Supplemental Online Content

REMAP-CAP Writing Committee; REMAP-CAP Investigators. Effect of antiplatelet therapy on survival and organ support–free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. Published online March 22, 2022. doi:10.1001/jama.2022.2910

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

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eAppendix 1. Supplementary Methods

1.1 Additional information about REMAP-CAP general design

REMAP-CAP is an international, multicenter, open-label adaptive platform trial to determine best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings. A full description of the trial design is provided elsewhere[1] and below is a short summary.

The trial uses a novel design entitled a randomized embedded multifactorial adaptive platform (REMAP).[2] The design has five key features: randomization, allowing causal inference; embedding of study procedures into routine clinical care, facilitating enrollment and generalizability; a multifactorial statistical model comparing multiple interventions across multiple patient subgroups; response-adaptive randomization with preferential assignment to those interventions that appear most favorable after regular adaptive analyses, and; a platform structured to permit continuous, potentially perpetual, enrollment.

Once the Covid-19 outbreak began, a new pandemic stratum was added within REMAP-CAP. Specifically, all patients hospitalized with suspected or proven Covid-19 are assigned to the pandemic stratum. They are further classified as being in either moderate (non-critically ill) or severe (critically ill) disease state. Severe disease state is defined by receiving respiratory or cardiovascular organ failure support in an intensive care unit (ICU). Respiratory support is defined as heated high flow oxygen delivery at ≥ 30 liters/min and FiO2 0.40, non-invasive positive pressure ventilation, or invasive mechanical ventilation. All other hospitalized patients are defined as being in the moderate state.

This report relates to the analysis of the in the Antiplatelet Therapy domain up to June 23, 2021. Other domains open to randomization within the pandemic stratum moderate and severe state up to this date were:

- Corticosteroid domain (open March 9, 2020, closed June 17, 2020)
- Immune Modulation version 1 domain (open April 19, 2020, closed April 10, 2021)
- Immune Modulation version 2 domain (open October 21, 2020)
- Covid-19 Antiviral domain (open March 9, 2020)
- Covid-19 Immunoglobulin domain (open April 29, 2020, and closed January 18, 2021)
- Therapeutic Anticoagulation version 1 domain (open May 6, 2020, and closed January 22, 2021)
- Therapeutic Anticoagulation version 2 (open April 7, 2021)
- Vitamin C domain (open October 16, 2020)
- Simvastatin domain (open October 10, 2020)
- ACE2 Renin Angiotensin System (RAS) domain (open Jan 25, 2021)

- Mechanical Ventilation (open March 28, 2021)

1.2 REMAP-CAP Eligibility Criteria for suspected or proven Covid-19

Platform inclusion criteria:

- Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (Covid-19) infection

Platform exclusion criteria:

- Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
- Patient is expected to be discharged from hospital today or tomorrow
- More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
- Previous participation in this REMAP within the last 90 days

Antiplatelet Therapy domain specific inclusion criteria:

- Covid-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Antiplatelet Therapy domain specific exclusion criteria:

- More than 48 hours has elapsed since ICU admission
- Clinical or laboratory bleeding risk or both that is sufficient to contraindicate antiplatelet therapy
- Patient is already receiving antiplatelet therapy or NSAID (non-steroidal anti-inflammatory drug) or a clinical decision has been made to commence antiplatelet or NSAID therapy
- Enrollment in a trial evaluating anticoagulation or antiplatelet therapy for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
- Patients older than 75 years AND otherwise eligible for the Therapeutic Anticoagulation Domain
- Creatinine Clearance <30 ml/min, or receiving renal replacement therapy or ECMO
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention specific exclusion criteria:

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent.
- Known or suspected pregnancy will result in exclusion from the P2Y12 inhibitor intervention
- Administration or intention to administer lopinavir/ritonavir will result in exclusion from the P2Y12 inhibitor intervention at sites that are using clopidogrel and ticagrelor as the P2Y12 inhibitor

1.3 Outcomes

1.3.1 Secondary outcomes:

- Survival to hospital discharge (dichotomous)
- 90-day mortality (time to event)
- Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death among those not on invasive mechanical ventilation or ECMO at baseline (dichotomous)
- Vasopressor/Inotrope-Free days
- Respiratory Support-Free days
- Duration of ICU stay
- Duration of hospital stay
- At least one serious adverse event
- WHO ordinal scale (range: 0-8, where 0 = no illness, 1-7 = increasing level of care, and 8 = death) assessed at day 14.[3] In this analysis categories 0,1,2 have been condensed into one category for all patients discharge from hospital.
- Major bleeding on or before day 14 as defined according to International Society of Thrombosis and Haemostasis (ISTH) criteria in non-surgical patients (see below for definition)
- Fatal bleeding on or before day 14
- Intracranial hemorrhage on or before day 14
- Deep venous thrombosis
- Pulmonary embolism
- Ischemic cerebrovascular event
- Acute myocardial infarction
- All thrombotic events
- Venous thrombotic event
- Arterial thrombotic event
- All thrombotic event or death
- Venous thrombotic event or death
- Arterial thrombotic event or death

1.3.2 Secondary outcome definitions

Major bleeding (according to International Society of Haemostasis and Thrombosis – ISTH - definition)[4]

Fatal bleeding, symptomatic or clinically manifest bleeding in a critical are or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome),

OR

Bleeding causing a fall in hemoglobin of ≥2g/dL, or leading to the transfusion of 2 or more whole blood or red cell units

Acute Myocardial Infarction (AMI)

The definition of an AMI requires detection of rise and fall or just a fall of cardiac biomarkers, such as any form of troponin assay, with at least one value above the upper reference limit (URL) PLUS evidence of myocardial ischemia with at least one of the following:

- Symptoms of cardiac ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):

- ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points of ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R waves or R/S ratio >1.

**Pathological Q waves:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 an any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, aVF; V7-V9).
- R-wave ≥ 0.04 s in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Confirmed deep vein thrombosis

Proximal deep vein thrombosis (DVT) is a thrombus located in axillary vein or more proximal, including the internal jugular vein, or a thrombus located in popliteal vein or more proximal. Confirmation requires imaging with techniques that include ultrasound or CT scan. Distal DVTs were excluded.

Confirmed pulmonary embolus

Segmental or multi-sub-segmental pulmonary emboli that is confirmed using CT pulmonary angiography or has a high probability ventilation: perfusion lung scan

Confirmed ischemic cerebrovascular event

An acute ischemic stroke is defined as central nervous system infarction defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on:

- Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; OR
- Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes types I and II hemorrhagic infarctions) OR
- Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

Mesenteric ischemia

Mesenteric Ischemia for arterial or venous mesenteric ischemia diagnosed on contrast imaging by CT or angiography or diagnosed at laparotomy or via laparoscopy.

Limb ischemia

Limb ischemia if evidence of acute limb ischemia sufficient to require surgical revascularization including bypass procedure, intraarterial thrombolysis, or embolectomy; amputation of a limb due to acute ischemia; or decision to withdraw of limit treatment because of acute limb ischemia. It is not sufficient for there to be evidence of limb ischemia that does not result in surgical intervention or determine a decision to institute palliative care. Ischemia attributed to vasopressor medication is insufficient unless also meets the above definition.

Systemic arterial thrombosis or embolism

Clinical evidence of sudden significant worsening of organ or limb perfusion and either confirmation of arterial obstruction (e.g. by imaging, hemodynamics, intraoperative findings or pathology evaluation) or requirement for intervention (thrombolysis, thrombectomy or urgent bypass).

