CLINICAL STUDY PROTOCOL

A Multicenter, Randomized-Controlled Trial to Evaluate the Efficacy and Safety of Antithrombotic Therapy for Prevention of Arterial and Venous Thrombotic Complications in Critically-Ill COVID-19 Patients

Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients Trial (COVID-PACT)

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1. Abbreviations

AC	Anticoagulation
AE	Adverse event
ALI	Acute limb ischemia
AP	Antiplatelet
aPTT	Activated Partial thromboplastin time
CEC	Clinical Events Committee
COVID-19	Coronavirus disease-2019
CrCl	Creatinine Clearance
CSP	Clinical study protocol
CV	Cardiovascular
DMC	Data Monitoring Committee
DVT	Deep venous thrombosis
EC	Ethics Committee
eCRF	Electronic Case Record Form
eGFR	Estimated glomerular filtration rate
FDAC	Full-dose anticoagulation
GCP	Good Clincial Practice
GUSTO	Global Utilization Of Streptokinase And tPA For Occluded Arteries
iCVA	Ischemic stroke
ICH	International Conference on Harmonization
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intention-to-treat
LMWH	Low molecular weight heparin
MI	Myocardial infarction
PE	Pulmonary embolism
PT	Prothrombin time
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus-2
SDPAC	Standard-dose prophylactic anticoagulation
SEE	Systemic embolic event
T1MI	Type 1 myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
UFH	Unfractionated heparin

2. Protocol Synopsis

Study sites and number of subjects planned

The study will be conducted at approximately 30 sites in the United States. It is estimated that approximately 750 patients will be enrolled during a recruitment period of approximately 6-12 months. Each participant will be followed through 28 days or hospital discharge, whichever comes first.

Study Initiation		Phase of development
Estimated date of first subject enrolled	Q2 2020	4

Study Design

This is a multicenter, open-label, 2x2 factorial, randomized-controlled trial in critically-ill patients with novel coronavirus disease 2019 (COVID-19) evaluating the efficacy and safety of full-dose vs. standard prophylactic dose anticoagulation and of antiplatelet vs. no antiplatelet therapy for prevention of venous and arterial thrombotic events. The trial will follow the principles of a prospective randomized open blinded end-point (PROBE) design.

Study Objectives

Primary Efficacy Objective:	Primary Efficacy Outcome Measure:
To assess the efficacy of: 1) full-dose anticoagulation (FDAC) versus standard-dose prophylactic anticoagulation (SDPAC) and 2) antiplatelet (AP) therapy versus no AP therapy on venous or arterial thrombotic events in critically-ill patients with COVID-19.	The hierarchical composite endpoint of: 1. Death due to venous or arterial thrombosis 2. Pulmonary embolism 3. Clinically evident deep venous thrombosis (DVT) 4. Type 1 myocardial infarction (MI) 5. Ischemic stroke 6. Systemic embolic event (SEE) or acute limb ischemia (ALI) 7. Clinically silent DVT

Key Secondary Efficacy Objective:	Key Secondary Efficacy Outcome Measure:
To assess the efficacy of: 1) FDAC versus SDPAC and 2) AP therapy versus no AP therapy on *clinically evident* venous or arterial thrombotic events in critically-ill patients with COVID-19.	The hierarchical composite endpoint of: 1. Death due to venous or arterial thrombosis 2. Pulmonary embolism 3. Clinically evident DVT 4. Type 1 MI 5. Ischemic stroke 6. SEE or ALI

Primary Safety Objective:	Primary Safety Outcome Measure:
To evaluate the safety of: 1) FDAC versus SDPAC and 2) AP therapy versus no AP therapy in critically-ill patients with COVID-19.	Composite endpoint of fatal or life-threatening bleeding

Target Population

Patients with COVID-19 requiring intensive care unit (ICU) admission (critically-ill) without an indication for full-dose anticoagulation.

Inclusion Criteria (See Section 6 for additional details)
Patients must meet all the following criteria to be eligible for enrollment:

1. Age ≥18 years (male or female)
2. Acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)
3. Currently admitted to an ICU

Key Exclusion Criteria (See Section 6 for complete listing)

1. Ongoing or planned full-dose (therapeutic) anticoagulation for any indication
2. Ongoing or planned treatment with dual antiplatelet therapy
3. Contraindication to antithrombotic therapy or high risk of bleeding

Investigational Product, Dosage, and Mode of Administration

Acceptable initial regimens for full-dose anticoagulation:

- Unfractionated heparin (UFH) administered intravenously with a nomogram targeting an aPTT of 1.5-2.5 times the control as per institutional therapeutic target for treatment of VTE
- Enoxaparin 1 mg/kg administered subcutaneously (SC) every 12 hours

Antiplatelet:

- Clopidogrel 300 mg administered once orally on the day of randomization, followed by 75 mg administered orally once daily on subsequent days

