A randomized controlled trial to investigate the use of acute coronary syndrome therapy in patients hospitalized with COVID-19

the COVID-19 Acute Coronary Syndrome trial

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ORIGINAL ARTICLE

A randomized controlled trial to investigate the use of acute coronary syndrome therapy in patients hospitalized with COVID-19: the COVID-19 Acute Coronary Syndrome trial

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Abstract

Background: Patients hospitalized with COVID-19 suffer thrombotic complications. Risk factors for poor outcomes are shared with coronary artery disease.

Objectives: To investigate the efficacy of an acute coronary syndrome regimen in patients hospitalized with COVID-19 and coronary disease risk factors.

Methods: A randomized controlled, open-label trial across acute hospitals (United Kingdom and Brazil) added aspirin, clopidogrel, low-dose rivaroxaban, atorvastatin, and omeprazole to standard care for 28 days. Primary efficacy and safety outcomes were 30-day mortality and bleeding. The key secondary outcome was a daily clinical status (at home, in hospital, on intensive therapy unit admission, or death).

Results: Three hundred twenty patients from 9 centers were randomized. The trial terminated early due to low recruitment. At 30 days, there was no significant difference in mortality (intervention vs control, 11.5% vs 15%; unadjusted odds ratio [OR], 0.73; 95% CI, 0.38-1.41; p = .355). Significant bleeds were infrequent and were not significantly different between the arms (intervention vs control, 1.9% vs 1.9%; $p > .999$). Using a Bayesian Markov longitudinal ordinal model, it was 93% probable that intervention arm participants were more likely to transition to a better clinical state each day (OR, 1.46; 95% credible interval [CrI], 0.88-2.37; Pr [beta > 0], 93%; adjusted OR, 1.50; 95% CrI, 0.91-2.45; Pr [beta > 0], 95%) and median time to discharge to home was 2 days shorter (95% CrI, −4 to 0; 2% probability that it was worse).

Conclusion: Acute coronary syndrome treatment regimen was associated with a reduction in the length of hospital stay without an excess in major bleeding. A larger trial is needed to evaluate mortality.

KEYWORDS
anticoagulant agent, antiplatelet agent, COVID-19 infection, ischemic heart disease, randomized controlled trial, thrombosis

1 | INTRODUCTION

Hospitalized patients with COVID-19 respiratory disease often develop thrombotic complications [1,2]. Observational studies have consistently found that a history of coronary artery disease and cardiovascular risk factors, such as hypertension and diabetes, is associated with severe disease and mortality from COVID-19 [3,4]. This would be a peculiar finding if COVID-19 was primarily a respiratory disease.

Cardiac biomarkers, such as troponin, are frequently elevated in hospitalized patients with COVID-19 and are associated with poor prognosis [5–7]. Although arterial thrombosis in atheromatous coronary vessels might be a potential explanation, these biomarkers do not allow differentiation between ischemic myocardial damage and

Essentials

- Thrombosis is often found in patients hospitalized with COVID-19, and risk factors for poor prognosis are shared with coronary artery disease.
- In a multinational randomized controlled trial, we tested if the addition of standard acute coronary syndrome therapy in 320 hospitalized patients with COVID-19 and cardiovascular risk factors improved clinical outcomes.
- No significant reduction in mortality was found with therapy.
- There was modest evidence of a reduction in the length of hospital stay without an increase in major bleeding.

myocarditis. However, myocardial infarction has been identified in nearly 20% of cases using late gadolinium enhancement magnetic resonance imaging after recovery of patients with severe COVID-19 and a raised troponin level [8,9]. Furthermore, immune-mediated vascular thrombosis and resultant cardiac injury through direct platelet reprogramming, indirect activation, and the development of antiplatelet, antiphospholipid, and anti–endothelial cell antibodies have been found in patients with COVID-19 [10]. These findings imply that myocardial damage from coronary arterial thrombosis may contribute to the morbidity and mortality in severe COVID-19 disease.