All thrombotic events

A composite dichotomous endpoint of deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular event, myocardial infarction, or systemic arterial thromboembolism diagnosed at any time during the index hospitalization or death in hospital

1.4 Classification of anticoagulation dosing

The dose of anticoagulation administered for all patients was classified as low dose prophylaxis, intermediate dose prophylaxis and therapeutic using the categories outlined in eTable 1. Patients who received a dose higher than intermediate, but lower than therapeutic dose, were classified as subtherapeutic. The first dose administered, excluding one-off or stat doses, after randomization and within first 48 hours was used to classify anticoagulation dosing. Anticoagulant doses were classified as either therapeutic or less than therapeutic for the analysis of interaction between antiplatelet intervention and anticoagulation strategy (Data presented in eTable 9).

eTable 1. Categories of Anticoagulation Intensity According to Anticoagulant and Dose

	Low dose prophylaxis	Intermediate dose prophylaxis	Therapeutic
Enoxaparin			
Weight <50kg			
CrCl ≥ 30 ml/min	20 or 30mg daily	1 mg/kg daily OR 20-40 mg BID	1 mg/kg BID OR ≥ 1.5 mg/kg daily
BMI < 40kg/m^2 OR weight 50-120 kg			
CrCl ≥ 30 ml/min	40mg daily	40mg OR 0.5 mg/kg BID OR 1 mg/kg daily	1 mg/kg BID OR 1.5 mg/kg daily
BMI ≥ 40 kg/m^2 OR weight ≥ 120 kg			
CrCl ≥ 30 ml/min	30-40 mg BID OR 40-60 mg daily	60mg OR 0.5 mg/kg BID OR 1 mg/kg daily	1 mg/kg BID or ≥ 1.5 mg/kg daily
Unfractionated heparin			
BMI < 40kg/m^2 OR weight < 120kg	2500-5000 units BID or TID	7500 units TID	Continuous infusion per protocol
BMI > 40kg/m^2 OR weight > 120kg	5000-7500 units BID or TID	10,000 units BID	Continuous infusion per protocol
Dalteparin			
BMI <40 kg/m^2 OR weight < 120 kg			
CrCl ≥ 30ml/min	2500-5000 units daily	5000 units BID OR 7500 units daily	100 units/kg BID OR 200 units/kg daily OR ≥ 18000 daily
BMI ≥ 40kg/m^2 OR weight ≥ 120kg			
CrCl ≥ 30 ml/min	5000-7500 units daily	5000-7500 units BID OR 100 units/kg daily	100 units/kg BID OR 200 units/kg daily OR ≥ 18000 daily
Tinzaparin			
BMI < 40kg/m^2 OR weight 50-120kg	≤ 4500 units daily	≤ 4500 units BID	175 units/kg daily OR ≥ 80 units/kg BID
BMI ≥ 40kg/m^2 OR weight ≥ 120kg	4500-8000 units daily	≤ 8000 units BID	175 units/kg daily OR ≥ 80 units/kg BID

Patients with CrCl < 30 mL/min were excluded from participation in the antiplatelet domain

1.5 Additional Statistical Methods:

Analysis populations:

As described in the Statistical Analysis Plan, the primary analysis was conducted on all patients with confirmed or suspected Covid-19 randomized in one or more domains within the pandemic stratum. Patients in both critically ill and non-critically ill groups were included in the model. The model estimated treatment effects for each of the patient groups (critically ill and non-critically ill), utilizing a Bayesian hierarchical approach that shares information across groups. When consistent effects are observed for the groups, the posterior distribution for each intervention group effect is shrunk towards the overall estimate, resulting in borrowing between groups. The model estimated a pooled treatment effect of the antiplatelet interventions in critically ill patients (following the equivalence trigger) and nested treatment effects of the antiplatelet interventions in non-critically ill patients using a Bayesian hierarchical approach. As the primary model included information about assignment in patient groups where randomization was ongoing and blinded to the investigators, the primary analysis was run by the fully unblinded Statistical Analysis Committee (SAC), who conduct all protocol-specified trial adaptive analyses and report results to the DSMB. The model included covariate terms reflecting each patient's domain eligibility and randomization, so that each treatment effect was estimated only from patients that were randomized within the domain and only directly comparing specific interventions available at each site. Patients enrolled outside the Antiplatelet Domain did not contribute to estimates of antiplatelet treatment effect but did contribute to the estimates of the covariate effects. As such, only patients randomized to the “no antiplatelet treatment” intervention within the Antiplatelet Domain served as controls for the analysis of antiplatelet therapeutic efficacy. In doing so, only concurrent controls were analyzed to determine efficacy of antiplatelet treatment. eFigure 1 depicts the randomized allocation of subjects to aspirin, P2Y12 inhibitor, or “no antiplatelet agent” throughout the duration of the trial in two-week increments.

In addition to the primary analysis conducted by the SAC, multiple sensitivity analyses were conducted by the investigator team who remain blinded to results of on-going randomization in concomitant domains. These analyses include only patients and interventions randomised in domains that have ceased recruitment (Unblinded ITT population). A sensitivity analysis of the primary outcome was repeated in independent models using data from patients in the critically ill and non-critically ill Covid-19 patient groups separately. As the primary analysis was conducted on pooled antiplatelet interventions, a sensitivity analysis was performed to understand independent effects of aspirin or P2Y12 inhibitors. For these analyses there was no adjustment for borrowing from the non-critically ill participants. The Bayesian probability distributions for the pooled antiplatelet odds ratio effect on the primary outcome in the Unblinded ITT analysis model are shown in eFigure 2.

Further sensitivity analyses assessed whether results were modified by excluding patients who were randomized as suspected Covid-19 but ultimately did not document SARS-CoV-2 PCR test positivity, or whether results were modified by excluding site and time effects from the model. As described in the statistical design plan, the analytical model includes site and time covariate terms to account for variability in treatment effect according to site (random effect) and to variation in the endpoint over time (fixed effect).

As the incidence of major bleeding is an important secondary outcome, additional sensitivity analyses included patients in the critically ill and non-critically ill who were also randomized in the therapeutic anticoagulation domain. In addition, as thrombotic complications may in part be mediated by inflammation, the use of interleukin-6 receptor antagonists may modulate thrombosis risk. Thus, the possibility of an interaction between interleukin-6 receptor antagonists and antiplatelet treatment was evaluated in a sensitivity analysis. Exploratory analyses were performed to assess interaction between antiplatelet interventions and all other unblinded domains with sufficient data available. The model was adjusted as described for the primary analysis.

Subgroup analyses

Treatment effect was examined in pre-specified subgroup analyses (See Protocol Appendix Statistical Analysis Plan) including age, sex, and requirement for invasive mechanical ventilation at baseline. Subgroups according to baseline serum troponin levels and chronic kidney disease were planned but data were not available at the time of analysis. To assess for potential heterogeneity of treatment effect according to anticoagulation dose, subgroups were predefined based on the baseline anticoagulation dose equivalent (low dose prophylaxis, intermediate dose prophylaxis, subtherapeutic/therapeutic dose anticoagulation). A second post-hoc subgroup analysis was performed on subgroups defined as therapeutic or “less than therapeutic” doses of anticoagulant (comprising low dose prophylaxis, intermediate dose prophylaxis, or sub-therapeutic anticoagulation). For each subgroup analysis, all subgroups were included in a single model that estimated a separate treatment effect by subgroup. The posterior distribution for each subgroup effect and 95% credible intervals are reported.

