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<u>A</u>nti<u>T</u>hrombotic <u>T</u>herapy to <u>A</u>meliorate <u>C</u>omplications of <u>C</u>OVID-19 (ATTACC**): study design and methodology for an international, adaptive Bayesian randomized controlled trial**

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ABSTRACT

BACKGROUND: Mortality from COVID-19 is high among hospitalized patients and effective therapeutics are lacking. Hypercoagulability, thrombosis and hyperinflammation occur in COVID-19 and may contribute to severe complications. Therapeutic anticoagulation may improve clinical outcomes through anti-thrombotic, anti-inflammatory, and anti-viral mechanisms.

PRIMARY OBJECTIVE: To evaluate whether therapeutic-dose anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) prevents mechanical ventilation and/or death in patients hospitalized with COVID-19 compared to usual care.

STUDY DESIGN: An international, open-label, adaptive randomized controlled trial. Using a Bayesian framework, the trial will declare results as soon as pre-specified posterior probabilities for either superiority, futility, or harm are reached. The trial uses response-adaptive randomization to maximize the probability that patients will receive the more beneficial treatment approach, as treatment effect information accumulates within the trial. By leveraging a common data safety monitoring board and pooling data with a second similar international Bayesian adaptive trial (REMAP-COVID anticoagulation domain), treatment efficacy and safety will be evaluated as efficiently as possible.

PRIMARY OUTCOME: The primary outcome is an ordinal endpoint with three possible outcomes based on the worst status of each patient through day 30: no requirement for invasive mechanical ventilation, invasive mechanical ventilation, or death.

FEASIBILTY AND SIGNIFICANCE: Using an adaptive trial design, the ATTACC trial will establish whether therapeutic anticoagulation can reduce mortality and/or avoid the need for mechanical ventilation in patients hospitalized with COVID-19. Leveraging existing networks to

recruit sites will increase enrollment and mitigate enrollment risk in sites with declining COVID-19 cases.

TRIAL REGISTRATION: NCT04372589

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel coronavirus that has rapidly spread across the globe causing severe respiratory infection.[1,2] With the possible exception of remdesivir, no therapies have proven efficacy.[3,4] Rapidly-deployable, safe and effective therapeutic agents are urgently needed. Coronavirus disease 2019 (COVID-19) is associated with activation of coagulation and inflammatory pathways (**Figure 1**), suggesting that therapeutic-dose anticoagulation may improve clinical outcomes.

Early observational reports suggest that that COVID-19 infection is associated with hypercoagulability and increased risk of thrombosis.[5-7] Thrombosis is closely linked to systematic vascular inflammation and, distinct from other respiratory viral syndromes, COVID-19 appears to be associated with a profound endotheliopathy.[8] D-dimer levels may signal this coagulopathy and predict poor prognosis.[5,9,10] D-dimers may also help identify patients most likely to benefit from anticoagulation.

Heparin is a commonly used anti-thrombotic agent that facilitates antithrombin-mediated inactivation of factors Xa and IIa. Heparin has diverse anti-inflammatory properties and is known to inhibit complement and adhesion molecule expression in the microvasculature,[11] and down-regulate IL-6.[12] Heparin may also exert direct anti-viral effects on SARS-CoV-2[13]. Upon binding heparin, the SARS-CoV-2 spike protein undergoes conformational changes that interfere with binding to angiotensin converting enzyme-2 (ACE2). A similar anti-viral effect of heparin has also been observed with SARS-CoV-1.[14,15]

A significant body of evidence including laboratory data[11,12], animal models[16], observational studies[17], randomized controlled trials in humans,[18,19] and meta-analyses[18,20] support the potential for heparin to reduce mortality in sepsis. Data are limited in COVID-19,

although an observational study from China suggested that the use of low-dose heparin may be associated with lower mortality in patients with elevated D-dimer levels.[21,22] A second observational cohort from New York observed that therapeutic anticoagulation was associated with longer survival among critically ill patients with COVID-19.[23] Both observational studies had important limitations and cited the need for randomized trials.