Coronary thrombosis and occlusion result in acute coronary syndromes (ACSs). Although the mechanism initiating thrombosis may differ in COVID-19 from conventional causes of ACS, it is possible that the shared risk factors result in a shared therapeutic target. Mortality from ACS has been transformed by the benefits of antiplatelet, anticoagulant, and statin therapies [11]. We hypothesized that a combination ACS treatment regimen may have a beneficial impact on patients hospitalized with COVID-19 by preventing myocardial damage. The additive effects of these drugs in ACS were tested incrementally in sequential trials over many years. Replicating such a strategy in COVID-19 would be impractical. We, therefore, opted for a pragmatic approach of testing an established ACS regimen that could be delivered orally rather than parenterally [12].

Herein, we report the safety and efficacy findings of a randomized, open-label, multicenter study evaluating the addition of a conventional ACS regimen (aspirin, clopidogrel, low-dose rivaroxaban, atorvastatin, and omeprazole) in patients hospitalized with COVID-19 who either were aged >40 years or had a history of coronary disease, diabetes, or hypertension.

2 | METHODS

2.1 | Trial design and oversight

COVID-19 Acute Coronary Syndrome (C19-ACS) was a multicenter, open-label, prospective, randomized control trial that compared the addition of ACS therapy in patients admitted to a hospital for treatment of COVID-19 who were at risk of cardiovascular complications to standard care. The study was overseen by the Trial Steering Committee (TSC) and an independent data and safety monitoring board. The trial was approved by the London – West London & Gene Therapy Advisory Committee Research Ethics Committee (Ref: 20/LO/0574) in the United Kingdom and the Comissao Nacional de Etica em Pesquisa (Ref: 4.171.639) in Brazil. The study was conducted in accordance with the Good Clinical Practice guidelines, and it was registered at ClinicalTrials.gov as NCT04333407. All patients (or appropriate surrogates if capacity lacking) provided informed consent.

The trial was funded by the Coronary Flow Charitable Trust and the Imperial College COVID-19 fund, which had no role in the design, analysis, or reporting of trial results. The members of the writing committee declare that the data are accurate, complete, and collected in adherence to the protocol. The trial protocol and statistical analysis plan are appended as Supplementary Materials.

2.2 | Recruitment

Recruitment started in the United Kingdom in April 2020 across 5 sites and then expanded to Brazil on September 24, 2020, across 4 sites. The study was terminated in November 2021. C19-ACS enrolled patients aged ≥18 years who were admitted for inpatient hospital treatment for COVID-19 with the presence of cardiovascular risk factors. Infection was confirmed by fulfillment of ≥1 of the following criteria: "positive test for COVID-19 viral infection (either rapid antigen testing or polymerase chain reaction tests), chest radiograph or CT suggestive of COVID-19 (based on local radiologist or clinician review), or typical lymphopenia (as per local laboratory reporting)."

Patients were required to have ≥1 of the following cardiovascular risk factors: diabetes mellitus, hypertension, known coronary artery disease, and age ≥40 years. Exclusion criteria included clear evidence of an ACS or myopericarditis that required specific treatment to preclude randomization, evidence of active bleeding, pregnancy, and age of <18 years. Participants were followed up for 30 days.

2.3 | Randomization

Participants were randomized 1:1 to intervention or control groups using an in-house, web-based, system with minimization across 4 clinical factors (age of ≥60 years, presence of diabetes mellitus, presence of coronary artery disease, and sex) and random factor (0.2). The intervention arm was aspirin 75 mg once daily (300-mg loading dose), clopidogrel 75 mg once daily (300-mg loading dose), rivaroxaban 2.5 mg twice daily, atorvastatin 80 mg once daily, and omeprazole 20 mg once daily. Modifications of this regimen to account for drug interactions (eg, statins with macrolide antibiotics), existing or new indication for anticoagulation, or need for parenteral routes are described in the Supplementary Materials, Protocol. Participants in the control arm continued any of these medications if they were already receiving them or if they developed a new indication for one during the study. Standard care in both arms was at the discretion of the admitting team and was not altered by the study team. Therapy was for 28 days, continuing after discharge. Participants could be enrolled into other clinical trials for COVID-19, unless they were testing antiplatelet, anticoagulant, or statin therapies.

