

Treatment-Dose LMWH versus Prophylactic/Intermediate Dose Heparins in High-Risk COVID-19 Inpatients: Rationale and Design of the HEP-COVID Trial

Mark Goldin^{1,2} Dimitrios Giannis¹ Wassim Diab² Janice Wang^{1,2} Sameer Khanijo²
 Gulru Sharifova² Marc Cohen³ Jeet M. Lund⁴ Andrea Mignatti^{2,5} Eugenia Gianos^{2,5}
 Alfonso Tafur^{6,7} Paul A. Lewis⁸ Kevin Cohoon⁹ John M. Kittelson¹⁰ Martin L. Lesser^{1,2}
 Cristina P. Sison^{1,2} Husneara Rahman¹ Kanta Ochani¹ William R. Hiatt^{†11,12} Rita A. Dale¹¹
 Victoria E. Anderson¹¹ Marc Bonaca^{11,12} Jonathan L. Halperin¹³ Jeffrey I. Weitz^{14–16}
 Alex C. Spyropoulos^{1,2}

¹Institute of Health Innovations and Outcomes Research, The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, United States

²Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, United States

³Department of Medicine, Newark Beth Israel Medical Center, Newark, New Jersey, United States

⁴Wellspan York Hospital, York, Pennsylvania, United States

⁵Department of Cardiology, Lenox Hill Hospital, Northwell Health, New York, New York, United States

⁶Department of Medicine and Vascular Medicine, NorthShore University Health System, Evanston, Illinois, United States

⁷Division of Cardiology, University of Chicago, Pritzker School of Medicine, Chicago, Illinois, United States

⁸Evidence Based Medicine, Baycare Health System, Clearwater, Florida, United States

⁹Division of Cardiovascular Medicine, Department of Medicine, Froedtert and Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Address for correspondence Alex C. Spyropoulos, MD, FACP, FCCP, FRCPC, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, 130 East 77th Street, New York, NY 10075, United States (e-mail: aspyropoul@northwell.edu).

¹⁰Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States

¹¹Biostatistics, Colorado Prevention Center (CPC) Clinical Research, Aurora, Colorado, United States

¹²Division of Cardiology, University of Colorado, School of Medicine, Aurora, Colorado, United States

¹³Department of Cardiovascular Medicine, The Cardiovascular Institute, Mount Sinai Medical Center, New York, New York, United States

¹⁴Department of Medicine, McMaster University, Hamilton, Ontario, Canada

¹⁵Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

¹⁶Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada

Thromb Haemost 2021;121:1684–1695.

Abstract

Keywords

- ▶ coronavirus disease-2019
- ▶ venous thromboembolism
- ▶ arterial thromboembolism
- ▶ thromboprophylaxis
- ▶ D-dimer

Coronavirus disease-2019 (COVID-19) has been associated with significant risk of venous thromboembolism (VTE), arterial thromboembolism (ATE), and mortality particularly among hospitalized patients with critical illness and elevated D-dimer (Dd) levels. Conflicting data have yet to elucidate optimal thromboprophylaxis dosing. HEP-COVID (NCT04401293) is a phase 3, multicenter, pragmatic, prospective, randomized, pseudo-blinded, active control trial to evaluate efficacy and safety of therapeutic-dose low-molecular-weight heparin (LMWH) versus prophylactic/intermediate-dose LMWH or unfractionated heparin (UFH) for prevention of a primary efficacy composite outcome of VTE, ATE, and all-cause mortality 30 ± 2 days post-enrollment. Eligible patients have COVID-19 diagnosis by nasal swab or serologic testing, requirement for supplemental oxygen per investigator judgment, and Dd >4 × upper limit of normal (ULN) or sepsis-induced coagulopathy score ≥4. Subjects are randomized to enoxaparin 1 mg/kg subcutaneous (SQ)/two times a day (BID) (creatinine

† Deceased.

received
January 22, 2021
accepted
April 1, 2021
published online
April 6, 2021

© 2021. Thieme. All rights reserved.
Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1475-2351>.
ISSN 0340-6245.

clearance [CrCl] \geq 30 mL/min) or 0.5 mg/kg (CrCl 15–30 mL/min) versus local institutional prophylactic regimens including (1) UFH up to 22,500 IU (international unit) daily (divided BID or three times a day), (2) enoxaparin 30 and 40 mg SQ QD (once daily) or BID, or (3) dalteparin 2,500 IU or 5,000 IU QD. The principal safety outcome is major bleeding. Events are adjudicated locally. Based on expected 40% relative risk reduction with treatment-dose compared with prophylactic-dose prophylaxis, 308 subjects will be enrolled (assuming 20% drop-out) to achieve 80% power. Distinguishing design features include an enriched population for the composite endpoint anchored on Dd $>4 \times$ ULN, stratification by intensive care unit (ICU) versus non-ICU, and the ability to capture asymptomatic proximal deep venous thrombosis via screening ultrasonography prior to discharge.

Introduction

The coronavirus disease-2019 (COVID-19) pandemic has led to nearly 80 million cases of acute viral illness and over 1.7 million deaths globally, and at the close of 2020, more than 500,000 new cases and 10,000 deaths were reported daily, both with steep upward trends. The United States accounts for nearly one-quarter of total cases and more than one-fifth of deaths, and currently over 118,000 individuals are hospitalized due to COVID-19.¹

Although SARS-CoV-2 is primarily a respiratory virus, COVID-19 that is caused by the virus has myriad systemic manifestations, and thrombosis is a major cause of morbidity and mortality in hospitalized patients. Thrombotic events in such patients include venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolism (ATE), such as myocardial infarction (MI) and ischemic stroke.^{2–5} Proposed risk factors for and mechanisms of thrombosis include acute illness with patient-related underlying risk factors and associated immobility, as well as cytokine storm and direct viral effects on the endothelium with coagulation activation.^{6–9}

Earlier studies reported VTE rates of 46% or greater in critically ill hospitalized patients with COVID-19, while more recent reports in larger U.S. studies suggest much lower rates of 1.7 to 3.6% in patients with COVID-19 admitted to medical wards.^{3,4,10} Alarming, autopsy data suggest that more than 60% of patients have undiagnosed DVT or in situ pulmonary microthrombi at the time of death.^{11,12} Additionally, there remain subgroups of hospitalized COVID-19 medical patients, especially those with critical illness, that experience “break-through thrombosis” despite standard thromboprophylaxis.^{2,13} Furthermore, elevated plasma levels of D-dimer—in addition to other laboratory parameters such as C-reactive protein and interleukin-6—have been associated with increased thrombotic risk and poor outcomes in patients hospitalized with COVID-19.¹⁴ Thus, hospitalized COVID-19 patients with high levels of D-dimer represent a critical cohort for studying optimal thromboprophylaxis dosing.

