JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2021

PUBLISHED BY ELSEVIER

JACC STATE-OF-THE-ART REVIEW

Recent Randomized Trials of Antithrombotic Therapy for Patients With COVID-19

JACC State-of-the-Art Review

Azita H. Talasaz, PharmD,[a,b] Parham Sadeghipour, MD,[c] Hessam Kakavand, PharmD,[a,b] Maryam Aghakouchakzadeh, PharmD,[a] Elaheh Kordzadeh-Kermani, PharmD,[a] Benjamin W. Van Tassell, PharmD,[d,e] Azin Gheymati, PharmD,[a] Hamid Ariannejad, MD,[b] Seyed Hossein Hosseini, PharmD,[a] Sepehr Jamalkhani,[c] Michelle Sholzberg, MDCM, MSc,[f,g] Manuel Monreal, MD, PhD,[h] David Jimenez, MD, PhD,[i] Gregory Piazza, MD, MS,[j] Sahil A. Parikh, MD,[k,l] Ajay J. Kirtane, MD, SM,[k,l] John W. Eikelboom, MBBS,[m] Jean M. Connors, MD,[n] Beverley J. Hunt, MD,[o] Stavros V. Konstantinides, MD, PhD,[p,q] Mary Cushman, MD, MSc,[r,s] Jeffrey I. Weitz, MD,[t,u] Gregg W. Stone, MD,[k,v] Harlan M. Krumholz, MD, SM,[w,x,y] Gregory Y.H. Lip, MD,[z,aa] Samuel Z. Goldhaber, MD,[j] Behnood Bikdeli, MD, MS[j,k,w]

ABSTRACT

Endothelial injury and microvascular/macrovascular thrombosis are common pathophysiological features of coronavirus disease-2019 (COVID-19). However, the optimal thromboprophylactic regimens remain unknown across the spectrum of illness severity of COVID-19. A variety of antithrombotic agents, doses, and durations of therapy are being assessed in ongoing randomized controlled trials (RCTs) that focus on outpatients, hospitalized patients in medical wards, and patients critically ill with COVID-19. This paper provides a perspective of the ongoing or completed RCTs related to antithrombotic strategies used in COVID-19, the opportunities and challenges for the clinical trial enterprise, and areas of existing knowledge, as well as data gaps that may motivate the design of future RCTs. (J Am Coll Cardiol 2021;■:■–■)

THROMBOEMBOLISM IN PATIENTS WITH CORONAVIRUS DISEASE-2019

Microvascular and macrovascular thrombotic complications, including arterial and especially venous thromboembolism (VTE), seem to be common clinical manifestations of coronavirus disease-2019 (COVID-19), particularly among hospitalized and critically ill patients (1–4). Pooled analyses have helped in providing aggregate estimates of thrombotic events (4,5). In a recent systematic review and meta-analysis, the overall incidence of VTE among inpatients with COVID-19 was estimated at 17% (95% confidence interval [CI]: 13.4 to 20.9), with variation based on study design and method of ascertainment; there was a four-fold higher incidence rate in patients

From the [a]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; [b]Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran; [c]Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran; [d]Department of Pharmacotherapy and Outcome Science, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia, USA; [e]Pauley Heart Center, Division of Cardiology, Department of Internal Medicine, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia, USA; [f]Departments of Medicine and Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Ontario, Canada; [g]Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada; [h]Department of Internal Medicine, Hospital Universitari Germans Trials i Pujol, Universidad Católica San Antonio de Murcia, Barcelona, Spain; [i]Respiratory Department, Hospital Ramón y Cajal and Medicine Department, Universidad de Alcalá (Instituto de Ramón y Cajal de Investigación Sanitaria), Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Madrid, Spain; [j]Cardiovascular Medicine Division,

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.02.035

ABBREVIATIONS AND ACRONYMS

BID = twice daily

CI = confidence interval

COVID-19 = coronavirus disease-2019

CrCl = creatinine clearance

DOAC = direct oral anticoagulant

HMGB1 = high-mobility group box protein 1

ICU = intensive care unit

LMWH = low-molecular-weight heparin

NET = neutrophil extracellular trap

PaO_2/FiO_2 = partial arterial pressure of oxygen/fraction of inspired oxygen

QD = once daily

RCT = randomized controlled trial

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

UFH = unfractionated heparin

VTE = venous thromboembolism

WHO = World Health Organization

in the intensive care units (ICUs) compared with non-ICU settings (28% vs. 7%) (6). In addition, postmortem studies show frequent evidence of microvascular thrombosis in patients with COVID-19 (7,8). The influence of these events on mortality rates remains unknown (9).

PATHOPHYSIOLOGY OF THROMBOEMBOLISM IN COVID-19: VIRCHOW'S TRIAD IN ACTION

COVID-19 can potentiate all 3 components of Virchow's triad and increases the risk of thrombosis (**Figure 1**). First, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection may trigger endothelial dysfunction. Using the angiotensin-converting enzyme 2, which is expressed on the surface of many cells, SARS-CoV-2 enters endothelial cells and may impair their intrinsic antithrombotic properties. It is proposed that viremia, hypoxia, the inflammatory response, increased expression of tissue factor, and elevated levels of neutrophil extracellular traps (NETs) can together disrupt the hemostasis equilibrium and promote endothelial activation (10–12). This induction of a procoagulant state along with the reduction in plasminogen activators further results in increased platelet reactivity (13–15). Inflammatory cytokines and endothelial activation can lead to downregulation of antithrombin and protein C expression. They can also lead to an increase in the levels of plasminogen activator inhibitor; fibrinogen; factors V, VII, VIII, and X; and von Willebrand factor (16). Increased platelet reactivity, NETosis, and alterations in the aforementioned hemostatic factors result in a hypercoagulable state (17–22).

Particularly in COVID-19, it is believed that the excessive inflammatory response plays an important role in the pathogenesis of thrombosis (thromboinflammation), including pulmonary microthrombosis and pulmonary intravascular coagulopathy (7,8). Antiphospholipid antibodies have been identified in some patients (23), but their clinical significance is uncertain (24). Finally, COVID-19 may predispose patients to venous stasis and increase the risk of (venous) thrombosis. Fatigue, hypoxemia, being connected to medical devices (for hospitalized patients), or acute illness (including pulmonary involvement, myocarditis with associated heart failure, or other forms of severe disease) can all lead to

HIGHLIGHTS

- Venous and arterial thrombosis are prevalent in patients with COVID-19.
- Optimal thromboprophylaxis has not been established for patients with this disease.
- Numerous randomized trials are evaluating antithrombotic regimens for outpatients and inpatients with COVID-19.
- Ongoing experience has influenced the design, conduct, analysis, and reporting the results of these trials.

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [k]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York, USA; [l]NewYork-Presbyterian Hospital/Columbia University Irving Medical Center, New York, New York, USA; [m]Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; [n]Hematology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [o]Haemostasis and Thrombosis Centre, St. Thomas' Hospital, London, United Kingdom; [p]Center for Thrombosis and Hemostasis, Johannes Gutenberg University of Mainz, Mainz, Germany; [q]Department of Cardiology, Democritus University of Thrace, Komotini, Greece; [r]Department of Medicine, University of Vermont Larner College of Medicine and University of Vermont Medical Center, Burlington, Vermont, USA; [s]Department of Pathology and Laboratory Medicine, University of Vermont Larner College of Medicine and University of Vermont Medical Center, Burlington, Vermont, USA; [t]Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [u]Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada; [v]Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [w]Center for Outcomes Research and Evaluation (CORE), Yale School of Medicine, New Haven, Connecticut, USA; [x]Department of Health Policy and Administration, Yale School of Public Health, New Haven, Connecticut, USA; [y]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA; [z]Liverpool Centre for Cardiovascular Science, Liverpool Heart and Chest Hospital, University of Liverpool, Liverpool, United Kingdom; and the [aa]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark. Paul F. Bray, MD, served as Guest Associate Editor for this paper. Christie Ballantyne, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 29, 2021; accepted February 5, 2021.

limited mobility and venous stasis (25,26). All the aforementioned mechanisms may increase the risk of arterial and venous thrombosis, thereby affecting the severity of illness.

ANTITHROMBOTIC PROPHYLAXIS IN COVID-19: PROS AND CONS

Bedside observations, pathophysiological investigations, and initial epidemiological data led to enthusiasm for antithrombotic prophylaxis in COVID-19 (27-31). The concern for thrombotic risk was heightened by reports of VTE in 13% to 56% of patients despite the use of standard prophylaxis (32-35). This led some experts to recommend empirical use of escalated doses of anticoagulant agents (36). However, the risks associated with intensified use of antithrombotic agents, such as bleeding, should be weighed against the presumptive benefits (22,27,31).

In addition, there have been variations in methodology and outcomes assessment for thrombotic events, including the concern about counting in situ thrombosis in small vessels (a recognized feature of acute lung injury also known as immunothrombosis) as pulmonary emboli. Due to these issues, as well as the concerns regarding excess bleeding, a number of guidance statements have not recommended empirical escalated-dose anticoagulation (27,37).

Multiple ongoing randomized controlled trials (RCTs) are evaluating a variety of antithrombotic regimens in patients with COVID-19 (**Figure 2**). These include trials of antiplatelet agents, anticoagulants, fibrinolytic agents, or combinations of these agents. In most trials, the intensity of antithrombotic therapy is proportional to the expected thrombotic event rates in the population under study. Less intensive therapies, including antiplatelet agents, oral anticoagulants, and standard prophylactic dose of low-molecular-weight heparin (LMWH), are typically studied in the outpatient or lower acuity hospital settings. In turn, more intensive therapies, including intermediate-dose or fully therapeutic doses of anticoagulants, or even fibrinolytic therapy, are under investigation in RCTs of hospitalized critically ill patients.

The aims of the current paper were to systematically summarize the ongoing and completed RCTs of antithrombotic therapy in patients with COVID-19 and to evaluate the strengths and limitations of the study designs, as well as the challenges and opportunities related to conducting and interpreting RCTs during a global pandemic.

METHODS

We conducted a systematic literature search of trials in ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform, with the pre-defined key words of COVID-19 and search terms for antiplatelet agents, anticoagulants, anticoagulation, fibrinolytic agents, and antithrombotic agents. The identified studies were screened, and those that were designed as RCTs with at least 1 active arm of antithrombotic therapy (date of last search December 16, 2020) were included. Supplemental Table 1 summarizes study-level inclusion and exclusion criteria for this review.

For the included studies, PubMed and MedRxiv were searched for design papers, study protocols, or published results of those studies. The list was complemented by hand-searching and discussion within the author group.