2.4 | Follow-up and data collection

Participants were followed up for 30 days. Due to the COVID-19 pandemic, all follow-up was conducted remotely. During their inpatient stay, study teams used hospital records to ascertain adverse events, escalation of care, and discharge details. After 30 days,

participants (or their preferred contact provided at enrolment) were telephoned to ascertain their status, collect further information on adverse events (such as readmission to a different hospital), and ensure that those in the intervention group returned to their preexisting medications.

2.5 | Outcomes

The primary efficacy outcome was mortality at 30 days. The primary safety outcome was bleeding (assessed using the Bleeding Academic Research Consortium [BARC] [13]) at 30 days. The key secondary outcome was participants' daily clinical status over the 30 days on a 4-point ordinal scale (at home, in hospital, on an intensive therapy unit (ITU) or equivalent environment, or dead), a simplification of the World Health Organization (WHO)–recommended ordinal scale for collecting data in COVID-19 trials [14]. Additional secondary efficacy outcomes included the time to discharge (duration/length of hospital stay). Additional safety outcomes included BARC 3 to 5 bleeds, BARC 5 bleeds (bleeds resulting in death), thromboembolic events, and cessation of therapy in the active arm.

2.6 | Monitoring and adjudication

The trial monitor performed reviewed documentation via videoconference and email to the national and international sites. All deaths, and 25% of the study data were subject to monitoring, and original source documentation reviewed. All deaths and bleeding and thrombosis events were submitted on digital adverse event forms and reviewed by a central adjudication committee who categorized bleeds according to the BARC classification.

2.7 | Statistical analysis

The primary analysis was conducted on the intent-to-treat population that included all participants who were allocated to the study arms regardless of the subsequent treatment received.

The effect size for the primary efficacy and safety outcomes are presented as odds ratios (ORs) and their associated 95% CIs and *p* values, calculated using logistic regression, including sex, age, recruitment site, presence of diabetes mellitus, coronary artery disease, and hypertension as covariates. Both unadjusted and adjusted results are presented.

The key secondary outcome of a daily ordinal scale was analyzed using Bayesian first-order Markov longitudinal ordinal model [15]. This method has been previously described and used in both COVID-19 and other trials [13,14]. The model includes the previous day's state, a flexible function of time since randomization (to allow a nonconstant hazard rate), nonproportional odds effect for time (as the mix of events can change over time), and a time by arm interaction (to allow for the effects of therapy to change over time), in addition to the aforementioned minimization and stratification covariates. This model was fitted using an Markov chain Monte Carlo algorithm and the "rmsb" package in the "R" (R Statistical Environment (v4.3.0; R Core Team 2021) statistical environment. The model used noninformative normal priors for the beta parameters with an SD of 100, and intercepts with a Dirichlet prior with a concentration parameter of 0.455. ORs, 95% credible intervals (CrIs), and the probability of the coefficient being >0 are reported. From sample draws of the fitted model, the median time to discharge was calculated.

No correction for multiple testing was made. Missing data were not imputed for any variables used in the analysis. The trial's detailed statistical analysis plan is included in Supplementary Material, Statistical Analysis Plan.

2.8 | Sample size

Sample size calculations during a pandemic of a novel disease are challenging. We originally calculated that on the basis of an estimated mortality rate of 25% in patients admitted to the hospital with COVID-19 [4], and approximately 3062 patients would provide 90% power at a 5% significance level to detect a reduction in mortality by 20% with an estimated 2% loss to follow-up. The key secondary outcome of an ordinal scale and longitudinal analysis was made without reference to unblinded data and was based on emerging statistical practices of other trials of therapies in COVID-19, public recommendations from health authorities (such as the WHO), and extensive work by biostatisticians involved in COVID-19 work. A detailed statistical analysis plan is included in the Supplementary Material, Protocol.