Comparator Product, Dosage, and Mode of Administration

Acceptable initial regimens for standard dose prophylactic anticoagulation:

- Enoxaparin 40 mg administered SC once daily (reduce to 30 mg if CrCl<30 ml/min)*
- Heparin 5,000 units administered SC three times daily

**Enoxaparin 30-40 mg administered SC twice daily may also be considered if CrCl≥30 ml/min and BMI≥35 kg/m^2.*

Antiplatelet:

- None

Statistical Methods

The primary efficacy assessments will involve on-treatment (OT) comparisons of the effect of 1) full-dose anticoagulation (FDAC) versus standard-dose prophylactic anticoagulation (SDPAC) (pooled across antiplatelet regimens) and 2) antiplatelet (AP) versus no AP therapy (pooled across anticoagulant regimens) on the composite endpoint of death due to venous or arterial thrombosis, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI, or clinically silent DVT through the follow-up period. Intention-to-treat (ITT) comparisons will also be performed as additional analyses.

The primary analysis will be conducted by estimating the unmatched win ratio evaluating the composite in a hierarchical manner. A win ratio greater than 1 will be in favor of the FDAC arm and AP arm, respectively. In a secondary analysis of the primary composite endpoint, clinical event rates will be calculated using the time to first event according to the cumulative incidence function. Differences in clinical outcomes between the two treatment groups will be assessed using the Gray's test for equality of cumulative incidence functions.

With a 2-sided alpha of 0.05, a 40% event rate in the group receiving both SDPAC and no AP therapy at a median follow-up of 14 days, a 10% competing risk of mortality, and a 1% dropout rate, approximately 750 patients would provide approximately 170 events and therefore at least 80% power to detect a hazard ratio of 0.65 using Gray's test for equality of cumulative incidence function. This approach is expected to be conservative with respect to the primary efficacy analysis, for which greater power is expected using the win-ratio analysis.

3. Study Background & Rationale

In addition to respiratory insufficiency, patients with coronavirus disease (COVID)-19, the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), have a range of serious cardiovascular (CV) complications[1-4], including venous and arterial thrombotic events.[5-8] Thrombotic event rates are believed to be substantially higher in patients requiring ICU-level care, among whom it is suggested that up to 2/3 may develop clinically evident or clinically silent venous thrombotic complications despite standard doses of thromboprophylaxis.[6-8] While an accurate estimate of the rate of arterial thrombotic events is unknown at this time, case reports describe acute arterial thrombotic events, including ischemic strokes, acute coronary syndromes and ischemic limb events.[5, 9, 10] Proposed mechanisms for the increased thrombotic risk in patients with COVID-19 include excessive inflammation and immobilization in the setting of aberrant coagulation parameters and diffuse intravascular coagulation (DIC).[11, 12] In addition, early autopsy series have been notable for the presence of megakaryocytes in affected organs, suggesting that platelet aggregation and platelet-rich clot formation may be important pathogenetic mechanisms.[13]

The benefit of thromboprophylaxis with low-dose anticoagulation for the prevention of venous thromboembolism (VTE) in acutely-ill hospitalized medical patients is well-established.[14] Moreover, in patients at very high risk for VTE (e.g., patients with a history of unprovoked VTE), thromboprophylaxis with full-dose anticoagulation has been shown to be more effective than low-dose anticoagulation in preventing thrombotic events.[15] Given the apparent very high risk of venous thrombotic complications in patients with severe COVID-19, FDAC may be a more effective thromboprophylaxis strategy than SDPAC, but may be associated with an increased risk of bleeding. The safety of this strategy in patients with COVID-19 has not yet been adequately studied.

Antiplatelet therapy is recommended for prevention of arterial thrombotic events in high-risk patient populations.[16-18] Antiplatelet therapy has also demonstrated benefit for prevention of new and recurrent VTE in high-risk patient populations.[19-21] The thienopyridine clopidogrel is superior to aspirin for prevention of atherothrombotic events with a similar safety profile and may be associated with less GI bleeding.[22] Thus, it is reasonable to hypothesize that in critically-ill patients with COVID-19, addition of antiplatlet therapy with clopidogrel may reduce the incidence of arterial and venous thrombotic events with an acceptable safety profile. However, the balance of safety (bleeding) and efficacy of this approach merits rigorous investigation.

The study described here, COVID-PACT, is a multicenter, open-label, 2x2 factorial, randomized-controlled trial evaluating the safety and efficacy of antithrombotic therapy (anticoagulation and antiplatelet) versus standard of care for prevention of venous and arterial thrombotic events in critically-ill patients with COVID-19.

4. Study Objectives

The primary objectives of this study are to assess the effect of:

1. FDAC as compared with SDPAC, and
2. AP therapy compared with no AP therapy,

on the clinical outcomes of venous and arterial thrombotic events in critically-ill patients with COVID-19.