There was no imputation of missing outcomes in either primary or secondary analyses. Cases were excluded on an analysis-by-analysis basis, i.e. patients missing outcome data were included in treatment compliance and safety analyses. The secondary outcomes were also analyzed in the unblinded ITT model. The primary safety analysis compared the proportion of patients who developed one or more serious adverse thrombotic or major bleeding events across groups. Patients with missing subgroup variables were included in a “Missing” subgroup.

eAppendix 2. Supplementary Results

Site Participation in the Antiplatelet Domain

During the study period, October 30, 2020 to June 23, 2021, 105 sites from 8 countries were open for enrollment in the antiplatelet domain.

Supplemental Data

Provided below are the secondary and sensitivity analyses of the primary outcome (days alive and free of organ support) and secondary outcomes of hospital mortality, death or major thrombotic events, and major bleeding in the critically ill participants where appropriate. Data from critically ill participants follow brief presentation of the primary and secondary analyses for the non-critically ill population.
eTable 2 presents the baseline characteristics of all participants in the antiplatelet domain (critically ill and non-critically ill). Supplemental data in all tables are presented as adjusted odds or hazard ratios where appropriate with 95% credible intervals, as well as the superiority of pooled antiplatelet group compared to no antiplatelet treatment unless otherwise noted.

Enrollment of non-critically ill participants was halted on June 23, 2021 at the same time as critically ill patients due to low recruitment and after release of RECOVERY trial data demonstrating futility of aspirin treatment in hospitalized patients with Covid-19. Baseline characteristics of non-critically ill participants are presented in eTable 2. Primary and secondary outcomes of the non-critically ill participants are shown in eTable 3 and serious adverse events, major bleeding, and thrombotic outcomes are presented in eTable 4. The non-critically ill population in the trial was too small to draw conclusions about therapeutic effects of antiplatelet interventions.

eTable 5 presents secondary outcomes of the critically ill subjects including progression of non-intubated participants to require invasive mechanical ventilation, ECMO, or death; freedom from respiratory or cardiovascular support; length of stay; and WHO scale at day 14. eTable 6 depicts the occurrence of serious adverse events, major bleeding, and thrombotic events for individual antiplatelet interventions in critically ill patients.

Interaction with Other Domains and Subgroups

The potential interaction of antiplatelet intervention and anticoagulation strategy was of particular importance in the analysis given the potential increased risk of bleeding in patients receiving combination antithrombotic therapy. Of note, patients >75 years of age were excluded from the Antiplatelet Domain if eligible for the Therapeutic Anticoagulation Domain given the increased bleeding risk in that age group. 122 participants were co-enrolled in the antiplatelet and anticoagulation domains with 35 patients randomized

to an active antiplatelet therapy and therapeutic anticoagulation. Analysis of the primary outcome (OSFD) and in-hospital mortality suggested a potentially harmful effect when receiving both antiplatelet treatment and therapeutic anticoagulation (eTable 8). Further post-hoc analysis of the effect of antiplatelet intervention stratified by anticoagulation dose suggested that antiplatelet therapy had a 97% posterior probability of improving in-hospital survival (OR 1.33 [0.99, 1.79]) in patients receiving prophylactic dose anticoagulant compared with likely harm (90% posterior probability) in patients receiving therapeutic anticoagulation (OR 0.63 [0.31, 1.28], eTable 9, eFigure 3). Analysis of the primary outcome of organ support free days by prespecified subgroups of ventilation status, age and baseline anticoagulation status is shown in eTable 7. Due to missing data, the other pre-specified subgroups defined by troponin levels and renal function, have yet not been analyzed but are planned for incorporation into subsequent manuscripts.

eTable 2. Participant Characteristics at Baseline

	Critically Ill Patients			Non-Critically Ill Patients		
	Aspirin (n = 565)	P2Y12 Inhibitors (n = 455)	Control [a] (n = 529)	Aspirin (n=90)	P2Y12 Inhibitors (n=67)	Control [a] (n=109)
Age in years, mean (SD)	55.5 (12.1)	56.3 (11.8)	55.0 (12.0)	52.0 (12.8)	53.9 (12.1)	53.4 (13.4)
Male sex, n (%)	366 (64.8)	316 (69.5)	346 (65.4)	57 (63.3)	43 (64.2)	75 (68.8)
Race / Ethnicity [b] - n / N (%)						
White	352 / 460 (76.5)	307 / 372 (82.5)	309 / 419 (73.7)	9 / 12 (75.0)	6 / 10 (60.0)	7 / 8 (87.5)
Asian	46 / 460 (10.0)	36 / 372 (9.7)	58 / 419 (13.8)	1 / 12 (8.3)	3 / 10 (30.0)	0 / 8 (0)
Black	16 / 460 (3.5)	9 / 372 (2.4)	16 / 419 (3.8)	1 / 12 (8.3)	0 / 10 (0)	0 / 8 (0)
Mixed	19 / 460 (4.1)	5 / 372 (1.3)	10 / 419 (2.4)	0 / 12 (0)	0 / 10 (0)	0 / 8 (0)
Other	27 / 460 (5.9)	15 / 372 (4.0)	26 / 419 (6.2)	1 / 12 (8.3)	1 / 10 (10.0)	1 / 8 (12.5)
Body-mass index [c], median (IQR)	31.7 (27.4, 37.6)	31.3 (26.9, 37.2)	31.1 (27.0, 35.9)	28.4 (25.3, 31.2)	29.4 (26.1, 32.8)	28.1 (25.2, 30.4)
APACHE II score, median (IQR)	12.0 (8.0, 17.0)	12.0 (8.0, 18.0)	12.0 (8.0, 17.0)	5.0 (2.0 - 8.0)	5.0 (3.0 - 9.0)	5.0 (3.0 - 8.0)
Confirmed SARS-CoV-2 infection [d], n / N (%)	505 / 519 (97.3)	400 / 415 (96.4)	465 / 477 (97.5)	79 / 80 (98.8)	61 / 63 (96.8)	97 / 98 (99.0)
Preexisting condition, n / N (%)						
Diabetes	134 / 562 (23.8)	93 / 449 (20.7)	112 / 521 (21.5)	18 / 90 (20.0)	18 / 67 (26.9)	18 / 106 (17.0)
Respiratory disease	113 / 562 (20.1)	88 / 449 (19.6)	97 / 522 (18.6)	9 / 90 (10.0)	15 / 67 (22.4)	16 / 106 (15.1)
Kidney disease	16 / 528 (3.0)	18 / 416 (4.3)	18 / 485 (3.7)	1 / 85 (1.2)	3 / 61 (4.9)	3 / 102 (2.9)
Severe cardiovascular disease	18 / 552 (3.3)	23 / 437 (5.3)	26 / 517 (5.0)	0 / 90 (0)	2 / 67 (3.0)	1 / 106 (0.9)
Any immunosuppressive condition	23 / 562 (4.1)	19 / 449 (4.2)	23 / 522 (4.4)	3 / 90 (3.3)	0 / 67 (0)	4 / 106 (3.8)
Liver cirrhosis / failure	1 / 552 (0.2)	3 / 437 (0.7)	0 / 517 (0.0)	0 / 90 (0)	0 / 67 (0)	0 / 106 (0)
Time to enrollment, median (IQR)						
From hospital admission, days	1.5 (0.9, 3.0)	1.8 (1.0, 3.5)	1.8 (0.9, 3.7)	1.0 (0.8, 1.9)	1.0 (0.7, 1.9)	1.0 (0.8, 1.6)
From ICU admission, hours	17.2 (9.8, 22.4)	17.9 (12.0, 23.5)	18.2 (10.7, 23.9)	19.0 (8.5, 22.1)	12.5 (5.4, 18.8)	17.6 (11.5, 22.2)
Acute respiratory support, n (%)						
None / supplemental oxygen	0 (0.0)	0 (0.0)	1 (0.2)	80 (88.9)	54 (80.6)	97 (89.0)
High-flow nasal cannula	125 (22.1)	121 (26.6)	132 (25.0)	2 (2.2)	5 (7.5)	1 (0.9)
Noninvasive ventilation only	227 (40.2)	173 (38.0)	202 (38.2)	8 (8.9)	8 (11.9)	11 (10.1)
Invasive mechanical ventilation	213 (37.7)	161 (35.4)	194 (36.7)	1 (1.1)	0 (0)	3 (2.8)
PaO_2 / FiO_2, median (IQR)	115 (86, 148)	118 (90, 163)	113 (89, 147)	129 (86, 198)	139 (104, 205)	128 (94, 171)
Vasopressor support - n (%)	121 (21.4)	72 (15.8)	88 (16.6)	0 (0)	0 (0)	0 (0)
Median laboratory values (IQR) [e]						
C-reactive protein, µg/mL	118 (62, 180)	109 (59, 179)	113 (60,180)	73 (31, 134)	81 (41, 126)	81 (51, 135)
D-dimer, ng/mL	972 (500, 2599)	850 (386, 2297)	898 (490, 2705)	500 (451, 827)	500 (444, 1065)	659 (500, 1515)
Platelet count, $x10^9$/L	251 (194, 313)	239 (184, 312)	253 (196, 327)	228 (193, 277)	234 (176, 298)	218 (185, 285)
Concomitant therapies within 48hr of randomization, n / N (%)						
Steroids	552 / 562 (98.2)	433 / 448 (96.7)	511 / 521 (98.1)	88 / 90 (97.8)	60 / 67 (89.6)	97 / 106 (91.5)
Remdesivir	113 / 562 (20.1)	87 / 448 (19.4)	126 / 521 (24.2)	28 / 90 (31.1)	13 / 67 (19.4)	25 / 106 (23.6)
Immunomodulators						
Tocilizumab	248 / 562 (44.1)	201 / 448 (44.9)	217 / 521 (41.7)	8 / 90 (8.9)	11 / 67 (16.4)	10 / 106 (9.4)
Sarilumab	66 / 562 (11.7)	45 / 448 (10.0)	54 / 521 (10.4)	2 / 90 (2.2)	0 / 67 (0)	0 / 106 (0)