Retrospective studies have suggested a possible role for empiric treatment-dose anticoagulant regimens for thromboprophylaxis, but there remains a paucity of high-quality

clinical trial data to confirm any potential net clinical benefit of this strategy.^{15–17} Given the unique characteristics of COVID-19 coagulopathy, guidance statements on hospitalized COVID-19 patients promote universal anticoagulant thromboprophylaxis and identify escalated anticoagulant dosing as a strategy to consider in high-risk groups, including those with critical illness.^{7,18–20} However, all guidance statements have noted an urgent need for high-quality randomized trials to test the hypothesis that escalated or treatment-dose anticoagulant therapy provides a net clinical benefit over conventional low-dose anticoagulant regimens for thromboprophylaxis in hospitalized COVID-19 patients.^{7,18–20}

This article describes the ongoing Systemic Anticoagulation with Full-Dose Low Molecular Weight Heparin (LMWH) versus Prophylactic or Intermediate-Dose LMWH/Unfractionated Heparin (UFH) in High-Risk COVID-19 Patients (HEP-COVID) trial including the (1) rationale and design, (2) main objectives, and (3) potential clinical implications.

Methods

Study Objectives and Hypothesis

The primary objective of the study is to evaluate the efficacy and safety of therapeutic-dose LMWH compared with prophylactic/intermediate doses of LMWH or UFH for the prevention of the primary composite efficacy endpoint of VTE, ATE, and all-cause mortality (ACM) at 30 ± 2 days after study enrollment. The key secondary objective includes testing the hypothesis that therapeutic-dose LMWH will be superior to prophylactic/intermediate doses of LMWH/UFH for the prevention of the composite of VTE, ATE, and ACM at day $10 + 4$ after hospital admission. Other secondary objectives include testing the hypothesis that therapeutic-dose LMWH will be superior to prophylactic/intermediate doses of LMWH/UFH for the prevention of progression to acute respiratory distress syndrome (ARDS), new-onset atrial fibrillation (AF), acute kidney injury (AKI), nonfatal cardiac arrest, need for intubation, and rehospitalization at day 30 ± 2 .

The principal safety endpoint is major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) at 30 ± 2 days after enrollment. The primary and secondary efficacy, principal safety, and other key secondary outcomes are summarized in ► **Table 1**.

Table 1 Outcomes of interest in the HEP-COVID trial

Primary efficacy outcome	
Composite of ATE, VTE, and ACM (30 ± 2 days after enrollment)	ATE: <ul style="list-style-type: none"> • Documented thromboembolic stroke by imaging (head CT, brain MRI) defined as a new focal neurologic defect lasting at least 24 hours that is not due to a readily identifiable nonvascular cause • Documented peripheral arterial thromboembolism by imaging (CT scan, arteriography, arterial Doppler of extremities) • Documented acute myocardial infarction defined by two of the three following conditions: (1) an appropriate clinical condition such as new EKG changes; (2) elevation of CK-MB or troponin-T or I $\geq 2 \times$ ULN (if CK-MB or troponin unavailable then total CK $\geq 2 \times$ ULN); (3) new significant (≥ 0.04 s) Q waves in ≥ 2 contiguous leads
	VTE: <p>Any new venous thromboembolic event (symptomatic DVT or asymptomatic proximal DVT found by screening ultrasonography or as an incidental finding of PE on CT scan) including DVT of upper or lower extremities, PE, splanchnic vein thrombosis, cerebral vein thrombosis defined by:</p> <ul style="list-style-type: none"> • One or more new filling defects at compression ultrasonography, venography, CT venography, or MR venography • A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion scan (V/Q scan) • A noncompressible venous segment on compression ultrasonography, or in patients with a history of previous DVT, either a new noncompressible segment or a substantial increase (4 mm or more) in the diameter of the vein during full compression in a previously abnormal segment on ultrasonography • In the absence of an imaging test in a hemodynamically unstable patient, evidence of right ventricular dysfunction by transthoracic or transesophageal echocardiogram (ESC Criteria)
	All-cause mortality
Secondary efficacy outcome	
Composite of ATE, VTE, and ACM (10 + 4 days after hospital admission)	Same as primary efficacy outcome + asymptomatic distal DVT of the lower extremity
Principal safety outcome	
Major bleeding	Documented major bleeding using ISTH criteria defined by: <ul style="list-style-type: none"> • A decrease in hemoglobin of 2 g/dL or more within 24 hours • A transfusion of 2 or more units of packed red blood cells • Critical site bleeding (including intracranial, intraocular, intra-articular, retroperitoneal, intramuscular with component syndrome, pericardial) • Bleeding that is fatal • Bleeding that necessitates surgical intervention
Other secondary outcomes	
Progression to acute respiratory distress syndrome (ARDS)	
Rehospitalization	
Need for intubation	
New-onset atrial fibrillation	
Nonfatal cardiac arrest	
Acute kidney injury	

Abbreviations: ACM; all-cause mortality; ATE; arterial thromboembolism; CK-MB, creatine kinase-myocardial band; CT, computed tomography; DVT, deep vein thrombosis; EKG, electrocardiogram; ESC, European Society of Cardiology; ISTH, International Society on Thrombosis and Haemostasis; MRI, magnetic resonance imaging; PE, pulmonary embolism; ULN, upper limit of normal; VTE, venous thromboembolism.

Study Overview

HEP-COVID (NCT04401293) is a phase 3, multicenter, pragmatic, prospective, randomized pseudo-blinded, active control trial that is conducted both in hospitals within the Northwell Health system in New York and in other health care systems in the United States. Study enrollment began in

May 2020 and is expected to continue for approximately 1 year until our target patient enrollment is achieved.