The key safety objectives are to assess the safety of:

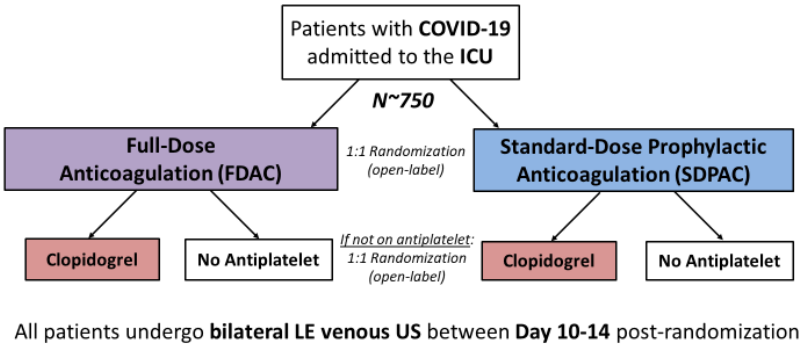
1. FDAC as compared with SDPAC, and
2. AP therapy compared with no AP therapy,

with respect to incidence of fatal or life-threatening bleeding.

See Section 8 (Study Outcomes) for additional secondary and exploratory objectives.

5. Study Design

This is a phase 4, multicenter, open-label, 2x2 factorial, randomized-controlled trial using a PROBE design. The trial will be conducted in approximately 30 sites in the United States. Approximately 750 patients will be enrolled. Patients will be randomized in a 1:1 allocation ratio to receive either FDAC or SDPAC. In patients without an ongoing indication for AP therapy at baseline, a second randomization will be performed in a 1:1 allocation ratio to either AP or no AP therapy. Randomization to FDAC vs. SDPAC will be stratified by whether or not the patient is planned to receive non-study AP therapy and therefore would not qualify for randomization in the second factorial treatment comparison. Patients will be assessed clinically and with bilateral lower extremity venous ultrasound between 10 and 14 days post-randomization. Patients will be followed through hospital discharge or 28 days, whichever occurs first, for a maximum follow-up of 28 days. The anticipated total duration of the study is 6-12 months.



6. Study Population

Inclusion Criteria

Patients must meet all the following criteria to be eligible for enrollment:

1. Age ≥18 years (male or female)
2. Acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)*
3. Currently admitted to an intensive care unit (ICU)**

**Acute SARS-CoV2 infection is defined as a documented, positive SARS-CoV2 RT-PCR, SARS-CoV2 IgM antibody test, or other accepted assay (see Manual of Site Operations) with active respiratory signs or symptoms during the current hospitalization.*

***Where ICU admission occurred ≤96 hours prior to randomization. ICU admission also includes patients requiring ICU-level care in other units. Criteria for ICU-level of care are defined in the Protocol Appendix.*

Exclusion Criteria

Patients who meet any of the following criteria are excluded from the study:

1. Ongoing (>48 hours) or planned full-dose (therapeutic) anticoagulation for any indication
2. Ongoing or planned treatment with dual antiplatelet therapy
3. Contraindication to antithrombotic therapy or high risk of bleeding due to conditions including, but not limited to, any of the following:
   a) History of intracranial hemorrhage, known CNS tumor or CNS vascular abnormality
   b) Active or recent major bleeding within the past 30 days with untreated source
   c) Platelet count <70,000 or known functional platelet disorder
   d) Fibrinogen <200 mg/dL
   e) International normalized ratio (INR) >1.9
4. History of heparin-induced thrombocytopenia
5. Ischemic stroke within the past 2 weeks
6. Pregnancy
7. Study staff or their family members
8. Any condition which in the investigator's assessment might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study
9. Subjects for whom further care is being forgone at the decision of the subject, family, and/or treating team ("comfort measures only")

Exclusion-based laboratory results are based on most recent values from within 2 days prior to randomization for platelet count and INR and within 3 days prior to randomization for fibrinogen.

Patients who meet the following criterion are excluded from the second randomization (antiplatelet therapy vs. no antiplatelet therapy):

1. Ongoing or planned antiplatelet therapy, including aspirin monotherapy

7. Study Intervention

7.1 Investigational Product Information:

Acceptable initial regimens for FDAC include the following:

- UFH administered intravenously with a nomogram targeting an aPTT of 1.5-2.5 times the control as per institutional therapeutic target for treatment of VTE
- Enoxaparin 1 mg/kg administered subcutaneously every 12 hours (if CrCl≥30 ml/min)

Acceptable initial regimens for SDPAC include the following:

- Enoxaparin 40 mg administered subcutaneously once daily (if CrCl≥30 ml/min)*
- Enoxaparin 30 mg administered subcutaneously once daily (if CrCl<30 ml/min)
- Heparin 5,000 units administered subcutaneous three times daily

**Enoxaparin 30-40 mg administered SC twice daily may also be considered if CrCl≥30 ml/min and BMI≥35 kg/m^2.*

Acceptable regimen for randomized antiplatelet therapy is:

- Clopidogrel 300 mg administered once orally on the day of randomization, followed by 75 mg administered once daily on subsequent days

7.2 Randomized Treatment Assignment: Randomization to FDAC versus SDPAC and AP therapy versus no AP therapy will be done via an Interactive Web-based Randomization System (IWRS). Treatment will be open-label and hospital-supplied by the institutional pharmacy per standard practice using local, standard formulations, concentrations and titration.