	Critically Ill Patients			Non-Critically Ill Patients		
	Aspirin	P2Y12 Inhibitors	Control [a]	Aspirin	P2Y12 Inhibitors	Control [a]

		(n = 565)	(n = 455)	(n = 529)	(n=90)	(n=67)	(n=109)
Anticoagulants Category							
	LMWH	512 / 565 (90.6)	395 / 455 (86.8)	480 / 529 (90.7)	81 / 90 (90.0)	57 / 67 (85.1)	92 / 109 (84.4)
	UFH	8 / 565 (1.4)	8 / 455 (1.8)	8 / 529 (1.5)	0 / 90 (0)	0 / 67 (0)	0 / 109 (0)
	DOAC	2 / 565 (0.4)	5 / 455 (1.1)	1 / 529 (0.2)	0 / 90 (0)	0 / 67 (0)	3 / 109 (2.8)
	Unknown	43 / 565 (7.6)	47 / 455 (10.3)	40 / 529 (7.6)	9 / 90 (10.0)	10 / 67 (14.9)	14 / 109 (12.8)
Dose							
	Low prophylactic dose	112 / 565 (19.8)	87 / 455 (19.1)	75 / 529 (14.2)	24 / 90 (26.7)	23 / 67 (34.3)	21 / 109 (19.3)
	Intermediate prophylactic dose	312 / 565 (55.2)	214 / 455 (47.0)	312 / 529 (59.0)	38 / 90 (42.2)	19 / 67 (28.4)	57 / 109 (52.3)
	Subtherapeutic	22 / 565 (3.9)	21 / 455 (4.6)	24 / 529 (4.5)	1 / 90 (1.1)	0 / 67 (0)	0 / 109 (0)
	Therapeutic	54 / 565 (9.6)	65 / 455 (14.3)	56 / 529 (10.6)	15 / 90 (16.7)	10 / 67 (14.9)	14 / 109 (12.8)
	Unknown	65 / 565 (11.5)	68 / 455 (14.9)	62 / 529 (11.7)	12 / 90 (13.3)	15 / 67 (22.4)	17 / 109 (15.6)

Percentages may not sum to 100 because of rounding. SD denotes standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation; DOAC, direct oral anticoagulants; LMWH, low-molecular weight heparin; UFH, unfractionated heparin.

[a] Control patients include all patient randomized to control who were also eligible to be randomized to antiplatelet.

[b] Data collection not approved in Canada and continental Europe. “Other” includes “declined” and “multiple”.

[c] Body-mass index is the weight in kilograms divided by the square of the height in meters.

[d] SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test.

[e] Laboratory results available when captured for clinical care. Number of patients varies with each test. Missingness ~15% for CRP, ~40% for D-Dimer, and ~4% for platelet count

