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Therapeutic considerations for prevention and treatment of thrombotic events in COVID-19

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ABSTRACT

Thrombosis is a known complication of SARS-CoV-2 infection, particularly within a severely symptomatic subset of patients with COVID-19 disease, in whom an aggressive host immune response leads to cytokine storm syndrome (CSS). The incidence of thrombotic events coinciding with CSS may contribute to the severe morbidity and mortality observed in association with COVID-19. This review provides an overview of pharmacologic approaches based upon an emerging understanding of the mechanisms responsible for thrombosis across a spectrum of COVID-19 disease involving an interplay between immunologic and pro-thrombotic events, including endothelial injury, platelet activation, altered coagulation pathways, and impaired fibrinolysis.

1. Overview of thrombosis in COVID-19

The clinical course and outcome of individuals infected with SARS-CoV-2 is decided, in part, by the now well-established risk of thrombotic complications, including pulmonary emboli [1]. Histopathological findings in fatal cases of COVID-19 disease revealed fibrinous thrombi deposited within pulmonary arterioles and endothelial tumefaction within pulmonary capillaries [2]. Although not completely understood, studies attribute increased levels of urokinase plasminogen activator (uPA), plasminogen activator inhibitor (PAI-1) and the presence of a positive lupus anticoagulant (LA) to this impairment of fibrinolytic function seen in individuals with COVID-19 disease [1]. Additional studies suggest hemostasis, endothelial injury, and hypercoagulability as likely contributors to observed fibrinolytic impairment and to clinical presentations of ischemic stroke, venous thromboembolism, and pulmonary embolism seen in individuals infected with SARS-CoV-2 [3].

A comprehensive review of COVID-19 cohorts globally supports an observed increase in thrombotic complications in individuals infected with SARS-CoV-2. Confirmed through imaging studies, a French cohort of over 100 patients, who presented with COVID-19 disease, found evidence of acute pulmonary embolism in nearly one-third of patients [4]. Additional cohorts worldwide have reported an increased risk of stroke and stroke syndrome severity in individuals infected with SARS-CoV-2, suggesting worsening COVID-19 clinical course and outcome [5–7]. Further, autopsy series have revealed features including endothelial injury, microthrombi and viral-mediated injury to the endothelium within the microvasculature of the lung, heart, liver, and kidney [8–10]. Therefore, multi-organ thrombotic disease in the setting of SARS-CoV-2 infections may involve the integrative effects of primary and secondary hemostasis, that is, platelet activation and aggregation and induction of coagulation cascade proteins, in addition to upregulation of the eicosanoid pathway, and impaired fibrinolysis. Consequently, SARS-CoV-2 infection may be a function of a simultaneous pro-thrombotic/anti-thrombotic dysfunction (Fig. 1). This observed

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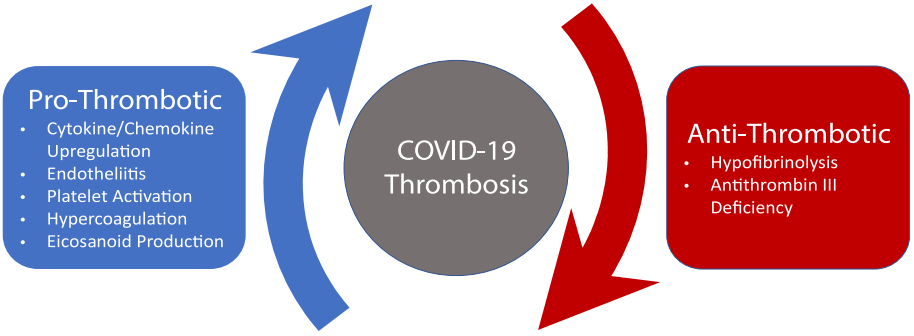

Fig. 1. Dysregulation of Pro-thrombotic and Anti-thrombotic Factors Contributing to COVID-19 Thrombosis. Thrombosis in COVID-19 results from a complex interplay involving a functional imbalance of pro-thrombotic and anti-thrombotic factors contributing to an increase in clinical thrombotic risk. Elevations in cytokines and chemokines promote endothelial injury, increased eicosanoid expression, and enhanced platelet interactions, leading to thrombosis. Downregulation or "escape" from anti-thrombotic mechanisms through impaired fibrinolytic pathways and reduction in anti-thrombin III potentiates this pro-thrombotic state.

thrombotic risk predominates as the acute hyperinflammatory, lymphocyte and macrophage rich immune response known as cytokine storm syndrome (CSS) [11].

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare syndrome observed in a small number of individuals who received adenoviral vector-based COVID-19 vaccines, such as ChAdOx1 CoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India) and Ad26.COV2.S vaccine (Janssen; Johnson & Johnson). VITT begins 5–10 days post-vaccination, and most commonly presents with cerebral venous thrombosis (CVT) [12,13]. However, isolated thrombocytopenia without thrombosis can also occur [14]. All individuals with VITT and thrombosis should receive full therapeutic dose anticoagulation with a non-heparin anticoagulant, especially if heparin induced thrombocytopenia (HIT) has not been ruled out. Urgent administration of high dose intravenous immunoglobulin (IVIG) may be used for two days [15]. In refractory cases, therapeutic plasma exchange can be used with concerning features such as platelet count <30,000/μL with CVT [16]. VITT remains extremely rare, and vaccination remains the primary means of preventing COVID-19. The risk of developing thrombosis from COVID-19 greatly exceeds the risk of VITT [17]. People who have recovered from the VITT should not receive another adenoviral vectored vaccine, but mRNA vaccines may be safe. The adenoviral vaccines appear to stimulate antibodies to platelet factor 4 (PF4), which activate platelets and cause thrombosis in the absence of heparin, similar to spontaneous or autoimmune heparin induced thrombocytopenia (HIT) [18]. Some studies postulate that the negatively charged viral DNA can bind to PF4, causing VITT [19]. Others hypothesize that thrombosis is related to a soluble spike protein variant, originating from splicing events, which cause important endothelial cells inflammatory events, binding to endothelial cells expressing angiotensin converting emzyme-2(ACE2) [20] This mechanism may also explain severe cases of SARS-CoV-2. Our group recently reported a mechanistic basis for thrombosis in CSS in COVID-19 that integrates these key features [21].