These data provide a compelling rationale to evaluate therapeutic anticoagulation with heparin in patients with COVID-19. The proposed **A**nti**T**hrombotic **T**herapy for **A**melioration of **C**omplications of **C**OVID-19 (**ATTACC**) trial will leverage an international network of over 30 sites across Canada, the U.S., Brazil, and Mexico to rapidly inform clinical practice.

METHODS

Trial objective

To establish whether therapeutic-dose parenteral anticoagulation with heparin prevents the need for mechanical ventilation and/or death in patients hospitalized with COVID-19.

Trial design

We will perform an international, open-label, pragmatic, adaptive randomized controlled trial enrolling adult patients hospitalized with confirmed COVID-19 infection.

ATTACC employs a Bayesian framework for statistical inference. This framework was chosen as it facilitates an adaptive trial design, providing needed flexibility within a rapidly evolving pandemic where uncertainty exists surrounding event rates and potential treatment effect sizes. The incorporation of response-adaptive randomization (RAR) according to baseline D-dimer facilitates allocation of a participant based on their observed probability of benefit

within a D-dimer-defined subgroup. In the context of emerging observational evidence suggesting potential benefit from therapeutic anticoagulation, RAR is useful to increase acceptance of the trial by both clinicians and patients given that patients have a higher probability of receiving therapeutic anticoagulation if there is early evidence of benefit in specific D-dimer subgroups.

Trial interventions

Intervention group: The active treatment arm will receive therapeutic-dose parenteral anticoagulation with either low molecular weight heparin (LWMH) or unfractionated heparin (UFH) at doses for the treatment of venous thromboembolism (VTE). Therapeutic anticoagulation will be continued for up to 14 days or until recovery (defined as hospital discharge or liberation from supplemental oxygen for >24 hours if oxygen was initially required), whichever comes first. The intervention arm is designed to be accessible, flexible and pragmatic. Heparin is an inexpensive drug that is accessible to practitioners in health systems around the world. The specific heparin formulation, decisions pertaining to anticoagulation monitoring, dosing, and dose adjustments will be conducted according to local practice. The choice of therapeutic (as opposed to intermediate) dose heparin is supported by observational studies of heparin in sepsis[17], and is associated with low bleeding rates[24]. Therapeutic dosing is required to provide separation between groups, especially given the heterogenous thromboprophylactic strategies employed in the care of patients with COVID-19[23].

Control group: The control arm will receive usual care that may include pharmacologic thromboprophylaxis (e.g., low dose LMWH or UFH) according to local practice. In some

centers, intermediate doses of LMWH or UFH for venous thromboprophylaxis are used, but remain below the therapeutic doses used in ATTACC; local practice may vary by center and over time, but will be recorded.

Co-enrollment

As anticoagulation is anticipated to be an ancillary supportive care strategy in patients with COVID-19, co-enrollment is permitted provided the co-enrolling trials are not evaluating anticoagulants or anti-platelet medications. This is intended to encourage the efficient conduct of alternative therapeutic trials in patients with COVID-19. Interactions with other potential COVID-19 therapies are not expected *a priori*, but will be explored *post hoc*.

Patient selection

Inclusion criteria: Patients ≥18 years of age admitted to hospital with laboratory-confirmed COVID-19. The anticipated duration of hospitalization must be >72 hours from randomization, and patients must be enrolled within 72 hours of hospital admission or confirmation of COVID-19.

Exclusion criteria: Major exclusions include invasive mechanical ventilation at the time of randomization, active bleeding, or risk factors for bleeding. The complete list of the exclusion criteria are presented in **Table 1**.

Trial outcomes

Primary outcome**:** The primary outcome is an ordinal categorical endpoint with three possible outcomes based on the worst status of each patient through day 30: no invasive mechanical ventilation, invasive mechanical ventilation, or death. This end-point was chosen because (a) invasive mechanical ventilation and death are clinically relevant outcomes with high importance to patients and healthcare systems; (b) the ordinal endpoint increases statistical power in comparison to a binary endpoint and is justified based on the clinical importance; and (c) the risk of ascertainment bias is low with this endpoint focused on objectively definable events. Venous thromboembolism (VTE) was not included in the primary outcome due to concerns for ascertainment bias, as patients on therapeutic anticoagulation may be less likely to receive imaging, which would therefore favor the intervention arm. Similarly, myocardial infarction (MI) was not included in the primary outcome as cardiac injury in COVID-19 patients can result from a variety of mechanisms, and it's unclear how or if heparin affects this. Both VTE and MI are captured as secondary outcomes.