Randomization and study treatment initiation should be done as soon as possible following ICU admission or the requirement for ICU-level of care and no longer than 96 hours after meeting ICU-level criteria.

7.3 Duration of Randomized Treatment: The study allocated regimen should be continued until hospital discharge (including after ICU discharge) or through 28 days post-randomization, whichever occurs first.

7.4 Transition in Randomized Treatment Assignment: The investigator may transition between acceptable regimens within the randomized treatment assignment as deemed appropriate clinically (e.g., transition from enoxaparin to subcutaneous heparin for SDPAC in the setting of new or worsening renal failure). Transitions to direct thrombin inhibitors, or fondaparinux are permitted if heparin-induced thrombocytopenia is confirmed or suspected. After a patient is transferred out of the ICU, transitions to oral anticoagulation are also permitted in the absence of significant renal or hepatic dysfunction (see Protocol Appendix for further details). Transitions in anticoagulant therapy will be recorded in the

eCRF. Refer to the Appendix for further guidelines regarding transitions in randomized treatment assignment including acceptable alternative regimens.

7.5 Blinding: Treatment will be open-label without blinding.

7.6 Concomitant Medications: All non-antithrombotic therapy is at the discretion of the patient's treating physicians. Non-study anticoagulant or antiplatelet therapy is not permitted while receiving the study allocated regimen unless there is a change in the patient's clinical status requiring an alternative regimen.

7.7 Discontinuation of Study Drug: Patients and healthcare providers may voluntarily discontinue study drug for any reason at any time. If adverse events occur that are believed to be due to study drug, or safety events occur that, in the opinion of the investigator, contraindicate further dosing of study drug, study drug may be temporarily interrupted or permanently discontinued. Whenever possible, restarting study drug should be encouraged, so long as the investigator judges that the potential benefit outweighs the risk. Situations that warrant temporary or permanent study drug discontinuation include:

- Active clinically significant bleeding
- Acute hemorrhagic or ischemic stroke at meaningful risk for hemorrhagic transformation
- Severe thrombocytopenia (platelet count <50,000)
- Evidence of overt disseminated intravascular coagulation (e.g. fibrinogen levels <150 mg/dl or INR >2.9 despite adequate vitamin K repletion). See Manual of Site Operations for guidelines to help discriminate DIC from sepsis induced coagulopathy.
- Need for invasive procedures requiring extended interruption of antithrombotic therapy

The investigator should contact the TIMI Hotline with any questions regarding study drug discontinuation and must update the eCRF with any study drug discontinuation and record it in the eCRF. Discontinuation of study drug does not mean discontinuation of follow-up. All study assessments should be continued even if study drug is discontinued.

In the course of the patient's participation, use of the alternative antithrombotic strategy (crossover) may be deemed clinically indicated due to a change in the patient's clinical status. Examples include: 1) a patient randomized to standard-dose prophylactic anticoagulation develops atrial fibrillation or deep venous thrombosis, requiring full-dose anticoagulation; or 2) a patient randomized to no antiplatelet therapy experiences an acute coronary syndrome requiring addition of an antiplatelet agent. The crossover in therapy will be recorded in the eCRF.

7.8 Withdrawal of Consent: Patients are free to completely withdraw from the study at any time (which means permanent discontinuation of IP and all follow-up assessments) without prejudice to further treatment. Withdrawal of consent should only occur if the patient refuses any further assessments or contact whatsoever. Patients who do not want in-person follow-up after cessation of IP should be offered alternative methods of follow-up including assessment of health status via treating physicians or medical records. Such patients would then not be viewed as withdrawals of consent. The investigator must explain to the patient all options for continued participation, and document which options were refused by the patient and the reason for refusal. Withdrawal of consent must be ascertained and documented in writing by the site investigator who must inform the TIMI Hotline and document the withdrawal of consent in the eCRF and medical records. Patients will be asked about the reason(s) for withdrawal of consent.