2. Therapeutic considerations for thrombotic events in COVID-19

Therapeutic options to prevent or treat thrombosis in COVID-19 are rapidly evolving with numerous studies enrolling patients. Further, the prevailing evidence supports the concept that all COVID-19 patients experiencing CSS are at increased risk for thrombosis [22,23]. Cytokine storm can be observed not only in viral infections, but also in association with autoimmune disorders or hemophagocytic lymphohistiocytosis (HLH). HLH can occur in the form of primary or familial syndromes as well as secondary or reactive HLH. This can include systemic lupus erythematosus (SLE) and macrophage activation syndrome (MAS) associated with systemic juvenile idiopathic arthritis. SARS-CoV-2 infected patients with CSS demonstrate a similar cytokine profile to reactive HLH, highlighting the similarity between these syndromes [24]. Coagulation disorders are reported in over half the patients with HLH, frequently attributed to hypofibrinogenemia. Although the mechanism of hypofibrinogenemia in HLH is not well defined, there is some suspicion that plasminogen activator inhibitor type 1 (PAI-1) may be a contributing factor, or that PAI-1 could be linked to fibrinogen consumption in DIC, frequently observed in severe cases of HLH as in CSS associated with COVID-19 [25].

The use of various thromboprophylaxis interventions in COVID-19 patients who have not yet experienced thrombotic events has been described. However,evidence of improved survival from the use of intermediate-dose heparin, therapeutic-dose heparin, or methylprednisolone has not been reported [26]. Additionally, the VAS-European Independent Foundation in Angiology/Vascular Medicine published thromboprophylaxis guidelines for COVID-19 patients with previous vascular disease and cardiovascular risk factors [22]. These guidelines suggest strict adherence to standing medications for previously diagnosed vascular disease, as well as administration of intermediate dose Low Molecular Weight Heparin (LMWH) or Unfractionated heparin (UFH) with heparin response testing in hospitalized patients. The International Society on Thrombosis and Haemostasis, the Anticoagulation Forum, and the American Society of Hematology (ASH) recommend prophylaxis in all non-ICU and ICU patients hospitalized with COVID-19 [27–30]. The ASH recently updated their position on prophylaxis recommending consideration of therapeutic, rather than prophylactic, anticoagulation in patients with COVID-19-related acute illness without known coagulopathy [29]. A question remains as to whether a more targeted approach to anticoagulation therapy with attention to the pro-thrombotic/anti-fibrinolytic mechanisms at play in COVID-19-related disease could improve outcomes among patients with the greatest risk of thrombotic events. It is possible that certain variants of SARS-CoV-2 may be associated with higher likelihood of thrombosis than other variants, however, further work is required to investigate this area.

To provide additional clarity of our discussion in this report, we encourage use of Fig. 2, which illustrates mechanisms of action of therapeutics summarized in this report and Table 1, which provides a summary of mechanisms of action of therapeutics studied in thrombosis-related COVID trials.

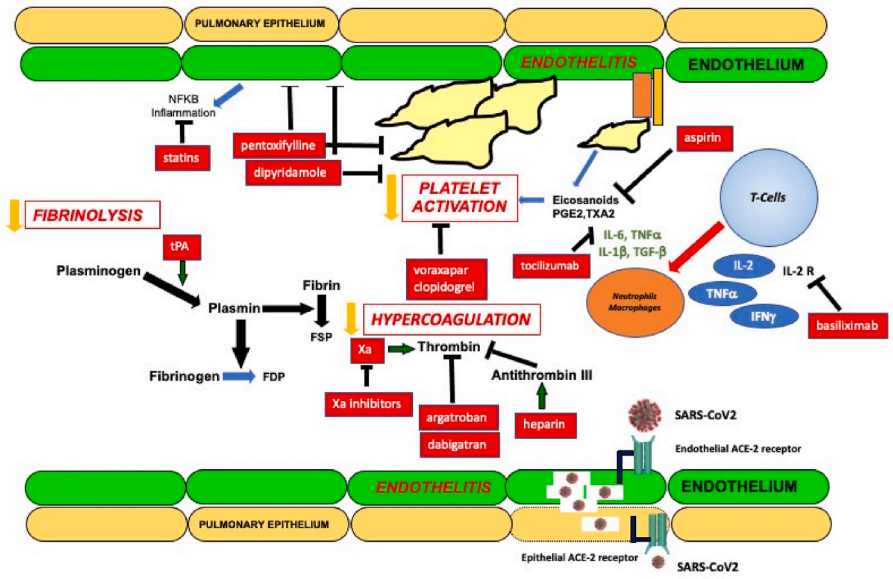

Fig. 2. Key therapeutic targets for anti-thrombotic therapies based on the integrated mechanisms of COVID-19 thrombosis. Strategies to treat thrombotic events in COVID-19 should be driven by the severity of thrombosis and established standards of care translated to patient specific needs. Studies are underway to determine if immunomodulation can reduce thrombosis risk. Inhibition of thromboxane A2 and prostaglandins by aspirin, inhibition of the P2Y1A receptor with clopidogrel, or inhibition of the protease activated receptor with vorapaxar may represent early preventative strategies for thrombosis in at risk COVID-19 patients. Intravenous use of argatroban or oral use of dabigatran to treat thrombosis in COVID-19 may offer significant benefit based on reduced levels of anti-thrombin III which may impair strategies centered around heparin or low molecular weight heparins. Intravenous tPA has been used successfully to treat cerebral embolism in COVID-19. Endothelitis may be potentially treated with pentoxifylline, dipyridamole, or statins.

Table 1
Summary of mechanisms of action of therapeutics studied in thrombosis-related COVID trials.