The study consists of a (1) screening phase (within 72 hours after hospital admission), (2) pseudo-blinded treatment phase beginning at the time of enrollment and ending at hospital discharge or the occurrence of a primary or

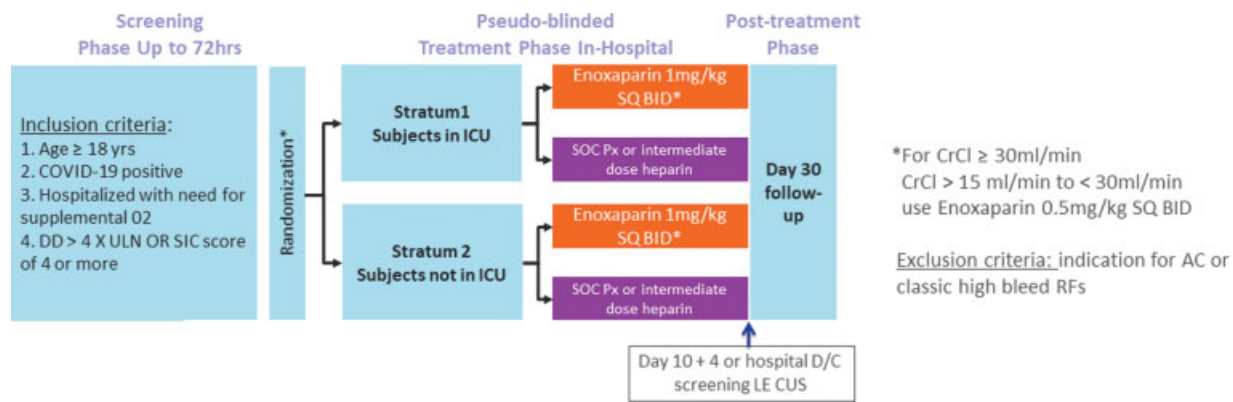


Fig. 1 The design of the HEP-COVID randomized pseudo-blinded active control trial (NCT04401293).

key secondary efficacy endpoint or principal safety endpoint requiring discontinuation of the study medication, with all patients receiving a lower extremity screening Doppler compression ultrasound (CUS) at hospital day 10 + 4 or sooner at the time of discharge, and (3) a 30 ± 2 day follow-up period (► **Fig. 1**).

The study is coordinated by the study co-principal investigators (PIs), an executive committee (EC) composed of members of the academic leadership of the study, and site PIs. An independent data and safety monitoring board (DSMB) monitors patient safety and outcomes at predetermined intervals during the study and makes recommendations to the EC regarding ongoing trial conduct.

The trial protocol was reviewed by regulatory authorities, including Northwell Institutional Review Board (IRB) and external IRBs at each center. Informed consent is obtained from eligible patients or their designates prior to enrollment.

Treatment Arms and Rationale

The optimal dose of heparin (either LMWH or UFH) in hospitalized COVID-19 patients is unknown because there are reports that patients receiving conventional prophylactic dose heparin (UFH or LMWH) as supported by international guidance statements on hospitalized COVID-19 patients remain at risk for thromboembolic events.¹⁸ There are data to support improved efficacy with treatment doses of twice-daily enoxaparin versus once-daily (QD) weight-adjusted enoxaparin for the management of VTE, especially with large thrombus burden.²¹ There are also data to support the concept that treatment-dose heparin reduces major cardiovascular events.²² Our current standard of care in the 24-hospital Northwell Health System, which has hospitalized a large number of patients with COVID-19, is to use enoxaparin 40 mg subcutaneous (SQ) QD for patients with a body mass index (BMI) <30 and creatinine clearance (CrCl) >15 mL/min, enoxaparin 40 mg SQ twice daily (BID) for patients with a BMI >30 and CrCl >15 mL/min, and UFH 5,000 U SQ BID or three times a day (TID) in patients with a CrCl <15 mL/min and BMI <30 and UFH 7,500 U SQ BID or TID with a CrCl <15 mL/min and BMI >30. Large health care institutions in the United States and elsewhere have protocols for in-patient thromboprophylaxis ranging from prophylactic to intermediate-dose UFH or LMWH

for the management of hospitalized patients with COVID-19-associated coagulopathy.²³

Patient Population and Eligibility

The patient population consists of adult (≥ 18 years of age) males and nonpregnant females at the time of enrollment, with a positive COVID-19 diagnosis by nasal swab or serologic testing, who require supplemental oxygen as per investigator's judgment and either have a D-dimer level $\geq 4 \times$ the upper limit of the local laboratory normal (ULN) or a sepsis-induced coagulopathy (SIC) score ≥ 4 . The patient (or a legally authorized representative) must be able to provide written informed consent prior to enrollment, and must understand and agree to comply with planned study procedures. The patient must consent to randomization within 72 hours after hospital admission or within 72 hours of index hospitalization if the patient was transferred from another facility.

Patients with a medical condition that requires administration of any parenteral or oral anticoagulant during the screening phase are not eligible for participation. Patients with an absolute contraindication to anticoagulation, including active bleeding, recent (within 1 month) history of bleeding, dual antiplatelet therapy, active gastrointestinal or intracranial cancer, history of bronchiectasis or pulmonary cavitation, liver failure with baseline international normalized ratio higher than 1.5, CrCl less than 15 mL/min, platelet count lower than 25,000, history of heparin-induced thrombocytopenia within the past 100 days in the presence of circulating antibodies using standardized definitions,²⁴ and hypersensitivity to enoxaparin/heparin/pork products/benzyl alcohol are not eligible for participation. In addition, patients participating in another blinded trial of investigational drug therapy for COVID-19 are excluded. The full list of inclusion and exclusion criteria is provided in ► **Table 2**.

Randomization and Stratification

The Feinstein Institutes Biostatistics Unit (Northwell Health) developed and implemented the randomization procedure using the Biostatistics Randomization Management System (BRMS). BRMS is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using their personal

Table 2 Inclusion and exclusion criteria

Inclusion criteria	
1	Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures
2	Understands and agrees to comply with planned study procedures
3	Male or nonpregnant female adult ≥ 18 years of age at the time of enrollment
4	Subjects with a positive COVID-19 diagnosis by nasal swab or serologic testing
5	Subject consents to randomization within 72 hours of hospital admission or transfer from another facility within 72 hours of index presentation
6	Hospitalized with a requirement for supplemental oxygen
7	D-Dimer $>4.0 \times \text{ULN}$ OR sepsis-induced coagulopathy (SIC) score of ≥ 4
Exclusion criteria	
1	A medical condition that requires administration of any parenteral or oral anticoagulant
2	Active bleeding
3	Recent (<1 month) history of bleeding
4	Dual antiplatelet therapy
5	Active gastrointestinal or intracranial cancer
6	History of bronchiectasis or pulmonary cavitation
7	Liver failure with a baseline INR >1.5
8	CrCl < 15 mL/min
9	PLT $< 25,000/\mu\text{L}$
10	History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies
11	Contraindications to enoxaparin including a hypersensitivity to enoxaparin sodium, hypersensitivity to heparin or pork products, hypersensitivity to benzyl alcohol
12	Pregnancy
13	Inability to give or designate to give informed consent
14	Participation in another blinded trial of investigational drug therapy for COVID-19

Abbreviations: CrCl, creatinine clearance; INR, international normalized ratio; PLT, platelet; ULN, upper limit of normal.

computer. BRMS allows for multicenter, stratified, and single/double-blinded RCTs, using permuted blocks.