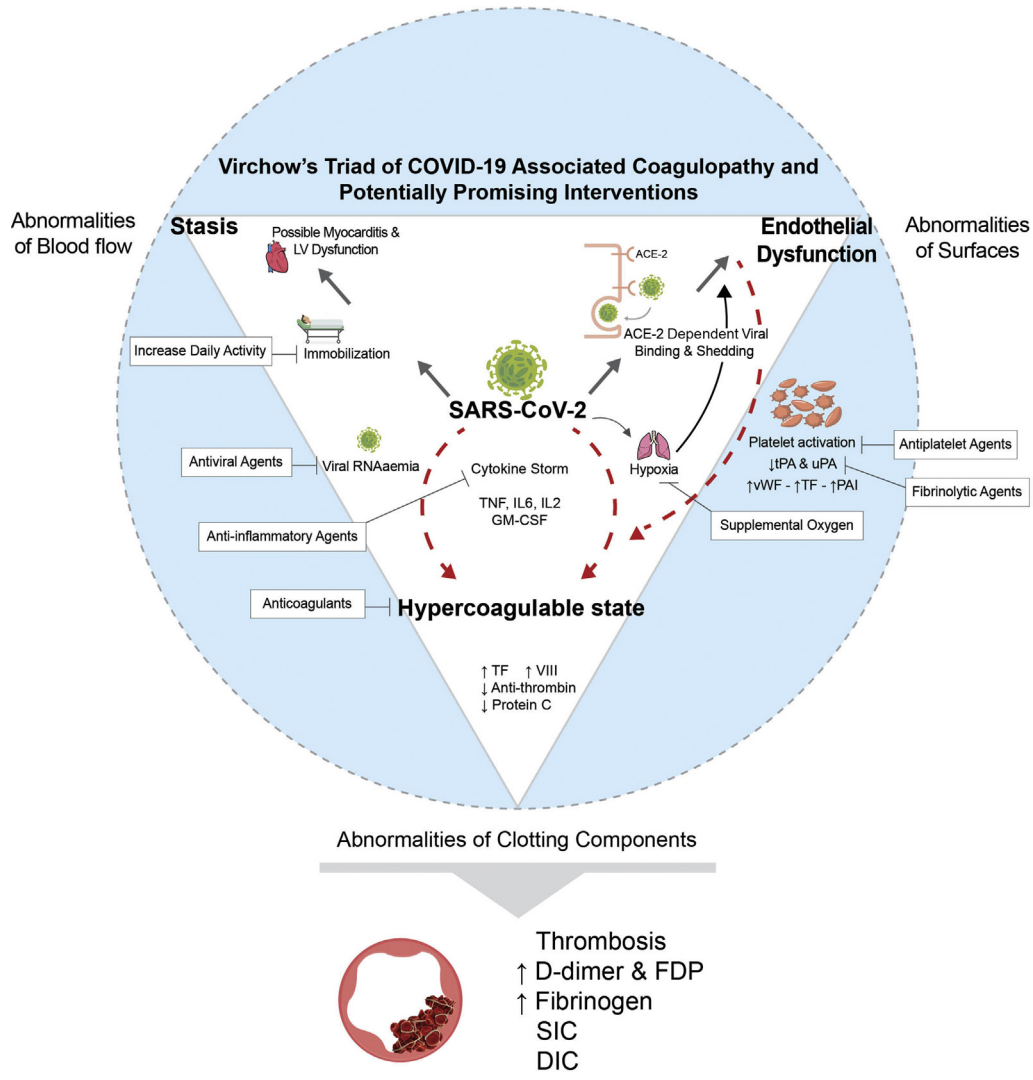
REVIEW OF ONGOING OR COMPLETED RCTs

After identification of 918 records and manual screening of 180 records, 75 RCTs were included in this study (Supplemental Figure 1). In 13 cases, a design paper and/or study protocol was available. Of all ongoing studies, 1 RCT reported the results in peer-reviewed literature (38) and 1 shared the findings on a pre-print server (39). For 3 RCTs, final results are unknown, but patient enrollment was paused in critically ill patients due to concern for futility and potential excess of safety events (40).

As of December 16, 2020, a total of 75 RCTs of antithrombotic agents for patients with COVID-19 were registered at the ClinicalTrials.gov or WHO International Clinical Trials Registry Platform databases. **Figure 2** provides a graphical summary of all RCTs of antithrombotic agents in COVID-19 in a pharmacological-based approach. Agents used in these trials include antiplatelet agents, unfractionated heparin (UFH) and heparin derivatives, parenteral direct thrombin inhibitors (DTIs), direct oral anticoagulants (DOACs), fibrinolytic agents, sulodexide (a mixture of heparin sulfate and dermatan sulfate) (39), dociparstat (a heparin derivative with anti-inflammatory properties), and nafamostat (a synthetic serine protease inhibitor with anticoagulant activity). A succinct discussion of the design features of these trials is provided in the following sections according to the clinical setting. Additional details are provided in Supplemental Tables 2 and 3.

In each section, the discussion begins with parenteral anticoagulants, followed by fibrinolytic therapy,

FIGURE 1 Virchow's Triad and COVID-19 Associated Coagulopathy

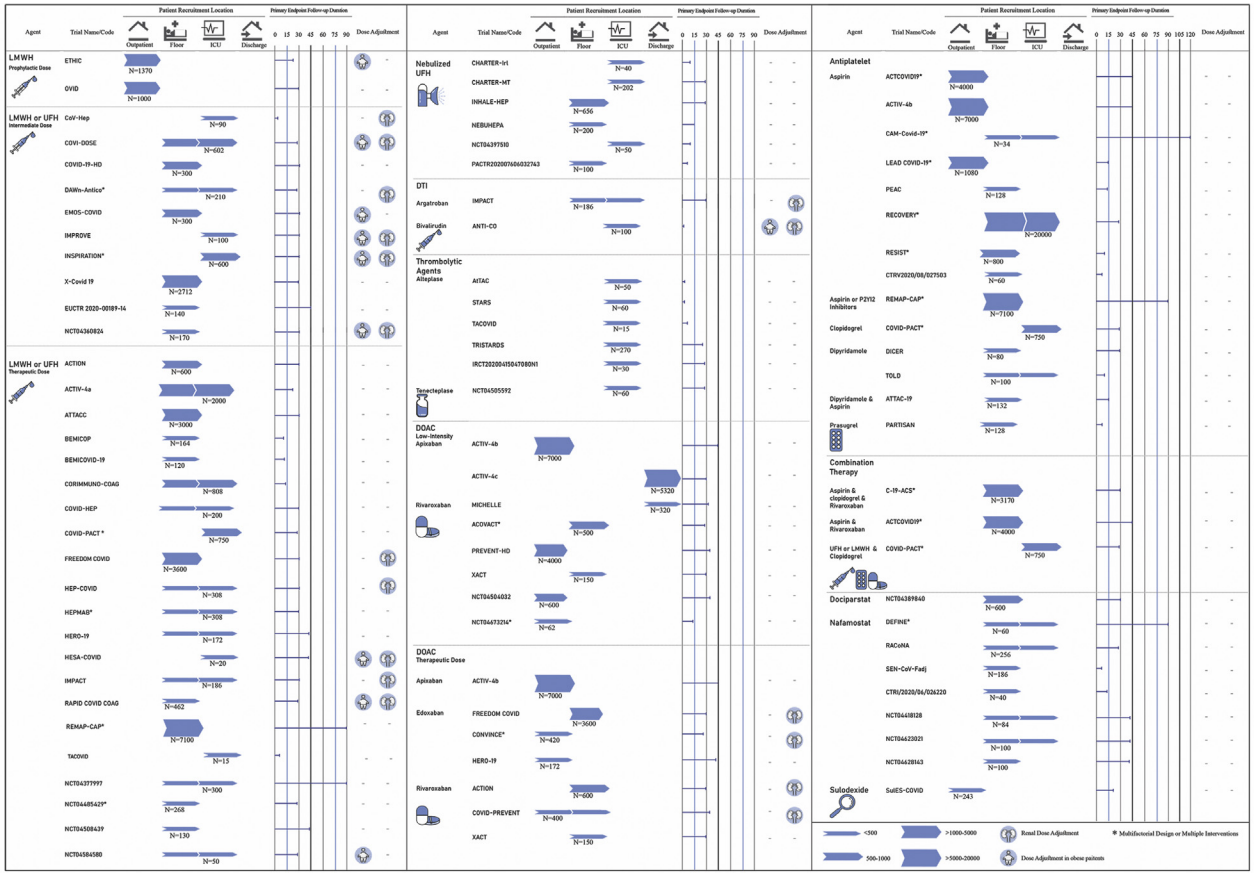


Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can potentiate all 3 sides of Virchow's triad, including endothelial dysfunction, blood flow stasis, and hypercoagulability. Angiotensin-converting enzyme-2 (ACE-2)–dependent viral entry and the virus-induced inflammatory response can lead to endothelial dysfunction. Bedridden status may lead to stasis; inflammation, viremia, and cytokine storm can produce a hypercoagulable state. Factor Xa may play a role in spike protein cleavage and endocytosis of the virus.
COVID-19 = coronavirus disease-2019; DIC = disseminated intravascular coagulopathy; FDP = fibrin degradation products; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; LV = left ventricular; PAI = plasminogen activator inhibitor; RNA = ribonucleic acid; SIC = sepsis-induced coagulopathy; TF = tissue factor; TNF = tumor necrosis factor; tPA = tissue type plasminogen activators; uPA = urokinase plasminogen activators; vWF = von Willebrand factor.

oral anticoagulants, antiplatelet agents, and investigational agents with antithrombotic properties. This sequence is arbitrary and does not indicate treatment preference. Figure 3 illustrates how RCTs of various agents can fill the knowledge gaps about antithrombotic therapy in COVID-19 in various settings of illness severity.

ONGOING CLINICAL TRIALS OF ANTITHROMBOTIC AGENTS IN THE OUTPATIENT SETTING. Eleven RCTs of antithrombotic therapy in outpatients with COVID-19 have been registered in clinical trials databases and are studying enoxaparin, DOACs, aspirin, and sulodexide compared with no treatment (6 of 11) or with placebo (5 of 11). These trials are mostly (8 of 11)

FIGURE 2 **Summary of RCTs of Antithrombotic Agents in COVID-19 Categorized Based on Pharmacological Class**



Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct thrombin inhibitors (DTIs), direct oral anticoagulants (DOACs), antiplatelets, fibrinolytic agents, and investigational agents are being evaluated in different settings, including outpatients, inpatients (intensive care unit [ICU] and non-ICU), and post-discharge. *Multifactorial designs or multiple interventions. COVID = coronavirus disease-2019; RCTs = randomized controlled trials.

open-label, with the number of participants ranging from 172 to 7,000 patients, and they include patients with a hyperinflammatory or procoagulant profile (including elevated levels of C-reactive protein [1 of 11] or D-dimer [2 of 11]) and exclude patients at high risk of bleeding (e.g., those with a history of recent gastrointestinal bleeding or intracranial hemorrhage). Pregnant women and patients with severe kidney dysfunction (creatinine clearance [CrCl] levels <30 ml/min) are excluded from 8 of 11 and 6 of 11 of these trials, respectively. The most common primary efficacy outcomes in the outpatient trials include the need for hospitalization, incidence of thromboembolic events, mortality, or composite outcomes inclusive of these factors. Bleeding events (5 of 11) constitute the most commonly assessed safety endpoints in the trials with an outpatient setting.