Secondary outcomes: The following safety and efficacy outcomes will be assessed:

Safety: The two major safety concerns associated with heparin anticoagulation relate to major bleeding and heparin induced thrombocytopenia (HIT).[25] As such, our safety outcomes include laboratory confirmed HIT, and major bleeding defined according to the International Society on Thrombosis and Haemostasis (ISTH).[26] This definition includes fatal bleeding, symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin of ≥2 g/dL, or leading to the transfusion of 2 or more whole blood or red cell units. The presence of HIT and/or major bleeding will be assessed on days 1, 3, 7, 14 and 21.

Efficacy: [Assessed at 21 days]: organ support-free days (days alive and without the need for invasive or non-invasive mechanical ventilation, high flow nasal cannula at ≥30 L/min flow, or vasopressor support); [Assessed at 30 days]: use of non-invasive ventilation or high-flow nasal cannula, intubation, ventilator-free days, ICU-free days, hospital-free days. For outcomes with "free-days" assessed at 21, 30 or 90 days, patients will be assigned a value of -1 if they die before 21, 30, or 90 days, respectively. [Assessed at 30 and 90 days]: VTE, myocardial infarction, ischemic stroke, and all-cause mortality.

Recruitment and patient consent

In response to pandemic-related infection control measures and policies that encourage the avoidance of unnecessary direct person-to-person contact, modifications to traditional written informed consent are required. Consent will be obtained as per Institutional Research Ethics Board / Institutional Review Board and FDA recommendations, but is anticipated to include verbal consent and consent obtained by telephone from either the patient or their designated substitute decision maker.

Methods of data collection, and the duration of follow-up

To maximize the operational feasibility of the trial, following randomization, collected data includes variables typically part of routine care. Laboratory investigations are not mandated, but will be ascertained using an electronic case report form as per the study schedule **(Appendix 1)**. Electronic data collection using an online case report form has been prioritized to minimize infectious exposure. Subjects will be followed until hospital discharge or 90-days, whichever

comes first. For those discharged before 90 days, telephone contact will be undertaken to ascertain the secondary 90-day outcomes.

Concomitant medications**:** Concomitant medications including proven or experimental COVID-19 treatments and anti-platelet agents will be collected from time of consent to 14 days or time of treatment discontinuation (whichever occurs first). Anticoagulant use following completion of the study protocol but prior to the 30-day assessment will also be collected.

Methods to protect against bias

Randomization and allocation concealment: A web-based, variable-block, randomization system will be used to allocate treatment assignments.

Outcome adjudication: The primary outcome will be independently verified by a central events adjudication committee. Given the importance of standardized definitions and reporting, major hemorrhage and laboratory confirmed HIT will be adjudicated without knowledge of treatment assignment. Venous and arterial thrombotic events will be adjudicated using similar methods.

Analytic plan

Sample size and power calculations: The trial design uses a Bayesian adaptive framework to reach a conclusion regarding superiority or futility in an efficient manner within three different baseline D-dimer-defined subgroups. D-dimer subgroups will be defined at the first interim analysis based on the 50th and 75th percentile values measured in the first 100 patients. The trial will enroll until the pre-specified stopping criterion for benefit (>99% posterior probability of

proportional odds ratio (OR) >1) or futility (<10% posterior probability of proportional OR>1.2) are reached within each D-dimer subgroup. An OR of 1.2 is used as the minimum treatment effect threshold to declare futility given it is approximately equivalent to an absolute risk reduction in mortality of ≤1% assuming a baseline event rate of 25% for intubation and 12.5% for death. We will enroll up to a maximum of 3,000 patients. Trial simulations indicate that the risk of Type I error remains below 5% at 3,000 patients and that enrolling 2,000 patients will give 90% power to detect an OR ≥ 1.5 for avoiding intubation or death (equivalent to a ≥5% absolute risk reduction in mortality). If the treatment is harmful (OR<1), there is a 60% chance that the trial will be halted after enrolling 200-300 patients based on the futility stopping criterion. Data will be analyzed based on the intention-to-treat principle.