Eligible patients will be stratified according to whether their level of care corresponds to intensive care unit (ICU) care or not. During the COVID-19 pandemic, a health system's ICUs may become overwhelmed so that critically ill patients with COVID-19 may be located outside a designated ICU. As such, the definitions of what constitutes a patient with ICU-level care at the time of randomization can include (1) subjects who require noninvasive ventilation acutely for their COVID-19-

related respiratory issues (high flow nasal cannula, bi-level ventilation, average volume-assured pressure support, or continuous positive airway pressure), (2) subjects who require vasopressor therapy, and (3) subjects who require vital sign monitoring more often than every 4 hours (q4h).

Subjects will be randomly assigned to the treatment arm (arm 0: treatment dose of LMWH) or the prophylactic-/intermediate-dose arm (arm 1: prophylactic/intermediate dose of LMWH or UFH) in a 1:1 ratio. The treatment-dose arm consists of enoxaparin 1 mg/kg SQ/BID in patients with CrCl ≥ 30 mL/min or enoxaparin 0.5 mg/kg in patients with CrCl ≥ 15 mL/min and <30 mL/min at the time of randomization. The prophylactic-/intermediate-dose LMWH or UFH arm follows the local institutional standard of care and includes the following regimens: (1) UFH up to 22,500 IU daily in BID or TID doses (i.e., UFH 5,000 IU SQ BID/TID or 7,500 IU BID/TID), (2) enoxaparin 30 and 40 mg SQ QD or BID (the use of weight-based enoxaparin, i.e., 0.5 mg/kg SQ BID for this arm is acceptable, but strongly discouraged), or (3) dalteparin 2,500 IU or 5,000 IU QD. The first dose of study drug is to be given as soon after randomization as possible and the treatment period will be for the duration of hospitalization or until a primary or key secondary efficacy or principal safety endpoint is met. If any of these study endpoints is met, the subject is taken off study drug and placed on open-label anticoagulant therapy.

Individual dose modification is not permitted unless the CrCl falls below 15 mL/min in the treatment arm (arm 0). In that case, conversion to dose-adjusted intravenous (IV) UFH is acceptable. The investigator is encouraged to convert back to treatment-dose enoxaparin as per protocol once the CrCl returns to values higher than or equal to 15 mL/min. Dose modification is allowed in the prophylactic/intermediate group (arm 1) if the CrCl falls below 15 mL/min so that UFH up to 22,500 U daily (i.e., UFH 5,000 U SQ BID or TID or 7,500 IU SQ BID or TID) can be used. The investigator is encouraged to convert back to prophylactic-/intermediate-dose LMWH/UFH as per protocol once the CrCl returns to values higher than or equal to 15 mL/min. If a subject requires permanent discontinuation of study medication, they will be withdrawn from the study and standard of care treatment will be initiated.

Due to the pragmatic nature of this study and pseudo-blinded trial design, at the time of randomization the study subject and corresponding site PIs will be blinded (unaware of specific treatment arm to which the patient is assigned). The study pharmacists as well as data abstractors and designated randomization personnel (i.e., research coordinators and/or research nurses performing the randomization process) will be unblinded.

After randomization and prior to administration of the study medication, blood will be collected to assess laboratory values and relevant medications will be recorded as per **Table 3**.

Primary and Secondary Efficacy Outcomes

The primary efficacy outcome is the composite of VTE (including symptomatic DVT of the upper or lower extremity,

Table 3 Laboratory values and relevant medications recorded at randomization and day 10 + 4 or discharge follow-up

	Randomization	Day 10 + 4 or discharge follow-up
Laboratory values		
Hemoglobin/hematocrit	X	X
PLT count	X	X
PT/INR	X	X
Serum creatinine	X	X
D-Dimer	X	X
C-Reactive protein	X	X
Fibrinogen	X	X
Troponin T/I	X	X
Protein C/protein S antigen	X	
Antithrombin activity	X	
Quick SOFA score	X	X
ISTH SIC score	X	X
IMPROVE VTE score	X	X
Medications		
Antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel, vorapaxar, cangrelor)	X	X
tPA	X	X
Steroids	X	X
Chloroquine	X	X
Hydroxychloroquine	X	X
Hormonal therapy	X	X
Famotidine	X	X
Immunosuppressant/immunomodulatory agents	X	X
Antivirals	X	X
Nonsteroidal anti-inflammatory drugs	X	X

Abbreviations: INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PLT, platelet; PT, prothrombin time; SIC, sepsis-induced coagulopathy; SOFA, Sequential Organ Failure Assessment; tPA, tissue plasminogen activator; VTE, venous thromboembolism.

asymptomatic proximal DVT of the lower extremity, nonfatal PE), ATE (including MI, stroke, systemic embolism, major adverse limb event, intracardiac thrombus), and ACM at 30 ± 2 days after enrollment as per ► **Table 1**.

The secondary efficacy outcomes include (1) the composite of VTE, ATE, and ACM at day 10 + 4 after hospital admission, (2) progression to ARDS, (3) the need for intubation, (4) rehospitalization, (5) new-onset AF, (6) AKI, and (7) nonfatal cardiac arrest at 30 ± 2 days after enrollment as per ► **Table 1**.

Safety Outcomes

Principal Safety Outcome

The principal safety outcome is major bleeding at 30 ± 2 days after enrollment using validated ISTH bleeding criteria as per ► **Table 1**. Major bleeding is defined as overt bleeding associated with a decrease in hemoglobin of 2 g/dL or more within 24 hours, or needing a transfusion of 2 or more units of packed red blood cells, or critical-site bleeding (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), fatal bleeding or bleeding that necessitates surgical intervention.

Serious Adverse Events

Serious adverse events of special interest will include hypersensitivity reactions, including Stevens–Johnson syndrome, evidence of hepatic toxicity with transaminase elevations greater than six times the ULN, heparin-induced thrombocytopenia using standardized definitions,²⁴ and bone marrow toxicity.

