REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix: COVID-19 Antiplatelet

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Antiplatelet Domain-Specific Appendix Version 2.0 dated 04 February 2022

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to one of three interventions:

- No Antiplatelet
- Aspirin
- P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

At this participating site the following interventions have been selected within this domain:

☐ No Antiplatelet

☐ Aspirin

☐ P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

- ☐ Clopidogrel
- ☐ Prasugrel
- ☐ Ticagrelor

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)			Pandemic infection neither suspected nor proven (PINSNP)
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol			REMAP-CAP Core Protocol
Illness Severity State	Moderate State		Severe State	Severe State
Interventions specified in this DSA	Not available		No Antiplatelet AspirinP2Y12 inhibitor	Not available
Interventions submitted for approval in this jurisdiction	Not available		☐ No Antiplatelet ☐ Aspirin ☐ P2Y12 inhibitor	Not available
Interventions offered at this site	Ward	ICU	ICU	ICU
	Not available	Not available	☐ No antiplatelet ☐ Aspirin ☐ P2Y12 inhibitor	Not available

REMAP-CAP: COVID-19 Antiplatelet Domain Summary	
Interventions	• No Antiplatelet therapy • Aspirin • P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) Note: Gastric protection with proton pump inhibition or H2 antagonist is recommended for patients receiving antiplatelet therapy.
Unit of Analysis, Strata, and State	This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection. Borrowing is permitted between strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	There is one nest comprising all active antiplatelet interventions. The nest will be converted to a pool if there is a statistical trigger for equivalence of the active antiplatelet interventions.
Timing of Reveal	Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support) • 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 • Patient is already receiving therapeutic dose anticoagulation or a clinical decision has been made to commence therapeutic dose anticoagulation • 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 • 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 Exclusions	Criteria that exclude a patient from one or more interventions are: • 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 of any agent known to have a significant interaction with an intervention in this domain will exclude a patient from receiving that agent

Outcome measures	Domain-specific primary endpoint: survival to hospital discharge, censored at day 90 Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Confirmed proximal deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Total red cell blood cell units transfused between randomization and the end of study day 15 • Acute myocardial infarction • Major bleeding • Other thrombotic event including mesenteric ischemia and limb ischemia • Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA

TABLE OF CONTENTS

1. ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
aPTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
CCP	Clinical Characterization Protocol
DSA	Domain-Specific Appendix
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
HIT	Heparin Induced Thrombocytopenia
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
LMWH	Low Molecular Weight Heparin
MERS-CoV	Middle East respiratory syndrome coronavirus
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolus
PISOP	Pandemic infection is suspected or proven
RCT	Randomized controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
UFH	Unfractionated heparin

VTE	Venous Thromboembolism
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (details of the current statistical analysis plan and models); Simulations Appendix (details of the current simulations of the REMAP); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions within each domain is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase

over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 ANTIPLATELET DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Antiplatelet Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Antiplatelet Domain-Specific Working Group (DSWG) on 24th August 2020

Version 2: Approved by the Antiplatelet DSWG on 04 February 2022

4. COVID-19 ANTIPLATELET DOMAIN GOVERNANCE

4.1. Domain members

Chair: Dr. Charlotte Bradbury

Deputy Chair: Dr. Patrick Lawler

Members:

Prof. Derek Angus

Dr. Scott Berry

Dr. Shailesh Bihari

Prof. Marc Carrier

A/Prof. Timothy Girard

Dr. Ewan Goligher

Prof. Anthony Gordon

A/Prof. Christopher Horvat

Prof. David Huang

Prof. Beverley Hunt

Dr. Colin McArthur

A/Prof. Bryan McVerry

Prof. John Marshall

Dr. Zoe McQuilten

A/Prof. Matthew Neal

Dr. Saskia Middeldorp

Prof. Alistair Nichol

A/Prof. Christopher Seymour

Prof. Simon Stanworth

Prof. Steve Webb

Dr. Ryan Zarychanski

4.2. Contact Details

Chair: Dr. Charlotte Bradbury

Bristol Hematology and Oncology Centre, Horfield Road, Bristol, UK. BS28ED

Email: c.bradbury@bristol.ac.uk

Phone: +44 7973353316

5. COVID-19 ANTIPLATELET DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Antiplatelet Domain-Specific Working Group have read the appendix and authorize it as the official COVID-19 Antiplatelet Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair Charlotte Bradbury Date 04 February 2022

Dr. Charlotte Bradbury

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of antiplatelet therapy for patients with acute illness due to suspected or proven COVID-19.

6.2. Domain-specific background

6.2.1. COVID-19 infection

COVID-19 is caused by a novel coronavirus designated SARS-CoV-2. In December 2019, COVID-19 was first reported when a cluster of patients with severe pneumonia of unknown cause was identified in Wuhan, China. SARS-CoV-2 quickly spread across the globe and the WHO declared COVID-19 a pandemic in March 2020 (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf). The spectrum of illness due to SARS-CoV-2 ranges from asymptomatic infection through to severe pneumonia, respiratory distress, multiorgan dysfunction, and death. A substantial proportion of patients admitted to hospital because of COVID-19 require provision of organ failure support in an Intensive Care Unit (ICU) and in-hospital mortality within this group is high (Tan et al., 2021). Early clinical management recommendations focus on supportive care, including organ support as needed, and the prevention of complications. Effective treatments are urgently needed. The WHO have recommended that "investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials" (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

6.2.2. Intervention strategy for this domain

This domain will test the potential benefits of antiplatelet therapy compared to no antiplatelet therapy. Version 2 of this DSA is a continuation of Version 1 but has evolved following a Platform Conclusion that occurred during Version 1. The period of recruitment and the results derived from that recruitment, using Version 1 of this DSA, are referred to as Stage 1, whereas Stage 2 refers to recruitment and analysis that will occur commencing with Version 2 of this DSA. Edits that apply to Stage 2 (this DSA) have occurred with the DSWG having full knowledge of the results from Stage 1. However, at the time of writing of this DSA Public Disclosure of the results from Stage 1 has not occurred. If this DSA is provided to one or more of participating sites, ethical review bodies, and

regulatory authorities prior to Public Disclosure of the results derived from Stage 1, a pre-print manuscript reporting the results from Stage 1 will also be provided.

If at any stage, evidence of harm or definitive evidence of absence of effectiveness for one or more interventions specified in this domain is observed, the ITSC, as advised by the DSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to the intervention will occur, so as to contribute additional weight of evidence in the public domain.

6.2.3. Thrombotic complications in COVID-19

Thrombotic complications are common in patients admitted to hospital with COVID-19 in spite of conventional thromboprophylaxis, with critically ill patients at highest risk (Shah et al., 2020, Spyropoulos et al., 2020, Bikdeli et al., 2020, Helms et al., 2020, Klok et al., 2020). Macrovascular COVID-19 related thrombotic complications are diverse and have been reported within the venous circulation (VTE, e.g. Pulmonary Embolism, PE) and arterial circulation (e.g. ischemic cardiac events or strokes or mesenteric ischemia, peripheral vascular ischemia) and are an independent predictor of poor outcome (Bilaloglu et al., 2020). Microvascular injury, activation, inflammation and thrombosis also contribute to organ dysfunction and are central to the development of acute respiratory distress syndrome (ARDS) seen in severe COVID-19 infection (Perlman and Dandekar, 2005, Blondonnet et al., 2016). Autopsies and histology from those who have died from COVID-19 have revealed widespread thrombosis in large and small blood vessels of the pulmonary vasculature (Buja et al., 2020). The pathogenesis of thrombosis in COVID-19 is intimately linked with the inflammatory response to the virus, endothelial infection, activation and injury as well as hypercoagulability (Shaw et al., 2021).

Multiple studies have looked at thrombotic rates in hospitalized patients with COVID-19 infection. For example, a multicenter, retrospective study in the US described the rate and severity of hemostatic and thrombotic complications in 400 hospitalized COVID-19 patients, including 144 critically ill patients (Al-Samkari et al., 2020a). These patients primarily received standard-dose prophylactic heparin anticoagulation, yet the overall thrombotic complication rate was reported at 9.5% (6.8-12.8%). The overall bleeding and major bleeding rates were 4.8% (2.9-7.3%) and 2.3% (1.0-4.2%) respectively. Patients at highest risk of thrombotic complications are those with severe COVID-19 admitted to intensive care units. In spite of standard thromboprophylaxis, in this cohort, reported VTE events occur in approximately 30% (most commonly PE) and arterial events in 4% (Klok et al., 2020, Helms et al., 2020). Similar rates of thrombosis (25%) in ICU patients have also been reported

in China where patients do not receive thromboprophylaxis routinely (Cui et al., 2020). Patients with COVID-19 related ARDS have been shown to have a higher risk of thrombotic complications than similar cohorts of patients with non-COVID-19 ARDS (Helms et al., 2020). As very few centers perform routine scans and post mortems are rarely performed, the actual incidence of thrombosis is likely higher than the proportion of patients who receive a diagnosis. Therefore, pulmonary emboli and other thrombotic complications may contribute to morbidity and mortality in those who never receive a diagnosis before death.