Analysis of primary and secondary outcomes: The primary analysis of the ordered categorical endpoint is a cumulative proportional odds model (OR>1 suggests treatment benefit). The effect of therapeutic anticoagulation is modeled within prespecified patient subgroups based on the baseline D-dimer levels. Each patient is classified by their baseline D-dimer levels as highest (top quartile), median (3rd quartile), and lowest (less than median). An additional category will be added for patients in whom D-dimer is not available at the time of randomization. Each conclusion for therapeutic anticoagulation is by subgroup, with a statistical model that borrows the effect across D-dimer subgroups. The baseline risks for each group are modeled with independent weak prior distributions with the lowest D-dimer group serving as the reference population.

In addition to an overall adaptive sample size, the trial also employs response-adaptive randomization for the effect of therapeutic anticoagulation within each of these 3 subgroups.

Interim analyses will be conducted after every 100 patients enrolled to re-weight allocation probabilities based on treatment responses. At each interim analysis, the trial may reach a conclusion of superiority or futility within any of the subgroups, which would stop randomization in that subgroup. If no conclusion within a subgroup is reached and randomization continues, the randomization probabilities will be re-weighted based on posterior probabilities of benefit or harm within the subgroup to a maximum of 90%. Post hoc analyses will be performed to investigate differential efficacy and safety by sex.

Risks to the safety of potential participants

As an open label trial of approved and commonly used drugs with well-established safety and side-effect profiles, adverse events and serious adverse events captured in this trial are events possibly related to the investigational agent, which includes major bleeding and laboratory confirmed HIT.

Study management and governance

Given the time sensitive nature of the pandemic, existing international expertise and capacity was leveraged to create a trial infrastructure with distributed roles amongst a number of academic institutions and organizations. The University of Manitoba (Winnipeg, Canada) is the study sponsor, and will support site contracts and payments. The Clinical Coordinating Centre (CCC) is Ozmosis@UHN (Toronto, Canada) who will be responsible for overall study management. The Data Coordinating Centre (DCC) is SOCAR Research (Nyon, Switzerland), an academic Clinical Research Organization in Switzerland. SOCAR will work closely with our

trial statistical consultant, Scott Berry (Austin, U.S.A) to prepare response-adaptive

randomization algorithms and data for frequent interim analyses.

The Executive Committee will consist of the Principal Investigators, country leads and

representatives from the CCC. The Executive Committee is responsible for the execution of the

trial according the study protocol. A Steering Committee will be responsible for providing

clinical and methodological guidance, including overall study design, execution, analysis, and

publication of the main study results.

Data safety monitoring board

An independent data safety monitoring board (DMSB) will regularly receive the results of

interim analyses as well as adverse events and serious adverse events reports. Based on

previously described trial conclusion parameters the DSMB may recommend stopping for

superiority, futility, or harm, of either the entire trial or the *a priori* defined d-dimer subgroups.

The DSMB is empowered to report independently to health authorities at their discretion.

To minimize the time to trial completion, and to garner robust estimates of safety, the

ATTACC investigators will combine data with patients enrolled in REMAP-COVID using a

common external DSMB. REMAP-COVID is a Bayesian adaptive platform trial that is currently

activating up to 200 sites in the U.S., United Kingdom, and European Union (EU) sites.

REMAP-COVID represents a sub-platform of the REMAP-CAP (Community Acquired

Pneumonia) international platform trial that specifically targets COVID-19 patients[27]. Although

this trial is operationally separate from ATTACC, the three principal investigators from

ATTACC serve on the working group for the Therapeutic Anticoagulation domain of REMAP-

COVID (RZ [chair], EG [deputy chair], and PL). Trial procedures and endpoints have thus been

harmonized between REMAP-COVID and ATTACC and the data will be combined to permit

shared interim analyses in the context of a shared external DMSB. This innovative and highly

collaborative data sharing structure permits evidence of efficacy and safety to be realized as

quickly and as robustly as possible.

Estimated duration of the trial

Based on projected enrolment rates (10 patients per month at, initially, 35 centres with

expansion as needed), we anticipate trial completion within 12 months. The inclusion of patients

from high volume sites in Canada, U.S., Brazil, and Mexico may shorten this estimate. Given the

Bayesian adaptive framework of ATTACC, the entire trial or specific subgroups of D-dimer

patients may be stopped earlier based on the results of interim analyses. Although the maximum

sample size is 3000 patients, trial simulations indicate a moderately high probability of stopping

for superiority before this sample size is attained.

Dissemination strategy

Results of the trial will be communicated rapidly to public health officials and policy

makers as well as the general medical community in order to inform urgent pandemic

management. We will work with our patient partners and knowledge users to prepare and

disseminate trial results via traditional publications, society recommendations, policy statements,

media, and social media. Results will be published in open access journals, with study data made

available in an open access repository.

Partnerships

ATTACC has broad international support. In Canada, ATTACC has partnered with the Canadian Critical Care Trials Group (CCCTG), the Canadian venous thromboembolism research (CanVECTOR) network and the Canadian trials for COVID (CATCO) trial network, a group of >50 hospitals participating in anti-viral therapeutic strategies for COVID-19 patients. Internationally ATTACC has partnered with REMAP-COVID, an international adaptive platform trial that is currently expanding to potentially include over 200 sites in the U.S., United Kingdom and EU. ATTACC has also partnered with the Worldwide Network for Innovation in Clinical Education and Research (WNICER) network, which includes our centers in Brazil and Mexico, and is endorsed by both the International Network of VENous Thromboembolism Clinical Research Network (INVENT) and the International Forum of Acute Care Trialists (InFACT). ATTACC has partnered with sites in Brazil and Mexico to increase the speed of recruitment and the generalizability of findings in low/middle income countries. These international partnerships have been developed to permit efficient site recruitment and promote swift trial completion in the face of a rapidly evolving pandemic with changing and unpredictable case volumes.

DISCUSSION

The ATTACC trial has been designed to urgently evaluate if therapeutic anticoagulation will benefit hospitalized patients with COVID-19 when compared with usual care. Multiple pandemic-specific design elements have been incorporated to promote the rapid recruitment of patients, and terminate the trial as soon as a clinically relevant conclusion has been achieved. By leveraging existing networks, the ATTACC investigators have further created an international network of committed sites with the necessary expertise and infrastructure to advance our

understanding of pathophysiologic mechanisms of thrombosis in COVID-19 and evaluate

antithrombotic strategies to improve clinical outcomes.

The use of a Bayesian adaptive trial design is well-suited for the pandemic where limited

information exists to inform *a priori* estimates of event rates and effect sizes. Frequent interim

analyses with the ability to terminate based on clinically important conclusions will allow the

trial to efficiently determine if heparin is efficacious, while monitoring safety. As an open trial,

our operational procedures and statistical analyses have been detailed *a priori* to ensure scientific

integrity, and reduced bias[28].

A unique feature of ATTACC is the use of a common external DSMB shared with a second

similar Bayesian adaptive international trial (REMAP-COVID)[27]. By harmonizing the two trial

procedures and outcomes, this innovative and highly collaborative data sharing structure permits

evidence of efficacy and safety to be realized as quickly and as robustly as possible.

The scope of ATTACC and diverse international partnerships have facilitated early

successes. Content experts from cardiology, hematology, thrombosis, intensive care, medication

safety and trial methodology have collaborated to design a trial that meets the unique situational

needs of the COVID-19 pandemic. Given the time-sensitive nature of the pandemic, roles were

distributed internationally based on the immediate capacity and expertise. Existing trial networks

were leveraged to recruit sites, which will increase enrollment and also mitigate enrollment risk

in sites with declining COVID-19 cases. The trial team and infrastructure established creates the

opportunity to test future hypotheses such as the role of anti-platelet agents, or other therapeutics.

