroups of patients.¹⁵³ Further experience and research, including results from a series of ongoing randomized trials, are needed to better understand the balance of pro- and anticoagulant properties of glucocorticoids in the setting of COVID-19.

Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline that has an immunomodulatory effect and antithrombotic activity that have been demonstrated in animal models and in patients with systemic lupus erythematosus, rheumatoid arthritis, and antiphospholipid syndrome.^{154–157}

In a mouse model, hydroxychloroquine reversed the thrombogenic properties of antiphospholipid antibodies.¹⁵⁸ Hydroxychloroquine may also have mild antiplatelet effects in patients with antiphospholipid antibodies, and may reduce blood viscosity.¹⁵⁴ An observational prospective study of patients with antiphospholipid antibody syndrome treated with hydroxychloroquine 200 mg daily demonstrated significant reduction in soluble tissue factor levels at 3 months compared with baseline.¹⁵⁹ Other potential antithrombotic mechanisms have led to its limited evaluation as a thromboprophylaxis modality in postoperative patients more than three decades ago.^{160,161} However, the exact mechanisms by which it exerts its antithrombotic effect remain largely unknown. Given the known adverse effects with hydroxychloroquine, including QTc prolongation and risk of arrhythmias,¹⁶² its routine use as an antithrombotic therapy in patients with COVID-19 cannot be recommended until further prospective data emerge.

Statins

HMG-CoA reductase inhibitors (statins) are widely used as cholesterol-lowering medications in patients with or at increased risk of atherosclerotic cardiovascular disease.¹⁶³ The pleiotropic effects of statins include improving endothelial function, decreasing inflammatory markers, and inhibiting thrombogenicity.¹⁶⁴ Because patients with COVID-19 may exhibit increased activation of the inflammatory cascade and

are prone to venous and arterial thrombosis, leveraging statins as a component of treatment has been proposed.^{5,165,166}

While no clinical studies have evaluated statin therapy in the management of COVID-19, there is biological plausibility and precedent for such investigation. Through inhibition of the MYD88 stress-response pathway, statins suppress NF- κ B-induced proinflammatory cytokines.¹⁶⁷ This may underlie their proposed utility in other viral pneumonias, including those caused by related coronaviruses.^{168–170} Besides mitigating inflammation, antiplatelet and anticoagulant properties can occur via downregulation of tissue factor, upregulation of thrombomodulin, and inhibition of thromboxane A₂.¹⁷¹ Prior reports have shown that use of statins is associated with reduced rates of VTE, and statins have stabilizing effects on atherosclerotic plaques.^{172,173} At least three clinical trials (NCT04348695, NCT04333407, and NCT04343001) are recruiting COVID-19 patients in randomized statin investigations.

Targeted Immunomodulatory Therapies

SARS-CoV-2 infection is associated with an inflammatory response marked by increased cytokine levels (e.g., IL-2, IL6, IL-10, tumor necrosis factor- α).¹⁷⁴ To treat the inflammatory response generated by severe COVID-19, some have proposed to repurpose immunomodulatory medications approved for other diseases.

One potential target is the complement cascade. A major component of innate immunity, the complement cascade has three independent pathways for activation (classical, lectin, and alternative), each culminating with formation of the lytic membrane attack complex. Eculizumab is an anti-C5 monoclonal antibody that blocks terminal complement activity. One of its clinical applications is complement-mediated thrombotic microangiopathy, namely atypical hemolytic uremic syndrome, which is thought to occur in some patients with COVID-19.^{20,175} In one study of five COVID-19 nonsurvivors, there was evidence of systemic activation of the alternative and lectin-based complement pathways and deposition of the membrane attack complex in both lung and skin.¹⁷⁵

Based on these data and evidence of efficacy of complement inhibition in murine models of SARS-CoV and MERS-CoV, the use of eculizumab in COVID-19 has been proposed.^{20,175} Potential barriers include a 1,000 to 2,000 times increased risk of meningococcal disease (requiring prior vaccination or antibiotic prophylaxis) and cost (\$20,000–\$25,000 per dose).

The Janus kinase (JAK)–signal transducer and activator of transcription pathway is another potential therapeutic target. JAK inhibitors target cytokine signaling pathways and have thus been proposed as a candidate to treat COVID-19. Baricitinib, a JAK1/JAK2 inhibitor approved for the treatment of rheumatoid arthritis, mitigates the systemic inflammatory response and has *in vitro* activity against SARS-CoV-2 through its numb-associated kinase inhibition that has a high affinity for AAK1, a regulator of clathrin-mediated endocytosis.¹⁷⁶ Notably, this therapy does carry a FDA warning for an increased incidence of VTE (6/997 patients with baricitinib vs. 0/1,070 controls),¹⁷⁷ and recent National Institutes of Health (NIH)

COVID-19 Treatment Guidelines recommends against the use of baricitinib outside of a clinical trial, such as the NIH-sponsored ACTT-2 trial comparing remdesivir ± baricitinib.¹⁷⁸ Ruxolitinib is a JAK2 inhibitor approved for patients with myelofibrosis and polycythemia vera. Similar to baricitinib (NCT04340232, NCT04320277, and NCT04346147), ruxolitinib is presently under investigation as a treatment for COVID-19 (NCT04334044, NCT04348071, NCT04337359, NCT04331665, NCT04348695, and NCT04338958).

Tocilizumab, an IL-6 receptor antagonist approved for the treatment of rheumatoid arthritis and cytokine release syndrome associated with chimeric antigen receptor-T cell therapy, is included in the Chinese National Health commission guidelines for treating COVID-19. While findings are yet to be published, a randomized trial of 129 hospitalized patients with moderate-to-severe COVID-19 pneumonia suggested that tocilizumab administration may significantly reduce rates of death or life support interventions.¹⁷⁹ It is thought that tocilizumab may mitigate the proatherothrombotic profile associated with rheumatoid arthritis. However, no specific data related to use of tocilizumab and VTE events in patients with COVID-19 have been published.

Future Directions and Conclusion

Despite the efforts of the international medical and scientific communities and recent declines in hospitalizations, COVID-19 continues to pose an unprecedented challenge. The prognosis for hospitalized patients with COVID-19, especially in the setting of critical illness, continues to be poor.^{180,181} While contributing factors to poor outcomes in patients with COVID-19 are likely multifactorial, thrombotic complications play a major role in the prognosis of these patients.⁵ The development of safe and effective thromboprophylaxis and treatment strategies for thrombotic disease is contingent on an improved understanding of the mechanistic and pathophysiological basis for such complications in COVID-19 patients. In this document, we have outlined several agents and mechanisms of action for potential for use as antithrombotic agents in the setting of COVID-19. Survey results from group of authors may be helpful for research priority settings for various agents and patient subgroups with COVID-19 (► **Table 3**). High-quality research investigations into the optimal drug, dose, and duration of therapies to prevent and treat thrombotic complications of COVID-19 offer the potential to improve outcomes of infected patients.

Conflict of Interest

No specific funding was sought or received for this manuscript. A list of Disclosures for co-authors is available online in the ► **Supplementary Material** (available in the online version).

Acknowledgment

The authors would like to acknowledge BioRender for providing templates and the platform that were used for creating ► **Fig. 1**.

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