Comorbid cardiovascular disease, diabetes and hypertension are distinct risk factors for COVID-19 associated mortality (Zhou et al., 2020). Patients with COVID-19 are also at increased risk of arterial events including reports of stroke in young patients. Stroke occurred in 2.8% (6 out of 214 patients, 41% male, mean age 53 years) in a cohort from Wuhan, China (Mao et al., 2020). Over a 2-week period from March 23 to April 7, 2020 in New York City, a total of five patients aged <50 years old presented with new-onset symptoms of large-vessel ischemic stroke. All five patients tested positive for COVID-19. By comparison, every 2 weeks over the previous 12 months, the same service treated on average, 0.73 patients <50 years with large-vessel stroke (Oxley et al., 2020). Ischemic injury of the fingers and toes has also been reported in patients with severe COVID-19 (Li et al., 2020). Acute cardiac injury (troponin >99th percentile of upper limit of normal) is a common feature of COVID-19 infection and associated with a poor prognosis (Shi et al., 2020b, Shi et al., 2020a). The underlying mechanism of cardiac injury includes direct infection via ACE2 of cardiac myocytes and coronary endothelium resulting in coronary and microvascular thrombosis as well as myocarditis. Elevated Troponin-I and arrhythmia are both associated with poor outcome (Guo et al., 2020). Of 416 hospitalized patients with COVID-19, approximately 20% had cardiac injury and cardiac injury was associated with an increased risk of complications including renal failure, as well as a 3.4-fold increase in mortality (Shi et al., 2020b). Reports of acute cardiovascular collapse with echocardiographic evidence of right heart strain has also been reported. In a consecutive case series of 184 COVID-19 positive patients admitted to a Dutch teaching hospital routinely receiving pharmacological thromboprophylaxis, the incidence of a composite outcome (symptomatic PE, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism) occurred in 31% of patients (Klok et al., 2020).

The pathogenesis of thrombosis in COVID-19 involves a combination of hypercoagulability, endothelial injury and inflammation. Patients with severe COVID-19 infection demonstrate hypercoagulability including high levels of fibrinogen, factor VIII, Von Willebrand factor, D-dimers, platelet activation, impaired fibrinolysis and low antithrombin (Helms et al., 2020). The

hypercoagulability in patients with severe COVID-19 infection is driven by the profound inflammatory response to COVID-19 and is an exaggerated version of the acute phase response commonly seen in patients unwell with infection, cancer or inflammatory disorders. Laboratory analysis of COVID-19 patients' blood demonstrates overt prothrombotic changes beyond the normal range and also beyond what is considered "normal" for non-COVID hospitalized patients with markedly hypercoagulable thromboelastography traces (Panigada et al., 2020). Derangements in coagulation laboratory parameters are strongly associated with worse outcomes and various lines of evidence suggest that the prothrombotic state is causally related to poor outcomes. In a series of 183 patients, patients who died (11%) exhibited markedly elevated D-dimers and elevated fibrin degradation products; 15 of the patients who died met criteria for disseminated intravascular coagulation (DIC), whereas only one survivor developed DIC (Tang et al., 2020). Similar derangements in hemostasis were documented in a separate case series of 94 patients (Lippi and Plebani, 2020). Development of DIC correlated with clinical deterioration. In multiple large case series, elevated D-dimer is consistently associated with a higher risk of ARDS and death (Wu and McGoogan, 2020, Zhou et al., 2020). However, in the majority of patients with COVID-19, raised D-dimers are not associated with low fibrinogen levels or thrombocytopenia or prolonged prothrombin times. Therefore, although there is microvascular thrombosis, COVID-19 coagulopathy is very rarely associated with DIC.

Given that thrombotic complications maybe a potentially preventable cause of significant number of COVID-19 related deaths and of morbidity in survivors, as well as a significant burden to health care resource, we hypothesize that more intensive thrombotic prevention strategies may have the potential to improve clinical outcomes.

6.2.4. Rationale for antithrombotic strategies in COVID-19

Recognition that thrombosis is a key contributor to clinical deterioration and death in COVID-19 has led to global interest in whether enhanced antithrombotic treatments improve patient outcomes (Gomez et al., 2021). Research has focused on all phases of illness, from the community, to hospital admission, when critically ill, and post-hospital discharge. Early in the pandemic, published guidelines were heterogeneous and not informed by evidence, with some recommendations including escalated antithrombotic treatment, dosing according to D-dimer results and/or extended post-discharge thromboprophylaxis (Gomez et al., 2021). From recent randomized trial evidence, it has become clear that efficacy and safety of antithrombotic treatments depends on timing with respect to illness severity, dose, duration of therapy, and that the mechanism of action may also be

of importance. For non-critically ill hospitalized patients, therapeutic dose heparin appears beneficial, with a high probability of reducing the need for organ support, progression to intubation and death, regardless of D-Dimer results (ATTACC Investigators et al., 2021). Results from two subsequent RCTs have also supported the role of therapeutic dose heparin in this cohort (Sholzberg et al., 2021). In contrast, in critically ill patients, therapeutic dose heparin did not improve outcomes with a high probability of harm (REMAP-CAP Investigators et al., 2021). The INSPIRATION trial also failed to demonstrate benefit of intermediate dose heparin compared to conventional low dose in this critically ill patient group (Inspiration Investigators et al., 2021).

A recent systemic review and meta-analysis of studies on the thrombotic and bleeding risk associated with COVID-19 demonstrated that thrombotic events occurred earlier after hospital admission than bleeding events (median 7.0 [IQR 5.9–8.2] vs 11.4 [8.6–14.1] days after admission and the authors suggested avoiding extended duration therapeutic dose anticoagulation (Tacquard et al., 2021). In the ACTION trial, in a mixed population of patients with mild, moderate and severe COVID-19, therapeutic dose rivaroxaban (in hospital and post-discharge) for 30 days was not superior to prophylactic dose heparin (mostly in hospital only) and was associated with higher risk of major bleeding (Lopes et al., 2021).

The Anticoagulation Domain in REMAP-CAP (currently Version 3) is restricted to the Severe State (critically ill patients) and is stratified by whether or not the patient is receiving therapeutic anticoagulation at time of assessment for eligibility. Patients in the No Prior Therapeutic Anticoagulation stratum are randomized to conventional low dose thromboprophylaxis or intermediate dose thromboprophylaxis. Patients in the Prior Therapeutic Anticoagulation stratum are randomized to one of three interventions comprising the same two interventions (low and intermediate dose) or continuation of therapeutic dose anticoagulation. The separate Anticoagulation and Antiplatelet Domains within REMAP will allow these interventions to be tested separately and also in combination.

6.2.5. Results from Stage 1 of the Antiplatelet Domain of REMAP-CAP

Platelets are activated and hyper-aggregable in patients with COVID-19 (Manne et al., 2020, Zaid et al., 2020). Autopsies have shown microvascular thrombi with megakaryocyte and platelet-fibrin deposition in the setting of organ failure (Wichmann et al., 2020, Lax et al., 2020, Rapkiewicz et al., 2020). Activated platelets reciprocally upregulate systemic inflammation, and therefore platelet inhibition may have antithrombotic and anti-inflammatory benefits (Akinosoglou and Alexopoulos, 2014, Morris et al., 2021). Observational data support an association between antiplatelet therapy and reduced lung injury, ICU requirement and mortality, without increased bleeding (Akinosoglou

and Alexopoulos, 2014, Chow et al., 2021). Accordingly, in the previous version of the Antiplatelet Domain of REMAP-CAP we evaluated the effect of antiplatelet therapy (aspirin or P2Y12 inhibitor) using an ordinal scale that is a composite of hospital survival and organ support provision up to day 21 in patients hospitalized with COVID-19, stratified by baseline illness severity.

The first patient was enrolled into the Antiplatelet Domain on October 30, 2020. On March 22, 2021, the pre-specified equivalence trigger for the aspirin and P2Y12 inhibitor groups (compared to each other) was reached in critically ill patients with 1016 patients enrolled with complete data (P2Y12 inhibitor to aspirin odds ratio 1.00, 95%CrI 0.80 to 1.23, posterior probability of equivalence 90.1%). These groups continued to enroll separately but were subsequently statistically pooled into a pooled antiplatelet group for all further adaptive analyses. On June 23, 2021, enrollment was discontinued after an adaptive analysis demonstrated that the pre-specified stopping criterion for futility had been reached in critically ill patients (REMAP-CAP Severe State) and patient follow up continued until July 26, 2021. At that time 1557 critically ill and 267 non-critically ill (REMAP-CAP Moderate State) patients had been enrolled and randomized. For non-critically ill patients, based on slow enrollment rates and external data (Recovery Collaborative Group, 2022), the REMAP-CAP International Trial Steering Committee decided to simultaneously stop enrollment in both critically ill and non-critically ill patients.

Among critically ill participants, the median organ support-free days was 7 (IQR –1, 16) in both the pooled antiplatelet and control groups. The median adjusted odds ratio for the effect of antiplatelet therapy compared with control was 1.02 (95% CrI 0.86 to 1.23), yielding a posterior probability of futility of 95.7%. Among critically ill patients, 723 participants (71.5%) in the pooled antiplatelet group and 354 participants (67.9%) in the control group survived to hospital discharge, yielding a median adjusted odds ratio for hospital survival of 1.27 (95% CrI 0.99 to 1.62) and a posterior probability of efficacy of 97.0% for antiplatelet therapy compared with control. The median adjusted absolute difference in survival to hospital discharge was 5.0% (95% CrI –0.2% to 9.5%). Similar effects of antiplatelet therapy on survival-time over 90 days were seen with a median adjusted hazard ratio of 1.22 (95%CrI 1.06 to 1.40) and 99.7% posterior probability of improved survival of the pooled antiplatelet group compared with control.

It is possible that there is lack of proportionality of treatment effect across all categories of the composite ordinal scale, raising the possibility that there is a beneficial effect of antiplatelet therapy on mortality with an off-setting increase in the duration of organ failure support among patients

who survive to hospital discharge but require only relatively short periods of organ failure support. However, this discrepancy between the ordinal primary end-point and the component of the ordinal primary end-point that relates to survival to hospital discharge could also have arisen due to chance. The primary objective of Stage 2 of the Antiplatelet Domain is to determine if there is a survival advantage from treatment of critically ill patients with an antiplatelet agent. This will be achieved by applying a domain-specific primary end-point of survival to hospital discharge (i.e., the -1 category in the primary end-point specified in the Pandemic Appendix to the Core Protocol, as a dichotomised variable).

Furthermore, in the pre-specified interaction analysis of patients co-enrolled in the Antiplatelet Domain and Therapeutic Anticoagulant Domain (n=122 critically ill patients), the odds ratio for the combination of antiplatelet therapy and therapeutic dose heparin anticoagulation, compared with no antiplatelet and standard thromboprophylaxis, was 0.73 (95% CrI 0.44 to 1.21) for organ support-free days and 0.72 (95% CrI 0.41 to 1.28) for hospital survival suggesting the possibility of harm with the combination of antiplatelet therapy and therapeutic dose heparin . The odds ratio for the interaction of antiplatelet therapy and therapeutic dose heparin anticoagulation was 0.79 (95% CrI 0.50 to 1.30) for organ support-free days and 0.64 (95% CrI 0.39 to 1.05) for hospital survival. Consistent with this, in a post-hoc subgroup analysis of hospital mortality according to baseline concomitant anticoagulation dose (randomized and usual care; n=1,360 with dose of anti-coagulation known) demonstrated that for patients receiving therapeutic dose anticoagulation (n=179), the adjusted odds ratio for hospital survival of antiplatelet therapy compared to control was 0.63 (95% CrI 0.31 to 1.28, 89.9% probability antiplatelet therapy led to harm in this context). In contrast, for patients receiving anticoagulation doses lower than therapeutic (n=1,181), the adjusted odds ratio for hospital survival was 1.33 (95% CrI 0.99 to 1.79, 97.1% probability pooled antiplatelet improved hospital survival in this context). If this interaction is real, it would have contributed to lowering the estimate of treatment effect for antiplatelet therapy (i.e. odds ratios for antiplatelet therapy alone are larger). Stage 2 of the Antiplatelet Domain will exclude patients who will commence or continue therapeutic anticoagulation and for sites that are participating in both the Anticoagulation Domain (Version 3 currently) and Stage 2 of the Antiplatelet Domain, for patients in the Prior Therapeutic Anticoagulation Stratum, randomization to the combination of Continuation of Therapeutic Anticoagulation and an active antiplatelet agent will be precluded.

In critically ill patients, major bleeding occurred in 21 of 1,002 participants (2.1%) in the pooled antiplatelet group (aspirin 2.0%, P2Y12 inhibitor 2.1%) and in 2 of 517 participants (0.4%) in the

control group. These frequencies appear lower than those reported in observational studies (Al-Samkari et al., 2020b, Shah et al., 2020), but are consistent with the recently reported anticoagulation study results (in critically ill patients, major bleeding occurred in 2.3% assigned to standard of care thromboprophylaxis and 3.8% in those assigned to therapeutic dose heparin) (REMAP-CAP Investigators et al., 2021).

6.2.6. REMAP-CAP antiplatelet results in the context of results from other trials

In the RECOVERY trial, 28 day mortality was not different in patients assigned to aspirin compared with control (17% in both groups), although a slightly higher proportion of patients were discharged from hospital alive within 28 days (75% vs. 74%; rate ratio 1.06; 95%CI 1.02-1.10; p=0.0062) (Recovery Collaborative Group, 2022). Unlike in REMAP-CAP, the majority of patients recruited to the RECOVERY trial were non-critically ill, and amongst those receiving non-invasive or invasive ventilation the relative risk for 28-day mortality was 0.95 (95%CI 0.87 to 1.03) with aspirin treatment (mortality for usual care 29.9% n=750/2505 vs aspirin 28.4% n=685/2415). It is noted that there is substantial overlap in the 95% confidence limits between the critically ill patients in RECOVERY and REMAP-CAP and the combined results include the possibility of clinically important survival benefit. Furthermore, the Kaplan-Meier curves for in-hospital mortality in REMAP-CAP continued to diverge after day-28, indicating the possibility that censoring at day 28 fails to capture clinically important outcomes. Compared to RECOVERY, other differences in REMAP-CAP included the recommendation for gastric protection, exclusion of patients at elevated risk for bleeding risk (including severe renal failure), and lower aspirin dose. The RECOVERY trial also did not control or record concurrent anticoagulation dose with a proportion of patients likely to have received therapeutic doses with potential negative interaction.

In the ACTIV 4a international, open-label, adaptive, controlled trial, non-critically ill hospitalized patients were randomized to receive P2Y12 inhibitor or no P2Y12 inhibitor (“usual care”) in a 1:1 ratio, in combination with recommended therapeutic-dose heparin, for 14 days or until hospital discharge, whichever was sooner (Berger et al., 2021). The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death and, for those who survived to hospital discharge, the number of index hospitalization days free of cardiovascular or respiratory organ support up to day 21. The design and analysis used a Bayesian approach. Enrollment was stopped and discontinued in the Moderate state (non-critically ill participants) on June 19, 2021, after a planned interim analysis demonstrated that the statistical criterion for futility was met. At that time, data on the primary outcome were available for 395 patients (206 assigned to P2Y12 inhibitors and 189 assigned to usual care). In the P2Y12 inhibitor arm, ticagrelor was used in 62% and

clopidogrel in 38% of participants. The median adjusted proportional odds ratio for the effect of P2Y12 inhibitor on organ support-free days was 0.73 (95% credible interval 0.44 to 1.18) favoring the control group, yielding a posterior probability of futility of 98%. Therefore, in non-critically ill hospitalized patients with COVID-19, use of P2Y12 inhibitors in conjunction with therapeutic dose heparin, did not result in a greater number of days alive and free of cardiovascular or respiratory organ support, with the direction of the treatment effect being towards harm. The REMAP-CAP results show a likely important and biologically plausible negative interaction between therapeutic dose anticoagulation and antiplatelet therapy that is consistent with the results from ACTIV 4a. In addition, in REMAP-CAP the predominant P2Y12 inhibitor chosen by sites was clopidogrel (>85% of patients received this) which is a less potent platelet inhibitor than ticagrelor, the preferred drug used in ACTIV-4a trial. Testing P2Y12 inhibitors in critically ill patients is ongoing in ACTIV-4a on a background of conventional low dose prophylactic anticoagulation).

6.2.7. Safety

Gastrointestinal (GI) bleeding is the commonest adverse event associated with any antiplatelet agent and peptic ulcers are the commonest cause. The main risk factors for this complication include older age, renal dysfunction, underlying pre-existing pathology, concurrent use of NSAIDs or anticoagulants (Pipilis et al., 2014). Lanas et al showed that the relative risk for upper GI bleeding was 3.7 for low-dose aspirin, 2.8 for clopidogrel and 16.4 for combination of aspirin with clopidogrel (Lanas et al., 2006). In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, aspirin plus clopidogrel combination prevented 23 new cardiovascular events in the place of 10 major bleeding episodes for every 1,000 patients; while in the case of ticagrelor they were 22 and 6, and for prasugrel the figures were 19 and 7 (Wiviott et al., 2007, Wallentin et al., 2009, Pipilis et al., 2014, Yusuf et al., 2001).

Results from Stage 1 of REMAP-CAP identified no unexpected safety concerns. As indicated, major bleeding occurred more frequently in patients receiving antiplatelet therapy but with no overall impact on the ordinal composite primary outcome and no evidence of increased mortality.

6.2.8. Stage 2 REMAP-CAP Antiplatelet Domain

Both Stage 1 of the REMAP-CAP Antiplatelet Domain and the sub-group of critically ill patients in RECOVERY, raise the important question of whether antiplatelet therapy administered to critically ill patients with COVID-19 can result in clinically meaningful survival benefit, even in the absence of improved organ support free days. As discussed above, there are several differences between the REMAP-CAP and the other trials that have evaluated antiplatelet agents (RECOVERY and ACTIV-4a) in

terms of patient cohorts, protocols and endpoints which could explain why these trials did not detect a consistent clinical benefit with antiplatelet therapy. Accordingly, the Antiplatelet Domain primary endpoint has been amended to survival to hospital discharge, with enrollment restarting only in critically ill patients. Patients receiving therapeutic dose anticoagulation will be excluded and other measures within the protocol have been introduced to avoid the combination of therapeutic dose anticoagulation and antiplatelet therapy. The aspirin and P2Y12 groups will continue to enroll separately, initially nested for statistical analysis but with pre-specification that the nest will be converted to a pool if equivalence is demonstrated for the updated domain-specific primary end-point. Treatment effects will be reported as nested (or pooled), as well as the treatment effect of each de-aggregated antiplatelet intervention, as a post-platform conclusion pre-specified sub-group.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of antiplatelet therapy for patients with acute illness due to suspected or proven pandemic infection.

We hypothesize that the probability of the occurrence of a domain-specific primary endpoint of survival to hospital discharge will differ based on allocation to antiplatelet therapy. The following interventions will be available:

- No Antiplatelet
- Aspirin
- P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

We hypothesize that the treatment effect of antiplatelet therapy is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be based on response adaptive randomization, as described in the core protocol documents.

8.1. Population

The REMAP enrolls patients with acute illness due to suspected or proven COVID-19 admitted to admitted to an intensive care unit.

8.1.1. State

This domain is available only to patients with acute illness due to suspected or proven pandemic infection in the Severe State at the time of assessment for this domain.

8.1.2. Domain-Specific Strata

No domain-specific strata are applied to patients at the time of assessment for this domain.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol + Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Antiplatelet Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since ICU admission unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more 48 hours has elapsed since commencement of sustained organ failure support in an ICU
- 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
- Patient is already receiving and will continue therapeutic dose anticoagulation or a clinical decision has been made to commence therapeutic dose anticoagulation

- 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
- 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

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site.

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from a one or more interventions are:

- 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 of any agent known to have a significant interaction with an intervention in this domain will exclude a patient from receiving that agent

For patients in the Prior Therapeutic Anticoagulation Stratum, randomization to the combination of Continuation of Therapeutic Anticoagulation in the Anticoagulation Domain and an active antiplatelet agent will be precluded.

8.3. Interventions

8.3.1. Antiplatelet Domain Interventions

Patients will be randomly assigned to receive either of the following open-label strategies. The interventions will be commenced immediately after allocation status is revealed.

☐ No Antiplatelet therapy

☐ Aspirin

☐ P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor)

Sites participating in the P2Y12 inhibitor intervention must choose one agent, either clopidogrel, prasugrel, or ticagrelor according to availability and local preference.

Note: Gastric protection with proton pump inhibition or H2 antagonist is recommended for patients receiving antiplatelet therapy.

8.3.2. No Antiplatelet therapy

Patients assigned to this intervention are not to receive any antiplatelet agent or NSAID for 14 days after randomization. Commencement of any agent that inhibits platelet function is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event. Commencement of such an agent in the absence of an accepted clinical indication is a protocol deviation. After 14 days, decisions regarding antiplatelet therapy are at the discretion of the treating clinician.

8.3.3. Aspirin

Aspirin will be administered daily by the enteral route at a dose from 75 to 100 mg per day according to local standard aspirin dose.

8.3.4. P2Y12 inhibitor

Each site will choose one P2Y12 inhibitor based on local availability and preference and administer as follows.

8.3.4.1. *Clopidogrel*

Clopidogrel will be administered daily via the enteral route at a dose of 75mg per day. No loading dose will be administered.

8.3.4.2. *Prasugrel*

Prasugrel will be administered daily by the enteral route as follows: If the patient's age is less than 75 years and measured or estimated weight is 60 kg or more, an initial loading dose of 60 mg will be administered followed by 10 mg per day. If the patient's age is more than 75 years or measured or estimated weight is less than 60 kg an initial loading dose of 60 mg will be administered followed by 5 mg per day.

8.3.4.3. *Ticagrelor*

Ticagrelor will be administered by the enteral route at a dose of 60 mg twice daily. No loading dose will be administered.

8.3.5. Duration of antiplatelet therapy

Patients assigned to aspirin or P2Y12 interventions are to receive the allocated antiplatelet agent until the end of study day 14 or hospital discharge, whichever occurs first. After 14 days decisions regarding antiplatelet therapy are at the discretion of the treating clinician.

8.3.6. Discontinuation of study intervention

Antiplatelet therapy may be discontinued if there is clinical bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Antiplatelet therapy may be recommenced if deemed appropriate by the treating clinician. Antiplatelet therapy should be discontinued if the patient commences therapeutic dose anticoagulation for any indication. Commencement of therapeutic dose anticoagulation in the absence of an accepted clinical indication (such as acute VTE or atrial fibrillation) is not permitted and is a protocol deviation. It is permitted to discontinue antiplatelet therapy if patients develop renal failure requiring renal replacement therapy and this is not a protocol deviation.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation, for the shortest period of time possible, to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of the study interventions for bleeding is not a protocol deviation.

8.3.7. COVID-19 antiplatelet strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive active antiplatelet but who subsequently test negative for COVID-19 infection may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision should take into account the known or suspected local population incidence of COVID-19 infection among hospitalized patients and sensitivity of testing for COVID-19 infection.

8.4. Concomitant care

Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. Commencement of therapeutic dose anticoagulation is not permitted unless the patient develops an accepted clinical indication. Commencement of any additional agent that inhibits platelet function is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event. Commencement of such an agent in the absence of an accepted clinical indication is a protocol deviation. Commencement of NSAIDs is also not permitted. After 14 days, decisions regarding antiplatelet therapy are at the discretion of the treating clinician. All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is survival to hospital discharge, censored at day 90.

8.5.2. Secondary endpoints

The primary endpoint and all secondary endpoints as specified from in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:

- Confirmed proximal deep venous thrombosis
- Confirmed pulmonary embolism
- Confirmed ischemic cerebrovascular event
- Total red cell blood cell units transfused between randomization and the end of study day 15
- Acute myocardial infarction
- Major bleeding defined as one or more of the following:
    - Fatal bleeding

  - Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome
  - Blood loss above 300mls, or bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or a requirement for transfusion of two or more units of whole blood or red cells because of bleeding
- Other thrombotic event including mesenteric ischemia and limb ischemia
- Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA

9. TRIAL CONDUCT

9.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected but no additional testing is specified in this protocol.

9.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Administration of anticoagulant agents
- Administration of agents that inhibit platelet function
- Transfusion of red cells
- Venous thrombotic events (including proximal deep vein thrombosis and pulmonary embolism and other venous thrombotic events)
- Arterial Thrombotic events (including ischemic cerebrovascular event and acute myocardial infarction (using fourth international definition), mesenteric ischemia, limb ischemia, and other arterial thrombotic events)
- Major bleeding (using the International Society on Thrombosis and Hemostasis definition)

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. Blinding

9.4.1. Blinding

All medication will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain for the domain-specific end-point of survival to hospital discharge:

- Inferiority for all interventions in the domain
- Superiority for an active antiplatelet intervention compared with all other interventions in the domain
- Effectiveness of one or more active antiplatelet intervention(s) compared with no antiplatelet intervention
- Futility of one or more active antiplatelet intervention(s) compared with no antiplatelet intervention
- Equivalence of a pair of active antiplatelet agents (which will result in further analysis being pooled)

A Platform Conclusion cannot occur until at least 300 patients have been enrolled in Stage 2. This minimum additional sample size was selected to control the probability of a positive finding without convincing evidence of a beneficial treatment effect in Stage 2.

In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.

10.2. Unit-of-analysis and strata

This domain is analyzed only in the pandemic statistical model utilizing the domain-specific primary endpoint, and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified

in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

10.2.1. Application of Response Adaptive Randomization

Randomization will commence with balanced randomization. At sites participating in both active antiplatelet interventions this will comprise 2:1:1 for the no antiplatelet intervention : aspirin : P2Y12 inhibitor. At sites participating in only one active antiplatelet intervention this will comprise 1:1 between the active antiplatelet intervention and the no antiplatelet intervention.

If RAR is applied, it will be applied according to probabilities derived from the domain-specific primary end-point. If RAR is applied after the active antiplatelet interventions are pooled (see section 10.5) the proportion applied to the pool will be split equally between aspirin and P2Y12 inhibitor at sites participating in both active interventions. At sites participating in only one active intervention the proportion applied to the pool will be applied completely to that active intervention.

If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization (RAR) will be applied to all PISOP patients, in the specified severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum.

If RAR is applied, the cap on the maximum proportion of patients assigned to an intervention that is specified in core protocol documents may be reduced by the SAC if needed to reduce the likelihood of sites being unblinded during a period of rapid recruitment. If a reduced maximum proportion for RAR assignment is applied this will be an operational decision of the SAC, who will inform the DSMB, but blinded trial personnel will not be informed. The decision to apply a modified strata cap will be an operational decision.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see relevant core protocol documents).

10.4. Interactions with interventions in other domains

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

It is noted that interaction between the current Anticoagulation Domain (Version 3) and this version of the Antiplatelet Domain will not be incorporated into the statistical model used to generate statistical triggers. However, interactions will be evaluated as a post-platform conclusion pre-specified sub-group but this will only occur after Platform Conclusions in both domains.

In the Prior Therapeutic Anticoagulation Stratum of the Anticoagulation Domain, patients can receive an assignment for the Continuation of Therapeutic Anticoagulation intervention. At sites participating in both the Anticoagulation Domain and the Antiplatelet Domain, randomization to the combination of Continuation of Therapeutic Anticoagulation and an active antiplatelet agent is precluded.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

10.5. Nesting of interventions

There is one nest comprising both active antiplatelet interventions. In the event of a trigger for equivalence of both active antiplatelet agents it is pre-specified that the nest will be converted to a single pooled active antiplatelet intervention with all subsequent triggers available comparing pooled active antiplatelet agents compared with the no antiplatelet intervention. The ITSC will not be informed if this equivalence trigger occurs.

10.6. Threshold probability for superiority, effectiveness, harm and inferiority

The threshold probability for statistical triggers for superiority, effectiveness, harm, and inferiority are those specified in the relevant core protocol documents.

10.7. Threshold odds ratio delta for equivalence and futility

The threshold odds ration delta for equivalence in this domain is that specified in the relevant core protocol documents but can be applied only to the pair of active antiplatelet interventions. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one-sided analysis for futility of antiplatelet therapy.

10.8. Informative priors

This domain will recommence with analysis including data derived from patients randomized in the Stage 1 of this domain (utilizing Version 1.0 of the DSA).

10.9. Relationship to Anticoagulation Domain

Randomization to active antiplatelet interventions in the Antiplatelet Domain and the continuation of therapeutic dose anticoagulation intervention in the Prior TAC stratum of the Anticoagulation Domain will not be permitted. At sites participating in both the Prior TAC stratum of the Anticoagulation Domain and the Antiplatelet Domain, patients who are eligible for both domains can receive an assignment for low or intermediate dose anticoagulation with an assignment to no antiplatelet intervention or an active antiplatelet intervention. A patient assigned to receive continuation of TAC will not receive an assignment in the Antiplatelet Domain.

There are no restrictions to randomization in the No Prior TAC stratum of the Anticoagulation Domain and the Antiplatelet Domain.

10.10. Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Treatment effect of aspirin or P2Y12 inhibitor, if equivalence is triggered
- Concomitant clinician-assigned anticoagulation dose

- Interaction with interventions in each domain-specific stratum of the Anticoagulation Domain, noting that this can occur only after a Platform Conclusion in both domains
- Receiving invasive mechanical ventilation at baseline
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, efficacy, inferiority, or futility of different interventions with respect to the primary endpoints are possible.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.

11.2. Potential domain-specific adverse events

For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE

- Major bleeding, including death due to bleeding

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of anticoagulation for COVID-19, the use of a usual care control is both appropriate and ethical.

Antiplatelet therapies are being used, off-trial, and typically without consent, for patients with proven or suspected COVID-19 infection. Clinicians may choose not to enroll individual patients if

they feel that participation is not in patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

Where all interventions that are available at a participating site and are regarded as being part of the acceptable spectrum of standard care and given the time imperative necessary to evaluate these interventions, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

All antiplatelet agents will be provided by participating hospitals. The cost of all agents specified in this domain are known to be inexpensive.

12.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

13.REFERENCES

AKINOSOGLOU, K. & ALEXOPOULOS, D. 2014. Use of antiplatelet agents in sepsis: a glimpse into the future. *Thromb Res,* 133**,** 131-8.

AL-SAMKARI, H., KARP LEAF, R. S., DZIK, W. H., CARLSON, J. C., FOGERTY, A. E., WAHEED, A., GOODARZI, K., BENDAPUDI, P., BORNIKOVA, L., GUPTA, S., LEAF, D., KUTER, D. J. & ROSOVSKY, R. P. 2020a. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. *Blood*.

AL-SAMKARI, H., KARP LEAF, R. S., DZIK, W. H., CARLSON, J. C. T., FOGERTY, A. E., WAHEED, A., GOODARZI, K., BENDAPUDI, P. K., BORNIKOVA, L., GUPTA, S., LEAF, D. E., KUTER, D. J. & ROSOVSKY, R. P. 2020b. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood,* 136**,** 489-500.

ATTACC INVESTIGATORS, ACTIV-4A INVESTIGATORS, REMAP-CAP INVESTIGATORS, LAWLER, P. R., GOLIGHER, E. C., BERGER, J. S., NEAL, M. D., MCVERRY, B. J., NICOLAU, J. C., GONG, M. N., CARRIER, M., ROSENSON, R. S., REYNOLDS, H. R., TURGEON, A. F., ESCOBEDO, J., HUANG, D. T., BRADBURY, C. A., HOUSTON, B. L., KORNBLITH, L. Z., KUMAR, A., KAHN, S. R., CUSHMAN, M., MCQUILTEN, Z., SLUTSKY, A. S., KIM, K. S., GORDON, A. C., KIRWAN, B. A., BROOKS, M. M., HIGGINS, A. M., LEWIS, R. J., LORENZI, E., BERRY, S. M., BERRY, L. R., ADAY, A. W., AL-BEIDH, F., ANNANE, D., ARABI, Y. M., ARYAL, D., BAUMANN KREUZIGER, L., BEANE, A., BHIMANI, Z., BIHARI, S., BILLETT, H. H., BOND, L., BONTEN, M., BRUNKHORST, F., BUXTON, M., BUZGAU, A., CASTELLUCCI, L. A., CHEKURI, S., CHEN, J. T., CHENG, A. C., CHKHIKVADZE, T., COIFFARD, B., COSTANTINI, T. W., DE BROUWER, S., DERDE, L. P. G., DETRY, M. A., DUGGAL, A., DZAVIK, V., EFFRON, M. B., ESTCOURT, L. J., EVERETT, B. M., FERGUSSON, D. A., FITZGERALD, M., FOWLER, R. A., GALANAUD, J. P., GALEN, B. T., GANDOTRA, S., GARCIA-MADRONA, S., GIRARD, T. D., GODOY, L. C., GOODMAN, A. L., GOOSSENS, H., GREEN, C., GREENSTEIN, Y. Y., GROSS, P. L., HAMBURG, N. M., HANIFFA, R., HANNA, G., HANNA, N., HEGDE, S. M., HENDRICKSON, C. M., HITE, R. D., HINDENBURG, A. A., HOPE, A. A., HOROWITZ, J. M., HORVAT, C. M., HUDOCK, K., HUNT, B. J., HUSAIN, M., HYZY, R. C., IYER, V. N., JACOBSON, J. R., JAYAKUMAR, D., KELLER, N. M., KHAN, A., KIM, Y., KINDZELSKI, A. L., KING, A. J., et al. 2021. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med,* 385**,** 790-802.

BERGER, J. S., CHEN, Y., KORNBLITH, L., GONG, M., CUSHMAN, M., KIM, K., REYNOLDS, H., LOPES, R. D., LOPEZ-SENDON, J. L., MAGGIONI, A., DE OLIVEIRA ANTUNES, M., ATASSI, B., BERRY, S., BOCHICCHIO, G., FARKOUH, M. E., GREENSTEIN, Y., HADE, E., HUDOCK, K., KAMEL, H., KHATRI, P., KIRWAN, B. A., KREUZIGER, L., LAWLER, P. R., LEIFER, E., MAIA, L., MCVERRY, B. J., NEWMAN, J. D., WAHID, L., WILSON, J., WISNIEWSKI, S., HOCHMAN, J. & NEAL, M. D. 2021. Late-Breaking Science Abstracts and Featured Science Abstracts From the American Heart Association's Scientific Sessions 2021 and Late-Breaking Abstracts in Resuscitation Science From the Resuscitation Science Symposium 2021: P2y12 Inhibitors in Noncritically Ill Hospitalized Patients With Covid-19. *Circulation,* 144**,** e564-e593.

BIKDELI, B., MADHAVAN, M. V., JIMENEZ, D., CHUICH, T., DREYFUS, I., DRIGGIN, E., NIGOGHOSSIAN, C., AGENO, W., MADJID, M., GUO, Y., TANG, L. V., HU, Y., GIRI, J., CUSHMAN, M., QUERE, I., DIMAKAKOS, E. P., GIBSON, C. M., LIPPI, G., FAVALORO, E. J., FAREED, J., CAPRINI, J. A., TAFUR, A. J., BURTON, J. R., FRANCESE, D. P., WANG, E. Y., FALANGA, A., MCLINTOCK, C., HUNT, B. J., SPYROPOULOS, A. C., BARNES, G. D., EIKELBOOM, J. W., WEINBERG, I., SCHULMAN, S., CARRIER, M., PIAZZA, G., BECKMAN, J. A., STEG, P. G., STONE, G. W., ROSENKRANZ, S., GOLDHABER, S. Z., PARIKH, S. A., MONREAL, M., KRUMHOLZ, H. M., KONSTANTINIDES, S. V., WEITZ, J. I., LIP, G. Y. H., GLOBAL COVID-19 THROMBOSIS

COLLABORATIVE GROUP, E. B. T. I. N. E., THE IUA, S. B. T. E. S. C. W. G. O. P. C. & RIGHT VENTRICULAR, F. 2020. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol,* 75**,** 2950-2973.

BILALOGLU, S., APHINYANAPHONGS, Y., JONES, S., ITURRATE, E., HOCHMAN, J. & BERGER, J. S. 2020. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA,* 324**,** 799-801.

BLONDONNET, R., CONSTANTIN, J. M., SAPIN, V. & JABAUDON, M. 2016. A Pathophysiologic Approach to Biomarkers in Acute Respiratory Distress Syndrome. *Dis Markers,* 2016**,** 3501373.

BUJA, L. M., WOLF, D. A., ZHAO, B., AKKANTI, B., MCDONALD, M., LELENWA, L., REILLY, N., OTTAVIANI, G., ELGHETANY, M. T., TRUJILLO, D. O., AISENBERG, G. M., MADJID, M. & KAR, B. 2020. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. *Cardiovasc Pathol,* 48**,** 107233.

CHOW, J. H., KHANNA, A. K., KETHIREDDY, S., YAMANE, D., LEVINE, A., JACKSON, A. M., MCCURDY, M. T., TABATABAI, A., KUMAR, G., PARK, P., BENJENK, I., MENAKER, J., AHMED, N., GLIDEWELL, E., PRESUTTO, E., CAIN, S., HARIDASA, N., FIELD, W., FOWLER, J. G., TRINH, D., JOHNSON, K. N., KAUR, A., LEE, A., SEBASTIAN, K., ULRICH, A., PENA, S., CARPENTER, R., SUDHAKAR, S., UPPAL, P., FEDELES, B. T., SACHS, A., DAHBOUR, L., TEETER, W., TANAKA, K., GALVAGNO, S. M., HERR, D. L., SCALEA, T. M. & MAZZEFFI, M. A. 2021. Aspirin Use Is Associated With Decreased Mechanical Ventilation, Intensive Care Unit Admission, and In-Hospital Mortality in Hospitalized Patients With Coronavirus Disease 2019. *Anesth Analg,* 132**,** 930-941.

CUI, S., CHEN, S., LI, X., LIU, S. & WANG, F. 2020. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost,* 18**,** 1421-1424.

GOMEZ, K., LAFFAN, M. & BRADBURY, C. 2021. Debate: Should the dose or duration of anticoagulants for the prevention of venous thrombosis be increased in patients with COVID-19 while we are awaiting the results of clinical trials? *Br J Haematol,* 192**,** 459-466.

GUO, T., FAN, Y., CHEN, M., WU, X., ZHANG, L., HE, T., WANG, H., WAN, J., WANG, X. & LU, Z. 2020. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*.

HELMS, J., TACQUARD, C., SEVERAC, F., LEONARD-LORANT, I., OHANA, M., DELABRANCHE, X., MERDJI, H., CLERE-JEHL, R., SCHENCK, M., FAGOT GANDET, F., FAFI-KREMER, S., CASTELAIN, V., SCHNEIDER, F., GRUNEBAUM, L., ANGLES-CANO, E., SATTLER, L., MERTES, P. M., MEZIANI, F. & GROUP, C. T. 2020. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med,* 46**,** 1089-1098.

INSPIRATION INVESTIGATORS, SADEGHIPOUR, P., TALASAZ, A. H., RASHIDI, F., SHARIF-KASHANI, B., BEIGMOHAMMADI, M. T., FARROKHPOUR, M., SEZAVAR, S. H., PAYANDEMEHR, P., DABBAGH, A., MOGHADAM, K. G., JAMALKHANI, S., KHALILI, H., YADOLLAHZADEH, M., RIAHI, T., REZAEIFAR, P., TAHAMTAN, O., MATIN, S., ABEDINI, A., LOOKZADEH, S., RAHMANI, H., ZOGHI, E., MOHAMMADI, K., SADEGHIPOUR, P., ABRI, H., TABRIZI, S., MOUSAVIAN, S. M., SHAHMIRZAEI, S., BAKHSHANDEH, H., AMIN, A., RAFIEE, F., BAGHIZADEH, E., MOHEBBI, B., PARHIZGAR, S. E., ALIANNEJAD, R., ESLAMI, V., KASHEFIZADEH, A., KAKAVAND, H., HOSSEINI, S. H., SHAFAGHI, S., GHAZI, S. F., NAJAFI, A., JIMENEZ, D., GUPTA, A., MADHAVAN, M. V., SETHI, S. S., PARIKH, S. A., MONREAL, M., HADAVAND, N., HAJIGHASEMI, A., MALEKI, M., SADEGHIAN, S., PIAZZA, G., KIRTANE, A. J., VAN TASSELL, B. W., DOBESH, P. P., STONE, G. W.,

LIP, G. Y. H., KRUMHOLZ, H. M., GOLDHABER, S. Z. & BIKDELI, B. 2021. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *JAMA,* 325**,** 1620-1630.

KLOK, F. A., KRUIP, M., VAN DER MEER, N. J. M., ARBOUS, M. S., GOMMERS, D., KANT, K. M., KAPTEIN, F. H. J., VAN PAASSEN, J., STALS, M. A. M., HUISMAN, M. V. & ENDEMAN, H. 2020. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res,* 191**,** 145-147.

LANAS, A., GARCIA-RODRIGUEZ, L. A., ARROYO, M. T., GOMOLLON, F., FEU, F., GONZALEZ-PEREZ, A., ZAPATA, E., BASTIDA, G., RODRIGO, L., SANTOLARIA, S., GUELL, M., DE ARGILA, C. M., QUINTERO, E., BORDA, F., PIQUE, J. M. & ASOCIACION ESPANOLA DE, G. 2006. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut,* 55**,** 1731-8.

LAX, S. F., SKOK, K., ZECHNER, P., KESSLER, H. H., KAUFMANN, N., KOELBLINGER, C., VANDER, K., BARGFRIEDER, U. & TRAUNER, M. 2020. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome : Results From a Prospective, Single-Center, Clinicopathologic Case Series. *Ann Intern Med,* 173**,** 350-361.

LI, T., LU, H. & ZHANG, W. 2020. Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect,* 9**,** 687-690.

LIPPI, G. & PLEBANI, M. 2020. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med,* 58**,** 1131-1134.

LOPES, R. D., DE BARROS, E. S. P. G. M., FURTADO, R. H. M., MACEDO, A. V. S., BRONHARA, B., DAMIANI, L. P., BARBOSA, L. M., DE AVEIRO MORATA, J., RAMACCIOTTI, E., DE AQUINO MARTINS, P., DE OLIVEIRA, A. L., NUNES, V. S., RITT, L. E. F., ROCHA, A. T., TRAMUJAS, L., SANTOS, S. V., DIAZ, D. R. A., VIANA, L. S., MELRO, L. M. G., DE ALCANTARA CHAUD, M. S., FIGUEIREDO, E. L., NEUENSCHWANDER, F. C., DRACOULAKIS, M. D. A., LIMA, R., DE SOUZA DANTAS, V. C., FERNANDES, A. C. S., GEBARA, O. C. E., HERNANDES, M. E., QUEIROZ, D. A. R., VEIGA, V. C., CANESIN, M. F., DE FARIA, L. M., FEITOSA-FILHO, G. S., GAZZANA, M. B., LIPORACE, I. L., DE OLIVEIRA TWARDOWSKY, A., MAIA, L. N., MACHADO, F. R., DE MATOS SOEIRO, A., CONCEICAO-SOUZA, G. E., ARMAGANIJAN, L., GUIMARAES, P. O., ROSA, R. G., AZEVEDO, L. C. P., ALEXANDER, J. H., AVEZUM, A., CAVALCANTI, A. B., BERWANGER, O. & INVESTIGATORS, A. C. C.-B. I. 2021. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet,* 397**,** 2253-2263.

MANNE, B. K., DENORME, F., MIDDLETON, E. A., PORTIER, I., ROWLEY, J. W., STUBBEN, C., PETREY, A. C., TOLLEY, N. D., GUO, L., CODY, M., WEYRICH, A. S., YOST, C. C., RONDINA, M. T. & CAMPBELL, R. A. 2020. Platelet gene expression and function in patients with COVID-19. *Blood,* 136**,** 1317-1329.

MAO, L., JIN, H., WANG, M., HU, Y., CHEN, S., HE, Q., CHANG, J., HONG, C., ZHOU, Y., WANG, D., MIAO, X., LI, Y. & HU, B. 2020. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*.

MORRIS, G., BORTOLASCI, C. C., PURI, B. K., OLIVE, L., MARX, W., O'NEIL, A., ATHAN, E., CARVALHO, A., MAES, M., WALDER, K. & BERK, M. 2021. Preventing the development of severe COVID-19 by modifying immunothrombosis. *Life Sci,* 264**,** 118617.

OXLEY, T. J., MOCCO, J., MAJIDI, S., KELLNER, C. P., SHOIRAH, H., SINGH, I. P., DE LEACY, R. A., SHIGEMATSU, T., LADNER, T. R., YAEGER, K. A., SKLIUT, M., WEINBERGER, J., DANGAYACH, N. S., BEDERSON, J. B., TUHRIM, S. & FIFI, J. T. 2020. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med,* 382**,** e60.

PANIGADA, M., BOTTINO, N., TAGLIABUE, P., GRASSELLI, G., NOVEMBRINO, C., CHANTARANGKUL, V., PESENTI, A., PEYVANDI, F. & TRIPODI, A. 2020. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost,* 18**,** 1738-1742.

PERLMAN, S. & DANDEKAR, A. A. 2005. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol,* 5**,** 917-27.

PIPILIS, A., MAKRYGIANNIS, S., CHRISANTHOPOULOU, E., SOURLAS, N., KALIAMBAKOS, S. & NTAILIANAS, P. 2014. Gastrointestinal bleeding in patients receiving antiplatelet and anticoagulant therapy: practical guidance for restarting therapy and avoiding recurrences. *Hellenic J Cardiol,* 55**,** 499-509.

RAPKIEWICZ, A. V., MAI, X., CARSONS, S. E., PITTALUGA, S., KLEINER, D. E., BERGER, J. S., THOMAS, S., ADLER, N. M., CHARYTAN, D. M., GASMI, B., HOCHMAN, J. S. & REYNOLDS, H. R. 2020. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *EClinicalMedicine,* 24**,** 100434.

RECOVERY COLLABORATIVE GROUP 2022. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet,* 399**,** 143-151.

REMAP-CAP INVESTIGATORS, ACTIV-4A INVESTIGATORS, ATTACC INVESTIGATORS, GOLIGHER, E. C., BRADBURY, C. A., MCVERRY, B. J., LAWLER, P. R., BERGER, J. S., GONG, M. N., CARRIER, M., REYNOLDS, H. R., KUMAR, A., TURGEON, A. F., KORNBLITH, L. Z., KAHN, S. R., MARSHALL, J. C., KIM, K. S., HOUSTON, B. L., DERDE, L. P. G., CUSHMAN, M., TRITSCHLER, T., ANGUS, D. C., GODOY, L. C., MCQUILTEN, Z., KIRWAN, B. A., FARKOUH, M. E., BROOKS, M. M., LEWIS, R. J., BERRY, L. R., LORENZI, E., GORDON, A. C., AHUJA, T., AL-BEIDH, F., ANNANE, D., ARABI, Y. M., ARYAL, D., BAUMANN KREUZIGER, L., BEANE, A., BHIMANI, Z., BIHARI, S., BILLETT, H. H., BOND, L., BONTEN, M., BRUNKHORST, F., BUXTON, M., BUZGAU, A., CASTELLUCCI, L. A., CHEKURI, S., CHEN, J. T., CHENG, A. C., CHKHIKVADZE, T., COIFFARD, B., CONTRERAS, A., COSTANTINI, T. W., DE BROUWER, S., DETRY, M. A., DUGGAL, A., DZAVIK, V., EFFRON, M. B., ENG, H. F., ESCOBEDO, J., ESTCOURT, L. J., EVERETT, B. M., FERGUSSON, D. A., FITZGERALD, M., FOWLER, R. A., FROESS, J. D., FU, Z., GALANAUD, J. P., GALEN, B. T., GANDOTRA, S., GIRARD, T. D., GOODMAN, A. L., GOOSSENS, H., GREEN, C., GREENSTEIN, Y. Y., GROSS, P. L., HANIFFA, R., HEGDE, S. M., HENDRICKSON, C. M., HIGGINS, A. M., HINDENBURG, A. A., HOPE, A. A., HOROWITZ, J. M., HORVAT, C. M., HUANG, D. T., HUDOCK, K., HUNT, B. J., HUSAIN, M., HYZY, R. C., JACOBSON, J. R., JAYAKUMAR, D., KELLER, N. M., KHAN, A., KIM, Y., KINDZELSKI, A., KING, A. J., KNUDSON, M. M., KORNBLITH, A. E., KUTCHER, M. E., et al. 2021. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med,* 385**,** 777-789.

SHAH, A., DONOVAN, K., MCHUGH, A., PANDEY, M., AARON, L., BRADBURY, C. A., STANWORTH, S. J., ALIKHAN, R., VON KIER, S., MAHER, K., CURRY, N., SHAPIRO, S., ROWLAND, M. J., THOMAS, M., MASON, R., HOLLAND, M., HOLMES, T., WARE, M., GURNEY, S. & MCKECHNIE, S. R. 2020. Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study. *Crit Care,* 24**,** 561.

SHAW, R. J., BRADBURY, C., ABRAMS, S. T., WANG, G. & TOH, C. H. 2021. COVID-19 and immunothrombosis: emerging understanding and clinical management. *Br J Haematol,* 194**,** 518-529.

SHI, S., QIN, M., CAI, Y., LIU, T., SHEN, B., YANG, F., CAO, S., LIU, X., XIANG, Y., ZHAO, Q., HUANG, H., YANG, B. & HUANG, C. 2020a. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J,* 41**,** 2070-2079.

SHI, S., QIN, M., SHEN, B., CAI, Y., LIU, T., YANG, F., GONG, W., LIU, X., LIANG, J., ZHAO, Q., HUANG, H., YANG, B. & HUANG, C. 2020b. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*.

SHOLZBERG, M., TANG, G. H., RAHHAL, H., ALHAMZAH, M., KREUZIGER, L. B., AINLE, F. N., ALOMRAN, F., ALAYED, K., ALSHEEF, M., ALSUMAIT, F., POMPILIO, C. E., SPERLICH, C., TANGRI, S., TANG, T., JAKSA, P., SURYANARAYAN, D., ALMARSHOODI, M., CASTELLUCCI, L. A., JAMES, P. D., LILLICRAP, D., CARRIER, M., BECKETT, A., COLOVOS, C., JAYAKAR, J., ARSENAULT, M. P., WU, C., DOYON, K., ANDREOU, E. R., DOUNAEVSKAIA, V., TSENG, E. K., LIM, G., FRALICK, M., MIDDELDORP, S., LEE, A. Y. Y., ZUO, F., DA COSTA, B. R., THORPE, K. E., NEGRI, E. M., CUSHMAN, M., JUNI, P. & INVESTIGATORS, R. T. 2021. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ,* 375**,** n2400.

SPYROPOULOS, A. C., LEVY, J. H., AGENO, W., CONNORS, J. M., HUNT, B. J., IBA, T., LEVI, M., SAMAMA, C. M., THACHIL, J., GIANNIS, D., DOUKETIS, J. D., SUBCOMMITTEE ON PERIOPERATIVE, C. C. T. H. O. T. S. S. C. O. T. I. S. O. T. & HAEMOSTASIS 2020. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost,* 18**,** 1859-1865.

TACQUARD, C., MANSOUR, A., GODON, A., GRUEL, Y., SUSEN, S., GODIER, A. & ALBALADEJO, P. 2021. Anticoagulation in COVID-19: not strong for too long? *Anaesth Crit Care Pain Med,* 40**,** 100857.

TAN, E., SONG, J., DEANE, A. M. & PLUMMER, M. P. 2021. Global Impact of Coronavirus Disease 2019 Infection Requiring Admission to the ICU: A Systematic Review and Meta-analysis. *Chest,* 159**,** 524-536.

TANG, N., LI, D., WANG, X. & SUN, Z. 2020. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost,* 18**,** 844-847.

WALLENTIN, L., BECKER, R. C., BUDAJ, A., CANNON, C. P., EMANUELSSON, H., HELD, C., HORROW, J., HUSTED, S., JAMES, S., KATUS, H., MAHAFFEY, K. W., SCIRICA, B. M., SKENE, A., STEG, P. G., STOREY, R. F., HARRINGTON, R. A., INVESTIGATORS, P., FREIJ, A. & THORSEN, M. 2009. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med,* 361**,** 1045-57.

WICHMANN, D., SPERHAKE, J. P., LUTGEHETMANN, M., STEURER, S., EDLER, C., HEINEMANN, A., HEINRICH, F., MUSHUMBA, H., KNIEP, I., SCHRODER, A. S., BURDELSKI, C., DE HEER, G., NIERHAUS, A., FRINGS, D., PFEFFERLE, S., BECKER, H., BREDEREKE-WIEDLING, H., DE WEERTH, A., PASCHEN, H. R., SHEIKHZADEH-EGGERS, S., STANG, A., SCHMIEDEL, S., BOKEMEYER, C., ADDO, M. M., AEPFELBACHER, M., PUSCHEL, K. & KLUGE, S. 2020. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med,* 173**,** 268-277.

WIVIOTT, S. D., BRAUNWALD, E., MCCABE, C. H., MONTALESCOT, G., RUZYLLO, W., GOTTLIEB, S., NEUMANN, F. J., ARDISSINO, D., DE SERVI, S., MURPHY, S. A., RIESMEYER, J., WEERAKKODY, G., GIBSON, C. M., ANTMAN, E. M. & INVESTIGATORS, T.-T. 2007. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med,* 357**,** 2001-15.

WU, Z. & MCGOOGAN, J. M. 2020. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*.

YUSUF, S., ZHAO, F., MEHTA, S. R., CHROLAVICIUS, S., TOGNONI, G., FOX, K. K. & CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL, I. 2001. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med,* 345**,** 494-502.

ZAID, Y., PUHM, F., ALLAEYS, I., NAYA, A., OUDGHIRI, M., KHALKI, L., LIMAMI, Y., ZAID, N., SADKI, K., BEN EL HAJ, R., MAHIR, W., BELAYACHI, L., BELEFQUIH, B., BENOUDA, A., CHEIKH, A., LANGLOIS, M. A., CHERRAH, Y., FLAMAND, L., GUESSOUS, F. & BOILARD, E. 2020. Platelets Can Associate with SARS-Cov-2 RNA and Are Hyperactivated in COVID-19. *Circ Res*.

ZHOU, F., YU, T., DU, R., FAN, G., LIU, Y., LIU, Z., XIANG, J., WANG, Y., SONG, B., GU, X., GUAN, L., WEI, Y., LI, H., WU, X., XU, J., TU, S., ZHANG, Y., CHEN, H. & CAO, B. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet,* 395**,** 1054-1062.

14. APPENDIX 1. OVERVIEW OF SIMULATIONS FOR STAGE 2 OF THE ANTIPLATELET DOMAIN

14.1. Introduction

In this section, we outline the simulations conducted for understanding the performance of Stage 2 (i.e. reopened) domain. The goal of these simulations is to understand the expected number of additional patients needed to reach a platform conclusion of efficacy of antiplatelet therapy to no antiplatelet.

14.2. Simulation Details

In these simulations, the effect for antiplatelet therapy is modeled as a pooled intervention. It is noted that the design in Stage 2 is nested evaluation but pooled analyses will correspond closely to those obtained for nested interventions.

For the purposes of modelling, these simulations utilize an informative prior for the effect of antiplatelet therapy that represents the effect observed in Stage 1 of the domain. This informative prior is centered on an odds ratio of 1.27 and has a prior 95% credible interval from 0.99 to 1.62. The simulations assume randomization is 1:1 between pooled antiplatelet and no antiplatelet. The primary analysis is based on a Bayesian logistic regression.

14.2.1. Standard-of-Care Rates and antiplatelet effect assumptions

Based on unblinded data from the Antiplatelet Domain, we assume that the in-hospital mortality rate on no antiplatelet is 32%. We created several possible scenarios for odds ratio effects (where OR>1 is beneficial) of pooled antiplatelet on in-hospital mortality:

Scenario	Odds ratio	No antiplatelet mortality rate (%)	Pooled antiplatelet mortality rate (%)	Absolute difference (%)
1	1.27	32	27	5
2	1.18	32	28.5	3.5
3	1.4	32	25	7
4	1	32	32	0

These scenarios represent a range of plausible values of the odds ratio effect based on the unblinded analyses of the initial stage of the Antiplatelet Domain. The first scenario is consistent with the estimated odds ratio effect of pooled antiplatelet on in-hospital mortality that adjusts for covariates and assignment to additional interventions. The second scenario is based on the unadjusted odds

ratio corresponding to the observed mortality rates of 32% and 28.5% on the no antiplatelet and pooled antiplatelet interventions, respectively. The third and fourth scenarios represent a larger and smaller odds ratio than observed on in-hospital mortality in the first stage of this domain.

For the simulations in this section, adaptive analyses are assumed to occur at 400 patients enrolled and then every 200 patients up to a maximum additional sample size of 2000.

14.3. Operating Characteristics

Figure 2 presents the cumulative probability to determine that an antiplatelet therapy is superior to no antiplatelet therapy as a function of the total number of patients enrolled in Stage 2 of the Antiplatelet Domain (x-axis) and the assumed effect sizes. After reopening, the domain has at least 80% power to demonstrate superiority of an antiplatelet therapy to no antiplatelet therapy by 1400 patients enrolled assuming an odds ratio effect size of 1.4. For an effect size of 1.27, the power is approximately 80% with 2000 patients enrolled in Stage 2. If there is no effect of antiplatelet therapy in the reopened domain, the cumulative probability of declaring antiplatelet therapy superior to no antiplatelet is 10% by 2000 patients enrolled.

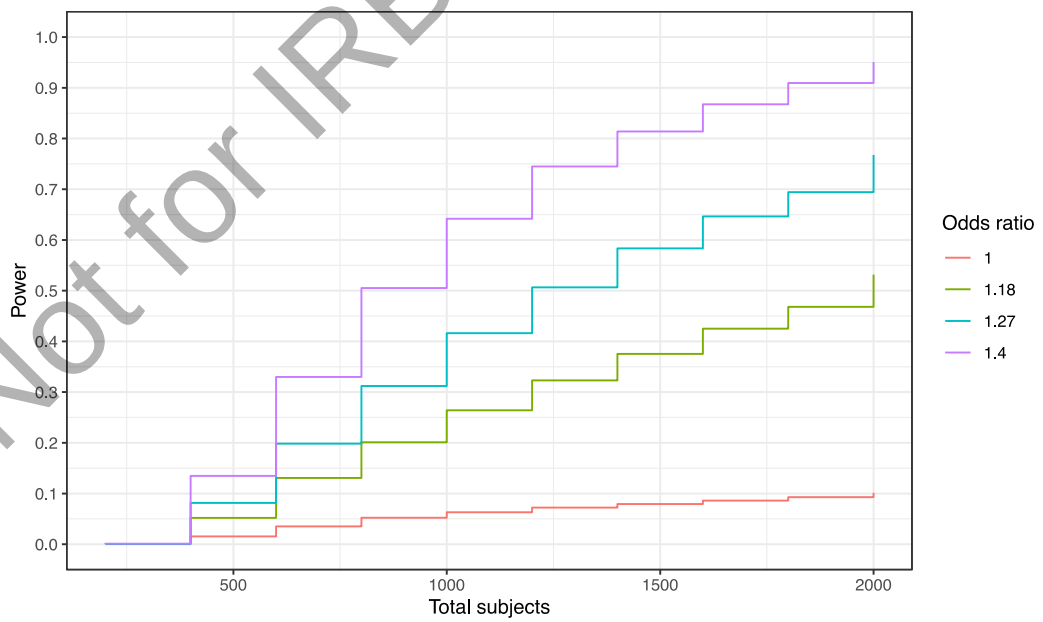

Figure 2: The cumulative power for each of the explored treatment effects (odds ratios of 1, 1.18, 1.27, and 1.4) versus the total number of subjects randomized to any intervention in the reopened domain.