Classic Anti-Thrombotic Mechanisms and Major Trials		
Therapeutic	Mechanism of Action	Major COVID-related Trials
Sulodexide	Releases tissue factor pathway inhibitor	N/A
Pentoxifylline	Phosphodiesterase inhibitor that reduces platelet aggregation via increased cAMP levels	N/A
Dipyridamole	Phosphodiesterase inhibitor that reduces platelet aggregation via increased cAMP levels	N/A
Aspirin	Inhibits thromboxane A2 formation in megakaryocytes and platelets	RECOVERY: Once daily 150 mg aspirin demonstrated no change in all-cause mortality, and no decreased risk of progression to invasive mechanical ventilation. It demonstrated moderately shorter hospitalization and a longer 28-day survival [55]. RECAP-MAP: No difference in organ support-free days or survival [56].
Clopidogrel	Irreversibly inhibits adenosine diphosphate binding of the $P2Y_{12}$ receptor of platelets	N/A
Voraxopar	Protease activated receptor antagonist that reduces platelet mobility and aggregation affinity	N/A
Tissue Plasminogen Activator	Mitigates platelet attachment at the endothelium and subsequent initiation of the coagulation cascade	N/A
Enoxaparin	Low molecular weight heparin that enhances binding of antithrombin III to factors IIa and Xa, enhancing thrombin clearance	INSPIRATION: No significant difference in intermediate versus standard-dose enoxaparin in selected patients admitted to the ICU with COVID-19 [82] OVID: No decrease in early hospitalization or deaths in outpatient primary thromboprophylaxis [83]. ETHIC: No decrease in all-cause mortality or hospitalization in the outpatient setting [84].
Heparin	Enhances binding of antithrombin III to factors IIa and Xa, enhancing thrombin clearance	REMAP-CAP, ATTACC, ACTIV-4a: Decreased use of respiratory and or cardiovascular organ support, increased survival to discharge in therapeutic versus standard prophylaxis in non-critically ill patients [88]. No difference in critically ill patients [89].
Argatroban	Direct thrombin inhibitor	Sathyamoorthy et al. FWCSWG. Direct Thrombin Inhibition using Argatroban for Treatment of Cytokine Storm Associated Thrombosis in COVID-19. (IRB pending)
Rivaroxaban	Factor Xa inhibitor	MICHELLE: Low-dose extended thromboprophylaxis showed improved clinical outcomes at 35-days versus no extended thromboprophylaxis [101]. ACTION: Therapeutic rivaroxaban showed no improved clinical outcomes compared to standard prophylaxis in hospitalized COVID-19 patients with elevated d-dimer [102].
Apixaban	Direct factor Xa inhibitor	ACTIV-4b: No improved clinical outcomes in the outpatient COVID-19 setting versus no intervention.
Anti-Inflammatory Antithrombotic Mechanisms and Major Trials		
Therapeutic	**Mechanism of Action**	**COVID-related Trials**
Pentoxifylline	Phosphodiesterase inhibitor that increases IL-10 production via downstream effects	N/A
Dexamethasone	Downregulates pro-inflammatory T-cell response; decreases PGE_2 and other pro-inflammatory eicosanoids	RECOVERY: A 10-day, 6 mg regimen plus standard care showed significant reduction of all-cause mortality for COVID-19 patients receiving invasive mechanical ventilation or non-mechanical oxygen support at time of randomization [108].
Toclizumab	Monoclonal antibody that inhibits IL-6 receptor signaling	COVACTA: Hospitalized patients with severe COVID-19 showed no significantly improved clinical outcomes or lower mortality versus placebo at 28 days.
Basiliximab	Monoclonal antibody that inhibits IL-2 receptor signaling	Sathyamoorthy et al. "Exploratory Regimen of Basilixamab for Treatment of Pulmonary Cytokine Storm in SARS-CoV-2 Hospitalized Adult Patients. FDA IND granted.
Statins	Increase ACE-2 levels and inhibit the cardiovascular toll-like receptor pathway	N/A

2.1. Complement pathway therapeutics

Complement activation is a frequent feature of the pathophysiology of acute respiratory distress syndrome and is prevalent in COVID-19. The spike and nucleocapsid proteins of SARS-CoV-2 can activate the complement system directly through the lectin pathway, while IgG and IgM antibodies directed against the receptor-binding domain of the spike protein initiates the classical pathway [31,32]. The spike protein can also compete with factor H, a key negative regulator of complement activity, and bind heparan sulfate, causing dysregulation of the alternative pathway [33]. Complement3(C3) and Complement5a(C5a) potentiate activation of leukocytes and neutrophils causing production of pro inflammatory cytokines and local neutrophil extracellular traps. SARS-CoV-2-primed endothelial cells upregulate C5a receptor 1 (C5aR1) causing pathological c5a activation and insertion of membrane attack complex (MAC) [34]. Simultaneously, complement induces the activation of platelets and the coagulation cascade. The cumulative effect of both mechanisms is loss of thromboresistance and detrimental thrombus formation. Pharmacological investigations are directed towards these pathways to reduce infection-induced extracellular and intracellular complement activation and thrombus formation. Current trials are underway to study the efficacy of monoclonal antibodies against c3 (AMY101), c5 (eculizumab and ravulizumab), c5a (BDB-001 and vilobelimab), and c5aR1 (avdoralimab) to reduce the inflammatory response [35].

2.2. Endothelial therapeutics

2.2.1. Pentoxifylline

Pentoxifylline is a methylxanthine derivative and a hemorheological agent. Pentoxifylline acts by reducing blood viscosity, increasing erythrocyte flexibility and increasing flow in the microcirculation, therefore increasing tissue perfusion by delivering oxygen to ischemic tissue [36]. It is currently prescribed to improve symptoms of patients diagnosed with intermittent claudication [36]. On a cellular level, pentoxifylline is a phosphodiesterase inhibitor that increases cyclic adenosine monophosphate (cAMP) levels leading to activation of protein kinase [37]. This leads to increased production of the cytokine IL-10, which then decreases production of pro-inflammatory cytokines such as IL-1, IL-6, IL-17, IFN-γ, and TNF-α, therefore inducing an anti-inflammatory response [37]. In vitro, pentoxifylline is also found to have a direct effect on the expression of the ACE-1 receptor [37]. In the setting of the SARS-CoV-2, pentoxifylline could potentially aid in treatment by reducing the extent of cytokine production without exerting an overt immunosuppressive response. In a randomized controlled trial (RCT), pentoxifylline was shown to reduce IL-6 levels in hospitalized patients with COVID-19, though it was not shown to have a significant effect on clinical outcomes [38,39]. This could allow viral clearance to be maintained while decreasing the extent of cytokine-induced inflammatory cascades that could be detrimental in these patients [37].

In the setting of overt sepsis, studies have demonstrated that pentoxifylline has proven effects on preservation of microvascular circulation and has protective effects on alveolar epithelial cells, vascular endothelial function and coagulation [37]. Animal models have demonstrated that pentoxifylline may preserve vascular function by improving the release of endothelium-derived nitric oxide as demonstrated in a study of polymicrobial sepsis in rats [40]. In the setting of a microvascular obstructive inflammatory thrombus syndrome presenting as severe hypoxia in the atypical acute respiratory distress syndrome (ARDS)-like presentation in COVID-19 patients, pentoxifylline has demonstrated improved ventilatory parameters by decreasing microvascular thrombosis [37].