Assessment of Outcomes and Follow-Up

All patients, including those who discontinued study medication, will be followed during their hospitalization and up to day 30 (±2 days) after study enrollment.

The day 10 + 4 visit will occur during hospitalization or at the time of hospital discharge (if this occurs sooner than day 10) and will include a mandatory screening Doppler lower extremity CUS and blood collection to assess laboratory values, as well as an updated list of relevant medications (► **Table 3**). Doppler CUS is performed because there is consistent evidence that asymptomatic proximal DVT correlates with ACM in hospitalized medically ill patients, including those with pneumonia or sepsis.²⁵ Doppler CUS also is recommended for objective diagnosis in symptomatic patients with suspected upper or lower extremity DVT. Where resource constraints or local institutional policies preclude use of full 5-point Doppler CUS of the lower extremities, point-of-care ultrasound using two-point compression can be substituted. There will be an assessment of all primary efficacy, principal safety, and secondary outcomes during this visit.

The day 30 ± 2 visit after enrollment will include an assessment of all primary efficacy, principal safety, and secondary outcomes via a face-to-face or telephone visit.

Data Collection, Sample Size, and Statistical Analysis

Study data obtained during the course of the clinical study will be recorded onsite on paper case report forms (CRFs) and then transferred to REDCap by trained study personnel. The accuracy, completeness, and timeliness of all study procedures will be monitored by the Data Coordinating Center, the EC, and the trial co-PIs, all of which will work together to ensure trial integrity. Copies of paper CRFs will be retained as part of the study record and available for inspection by regulatory authorities. The electronic systems used for data management employ an audit trail that will identify any changes made to study records.

The effect of therapeutic anticoagulation will be measured by the absolute risk reduction (ARR) defined as the difference in the risk of the primary efficacy endpoint difference between the two treatment arms (arm 0 minus arm 1). The study sample size is determined by an expected 40% relative risk reduction in the primary efficacy endpoint from 42% in the prophylactic/intermediate arm (arm 1) to 25.2% in the treatment arm (arm 0) based on earlier reports in sick, hospitalized COVID-19 patients.¹⁰ Under these assumptions a total of 246 patients (123 in each arm) are needed to provide 80% power with a two-sided significance level of 0.05. Assuming a 20% drop-out rate, 308 patients will be recruited and randomized.

The intent-to-treat (ITT) population will consist of all subjects who were randomized. The safety (SAF) and modified ITT (mITT) populations will consist of all randomized patients who received at least one dose of study drug. Reporting of the SAF population will be done according to the majority treatment received (as treated). The Per Protocol (PP) Population will consist of all patients who received at least 80% of planned therapy and did not have any major protocol deviations. Planned therapy will be calculated as the duration in days that the subject received study treatment according to the randomization arm divided by the duration of hospitalization after randomization, in days.

Major protocol deviations can be assessed from the database and will include those patients who did not meet inclusion criteria or met exclusion criteria, permanently discontinued assigned study medication after randomization not due to an outcome event, and did not undergo the day 10 + 4 or discharge screening Doppler lower extremity CUS.

The primary analysis will be done in the PP and mITT populations. The criteria for establishing a significant difference are chosen according to an O'Brien–Fleming design²⁶ that includes one interim analysis with early stopping for efficacy of therapeutic-dose anticoagulation compared with the prophylactic/intermediate dose. Under the design assumptions, with 246 patients treatment-dose LMWH will be deemed to be superior to prophylactic/intermediate-dose UFH or LMWH treatment (with two-sided α less than 0.05) if upon trial completion there are 15 or more primary outcome events in the prophylactic/intermediate anticoagulation-dose group than there are in the therapeutic LMWH-dose group, which with 123 patients per group corresponds to an ARR greater than 12.2%.

An interim analysis for efficacy will be conducted after the primary outcome status is observed on approximately 123 randomized patients (~50% of the ITT population). As at the final analysis, the O'Brien–Fleming decision criteria at the interim analysis are the same as at the final analysis, that is, therapeutic anticoagulation will be deemed to be superior to prophylactic/intermediate anticoagulation if there are 15 or more primary outcome events in the prophylactic/intermediate anticoagulation-dose group than there are in the therapeutic LMWH dose group, which with 61 patients per arm corresponds to an ARR greater than 25.6%.

Every effort will be made to minimize the amount of missing data. Due to the time-sensitive nature, the focus will be on three outcome variables: day 10 + 4 primary efficacy

and principal safety outcomes or discharge Doppler screening lower extremity CUS and day 30 \pm 2 primary efficacy and principal safety outcomes. There should be no missing data on the most important component of the primary efficacy endpoint, ACM.

DSMB and EC Activities

An independent external DSMB will actively monitor interim data to review the ongoing safety of patients and will make recommendations about early study closure or changes to the protocol. The DSMB members will include three voting members, two physicians with relevant medical specialty training and experienced in clinical trials research and one clinical trial statistician. An external DSMB support team will prepare unblinded safety reports and the interim analysis for the DSMB. Adjudication of primary and secondary efficacy and principal safety outcomes will be done locally, with periodic quality assessments by the study co-PIs and EC.

All DSMB members will be free of both substantial intellectual and financial conflicts of interests. The DSMB chair reviews subject safety results every 2 weeks by group assignment, judges whether the overall safety of the project remains acceptable, has ongoing access to unblinded information, and makes recommendations after discussion with the DSMB committee. Upon review of the interim analysis results, the DSMB committee makes recommendations about early study closure or changes to the protocol to the study co-PIs and EC, who have the responsibility to accept, reject, or to modify DSMB recommendations. The DSMB meeting frequency will be at ~25, ~50, ~75, and ~100% enrollment. Furthermore, the detailed operation of the DSMB is governed by a charter describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring), and requirements for reporting.

The EC consists of one study PI as Chair and other study investigators, as well as up to four external members with expertise in antithrombotic trials. This EC will assist the study Chair in managing quality oversight of trial-related activities during the conduct of the clinical trial.