2.9 | Protocol changes and early termination

Throughout the trial, the Trial Management Group took recommendations from the TSC, which was advised by the Data Monitoring Committee. Initially, the trial was designed with an initial phase based on biochemical markers (including D-dimer and troponin), with a target of 3062. Due to difficulties obtaining regular blood tests during the pandemic, this was dropped, and due to tapering recruitment, as we emerged from the first wave of COVID-19 and methodical recommendations from the WHO and other clinical trials, we switched to the longitudinal Bayesian ordinal model for the key secondary end point. Finally, the TSC, on the basis of a recommendation of the Data Monitoring Committee terminated the trial early for futility based on the recruitment and event rate for the primary end point (Supplementary Materials, Statistical Analysis Plan). This occurred after 320 patients had been enrolled.

TABLE 1 Baseline characteristics.

	Intervention *N* = 159	Control *N* = 160	All *N* = 319
Recruitment country			
United Kingdom	73 (46%)	73 (46%)	146 (46%)
Brazil	86 (54%)	87 (54%)	173 (54%)
Inclusion risk factors			
Age ≥40 y	158 (99%)	159 (99%)	317 (99%)
Diabetes	62 (39%)	61 (38%)	123 (39%)
Hypertension	97 (61%)	95 (59%)	192 (60%)
Coronary artery disease	28 (18%)	39 (24%)	67 (21%)
Demographics			
Age (y), mean ± SD	63.9 ± 11.6	63.3 ± 11.9	63.6 ± 11.7
Median (IQR)	65 (IQR, 55-72)	63.5 (IQR, 55-73)	64 (IQR, 55-73)
Male	97 (61%)	101 (63%)	198 (62%)
Female	62 (39%)	59 (37%)	121 (38%)
Angina	9 (6%)	11 (7%)	20 (6.3%)
Myocardial infarction	19 (12%)	26 (16%)	45 (14.1%)
Percutaneous coronary intervention	16 (10%)	17 (11%)	33 (10.3%)
Coronary artery bypass graft	10 (6%)	12 (8%)	22 (6.9%)
Asthma	14 (9%)	11 (7%)	25 (7.8%)
Active cancer	5 (3%)	5 (3%)	10 (3.1%)
Current smoker	4 (3%)	3 (2%)	7 (2.2%)
Ex-smoker	37 (23%)	42 (26%)	79 (25%)
Never smoked	55 (35%)	54 (34%)	109 (34%)
Unknown smoking status	63 (40%)	61 (38%)	124 (39%)
Troponin (baseline)			
Value available	130 (82%)	131 (82%)	261 (82%)
Median	10	11	10.8
IQR	(5-21.8)	(5-33.0)	(5-27.9)
Positive (≥32)	29/130 (22%)	33/132 (25%)	62/261 (24%)

3 | RESULTS

3.1 | Recruitment and follow-up

Three hundred and twenty patients were enrolled and randomized to 2 study arms, 160 to the intervention arm and 160 to the control arm (Figure 1). One participant randomized to the intervention arm withdrew from the study immediately after randomization and provided no baseline or follow-up data. Two participants randomized to the intervention arm withdrew from the study at the time of discharge from the hospital and contributed data until this point. All other participants completed the 30-day phone call.

3.2 | Baseline characteristics

Patients were enrolled from 5 hospitals in the United Kingdom (46%) and 4 hospitals in Brazil (54%). The mean age was 64 years, with 99% of participants aged ≥40 years, and 62% of participants were male. Cardiovascular risk factors were common; 60% had a history of hypertension, 39% had diabetes, and 21% had coronary artery disease. A valid troponin was available at baseline (within 6 days before to 2 days after randomization) in 82% of participants. Baseline troponin was positive (≥32 ng/L) in 24% of these participants (median, 10.8; IQR, 5.0-27.9). Other baseline characteristics are shown in Table 1.