In a study focusing on macrophage-induced TNFα and nitric oxide production following gastric acidic injury of alveolar cells in an animal model, pre-treatment with pentoxifylline interfered with TNFα production while preserving nitric oxide production and function [41]. Alveolar macrophage stimulation of TNFα during acute lung injury incites an inflammatory cascade that can ultimately lead to ARDS. When pre-treated with pentoxifylline and exposed to bacterium or lipopolysaccharides, the antimicrobial effects of TNFα on alveolar macrophages were preserved [41]. This is yet another example of pentoxifylline's ability to reduce the hazards of immune-induced inflammation, while preserving the host's protective mechanisms.

2.2.2. Sulodexide

Sulodexide is a purified mixture of glycosaminoglycan that includes heparan and dermatan sulfate. It has effects on the fibrinolytic system, platelets, endothelial cells, and inflammation. Like heparin, it releases tissue factor pathway inhibitor (TFPI) which contributes to its antithrombotic and anti-inflammatory properties, however, it has better oral bioavailability, longer half-life and it is associated with less bleeding compared with heparin [42]. Given its anticoagulant and anti-thrombotic actions, it is a potential therapeutic in COVID-mediated thrombosis. Gonzalez-Ochoa et al. assessed the effects of giving sulodexide within 3 days of clinical onset of COVID-19 [43]. When compared to placebo, the use of sulodexide, when provided within 3 days of clinical onset, was associated with a lower need for hospitalizations, supplemental oxygen, a lower proportion of patients with d-dimer >500 ng/dL (22 vs 47% $p < 0.01$) and lower mean CRP levels (12.5 vs 17.8 mg/dL $p < 0.01$) [43]. In a recent study, Charfeddine et al. looked at the beneficial endothelial effects of sulodexide in patients with long COVID-19 [44]. When compared to placebo, patients experienced improved chest pain (83.7 vs 43.6%, $p < 10^{\wedge}$-3) and palpitations (85.2 vs 52.9%, $p = 0.009$), both of which were correlated to improved endothelial function. This suggests that use of sulodexide improves long-lasting post-COVID-19 endothelial dysfunction, thereby alleviating chest pain and palpitations.

2.2.3. Dipyridamole

There is evidence-based use for dipyridamole (DMP) as an antithrombotic;.When used in combination with aspirin, it has been found to be superior to aspirin monotherapy in secondary prevention of stroke without increasing the risk of bleeding; the benefit of DMP is due to concomitant effects on blood pressure, and circulating Von Willebrand factor (vWF) [45]. DMP is a phosphodiesterase inhibitor that increases intercellular cAMP/cGMP and red cell uptake of adenosine [45,46]. DMP reversibly inhibits platelet aggregation and thus platelet-mediated thrombotic disease by increasing cAMP and cGMP levels in platelets [45]. Studies also suggest DMP preserves endothelial nitric oxide production, thus allowing for nitric oxide's ability to regulate blood flow, maintain vascular tone and increase tissue perfusion [45]. Antioxidant properties of DMP may prevent oxidation of low-density lipoprotein and stabilize platelet and vascular membranes [47]. DMP has other vascular-endothelial protective factors by inhibiting endothelial-leukocyte interaction in the setting of inflammation [45]. DMP also inhibits smooth muscle proliferation and, by increasing local concentration of prostacyclin and adenosine, may inhibit vascular inflammation and promote vascular tone [45].

Although DMP is known primarily as an antiplatelet and vasodilating agent, recent studies demonstrated that it may have broad spectrum antimicrobial and anti-viral properties as well [46,48]. After SARS-CoV-2 enters epithelial cells, viral RNA is translated by two proteinases to promote replication. DMP may be effective in COVID-19 due to inhibitory effects on positive-stranded RNA viruses like SARS-CoV-2. However, in vitro studies evaluating the role of DMP as an inhibitor of the SARS-CoV-2 main protease have shown mixed results [49].

DMP administrated early in a SARS-CoV-2 disease state may aid in suppression of inflammation, promote mucosal healing, and, via broad phosphodiesterase inhibition, may decrease acute local and systemic injury and progression of fibrosis in the lungs, kidney, heart, and liver. In patients infected with SARS-CoV-2, elevated d-Dimer levels >1 mg/dL

were associated with worse prognosis [46]. In a study involving 31 SARS-CoV-2-infected patients, DMP initiation of 50 mg three times a day for 14 days was found to significantly decrease concentrations of D-dimer levels and increase recovery of circulatory leukocytes and platelets [46]. Most importantly, DMP substantially improved clinical outcomes compared to controls, and all 8 of the most-severely ill patients included in the treatment arm of the study achieved clinical cure (7 patients) or remission (1 patient). All patients in this study were also treated with glucocorticoids, ribavirin, oxygen therapy and some received intravenous immunoglobulin and antibiotics [46].

2.3. Antiplatelet therapeutics

2.3.1. Aspirin

Acetylsalicylic acid (ASA), or aspirin, exerts its effects though the irreversible inhibition of the COX-1 enzyme in the eicosanoid pathway. Aspirin serves as an anti-platelet/anti-thrombotic therapy by inhibition of thromboxane A2 formation in megakaryocytes and platelets [50]. Aspirin may play a role in reducing disease severity and overall mortality rates in patients admitted to the intensive care unit (ICU) with ARDS [51].

In a prospective analysis that focused on aspirin treatment in patients who had either been taking aspirin prior to admission to intensive care or initiated at onset of the acute illness, aspirin therapy was superior to non-therapy [51]. By inhibiting platelet aggregation, aspirin also prevents the signaling pathway that triggers neutrophil migration leading to neutrophil extracellular traps [51]. In this pathway it triggers an anti-inflammatory lipid mediator (resolvin D1) via the acetylation of cyclo-oxygenase-2 [51]. This compound generated via aspirin is known to decrease neutrophil and macrophage migration recruitment, restoring the capillary-endothelial alveolar-epithelial barrier function, thus decreasing the severity of ARDS and possibly contributing to the resolution of the disease state [51]. In addition, the anti-inflammatory lipid mediator, 15-epi-lipoxin A4, is triggered via aspirin therapy, and displays preservation of neutrophil apoptosis, promoting restoration of effective immune function and contributes to alveolar inflammation resolution [51].

