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BRIEF REPORT

Use of novel antithrombotic agents for COVID-19: Systematic summary of ongoing randomized controlled trials

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with macro- and micro-thromboses, which are triggered by endothelial cell activation, coagulopathy, and uncontrolled inflammatory response. Conventional antithrombotic agents are under assessment in dozens of randomized controlled trials (RCTs) in patients with COVID-19, with preliminary results not demonstrating benefit in several studies.

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Objectives: Given the possibility that more novel agents with antithrombotic effects may have a potential utility for management of patients with COVID-19, we assessed ongoing RCTs including these agents with their potential mechanism of action in this population.

Methods: We searched clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform to identify RCTs of novel antithrombotic agents in patients with COVID-19.

Results: Based on a systematic literature search, 27 RCTs with 10 novel antithrombotic agents (including nafamostat, dociparstat, rNAPc2, and defibrotide) were identified. The results from these trials have not been disseminated yet. The studied drugs in the ongoing or completed RCTs include agents affecting the coagulation cascade, drugs affecting endothelial activation, and mixed acting agents. Their postulated antithrombotic mechanisms of action and their potential impact on patient management are summarized.

Conclusion: Some novel antithrombotic agents have pleiotropic anti-inflammatory and antiviral effects, which may help reduce the viral load or fibrosis, and improve oxygenation. Results from ongoing RCTs will elucidate their actual role in the management of patients with COVID-19.

KEYWORDS
anti-inflammatory, antithrombotic, antiviral, COVID-19, RCT

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is associated with venous and arterial thrombosis.[1–3] Dozens of randomized controlled trials (RCTs) are evaluating the utility of conventional antithrombotic agents in COVID-19.[4] Results from the available RCTs of the conventional antithrombotic agents have not yet led to definitive answers. In patients admitted to the intensive care unit (ICU), intermediate-dose or full-dose prophylactic anticoagulation did not lead to improvement in clinical outcomes.[5–8] Among patients hospitalized in medical wards, the results for heparin-based regimens are promising, although some details are yet to be clarified. Escalated-dose prophylaxis with rivaroxaban was not associated with improvement in outcomes.[9] It is in this setting that there has been interest in novel agents with antithrombotic effects (with coexisting anti-inflammatory and/or antiviral properties) in patients with COVID-19. We summarized the ongoing RCTs of novel antithrombotic agents being tested in COVID-19 and their potential mechanisms of action.

ESSENTIALS

- Dozens of randomized controlled trials (RCTs) are evaluating the utility of conventional antithrombotic agents in coronavirus disease 2019 (COVID-19).
- Novel antithrombotic agents with pleiotropic properties are under evaluation in 27 RCTs with 10 distinct agents.
- Novel antithrombotic agents could be classified as drugs affecting the coagulation cascade, drugs affecting endothelial activation, and those with mixed mechanisms of action.
- Results from these RCTs may help expand therapeutic options in COVID-19.

2 | METHODS

We searched clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform, to identify RCTs of novel antithrombotic agents (last updated on February 26, 2021) using pre-defined keywords containing COVID-19, and keyword permutations for antithrombotic agents. The search strategy and screening of the studies is described in Figure 1. RCTs of conventional antithrombotic agents (such as heparin-based regimens, direct oral anticoagulants, fibrinolytic therapy, aspirin, and $P2Y_{12}$ inhibitors) were excluded.

3 | RESULTS

We identified 998 records, of which 27 RCTs met the eligibility criteria (Figure 1). We did not identify registered RCTs for danaparoid, soluble thrombomodulin, or activated protein C.