eTable 3. Primary and Secondary Analyses of Non-Critically Ill Patients

	Pooled Antiplatelet	Aspirin	P2Y12 Inhibitor	No Antiplatelet Therapy
Organ Support Free Days to Day 21 [1,2]				
Number of patients with known outcome		90	67	106
Median (IQR)		22 (18, 22)	22 (22, 22)	22 (18.5, 22)
Adjusted proportional odds ratio (95% CrI)		0.94 (0.56, 1.35)	0.97 (0.59, 1.50)	1 (Reference)
Probability of futility[3], %		90.9	85.8	-
Probability of efficacy[4], %		36.4	43.7	-
Survival to Hospital Discharge				
Number of patients/total number (%)		78/90 (86.6)	63/67 (94.0)	87/106 (82.1)
Adjusted odds ratio (95% CrI)		1.23 (0.70, 2.04)	1.29 (0.77, 2.52)	1 (Reference)
Adjusted absolute risk difference (%, 95% CrI)		3.2 (-4.7, 12.9)	4.1 (-3.5, 17.6)	-
Probability of efficacy[4], %		79.50	85.6	-
90-Day Mortality				
Adjusted hazard ratio				
Mean (SD)	1.2 (0.44)	-	-	1 (Reference)
Median (95% CrI)	1.13 (0.57, 2.27)	-	-	1 (Reference)
Probability of efficacy[4], %	63.7	-	-	-
Progression to Intubation, ECMO, or Death [5]				
Number of patients/total number (rate)[6]	11/76 (0.145)	10/53 (0.189)	1/23 (0.043)	19/66 (0.288)
Death, n (%)	10 (13.2)	9 (17)	1 (4.3)	17 (25.8)
Intubation, n (%)	10 (13.2)	9 (17)	1 (4.3)	12 (18.2)
ECMO, n (%)	1 (1.3)	1 (1.9)	0 (0)	1 (1.5)
Adjusted odds ratio (95% CrI)	1.15 (0.87, 1.53)	-	-	1 (Reference)
Probability of efficacy[4], %	83.1	-	-	-
Days Free from Organ Support Respiratory				
Median (IQR)		22 (18, 22)	22 (22, 22)	22 (20,22)
Adjusted odds ratio				
Mean (SD)	0.93 (0.29)	-	-	1 (Reference)
Median (95% CrI)	0.89 (0.49, 1.60)	-	-	1 (Reference)
Probability of efficacy[4], %	41.2	-	-	-
Cardiovascular				
Median, (IQR)		22 (22, 22)	22 (22, 22)	22 (22,22)
Adjusted odds ratio				
Mean (SD)	0.96 (0.36)	-	-	1(Reference)
Median (95% CrI)	0.9 (0.44, 1.85)	-	-	1 (Reference)
Probability of efficacy[4], %	40.0	-	-	-
Length of Stay - Hospital				
Adjusted odds ratio				
Mean (SD)	0.94 (0.14)	-	-	1 (Reference)
Median (95% CrI)	0.93 (0.70, 1.24)	-	-	1 (Reference)
Probability of efficacy[4], %	30.2	-	-	-
WHO Scale at Day 14				
Adjusted odds ratio				
Mean (SD)	0.91 (0.29)	-	-	1 (Reference)
Median (95% CrI)	0.87 (0.48, 1.59)	-	-	1 (Reference)
Probability of efficacy[4], %	32.2	-	-	-

[1]Composite ordinal scale consisting of survival to hospital discharge and days free of organ support to day 21. Odds ratio>1 indicates a benefit from treatment. Probabilities of efficacy (proportional odds ratio>1), harm (proportional odds ratio<1), and futility (proportional odds ratio<1.2) are computed from the posterior distribution.

[2]Dynamic borrowing was used across illness severity (i.e. critically and non-critically ill patients), whereby like treatment effects are shrunk together based on their degree of similarity - accordingly, observations about treatment effect are shared between groups

[3] Futility defined by OR < 1.2

[4] Efficacy defined by OR >1

[5]Data and analysis are restricted to patients free of intubation and ECMO at baseline

[6]One subject may progress on more than one component of the composite outcome

eTable 4. Serious Adverse Events, Major Bleeding, and Thrombotic Events in Non-Critically Ill Patients

	Pooled Antiplatelet	Aspirin	P2Y12 Inhibitor	No Antiplatelet Therapy
Serious Adverse Events				
Number of Events/Number of Patients (Rate)	0/157 (0)	0/90 (0)	0/67 (0)	0/109 (0)
Major Bleeding				
Number of Events/Number of Patients (Rate)	1/157 (0.006)	1/90 (0.004)	0/67 (0)	0/105 (0)
Thrombotic Events or Death				
Number of Events/Number of Patients (Rate)	20/157 (0.127)	13/90 (0.144)	7/67 (0.104)	21/106 (0.198)
Adjusted odds ratio				
Mean (SD)	1.11 (0.44)	1.18 (0.51)	1.15 (0.67)	1 (Reference)
Median (95% CrI)	1.03 (0.49, 2.18)	1.09 (0.49, 2.44)	0.99 (0.36, 2.86)	1 (Reference)
Probability of efficacy[1], %	53.4	58.4	49.6	-
Thrombotic Events[2]				
Number of Patients with at least one event (Rate)	6/157 (0.038)	2/90 (0.03)	4/67 (0.022)	2/106 (0.019)
Adjusted odds ratio				
Mean (SD)	-	1.11 (0.97)	0.58 (0.46)	1 (Reference)
Median (95% CrI)	-	0.82 (0.21, 3.66)	0.46 (0.12, 1.79)	1 (Reference)
Probability of efficacy[1], %	-	39.7	12.6	-
Thrombotic Event Breakdown (n)[3]	7	2	5	2
Pulmonary Embolism	5	1	4	1
Myocardial Infarction	1	1	0	1
Ischemic Cerebrovascular Accident	0	0	0	0
Systemic Arterial Thromboembolism	0	0	0	0
Deep Vein Thrombosis	1	0	1	0

[1] Efficacy defined by odds ratio >1

[2] Number of participants experiencing thrombotic events are presented for each individual intervention.

[3] Participants may have experienced more than one thrombotic event.

eTable 5. Other Secondary Outcomes for Critically Ill Patients

	Pooled Antiplatelet[1]	No Antiplatelet
Progression to Intubation, ECMO, or Death[2]	N=636	N=326
Progressors, Number of patients (%)	265 (41.7)	148 (45.4)
Death (Number of patients (%))	155 (24.4)	98 (30.1)
Intubation, Number of patients (%)	230 (36.2)	133 (40.8)
ECMO, Number of patients (%)	4 (0.6)	1 (0.3)
Adjusted odds ratio		
Mean (SD)	1.15 (0.17)	1 (Reference)
Median (95% CrI)	1.14 (0.86, 1.51)	1 (Reference)
Probability of efficacy [3], %	82.2	-
Days Free from Organ Support		
Respiratory		
Median (IQR)	7 (-1, 16)	7 (-1, 16)
Adjusted odds ratio		
Mean (SD)	1.04 (0.1)	1 (Reference)
Median (95% CrI)	1.04 (0.85, 1.26)	1 (Reference)
Probability of efficacy [3], %	65.2	-
Cardiovascular		
Median, (IQR)	19 (-1, 21)	19 (-1, 21)
Adjusted odds ratio		
Mean (SD)	1.12 (0.12)	1 (Reference)
Median (95% CrI)	1.11 (0.9, 1.37)	1 (Reference)
Probability of efficacy [3], %	83.7	-
Length of Stay		
ICU		
Adjusted odds ratio		
Mean (SD)	1.05 (0.07)	1 (Reference)
Median (95% CrI)	1.05 (0.92, 1.20)	1 (Reference)
Probability of efficacy [3], %	76.8	-
Hospital		
Adjusted odds ratio		
Mean (SD)	1.05 (0.07)	1 (Reference)
Median (95% CrI)	1.05 (0.92, 1.20)	1 (Reference)
Probability of efficacy [3], %	74	-
WHO Scale at Day 14		
Adjusted odds ratio		
Mean (SD)	1.0 (0.1)	1 (Reference)
Median (95% CrI)	1.00 (0.82, 1.21)	1 (Reference)
Probability of efficacy [3], %	48.6	-

IQR – Interquartile Range, CrI – Credible Interval

[1] Aspirin (N=349) and P2Y12 inhibitor (N=287) equivalent

[2] Analysis restricted to patients not receiving mechanical ventilation or ECMO at baseline

[3] Efficacy defined by odds ratio >1

eTable 6. Serious Adverse Events, Major Bleeding, and Thrombotic Events in Critically Ill Patients