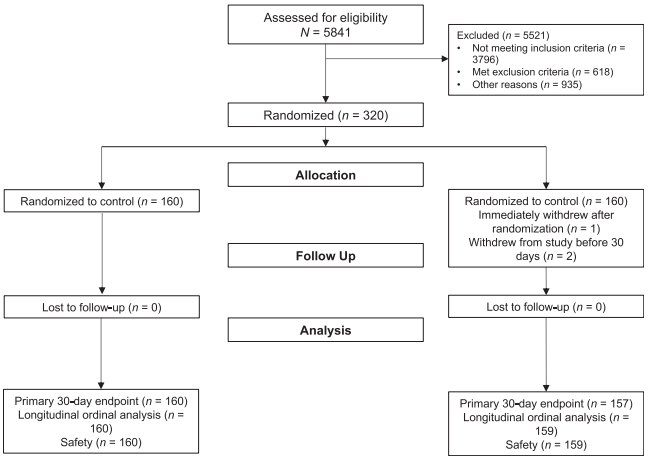

FIGURE 1 CONSORT diagram.

3.3 | Exposure to intervention

As a pragmatic open-label trial of 5 drugs, participants randomized to the intervention arm may not have received all 5 drugs. For example, if a patient declined a statin, atorvastatin was not started but other trial drugs were. Conversely, some participants randomized to the control group were already on some of the trial drugs (eg, due to a history of coronary artery disease). These medications were continued. Of the participants randomized to the intervention arm, 91% received aspirin, 92% received clopidogrel, 77% received rivaroxaban 2.5 mg twice daily, 87% received atorvastatin or another statin, and 93% received omeprazole or another proton pump inhibitor (PPI). Among participants randomized to the control group, 31% received aspirin, 13% received clopidogrel, 0 received rivaroxaban 2.5 mg twice daily, 53% received atorvastatin or another statin, and 62% received omeprazole or another PPI. Overall, 58% (93 of 159) of the intervention group and 0 (0 of 160) of the control group received at some point one of all 5 therapy classes: any 2 antiplatelets, rivaroxaban 2.5 mg twice daily, any statin, and any PPI. Further details are shown in Table 2.

3.4 | Primary outcome

At 30 days, 18 of 157 (11.5%) of participants in the intervention group, and 24 of 160 (15.0%) in the control group had died. There was no significant difference between the groups (unadjusted OR, 0.73; 95% CI, 0.38-1.41; p = .355; adjusted OR, 0.71; 95% CI, 0.36-1.42; p = .337). Bayesian analyses are reported in the Supplementary Materials, Additional Result 1.

3.5 | Secondary outcomes

The daily clinical state (at home, in hospital, on ITU, or dead) over 30 days was tabulated, with the proportion in each category shown in Figure 2. Using a Bayesian Markov longitudinal ordinal model, it is 93% probable that participants randomized to the intervention arm are more likely, compared with those randomized to the control arm, to transition to a better clinical state each day (OR, 1.46; 95% CrI, 0.88-2.37; Pr [beta > 0], 93%; adjusted OR, 1.50; 95% CrI, 0.91-2.45; Pr [beta > 0], 95%). The median time to discharge home was 2 days shorter in the intervention group (95% CrI, −4 to 0), with only a 2% probability that it was worse.

TABLE 2 Trial medication exposure.