LMWHs (at standard prophylactic dose), DOACs (at both low intensity and high intensity), aspirin, and sulodexide are the agents under investigation in the outpatient setting. ETHIC and OVID RCTs are comparing the effect of a standard prophylactic dose of enoxaparin versus no intervention on the primary outcome of hospitalization or mortality in 2,370 individuals (41). Low-intensity rivaroxaban (10 mg once daily [QD]) is being evaluated in a total of 4,600 patients in 2 ongoing RCTs (PREVENT-HD [A Study of Rivaroxaban to Reduce the Risk of Major Venous and Arterial Thrombotic Events, Hospitalization and Death in Medically Ill Outpatients With Acute, Symptomatic Coronavirus Disease 2019 (COVID-19) Infection; NCT04508023] and Study to Evaluate Safety and Efficacy of Rivaroxaban for High Risk People With Mild COVID-19 [NCT04504032]). Low-intensity apixaban (2.5 mg twice daily [BID]) is also

FIGURE 3 **Graphical Summary of Ongoing RCTs of Antithrombotic Therapy in COVID-19 Based on Patient Settings**

Categorizing the RCTs evaluating different agents in various settings, including those treated entirely as outpatients, patients in the non-ICU hospital wards, critically ill patients in the ICU, and post-hospital discharge. Others: dociparstat, nafamostat, and sulodexide. Abbreviations as in Figure 2.

under investigation in the ACTIV-4b (Anti-thrombotics for Adults Hospitalized With COVID-19) trial in up to 7,000 patients. High-intensity DOACs, including rivaroxaban (20 mg QD), apixaban (5 mg BID), and edoxaban (60 mg QD), are being investigated among 7,992 patients in 4 RCTs (COVID-PREVENT, ACTIV-4b, HERO-19 [Health Care Worker Prophylaxis Against COVID-19], and CONVINCE [Corona Virus Edoxaban Colchicine]). The primary outcome for the COVID-PREVENT, HERO-19, and CONVINCE trials is the composite of mortality and arterial and venous thromboembolism; the primary outcome for the

randomized, double-blind, placebo-controlled ACTIV-4b trial is a composite of venous and arterial thromboembolism, hospitalization for cardiovascular/pulmonary events, and all-cause mortality. The impact of low-dose aspirin on the composite rate of hospitalizations and mortality is being evaluated in 3 RCTs with a total of 12,080 patients with COVID-19 (ACT-COVID19 [Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial], LEAD COVID-19 [Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations], and ACTIV-4b).

SulES-COVID (Sulodexide in the Treatment of Early Stages of COVID-19) is the only completed trial of antithrombotic therapy in outpatients with COVID-19 (39). This single-center study of 243 participants assessed the efficacy of sulodexide compared with placebo on 21-day rates of hospitalization and need for use of supplemental oxygen. Use of sulodexide was associated with reduced hospital admissions (relative risk: 0.6; 95% CI: 0.37 to 0.96; $p = 0.03$) and need for oxygen support (relative risk: 0.71; 95% CI: 0.5 to 1; $p = 0.05$), with no significant effect on mortality. The study has limitations, including frequent (22.1%) post-enrollment exclusions due to negative SARS-CoV-2 test results or loss to follow-up.

Many of the outpatient antithrombotic therapy trials for COVID-19 are large, and the follow-up windows are sufficient to capture the intended primary outcomes. An issue with some of these trials is an open-label design, which is a pragmatic feature facilitating the design and enrollment but potentially limits the internal validity, especially for outcomes that may be less bias resistant. In addition, the available data do not clarify whether dose adjustments are made for renal or liver dysfunction.

ONGOING CLINICAL TRIALS OF ANTITHROMBOTIC AGENTS IN HOSPITALIZED NON-ICU PATIENTS. We identified 50 ongoing RCTs related to antithrombotic therapy in hospitalized non-ICU patients with COVID-19. Most trials (44 of 50) are open-label. The antithrombotic agents under investigation include heparin (both systemic and inhaled), DOACs, aspirin, $P2Y_{12}$ inhibitors, dipyridamole, dociparstat, nafamostat, and a combination of these drugs. The planned sample sizes range between 34 and 20,000 patients. Considering the potential link between elevated D-dimer levels, microthrombosis, macrothrombosis, and worse outcomes in COVID-19 (42-44), many RCTs (16 of 50) include patients with elevated D-dimer levels with cutoffs ranging from >500 ng/ml to >1,500 ng/ml (or defined as >2 to 4 times the upper limit of normal per the local laboratory). Most trials exclude pregnant women (41 of 50) and patients with active bleeding or history of intracranial or gastrointestinal bleeding (39 of 50). Many trials also exclude patients with CrCl levels <30 ml/min (20 of 50). In most trials, the time frame for the primary outcome assessment is 28 to 30 days, although a few studies are designed to assess the primary outcomes at earlier or longer durations. These RCTs are focused on primary efficacy outcomes, including all-cause mortality, VTE, arterial thrombosis, requirement for respiratory support, or a composite of these outcomes.

Twenty-eight ongoing studies are being conducted to examine the efficacy of heparin-based regimens on primary outcomes such as all-cause mortality, venous and arterial thrombosis, re-hospitalization, the need for invasive mechanical ventilation, or composite outcomes inclusive of these factors in hospitalized patients with COVID-19. Bleeding events is the most common (17 of 28) primary safety endpoint used in these trials. The majority of these RCTs have chosen a standard-dose prophylactic anticoagulation regimen as the comparator. Intermediate-dose anticoagulation will be tested in DAWn-Antico (Direct Antivirals Working Anticoagulation) (45), X-COVID-19, COVID-19 HD (Randomised controlled trial comparing efficacy and safety of high versus low Low-Molecular Weight Heparin dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation), COVI-DOSE (Weight-Adjusted vs Fixed Low Doses of Low Molecular Weight Heparin for Venous Thromboembolism Prevention in COVID-19), EMOS-COVID (Enoxaparin at Prophylactic or Therapeutic Doses in COVID-19), COVID-19-associated Coagulopathy: Safety and Efficacy of Prophylactic Anticoagulation Therapy in Hospitalized Adults With COVID-19 (NCT04360824), and Impact of the use of low molecular weight heparins (LMWH), at prophylactic versus intermediate doses, on SARS-CoV2 infection (COVID-19) [EUCTR2020-001891-14-ES] with 4,434 patients in total. Conversely, a total of 18 RCTs with 19,776 patients will evaluate the efficacy of therapeutic anticoagulation in non-ICU hospitalized patients (46). Only 2 trials totaling 494 patients (IMPACT [InterMediate ProphylACtic Versus Therapeutic Dose Anticoagulation in Critically Ill Patients With COVID-19: A Prospective Randomized Study; NCT04406389] and HEP-COVID [Systemic Anticoagulation With Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients; NCT04401293]) will directly compare therapeutic and intermediate doses of heparin. The different

intensities of heparin derivatives are summarized in Supplemental Table 3.

Recognizing that heparin has an anticoagulant effect but also an antiviral and anti-inflammatory effect (47,48), INHALE-HEP (Inhaled Nebulised Unfractionated Heparin for the Treatment of Hospitalised Patients With COVID-19) and NEBUHEPA (Nebulized Heparin in Severe Acute Respiratory Syndrome COVID-19) are evaluating the impact of nebulized UFH on the rate of intubation in 856 hospitalized patients with COVID-19. PACTR202007606032743 evaluates the impact of nebulized UFH on the partial arterial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio in 100 hospitalized patients. Standard of care (for INHALE-HEP and PACTR202007606032743) and standard-dose prophylaxis with LMWH (NEBUHEPA) are the comparators.

The use of DOACs in hospitalized ward patients with COVID-19 is under investigation in 5 RCTs. Low-intensity rivaroxaban is being investigated in 650 planned participants in the ACOVACT (Austrian Coronavirus Adaptive Clinical Trial) and XACT (Factor Xa Inhibitor Versus Standard of Care Heparin in Hospitalized Patients With COVID-19) trials of hospitalized patients to assess outcomes such as all-cause mortality, ICU admission, and intubation. High-intensity (but not loading-intensity) DOACs, including rivaroxaban and apixaban, are being evaluated in large RCTs that will enroll a total of 4,750 participants (ACTION [Randomized Clinical Trial to Evaluate a Routine Full Anticoagulation Strategy in Patients With Coronavirus (COVID-19); NCT04394377], COVID-PREVENT [Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19], FREEDOM [FREEDOM COVID Anticoagulation Strategy Randomized Trial; NCT04512079] COVID, and XACT [Factor Xa Inhibitor Versus Standard of Care Heparin in Hospitalized Patients With COVID-19; NCT04640181]). Major bleeding is the primary safety endpoint in 3 of 6 trials addressing DOACs in hospitalized non-ICU patients.

C-19-ACS (Preventing Cardiac Complications of COVID-19 Disease with Early Acute Coronary Syndrome Therapy) is an adaptive RCT conducted to evaluate the impact of the combination of low-dose rivaroxaban (2.5 mg BID) plus aspirin 75 mg/day plus clopidogrel 75 mg/day along with atorvastatin and omeprazole on 30-day all-cause mortality in 3,170 hospitalized patients with COVID-19. Patients with definite acute coronary syndromes are excluded from this RCT. The effect of dual pathway inhibition using the combination of low-dose rivaroxaban and aspirin is being evaluated in the adaptive ACTCOVID19 inpatient study. In this RCT of 4,000 patients, the rate of invasive mechanical ventilation or death is assessed at 45 days' post-randomization.

The potential protective effect of antiplatelet agents in hospitalized patients with COVID-19 is being evaluated in 11 RCTs. REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) is a large global RCT with a multifactorial adaptive design that is planning to randomize 7,100 patients to receive multiple therapeutic interventions, including an anticoagulant arm and an antiplatelet agent arm evaluating aspirin and the $P2Y_{12}$ inhibitors clopidogrel, ticagrelor, or prasugrel (49). PEAC (Protective Effect of Aspirin on COVID-19 Patients; NCT04365309) aims to test the efficacy of aspirin in shortening clinical recovery time. The impact of aspirin on all-cause mortality among hospitalized patients is also under evaluation in the largest adaptive platform RCT for COVID-19 (RECOVERY [Randomised Evaluation of COVID-19 Therapy]) with 20,000 participants (50). RESIST (CTRI/2020/07/026791) aims to evaluate the role of aspirin plus atorvastatin in clinical deterioration characterized by progression according to the WHO clinical improvement ordinal score in 800 hospitalized patients with COVID-19 (51). CAM-Covid-19 evaluates the impact of a higher dose of aspirin (325 mg 4 times a day) along with colchicine and montelukast on inflammatory markers such as high-sensitivity C-reactive protein in 34 patients. PARTISAN (Prasugrel in Severe COVID-19 Pneumonia; NCT04445623) will be comparing the effect of prasugrel versus placebo among 128 patients with COVID-19 on the primary outcome of improved oxygenation expressed as the PaO_2/FiO_2 ratio at 7-day follow-up. Some RCTs are evaluating the impact of dipyridamole in hospitalized patients with COVID-19. Dipyridamole 100 mg 4 times a day and the combination of dipyridamole extended-release 200 mg twice daily and aspirin 25 mg twice daily are being evaluated in 3 small RCTs (TOLD, DICER [Dipyridamole to Prevent Coronavirus Exacerbation of Respiratory Status], and ATTAC-19 [Aggrenox To Treat Acute Covid-19]) for primary outcomes such as D-dimer level changes (for the first 2 trials) and improvement in the COVID-19 WHO ordinal scale (a scale indicting severity of illness, from 0 [not infected] to 8 [death]) (ATTAC-19).

High-mobility group box protein 1 (HMGB1) is a protein involved in the pathogenesis of inflammation. Elevated levels of HMGB1 are associated with worse outcomes in COVID-19 (52). Dociparstat, a heparin derivative with presumed anticoagulant and anti-inflammatory properties, inhibits HMGB1 and may reduce the formation of NETs and the risk of

thrombosis. The drug is being studied in the Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure study [NCT04389840] to assess its impacts on all-cause mortality and need for mechanical ventilation in 600 patients with severe COVID-19 (53).

Nafamostat is a synthetic serine protease inhibitor with antiviral, anti-inflammatory, and anticoagulant activity previously used for anticoagulation during hemodialysis (54). Nafamostat is under evaluation in hospitalized patients with COVID-19 in 7 RCTs with 826 individuals in total. The primary efficacy outcome in 5 of these 7 trials is time to recovery.

The strengths of many of the antithrombotic trials among inpatients with COVID-19 include relatively large sample sizes and ample follow-up for detection of events. With multiple large clinical trials underway, robust evidence should soon be available comparing the intermediate/therapeutic doses of heparinoids versus usual care. However, studies such as PARTISAN and Clinical Trial on the Efficacy and Safety of Bemiparin in Patients Hospitalized Because of COVID-19 (NCT04420299) have relatively small sample sizes and short periods of follow-up (7 and 10 days, respectively), rendering them susceptible to a type II error. There is also variability across the trials in methods for identification and ascertainment of thrombotic outcomes. Lack of blinding and blinded outcome adjudication are practical limitations for some of these trials.

ONGOING CLINICAL TRIALS OF ANTITHROMBOTIC AGENTS IN CRITICALLY ILL PATIENTS. The risk of thrombotic events seems to be highest among critically ill patients with COVID-19. A systematic review estimated that VTE event rates in critically ill patients with COVID-19 would be estimated at 27.9% (95% CI: 22.1 to 34.1) (6). Currently, there are 33 ongoing RCTs evaluating the role of antithrombotic agents in critically ill patients with COVID-19, of which 18 RCTs enrolled mixed non-ICU and ICU populations and 15 RCTs solely enrolled ICU patients. The sample size of these studies range from 15 to 20,000 patients. These trials are studying the role of systemic anticoagulants (intermediate- to full-therapeutic-dose of heparin and direct thrombin inhibitors), inhaled UFH, fibrinolytic agents (tenecteplase and alteplase), antiplatelet agents (aspirin, clopidogrel, and dipyridamole), and nafamostat. Inclusion criteria in 11 of 33 RCTs require D-dimer cutoffs ranging from >500 ng/ml to >3,000 ng/ml (or defined as >2 to 6 times the upper limit of normal limit). All-cause mortality, venous and arterial thrombotic complications, and oxygenation (expressed mostly as PaO_2/FiO_2) status are the most common components of the primary efficacy outcomes. Bleeding complications are the most widely used primary safety outcome among these studies.

UFH and/or LMWH (19 studies) are the most common antithrombotic regimens under investigation in the ongoing trials in critically ill patients. INSPIRATION (The Intermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial) (55), IMPROVE (Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19: A Cluster Based Randomized Selection Trial; NCT04367831), DAWn-Antico, and COVI-DOSE are testing intermediate-dose versus standard prophylactic dose anticoagulation in more than 1,500 participants in total. INSPIRATION has recently completed enrollment of 600 patients (55). Preliminary analyses indicate that intermediate-dose compared with standard-dose anticoagulation did not reduce a composite of venous or arterial thrombosis or death. The full results are imminent. IMPACT and HEP-COVID are comparing therapeutic anticoagulation with intermediate-dose anticoagulation in a total of 494 individuals. Finally, 11 RCTs are evaluating the potential role of therapeutic-dose versus standard prophylactic dose anticoagulation in 5,142 patients. In December 2020, preliminary results of an interim analysis of pooled critically ill patients enrolled in 3 trials (ACTIV-4a, REMAP-CAP, and ATTACC [Antithrombotic Therapy to Ameliorate Complications of COVID-19]) prompted the Data Safety and Monitoring Boards to pause enrollment due to futility for the endpoint of freedom from organ support at 21 days and a potential for harm due to possibly higher rates of bleeding. More details are forthcoming (40). Conversely, in January 2021, the same study groups paused enrollment into the strata of moderately ill hospitalized patients with COVID-19 not requiring ICU level of care, in whom a preliminary analysis showed a reduction in the need for ventilatory support or other organ-supportive interventions with therapeutic-dose enoxaparin (56). Data supporting these decisions have not yet been finalized or peer reviewed, and they are anxiously awaited.

The only published RCT in critically ill patients with COVID-19 is HESACOVID (Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial), a single-center study of 20 patients requiring invasive mechanical ventilation randomized to receive therapeutic-dose versus standard-dose anticoagulation. Therapeutic-dose anticoagulation significantly increased PaO_2/FiO_2

and ventilator-free days (15 days [interquartile range: 6 to 16 days] vs. 0 days [interquartile range: 0 to 11 days]; p = 0.028) (38). The study did not have sufficient power to compare all-cause mortality between the study groups. Bleeding may have been underestimated due to barriers in performing imaging testing, including computed tomography scanning to identify a source, in critically ill patients (57).

CHARTER-Irl (Patients with SARS-CoV-2 Requiring Mechanical Ventilation in Ireland), CHARTER-MT (Can Nebulised Heparin Reduce Mortality and Time to Extubation in Patients With COVID-19 Requiring Mechanical Ventilation Meta-Trial), and Nebulized Heparin for the Treatment of COVID-19 Induced Lung Injury (NCT04397510) are evaluating the utility of nebulized UFH in 292 mechanically ventilated critically ill patients with COVID-19. The primary outcome for CHARTER-Irl is the alterations in D-dimer area under the curve within a 10-day follow-up, and for CHARTER-MT is ventilator-free days with a follow-up duration of 28 days; the primary outcome for the Nebulized Heparin for the Treatment of COVID-19 Induced Lung Injury study (NCT04397510) is improvement in the PaO_2/FiO_2 ratio within 10 days.

The use of parenteral anticoagulant agents other than UFH and LMWHs in COVID-19 is being studied in 2 trials. IMPACT will randomize 100 ICU patients with COVID-19 into 4 arms to compare fondaparinux, argatroban, intermediate-dose heparin, and therapeutic-dose heparin (UFH/LMWH) with the primary outcomes of 30-day mortality. In ANTICO, bivalirudin is being investigated in 100 critically ill patients for the primary outcome of improvement in oxygenation as determined by the PaO_2/FiO_2 ratio (58).