	Pooled Antiplatelet	Aspirin	P2Y12 Inhibitor	No Antiplatelet
Serious Adverse Events				
Number of Events/Number of Patients (Rate)		5/565 (0.009)	4/455 (0.009)	3/529 (0.006)
Adjusted odds ratio				
Mean (SD)	-	1.49 (0.95)	1.33 (0.87)	1 (Reference)
Median (95% CrI)	-	1.26 (0.42, 3.90)	1.11 (0.35, 3.53)	1 (Reference)
Probability of efficacy [1], %	-	34.3	41.9	-
Major Bleeding				
Number of Events/Number of Patients (Rate)	21/1002 (0.02)	11/559 (0.02)	10/443 (0.023)	2/517 (0.004)
Adjusted odds ratio				
Mean (SD)	3.45 (1.88)	2.63 (1.32)	2.81 (1.47)	1 (Reference)
Median (95% CrI)	2.97 (1.23, 8.28)	2.34 (0.93, 5.93)	2.50 (0.95, 6.56)	1 (Reference)
Probability of efficacy [1], %	0.1	3.5	3.1	-
Thrombotic Events or Death				
Number of Events/Number of Patients (Rate)	355/1011 (0.351)	204/563 (0.362)	151/448 (0.337)	212/521 (0.407)
Adjusted odds ratio				
Mean (SD)	0.71 (0.09)	0.70 (0.10)	0.73 (0.12)	1 (Reference)
Median (95% CrI)	0.70 (0.54, 0.90)	0.69 (0.52, 0.93)	0.73 (0.53, 0.99)	1 (Reference)
Probability of efficacy [1], %	99.7	99.3	98.0	-
Thrombotic Events[2]				
Number of Patients with at least one event (Rate)[3]		69/556 (0.124)	43/440 (0.098)	65/513 (0.127)
Adjusted odds ratio [4]				
Mean (SD)	-	1.08 (0.23)	0.78 (0.19)	1 (Reference)
Median (95% CrI)	-	1.07 (0.71, 1.59)	0.75 (0.47, 1.21)	1 (Reference)
Probability of efficacy [1], %	-	38.2	88.3	-
Thrombotic Event Breakdown (n)	-	76	49	67
Pulmonary Embolism	-	47	25	49
Myocardial Infarction	-	9	7	5
Ischemic Cerebrovascular Accident	-	10	6	4
Systemic Arterial Thromboembolism	-	2	2	1
Deep Vein Thrombosis	-	8	9	8

[1] Efficacy defined by odds ratio <1

[2] Number of participants experiencing thrombotic events are presented for each individual intervention.

[3] Participants may have experienced more than one thrombotic event.

[4] OR>1 indicates harm and OR <1 indicates benefit in analysis of thrombotic events

eTable 7. Organ Support Free Days (OSFD) Within 21 Days by Age, Mechanical Ventilation Status and Baseline Anticoagulation Dose in Critically Ill Patients

	Pooled Antiplatelet	No Antiplatelet
Ventilation	N=1020	N=529
No Invasive Mechanical Ventilation, Number (%)	646 (63.3)	335 (63.3)
Median (IQR)	13 (0, 17)	12 (-1, 18)
Adjusted OR, Median (95% CrI)	1.05 (0.84, 1.31)	1 (Reference)
Probability of efficacy [1], %	67.4	-
Deaths, Number (%)[2]	155 (24.3)	98 (29.9)
Invasive Mechanical Ventilation, Number (%)	374 (36.7)	194 (36.7)
Median (IQR)	0 (-1, 11)	0 (-1, 12)
Adjusted OR, Median (95% CrI)	0.97 (0.75, 1.24)	1 (Reference)
Probability of efficacy [1], %	39.8	-
Deaths, Number (%)[2]	133 (35.8)	69 (35.8)
Age	N=1011	N=521
Age <50, Number (%)	277 (27.4%)	148 (28.4%)
Median (IQR)	13 (0, 17)	14 (0, 18)
Adjusted OR, Median (95% CrI)	0.91 (0.7, 1.2)	1 (Reference)
Probability of efficacy [1], %	25.7	-
Deaths, Number (%)	33 (11.9)	24 (16.2)
Age 50-70, Number (%)	614 (60.7)	326 (62.6)
Median (IQR)	4 (-1, 16)	2.5 (-1, 16)
Adjusted OR, Median (95% CrI)	1.03 (0.82, 1.27)	1 (Reference)
Probability of efficacy [1], %	59.5	-
Deaths, Number (%)	195 (31.8)	121 (37.1)
Age ≥70, Number (%)	120 (11.9%)	47 (9.0%)
Median (IQR)	-0.5 (-1,13)	0 (-1,11)
Adjusted OR, Median (95% CrI)	1.49 (1.00, 2.22)	1 (Reference)
Probability of efficacy [1], %	97.5	-
Deaths, Number (%)	60 (50.0)	22 (46.8)
Anticoagulation		
Low dose	N=199	N=75
Median (IQR)	9 (-1,16)	0 (-1, 16.5)
Adjusted OR, Median (95% CrI)	1.13 (0.71, 1.81)	1 (Reference)
Probability of efficacy [1], %	69.6	-
Deaths, Number (%)	56 (28.1)	28 (37.3)
Intermediate dose	N=525	N=312
Median (IQR)	7 (-1, 16)	9 (-1, 17)
Adjusted OR, Median (95% CrI)	0.97 (0.74, 1.25)	1 (Reference)
Probability of efficacy [1], %	39.2	-
Deaths, Number (%)	141 (26.9)	100 (32.1)
Sub-therapeutic/Therapeutic	N=162	N=80
Median (IQR)	6.5 (-1, 15)	7 (-1,15)
Adjusted OR, Median (95% CrI)	0.98 (0.62, 1.56)	1 (Reference)
Probability of efficacy [1], %	46.9	-
Deaths, Number (%)	51 (31.5)	21 (26.2)
Unknown dose	N=125	N=54
Median (IQR)	6 (-1,17)	0 (-1,13)
Adjusted OR, Median (95% CrI)	1.00 (0.58, 1.78)	1 (Reference)
Probability of efficacy [1], %	50.2	-
Deaths, Number (%)	40 (32.0)	18 (33.3)

Probabilities represent posterior probabilities of pooled antiplatelet interventions compared to no antiplatelet intervention

SD – Standard Deviation, IQR – Interquartile Range, CrI – Credible Interval, OR -odds ratio

[1] Efficacy defined by odds ratio >1

[2] Number of participants with known outcome slightly less than number randomized. Missingness ≤ 2% in all cases

eTable 8. Treatment Effects on Organ Support-Free Days and Hospital Survival Among Critically Ill Patients Enrolled in the Antiplatelet Domain and/or Therapeutic Anticoagulation Domain

Organ Support Free Days at Day 21		**Reference**
Pooled Antiplatelet Therapy[1]	N=1020	N=529
Adjusted odds ratio, median (IQR)	1.02 (0.86 to 1.23)	No Antiplatelet
Probability of efficacy[2], %	58	-
Therapeutic Anticoagulation[3]	N=499	N=511
Adjusted odds ratio, median (IQR)	0.90 (0.72 to 1.14)	Usual Care Thromboprophylaxis
Probability of efficacy[2], %	19	-
Antiplatelet/Anticoagulation Combination [4]	N=35	N=26
Adjusted odds ratio, median (IQR)	0.73 (0.44 to 1.21)	No Antiplatelet / Usual Care Thromboprophylaxis
Probability of efficacy[2], %	12	-
Hospital Survival		Reference
Antiplatelet Therapy[1]	N=1020	N=529
Adjusted odds ratio, median (IQR)	1.27 (0.99 to 1.62)	No Antiplatelet
Probability of efficacy[2], %	97	-
Therapeutic Anticoagulation[3]	N=499	N=511
Adjusted odds ratio, median (IQR)	0.88 (0.66 to 1.16)	Usual Care Thromboprophylaxis
Probability of efficacy[2], %	19	-
Antiplatelet/Therapeutic Anticoagulation Combination [4]	N=35	N=26
Adjusted odds ratio, median (IQR)	0.72 (0.41 to 1.28)	No Antiplatelet / Usual Care Thromboprophylaxis
Probability of efficacy[2], %	12	-

[1] Estimate for all critically ill patients randomized in the Antiplatelet Domain

[2] Efficacy defined by OR > 1.