In the setting of SARS-CoV-2 infection, aspirin may play a role in treating patients at all levels of disease severity as growing knowledge suggests that even asymptomatic individuals displayed inflammatory lung injuries on computerised tomography (CT) imaging [52]. In addition to the effect of aspirin on neutrophil migration, aspirin plays a direct role in reducing pro-coagulation mediators. Aspirin administered at 500 mg per day for three days, results in significantly reduced release of PAI-1 from platelets [53]. Similar studies have shown a peak reduction of plasma PAI-1 levels 2-h post-administration of a single dose of 650 mg of aspirin [54]. The aspirin RECOVERY randomized multicenter trial found that the addition of 150 mg aspirin (once daily) did not improve all-cause mortality or decrease the risk of progression to invasive mechanical ventilation in hospitalized COVID-19 patients compared with standard therapy. Aspirin was associated with slightly shorter hospital stay and a modest increase in 28-day survival [55]. The REMAP-CAP trial was a large study investigating the use of aspirin in COVID-19 patients that additionally found no difference in organ support-free days or survival versus placebo [56]. Conversely, a large cohort study of hospitalized, non-ICU COVID-19 patients with moderate disease severity found aspirin use was associated with lower in-hospital mortality [57]. Thus, aspirin may offer a broad spectrum of benefits when used in the treatment of SARS-CoV-2, specifically in patients with less severe COVID-19 disease, through direct effects on inflammatory, cell migratory, and thrombosis pathways.

2.3.2. Clopidogrel

Clopidogrel is administered as a prodrug that undergoes hepatic metabolism to active drug, and acts as inhibitor of platelet aggregation by irreversibly blocking adenosine diphosphate (ADP) binding to the P2Y12 receptor of platelets. This prevents glycoprotein-IIb/IIIa complex activation and platelet aggregation [58]. In a recent meta-analysis comparison, Clopidogrel was found to have similar efficacy and safety outcomes when compared with ticagrelor, a direct-acting $P2Y_{12}$ platelet receptor modulator, in the treatment of acute coronary syndrome, though with a reduced incidence of dyspnea due to ticagrelor's increased $P2Y_{12}$ inhibition on sensory neurons [59]. A recent RCT comparing clopidogrel or ticagrelor in combination with heparin versus heparin monotherapy showed no improvement in organ support-free days in hospitalized non-ICU COVID-19 patients [60]. Given the well-established clinical experience with this agent, along with its reduced major bleeding risk when compared with more contemporary ADP receptor antagonists such as ticagrelor or prasugrel, clopidogrel could serve as a monotherapy. Alternatively, in combination with aspirin, clopidogrel could reduce the potential for thrombosis in at-risk COVID-19 patients.

2.3.3. Vorapaxar

Vorapaxar is the only commercially available protease activated receptor-1 (PAR-1) antagonist, and is indicated for secondary prevention in patients who have suffered from ischemia and infarction [61], However, it is contraindicated in patients with a history of stroke or transient ischemic attack [61]. Vorapaxar is given in addition to a $P2Y_{12}$ inhibitor and aspirin in an effort to prevent thromboembolic events in high-risk patient populations. Vorapaxar has not gained widespread use in clinical practice, largely due to the observed major bleeding risks observed when this agent was added to standard dual antiplatelet therapy in acute coronary syndrome [62]. However, based on the *potent* mechanism of action of inhibition of thrombin mediated platelet activation, we believe this agent could serve as a potential monotherapy or, in combination with low dose aspirin, could prevent or even treat microangiopathic thrombosis in COVID-19, and deserves hypothesis driven investigation through clinical studies.

PAR-1 is a G protein-coupled receptor located largely in platelets and endothelial cells [63]. Thrombin is a high potency activator of platelets, in which activation of the PAR-1 receptor occurs even at trace levels [63]. Platelets increase both mobility and aggregation affinity via through granulation release when PAR-1 is activated [63]. When this G protein is further coupled with another PAR receptor, PAR-4, increased calcium ion influx mediated through Inositol triphosphate (IP_3) leads to increased platelet activation [63]. Protein kinase C is also activated, causing further platelet aggregation and triggering of the coagulation cascade [63]. As such, the inhibition of PAR-1 leads to decreased thrombin-mediated platelet activation.

2.4. Anti-fibrinolytic therapeutics

2.4.1. Tissue plasminogen activator (t-PA)

Tissue plasminogen activator is a critical anti-thrombotic that is secreted by the endothelium and functions by mitigating platelet attachment and subsequent initiation at this site of the coagulation cascade. Serving as the molecular knife tPA cleaves the inactive zymogen plasminogen to the active fibrinolytic plasmin, which converts fibrin/fibrinogen polymers into fibrin split and degradation products [64]. Administration of tPA has historically been used to treat myocardial infarction, ischemic stroke, pulmonary emboli, or peripheral arterial thrombosis. Two case studies have showed improved outcomes with tPA administration in patients suffering from Acute Respiratory Distress Syndrome (ARDS) due to COVID-19 [65,66]. Studies using tPA in COVID-19 patients experiencing acute ischemic stroke are being evaluated [67]. A small RCT of tPA in patients with COVID-19 associated respiratory failure showed significantly improved oxygenation among treated individuals, but no difference in mortality versus standard of care [68]. Similarly, a small, open-label 3-arm pilot RCT evaluating tPA for the treatment of adults with critical COVID-19 showed statistical improvement in PaO2/FiO2 (P/F) ratios and Sequential Organ Failure

Assessment (SOFA) scores during the first 48 h of enrollment [69]. In patients receiving thrombolytic therapy (tPA), the average length of ICU stay was 7 days, though none of the patients were discharged from the ICU alive. In patients receiving therapeutic-dose anticoagulation, however, the average length of ICU stay was 8 days, and 3 patients of this group were discharged from the ICU alive. Finally, in patients receiving standard dose anticoagulation, average length of ICU stay was 11 days and only 1 patient of this group was discharged alive. Despite initial improvements in P/F ratios and SOFA scores, secondary study outcomes (ICU length of stay, ICU discharge %, increased risk of bleeding) give pause to the therapeutic benefit of tPA as treatment in adults with critical COVID-19.

Exogenous tPA can be administered intravenously, intraosseous, or via catheter-direction, depending on severity or accessibility. Given the elevated levels of PAI-1 in COVID-19 patients, the resulting hypofibrinolytic state may especially benefit from systemic or catheter-directed tPA administration for patients [70,71]. Catheter-directed tPA administration is highly effective in the treatment of thrombotic events, and is safely used in combination with direct thrombin inhibitors such as Argatroban [72,73].