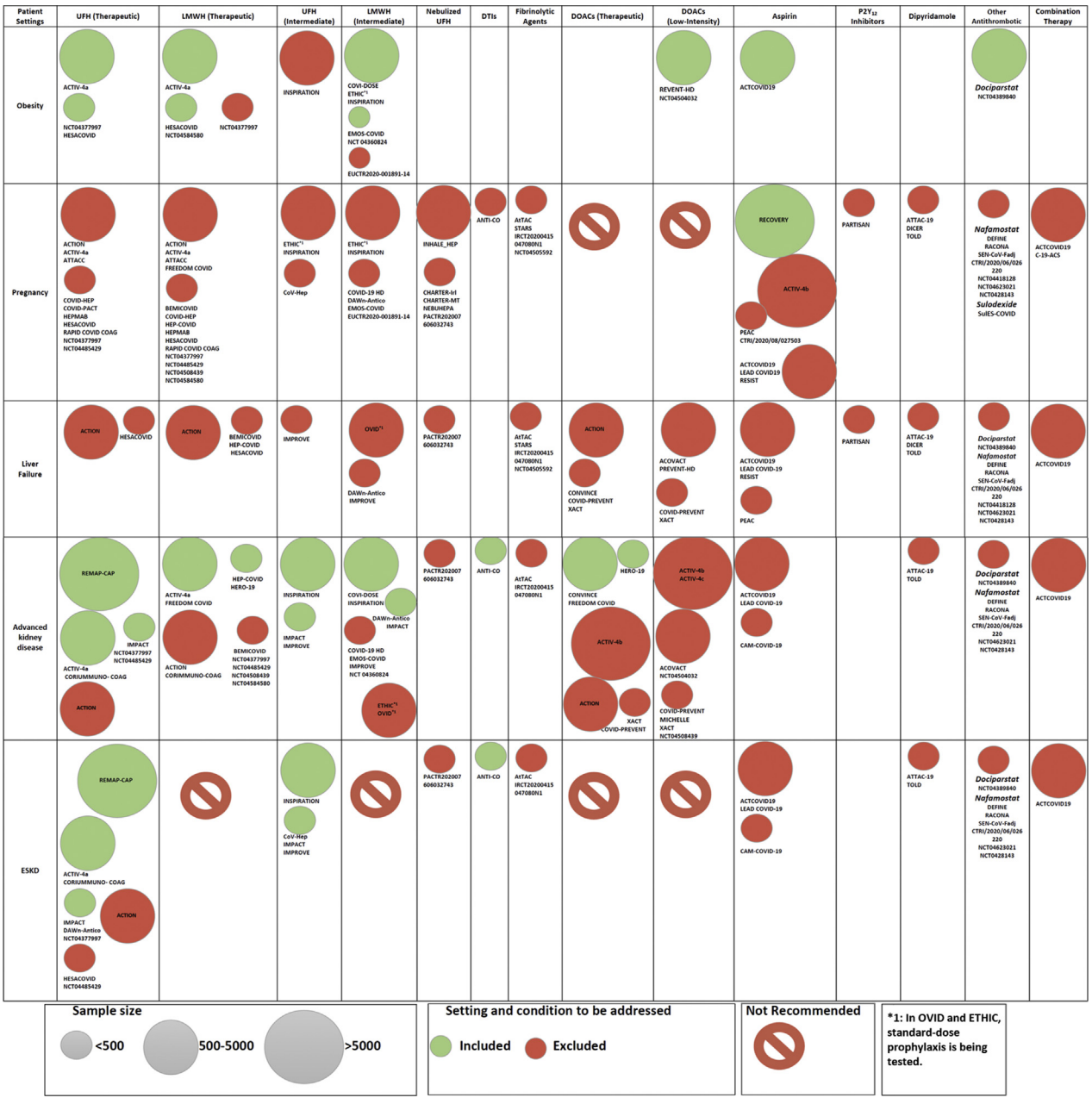
There are 6 RCTs (AtTAC [Tissue Plasminogen Activator (tPA) Treatment for an Atypical Acute Respiratory Distress Syndrome (Microvascular COVID-19 Lung Vessels Obstructive Thromboinflammatory Syndrome (MicroCLOTS): A Multicentral Randomized; NCT04453371), STARS [Fibrinolytic Therapy to Treat ARDS in the Setting of COVID-19 Infection; NCT04357730], TRISTARDS [ThRombolysIS Therapy for ARDS A Phase IIb/III Operationally Seamless, Open-label, Randomised, Sequential, Parallel-group Adaptive Study to Evaluate the Efficacy and Safety of Daily Intravenous Alteplase Treatment Given up to 5 Days on Top of Standard of Care (SOC) Compared With SOC Alone, in Patients With Acute Respiratory Distress Syndrome (ARDS) Triggered by COVID-19; NCT04640194], TACOVID [Evaluation of Tissue Plasminogen Activator (tPA) in comparition of anticoagulation for treatment of critical COVID 19 patient; 48929], Tenecteplase in Patients With COVID-19 [NCT04505592], and the Evaluation of Tissue Plasminogen Activator (tPA) in comparition of anticoagulation for treatment of critical COVID 19 patient [IRCT20200415047080N1]) evaluating the safety and efficacy of fibrinolytic therapy (tenecteplase or alteplase) on COVID-19-related respiratory failure in a total of 485 patients (59). Most of these trials include patients with severe disease (severe acute respiratory distress syndrome, elevated troponin levels, and elevated D-dimer levels). The primary outcomes in 5 of these trials include the improvement in PaO_2/FiO_2 ratio or ventilator-free days. The time frame for studies evaluating the change in PaO_2/FiO_2 ratio is between 48 and 72 h; for those evaluating ventilator-free days, it is 28 days. Patients receiving therapeutic anticoagulation, and those with thrombocytopenia or a history of intracranial or gastrointestinal bleeding, are excluded from fibrinolytic therapy trials.

The role of antiplatelet agents is under investigation in critically ill patients in 4 trials. As previously described, dipyridamole (TOLD) and aspirin (RECOVERY and CAM-Covid-19) are under evaluation. COVID-PACT is a multicenter, open-label study that will randomize 750 patients with a 2×2 factorial design trial to receive full-dose anticoagulation versus standard-dose prophylactic anticoagulation with heparin-based regimens (first randomization) and to antiplatelet therapy with clopidogrel versus no antiplatelet therapy (second randomization). The primary efficacy outcome is the incidence of VTE or arterial thrombosis incidence 28 days after enrollment.

Nafamostat is under evaluation in 4 studies in critically ill patients with COVID-19 (DEFINE [Rapid Experimental Medicine for COVID-19; NCT04473053], RACONA [RAndomized Clinical Trial in COvid19 Patients to Assess the Efficacy of the Transmembrane Protease Serine 2 (TMPRSS2) Inhibitor NAfamostat; NCT04352400], 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]) with 650 participants in total.

Research in the ICU faces several challenges for study design, data/sample collection, and patient follow-up (60). In many cases, patients are unconscious, and obtaining informed consent requires discussion with health care proxies. This situation is further complicated because visitors are prohibited. The strengths of the aforementioned studies in the ICU include the diversity of studied antithrombotic agents and sample size in many RCTs. There are also a number of notable limitations to these trials.

FIGURE 4 **Illustration of How Vulnerable Populations Were or Were Not Included in the Existing Trials**

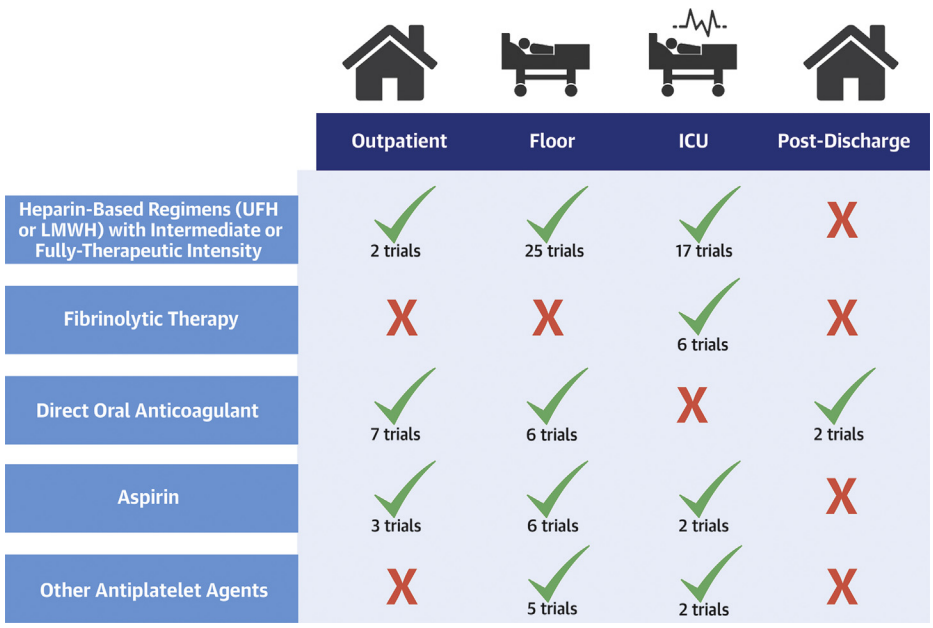


Categorizing the RCTs evaluating different agents in vulnerable populations, including patients with advanced kidney disease, end-stage kidney disease (ESKD), patients with liver failure, and obese patients. Further details are illustrated in Supplemental Figure 1. Obesity is defined differently in different RCTs; body mass index >30, 35, and 40 kg/m^2 and weight >100 and 120 kg are among the most-used definitions among RCTs. Others: dociparstat, nafamostat, and sulodexide. Abbreviations as in **Figure 2**.

The most important limitation is the small sample size in several studies, raising the possibility of a type II error. The small sample size will mostly influence trials of thrombolytic therapy and nonheparin anticoagulants.

ONGOING CLINICAL TRIALS IN POST-DISCHARGE PATIENTS. ACTIV-4c (COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis; NCT04650087) is a double-blind, placebo-controlled RCT that will evaluate the impact of apixaban 2.5 mg

CENTRAL ILLUSTRATION **Simplified Summary of Ongoing Antithrombotic Therapy Trials in Coronavirus Disease-2019***



Talasaz, A.H. et al. J Am Coll Cardiol. 2021;■(■):■–■.

Heparin-based regimens are the most frequently studied antithrombotic agents in patients with coronavirus disease-2019. Trials of fibrinolytic therapy are reserved for patients admitted to the intensive care unit (ICU). *Additional details are provided in **Figure 2 and Supplemental Table 2**. LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

BID on the rate of all-cause mortality and arterial and venous thromboembolism on 5,320 post-discharge patients. MICHELLE (Medically Ill Hospitalized Patients for COVID-19 THrombosis Extended Prophy-Laxis With Rivaroxaban ThErapy: The MICHELLE Trial; NCT04662684) is an open-label RCT with 320 participants; it aims to evaluate the safety and efficacy of rivaroxaban 10 mg QD for 35 ± 4 days versus no intervention after hospital discharge with a composite efficacy outcome of VTE and VTE-related death.

In addition, there are 7 RCTs with a projected total of 1,452 participants that will continue the already assigned antithrombotic therapy after discharge in patients who were randomized in the general medical wards or in the ICU. In the INSPIRATION study, an intermediate or standard prophylactic dose of enoxaparin will be continued after discharge in 600 patients who were randomized in the ICU to evaluate the rate of VTE. In the COVID-PREVENT, XACT, and Effect of the Use of Anticoagulant Therapy During Hospitalization and Discharge in Patients With COVID-19 Infection (NCT04508439) RCTs, post-discharge thromboprophylaxis with rivaroxaban (10 or 20 mg QD) is being investigated in 680 participants enrolled in general medical wards to measure the incidence of VTE at 30 to 35 days after discharge. In the HERO-19 study, edoxaban 60 mg QD or placebo will continue after discharge in 172 patients who were randomized to treatment in the ICU or non-ICU settings to evaluate all-cause mortality rate and VTE incidence at 42 days. Finally, aspirin in the PEAC study, and dipyridamole extended-release plus aspirin in the ATTAC-19 study, will be continued after discharge in patients randomized to treatment in the non-ICU general wards.