8. Study Outcomes

Efficacy Outcomes

Primary Efficacy Outcome

The hierarchical composite endpoint of:

1. Death due to venous or arterial thrombosis
2. Pulmonary embolism
3. Clinically evident DVT
4. Type 1 MI
5. Ischemic stroke
6. Systemic embolic event (SEE) or acute limb ischemia (ALI)
7. Clinically silent DVT

Key Secondary Efficacy Outcome

The hierarchical composite endpoint of:

1. Death due to venous or arterial thrombosis
2. Pulmonary embolism
3. Clinically evident DVT
4. Type 1 MI
5. Ischemic stroke
6. SEE or ALI

Secondary Efficacy Outcomes

- Composite of venous thrombotic events (PE or clinically evident or silent DVT)
- Composite of arterial thrombotic events (ischemic stroke, SEE or ALI, or T1MI)
- Each of the individual components of the primary efficacy outcome
- Cardiovascular death

Exploratory Efficacy Outcomes

- Clinical improvement on COVID ordinal scale recommended by WHO R&D Blueprint Group
- Ventilator-free days (at 28 days post-randomization)
- Time from ICU admission to ICU discharge
- Acute kidney injury
- Need for new renal replacement therapy
- Pulseless electrical activity cardiac arrest
- Catheter thrombosis
- Myocardial dysfunction
- All-cause mortality

Safety Outcomes

Primary Safety Outcome

Time to first occurrence of fatal or life-threatening bleeding

Secondary Safety Outcome

- GUSTO moderate or severe bleeding

9. Study Procedures

Screening and Randomization

- Obtain written informed consent from patient or legal authorized representative
- Review inclusion/exclusion criteria (including pregnancy testing for women of child bearing potential), relevant medical history, vital signs (including weight), and medications
- Review or obtain labs (platelet count, INR and fibrinogen)
- Randomize (Day 0) using the Interactive Web Randomization System (IWRS)
- Initiate randomized anticoagulant strategy and, if applicable, antiplatelet therapy

Follow-up (through day 28 or hospital discharge, whichever occurs first)

- Continue randomized antithrombotic therapy
- Monitor anticoagulation as per local practice; obtain INR daily and fibrinogen at least every 3 days while receiving ICU-level care (see Appendix for details)
- Obtain bilateral lower extremity venous ultrasound as a single assessment any time between days 10-14. If a patient crosses over or discontinues randomized anticoagulation strategy on Day 4 through Day 9, this assessment should be performed as close to the date of discontinuation as possible (and no longer than 3 days after discontinuation). For crossover or permanent discontinuation prior to Day 4, this assessment is not required.
- Assess for efficacy and safety events

Additional details about study operations can be found in the Manual of Site Operations

10. Site Training and Monitoring

10.1 Training of Study Site Personnel: Before enrolling patients into the study, the requirements of the Clinical Study Protocol and related documents will be reviewed with the investigational staff who will be trained in any study-specific procedures. The site principal investigators will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The site principal investigator will also maintain a record of all individuals involved in the study.

10.2 Monitoring of Study Sites

Site monitoring will be performed based on the Monitoring Plan. Site monitoring will occur on a regularly scheduled basis and, as needed, based on site performance and perceived training needs. The purpose of such monitoring will be to ensure that the study is being conducted in accordance with the protocol, particularly through helping study site staff resolve any local problems and providing extra training focused on specific needs. Particular attention will be given to the effectiveness of strategies to recruit appropriate participants, the completeness of follow-up, the maintenance of participant adherence to study treatment, and the reporting of study outcomes and collection of relevant supporting documentation. Details are provided in the Monitorting Plan.

11. Data Analysis Plan

Further details can be found in the Statistical Analysis Plan (SAP).

11.1 Analysis Sets

a) The On-Treatment Analysis Set will consist of all randomized patients who received at least one dose of study drug. However, only those events/observations occuring during therapy with the randomized treatment strategy or within 3 days of the last dose of randomized treatment will be a part of this analysis set. A transition in randomized treatment as defined in Section 7.4 is not considered a deviation in therapeutic strategy and observations occurring after the transition will be a part of this analysis set. Crossovers and permanent discontinuations (Section 7.7) of randomized treatment are considered an end to the randomized anticoagulant or antiplatelet therapeutic strategy; only observations occurring up to 3 days after crossovers or discontinuations of randomized treatment will be a part of this analysis set. The primary assessement for efficacy outcomes will be analyzed based on the On-Treatment Analysis Set.

b) The Intention-to-Treat Analysis Set will consist of all randomized patients with the exception of those who did not qualify for randomization and did not receive study drug but were inadvertently randomized into the study. Following the intention-to-treat

principle, patients will be analyzed according to the treatment group to which they were assigned at randomization. Additional assessments for efficacy outcomes will be analyzed based on the Intention-to-Treat Analysis Set.

11.2 Analyses

The primary efficacy analysis will be performed using the On-Treatment Analysis Set. The primary efficacy assessments will involve on-treatment comparisons of the effect of allocation to: 1) FDAC versus SDPAC (pooled across AP regimens); and 2) AP therapy versus no AP therapy (pooled across anticoagulation regimens) on the primary composite endpoint of death due to venous or arterial thrombosis, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI, or clinically silent DVT through the follow-up period. Clinical event rates will be calculated according to the cumulative incidence function. Intention-to-treat comparisons will also be performed as additional analyses.