2.4.2. Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor that is used for treatment of peripheral and cerebrovascular diseases that targets the endothelium and the fibrinolytic system. [74]. As noted in the discussion on therapies targeting the endothelium, pentoxifylline improves rheological properties of blood with effects on blood viscosity and improved microcirculation flow [36]. Pentoxifylline has anti-thrombotic effects including increasing the flexibility of erythrocytes and decreasing platelet aggregation via anti-inflammatory modalities [74]. Suppression of neutrophil activation with amplification of IL-10 by pentoxifylline protects against endothelial damage and development of a nidus for coagulation. When modulating leukocyte-endothelium adhesion with complete inhibition of intercellular adhesion molecule-1 expression, it sufficiently regulates leukocyte-platelet interactions relevant in thrombosis [75]. A study of the use of pentoxifylline for lysis of intraperitoneal adhesions in rats demonstrated increased levels and activity of tissue plasminogen activator when compared with a control group [76]. Further, the study demonstrated a significant decrease in PAI-1 in rats given doses of pentoxifylline. Pentoxifylline has regularly been administered as a fibrinolytic medication in varying thrombotic pathologies; these mechanisms could prove vital in the treatment of COVID-19 infections.

2.5. Anticoagulant therapeutics

2.5.1. Indirect thrombin inhibitors: heparins

Heparin is a standard treatment for patients with venous and arterial thrombosis, both of which have been reported in COVID-19. UFH and LMWH are antithrombin III (AT3) enzymatic catalysts that enhance the binding of AT3 to Factor IIa (FIIa) and Factor Xa(FXa) by a log scale. The heparin-antithrombin complex allows for rapid clearance of thrombin (factor IIa) and factor Xa, while also inhibiting factors IXa, XIa, and XIIa, although at a weaker level. UFH and LMWH are the most widely-used anti-coagulants in the hospitalized patient [77].

Thrombotic events continue to be observed in cases of COVID-19 [78]. However, the optimal regimen of antithrombotic treatment in these patients has yet to be determined. Inflammation associated with COVID-19 ARDS [79] may be partially treated with statin therapy [80]. Therefore, to explore the effects of anticoagulation therapy *and* statin treatment on critically ill patients infected with COVID-19, Bikdeli et al. initiated the INSPIRATION (intermediate versus standard-dose prophylactic anticoagulation in critically ill patients with COVID-19: an open label RCT) and INSPIRATION-statin (INSPIRATION-S) studies [81]. The study used a 2x2 factorial design to compare treatment with either standard-dose prophylaxis (40 mg/day) or intermediate dosing (based on patient weight) of the LMWH enoxaparin. Additionally, each of the two experimental groups were divided to compare the effects of statin therapy (atorvastatin 20 mg/day) to a placebo [81]. Findings from the INSPIRATION study revealed no difference in intermediate versus standard-dose enoxaparin in selected patients admitted to the ICU with COVID-19 [82]. Meanwhile, the impact of statin therapy has yet to be reported. It is anticipated that this may uncover a potential benefit in patients critically affected by COVID-19.

In the outpatient setting, the OVID trial, a randomized, open-label phase 3 controlled trial was terminated early when it failed to show that enoxaparin was beneficial as primary prophylaxis in preventing early hospitalizations or deaths in elderly patients with symptomatic COVID-19 compared to standard of care (no enoxaparin) [83]. Similarly, the ETHIC trial, a randomized, open-label phase 3 controlled trial investigating enoxaparin as primary thromboprophylaxis in the outpatient setting was terminated early due to a low event rate and slow enrollment of participants [84]. The authors of the ETHIC trial concluded that enoxaparin as primary thromboprophylaxis was not warranted in the outpatient setting for at-risk COVID-19 patients versus no enoxaparin when assessing for all-cause hospitalizations or mortality at 21 days. These two studies highlight that thromboprophylaxis in patients not experiencing CSS likely is unwarranted, as these patients may not face elevated thrombosis risk.

The ACTIV-4 master protocol is a series of trials examining antithrombotic use in prevention and treatment of COVID-19-associated coagulopathy. The ACTIV-4 inpatient trial is a phase 3 randomized, open-label, adaptive platform study examining the effects of either prophylactic or therapeutic anticoagulation treatment with heparin on 268 participants over 18 years old hospitalized with complications of COVID-19. A multiplatform study, including ACTIV-4a (Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE) found that utilization of therapeutic-dose heparin decreased use of respiratory or cardiovascular organ support and increased survival to discharge when compared with traditional hospital thromboprophylaxis methods in non-critically ill COVID-19 patients [87]. Similarly positive results were observed in non-critically ill COVID-19 patients when the study expanded to include investigations by ATTACC, ACTIV-4a, and REMAP-CAP investigators [88].

To determine whether therapeutic-dose anticoagulation would improve outcomes in critically ill COVID-19 patients, REMAP-CAP Investigators joined with the ACTIV-4a and ATTACC investigators to conduct an international, multiplatform RCT with over 1000 patients with severe infection. Severe infection was defined as symptoms in patients with a positive COVID-19 test that led to administration of ICU-level respiratory or cardiovascular organ support [89]. These patients were anticoagulated after random assignment to a regimen of either therapeutic-dose unfractionated heparin or usual-care pharmacologic thromboprophylaxis with the primary outcome being the number of organ-support free days. After terminating the eight-month long study and meeting the statistical criteria for futility, it was concluded that using therapeutic-dose anticoagulation does not effectively increase the probability of survival to discharge or the number of organ-support free days. In fact, the analysis showed a 95% probability that therapeutic dose anticoagulation is inferior to usual care thromboprophylaxis treatment [90]. This calls into question the reported association with improved outcomes identified in previous studies that showed its apparent effectiveness [90,91].

We believe there are potentially serious limitations to the efficacy of UFH and/or LMWH in SARS-CoV-2, based on an emerging understanding of reduced levels of circulating AT3 in COVID-19 patients. Approximately 50 IU/dl of AT3 must be present to reach therapeutic effects of UFH [92]. In its absence, UFH has limited anticoagulant activity. Administration of UFH or LMWH was demonstrated recently to be ineffective in COVID-19 patients in the ICU [93]. Deficiency in AT3, whether through increased consumption or reduced production, has been problematic in severe presentations of COVID-19. This accounts for

argatroban, a direct thrombin inhibitor that is independent of AT3, being a more effective therapeutic than heparin [94].