Adjusted OR based on analysis of critically ill patients randomized in the Antiplatelet Domain, critically ill patients randomized in the Therapeutic Anticoagulation Domain and 122 patients who were co-enrolled in both Anitplatelet Domain and Therapeutic Anticoagulation Domain

[3] Estimate for all critically ill patients randomized in the Therapeutic Anticoagulation Domain

[4] Estimate includes 122 patients co-enrolled in the Antiplatelet Domain and the Therapeutic Anticoagulation Domain. 35 patients were randomized to antiplatelet treatment (either aspirin or P2Y12 inhibitor) and therapeutic-dose heparin. 26 patients were randomized to no antiplatelet and usual care thromboprophylaxis. 49 patients were randomized to antiplatelet treatment and usual care thromboprophylaxis. 12 patients were randomized to therapeutic-dose heparin and no antiplatelet.

eTable 9. In-Hospital Survival and Organ Support by Differential Anticoagulant Dose Given (Randomized and Clinical Decision) in Critically Ill Patients

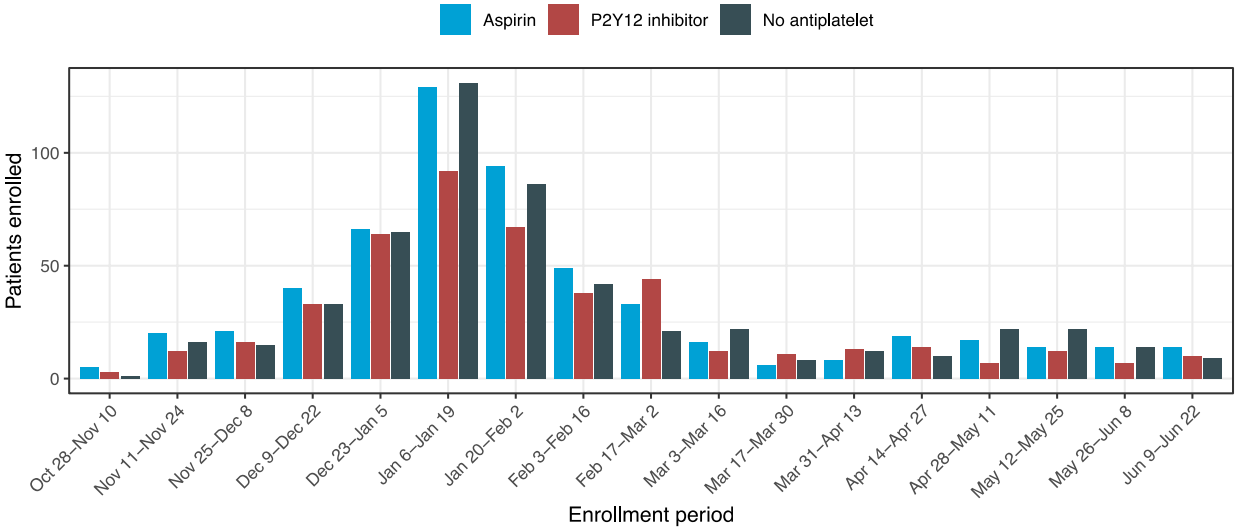
	Pooled Antiplatelet	Aspirin	P2Y12 Inhibitor	No Antiplatelet Therapy
Less than Therapeutic Dose Anticoagulation				
Number of Deaths (%)	205/767 (26.7)	124/444 (27.9)	81/323 (25.1)	136/414 (32.9)
OSFD, Median (95% CrI)	8 (−1, 16)	8 (−1, 16)	9 (−0.5, 16)	7.5 (−1, 16)
OSFD in survivors, Median (95% CrI)	14 (4, 17)	14 (4, 17)	14 (4, 17.75)	15 (7, 18)
Adjusted OR for Survival (Median, 95% CrI)	1.33 (0.99, 1.79)	-	-	Reference (1)
Probability of efficacy[1] (%)	97.1	-	-	-
Patients with major bleeding events (%)	17/761 (2.2)	10/441 (2.3)	7/320 (2.2)	1/410 (0.2)
Therapeutic Dose Anticoagulation				
Number of Deaths (%)	46/124 (37.1)	20/60 (33.3)	26/64 (40.6)	13/55 (23.6)
OSFD, Median (95% CrI)	0 (−1, 14)	4 (−1, 13)	0 (−1, 15)	7 (0, 15.5)
OSFD in survivors, Median (95% CrI)	12.5 (4.25, 17)	12 (4.5, 16)	14 (4.5, 17.75)	14 (6.25, 17)
Adjusted OR for Survival (Median, 95% CrI)	0.63 (0.31, 1.28)	-	-	Reference (1)
Probability of efficacy[1] (%)	10.1	-	-	-
Patients with major bleeding events (%)	3/123 (2.4)	0/60 (0.0)	3/63 (4.8)	1/55 (1.8)
Unknown Dose Anticoagulation				
Number of Deaths (%)	37/120 (30.8)	17/59 (28.8)	20/61 (32.8)	18/52 (34.6)
OSFD, Median (95% CrI)	6.5 (−1, 17)	9 (−1, 17)	6 (−1, 16)	0 (−1, 13.75)
OSFD in survivors, Median (95% CrI)	14 (6, 17)	15.5 (6, 18)	13 (6, 17)	11.5 (0.75, 17.75)
Adjusted OR for Survival (Median, 95% CrI)	1.09 (0.53, 2.17)	-	-	Reference (1)
Probability of efficacy[1] (%)	59.6	-	-	-
Patients with major bleeding events (%)	1/118 (0.8)	1/58 (1.7)	0/60 (0.0)	0/52 (0)