ATTACC is planning an ancillary biomarker study and creation of a biobank that will

advance our understanding of the pathophysiology of COVID-19 infection, the interplay between

infection, inflammation and coagulation, and the mechanistic role of heparin. The biobank will be leveraged for further research, extending beyond the duration of the trial.

In the context of an evolving global pandemic, the ATTACC trial has been designed to efficiently address a clinical question of global priority. To launch the trial as quickly as possible we chose to evaluate and repurpose an existing, widely accessible, and inexpensive class of medications with strong biologic plausibility. If therapeutic anticoagulation is found to be superior to usual care, treatment can be rapidly instituted for patients hospitalized with COVID-19 around the world.

Table 1. Exclusion criteria

Mechanical ventilation (at time of randomization)
No intention to use pharmacologic thromboprophylaxis*
Active bleeding
Risk factors for bleeding
Intracranial surgery or stroke within 3 months
History of intracranial arteriovenous malformation
Cerebral aneurysm or mass lesions of the central nervous system
Intracranial malignancy
History of bleeding diatheses (e.g., haemophilia)
Gastrointestinal bleeding within 3 months
Thrombolysis within 7 days
Presence of an epidural or spinal catheter
Major surgery within 14 days
Uncontrolled hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg)
Other contraindications to therapeutic anticoagulation
Platelet count <50 x10^9/L, international normalized ratio (INR) >2.0, or baseline activated partial thromboplastin time (aPTT) >50 seconds
Hemoglobin <8 g/dL (to minimize the likelihood of transfusion if bleeding were to occur)
Acute or subacute bacterial endocarditis
History of heparin induced thrombocytopenia (HIT) or other heparin allergy or hypersensitivity
Current use of dual antiplatelet therapy (e.g., aspirin plus clopidogrel or ticagrelor or prasugrel)
Patients with an independent indication for therapeutic anticoagulation
Patients in whom imminent demise is anticipated and there is no commitment to active intervention
Anticipated transfer to a non-study site within 72 hours
Enrollment in other trials related to anticoagulation or antiplatelet therapy
Refusal of the treating physician

*At U.S. sites only.

Figure 1. Proposed pathophysiologic mechanisms of thrombosis in COVID-19 infection.
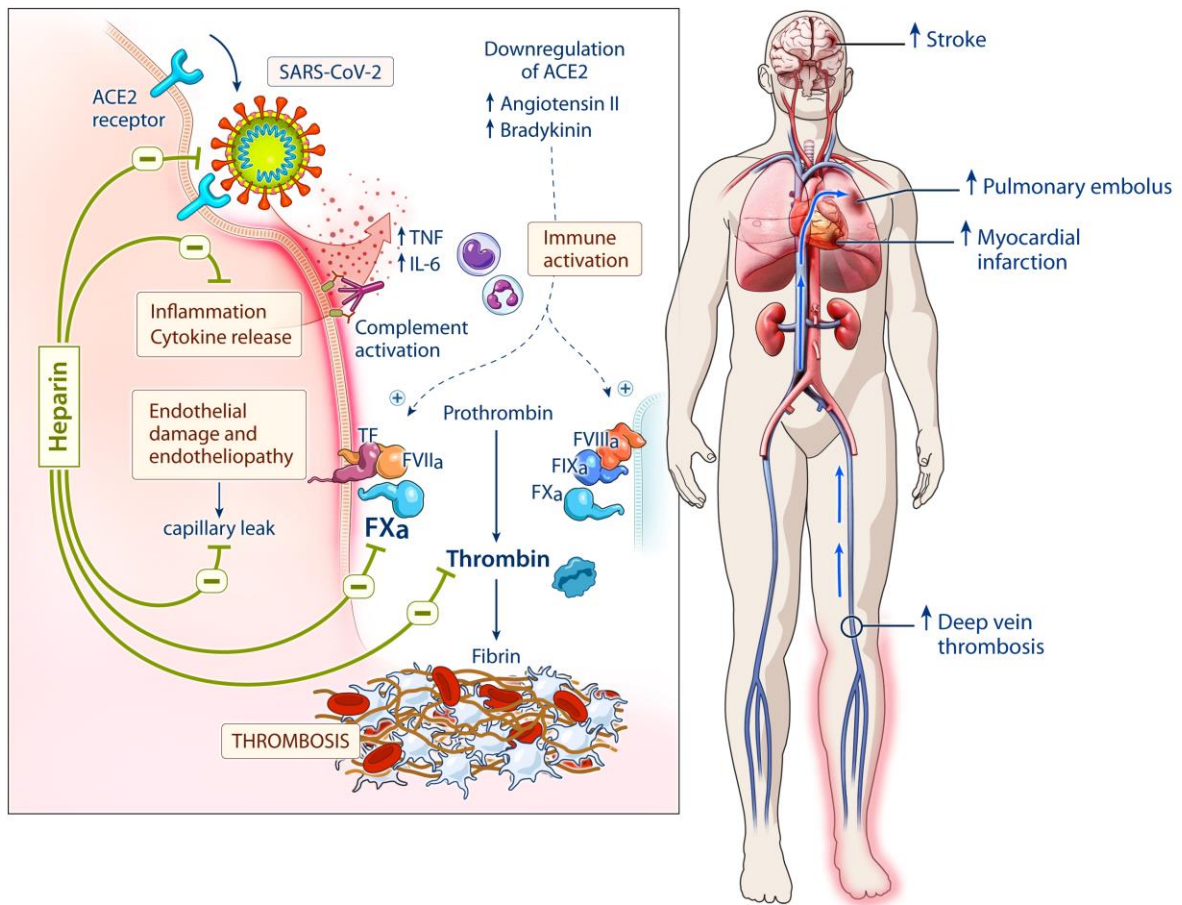
ACE-2 = angiotensin-converting enzyme II; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF = tumor necrosis factor; IL-6 = interleukin 6; TF = tissue factor

Appendix 1. Study Schedule

Participants will be given therapeutic-dose parenteral anticoagulation daily, up to 14 days or until *recovery*, defined as hospital discharge or liberation from supplemental oxygen >24 hours (provided supplemental oxygen was originally required), whichever comes first. Subjects will be followed until hospital discharge, after which time telephone contact will be undertaken to ascertain vital status following hospital discharged. (Schedule days refer to post-randomization days.) All post-discharge follow-up is telephone-/remote.

Investigations	Pre-Treatment (Baseline)	Day 1	Day 3	Day 7	Day 14	Day 21	Day 30	Day 90
Windows		+/- 3 days					+/- 3 days	+/- 7 days
Consent & Registration	X							
Demographics	X							
Medical History	X							
Weight	X							
SOC Vitals documented (SpO2 and FiO2, heart rate, blood pressure, respiratory rate, temperature)[1]	X	X	X	X	X			
Hematology bloodwork (SOC)[1]	X	X	X	X	X			
Biochemistry bloodwork (SOC)[1]	X	X	X	X	X			
Troponin (SOC)[1]	X	X	X	X	X			
D-dimer (SOC)[1]	X	X	X	X	X			
Anticoagulant Administration[2]		X[2]	X[2]	X[2]	X[2]			
Organ-free support outcome						X		
Primary and secondary outcomes[3]				X				
Survival, DVT, PE, MI, stroke (by phone)[3]								X
Adverse events[4]				X				
Concomitant medications[4]				X				

Footnotes:
[1]As per routine standard of care, collected while on therapy (until discharge or up to 14d or recovery); record the "worst" value observed during internal since last assessment;
[2] Participants randomized to the <u>investigational arm</u> will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from supplemental oxygen >24 hours if

previously required, whichever comes first) with heparin, with preference for subcutaneous low molecular weight heparin (enoxaparin preferred, although dalteparin or tinzaparin are also acceptable, as available) if no contraindication is present; alternatively, intravenous unfractionated heparin infusion may be used.

Participants randomized to the <u>control arm</u> will receive usual care, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.

[3]All post-discharge follow-up is telephone-/remote.

[4]Treatment-related adverse events and concomitant medications assessed only while on therapy.

Abbreviations: SOC=standard of care; SpO2=oxygen saturation; FiO2=fractional inspired oxygen; DVT=deep venous thrombobosis; PE=pulmonary embolism; MI=myocardial infarction.

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