2.5.2. Direct thrombin (IIa) inhibitors: argatroban

A limitation in the above studies may be the observed refractory thromboembolic events, such as deep vein thrombosis and pulmonary embolism in COVID-19 patients despite treatment with heparins. In a recently-published study of 10 patients, nine of whom had confirmed thrombosis despite prophylaxis with LMWH, all were found to have reduced levels of AT3 [94]. Mechanistically, UFH and LMWH serve as catalysts for the binding of AT3 to factor IIa or Xa and, therefore, would theoretically be less effective in treating COVID-19 patients if they were deficient in AT3 [95].

Argatroban is a direct thrombin inhibitor that reversibly binds directly to the catalytic site of both clot-bound and unbound thrombin molecules to reduce the conversion of fibrinogen to fibrin [97]. The elimination half-life of argatroban is 52 ± 16 min. It is activated through a dose response, which is monitored by assessment of the activated partial thromboplastin time (aPTT) and activated clotting time. Due to its pharmacokinetic properties and mechanism of action, this drug can be used as an alternative to other intravenous anticoagulants. Argatroban is used to treat HIT and has been studied in the treatment of acute coronary syndrome, in association with percutaneous coronary intervention. It has also been used in treatment of arterial thrombosis [98]. Recently-published evidence supports the effectiveness of argatroban for treatment of organ system thrombosis, rescue from ineffective treatment with heparins, and for prevention of CRRT filter clotting in COVID-19 patients [94]. Similarly, an unpublished case series reported to the Fort Worth COVID-19 Clinical Sciences Working Group (FWCSWG) demonstrated that nine consecutive COVID-19 patients hospitalized in the ICU demonstrated consistently low levels of AT3.

2.5.3. Direct oral anticoagulants (DOACs)

Direct oral anticoagulation agents have become the standard of care and preferred agents in clinical practice for treatment of various types of clinical thrombosis. These agents include dabigatran, apixaban, rivaroxaban, and edoxaban [99]. DOACs offer an oral anticoagulant alternative to warfarin. They are indicated for: prevention of deep vein thrombosis and pulmonary embolism after orthopedic surgery; treatment of deep vein thrombosis and pulmonary embolism unrelated to orthopedic surgery; and for the prevention of stroke and systemic thromboembolism in patients with nonvalvular atrial fibrillation. DOACs do not require laboratory monitoring, have less food or drug interactions and can be used at fixed doses DOACs achieve rapid peak concentration (C-max), and have short half-lives; and have dramatically simplified oral anticoagulation [99]. Several phase 3 clinical trials comparing DOACs and warfarin have demonstrated non-inferiority to warfarin for stroke prevention, decreased risk of intracranial hemorrhage, and all-cause mortality [99]. DOACs now have approved reversal agents: andexanet alfa for apixaban and rivaroxaban and idarucizumab for dabigatran [100].

The two classes of DOACs include direct thrombin inhibitors and factor Xa inhibitors. Factor Xa inhibitors include apixaban, rivaroxaban, and edoxaban. These agents selectively inhibit free and clot-bound factor Xa while also interfering with prothrombinase activity, ultimately inhibiting formation of thrombin [100]. Dabigatran, the only direct oral thrombin inhibitor, is a reversible inhibitor of thrombin that can bind to thrombin that is free in the bloodstream or clot-bound [100]. When dabigatran binds to thrombin, fibrinogen cannot be converted into fibrin. In addition, dabigatran inhibits the activation of factor XIII, which inhibits the conversion of soluble fibrinogen to insoluble fibrin [100].

The therapeutic effects of DOACs are AT3-independent. Patients infected with SARS-COV-2 may demonstrate low levels of AT3, and this may partially explain why heparins, although often a first-line agent, have not produced consistent results in decreasing clot burden in these patients [94,95]. Therefore DOACs may serve as an anticoagulant of choice in appropriately selected COVID-19 patients with deep vein thrombosis and pulmonary embolism. The multi-center, randomized, controlled MICHELLE trial revealed that use of low-dose (10 mg/day) rivaroxaban for 35 days in patients at high risk of venous thromboembolism following hospital discharge due to COVID-19 had improved clinical outcomes compared with no extended thromboprophylaxis [101]. The ACTION trial, however, failed to demonstrate improvement with therapeutic doses (20 mg/day or 15 mg/day) of rivaroxaban versus standard hospital prophylaxis in hospitalized COVID-19 patients with elevated d-dimer [102]. Similarly, the ACTIV-4b outpatient clinical trial, studying patients with mild COVID-19 disease, concluded that prophylactic therapy with apixaban was not necessary in clinically stable patients [103,104].

2.6. Anti-cytokine therapeutics

2.6.1. Corticosteroids

Dexamethasone, a potent glucocorticoid, leads to suppression of the immune system and inflammation in a multitude of ways. Dexamthasone decreases proliferation and differentiation of naïve T-cells via downregulation of the CD28 co-activation pathway [105]. In addition to downregulation of pro-inflammatory T-cell response, a known contributor to CSS, it has long been shown to decrease PGE_2 and other pro-inflammatory eicosanoids in human endothelial cells, most likely through ablation of arachidonic acid production [106]. The dexamethasone RECOVERY trial demonstrated that a 10-day regimen of 6 mg dexamethasone plus standard care resulted in a significant reduction of all-cause mortality in COVID-19 patients, from 25.7% to 22.9%, who were receiving either invasive mechanical ventilation or non-mechanical oxygen support at the time of randomization. No difference was noted in those not requiring oxygen support at time of randomization [107]. This shows that dexamethasone may be protective in those with more serious disease, potentially through ablation of the cytokine storm. The REACT working group performed a meta-analysis, largely pooling data from the RECOVERY trial, that revealed lower 28-day all-cause mortality with administration of systemic corticosteroids in critically ill COVID-19 patients compared to treatment with usual care or placebo [108]. Further analysis by Ma et al. supported this conclusion, adding that there was no increase in serious adverse events in patients treated with corticosteroids compared to those with no corticosteroids [109]. In a separate meta-analysis that studied COVID-19 patients with different illness severity, Pasin et al. suggested that corticosteroid may be considered in severe illness [110]. However, they discouraged its use for mild illness not requiring oxygen therapy, as it increased mortality [110]. In conclusion, the evidence states that corticosteroids may be considered in severely ill COVID-19 patients, thereby reducing all-cause mortality, but is only beneficial in those requiring oxygen therapy. Part of this effect may occur through reduction in micro-thrombotic events in COVID-19, although further study is needed. These clinical trials may be used to guide treatment of COVID-19 based on severity of disease state.