Discussion

The HEP-COVID trial (NCT04401293) is a phase 3 multicenter, pragmatic, prospective, randomized, pseudo-blinded, active control trial that was designed to answer an important question in the COVID-19 pandemic, namely whether there is improved efficacy and acceptable safety of therapeutic-dose LMWH versus prophylactic/intermediate-dose LMWH/UFH in reducing major thromboembolism or mortality in high-risk hospitalized COVID-19 patients. The trial is randomizing patients into two strata at the time of randomization: whether they require ICU level of care or not. Lastly, the pragmatic design of the trial and accelerated study startup timeframe is meant to maximize patient enrollment and efficiency of study-specific procedures during the time of the COVID-19 pandemic in a hospitalized setting.

There are consistent data that the risk of both VTE and ATE is elevated in sick hospitalized COVID-19 patients, with a

significant proportion of mortality presumed to be secondary to subclinical thrombosis.^{2-4,10-12} Very elevated thrombotic event rates of 31% or more and ACM rates of 13% or more have been described in hospitalized COVID-19 patients requiring ICU level of care.^{2,27} In addition, D-dimer levels greater than four or six times the ULN or elevated SIC scores have been recognized as independent predictors of thrombotic events and poor outcomes.¹⁴ Consistent with these findings, multivariate analysis using data from a cohort of 9,407 patients with COVID-19 hospitalized at Northwell Health revealed that compared with lower levels, D-dimer levels four to six times the ULN were associated with a 2.1-fold higher risk of VTE or mortality.²⁸ Accordingly, this trial uses inclusion criteria anchored on D-dimers at least four times the ULN or an SIC score of 4 or more to ensure enrollment of a high-risk population. The success of this approach is evidenced by the current blinded pooled primary efficacy event rate of 27%. Lastly, a key design feature of the HEP-COVID trial is the inclusion of a screening Doppler lower extremity CUS to capture asymptomatic proximal DVT as a key component of the primary efficacy outcome. There are now consistent data from three large-scale thromboprophylaxis trials that asymptomatic proximal DVT captured by screening ultrasonography is a relevant endpoint in thromboprophylaxis trials and is significantly associated with ACM, with the most recent analysis showing a hazard ratio (HR) of 2.31²⁵.

The key trial hypothesis is that treatment-dose anticoagulation with LMWH versus standard of care prophylactic-to-intermediate doses of LMWH/UFH will be more efficacious and have an acceptable safety profile as thromboprophylaxis of major thromboembolic events and ACM in sick, hospitalized COVID-19 patients. A unique feature of COVID-19 coagulopathy is the observation that “breakthrough thrombosis” occurs despite standard thromboprophylaxis, especially in critically ill patients.²⁹ Despite prophylactic-dose anticoagulation, a thrombotic complication rate of 16.7% in COVID-19 patients with ARDS was seen in one study, whereas another study revealed that despite standard thromboprophylaxis in the ICU, VTE rates of 27%, ATE rates of 3.7%, and ACM of 13% were noted.^{2,13} Preliminary data suggested that exposure to escalated/treatment-dose anticoagulation over standard-of-care dosing for thromboprophylaxis at index hospitalization for COVID-19 conferred a mortality advantage at 28 days (32.8 vs. 52.4%, $p = 0.017$) and that therapeutic-dose anticoagulation reduced hospital-based thrombotic complications (HR: 0.29, 95% confidence interval: 0.091–0.92).^{10,15} Moreover, a recent small randomized trial of therapeutic versus prophylactic anticoagulation in patients with severe COVID-19 revealed that therapeutic anticoagulation improved ventilator-free days.³⁰ However, more recent studies have found either no benefit between prophylactic and therapeutic anticoagulation or have found that in-hospital mortality was 2.3 times greater with preemptive treatment-dose anticoagulation from the time of hospital admission.^{15,31} Lastly, whether the mechanisms of thrombosis in COVID-19 are due primarily to *in situ* immunothrombosis or classic thromboembolic macrovessel disease continues to be a matter of debate, with the former theoretically less susceptible and more resistant

to heparin-based strategies for management, even with escalating or treatment doses.³² In short, there continues to remain true clinical equipoise for both the efficacy and safety of using treatment-dose anticoagulation for primary thromboprophylaxis in this high-risk hospitalized COVID-19 population.

Limitations of the HEP-COVID trial include the pseudo-blinded trial design, although unlike a complete open-label design, we have attempted to mitigate any impact on outcomes by blinding both study investigators and participants. We acknowledge that blinding the receipt of some of the study medications (i.e., IV UFH using a nomogram) may be difficult to do. In addition, the pragmatic design of the trial allows flexibility of investigators to utilize local thromboprophylactic regimens and doses (including both UFH and LMWH from prophylactic-to-intermediate doses) for the standard-of-care thromboprophylactic arm. Although this may enhance the external generalizability of trial results, this also introduces heterogeneity of regimens and doses used to define the standard-of-care thromboprophylactic arm. Another potential limitation is the use of local adjudication to define primary and key secondary as well as principal safety outcomes, although we have attempted to mitigate any reporting inconsistencies by utilizing standardized definitions and performing periodic quality assessments. Lastly, we acknowledge the potential that the trial may be underpowered to answer the clinical question based on our trial’s hypothesis of a 42% event rate of major thromboembolism and ACM in the control group, although to date our pooled primary efficacy event rate of 27% suggests that we have been successful in enrolling a high-risk subgroup of hospitalized COVID-19 patients.

The HEP-COVID trial is among 20 high-quality global trials (representing a total of 12,568 subjects), including the large multiplatform ATTACC, REMAP-CAP, and ACTIVE-IV trials that at the present time are assessing efficacy and safety of escalated or treatment-dose anticoagulant regimens versus standard-of-care anticoagulant regimens to reduce COVID-19 coagulopathy in hospitalized patients (– Table 4).³³ Some of these trials only include critically ill hospitalized COVID-19 patients while others include both ICU and medical-ward patients.³³ The HEP-COVID trial design where subjects are stratified at the time of randomization to ICU versus non-ICU level of care is designed to potentially stop the trial early in either ICU versus non-ICU populations separately if there is evidence of overwhelming efficacy or futility using prespecified stopping criteria during the interim analysis. At the time of this writing, trial investigators of the multiplatform ATTACC, REMAP-CAP, and ACTIVE-IV trials have paused trial enrollment in the ICU population due to futility concerns as well as potential for harm.³⁴ Due to the urgent nature of the clinical question and magnitude of the current COVID-19 pandemic, many investigator groups including ours that are assessing different dosing regimens of anticoagulant interventions in hospitalized COVID-19 patients recognize the need for collaboration to complete trials as soon as possible, pool relevant data when feasible, and disseminate effective interventions as rapidly as possible. Toward this goal, there is a collaborative effort led by the World Health Organization and supported by the INVENT-VTE network (www.INVENT-VTE.com) to conduct a