OR - Odds Ratio, OSFD – Organ Support Free Days

[1] Efficacy defined by OR >1

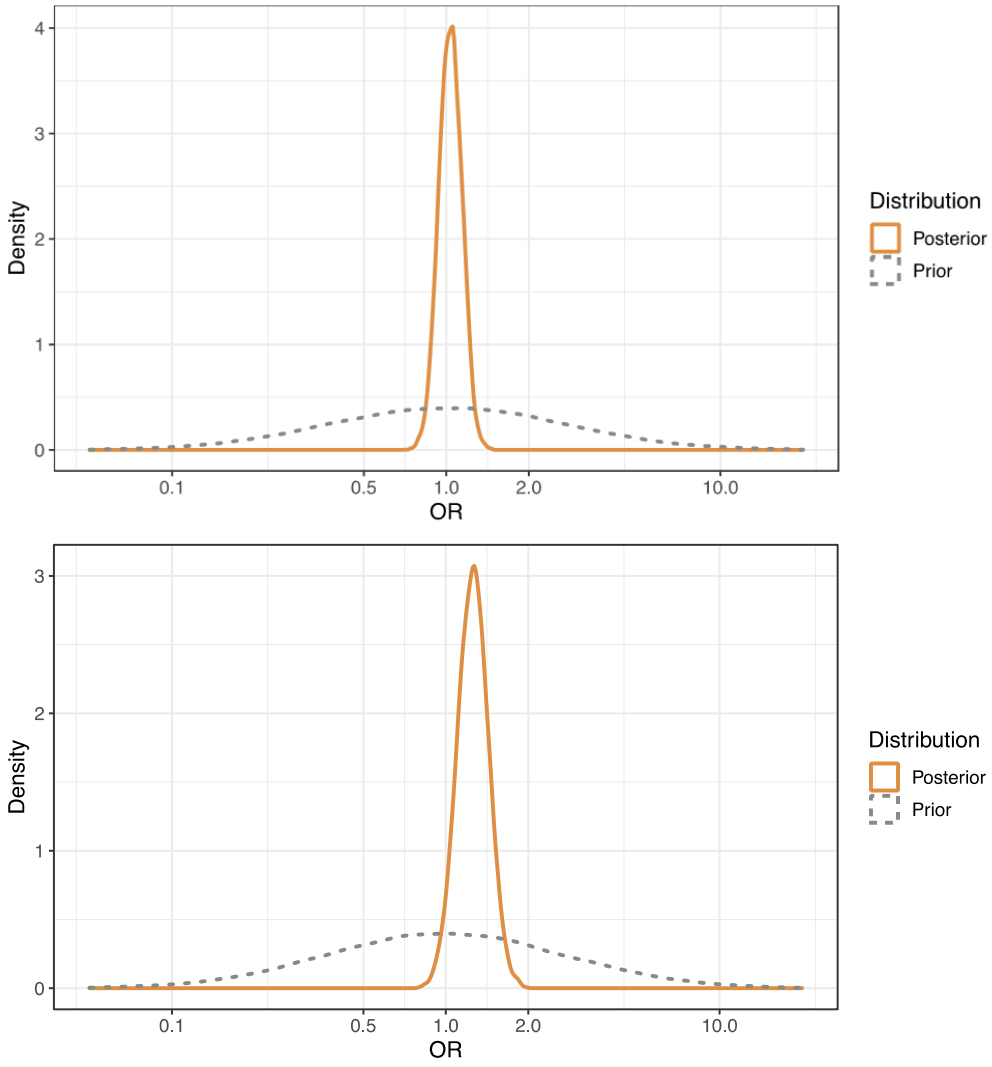
eFigure 1. Patient Enrollment by Intervention and Time-Period

Number of patients randomized (y axis) to an antiplatelet intervention (color) during two-week time periods (x axis).

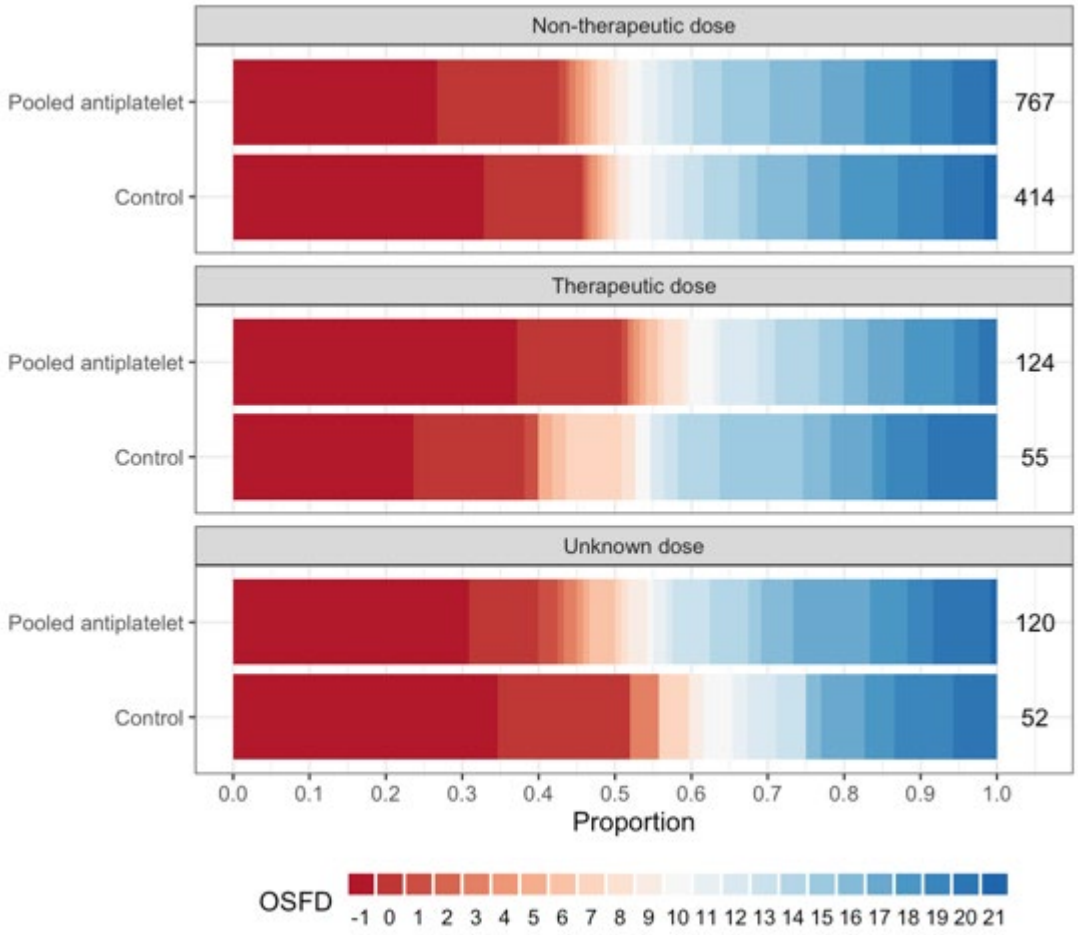


eFigure 2. Distributions of OSFD Odds Ratio for Pooled Antiplatelet

Summary of Bayesian probability distributions for the pooled antiplatelet odds ratio effect on organ support-free days (upper panel) and in-hospital mortality (lower panel) in the Unblinded ITT analysis model. The panels present density estimates of the probability density function for the prior and posterior distribution of the pooled antiplatelet odds ratio. The estimated density (y axis) is shown for a range of odds ratio values (x axis). The x-axis is log-transformed so that equivalent-size relative effects are equidistant from 1 (*i.e.,* 0.5 and 2 are the same distance from 1). The gray dashed line represents the density of the prior distribution (a standard normal prior on the log odds ratio). With the log-transformed x-axis, the prior is centered on 1 (no effect of antiplatelet therapy) and symmetric and nearly all of the prior mass (98%) falls between odds ratios of 0.1 to 10. The yellow solid line represents the density of the posterior distribution estimated using samples produced by Markov Chain Monte Carlo (MCMC) methods. In the upper panel, the mode of the posterior distribution is close to 1 and, compared to the prior distribution, the distribution has substantially shrunk towards an odds ratio of 1 with 95% of the posterior mass falling between 0.86 and 1.25. In the lower panel, the mode of the posterior distribution is above 1 and 95% of the posterior mass falls between 0.97 and 1.62.



eFigure 3. Interaction Between Antiplatelet Allocation and Anticoagulation Dose for OSFD



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