2.6.2. IL-6 inhibition

Tocilizumab, a recombinant monoclonal antibody that binds to the IL-6 receptor and inhibits IL-6-mediated signaling, may have potential for reducing thrombosis risk in COVID-19 patients [111]. IL-6 is implicated in the upregulation of pro-thrombotic PAI-1, making it a potential target for reducing the risk of coagulopathy. A 2019 study found that rheumatoid arthritis patients who responded to tocilizumab treatment observed a reduction of their pro-thrombotic state via a reduction of circulating clotting factors [112]. Tocilizumab may be both effective in areas of reduced inflammation and reduced coagulation in the setting of SARS-CoV-2 infection.

An early study from Wuhan at the outset of the COVID-19 pandemic demonstrated significant elevations of IL-6 in patients presenting with

severe disease that led to a small, non-randomized study of 21 consecutive patients that suggested a clinical benefit [113]. This led to Phase 2/3 randomized trials studying the use of tocilizumab and sarilumab, another IL-6 receptor antagonist, in SARS-CoV-2 which, unfortunately, did not meet their prespecified clinical endpoints [114–116]. Importantly, these trials did not appear to include or specify thrombosis endpoints, although, based on mechanisms outlined, a potential benefit may be anticipated; retrospective analyses of these trials should be considered.

2.6.3. IL-2 inhibition

Although studies published to date have targeted the Th2 cytokine IL-6, the Th1 cytokine profile is more consistently demonstrated in early viral infection. Multiple recent reports demonstrate consistently elevated Th1 genomic and immunophenotypic signatures in symptomatic SARS-CoV-2 patients. Long et al. demonstrated a multi-fold higher expression of Th-1 cytokines, in particular TNF alpha and IL-2, and significant expression of the IL-2 receptor subunit alpha in symptomatic COVID-19 patients in Wuhan [52]. A subsequent report by Lee et al demonstrated similar results through transcriptional and immuno-profiling techniques [117]. An additional report by Long et al did reported similar results [52,117]. Therefore, potential key targets for the treatment of COVID-19-associated CSS may include IL-2. Basiliximab is a monoclonal antibody agent that inhibits T-cell proliferation by binding to IL-2 receptors on the surface of T-helper cells. It is a non-depleting immunosuppressive agent approved for induction therapy in kidney transplantation. Compared with T-cell depletive immunotherapy, IL-2 induction therapy does not increase the risk of infection or cancer. There is evidence supporting its use in EBV-mediated secondary HLH syndromes [119].

The Fort Worth Clinical Sciences Working Group developed a COVID-19 immunotherapy study that recently received an FDA IND. This will permit a study to randomize COVID-19 patients with hypoxemia requiring high-flow oxygen meeting cytokine storm criteria for treatment with basiliximab or placebo in a double-blind design to determine ventilator-free survival as the primary, prespecified endpoint [120]. The study will further *prospectively* assess multiple parameters of thrombosis at various timepoints throughout the study, including coagulation factor levels, isolated and integrated parameters of platelet function, and fibrinolytic (PAI-1/tPA) protein antigen and activity levels. It will be important to determine if inhibition of IL-2 mitigates *pre-specified* thrombosis endpoints.

2.7. Potential therapeutics

2.7.1. Eicosanoids

Targeting of eicosanoids in COVID-19 may impact thrombotic endpoints. As noted earlier, Gross et al. (2007) and Hammock et al. (2019) reported that prostaglandin E (PGE_2) upregulation is noted in inflammation [121,122]. It plays a major role in initiation of coagulation and mediates these effects via binding four G-protein coupled receptors: EP1, EP2, EP3 and EP4 [121,122]. Selective silencing of each of the four known heptahelical receptors has supported platelet activation by PGE2 effects, utilizing EP3: inhibiting adenylate cyclase, decreasing intracellular cAMP levels, and thus decreasing corresponding platelet threshold of activation [123]. Hence, it may be beneficial to monitor PGE_2 and pro-inflammatory eicosanoids (PGE_2, PGI_2, PGD_2, PGF_2a, TXA_2) in COVID-19 patients [121,124]. In addition to prostaglandin targets, given the significant effects of eicosanoids via COX-2 and TXA2 pathways, a simple yet mechanistically feasible strategy would be to consider early "upstream" use of aspirin as an antiplatelet strategy targeting cyclo-oxygense (COX-1) and its downstream target, thromboxane A2 (TXA2).

2.7.2. Statins

Statins may exert another pleiotropic, anti-inflammatory effect by increasing ACE-2 levels and inhibiting the cardiovascular toll-like receptor (TLR)-MYD88-NF-kappaB pathway. Prior studies on the effects of statins on this cardiovascular TLR pathway have found decreased levels of C-reactive protein, linking the efficacy of statins to the anti-inflammatory pathway outside their cholesterol lowering effects [125,126]. In a study following thrombotic events in patients with inflammatory autoimmune conditions such as Systemic Lupus Erythamatosis (SLE) or antiphospholipid antibodies, statin therapy was shown to be protective against thrombotic events [127]. Given the pleiotropic, anti-inflammatory effects of statins, and downstream effects on thrombosis, these agents may be investigated as low-risk preventative therapeutic to mitigate some aspects of thrombosis in COVID-19 patients. Retrospective meta-analyses of published COVID-19 trials to date may offer some evidence.

3. Conclusion

In summary, SARS-CoV-2 induces cytokine storm through direct and indirect effects on host immunity. This process leads to a series of events involving damage to the endothelium, activation of platelets, activation of coagulation factors, and hypo-fibrinolysis though induction of PAI-1 that our group presented as a mechanistic basis for thrombosis in COVID-19 [21]. In this report, we build on this reported mechanistic basis to describe potential therapeutic interventions to prevent or treat thrombotic events in COVID-19 patients using this integrated model of thrombosis (Fig. 2). We believe that this review provides a comprehensive and up to date review of the literature in this area whilst providing a strategic template for investigators to help visualize hypothesis-driven investigations for therapeutic interventions for prevention or treatment of thrombosis in COVID-19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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