Table 4 Main characteristics of trials comparing different doses of anticoagulants in hospitalized COVID-19 patients

Study name or site	Country	Registry trial number	Registration date	Estimated study completion date	Intervention arm	Control arm	Primary outcomes
COVID-HEP	Switzerland	NCT04345848	April 2020	March 2021	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH	Composite outcome: arterial or venous thrombosis, DIC, and all-cause mortality at 30 days
CORIMMUNO-COAG	France	NCT04344756	April 2020	September 2020	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH	Survival without ventilation at 14 days (group 1) or at 28 days (group 2)
RAPID COVID COAG	Multinational	NCT04362085	April 2020	December 2020	Therapeutic LMWH or UFH	Prophylactic LMWH, UFH, or fondaparinux	Composite outcome: ICU admission, noninvasive positive pressure ventilation, invasive mechanical ventilation, or all-cause mortality at 28 days
HeSAcovid	Brazil	RBR-949z6v (REBEC)	May 2020	July 2020	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH	Evaluation of PaO ₂ /FIO ₂ ratio at baseline, 7, and 14 days and days without mechanical ventilation at 28 days
COALIZAO ACTION	Brazil	NCT04394377	May 2020	December 2020	Therapeutic rivaroxaban, LMWH, or UFH	Prophylactic LMWH	Composite outcome: mortality, number of days alive, number of days in the hospital, and number of days with oxygen therapy at 30 days
COVID PACT	United States	NCT04409834	May 2020	May 2021	Therapeutic LMWH or UFH ± clopidogrel	Prophylactic LMWH or UFH ± clopidogrel	Venous or arterial thrombosis at 28 days
PROTECT	United States	NCT04359277	April 2020	April 2021	Therapeutic LMWH or UFH	BMI- and weight-adjusted prophylactic dose LMWH	All-cause mortality at 1 year; incidence of cardiac arrest, symptomatic, deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, hemodynamic shock at 21 days
ACTIV-4	United States	NCT04505774	August 2020	December 2021	Therapeutic heparin (unfractionated heparin, enoxaparin, dalteparin, tinzaparin, heparin)	Prophylactic heparin (enoxaparin, dalteparin, tinzaparin, fondaparinux, heparin)	Organ support (respiratory or vasopressor) free days at 21 days. Organ support: receipt of noninvasive mechanical ventilation, high flow nasal cannula oxygen, mechanical ventilation, or vasopressor therapy, with death at any time during the index hospitalization assigned -1 day.
REMAP-CAP	Multinational	NCT02735707	April 2020	December 2021	Therapeutic LMWH or UFH	Local standard thromboprophylaxis	Days alive and outside ICU at 21 days
ATTACC	Multinational	NCT04372589	April 2020	January 2021	Therapeutic LMWH or UFH	Local standard thromboprophylaxis	Mortality and days free of organ support at 21 days (in collaboration with ACTIV-4)
MGH (Albarghaddi et al)	United States	NCT04377997	May 2020	January 2021	Therapeutic LMWH or UFH	Local standard thromboprophylaxis	Composite endpoint: death, cardiac arrest, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, or hemodynamic shock at 12 weeks, ISTH major bleeding at 12 weeks

Table 4 (Continued)

Study name or site	Country	Registry trial number	Registration date	Estimated study completion date	Intervention arm	Control arm	Primary outcomes
IMPACT	United States	NCT04406389	May 2020	June 2021	Therapeutic LMWH, UFH, fondaparinux, or argatroban	Intermediate-dose LMWH, UFH, or fondaparinux	Mortality at 30 days
COVID-19 HD	Italy	NCT04408235	May 2020	June 2021	Subtherapeutic LMWH	Prophylactic LMWH	Composite outcome: mortality, acute myocardial infarction, symptomatic arterial or venous thromboembolism, and need for noninvasive or invasive mechanical ventilation at 30 days
COV-DOSE	France	NCT04373707	May 2020	October 2020	Weight-based intermediate-dose LMWH	Prophylactic LMWH (augmented dose for ICU patients)	Venous thromboembolism at 28 days
X-Covid 19	Italy	NCT04366960	April 2020	November 2020	Intermediate-dose LMWH	Prophylactic LMWH	Venous thromboembolism at 30 days
Heparin-SARS-CoV2	Spain	EUCTR2020-001891-14ES	May 2020	Not provided	Intermediate-dose LMWH	Prophylactic LMWH	Need for oxygen therapy escalation or invasive mechanical ventilation or mortality during admission and up to 30 days
University of Iowa (Perepu et al)	United States	NCT04360824	April 2020	April 2021	Intermediate-dose LMWH	BMI-adjusted prophylactic-dose LMWH	All-cause mortality at 30 days
IMPROVE-COVID	United States	NCT04367831	April 2020	April 2021	Intermediate-dose LMWH or UFH	BMI- and weight-adjusted prophylactic-dose LMWH	Clinically relevant venous or arterial thrombosis in ICU at 30 days
COVID-PREVENT	Germany	NCT04416048	June 2020	May 2021	Therapeutic rivaroxaban	Prophylactic LMWH or UFH	Composite outcome: venous or arterial thromboembolism, myocardial infarction, nonhemorrhagic stroke, mortality, or progression to intubation and invasive ventilation at 35 days
ACOVACT	Austria	NCT04351724	April 2020	December 2020	Rivaroxaban 5 mg twice daily	Local standard thromboprophylaxis	Sustained improvement (>48 hours) of one point on the World Health Organization Scale at 29 days

Abbreviations: BMI, body mass index; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

prospective meta-analysis to combine key study populations and relevant outcomes from the previously mentioned anticoagulant intervention trials in hospitalized COVID-19 patients. Thus high quality and definitive conclusions from the pooled results of these trials may result in their rapid dissemination to the global clinical community and inform clinical practice antithrombotic guidelines on the topic.

In conclusion, the HEP-COVID trial is a high-quality multicenter randomized trial that is pseudo-blinded and aims to answer a key clinical question, namely, is there net clinical benefit for using treatment-dose LMWH versus prophylactic- or intermediate-dose LMWH/UFH for thromboprophylaxis in high-risk hospitalized COVID-19 patients. It has unique design features and is pragmatic in design. The results of this trial, coupled with other high-quality trials of anticoagulant interventions in this population, has the potential to inform best clinical practice in managing the coagulopathy and potentially reducing the ensuing morbidity and mortality seen in hospitalized COVID-19 patients.