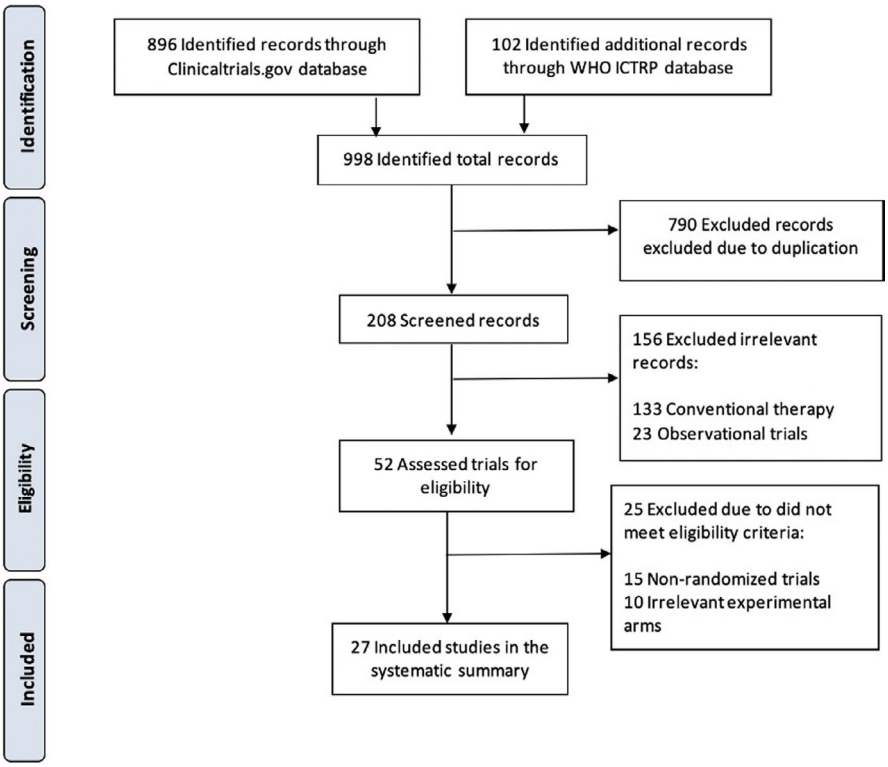


FIGURE 1 PRISMA flow diagram. Keywords used for search of clinicaltrials.gov and WHO ICTRP included: COVID-19 or SARS-CoV-2 or Coronavirus disease 2019 and coagulation, thrombosis, thrombotic, thromboembolism, thromboembolic, anticoagulation, anticoagulant, antithrombotic, antiplatelet, aspirin, dipyridamole, Aggrenox, cilostazol, P2Y12 inhibitor, clopidogrel, ticagrelor, prasugrel, ticlopidine, cangrelor, vorapaxar, eptifibatide, tirofiban, abciximab, heparin, UFH, LMWH, enoxaparin, dalteparin, tinzaparin, bemiparin, nadroparin, fondaparinux, danaparoid, DTI, bivalirudin, argatroban, lepirudin, desirudin, DOAC, apixaban, rivaroxaban, edoxaban, betrixaban, dabigatran, sulodexide, thrombolytic, fibrinolytic, alteplase, reteplase, tenecteplase, dociparstat, DSTAT, nafamostat, ulinastatin, defibrotide, crizanlizumab, rNAPc2, antithrombin, recombinant antithrombin, human antithrombin, ATryn, thrombomodulin, activated protein C, drotrecogin alpha, eculizumab, ravulizumab, isoquercetin, isotrifoliin, and quercetin. COVID-19, coronavirus disease 2019; DOAC, direct iral anticoagulant; DSTAT, dociparstat sodium; DTI, direct thrombin inhibitor; LMWH, low molecular weight heparin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; rNAPc2, recombinant nematode anticoagulant protein c2; UFH, unfractionated heparin; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform

The presumed mechanism of action relevant to COVID-19 of novel agents with antithrombotic properties is illustrated in Figure 2. Some of these agents have anticoagulant properties, some have profibrinolytic functions, and others may impact thromboinflammation by reduction in the formation of neutrophil extracellular traps (NETs).

Table 1 summarizes the ongoing RCTs of 10 novel agents and comparator arms in each RCT, and their respective clinical trial registration number. A summary of ongoing or completed trials are described in Figure 3. These completed or ongoing RCTs have focused only on hospitalized patients with COVID-19, except one trial of quercetin, which includes outpatients. Although there may be some overlap in the putative mechanisms of action, for simplicity, these agents are grouped as those drugs affecting the coagulation cascade, drugs affecting endothelial activation, and agents with mixed mechanisms of action.[4,10] A brief discussion of these agents and their trials is provided in the following sections.

3.1 | Drugs affecting the coagulation cascade

The hypercoagulopathy in COVID-19 is associated with increased levels of tissue factor (TF), thrombin, von Willebrand factor (VWF), and type-1 plasminogen activator inhibitor (PAI-1), as well as reduced levels of plasminogen activators and antithrombin.[4] Drugs affecting the coagulation cascade in this review can be divided into three groups: tissue factor pathway inhibitors (recombinant nematode anticoagulant protein c2 [rNAPc2] and quercetin), serine protease inhibitors (antithrombin, nafamostat, and ulinastatin), and those that augment fibrinolysis (defibrotide). Due to multiple properties of defibrotide, it will be described in a distinct section, subsequently.

3.1.1 | Tissue factor inhibitors: rNAPc2 and quercetin

rNAPc2 inhibits TF/factor VIIa complex and may decrease the interleukin-10 response and dampen the cytokine storm.[11]

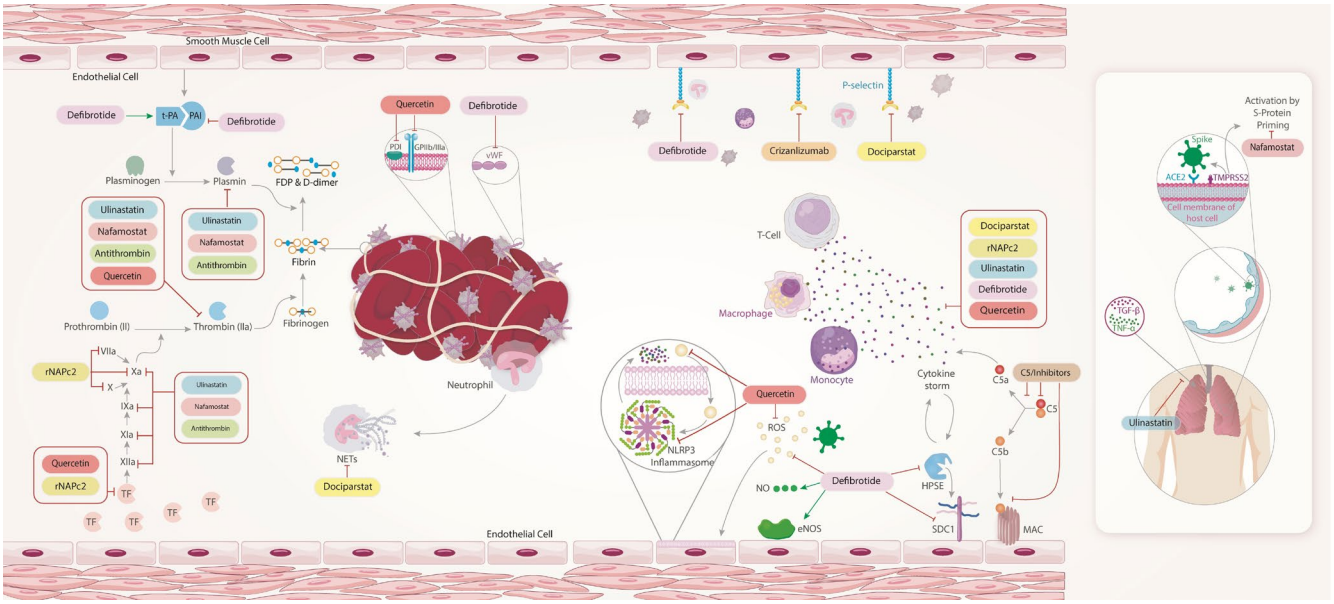


FIGURE 2 The presumed mechanism of action of the investigational antithrombotic agents in patients with COVID-19. Antithrombin inhibits serine proteases, coagulation factors, thrombin, and plasmin. Nafamostat affects coagulation cascade, endothelial dysfunction, and inhibits serine proteases. Also, it blocks TMPRSS2 activity—essential for spike protein (S-protein) priming of SARS-CoV-2. Blocking of TMPRSS2 activity leads to lack of S-protein priming and inhibits cell entry by angiotensin converting enzyme 2. Ulinastatin blocks serine proteases and inhibits the cytokine storm. In addition, it exerts antifibrotic effects on lung parenchyma by inhibiting the expression of inflammatory markers and fibrotic factors such as transforming growth factor β. Recombinant nematode anticoagulant protein c2 (rNAPc2) inhibits the cytokine storm and blocks TF/FVIIa by binding to activated or zymogen factor X. Quercetin derivatives inhibit protein disulfide isomerase, TF, glycoprotein IIb/IIIa activation, platelet aggregation, and decrease thrombin generation. Furthermore, quercetin can diminish reactive oxygen species and inhibit NLRP3 inflammasome. Defibrotide inhibits plasminogen activator inhibitor, induces tissue-plasminogen activator, and reduces von Willebrand factor expression and platelet aggregation. In addition, it can suppress viral attachment and viral dissemination by inhibition of syndecan-1 and heparanase. Defibrotide can also inhibit endothelial cell activation. Defibrotide, crizanlizumab, and dociparstat block P-selectin, thereby reducing platelet aggregation. Dociparstat can also inhibit cytokine storm and decreases the risk of thrombosis by reducing the formation of neutrophil extracellular traps (NETs). C5 inhibitors block C5 and cleavage into C5a and C5b, therefore they can inhibit cytokine storm and endothelial cell damage. ACE2, angiotensin-converting enzyme 2; C5, complement 5; eNOS, endothelial nitric oxide synthase; FDP, fibrin degradation products; GP IIb/IIIa, glycoprotein IIb/IIIa; HPSE, heparanase; ICU, intensive care unit; MAC, membrane attack complex; NLRP3, nod-like receptor family pyrin domain containing 3; NO, nitric oxide; PD, protein disulfide isomerase; RCT, randomized controlled trial; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SDC-1, syndecan-1; SOC, standard of care; TF, tissue factor (factor III); TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor-α; TMPRSS2, transmembrane protease serine 2

rNAPc2 is being studied in ASPEN-COVID-19 (Assessing Safety, Hospitalization and Efficacy of rNAPc2 in COVID-19) among 160 patients with COVID-19 to determine its effect on the time to recovery, change of D-dimer level, and bleeding events as co-primary outcomes.

Quercetin and isoquercetin have anti-inflammatory and antithrombotic properties. Quercetin derivatives are the protein disulfide isomerase inhibitors, which suppresses TF, inhibit glycoprotein IIb/IIIa activation and platelet aggregation, and decrease thrombin generation and D-dimer level.[12] These agents decrease reactive oxygen species (ROS) levels and pro-inflammatory cytokines. By decreasing ROS levels, quercetin can inhibit nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation. In addition, quercetin can suppress NLRP3 inflammasome directly.[13]

Quercetin and its derivatives are being evaluated in five RCTs, including four in hospitalized patients. The primary outcome of three ongoing RCTs, conducted in a total of 600 hospitalized non-ICU patients, is disease progression (Study of Isoquercetin Plus Standard of Care Versus Standard of Care Only for the Treatment of COVID-19 [NCT04536090], Masitinib Combined With Isoquercetin and Best Supportive Care in Hospitalized Patients With Moderate and Severe COVID-19 [NCT04622865], and Study to Investigate the Clinical Efficacy of Isoquercetin in Patients With COVID-19 [NCT04733651]). The assessment of positivity of the nasopharyngeal polymerase chain reaction swab is the primary outcome of one RCT of isoquercetin in 60 hospitalized (non-ICU and ICU) patients (IRCT20200419047128N2). Trial to Study the Adjuvant Benefits of Quercetin Phytosome in Patients With COVID-19 (NCT04578158) is assessing the effect of quercetin on hospitalization rates in 152 outpatients with COVID-19.

TABLE 1 Review of RCTs categorized based on the mechanism of action

aTable 1. Review of RCTs Categorized Based on the Mechanism of Action

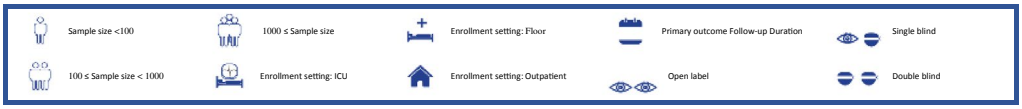
	Trial Code/ Name	Blinding status	Patient recruitment location	Actual Dose Used (daily)	Major Inclusion Criteria	Sample Size	Major Exclusion Criteria	Primary Endpoint Follow-up Duration (days)	Efficacy Outcomes: Primary: Composite clinical endpoint	Efficacy Outcomes: Primary: Other	Efficacy Outcomes: Secondary: Mortality	Efficacy Outcomes: Secondary: Anti-viral outcome	Efficacy Outcomes: Secondary: Inflammatory or other surrogate markers
Drugs Affecting Coagulation Cascade													
Tissue Factor Inhibitors													
rNAPc2	ASPEN-COVID-19 NCT04655586†			Higher dose: 7.5 µg/kg SC on Day 1, 3, and 5 Lower dose: 5 µg/kg SC on Day 1, 3, and 5	Adult PCR confirmed COVID-19 with evidence of systemic inflammation	160	History of APS, High bleeding risk, CKD, Liver disease	30	-	D-dimer level, bleeding	✓	-	✓
Quercetin and Quercetin derivatives	IRCT20200419047128N2			1 g PO daily for 7 days	PCR confirmed COVID-19	60	Autoimmune diseases (lupus, MS, etc.), HBV or HCV	14	-	Assessment of PCR	-	-	✓
	NCT04536090			1 g PO BID on day 1, then 500 mg BID for 27 days	Adult confirmed COVID-19	150	High bleeding risk, Antecedent intensified Heparin derivatives or DAPT, CKD	28	-	Clinical status improvement	✓	✓	✓
	NCT04578158			400 mg PO daily for 30 days	Adult RT-PCR confirmed COVID-19	152	Hypersensitivity reaction to quercetin	30	-	Clinical status improvement	-	-	-
	NCT04622865			1 g PO daily	Adult confirmed COVID-19	200	-	15	-	Clinical status improvement	-	-	-
	NCT04733651			1 g PO daily for 28 days	Adult PCR/RT-PCR confirmed COVID-19	250	High bleeding risk, Antecedent antiplatelet, Strong CYP3A4 inducer, CKD, Liver disease	28	-	Clinical status improvement	✓	-	-
Serine Protease Inhibitors													
Antithrombin	ANTITROMBINA NCT04745442			50 IU/Kg IV BID for 3 days	Adult confirmed COVID-19 with evidence of systemic inflammation	48	High bleeding risk, Immunosuppression by cancer or transplant	31	✓	-	✓	-	✓
Nafamostat	ASCOT-ADAPT NCT04483960			0.2mg/kg/hour IV for 7 days or until DC	Adult PCR/RT-PCR confirmed COVID-19	2400	High bleeding risk, Decompensated HF, Currently receiving acute intensive respiratory support, CKD, Liver disease	28	✓	-	✓	✓	-
	DEFINE NCT04473053			0.2mg/kg/hour IV for 7 days or until DC	Adult confirmed COVID-19	60	Decompensated HF, Antecedent AC or Antiplatelet, K sparing diuretics, CKD, Liver disease	90	-	Adverse events	-	✓	✓
	RACONA NCT04352400‡			Not provided	Adult confirmed COVID-19	256	High bleeding risk, Requiring ECMO, Chronic ILD, Long QTc, Requiring high dose of loop diuretic or immunosuppressive therapy, CKD, Liver disease	28	-	Clinical status improvement	✓	-	-
	CTRI/2020/06/026220			0.1mg/kg/hour IV for 10 days or until DC	Adult RT-PCR confirmed COVID-19 with pneumonia and respiratory failure	41	High bleeding risk, Requiring ECMO or MV, Chronic ILD, Long QTc, Requiring high dose of loop diuretic or immunsuppressive therapy, Decompensated HF, CKD, Liver disease	14	-	Clinical status improvement	✓	✓	-
	jRCTs031200026			0.1mg/kg/hour IV for 10 days or until DC	Age 20-75 years, confirmed COVID-19 with evidence of pneumonia	160	Cardiac dysfunction, Antecedent treatment of gout or hyperuricemia, CKD, Liver disease	7	-	Clinical status improvement	-	✓	-
	NCT04418128			0.1-0.2 mg/kg/hour IV for 10 - 14days	Age 18-85 years, RT-PCR confirmed COVID-19	84	History of HIV or AIDS, Liver disease	28	-	Clinical status improvement	✓	✓	-
	NCT04623021			0.1mg/kg/hour IV for 10 days or until DC	Adult confirmed COVID-19 (104)	104	High bleeding risk, History of long QTc, Ventricular arrhythmia, CKD, Liver disease	28	-	Clinical status improvement	✓	-	✓
	NCT04628143			Not provided	Adult years, RT-PCR confirmed COVID-19 with evidence of pneumonia	100	Long QTc, Antecedent immunosuppressive therapy or corticosteroids, CKD, Liver disease	28	-	Clinical status improvement	✓	-	-
Ulinastatin	ChiCTR2000030779			200,000 U IV infusion every 8 hours for 5 days or until DC	Age 18-75 years, confirmed COVID-19	100	Using urinary trypsin inhibitors	NP	-	Clinical status improvement	✓	-	-
	ChiCTR2000032135			300,000 U IV infusion every 12 hours for mild cases and 1 or 1.6 MU for severe or critical cases	Age 18-75 years, confirmed COVID-19	50	Using civerex and gabexate	14	-	The changes of PaO_2/FiO_2, safety outcomes	-	✓	-
	CTRI/2020/06/025704			200,000 U IV infusion every 8 hours for 7 days	Age 18-65 years, RT-PCR confirmed COVID-19 with mild to moderate ARDS	120	History of HIV/HCV/HBV or TB, Antecedent immunosuppressant or immunotherapy	14	-	Changes of PaO_2/FiO_2	✓	-	✓
	NCT04393311‡			200,000 U IV infusion every 8 hours for 5 days or until DC	Adult confirmed COVID-19	160	Using antibody immunotherapy, CKD, Liver disease	29	-	Clinical status improvement	✓	-	-

(Continues)

TABLE 1 (Continued)

Table 1. Review of RCTs Categorized Based on the Mechanism of Action (continued)

	Trial Code/ Name	Blinding status	Patient recruitment location	Actual Dose Used (daily)	Major Inclusion Criteria	Sample Size	Major Exclusion Criteria	Primary Endpoint Follow-up Duration (days)	Efficacy Outcomes: Primary: Composite clinical endpoint	Efficacy Outcomes: Primary: Other	Efficacy Outcomes: Secondary: Mortality	Efficacy Outcomes: Secondary: Anti-viral outcome	Efficacy Outcomes: Secondary: Inflammatory or other surrogate markers
Drugs Affecting Endothelial Activation													
P-selectin Inhibitors													
Crizanlizumab	**CRITICAL NCT04435184‡**			5 mg/kg IV single dose	Adult, RT-PCR confirmed COVID-19 with evidence of pulmonary infiltrates and respiratory failures	50	INR> 3, aPTT> 60	3 or until DC	-	P-selectin levels	-	-	✓
Dociparstat	**NCT04389840‡**			4 mg/kg IV bolus on Day 1, followed by continuous IV infusion daily for 7 days	Age 18-85 years, RT-PCR confirmed COVID-19	3	High bleeding risk, Long QTc, Antecedent corticosteroids, Immunosuppressive therapy, CKD, Liver disease	28	-	Mechanical ventilation-free survival	✓	-	✓
Complement Component 5 Inhibitors													
Eculizumab	**CORIMUNO19-ECU NCT04346797**			1200 mg IV on Days 1, 4, 8 then 1200 mg or 900 mg on Day 12, 900 mg on Days 15, 18 and 22	Age 18-70 years, confirmed COVID-19	120	History or unresolved Neisseria meningitides infection	14	-	The survival without needs of intubation	✓	✓	-
Ravulizumab	**TACTIC-R NCT04390464**			Weight based IV single dose	Confirmed COVID-19	1167	History of Neisseria Meningitides infection, TB, HBV, HCV, Chronic IVIG treatment, CKD, Liver disease	14	✓	-	✓	✓	-
	NCT04369469			Weight based IV on Days 1, 5, 10, and 15	PCR confirmed COVID-19 with evidence of respiratory failure	270	Decompensated HF, History of unresolved Neisseria meningitides infection, Antecedent IVIG treatment	29	-	Mortality	✓	-	-
	NCT04570397			Weight based IV on Days 1, 5, 10, and 15	Confirmed COVID-19 with clinical diagnosis of thrombotic microangiopathy	32	Unresolved Neisseria Meningitides infection	30	-	Improvement of AKI	-	-	-
Mixed Acting Agents													
Defibrotide	**DEFACOVID NCT04348383‡**			25 mg/kg 24 hours continuous IV infusion for 15 days	PCR confirmed COVID-19 with levels of IL-6 ≥ 3 ULN	150	Acute bleeding, Antecedent thrombolytic or therapeutic anticoagulant treatment	30	-	Clinical status improvement	✓	-	✓



Abbreviations: AC, anticoagulation; AIDS, acquired immune deficiency virus; AKI, acute kidney injury; APS, antiphospholipid syndrome; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; BID, twice daily; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DC, discharge; ECMO, extracorporeal membrane oxygenation; HBV, hepatitis B virus; HCV, hepatitis C virus; HF, heart failure; HIV, human immunodeficiency virus; ICU, intensive care unit; IL, interleukin; ILD, interstitial lung disease; INR, international normalized ratio; IV, intravenous; IVIG, intravenous immunoglobulin; MS, multiple sclerosis; MV, mechanical ventilation; PCR, polymerase chain reaction; PO, taken by mouth; QTc, heart-rate corrected QT; RT-PCR, real-time polymerase chain reaction; SC, subcutaneous; TB, tuberculosis; ULN, upper limit of normal.

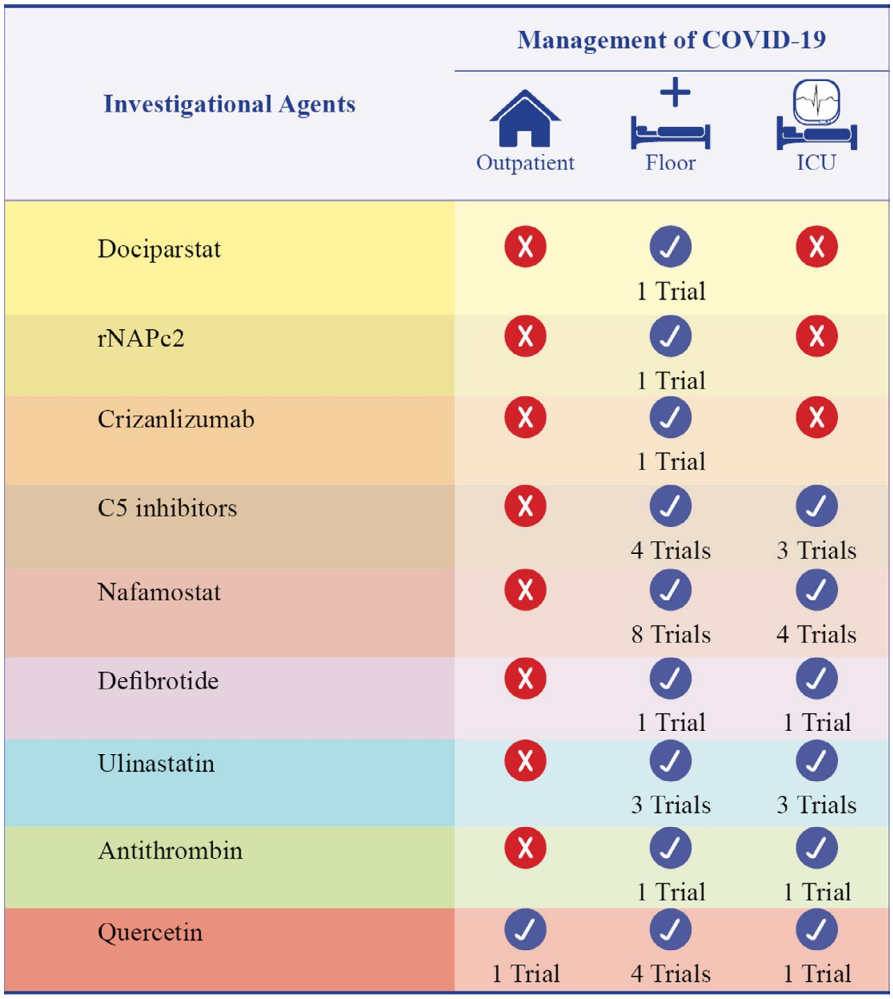
† The comparator of this trial is heparin.

‡ The comparator of these trials is placebo.

3.1.2 | Serine protease inhibitors: antithrombin, nafamostat, and ulinostatin

Antithrombin inactivates clotting enzymes, particularly factor II (FII)a and factor X (FX)a. Disruption of the endothelial cell glycocalyx with COVID-19 may lead to loss of heparan sulfate and hypercoagulability.[4] ANTITROMBINA (Pilot Study of Antithrombin as Prophylaxis of Acute Respiratory Distress Syndrome in Patients With COVID-19) is evaluating the effect of antithrombin in 48 patients with COVID-19 for a primary composite outcome of all-cause mortality or need for mechanical ventilation.

As a synthetic serine protease inhibitor, nafamostat inhibits thrombin, FXa, and FXIIa. Moreover, it has anti-inflammatory and antiviral effects by blocking protease serine 2 activity and viral entry.[14] Nafamostat is being studied in nine RCTs. Out of these nine, in five RCTs including a total of 2887 hospitalized non-ICU patients, the impact of nafamostat on death, need for mechanical ventilation, vasopressor therapy, clinical improvement or viral load is being assessed (ASCOT-ADAPT [Australasian COVID-19 Trial Adaptive Platform Trial], SEN-CoV-Fadj [Efficacy and Safety Evaluation of Treatment Regimens in Adult COVID-19 Patients in Senegal], A Study to Evaluate the Efficacy and Safety of Nafamostat Mesilate in Treatment of Coronavirus Infection [CTRI/2020/06/026220], Combination Therapy of Favipiravir and Nafamostat Mesilate in Patients with COVID-19 Pneumonia [jRCTs031200026], and A Study Evaluating the Efficacy and



There are a total of 27 trials. 11 trials enroll from floor and ICU. All these agents are being investigated only in the setting of hospitalized patients, except for one RCT of quercetin. For more details please review Table 1. COVID-19: Coronavirus Disease 2019, ICU: Intensive Care Unit, rNAPc2:recombinant nematode anticoagulant protein c2.

FIGURE 3 Graphical summary of investigational antithrombotic agents used in Completed or ongoing randomized trials (RCTs) in patients with COVID-19. All these agents are being investigated only in the setting of hospitalized patients, except for one RCT of quercetin. For more details, please review Table 1. COVID-19, coronavirus disease 2019; ICU, intensive care unit; rNAPc2,recombinant nematode anticoagulant protein c2

Safety of CKD-314 in Hospitalized Adult Patients Diagnosed With COVID-19 Pneumonia [NCT04628143]). ASCOT-ADAPT, as the trial with the largest number of participants in this group, is evaluating nafamostat in an adaptive platform trial with 2400 participants for a primary composite outcome of all-cause mortality or need for invasive or non-invasive ventilation or vasopressor or inotropic support. This drug is being assessed in another four RCTs with a total of 504 hospitalized patients (DEFINE [Rapid Experimental Medicine for COVID-19], RACONA [Efficacy of Nafamostat in Covid-19 Patients], Clinical Efficacy of Nafamostat Mesylate for COVID-19 Pneumonia [NCT04418128], and A Study Evaluating the Efficacy and Safety of CKD-314 [Nafabelltan] in Hospitalized Adult Patients Diagnosed With COVID-19 Pneumonia [NCT04623021]). The most common primary efficacy outcome (6/9) is time to clinical improvement. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load level and safety of nafamostat are the primary outcomes in SEN-CoV-Fadj and DEFINE trials, respectively.

Ulinastatin inhibits elastase and thrombin, factor IX (FIX)a, FXa, FXIa, FXIIa, and interleukin-6, but upregulates angiotensin-converting enzyme 2.[15] Ulinastatin may attenuate lung injury by inhibiting transforming growth factor-β1, tumor necrosis factor-α (TNF-α), and nuclear factor-κB.[16] Ulinastatin is being investigated in four RCTs (A Clinical Trial for Ulinastatin Injection in the Treatment of Patients with Severe Novel Coronavirus Pneumonia (COVID-19) [ChiCTR2000030779], Efficacy and Safety of Ulinastatin in the Treatment of Novel Coronavirus Pneumonia [COVID-19] [ChiCTR2000032135], Ulinastatin for COVID-19 in Patients with Breathlessness [CTRI/2020/06/025704], and Ulinastatin for the Treatment of COVID-19 in Hospitalized Patients [NCT04393311]) among a total of 430 participants. The primary outcomes are change from baseline PaO_2/FiO_2 ratios in two RCTs and time to recovery in NCT04393311 trial. Blood gas and the Sequential Organ Failure Assessment (SOFA) score are being assessed as the co-primary outcome in the ChiCTR2000030779 trial.

3.2 | Drugs affecting endothelial activation

COVID-19 may lead to endothelial activation[17,18] and drugs affecting endothelial activation can be divided into two groups: P-selectin inhibitors and complement inhibitors.

Soluble P-selectin levels are elevated in patients with COVID-19 and increased P-selectin expression on endothelial cells can tether tissue factor expressing monocytes or microparticles to the vessel wall, which may contribute to thromboinflammation.[19] Crizanlizumab and defibrotide are the agents acting against P-selectin that block leukocyte tethering. Another drug, dociparstat, is a heparin derivative with modest anticoagulant activity but with the capacity to block P-selectin–mediated cell adhesion. Activation of complement system during SARS-CoV-2 infection is associated with increasing the pro-inflammatory complement such as C5, C5a, and C5b, which may exacerbate endothelial damage. An increase in activated C5a is associated with viral mediated acute lung injury. Reduced C5a generation may prevent lung damage during SARS-CoV-2 infection. Eculizumab and ravulizumab are human monoclonal antibodies with immunoregulatory effects by blocking complement C5 and cleavage into C5a and C5b. In addition, C5 inhibitors including eculizumab and ravulizumab can prevent the activation of endothelial cells by inhibition of C5b formation, production of ROS, and the initiation of cytokine storm. Preventing membrane attack complex formation on the vascular endothelial cells due to inhibition of C5b may protect endothelial cells from further damage leading to thrombotic microangiopathy (TMA).[20–22]

3.2.1 | P-selectin inhibitors: crizanlizumab and dociparstat

Crizanlizumab is a monoclonal antibody that blocks the adhesion of leukocytes and platelets to the vessel wall.[19] The CRITICAL (Crizanlizumab for Treating COVID-19 Vasculopathy) trial is evaluating its effect on P-selectin levels in 50 hospitalized non-ICU patients with COVID-19.

Dociparstat may reduce the release of pro-inflammatory cytokines and decrease neutrophil NET formation by inhibiting high mobility group box protein 1 and platelet factor 4.[4] NETs can enhance the activity of fibrinogen, VWF, and other protein components involved in thrombosis, and may also trap red blood cells, promote platelet aggregation, and finally induce thrombus formation. Dociparstat is being studied in NCT04389840 (Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure), a pilot RCT of three patients hospitalized with COVID-19.

3.2.2 | Complement component 5 inhibitors: eculizumab and ravulizumab

Use of eculizumab in patients with severe COVID-19 is associated with reduced D-dimer level and inflammatory markers.[23] Therefore, some investigators hypothesize that it may improve hypoxia and patient outcomes such as survival. The CORIMUNO19-ECU (Trial Evaluating Efficacy and Safety of Eculizumab [Soliris] in Patients With COVID-19 Infection, Nested in the CORIMUNO-19 Cohort) trial is evaluating the impact of eculizumab on survival without the need for intubation as the primary outcome in 120 hospitalized patients with COVID-19.

Ravulizumab has a longer half-life compared to eculizumab with the advantage of a single-dose administration. This drug is being studied in three ongoing RCTs with a total of 1469 hospitalized patients (TACTIC-R [Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted With Covid-19—Repurposed Drugs], Efficacy and Safety Study of IV Ravulizumab in Patients With COVID-19 Severe Pneumonia [NCT04369469], and Ravulizumab and COVID-19 [NCT04570397]). A composite of mortality, and improvement in SARS-CoV-2-induced acute kidney injury, are the main outcomes in these RCTs.

3.3 | Mixed-acting agents: defibrotide

Defibrotide is a polydispersed oligonucleotide synthesized by depolymerization of DNA extracted from porcine intestinal mucosa. It has a complex mechanism of action with antiviral activity, antithrombotic properties, and anti-inflammatory effects via reducing TNF-α and IL-6, and vascular endothelial growth factor levels. Defibrotide upregulates tissue plasminogen activator expression, decreases PAI-1 levels, and enhances plasmin activity.[24,25] Defibrotide can inhibit viral attachment by suppression of syndecan-1 directly and indirectly via inhibiting heparanase. Also, defibrotide can diminish viral dissemination by heparanase. Furthermore, it can inhibit endothelial cell activation through a number of mechanisms including enhancing endothelium-derived nitric oxide/nitric oxide synthase activity, diminishing the generation of the macrophage-derived ROS, and downregulating P-selection.[26,27] The DEFACOVID trial (Defibrotide as Prevention and Treatment of Respiratory Distress and Cytokine Release Syndrome of Covid 19) is evaluating whether defibrotide results in clinical improvement in 150 hospitalized patients with COVID-19.

4 | CONCLUSIONS

Multiple novel therapies possessing antithrombotic properties are under investigation in RCTs of patients with COVID-19. Several of these agents have pleiotropic anti-inflammatory and antiviral effects, which may help reduce the viral load or fibrosis, and improve oxygenation. Results from these trials will improve our understanding of the disease pathophysiology and may help expand therapeutic options in COVID-19.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

All authors contributed substantially to the conception of the work, revising it critically for important intellectual content, approved the final version to be published, and agreed to all aspects of the work being accurate and integrative. AHT, PS, MA, and BB drafted the manuscript. AHT, PS, MA, HK, HA, and BB designed the figures. BB supervised the work. JMC, BJH, JSN, BVT, SM, GP, JIW, MC, GYL, SZG, and BB made critical revisions to the manuscript.

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