INCORPORATION OF VULNERABLE POPULATIONS IN THE ONGOING TRIALS. Most of the ongoing RCTs are excluding patients at increased risk of bleeding, or with acute and chronic hepatic failure. In >50% of the trials designed to evaluate escalated dose anticoagulation, patients with CrCl levels <15 ml/min are excluded. CoV-Hep is an open-label study that evaluates the role of low-dose (10 IU/kg per hour) intravenous UFH on the rate of clotted dialyzers in 90 critically ill patients with COVID-19 undergoing continuous venous-venous hemodialysis with a

TABLE 1 Expected Knowledge Gains From Ongoing Antithrombotic Therapy Trials in COVID-19 and Ongoing Knowledge Gaps

Outpatient	Noncritical Inpatient	ICU	Post-Discharge
Expected knowledge gain			
The safety/efficacy of standard prophylactic doses of LMWHs and DOACs compared with standard of care or placebo in high-risk patients with early stages of COVID-19 The impact of aspirin administration on rate of MACE, disease progression, hospitalization, and death in patients with acute, symptomatic COVID-19 The safety/efficacy of sulodexide in patients with acute, symptomatic COVID-19	The safety/efficacy of intermediate-dose and therapeutic-dose heparin derivatives or DOACs compared with standard prophylactic anticoagulation Proof-of-concept data of the role of inhaled antithrombotic therapy in patients with COVID-19 The impacts of antiplatelet agents on all-cause mortality The safety/efficacy of dociparstat and nafamostat in hospitalized patients with COVID-19	The safety/efficacy of intermediate-dose and therapeutic-dose anticoagulation compared with prophylactic anticoagulation Effects of short-term infusion of bivalirudin on the PaO_2/FiO_2 ratio The impacts of antiplatelet agents on thrombotic outcomes and mortality Proof-of-concept data on the role of fibrinolytic therapy in critically ill patients Proof-of-concept data on the role of inhaled antithrombotic therapy in mechanically ventilated patients with COVID-19	The safety/efficacy of extended anticoagulation with DOACs or LMWHs after hospital discharge
Remaining knowledge gap			
PMA needed to understand the relative efficacy of antiplatelet agents, standard prophylactic dose of enoxaparin compared with DOACs The safety/efficacy of antithrombotic therapy regimens in vulnerable subgroups, including obese patients, pregnant women, and those with advanced kidney disease	The efficacy/safety of fondaparinux, DTIs, and danaparoid compared with standard prophylactic anticoagulation PMA needed to understand the tradeoffs of various investigational antithrombotic regimens Best assay for LMWH/UFH monitoring in noncritically ill patients with COVID-19 The safety/efficacy of antithrombotic therapy regimens in vulnerable subgroups, including obese patients, pregnant women, and those with advanced kidney disease	The impact of antiplatelet therapy on survival in critically ill patients with COVID-19 PMA needed to understand the tradeoffs of various investigational antithrombotic regimens Best assay for LMWH/UFH monitoring in critically ill patients with COVID-19 The safety/efficacy of antithrombotic therapy regimens in vulnerable subgroups, including obese patients, pregnant women, and those with advanced kidney disease	The role of antiplatelet agents on VTE incidence in post-discharge patients The safety/efficacy of antithrombotic therapy regimens in vulnerable subgroups, including obese patients, pregnant women, and those with advanced kidney disease

COVID-19 = coronavirus disease-2019; DOAC = direct oral anticoagulants; DTI = direct thrombin inhibitor; ICU = intensive care unit; LMWH = low-molecular-weight heparin; MACE = major adverse cardiovascular events; PaO_2/FiO_2 = partial arterial pressure of oxygen/fraction of inspired oxygen; PMA = prospective meta-analysis; UFH = unfractionated heparin; VTE = venous thromboembolism.

follow-up duration of 3 days. Specific dose adjustment for obesity is considered for 10 of 34 trials of systemic heparin compounds. Pregnant women are excluded from 25 of 34 trials of systemic heparin compounds. Although patient selection in these studies is based on practical considerations, it is unlikely that high-quality evidence will soon be available for antithrombotic therapy in such vulnerable subgroups (**Figure 4,** Supplemental Figure 2). With limited high-quality data on the horizon for these vulnerable and high-risk subgroups, decision-making for optimal management in these patients will continue to be challenging.

THE IMPACT OF RCTs ON THE FUTURE PRACTICE OF ANTITHROMBOTIC THERAPY. A large number of RCTs will help to delineate the efficacy and safety of antithrombotic agents in patients with COVID-19 (**Central Illustration**). Until the results accrue, participation in these RCTs is encouraged. Efficacy outcomes vary based on the location of enrollment (i.e., between outpatient trials and inpatient trials). As for safety outcomes, many of the trials are systematically assessing major bleeding by using the International Society on Thrombosis and Haemostasis criteria or the Bleeding Academic Research Consortium definitions (61,62). Although observational evidence suggests low rates of major bleeding (33,63), observational studies have the potential for under-reported outcomes, and therefore RCTs with systematic and prospective capture of both thrombotic and bleeding events will help determine the true risk-benefit ratio for treatments. This is especially the case because risk factors for thrombosis in COVID-19 (e.g., D-dimer) may also predict bleeding (33).

Although results from the individual trials may inform interim practice, some challenges persist. The large number of antithrombotic agents under investigation, the variable dosing regimens tested, and variability in trial conduct as well as methods of outcome detection and adjudication may complicate the identification of the optimal regimens. A prospective meta-analysis of RCTs, ideally with individual participant data, will help to assess the effects of distinct agents across the spectrum of disease severity and may address the clinical and statistical heterogeneity of the upcoming results. Efforts to harmonize endpoints have been advocated, with creation of common data elements for VTE, for example, to aid in pooling trial results (64,65). In addition, there are few head-to-head

TABLE 2 Antithrombotic Therapy Trial Design Before and During the COVID-19 Pandemic

	Before COVID-19 Pandemic	During COVID-19 Pandemic
Investigators	• Single specialty-based collaboration common • Focused, often established study groups	• Specialty-based and multispecialty collaboration common • Frequent ad hoc collaborations within and between institutions and countries
Study design	• Diverse research priorities • Patient enrollment over a long time period; recruitment time could be slow or fast • Long-term follow-up a routine feature of many trials	• Distinct focus on COVID-19–related trials; some adaptations required for pre-COVID-19 trials • Time-sensitive trial design (to provide rapid access to high-quality evidence). Trial design in short period of time may lead to multiple smaller and underpowered trials rather than larger multicenter collaborations. • Urgently needed medical solutions necessitate relatively fast patient enrollment • Incorporation of pragmatic design features • Multiple projects around the world occasionally leading into several smaller trials rather than fewer large-scale trials • Short-term follow-up most common • Applicability for adaptive platform design for multiple aspects of COVID-19 trials. Multiple interventions, quick enrollment, and the possibility of re-estimation of the optimal sample size during the study • Higher certain event rates (death or re-admission) than excepted from protocol
Funding/ financial support	• Time-consuming review and approval process for funding allocation	• Accelerated review, prioritizing trials that affect the response to the pandemic
IRB approval	• Time-consuming process with occasional long delays before approval	• IRBs meeting more frequently, often resulting in rapid review and approval • More permissive regulations may expedite trial initiation
Informed consent	• Based on paper forms; may be cumbersome	• In-person or remote electronic informed consent available in many trials
Participant enrollment and engagement	• Variable willingness for trial participation by patients	• Patients willing to participate and engage in trials as partners • Periodic slowdown or interruptions in enrollment for some non–COVID-19 trials; in COVID-19 trials, there may be changes in enrollment rate with COVID-19 disease waves
Monitoring and auditing	• On-site session for multiple predefined monitoring visits • On-site or in-person data audits	• Frequent off-site online sessions with more restricted on-site visits • Remote monitoring and follow-up • Rapid enrollment makes keeping up to date with monitoring difficult, with risk of greater numbers of protocol deviations going unnoticed • Ascertainment of events other than all-cause mortality may be challenging due to limitations in testing strategies during the pandemic
Clinical events adjudication	• Central blinded outcome adjudication common • Face-to-face meetings • High costs • Time-consuming process to request ad hoc data from sites, summarize, and send back to adjudication meetings	• Some trials not able to incorporate endpoint adjudication (not recommended if resources allow) • Systematic and blinded adjudication in online meeting for assessment endpoints • Remote periodic meetings • Less expensive and quicker than face-to-face adjudication
DSMB meetings	• Face-to-face meetings • High costs	• Many trials using online platforms for DSMB meetings • Less costly
Follow-up	• Face-to-face visits or telephone calls • More costly	• Remote monitoring and follow-up in many trials by telephone calls and use of digital technology • Cost-saving and more efficient
Dissemination of results	• Longer peer review process • More strict criteria for publication • Uncommon use of pre-print servers	• Fast-track peer review process expedites the dissemination of completed studies. However, very quick peer review has occasionally missed important flaws of submitted reports • Frequent use of pre-print servers to share the early results of the studies The benefits of rapid dissemination and potential limitations with lack of peer review should be considered among the audience of the results • Similar to the pre-COVID-19 era, some studies may report preliminary results by press release, with full results becoming available days or weeks later

COVID-19 = coronavirus disease-2019; DSMB = Data and Safety Monitoring Board; IRB = institutional review board; RCT = randomized controlled trial.

comparisons for many of the experimental therapies, such as intermediate-dose regimens compared with fully therapeutic heparin-based regimens. Network meta-analytic techniques might generate insights into the comparative tradeoffs of these regimens (66). Additional biomarker and clinical risk prediction substudies can also further elucidate subgroups with more favorable net benefit profiles from distinct regimens. Moreover, the remaining knowledge gaps summarized in **Table 1** should be kept in mind so that the design of additional studies could be considered.

Anti-inflammatory properties and activity against thromboinflammation have been attributed to several antithrombotic regimens, including heparin derivatives and antiplatelet agents (30,67,68), with the potential to reduce large-vessel thrombosis and improve outcomes. Another evolving concept is the role of microthrombosis and pulmonary intravascular coagulopathy (7,8,69) in the pathophysiology of respiratory failure in COVID-19 (70). Results from the small HESACOVID study suggested improved arterial oxygenation (PaO_2/FiO_2) with therapeutic versus standard-dose prophylaxis anticoagulation in

critically ill patients with COVID-19 (38). However, combined investigation of 3 large-scale randomized trials of therapeutic anticoagulation (ACTIV-4a, REMAP CAP, and ATTACC) paused enrollment of critically ill patients for futility; we await further clarifications (40).

Therapeutic drug monitoring of the investigational agents is also important. Even when an agent is selected (e.g., UFH), the best method for dose titration or adjustment remains uncertain (71). Some experts recommend measuring anti-factor Xa levels in those receiving intravenous UFH, because the high levels of factor VIII observed among critically ill patients with COVID-19 may interfere with activated partial thromboplastin time assays. The necessity and optimal method for dosing and monitoring of heparins and LMWHs, in particular for patients with kidney disease or obesity, have yet to be elucidated and are even understudied outside COVID-19 (72). Ideally, future strategy trials should test the merits and limitations of these monitoring tests.

CLINICAL TRIAL ENTERPRISE DURING COVID-19 PANDEMIC: IS A QUANTUM LEAP TAKING PLACE?

The clinical trial enterprise has been significantly affected during the COVID-19 pandemic (73). Patient recruitment in many ongoing pre-COVID-19 trials was temporarily halted. Notable challenges such as barriers to follow-up and site monitoring persist. However, the desire to provide an evidence-based response has been one of the key drivers of positive changes during the pandemic (74). These changes include multispecialty study teams, harmonization of multicenter protocols, expedited multi-institutional agreement execution and institutional review board and governmental agency approvals, accelerated informed consent, and enrollment with digital contact-free technology, expeditious outcomes ascertainment, remote monitoring, and dissemination of the findings via fast-track publications, preprints, and social media accounts from scientific societies or investigators (**Table 2**) (75-77).