The primary analysis will be conducted by estimating the unmatched win ratio by comparing 1) every participant in the FDAC arm to every participant in the SDPAC arm to determine a winner, and 2) every participant in the AP therapy to every participant in the no AP therapy arm to determine a winner. The estimated win ratio (the total number of wins in the FDAC arm divided by the total number of wins in the SDPAC arm, and the total number of wins in the AP therapy arm divided by the total number of wins in the no antiplatelet therapy arm) will be calculated evaluating the composite in a hierarchical manner. A win ratio greater than 1 will be in favor of the FDAC arm and AP therapy arm, respectively.

The corresponding two-sided 95% confidence intervals will be calculated. The analysis will be performed using the unmatched pair win ratio approach.[23] For the comparison of FDAC vs. SDPAC, the analysis will be stratified by ongoing or planned AP therapy and the second factorial treatment comparison of AP therapy vs. no AP therapy for those eligible. For the analysis of AP therapy vs. no AP therapy, the analysis will be stratified by FDAC vs. SDPAC randomization. Contributions of each component of the composite endpoint to total number of winners used in estimation of the win ratio will be reported.

In a secondary analysis of the primary composite endpoint, differences in clinical outcomes between the treatment groups will be assessed using the Gray's test for equality of cumulative incidence functions, incorporting stratification in the analysis as outlined for the primary analysis. Hazard ratios and 95% confidence intervals will be calculated using a Fine-Gray model to account for the competing risk of mortality. Analogous analyses will be performed for the secondary and exploratory efficacy outcomes involving time-to-event comparisons. Additional details of the analytic approach can be found in the Statistical Analysis Plan (SAP).

11.3 Subgroup Analyses

Subgroups will be analyzed for the primary and secondary efficacy outcomes, including, but not limited to:

a) Age
b) Sex
c) Body-mass index (BMI)
d) Diabetes mellitus
e) History of cardiovascular disease
f) Baseline indication for antiplatelet therapy (i.e., eligible for 2nd randomization) (only for comparison of FDAC vs. SDPAC)
g) D-dimer
h) Need for mechanical ventilation at randomization
i) High-sensitivity C-reactive protein (hsCRP)
j) Prior history of VTE

Further details can be found in the Statistical Analysis Plan.

11.5 Sample Size Considerations

The sample size is based on the secondary analysis of the primary efficacy endpoint. With a 2-sided alpha of 0.05, a 40% event rate in the control arm rate in the group receiving both SDPAC and no AP therapy (estimated based on 3 recent case series of critically-ill patients with COVID-19), [6-8] a 10% competing risk of mortality, and a 1% dropout rate (e.g., withdrawal of consent, loss-to-follow-up), approximately 750 patients should provide at least 170 events and therefore at least 80% power to detect a 35% relative risk reduction (RRR) for the FDAC vs. SDPAC comparison using Gray's test for equality of cumulative incidence function. The power for the AP therapy comparison is expected to be slightly less (~70%) as it is assumed that 10% of patients will not be eligible for the AP randomization. The approach of powering the trial based on the secondary analysis of the primary efficacy endpoint (i.e., cumulative incidence function) is expected to be conservative with respect to the primary analysis of the primary efficacy endpoint (i.e., unmatched win ratio), for which larger power is expected.

During the course of the trial, trial leadership will monitor the aggregate event rate and proportion of patients who proceed to the second randomization to ensure consistency with the initial assumptions and preserve the planned power for the trial. The target sample size may be increased to ensure accrual of an adequate number of efficacy endpoint events to preserve the overall initial planned power. Refer to the SAP for further details.

12. Data and Safety Monitoring and Review

12.1 Data Collection

An electronic case record form (eCRF) will be used for data collection and query handling. The site investigator will ensure that data are recorded in the eCRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness, and timeliness of the data recorded. The investigator will sign the completed eCRF. Data will be reviewed as defined in the Data Management Plan.

12.2 Safety Monitoring

As all study therapies have been approved for use in patients at risk for venous and arterial thrombotic events, this study has received an exemption from the need for an Investigational New Drug (IND). Investigators are required to report: (1) Serious Adverse Events Related to Study Drug, (2) Unexpected Problems, and (3) Adverse Events Leading to Drug Discontinuation.

1. Reporting of Serious Adverse Events Related to Study Drug
   A serious adverse event (SAE) related to study drug must meet the following criteria:
   a) Be serious, meaning that in the view of either the local investigator or the TIMI Study group physician, the adverse event results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

   b) Be related to study drug, meaning that there is a reasonable possibility that the drug caused the adverse event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. In making this assessment, there should be consideration, based on the available information, of the probability of an alternative cause, the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

   Events that qualify as an SAE related to study drug and occur after the first dose of study drug has been administered (through the end of the study period), should be reported in the eCRF on the appropriate pages. SAEs related to study drug must be reported within 24 hours of knowledge of their occurrence. They should be clinically followed

until the event has resolved or stabilized. All confirmed SAEs related to study drug will be reported to relevant ethics committees, Institutional Review Boards, and investigators in an expedited manner in accordance with regulatory requirements.

2. Reporting of Unexpected Problems (UPs):
   To qualify as a UP, an event must meet all of the following criteria:

   a) Be unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
   b) Be related or possibly related to participation in the research. "Possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.
   c) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

3. Reporting of Adverse Events Leading to Drug Discontinuation: All adverse events (AEs) leading to investigational product discontinuation should be reported via the eCRF within 3 working days of knowledge of their occurrence.

4. Pregnancy: If any pregnancy is discovered during the course of the study, then investigators or other site personnel should contact the TIMI Hotline immediately but no later than 24 hours after knowledge of its occurrence. Investigational product should be discontinued immediately. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up (even if after trial completion) and documented on the paper Pregnancy Outcome Report form and sent to the TIMI Safety Desk.

12.3 Data Monitoring Committee (DMC)

An independent DMC will be appointed by the TIMI Study Group. The DMC will be responsible for safeguarding the interests of the patients in the study by assessing the efficacy and safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. They will review overall safety in the trial and specifically the incidence of fatal or life-threatening bleeding. The DMC statistician will be able to have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. The DMC Charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data.

12.4 Clinical Events Committee (CEC)

Suspected outcome events in the study including the components of the primary and key secondary efficacy and primary and secondary safety endpoints will be centrally adjudicated by an independent clinical events committee. Suspected outcome events in the study will be identified either by the site investigator or by electronic review of reported AEs. For all events identified for adjudication, the investigator will complete the appropriate modules of the eCRF and provide required source documentation.

13. Ethics and Dissemination

13.1 Ethical Conduct of the Study

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the most recent version of the Declaration of Helsinki.

An Ethics Committee (EC) or Institutional Review Board (IRB) will approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to patients.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure).

13.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the TIMI Study Group and the IRB prior to implementation.

13.3 Informed Consent Procedures

a) Eligible patients may only be included in the study after providing written informed consent, or, if applicable, after such consent has been provided by a legally acceptable representative(s) of the patient. Verbal or electronic consent (eConsent) may be used where consistent with local regulations.
b) Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in the protocol)

13.4 Publications

The Principal Investigators, in collaboration with the other Steering Committee members, will be responsible for drafting the main report from the trial for publication and for secondary and supplementary analyses.

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15. Appendices

1. Study Organization and Oversight

This study was initiated by independent scientists in the Critical Care Cardiology Trial Networks, TIMI Study Group, at Brigham and Women's Hospital and Harvard Medical School. The TIMI Study Group will act as the sponsor for the trial.

TIMI Principal Investigators

The Principal Investigators have overall responsibility for:

a) Design and conduct of the study in collaboration with the Steering Committee;
b) Preparation of the protocol and subsequent revisions;
c) Development of the eCRF;
d) Development of the statistical analysis plan;
e) Interpretation of the final data and reporting of the study.

Steering Committee

The Steering Committee is responsible for:

a) Reviewing and commenting on the final protocol and statistical analysis plans;
b) Reviewing progress of the study and, if necessary, advising on protocol revisions;
c) Reviewing study publications and substudy proposals;
d) Reviewing external new studies that may be of relevance.

Data Monitoring Committee

The indepedendent Data Monitoring Committee is responsible for:

a) Reviewing unblinded data as per the DMC charter;
b) Advising the Principal Investigators if, in its view, the data provide evidence that may warrant modification of the trial protocol or early termination for either efficacy or safety.

Clinical Events Committee

The Clinical Events Committee is responsible for independently reviewing, interpreting, and adjudicating potential endpoints that are experienced by the patients. (NB: The precise responsibilities and procedures applicable to the CEC will be detailed in the CEC Charter.)

2. Guidelines for Monitoring Coagulation Parameters

Treatment will be open-label and hospital-supplied by the institutional pharmacy per standard practice using local, standard formulations, concentrations and titration. Unfractionated heparin (UFH) should be administered intravenously with an institution- or provider-determined nomogram targeting an aPTT of 1.5-2.5 times the control as per institutional therapeutic target for treatment of VTE. Similarly, if heparin-induced thrombocytopenia is confirmed or suspected, and a patient is transitioned to a direct thrombin inhibitor (bivalirudin or argatroban), these should be administered intravenously with an institution- or provider-determined nomogram targeting an aPTT of 1.5-2.5 times the control as per institutional therapeutic target for treatment of VTE. It is also acceptable

to use an institution- or provider-determined nomogram targeting an anti-Factor Xa level of 0.3-0.7 IU/ml for any of the intravenous FDAC regimens. Prothrombin time(PT)/international normalized ratio (INR) should be monitored daily, and fibrinogen level should be monitored at least every 3 days while the subject requires ICU level care.

3. **Guidelines for Transitions in Randomized Treatment**

The investigator may transition between acceptable regimens within the randomized treatment assignment as deemed appropriate clinically (e.g., transition from enoxaparin to subcutaneous heparin for standard-dose prophylactic anticoagulation in the setting of new or worsening renal failure). In addition, transitions to direct thrombin inhibitors are permitted if heparin-induced thrombocytopenia is confirmed or suspected.

Accepatable alternative regimens for FDAC include:

- Bivalirudin administered intravenously with a nomogram targeting an aPTT of 1.5-2.5 times the control as per institutional therapeutic target for treatment of VTE
- Argatroban administered intravenously with a nomogram targeting an aPTT of 1.5-2.5 times the control as per institutional therapeutic target for treatment of VTE
- Fondaparinux administered subcutaneously once daily with dosing according to weight (<50 kg: 5 mg once daily; 50-100 kg: 7.5 mg once daily; >100 kg: 10 mg once daily)

Review with the Central Coordinating Center any modifications in dosing in your hospital guidelines for patients at the extremes of body weight. Equivalent dosing of alternative LMWH preparations is detailed in the Manual of Site Operations.

Acceptable alternative regimens for SDPAC include:

- Fondaparinux administered subcutaneously 2.5 mg once daily

After a patient is transferred out of the ICU, transitions to oral anticoagulation are also permitted.

Acceptable alternative regimens for FDAC outside of the ICU and prior to hospital discharge include:

- Apixaban administered orally 5 mg twice daily
- Rivaroxaban administered orally 20 mg once daily
- Edoxaban administered orally 60 mg once daily (if body weight >60 kg) or 30 mg once daily (if body weight <60 kg or CrCl 30-50 ml/min)
- Dabigatran 150mg orally twice daily
- Warfarin with a target International Normalized Ratio (INR) of 2-3

Note that, in general, NOACs should not be used in patients with significant renal dysfunction or with Child-Pugh B/C hepatic dysfunction. Refer to package insert recommendations for DVT/PE treatment dosing for each individual NOAC for patients with renal or hepatic dysfunction.

The decision to transition therapy is left to the discretion of the investigator. Transitions in randomized treatments do not constitute a deviation in treatment strategy. All transitions in anticoagulant therapy will be recorded in the eCRF. The indications for antithrombotic therapy at the time of hospital discharge are determined by the managing clinician according to local standards of care.

4. Criteria for ICU-Level of Care

Patients are considered to have been admitted to an ICU if they were either admitted to a regular ICU room or if they were in a non-ICU room that is functioning as an ICU room to accommodate surge capacity. Non-ICU rooms are considered to be functioning as an ICU under any of the following conditions:

- The patient is being treated by an ICU team
- The patient is receiving advanced respiratory support (i.e, invasive mechanical ventilation, non-invasive positive pressure ventilation for respiratory insufficiency, or high flow nasal canula of at least 10L/min), vasopressors for at least 1 hour, continuous renal replacement therapy or mechanical circulatory support.

16. Changes to the Protocol

16.1 Protocol Amendment 1 – October 28, 2020

- Acceptable initial regimens for standard dose prophylactic anticoagulation

  To be consistent with accepted dose modifications for obesity, enoxaparin 40 mg SC twice daily is added as an alternative for individuals with CrCl≥30 ml/min and BMI≥35 kg/m^2.

- Inclusion criteria
  - Given emerging new technology for high specificity testing, confirmation of SARS-CoV2 may include acceptable alternatives to SARS-CoV2 RT-PCR or SARS-CoV2 IgM antibodies
  - To accommodate the range of turn-around times for SARS-CoV2 testing, the time window from ICU admission to randomization is increased from 72 hours to 96 hours.
  - Clarification that ICU admission also includes patients requiring ICU-level care in other units. Criteria for ICU-level of care are defined in the Protocol Appendix.

- Exclusion criteria
  - Clarification that study staff rather than any employee of the hospital system are excluded from participation in the study.
  - For clarity, time windows for exclusions based on local laboratory results are added.

- Study procedures
  - Review of laboratory results during screening added as an explicit procedure.
  - To reduce the burden of testing when not needed for safety, the time period for performance of INR daily and fibrinogen every 3 days is modified to the duration of ICU-level care. Outside this time window, testing is according to local standard practice.
  - To mitigate exposures to COVID-19, verbal or electronic consent (eConsent) may be used where consistent with local regulations.

- Acceptable alternative regimens for FDAC outside of the ICU and prior to hospital discharge
  - Updated to include dabigatran and warfarin, both of which are acceptable anticoagulants.
  - For consistency with standard practice, cautions for subjects with renal or hepatic dysfunction are updated to refer to individual package labeling.

- Correction of grammatical and typographic errors