Conflict of Interest

M.G.: research grant from Janssen; M.C.: speakers bureau Sanofi; A.T.: educational grant: Janssen, research grant: Janssen, Bristol Meyers Squibb, Idorsia, consultant: Recovery Force, J.M.K.: consultant for Bayer Healthcare, Jansen, the ATLAS Group, AMAG pharmaceuticals, Agile Therapeutics for advisory and steering committee activities. Data and safety monitoring committees for Cystic Fibrosis Foundation Therapeutics, Novo Nordisk, Pfizer, Genentech, and BioMarin pharmaceuticals. M.B.: research grant support to CPC Clinical Research from Amgen, AstraZeneca, Bayer, Janssen, Merck, NovoNordisk; J.L.H.: consultancies with the ATLAS Group, Bayer Healthcare, Boehringer Ingelheim, and Population Health Research Institute; J.I.W.: consultant for Anthos, ATLAS Group, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Ionis, Janssen, Johnson and Johnson, Merck, Pfizer, PhaseBio, and Servier, institutional research grants from Bayer and Boehringer Ingelheim; A.C.S.: Janssen, Boehringer Ingelheim, Bayer, BMS, Portola, ATLAS Group; consultancy; Janssen, Boehringer Ingelheim; research funding. D.G., W.D., J.W., S.K., G. S., J.M.L., A.M., E.G., P.A.L., K.C., M.L., C.P.S., H.R., K.O., W.R.H., R.A.D., V.E.A.: no conflict of interest.

Acknowledgments

The HEP-COVID trial is dedicated to the memory of Dr. Will Hiatt who as part of the trial's Executive Committee and President of CPC Clinical Research was instrumental in initiation of trial activities as well as serving as an inspiration to trial investigators. We would also like to acknowledge Drs. Jim Douketis and Sam Schulman, who as Chair and Member of the trial's DSMB, respectively, have worked tirelessly in their activities. We would finally like to acknowledge all of the local principal investigators, clinical research coordinators (including Damian Inall who assisted in study initiation activities), and study personnel who have contributed greatly to the HEP-COVID trial. This trial is partly funded from the Broxmeyer

Fellowship in Clinical Thrombosis, as well as by generous donors in our Northwell Health community.

References

- 1 Novel Coronavirus. (2019-nCoV) situation reports [Internet] [cited 2020 Dec 28]. Accessed April 18, 2021 at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
- 2 Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020;191:148–150
- 3 Hanif A, Khan S, Mantri N, et al. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience. *Ann Hematol* 2020;99(10):2323–2328
- 4 Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. *JAMA* 2020;324(08):799–801
- 5 Spyropoulos AC, Weitz JI. Hospitalized COVID-19 patients and venous thromboembolism: a perfect storm. *Circulation* 2020;142(02):129–132
- 6 Bikdeli B, Madhavan MV, Gupta A, et al; Global COVID-19 Thrombosis Collaborative Group. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. *Thromb Haemost* 2020;120(07):1004–1024
- 7 Bikdeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATE, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. 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(23):2950–2973
- 8 Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. *Blood* 2020;136(11):1317–1329
- 9 Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020;127:104362
- 10 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020;18(05):1094–1099
- 11 Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020;173(04):268–277
- 12 Lax SF, Skok K, Zechner P, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med* 2020;173(05):350–361
- 13 Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis) High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020;46(06):1089–1098
- 14 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18(04):844–847
- 15 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(01):122–124
- 16 Stessel B, Vanvuchelen C, Bruckers L, et al. Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: a longitudinal controlled before-after study. *Thromb Res* 2020;194:209–215
- 17 Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020;76(16):1815–1826

- 18 Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020;18(08):1859–1865
- 19 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(03):1143–1163
- 20 Fernández-Capitán C, Barba R, Díaz-Pedroche MDC, et al. Presenting characteristics, treatment patterns, and outcomes among patients with venous thromboembolism during hospitalization for COVID-19. *Semin Thromb Hemost* 2021;47(04):351–361
- 21 Merli G, Spiro TE, Olsson CG, et al; Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134(03):191–202
- 22 Gargiulo G, Carrara G, Frigoli E, et al. Bivalirudin or heparin in patients undergoing invasive management of acute coronary syndromes. *J Am Coll Cardiol* 2018;71(11):1231–1242
- 23 Cohoon KP, Mahé G, Tafur AJ, Spyropoulos AC. Emergence of institutional antithrombotic protocols for coronavirus 2019. *Res Pract Thromb Haemost* 2020;4(04):510–517
- 24 Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv* 2018;2(22):3360–3392
- 25 Raskob GE, Spyropoulos AC, Cohen AT, et al. Association between asymptomatic proximal deep vein thrombosis and mortality in acutely ill medical patients. *J Am Heart Assoc* 2021;10(05):e019459
- 26 Emerson SS, Fleming TR. Symmetric group sequential test designs. *Biometrics* 1989;45(03):905–923
- 27 Poissy J, Goutay J, Caplan M, et al; Lille ICU Haemostasis COVID-19 Group. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. *Circulation* 2020;142(02):184–186
- 28 Cohen SL, Gianos E, Barish MA, et al; Northwell Health COVID-19 Research Consortium. Prevalence and predictors of venous thromboembolism or mortality in hospitalized COVID-19 patients. *Thromb Haemost* 2021;121(08):1043–1053
- 29 Spyropoulos AC, Weitz JI. Hospitalized COVID-19 patients and venous thromboembolism: a perfect storm. *Circulation* 2020;142(02):129–132
- 30 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;196:359–366
- 31 Motta JK, Ogunnaike RO, Shah R, et al. Clinical outcomes with the use of prophylactic versus therapeutic anticoagulation in COVID-19. *medRxiv* [Internet] Cold Spring Harbor Laboratory Press; 2020 [cited 2020 Sep 14]. Accessed April 18, 2021 at: <https://www.medrxiv.org/content/10.1101/2020.07.20.20147769v1>
- 32 Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. *Thorax* 2021;76:412–420
- 33 Tritschler T, Mathieu M-E, Skeith L, et al; International Network of Venous Thromboembolism Clinical Research Networks INVENT-VTE. 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(11):2958–2967
- 34 National Institutes of Health. NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients [Internet]. Natl. Inst. Health NIH. 2020 [cited 2021 Jan 15]. Accessed April 18, 2021 at: <https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients>