SUPPLEMENTAL MATERIAL

This appendix has been provided by the authors to give readers additional information about their work.

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Anticoagulation and Antiplatelet Therapy For Prevention of Venous and Arterial Thrombotic Events in Critically Ill Patients with COVID-19: COVID-PACT

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SUPPLEMENTARY METHODS

STUDY ELIGIBILITY CRITERIA

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 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.

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.

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

RANDOMIZATION SCHEME
Randomization was performed in the electronic database within a site using blocks of 8 for patients eligible for the antiplatelet randomization (i.e., in the case of 4 possible treatment assignments) and blocks of 4 for patients ineligible for the antiplatelet randomization (i.e., in the case of 2 possible treatment assignments).

ACCEPTABLE INITIAL STUDY DRUG REGIMENS
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 subcutaneously three times daily

*Enoxaparin 30-40 mg administered SC twice daily may also be considered if CrCl ≥ 30 ml/min and BMI ≥ 35 kg/m².

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

STUDY DRUG MANAGEMENT
Transition Between Regimens within Randomized Study Drug Strategy
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.

Acceptable alternative regimens for full-dose anticoagulation 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)

Acceptable alternative regimens for standard prophylactic dose anticoagulation 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 full-dose anticoagulation 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, direct oral anticoagulants 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 direct oral anticoagulants for patients with renal or hepatic dysfunction.

The decision to transition therapy was left to the discretion of the investigator. Transitions in randomized treatments did not constitute a deviation in treatment strategy. The indications for antithrombotic therapy at the time of hospital discharge are determined by the managing clinician according to local standards of care.

Discontinuation of Randomized Study Drug Strategy
Patients and healthcare providers could voluntarily discontinue study drug for any reason at any time. If adverse events occurred that were believed to be due to study drug, or safety events occurred that, in the opinion of the investigator, contraindicated further dosing of study drug, study drug could be temporarily interrupted or permanently discontinued. Whenever possible,
restarting study drug was encouraged, so long as the investigator judged that the potential benefit outweighed the risk. Situations that may have warranted 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).
- Need for invasive procedures requiring extended interruption of antithrombotic therapy

In the course of the patient’s participation, use of the alternative antithrombotic strategy (crossover) may have been 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 was recorded in the eCRF.

ADDITIONAL STUDY PROCEDURES
Patients were to have bilateral lower extremity venous ultrasound as a single assessment any time between days 10-14. If a patient crossed over or discontinued randomized anticoagulation strategy on Day 4 through Day 9, this assessment should have been 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 was not required.

ADDITIONAL STATISTICAL METHODS

Efficacy and Safety Endpoints
Other secondary efficacy outcomes of the study include:

- Composite of venous thrombotic events (PE or clinically evident or silent DVT)
- Composite of arterial thrombotic events (ischemic stroke, SEE or ALI, or type 1 MI)
- Each of the individual components of the primary efficacy outcome
- Cardiovascular death

Other efficacy variables
Other exploratory efficacy variables of the study include all-cause mortality.

Additional Details on Analytic Methods

Tabulation of events and censoring
Only events adjudicated and confirmed by the CEC will be included in the analyses of primary and secondary efficacy outcomes.

A patient may have one or more events. For composite endpoints, the time to first event within the composite list will be used for survival analysis, and a pre-specified hierarchy was used for the win ratio for the primary and secondary outcomes. For each component of a
composite (e.g., PE), the time to first component event will be used, regardless of other events occurring earlier (e.g., if a DVT precedes a PE in a patient, then the DVT counts in the composite as the first event, but the PE counts in the time to first PE analysis).

The end-of-study was defined as the time of hospital discharge or 28 days post-randomization (whichever occurs first) for each individual patient. If no endpoint event occurred during the study period, withdrawal of consent, hospital discharge, 28 days post-randomization, or death (whichever is earliest) was treated as the censoring event for the intention-to-treat analysis.

For the analyses of death due to arterial or venous thrombosis and of cardiovascular death, a patient who dies of a non-thrombotic death and non-cardiovascular death (or undetermined cause), would be censored at the time of death. Censoring occurred according to the same pattern for both the on-treatment analysis set and intention-to-treat analysis set, with the exception that only observations occurring up to 72 hours after crossovers or discontinuations of randomized treatment were a part of the on-treatment analysis set.

**Unmatched pair win ratio**

For the primary endpoint, the following hypotheses were tested at the two-sided 0.05 level in the primary analysis:

H01: Win ratio [FDAC:SDPAC] =1 vs

H11: Win ratio [FDAC:SDPAC] ≠1

and

H02: Win ratio [AP therapy:no AP therapy] =1 vs

H12: Win ratio [AP therapy:no AP therapy] ≠1

The win ratio analysis of both the primary and key secondary endpoints were conducted 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) was calculated by evaluating the composite in a hierarchical manner. A win ratio greater than 1 is in favor of the FDAC arm and AP therapy arm, respectively.

The corresponding two-sided 95% confidence intervals were calculated. The analysis was to be performed using the unmatched pair win ratio approach (Pocock SJ et al. Eur Heart J 2012; 33(2): 176-82). 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 was 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 are reported.

**Fine-Gray proportional hazards model**

In time-to-event comparisons of the primary and key secondary composite endpoints, as well as the secondary and exploratory efficacy endpoints, differences in clinical outcomes between the treatment groups were assessed using the Gray’s test for equality of cumulative incidence functions, incorporating stratification in the analysis as outlined for the win ratio analysis. Hazard ratios and 95% confidence intervals were calculated using a Fine-Gray model to account for the competing risk of mortality.

With respect to randomized treatment, hazard ratio estimates and 2-sided confidence intervals (CIs) are presented. P-values are presented from the Wald’s test. A patient may have one or more events. However, only a patient’s first applicable event contributed to the analysis of each specified endpoint.

The assumption of proportional hazards for the factor for treatment groups were assessed without any significant departures. Based on the proportional hazards test (z-test) using weighted Schoenfeld residuals (as well as examining log-log plots and residual-vs-time plots), we did not observe any violation of proportional hazards assumptions for any of the three endpoints for the randomized anticoagulation (p-value=0.7855 for the primary efficacy endpoint, p-value=0.5381 for the key secondary, and p-value=0.2118 for all-cause mortality).

Additionally, we examined the plots of the Schoenfeld residuals versus time from Fine-Gray model, and did not observe time-dependency, implying the absence of proportional hazards violation.

The contribution of each component of the primary composite endpoints to the overall treatment effect was examined. Methods similar to those described for the primary and key secondary composite endpoints were used to separately analyze the time from randomization to the first occurrence of the composite of venous thrombotic events (PE or clinically evident or silent DVT), the composite of arterial thrombotic events (ischemic stroke, SEE or ALI, or type 1 MI), each of the individual components of the primary efficacy outcome, and cardiovascular death. Nominal p-values are presented.

**Bayesian analysis**

In a Bayesian analysis of the primary composite endpoint, the probability that FDAC compared with SDPAC decreases the risk of venous and arterial thrombotic events in critically ill patients with COVID-19 was evaluated. A Bayesian robust mixture approach was used, which combines informative and non-informative normal distributions. The informative prior distribution had a
mean that is equal to the meta-analyzed log risk ratio derived from a fixed effects model of published outcomes trials of anticoagulation in critically ill patients with COVID-19. The non-informative distribution had a mean 0, which is consistent with equality between treatment arms, and a standard deviation set to be consistent with only 1 patient’s worth of information. The mixture prior distribution was updated with the observed COVID-PACT results to produce a posterior distribution of the treatment effect of FDAC compared with SDPAC.

The results from the time-to-first event analysis were incorporated into a Bayesian analysis of the efficacy of FDAC compared with SDPAC using a trial level meta-analysis of data from published outcome trials of full-dose anticoagulation in critically ill patients with COVID-19 to derive informative prior distributions. The analysis was conducted by replicating the Cox model for primary efficacy endpoint including prior information on the treatment effect. A normal distribution was used as prior for the log(HR) using results from an internally conducted meta-analysis on 2 published studies of FDAC versus SDPAC in critically ill COVID-19 patients (HR=0.60, 95% CI: 0.40-0.88) to derive a mean and standard deviation (Goligher EC et al. N Engl J Med 2021;385(9):777-789; Lemos ACB et al. Thromb Res 2020; 196:359-66). The posterior HR and the 95% credible interval were estimated using a Markov Chain Monte Carlo procedure with 12,000 iterations and excluding the first 2,000 iterations for burn-in. A sensitivity analysis was conducted for the primary efficacy endpoint using 4 published studies in critically ill COVID-19 patients, including 2 studies of intermediate dose anticoagulation versus SDPAC (meta-analysis prior HR=0.58, 95% CI: 0.42-0.78; Goligher EC et al. N Engl J Med 2021;385(9):777-789; Lemos ACB et al. Thromb Res 2020; 196:359-66; Sadeghipour P et al. JAMA 2021; 325(16):1620-30; Perepu US et al. J Thromb Haemost 2021; 19(9):2225-34). All-cause mortality was assessed in the same 4 trials using a Bayesian approach with a prior HR of 1.03 (95% CI: 0.92-1.16).

Interaction between factorial treatment comparisons

The quantitative interaction between the two treatment interventions, FDAC vs. SDPAC and antiplatelet therapy vs. no antiplatelet therapy, was tested and was found not to be significant. For the anticoagulation comparison, the interaction p-value by antiplatelet randomization was 0.73; for the antiplatelet comparison, the interaction p-value by anticoagulation randomization was 0.60.

Subgroup analyses

HRs and CIs for the overall analysis and subgroups are presented with forest plots. Cumulative incidence functions of the first occurrence of any event in the primary and secondary endpoints were calculated and plotted, for the overall analysis and for the individual components, according to treatment group.

Subgroup analyses to evaluate variation in treatment effect were performed based on tests for interaction using the Fine-Gray model. The p-values for the subgroup analyses were not adjusted for multiple comparisons as the tests are exploratory and are to be interpreted
descriptively. Event rates by treatment and HRs with 95% confidence intervals were reported for each subgroup.

Subgroup analyses were to be performed for the stratification factors as well as for the following variables:

- Age
- Sex
- Body-mass index (BMI)
- Diabetes mellitus
- History of cardiovascular disease
- D-dimer
- Need for mechanical ventilation at randomization
- High-sensitivity C-reactive protein (hsCRP)
- Prior history of VTE [not done due to small N with prior VTE]
ENDPOINT DEFINITIONS

DEATH

All deaths will be recorded in the eCRF. A subset relevant to the primary efficacy and safety endpoints will be adjudicated.

DEATH DUE TO ARTERIAL OR VENOUS THROMBOSIS

The classification of deaths as due to arterial or venous thrombotic events is aimed at capturing cases where such events are considered to be a major contributor to or direct precipitant of death in the setting of COVID-19. In cases where arterial and venous thrombotic contributions may be multifactorial, the CEC will select the major or primary acute contributor to death. It is appreciated that in most cases, the primary cause of death (i.e., the underlying disease that initiated the train of events resulting in death) is COVID-19.

All deaths in patients with a reported or CEC-identified arterial or venous thrombotic event will be reviewed.

Death due to arterial or venous thrombosis includes death where any of the following are determined to be a major contributor to death: acute myocardial infarction (MI), ischemic stroke, systemic embolic event (SEE) or acute limb ischemia (ALI) or venous thrombotic event (VTE) (i.e., pulmonary embolism).

1. Death due to Acute Myocardial Infarction refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, or heart failure) that is either a direct consequence of or substantially contributed to by an acute type 1 MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia.

   Note:
   - Acute type 1 MI should be verified to the extent possible by the diagnostic criteria outlined for acute type 1 MI or by autopsy findings showing recent MI or recent coronary thrombosis.
   - Death resulting from a procedure to treat a type 1 MI (PCI or CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI.

2. Death due to Ischemic Stroke refers to death after an ischemic stroke (with or without hemorrhagic transformation) that is either a direct consequence of or substantially contributed to by the stroke or a complication of the stroke.

3. Death due to SEE or ALI refers to death after a SEE or ALI event that is either a direct consequence of or substantially contributed to by the SEE or ALI event or a complication of the event.

4. Death due to VTE refers to death after a venous thrombotic event that is either a direct consequence of or substantially contributed to by the VTE or a complication of the event.

   Note:
- VTE should be verified by imaging (e.g. ultrasound or contrast-enhanced CT) or by autopsy findings showing a recent VTE.
- Death resulting from a procedure to treat a VTE (e.g. systemic or catheter-directed thrombolysis, surgical embolectomy or IVC filter placement), or to treat a complication resulting from VTE, should also be considered death due to VTE.

**FATAL BLEEDING**

Potential fatal bleeding events will be adjudicated. These potential events will be identified through investigator report and review of all deaths in patients with a bleeding event.

**Relationship of Death to Bleeding (categories are mutually exclusive)**

1. Fatal bleeding: death in which a bleeding event directly led to death. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death or such a poor neurologic prognosis that care was withdrawn, death from hemopericardium, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. Typically, these events are within 7 days of the bleed.

2. Bleeding contributed to death: a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death (typically within 30 days of the bleed), but bleeding was not directly and/or immediately related to subject’s death. An example of bleeding contributing to death is an intracranial hemorrhage that leads to intubation and mechanical ventilation which is then complicated by ventilator-associated pneumonia and death, or a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as “fatal”), then the cause of death must be recorded as something other than bleeding.

**CARDIOVASCULAR DEATH, NON-CARDIOVASCULAR AND UNKNOWN DEATHS**

Deaths will be classified as cardiovascular vs. non-cardiovascular or unknown by the local investigator, except that when the CEC has classified a death as due to an arterial or venous thrombotic event, the event will be deemed cardiovascular irrespective of the investigator’s classification.

**MYOCARDIAL INFARCTION**

*(Based on Thygeson K. et al. (2018). Fourth Universal Definition of Myocardial Infarction. Circulation, 138:e618-e651.)*

The term myocardial infarction (MI) (for types 1, 2 and 3 MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following:

- Symptoms of myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
• Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs)

Criteria for Universal Classification of Myocardial Infarction

Note: Although language below states troponin, CKMB can be used with similar cut points.

Type 1 Myocardial Infarction

MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion). The relative burden of atherosclerosis and thrombosis in the culprit lesion varies greatly, and the dynamic thrombotic component may lead to distal coronary embolization resulting in myocyte necrosis. Plaque rupture may not only be complicated by intraluminal thrombosis but also by hemorrhage into the plaque through the disrupted surface. This classification requires:

a) Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least one value >99th percentile URL and
b) At least 1 of the following:
   1) Symptoms of acute myocardial ischemia
   2) New ischemic ECG changes
   3) Development of pathological Q waves
   4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
   5) Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy*

*Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values.

Type 2 Myocardial Infarction

The pathophysiological mechanism leading to ischemic myocardial injury in the context of a mismatch between oxygen supply and demand. By definition, acute atherothrombotic plaque disruption is not a feature of type 2 MI. In patients with stable known or presumed CAD, an acute stressor such as an acute gastrointestinal bleed with a precipitous drop in hemoglobin or a sustained tachyarrhythmia with clinical manifestations of myocardial ischemia, may result in myocardial injury and a type 2 MI. These effects are due to insufficient blood flow to the ischemic myocardium to meet the increased myocardial oxygen demand of the stressor. Ischemic thresholds may vary substantially in individual patients depending upon the magnitude of the stressor, the presence of noncardiac comorbidities, and the extent of underlying CAD and cardiac structural abnormalities.

Type 2 MI classification requires:
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a) Detection of a rise and/or fall of cTn values with at least 1 value >99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, and

b) At least 1 of the following:
   1) Symptoms of acute myocardial ischemia
   2) New ischemic ECG changes
   3) Development of pathological Q waves
   4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

Type 3 Myocardial Infarction

Patients who suffer cardiac death with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4a Myocardial Infarction – related to percutaneous coronary intervention (PCI)

PCI-related MI ≤48 hours after the index procedure arbitrarily defined by an elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values. In patient with elevated pre-procedure cTn in whom the troponin level are stable (≤20% variation) or falling, the post-procedure troponin must rise by >20%. However, the absolute postprocedural value must still be at least 5 times the 99th percentile URL. This classification also requires at least (1) of the following:
   a) New ischemic ECG changes
   b) Development of new pathological Q waves
   c) Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization
   d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

Type 4b Myocardial Infarction – related to stent thrombosis

MI associated with stent/scaffold thrombosis as documented by coronary angiography or autopsy using the same criteria utilized for type 1 MI.
Type 4c Myocardial Infarction – related to (stent) restenosis

MI associated with focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying the same criteria utilized for type 1 MI.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with and occurring within 48 hours of CABG surgery with elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In patients with elevated pre-procedure cTn in whom levels are stable or falling, the post-procedure cTn level must rise by >20%. However, the absolute post-procedural value still must be >10 times the 99th percentile URL. This classification also requires at least (1) of the following:
  a) New pathological Q waves
  b) Angiographic documented new graft or new native coronary artery occlusion
  c) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

General Considerations

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

MYOCARDITIS

General: Myocarditis will be diagnosed in the setting of acute cardiac conditions without an alternative primary diagnosis (e.g. acute coronary syndrome, trauma).

Definitions:
  a. Clinical Presentation
     The clinical syndrome associated with myocarditis is broad and can encompass a spectrum of symptoms including palpitations, chest pain, acute or chronic heart failure as well as findings including pericardial effusion. Patients with symptoms that are entirely
attributable to another non-myocarditis diagnosis will not be counted as having a clinical syndrome.

b. **Biomarker Elevations**

Biomarkers for myocarditis are markers of myonecrosis including cardiac troponin, CK-MB or total CK. For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer’s listed reference limits in an assay’s instructions for use.

In general, cardiac troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

c. **Electrocardiogram (ECG) Changes**

Electrocardiographic (ECG) changes can be used to support or confirm a diagnosis of myocarditis. ECG changes should be dynamic (change from baseline) in a timeframe consistent with the onset of the myocarditis syndrome. Possible changes are broad including arrhythmias, ST-T wave abnormalities, PR segment changes, or new arrhythmias (e.g. new heart block or ectopy). ECG findings diagnostic for an alternative diagnosis (e.g. regional ST segment elevation in the context of known ACS) should not be counted as changes consistent with myocarditis.

**Definite Myocarditis:**

1) Any pathology diagnostic of myocarditis
2) Cardiac magnetic resonance imaging (CMR) diagnostic of myocarditis, a clinical syndrome and one of following:
   a) Elevated biomarker of cardiac myonecrosis
   b) ECG evidence of myo-pericarditis
3) New wall motion abnormality (WMA) on echocardiogram not explained by another diagnosis (e.g. ACS ruled out by angiography, trauma, stress induced cardiomyopathy, sepsis) and all of the following:
   a) Clinical syndrome consistent with myocarditis
   b) Elevated biomarker of cardiac myonecrosis
   c) ECG evidence of myo-pericarditis
   d) Negative angiography or other testing to exclude obstructive coronary disease
Probable Myocarditis: Any of the scenarios below that are not explained by another diagnosis (e.g. ACS, trauma, stress induced cardiomyopathy)
   1) CMR with findings diagnostic of myocarditis without any of the following:
      a) Clinical syndrome consistent with myocarditis
      b) Elevated biomarker of cardiac myonecrosis
      c) ECG evidence of myo-pericarditis

   2) Non-diagnostic CMR findings suggestive of myocarditis with any 1 of the following:
      a) Clinical syndrome consistent with myocarditis
      b) Elevated biomarker of cardiac myonecrosis
      c) ECG evidence of myo-pericarditis

   3) New WMA on echocardiogram with a clinical syndrome consistent with myocarditis and either:
      a) Elevated biomarker of cardiac myonecrosis
      b) ECG evidence of myo-pericarditis

   4) A scenario meeting criteria for Possible Myocarditis (see below) with 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) imaging showing patchy cardiac FDG uptake without another explanation

Possible Myocarditis: Any of the scenarios below that are not explained by another diagnosis (e.g. ACS, trauma, stress induced cardiomyopathy)
   1) Non-diagnostic CMR findings suggestive of myocarditis with none of the following:
      a) Clinical syndrome consistent with myocarditis
      b) Elevated biomarker of cardiac myonecrosis
      c) ECG evidence of myo-pericarditis

   2) New WMA on echocardiogram and 1 of the following:
      a) Clinical syndrome consistent with myocarditis
      b) ECG evidence of myo-pericarditis

   3) New elevated biomarker (beyond baseline) and 1 of the following:
      a) Clinical syndrome consistent with myocarditis
      b) ECG evidence of myo-pericarditis

For the purpose of this trial, myocarditis should be indicated in the setting of definite or probable myocarditis. Possible myocarditis should be adjudicated as “no myocarditis.”
For myocarditis, if other diagnostic information (e.g. cardiac PET scan or serial imaging) is available, it should be reviewed and integrated into the overall adjudication and may result in upgrade or downgrade by not more than 1 level.

**STRESS CARDIOMYOPATHY**

Stress cardiomyopathy will be confirmed in the presence of acute cardiac injury meeting each of the following criteria:

a) Does not meet criteria for myocardial infarction or myocarditis

b) Biomarker elevation (as defined for myocarditis) with a dynamic pattern (at least 20% change if serial values available)

c) Cardiac imaging with characteristic LV regional wall motion abnormalities: apical or mid-ventricular akinesis or hypokinesis in a circumferential pattern involving >1 coronary artery territory

Other diagnostic testing (i.e. cardiac MRI, Cath, CTA, and ECG findings) should be reviewed and integrated into the overall adjudication.

ECG abnormalities (ST-segment elevation, ST-segment depression, or deep symmetric T-wave inversions) that are out of proportion to the degree of elevation of cardiac biomarkers of necrosis are supportive of the diagnosis of stress cardiomyopathy.

**CEREBROVASCULAR EVENT**

**Stroke**

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Infarction may be documented by the following:

- brain imaging or,
- persistence of symptoms beyond 24 hours or
- death within 24 hours

AHA/ASA recommends duration ≥24 hours as an operational definition of persisting symptoms of stroke rather than TIA, based mostly on consensual practice rather than objective evidence.

**Classification:**

- **Ischemic Stroke** is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.
- **Hemorrhagic Stroke** is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Note: Subdural hematomas are intracranial hemorrhagic events and not strokes.

- **Undetermined Stroke** is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either (A) ischemic or (B) hemorrhagic.

**SYSTEMIC EMBOLIC EVENTS**

A Systemic Embolic Event (SEE) is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but will be classified respectively as stroke, myocardial infarction, and pulmonary embolism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion. Acute limb ischemia will overlap with this endpoint and can be a subset of SEE.

**ACUTE LIMB ISCHEMIA (ALI)**

Acute limb ischemia may be caused by arterial emboli, arterial thrombosis, arterial trauma from a vascular procedure, or other acute cause of malperfusion (e.g. microvascular thrombosis) with

- Clinical scenario suggesting a rapid or sudden decrease in limb perfusion AND
  - A. New pulse deficit with associated rest pain, pallor, paraesthesias, or paralysis,
  - Or
  - B. Confirmation of arterial obstruction by imaging (including ultrasound, CT, MRI, or conventional angiography), surgical findings, or pathology

**VENOUS THROMBOEMBOLISM**

**Deep Vein Thrombosis**

A deep venous thrombosis is defined as an acute or subacute thrombus in the venous system, including in the distal or proximal lower extremities, upper extremities, or central veins (e.g. internal jugular, superior vena cava, hepatic veins, inferior vena cava, or right heart) that is confirmed with imaging, such as ultrasound or venography (e.g. invasive, CT or MR).
Clinically evident DVT requires the presence of clinical signs or symptoms consistent with a DVT, including, but not limited to:
- Pain
- Swelling/edema
- Palpable cord

A clinically silent DVT is one that was identified through screening or surveillance imaging (e.g. day 10-14 bilateral lower extremity ultrasound) in the absence of clinical signs or symptoms of a DVT. Symptoms will be considered to be any VTE-related symptoms as reported by the investigator. The CEC will classify whether a lower-extremity DVT was proximal or distal (entirely below the popliteal vein).

**Pulmonary Embolism**
A pulmonary embolism is defined as an acute or subacute thrombus in the pulmonary arterial system or in-transit through the right-sided cardiac structures (e.g. right atrium or right ventricle). Pulmonary embolism may be confirmed in the following manner:
- Thrombus in the subsegmental or more proximal branches at autopsy
- An intraluminal defect in the subsegmental or more proximal branches on spiral CT scan or invasive pulmonary angiography
- A high probability finding on ventilation/perfusion lung scan
- Intracardiac thrombus in the right atrial, right ventricle or pulmonary arteries by echocardiogram, cardiac or chest CT or MRI.

Notes:
- Evidence of right ventricular dysfunction alone (i.e., without other imaging confirming the presence of a pulmonary embolism) is not sufficient to support a diagnosis of pulmonary embolism.
- Sudden cardiac arrest without imaging or autopsy confirmation of a hemodynamically significant pulmonary embolism (as defined above) is not sufficient to support a diagnosis of pulmonary embolism.

**BLEEDING**

Fatal/Life-threatening includes bleeding events that meet any of the following criteria
- Fatal bleeding – See Relationship of Death to Bleeding Section in Death Section
- Intracranial bleeding (ICH), including all CNS bleeding events (e.g. intraparenchymal, intraventricular, subarachnoid, subdural, and epidural).
- Intrapericardial bleeding with cardiac tamponade
- Hypovolemic shock or severe hypotension (systolic blood pressure < 90mm Hg) due to bleeding and requiring vasopressors/inotropes, fluid resuscitation, surgery, or other invasive intervention
- Transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding over 24 hours

**GUSTO Bleeding Classification:**
Severe: Clinically overt bleeding that was fatal, intracranial*, or that caused hemodynamic compromise requiring intervention (e.g. systolic blood pressure <90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support**, or procedural intervention)

Moderate: Clinically overt bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise (as defined above)

Mild: Clinically overt bleeding without blood transfusion or hemodynamic compromise

*Intracranial bleeding (ICH), including all CNS bleeding events (e.g. intraparenchymal, intraventricular, subarachnoid, subdural, and epidural).
**Need for vasopressor/inotropic support for hemodynamic compromise, even if blood pressure is >90 mm Hg with treatment.
SUPPLEMENTARY DATA

Bayesian Analyses
The Bayesian analysis for the primary efficacy endpoint yielded a hazard ratio of 0.56 with a 95% credible interval of 0.29-0.96. A sensitivity analysis including trials of intermediate-dose anticoagulation as well as FDAC in critically ill COVID-19 patients for the primary efficacy endpoint yielded a hazard ratio of 0.55 with a credible interval of 0.33-0.90. A Bayesian analysis for all-cause mortality yielded a hazard ratio of 0.82 with a credible interval of 0.55-1.16.
SUPPLEMENTARY FIGURES
FIGURE S1. Consort Diagram for Anticoagulation Randomization

398 Screened
390 Randomized
8 Screen Failed

197 Randomized to FDAC
6 Never Received FDAC

193 Randomized to SDPAC
2 Never Received SDPAC

Premature Discontinuation Before Study Completion
62 Premature d/c after initiating
32 Crossover to SDPAC
30 Discontinuation of all AC

Study Completion Status
0 Did not complete study
0 Withdrawal of consent
0 Loss to follow-up
55 Died during follow up
142 Completed study alive
29 In-hospital at day 28
113 Discharged alive prior to day 28

Premature Discontinuation Before Study Completion
72 Premature d/c after initiating
65 Crossover to FDAC
7 Discontinuation of all AC

Study Completion Status
0 Did not complete study
0 Withdrawal of consent
0 Loss to follow-up
62 Died during follow up
131 Completed study alive
24 In-hospital at day 28
107 Discharged alive prior to day 28

191 On-Treatment Analysis Population*
197 ITT Analysis Population

191 On-Treatment Analysis Population*
193 ITT Analysis Population

*On-Treatment Analysis Population includes all randomized patients who received at least one dose of randomly allocated strategy. Only those events/observations occurring during therapy with randomized treatment strategy or within 72 hours after the last dose of randomized strategy are included in the analysis set.
FIGURE S2. Consort Diagram for Antiplatelet Randomization

398 Screened
8 Screen failed for overall study
292 Randomized
98 not eligible for AP randomization

152 Randomized to clopidogrel
2 Never received clopidogrel

140 Randomized to no clopidogrel
0 Received clopidogrel

Premature Discontinuation Before Study Completion
47 Premature d/c after initiating
1 Temporary clopidogrel d/c >72 hrs then restarted
1 Crossover to other AP
45 Discontinuation of all AP

Premature Discontinuation Prior to Study Completion
0 Crossover to clopidogrel or other AP

Study Completion Status
0 Did not complete study
0 Withdrawal of consent
0 Loss to follow-up
41 Died during follow up
111 Completed study alive
16 In-hospital at day 28
95 Discharged alive prior to day 28

Study Completion Status
0 Did not complete study
0 Withdrawal of consent
0 Loss to follow-up
34 Died during follow up
106 Completed study alive
22 In-hospital at day 28
84 Discharged alive prior to day 28

150 On-Treatment Analysis Population*
152 ITT Analysis Population

140 On-Treatment Analysis Population*
140 ITT Analysis Population

*On-Treatment Analysis Population includes all randomized patients who received at least one dose of randomly allocated therapy. Only those events/observations occurring during therapy with randomized treatment strategy or within 72 hours after last dose of randomized strategy are included in the analysis set.
FIGURE S3. Cumulative Incidence Function Curves for Primary Efficacy Outcomes in Intention-to-Treat

Cumulative incidence function curves accounting for competing non-thrombotic deaths. Primary efficacy endpoint for full-dose anticoagulation (FDAC) versus standard dose prophylactic anticoagulation (SDPAC) (Panel A) and for clopidogrel versus no clopidogrel (Panel B) in the Intention-to-Treat analysis set.

S3A: Primary Efficacy Endpoint for Anticoagulant Randomization using ITT Analysis Set

A)

HR 0.72 (0.43, 1.19)
P-value=0.21
S3B: Primary Efficacy Endpoint for Antiplatelet Randomization using ITT Analysis Set

B)

**Cumulative Incidence Function for Primary Efficacy Endpoint**

**At-Risk**

|         | Clopi | No Clopi |
|---------|-------|----------|
| Days    | 152   | 140      |
| Days 7  | 120   | 115      |
| Days 14 | 53    | 59       |
| Days 21 | 25    | 36       |

**HR 1.13 (0.63, 2.03)**

**P-value=0.68**
FIGURE S4. Cumulative Incidence Function Curves for Key Secondary Safety Outcomes in On-Treatment

Cumulative incidence function curves accounting for competing non-thrombotic deaths in the on-treatment analysis set. Key secondary safety endpoint of GUSTO moderate or severe bleeding for full-dose anticoagulation (FDAC) versus standard dose prophylactic anticoagulation (SDPAC) (Panel A) and for clopidogrel versus no clopidogrel (Panel B) in the On-Treatment analysis set.

S4A: Key Secondary Safety Endpoint for Anticoagulation Randomization using On-Treatment Analysis Set

| At-Risk | FDAC | SDPAC |
|---------|------|-------|
| Days    | 0    | 163   | 137   |
|         | 7    | 78    | 56    |
|         | 14   | 29    | 22    |
|         | 21   |       | 17    |
|         | 28   |       | 13    |

HR 12.30 (1.64, 92.08)
P-value=0.002
S4B: Key Secondary Safety Endpoint for Antiplatelet Randomization using On-Treatment Analysis Set

**B)**

Cumulative Incidence Function for GUSTO Moderate or Severe Bleeding

- **No Clopidogrel**
- **Clopidogrel**

**HR 0.87 (0.30, 2.55)**

**P-value=0.83**

| Days | Clopi At-Risk | Clopi | No Clopi At-Risk | No Clopi |
|------|--------------|-------|-----------------|----------|
| 0    | 150          | 111   | 140             | 115      |
| 7    | 111          | 44    | 59              | 36       |
| 14   | 44           | 12    | 36              | 21       |
| 21   | 12           | 5     |                 |          |
| 28   | 5            |       |                 |          |
### TABLE S1: Advanced ICU Care During Follow-Up in the On-Treatment Population

|                        | Total for Anticoagulation Randomization (N=382) | Total for Antiplatelet Randomization (N=290) |
|------------------------|-----------------------------------------------|---------------------------------------------|
|                        | FDAC (N=191)                                  | SDPAC (N=191)                               | Clopidogrel (N=150) | No Clopidogrel (N=140) |
| Any Use Advanced Respiratory Therapy |                                  |                                          |                  |                        |
| Any high-flow nasal cannula | 190 (99.5)                                    | 191 (100)                                   | 150 (100)         | 139 (99.3)             |
| Any non-invasive positive pressure ventilation | 185 (97.4)                                    | 186 (97.4)                                   | 146 (97.3)         | 135 (97.1)             |
| Any invasive mechanical ventilation | 104 (54.7)                                    | 97 (50.8)                                    | 74 (49.3)          | 67 (48.2)              |
| Any venovenous EMCO      | 2 (1.1)                                       | 2 (1.0)                                     | 1 (0.7)           | 1 (0.7)                |
| Other Advanced ICU Care |                                  |                                          |                  |                        |
| IV vasoactive therapy    | 70 (36.6)                                     | 76 (39.8)                                    | 56 (37.3)         | 48 (34.3)              |
| Renal replacement therapy | 15 (7.9)                                      | 20 (10.5)                                    | 16 (10.7)         | 9 (6.4)                |

*P-value > 0.05 for all comparisons.*
### TABLE S2. Baseline Characteristics in ITT Analytic Population

| Demographics | Total for Anticoagulation Randomization (N=390) | Total for Antiplatelet Randomization (N=292) |
|--------------|-----------------------------------------------|---------------------------------------------|
|              | FDAC (N=197) | SDPAC (N=193) | Clopidogrel (N=152) | No Clopidogrel (N=140) |
| Age, years   | 59 [51, 70] | 62 [51, 68] | 58 [49, 67] | 58 [47, 67] |
| Age > 65     | 70 (36)    | 71 (37)    | 44 (29)    | 39 (28)    |
| Male         | 122 (62)   | 109 (57)   | 93 (61)    | 80 (57)    |
| Race         |            |            |            |            |
| White        | 135 (74)   | 140 (79)   | 117 (83)†  | 91 (71)†   |
| Hispanic     | 31 (18)    | 27 (16)    | 28 (21)    | 25 (20)    |
| BMI, kg/m²   | 34 [29, 40] | 34 [29, 41] | 34 [29, 42] | 34 [29, 40] |
| BMI ≥ 30     | 126 (64)   | 137 (71)   | 105 (69)   | 97 (70)    |
| Medical History |         |            |            |            |
| Hypertension | 109 (55)   | 119 (62)   | 77 (51)    | 76 (54)    |
| Diabetes     | 75 (38)†   | 49 (25)†   | 40 (26)    | 41 (29)    |
| ASCVD        | 29 (15)    | 25 (13)    | 10 (6.6)   | 9 (6.4)    |
| Active cancer| 10 (5.1)   | 7 (3.6)    | 8 (5.3)    | 5 (3.6)    |
| Current or past smoking | 84 (43)   | 73 (38)    | 56 (37)    | 49 (35)    |
| Chronic kidney disease | 20 (10)    | 20 (10)    | 10 (6.6)   | 11 (7.9)   |
| Pulmonary disease | 45 (23)    | 36 (19)    | 31 (20)    | 29 (21)    |
| COVID-19 Status at Randomization |         |            |            |            |
| Time from admission to randomization, days | 2.3 [1.6-3.7] | 2.1 [1.5-3.3] | 2.1 [1.6-3.6] | 2.1 [1.4-3.2] |
| WHO Ordinal Scale |         |            |            |            |
| No oxygen therapy | 0 (0)   | 0 (0)     | 0 (0)     | 0 (0)     |
| Oxygen by mask or NC | 3 (1.5) | 1 (0.5) | 1 (0.7) | 3 (2.1) |
| NIV or HFNC | 156 (79)† | 170 (88)† | 130 (86) | 115 (82) |
| Invasive ventilation | 38 (19)† | 22 (11)† | 21 (14) | 22 (16) |
| P/F ≥ 150 | 10 (5.1) | 5 (2.6) | 5 (3.3) | 8 (5.7) |
| P/F < 150 or vasopressor | 25 (12.7) | 14 (7.3) | 14 (9.2) | 11 (7.9) |
| P/F < 150 and organ support* | 3 (1.5) | 3 (1.6) | 2 (1.3) | 3 (2.1) |
| Laboratories |         |            |            |            |
| eGFR, ml/min/1.73² | 88 [66, 102] | 86 [66, 101] | 91 [75, 107] | 90 [69, 103] |
| Hemoglobin, g/dL | 13.2 [11.9, 14.2] | 13.0 [11.9, 14.3] | 13.2 [12.2, 14.2] | 13.3 [11.8, 14.3] |
| D-dimer, ng/mL | 962 [616, 1780] | 950 [546, 1780] | 807 [500, 1450] | 902 [551, 1439] |

Counts (percent) or median (25th, 75th percentile) presented. FDAC indicates full dose anticoagulation; SDPAC, standard dose prophylactic anticoagulation; ASCVD, atherosclerotic cardiovascular disease; WHO, World Health Organization; NC, nasal canula; HFNC, high-flow nasal canula; P/F, PaO₂ over fraction inspired oxygen; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal. *organ support refers to vasopressor, renal replacement therapy or extracorporeal membrane oxygenation. †p-value for comparison between arms within strategy < 0.05.
TABLE S3. Antithrombotic Therapy Prior to Randomization in On-Treatment Population

| Antithrombotic therapy prior to Hospitalization | Total for Anticoagulation Randomization (N=382) | Eligible for Antiplatelet Randomization (N=290) |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                               | FDAC (N=191)                                   | Clopidogrel (N=150)                           |
|                                               |                                               | No Clopidogrel (N=140)                        |
| Full dose anticoagulation                     | 0 (0)                                         | 0 (0)                                         |
| Any antiplatelet therapy                      | 44 (23.0)                                     | 6 (4.0)                                      |
| Aspirin                                       | 38 (19.9)                                     | 6 (4.0)                                      |
| Clopidogrel                                   | 6 (3.1)                                       | 1 (0.7)                                      |
| Other                                         | 0 (0)                                         | 0 (0)                                         |

Antithrombotic therapy in-hospital prior to randomization

| Any anticoagulation                          | 187 (97.9)                                     | 144 (96.0)                                   |
| Low dose prophylaxis                         | 128 (68.4)                                     | 98 (68.1)                                    |
| Intermediate dose prophylaxis               | 50 (26.7)                                      | 39 (27.1)                                    |
| Full dose anticoagulation                    | 9 (4.8)                                       | 7 (4.9)                                      |

Indication for FDAC

| Prophylaxis only                             | 7 (77.8)                                       | 6 (85.7)†                                   |
| Any antiplatelet                             | 46 (24.1)                                      | 3 (2.0)                                     |

Counts (percent) or median (25th, 75th percentile) presented. FDAC indicates full dose anticoagulation. †p-value < 0.05.
TABLE S4. Initial Anticoagulant Used After Randomization in On-Treatment Population

| Anticoagulant                        | Total for Anticoagulation Randomization (N=382) | Eligible for Antiplatelet Randomization (N=288) | Not Eligible for Antiplatelet Randomization (N=94) |
|--------------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------------------------------------|
|                                      | FDAC (N=191) SDPAC (N=191)                      | FDAC (N=143) SDPAC (N=145)                      | FDAC (N=48) SDPAC (N=46)                         |
| IV UFH or subcutaneous heparin       | 36 (18.8) 31 (16.2)                             | 21 (14.7) 18 (12.4)                             | 15 (31.3) 13 (28.3)                             |
| Low molecular weight heparin         | 155 (81.2) 159 (83.2)                           | 122 (85.3) 126 (86.9)                           | 33 (68.8) 33 (71.7)                             |
| Other                                | 0 (0) 1 (0.5)                                  | 0 (0) 1 (0.7)                                   | 0 (0) 0 (0)                                     |

Counts (percent) presented.

p-value

0.49

0.53

0.75
TABLE S5. Study Drug Administration in the On-Treatment Population

| Duration of exposure to any anticoagulation* | Total for Anticoagulation Randomization (N=382) | Total for Antiplatelet Randomization (N=290)† |
|---------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Median [IQR], days                          | FDAC (N=191)                                  | SDPAC (N=191)                               |
|                                             | 10.6 [7.0, 17.3]                              | 10.6 [6.0, 17.5]                            |
|                                             | 0.51                                          |                                             |
| Duration of exposure to randomized therapy strategy** | Median [IQR], days | 9.9 [6.2, 14.3]                              | 6.6 [3.5, 12.8] |
|                                             | <0.0001                                       |                                             |
|                                             | 8.6 [4.6, 13.7]                               |                                             |
|                                             | 4 days                                        |                                             |
|                                             | 26 (14)                                       | 57 (30)                                     |
|                                             | 0.0004                                        |                                             |
|                                             | 35 (24)                                       |                                             |
|                                             | 4-<10 days                                    |                                             |
|                                             | 72 (38)                                       | 72 (38)                                     |
|                                             | 0.0004                                        |                                             |
|                                             | 55 (37)                                       |                                             |
|                                             | 10-14 days                                    |                                             |
|                                             | 40 (21)                                       | 24 (13)                                     |
|                                             | 25 (17)                                       |                                             |
|                                             | >14 days                                      |                                             |
|                                             | 53 (28)                                       | 38 (20)                                     |
|                                             | 34 (23)                                       |                                             |
| Crossover or discontinuation                | 62 (33)                                       | 71 (37)                                     |
|                                             | 0.33                                          | 46 (31)                                     |
| Discontinued all meds in class              | 30 (16)                                       | 7 (3.7)                                     |
|                                             | <0.0001                                       | 46 (31)                                     |
| Crossover to the alternative strategy       | 32 (17)                                       | 64 (34)                                     |
|                                             | 0.0002                                        | N/A                                         |
| Reason for discontinuation or crossover     | <0.0001                                       |                                             |
| Provider preference                         | 7 (11)                                        | 22 (31)                                     |
| New indication for FDAC or AP               | N/A                                           | 42 (59)                                     |
| New contraindication to AC or AP            | 11 (18)                                       | 2 (2.8)                                     |
| Concern for clinically significant bleeding | 36 (58)                                       | 2 (2.8)                                     |
| Coagulation parameter met study criteria for discontinuation | 1 (1.6)                          | 0 (0)                                        |
|                                             | 0 (0)                                         |                                             |
| Patient wishes                              | 4 (6.5)                                       | 3 (4.2)                                     |
| Unknown                                     | 3 (4.8)                                       | 0 (0)                                       |
| Transitions in therapy within randomized strategy | 51 (27)                        | 35 (18)                                     |

Counts (percent) or median [25th, 75th percentile] presented unless otherwise indicated. FDAC indicates full dose anticoagulation; SDPAC, standard dose prophylactic anticoagulation; AP, antiplatelet; IQR, interquartile range; SD, standard deviation. †There were no crossovers to clopidogrel in patients randomized to no antiplatelet therapy. *Defined as time from randomization to premature discontinuation of all anticoagulation or study completion. **Defined as time from randomization to crossover to other strategy, premature discontinuation of all anticoagulation or study completion.
### TABLE S6. Study Drug Management in Intention-to-Treat Population

| Duration of exposure to initial randomized therapy | Total for Anticoagulation Randomization (N=390) | Total for Antiplatelet Randomization (N=292) |
|--------------------------------------------------|-----------------------------------------------|---------------------------------------------|
|                                                  | FDAC (N=197)      | SDPAC (N=193)   | p-value | Clopidogrel (N=152) | No Clopidogrel (N=140) | p-value |
| Median [IQR], days                               | 10.0 [6.3, 14.3] | 6.6 [3.5, 12.8] | <0.0001 | 8.6 [4.6, 13.7]     | 0 (0)                    | -       |
| <4 days                                          | 26 (13)           | 58 (30)         | 0.0002  | 35 (24)             | 0 (0)                    | -       |
| 4-<10 days                                       | 72 (37)           | 72 (38)         | 0.0002  | 55 (37)             | 0 (0)                    | -       |
| 10-14 days                                       | 42 (22)           | 24 (13)         |         | 25 (17)             | 0 (0)                    |         |
| >14 days                                         | 54 (28)           | 38 (20)         |         | 34 (23)             | 0 (0)                    |         |
| Crossover or discontinuation                     | 62 (32)           | 72 (37)         | 0.23    | 46 (30)             | 0 (0)                    | <0.0001 |
| Discontinued all meds in class                   | 30 (15)           | 7 (3.6)         | <0.0001 | 46 (30)             | N/A                      | -       |
| Crossover to the alternative strategy            | 32 (16)           | 65 (34)         | <0.0001 | N/A                 | 0 (0)                    | -       |
| Reason for discontinuation or crossover          |                  |                  | <0.0001 |                    |                          | 0.75    |
| Provider preference                              | 7 (11)            | 23 (32)         |         | 13 (28)             | 0 (0)                    |         |
| Patient wishes                                   | 4 (6.5)           | 3 (4.2)         |         | 1 (2.2)             | 0 (0)                    |         |
| New indication for FDAC or AP                    | N/A               | 42 (58)         |         | N/A                 | 0 (0)                    |         |
| New contraindication to AC or AP                 | 11 (18)           | 2 (2.8)         |         | 10 (22)             | N/A                      |         |
| Coagulation parameter met study criteria for discontinuation | 1 (1.6) | 0 (0) | | 0 (0) | N/A | |
| Concern for clinically significant bleeding      | 36 (58)           | 2 (2.8)         |         | 21 (46)             | N/A                      |         |
| Unknown                                          | 3 (4.8)           | 0 (0)           |         | 1 (2.2)             | 0 (0)                    |         |
| Transitions in therapy within randomized strategy| 51 (26)           | 36 (19)         | 0.086   | N/A                 | N/A                      | -       |

Counts (percent) or median [25th, 75th percentile] presented unless otherwise indicated. FDAC indicates full dose anticoagulation; SDPAC, standard dose prophylactic anticoagulation; AP, antiplatelet; IQR, interquartile range; SD, standard deviation.
TABLE S7. Exploratory Analysis of Primary and Key Secondary Efficacy Outcomes Using Win Ratio Approach with All-Cause Mortality in the On-Treatment Analytic Set

| Anticoagulation Strategy | FDAC Wins (%) | SDPAC Wins (%) | Stratified Win Ratio (95% CI) (FDAC/SDPAC) | P-value |
|--------------------------|---------------|----------------|------------------------------------------|---------|
| On-Treatment             |               |                |                                          |         |
| Primary efficacy         | 7,667 (21.0)  | 4,406 (12.1)   | 1.74 (1.13, 2.67)                        | 0.011   |
| Key secondary efficacy   | 6,856 (18.8)  | 4,106 (11.3)   | 1.64 (1.05, 2.56)                        | 0.03    |

On-treatment analysis set used with events included that occurred while on randomized treatment strategy or within 72 hours of last dose of randomized treatment strategy. Primary outcome is a hierarchical composite of venous and arterial thrombotic events in the following order: 1) all-cause mortality, 2) pulmonary embolism, 3) clinically evident DVT, 4) type 1 MI, 5) ischemic stroke, 6) SEE or ALI, and 7) clinically silent DVT. Key secondary outcome is a hierarchical composite of clinically evident venous and arterial thrombotic events, including the following events: 1) all-cause mortality, 2) pulmonary embolism, 3) clinically evident DVT, 4) type 1 MI, 5) ischemic stroke, and 6) SEE or ALI.
TABLE S8. Cumulative Incidence Functions at Day 14 for Primary and Key Secondary Efficacy and Safety Outcomes in On-Treatment Analysis Set

|                                | Total for Anticoagulation Randomization (N=382) | Total for Antiplatelet Randomization (N=290) |
|--------------------------------|------------------------------------------------|---------------------------------------------|
|                                | FDAC (N=191) | SDPAC (N=191) | Clopidogrel (N=150) | No Clopidogrel (N=140) |
| Efficacy Endpoints             |              |               |                    |                         |
| Primary efficacy               | 13.4         | 20.2          | 14.7               | 18.3                    |
| Key secondary efficacy         | 8.7          | 15.7          | 13.7               | 10.5                    |
| Safety Endpoints               |              |               |                    |                         |
| Primary safety                 | 2.3          | 0.5           | 1.4                | 1.4                     |
| Secondary safety               | 8.9          | 0.5           | 6.2                | 7.9                     |

14-day cumulative incidence function rate presented. On-treatment analysis set used with events included that occurred while on randomized treatment strategy or within 72 hours of last dose of randomized treatment strategy. Primary efficacy endpoint is a composite of venous and arterial thrombotic events (death due to venous or arterial events, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI, and clinically silent DVT). Key secondary efficacy endpoint is a composite of clinically evident venous and arterial thrombotic events (death due to venous or arterial events, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI). The primary safety endpoint is a composite of fatal or life-threatening bleeding. The secondary safety endpoint is a composite of GUSTO moderate or severe bleeding.
### TABLE S9. Efficacy and Safety Outcomes Using Time-to-Event Approach in Intention-to-Treat Analysis Set

|                              | Total for Anticoagulation Randomization (N=390) | Total for Antiplatelet Randomization (N=292) |
|------------------------------|-----------------------------------------------|--------------------------------------------|
|                              | FDAC (N=197) | SDPAC (N=193) | Hazard Ratio (95% CI) | P-value | Clopidogrel (N=152) | No Clopidogrel (N=140) | Hazard Ratio (95% CI) | P-value |
| **Efficacy Endpoints**       |              |              |                     |         |                  |                          |                     |         |
| Primary efficacy             | 26 (13.2)    | 32 (16.6)    | 0.72 (0.43, 1.19)   | 0.21    | 23 (15.1)         | 21 (15.0)               | 1.13 (0.63, 2.03)     | 0.68    |
| Key secondary efficacy       | 18 (9.1)     | 25 (13.0)    | 0.66 (0.36, 1.20)   | 0.17    | 20 (13.2)         | 13 (9.3)                | 1.55 (0.77, 3.10)     | 0.21    |
| **Efficacy Endpoint Components** |        |              |                     |         |                  |                          |                     |         |
| Venous thrombotic events (VTE) | 25          | 30           | 0.74 (0.44, 1.24)   | -       | 22                | 21                       | 1.08 (0.60, 1.95)     | -       |
| Arterial thrombotic events (ATE) | 1           | 3            | 0.36 (0.03, 3.66)   | -       | 2                 | 0                        | -                    | -       |
| Pulmonary embolism           | 7            | 8            | 0.81 (0.29, 2.24)   | -       | 7                 | 6                        | 1.14 (0.38, 3.42)     | -       |
| Clinically evident DVT       | 12           | 17           | 0.65 (0.31, 1.36)   | -       | 13                | 9                        | 1.45 (0.62, 3.41)     | -       |
| Clinically silent DVT        | 8            | 7            | 0.98 (0.36, 2.65)   | -       | 3                 | 8                        | 0.42 (0.11, 1.64)     | -       |
| Death due to VTE or ATE      | 1            | 1            | -                   | -       | 1                 | 0                        | -                    | -       |
| Type 1 MI                    | 1            | 0            | -                   | -       | 0                 | 0                        | -                    | -       |
| Ischemic stroke              | 0            | 1            | -                   | -       | 1                 | 0                        | -                    | -       |
| SEE or ALI                   | 0            | 2            | -                   | -       | 1                 | 0                        | -                    | -       |
| All-cause mortality          | 55 (27.9)    | 62 (32.1)    | 0.80 (0.56, 1.16)   | 0.24    | 41 (27.0)         | 34 (24.3)               | 1.33 (0.84, 2.09)     | 0.22    |
| **Safety Endpoints**         |              |              |                     |         |                  |                          |                     |         |
| Primary safety               | 4 (2.0)      | 2 (1.0)      | 2.05 (0.39, 10.74)  | 0.39    | 2 (1.3)           | 2 (1.4)                 | 0.98 (0.14, 7.03)     | 0.99    |
| Fatal bleeding               | 0            | 0            | -                   | -       | 0                 | 0                        | -                    | -       |
| Life-threatening bleeding     | 4            | 2            | -                   | -       | 2                 | 2                        | -                    | -       |
| Secondary safety             | 15 (7.6)     | 6 (3.1)      | 2.37 (0.91, 6.14)   | 0.066   | 7 (4.6)           | 9 (6.4)                 | 0.79 (0.29, 2.13)     | 0.64    |
| GUSTO severe bleeding        | 4            | 2            | -                   | -       | 2                 | 2                        | -                    | -       |
| GUSTO moderate bleeding      | 11           | 4            | -                   | -       | 5                 | 7                        | -                    | -       |

Number of events +/- n/N rate presented. Primary efficacy endpoint is a composite of venous and arterial thrombotic events (death due to venous or arterial events, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI, and clinically silent DVT). Key secondary efficacy endpoint is a composite of clinically evident venous and arterial thrombotic events (death due to venous or arterial events, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, SEE or ALI). Venous thrombotic events include PE and any DVT (clinically evident and clinically silent). Arterial thrombotic events include ischemic stroke, SEE, ALI or type 1 MI. The primary safety endpoint is a composite of fatal or life-threatening bleeding. The secondary safety endpoint is a composite of GUSTO moderate or severe bleeding. Hazard ratio and 95% confidence intervals are from Fine and Gray’s subdistribution regression accounting for any non-thrombotic death as a competing event with stratification by randomization stratification factors (status of receiving or planned to receive antiplatelet therapy at screening and status of randomized to antiplatelet therapy). P-values are from the stratified Gray’s test for equality of cumulative incidence functions. All-cause mortality analysis used Cox proportional hazards regression with stratification by randomization stratification factors; p-values are from the stratified log-rank test.
### TABLE S10. Adverse Events in the ITT Population

| Event                                      | Total for Anticoagulation Randomization (N=390) | Total for Antiplatelet Randomization (N=292) | P-value |
|--------------------------------------------|------------------------------------------------|---------------------------------------------|---------|
|                                            | Full Dose Anticoagulation (N=197) | Standard Dose Prophylactic Anticoagulation (N=193) | P-value | Clopidogrel (N=152) | No Clopidogrel (N=140) | P-value |
| Any AE                                     | 66 (33.5) | 50 (25.9) |                  | 0.10 | 43 (28.3) | 44 (31.4) |                  | 0.56 |
| Adverse event leading to study drug regimen discontinuation | 43 (21.8) | 29 (15.0) |                  | 0.083 | 26 (17.1) | 0 (0) | <0.0001 |
| Any SAE                                    | 27 (13.7) | 21 (10.9) |                  | 0.40 | 19 (12.5) | 14 (10.0) |                  | 0.50 |
| Serious adverse event thought to be related to study drug regimen | 16 (8.1) | 3 (1.6) |                  | 0.0016 | 6 (3.9) | 0 (0) | 0.02 |
| Bleeding                                   | 12 (6.1) | 2 (1.0) |                  | - | 5 (3.3) | 0 (0) | - |
| Non-bleeding                               | 4 (2.0) | 1 (0.5) |                  | - | 1 (0.6) | 0 (0) | - |
| Unexpected event                           | 0 (0) | 0 (0) |                  | - | 0 (0) | 0 (0) | - |

*Number of events during follow up and incidence rate (n/N) presented. All events are investigator-reported.*