Although traditional RCTs have provided a great deal of knowledge for modern medicine, they are confined to testing a limited number of interventions. Because COVID-19 has multiorgan involvement and broad manifestations (including inflammation, acute respiratory distress syndrome, thrombosis, and others), adaptive platform trials, which allow for testing multiple interventions in a single disease based on a decisive algorithm, have gained attention (78). This type of trial has a perpetual and multiarm, multistage design (79). The RECOVERY trial (80) and the World Health Organization Solidarity trial (81) have tested different steroid and antiviral regimens, respectively, and have some additional agents under investigation, including aspirin in one of the hypotheses from RECOVERY. REMAP-CAP is testing several interventions, including steroids, antiviral agents, biologic agents, simvastatin, and antiplatelet therapy. The ACTIV4 platform is similarly using an adaptive design for antithrombotic agents.

Notwithstanding the good will of investigators, the constant pressure to provide a rapid pandemic response may pose challenges as well. In some cases, multiple small single-center RCTs underpowered for their clinical points or using surrogate endpoints with short follow-up have been designed (74,82) and may compete against larger multicenter, and potentially more definitive, studies. The large numbers of these trials alone, in addition to the intense pressure to present broadly and publish these findings, suggests at least some potential for type I error with amplification of these results through rapid dissemination of the results.

Additional methodological aspects deserve attention. Interpretation of these trial results may be limited by underutilization of placebo (perhaps except for the outcome of mortality) (57,82). Some experts consider that the pressures of working during a global pandemic make the use of placebo more aspirational than realistic. Nevertheless, when feasible, placebo control improves the internal validity of a trial. Furthermore, appropriate endpoint assessment, including blinded adjudication when feasible, and pre-specified analysis methods will remain of importance (57).

Institutional Review Boards and independent ethics committees may experience the burden of numerous protocol submissions and amendments during the pandemic. Burnout of health care systems during the pandemic, and the risks to the research teams are unique challenges that should also be considered when designing and executing study protocols (75). Investigators should attempt to foresee some of the challenges to minimize the need for protocol amendments (83-85). Moreover, the informed consent process has become adapted to facilitate discussions by telephone or video conference, followed by verbal confirmation, and documentation of consent using approved software programs and electronic signature, where acceptable (83,86).

Monitoring of efficacy and safety outcomes is also critical. Execution of online Clinical Event Committee and Data and Safety Monitoring Board meetings for assessing the adverse events is a fast, safe, and efficient alternative to face-to-face meetings. If done

with appropriate planning to adhere to standards of high-quality Clinical Event Committee and Data and Safety Monitoring Board meetings, such approaches may be considered even when society transitions out of the pandemic (84,86).

Peer review and dissemination of the studies have had unique challenges and advancements as well. Journal editors and reviewers have been pressured for rapid release of the results of completed studies. This has activated the fast-track peer review process more than ever. Despite its merits, the "COVID-19 fatigue" created by the fast-track review process might negatively affect the quality of peer review, as noted by occurrence of post-publication major revisions and retractions, including in major journals (87). In a recent study, only 29% of the clinical trials of patients with COVID-19 reviewed on ClinicalTrials.gov met the Oxford Centre for Evidence-Based Medicine Level 2 evidence (88). The process of peer review remains an imperfect, yet essential, step in the evaluation and reporting of results (89). Pre-print servers include full drafts of research studies shared publicly before peer review. Pre-prints have the potential benefit of early dissemination and opportunity for feedback and discussion, and could be of substantial benefit during the pandemic. With a pre-print, key researchers in the field can discover findings sooner, indicate critical errors, or suggest new studies or data that strengthen the argument (90). The limitations of pre-prints should be also communicated transparently, so that similar weight is not placed on pre-print and peer-reviewed literature by the lay people, the press, health care workers, or policy makers. Indeed, many retracted papers were from pre-print servers (87).

Prospectively planned meta-analyses would be of particular help during the pandemic. Such studies can help understand the heterogeneity of the findings between interventions, between distinct studies, and within subgroups. Prospective meta-analysis can also help with pooled comparisons for interventions with small individual studies, as well as indirect comparisons for interventions that do not have sufficiently large head-to-head comparisons in existing studies.

CONCLUSIONS

Optimal antithrombotic therapy in patients with COVID-19 has yet to be determined. Results of these ongoing RCTs, and prospective meta-analyses of the completed studies, will help clarify whether any of the plentiful antithrombotic regimens under investigation can safely mitigate thrombotic complications and improve patient outcomes.

ACKNOWLEDGMENT The authors express their sincere gratitude to Fatemeh Esmaeili, MS, for her kind assistance in graphic designs.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Van Tassell has received research support from Novartis, Swedish Orphan Biovitrum, Olatec Therapeutics, and Serpin Pharma; and is a consultant of R-Pharm and Serpin Pharma. Dr. Monreal has served as an advisor or consultant for Sanofi, Leo Pharma, and Daiichi-Sankyo; and has received a nonrestricted educational grant by Sanofi and Bayer to sponsor the Computerized Registry of Patients with Venous Thromboembolism. Dr. Jimenez has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Leo Pharma, Pfizer, ROVI, and Sanofi; has served as a speaker or a member of a speaker bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Leo Pharma, ROVI, and Sanofi; and has received grants for clinical research from Daiichi-Sankyo, Sanofi, and ROVI. Dr. Piazza has received research grant support from Boston Scientific Corporation, Bayer, Bristol Myers Squibb/Pfizer, Portola/Alexion Pharmaceuticals, and Janssen Pharmaceuticals; and has received consulting fees from Amgen, Pfizer, Agile, and Prairie Education and Research Cooperative. Dr. Parikh has received institutional research support from Abbott Vascular, TriReme Medical, SurModics, and Shockwave Medical; is an advisory board member for Abbott Vascular, Boston Scientific, Cardinal Health, Medtronic, Janssen, CSI, and Philips; and receives honoraria from Abiomed and Terumo. Dr. Kirtane has received institutional funding from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, and ReCor Medical; and has received travel expenses/meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron, all outside the submitted work. Dr. Eikelboom has received honoraria and grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Sanofi, and Eli Lilly, as well as a personal award from the Heart and Stroke Foundation. Dr. Konstantinides has received research grants from Bayer AG, Boehringer Ingelheim, and Actelion-Janssen; has received educational grants from Biocompatibles Group UK, Boston Scientific, and Daiichi-Sankyo; and has received lecture fees from Bayer AG, Bristol Myers Squibb/Pfizer, and Merck Sharp and Dohme. Dr. Weitz serves as a consultant and has received honoraria from Bayer, Janssen, Johnson & Johnson, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Novartis, Daiichi-Sankyo, Merck, Servier, Anthos, Ionis, and PhaseBio. Dr. Stone has received speaker or other honoraria from Cook, Terumo, and Orchestra Biomed; has been a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, and CardioMech; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. Dr. Krumholz has received personal fees from UnitedHealth, IBM Watson Health, Element Science, Aetna, Facebook, Siegfried & Jensen Law Firm, Arnold & Porter Law Firm, Ben C. Martin Law Firm, and the National Center for Cardiovascular Diseases (Beijing, China); has ownership in Hugo Health and Refactor Health; and has contracts from the U.S. Centers for Medicare & Medicaid Services; and has received grants from Medtronic, the U.S. Food and Drug Administration, Johnson & Johnson, and the Shenzhen Center for Health Information, outside the submitted work. Dr. Lip is a consultant for Bayer/Janssen, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; and is a speaker for Bayer, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo (no

fees are directly received personally). Dr. Goldhaber has received research support from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Boston Scientific, Daiichi-Sankyo, Janssen, the National Heart, Lung, and Blood Institute, and the Thrombosis Research Institute; and has received consulting fees from Bayer, Agile, Boston Scientific, and Boehringer Ingelheim. Dr. Bikdeli is a consulting expert, on behalf of the plaintiff, for litigation related to 2 specific brand models of inferior vena cava filters. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Behnood Bikdeli, Cardiovascular Medicine Division, Brigham and Women's Hospital, 75 Francis Street, Shapiro 5, Suite 5156, Boston, Massachusetts 02115, USA. E-mail: bbikdeli@bwh.harvard.edu OR Behnood.bikdeli@yale.edu. Twitter: @AzitaTalasaz, @bbikdeli, @BrighamResearch, @harvardmed, @crfheart.

REFERENCES

1. Piazza G, Campia U, Hurwitz S, et al. Registry of arterial and venous thromboembolic complications in patients with COVID-19. J Am Coll Cardiol 2020;76:2060–72.

2. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: a single health system study. J Am Coll Cardiol 2020;76:1815–26.

3. Schulman S, Hu Y, Konstantinides S. Venous thromboembolism in COVID-19. Thromb Haemost 2020;120:1642–53.

4. Voicu S, Bonnin P, Stépanian A, et al. High prevalence of deep vein thrombosis in mechanically ventilated COVID-19 patients. J Am Coll Cardiol 2020;76:480–2.

5. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Res Prac Thromb Haemost 2020;6:1178–91.

6. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of venous thromboembolism and bleeding among hospitalized patients with COVID-19: a systematic review and meta-analysis. Chest 2020 Nov 17 [E-pub ahead of print].

7. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–8.

8. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173:268–77.

9. Fernández-Capitán C, Barba R, del Carmen Díaz-Pedroche M, et al. Presenting characteristics, treatment patterns, and outcomes among patients with venous thromboembolism during hospitalization for COVID-19. Semin Thromb Hemost 2020 Oct 21 [E-pub ahead of print].

10. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020;41:3038–44.

11. Giustino G, Pinney SP, Lala A, et al. Coronavirus and cardiovascular disease, myocardial injury, and arrhythmia: JACC Focus Seminar. J Am Coll Cardiol 2020;76:2011–23.

12. Skendros P, Mitsios A, Chrysanthopoulou A, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Investig 2020;130:6151–7.

13. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135:2033–40.

14. Koupenova M. Potential role of platelets in COVID-19: implications for thrombosis. Res Prac Thromb Haemost 2020;4:737–40.

15. Siddiqi HK, Libby P, Ridker PM. COVID-19—a vascular disease. Trends Cardiovasc Med 2021;31:1–5.

16. Stefely JA, Christensen BB, Gogakos T, et al. Marked factor V activity elevation in severe COVID-19 is associated with venous thromboembolism. Am J Hematol 2020;95:1522–30.

17. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolys 2020;50:54–67.

18. Zuo Y, Zuo M, Yalavarthi S, et al. Neutrophil extracellular traps and thrombosis in COVID-19. J Thromb Thrombolysis 2020;5:e138999.

19. Singhania N, Bansal S, Nimmatoori DP, Ejaz AA, McCullough PA, Singhania G. Current overview on hypercoagulability in COVID-19. Am J Cardiovasc Drugs 2020;20:393–403.

20. Jin S, Jin Y, Xu B, Hong J, Yang X. Prevalence and impact of coagulation dysfunction in COVID-19 in China: a meta-analysis. Thromb Haemost 2020;120:1524–35.

21. Katneni UK, Alexaki A, Hunt RC, et al. Coagulopathy and thrombosis as a result of severe COVID-19 infection: a microvascular focus. Thromb Haemost 2020;120:1668–79.

22. Marchandot B, Trimaille A, Curtiaud A, et al. Staging severity of COVID-19 according to hemostatic abnormalities (CAHA Score). Thromb Haemost 2020;120:1716–9.

23. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med 2020;12:eabd3876.

24. Borghi MO, Beltagy A, Garrafa E, et al. Anti-phospholipid antibodies in COVID-19 are different from those detectable in the anti-phospholipid syndrome. Frontiers Immunol 2020;11:2692–9.

25. Szekely Y, Lichter Y, Taieb P, et al. The spectrum of cardiac manifestations in coronavirus disease 2019 (COVID-19)—a systematic echocardiographic study. Circulation 2020;142:342–53.

26. Giustino G, Croft LB, Stefanini GG, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol 2020;76:2043–55.

27. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST Guideline and Expert Panel Report. Chest 2020;158:1143–63.

28. Andreini D, Arbelo E, Barbato E, et al. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. ESC. June 2020. Available at: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. Accessed October 1, 2020.

29. National Institutes of Health. The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Convalescent Plasma for the Treatment of COVID-19. September 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed October 1, 2020.

30. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023–6.

31. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:2950–73.

32. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18:1743–6.

33. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID and coagulation: bleeding and thrombotic manifestations of SARS-CoV2 infection. Blood 2020;136:489–500.

34. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18:1995–2002.

35. Klok F, Kruip M, Van der Meer N, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.

36. Spyropoulos AC. The management of venous thromboembolism in hospitalized patients with COVID-19. Blood Adv 2020;4:4028.

37. National Institutes of Health. Antithrombotic therapy in patients with COVID-19. December 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/. Accessed December 28, 2020.

38. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID). Thromb Res 2020;196:359–66.

39. Gonzalez-Ochoa AJ, Raffetto JD, Hernández AG, et al. Sulodexide in the treatment of patients with early stages of COVID-19: a randomised controlled trial. medRxiv 2020 Dec 7 [E-pub ahead of print].

40. National Institutes of Health. NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients. December 2020 December 2020. Available at: https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients. Accessed December 24, 2020.

41. Barco S, Bingisser R, Colucci G, et al. Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus disease-2019 (the OVID study): a structured summary of a study protocol for a randomized controlled trial. Trials 2020;21:1–3.

42. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.

43. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18:1324–9.

44. Weinberg I, Fernández-Capitán C, Quintana-Díaz M, et al. Systematic testing for venous thromboembolism in hospitalized patients with COVID-19 and raised D-dimer levels. Thrombosis Update 2021;2:100029.

45. Vanassche T, Engelen MM, Van Thillo Q, et al. A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19: the DAWn-Antico study. Trials 2020;21:1–14.

46. Houston BL, Lawler PR, Goligher EC, et al. Anti-Thrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC): study design and methodology for an international, adaptive Bayesian randomized controlled trial. Clin Trials 2020;17:491–500.

47. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. Am J Physiol Lung Cell Mol 2020;319:L211–7.

48. Conzelmann C, Müller JA, Perkhofer L, et al. Inhaled and systemic heparin as a repurposed direct antiviral drug for prevention and treatment of COVID-19. Clin Med 2020;20:e218.

49. Angus DC, Berry S, Lewis RJ, et al. The randomized embedded multifactorial adaptive platform for community-acquired pneumonia (REMAP-CAP) study: rationale and design. Ann Am Thorac Soc 2020;17:879–91.

50. Normand SLT. The RECOVERY platform. N Engl J Med 2020 Jul 21 [E-pub ahead of print].

51. Ghati N, Roy A, Bhatnagar S, et al. Atorvastatin and aspirin as adjuvant therapy in patients with SARS-CoV-2 infection: a structured summary of a study protocol for a randomised controlled trial. Trials 2020;21:1–3.

52. Chen L, Long X, Xu Q, et al. Elevated serum levels of S100A8/A9 and HMGB1 at hospital admission are correlated with inferior clinical outcomes in COVID-19 patients. Cell Mol Immunol 2020;17:992–4.

53. Lasky JA, Fuloria J, Morrison ME, et al. Design and rationale of a randomized, double-blind, placebo-controlled, phase 2/3 study evaluating dociparstat in acute lung injury associated with severe COVID-19. Adv Ther 2021;38:782–91.

54. Maruyama Y, Yoshida H, Uchino S, et al. Nafamostat mesilate as an anticoagulant during continuous veno-venous hemodialysis: a three-year retrospective cohort study. Int J Artif Organs 2011;34:571–6.

55. Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: rationale and design of the INSPIRATION/INSPIRATION-S studies. Thromb Res 2020;196:382–94.

56. Interim presentation. ATTACC, ACTIV-4a & REMAP-CAP multiplatform RCT: Results of interim analysis. Available at: https://www.attacc.org/presentations. Accessed January 28, 2021.

57. Bikdeli B. Anticoagulation in COVID-19: randomized trials should set the balance between excitement and evidence. Thromb Res 2020;196:638–40.

58. Kharma N, Roehrig S, Shible AA, et al. Anticoagulation in critically ill patients on mechanical ventilation suffering from COVID-19 disease, The ANTI-CO trial: a structured summary of a study protocol for a randomised controlled trial. Trials 2020;21:1–2.

59. Moore HB, Barrett CD, Moore EE, et al. Study of alteplase for respiratory failure in SARS-Cov2/COVID-19: study design of the Phase IIa STARS Trial. Res Prac Thromb Haemost 2020;4:984–96.

60. Dahlberg J, Eriksen C, Robertsen A, Beitland S. Barriers and challenges in the process of including critically ill patients in clinical studies. Scand J Trauma Resusc Emerg Med 2020;28:1–8.

61. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.

62. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

63. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:122–4.

64. Siegal DM, Barnes GD, Langlois NJ, et al. A toolkit for the collection of thrombosis-related data elements in COVID-19 clinical studies. Blood Adv 2020;4:6259–73.

65. Tritschler T, Mathieu ME, Skeith L, et al. Anticoagulant interventions in hospitalized patients with COVID-19: a scoping review of randomized controlled trials and call for international collaboration. J Thromb Haemost 2020;18:2958–67.

66. Lopes RD, Fanaroff AC. Anticoagulation in COVID-19: it is time for high-quality evidence. J Am Coll Cardiol 2020;76:1827–9.

67. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-inflammatory effects of heparin and its derivatives: a systematic review. Adv Pharmacol Sci 2015;2015:507151.

68. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemost 2020;120:1004–24.

69. Deshpande C. Thromboembolic findings in COVID-19 autopsies: pulmonary thrombosis or embolism? Ann Intern Med 2020;173:394–5.

70. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet 2020;2:e437–45.

71. Lawlor M, Gupta A, Ranard LS, et al. Discordance in activated partial thromboplastin time and anti-factor Xa levels in COVID-19 patients on heparin therapy. Thromb Res 2020;198:79–82.

72. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2018;2:3198–225.

73. Selvaraj S, Greene SJ, Khatana SAM, Nathan AS, Solomon SD, Bhatt DL. The landscape of cardiovascular clinical trials in the United States initiated before and during COVID-19. J Am Heart Assoc 2020;9:e018274.

74. Kimmel SE, Califf RM, Dean NE, Goodman SN, Ogburn EL. COVID-19 clinical trials: a teachable moment for improving our research infrastructure and relevance. Ann Intern Med 2020;173:652–4.

75. Tuttle KR. Impact of the COVID-19 pandemic on clinical research. Nat Rev Nephrol 2020;16:562–4.

76. Bagiella E, Bhatt DL, Gaudino M. The consequences of the COVID-19 pandemic on non-COVID-19 clinical trials. J Am Coll Cardiol 2020;76:342–5.

77. Makris M. Staying updated on COVID-19: social media to amplify science in thrombosis and hemostasis. Res Prac Thromb Haemost 2020;4:722–6.

78. Angus DC, Alexander BM, Berry S, et al. Adaptive platform trials: definition, design, conduct and reporting considerations. Nat Rev Drug Discov 2019;18:797–808.

79. Park JJ, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 2019;20:1–10.

80. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med 2021;384:693–704.

81. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. N Engl J Med 2021;384:497–511.

82. Varshney AS, Wang DE, Bhatt AS, et al. Characteristics of clinical trials evaluating cardiovascular therapies for coronavirus disease 2019 registered on ClinicalTrials.gov: a cross sectional analysis. Am Heart J 2020;232:105–15.

83. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency September 2020. FDA Guidance Document, September 2020. Available at: https://www.fda.gov/media/136238/download. Accessed October 30, 2020.

84. Spitzer E, Ren B, Brugts JJ, et al. Cardiovascular clinical trials in a pandemic: immediate implications of coronavirus disease 2019. Card Fail Rev 2020;6:e09.

85. Vaduganathan M, Butler J, Krumholz HM, Itchhaporia D, Stecker EC, Bhatt DL. Regulation of cardiovascular therapies during the COVID-19 public health emergency. J Am Coll Cardiol 2020;76:2517–21.

86. Gaba P, Bhatt DL. The COVID-19 pandemic: a catalyst to improve clinical trials. Nat Rev Cardiol 2020;17:673–5.

87. Retracted coronavirus (COVID-19) papers 2020. Available at: https://retractionwatch.com/retracted-coronavirus-covid-19-papers/. Accessed December 28, 2020.

88. Pundi K, Perino AC, Harrington RA, Krumholz HM, Turakhia MP. Characteristics and strength of evidence of COVID-19 studies registered on ClinicalTrials. gov "letter. JAMA Intern Med 2020;180:1398–400.

89. Dean NE, Gsell PS, Brookmeyer R, et al. Creating a framework for conducting randomized clinical trials during disease outbreaks. N Engl J Med 2020;382:1366–9.

90. Sarabipour S, Debat HJ, Emmott E, Burgess SJ, Schwessinger B, Hensel Z. On the value of preprints: an early career researcher perspective. PLoS Biol 2019;17:e3000151.

KEY WORDS COVID-19, anticoagulant, antiplatelet, clinical trial, RCT, thrombosis

APPENDIX For supplemental tables and figures, please see the online version of this paper.