	Intervention (n = 159)	Control (n = 160)
Aspirin	145 (91%)	49 (31%)
Clopidogrel	147 (92%)	21 (13%)
Other antiplatelet	1 (1%)	0 (0%)
No. of antiplatelets		
None	7 (4%)	103 (64%)
1 antiplatelet agent	11 (7%)	44 (28%)
2 antiplatelet agents	141 (89%)	13 (8%)
Any anticoagulant	147 (92%)	116 (73%)
First anticoagulant received		
Rivaroxaban trial dose (2.5-mg dose twice daily)	108 (68%)	0 (0%)
UFH 5000 units	1 (1%)	5 (3%)
LMWH prophylaxis	10 (6%)	45 (28%)
LMWH as part of a local COVID protocol	4 (3%)	15 (9%)
LMWH Rx	7 (4%)	22 (14%)
Warfarin Rx	3 (2%)	11 (7%)
Apixaban Rx	2 (1%)	9 (6%)
Rivaroxaban Rx	11 (7%)	7 (4%)
LMWH unspecified	1 (1%)	2 (1%)
Rivaroxaban trial dose (2.5 mg twice daily) at any time	123 (77%)	0 (0%)
Any statin	138 (87%)	86 (53%)
Any PPI	148 (93%)	99 (62%)
Any 2 antiplatelets, rivaroxaban trial (2.5-mg dose twice daily), any statin, any PPI	93 (58%)	0 (0%)

Trial medication exposure is exposure to the trial medications (or associated classes) at any point during the 28 days of the trial.

LMWH, low molecular weight heparin; Rx, dosage to achieve therapeutic anticoagulation; UFH, unfractionated heparin; PPI, proton pump inhibitor.

3.6 | Safety

There was no significant difference in bleeding (across BARC grades) between the intervention and control arms (13 of 159 [8.2%] vs 9 of 160 [5.6%]; p = .5). Major bleeds (those adjudicated BARC 3 or above)

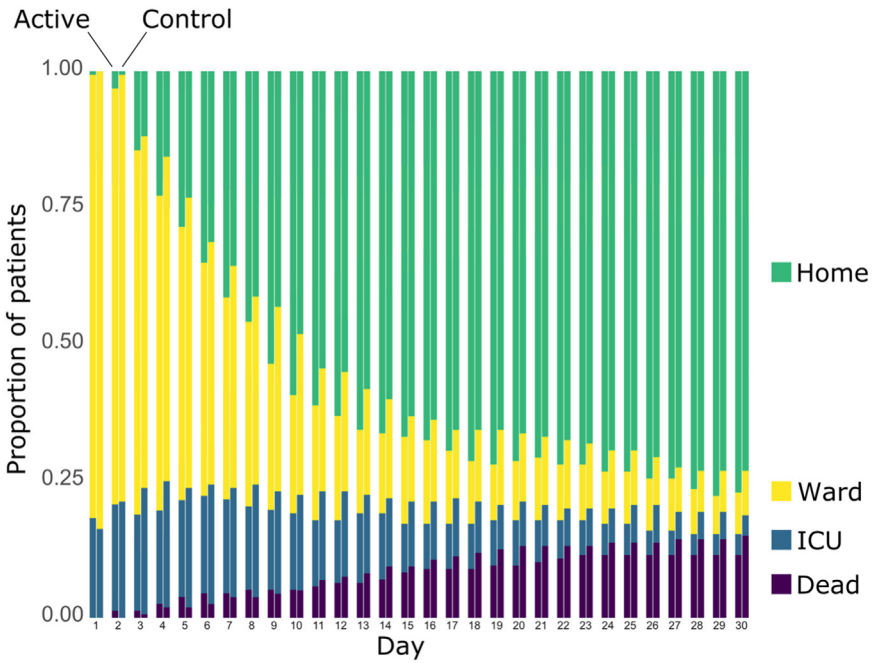

FIGURE 2 The proportion of participants in each of the 4 clinical states, split by the active and control arms (pairs of columns, active left and control right), over the 30 days after randomization. ICU, intensive care unit.

were infrequent, and not significantly different between the arms (intervention, 3 of 159 [1.9%]; control, 4 of 160 [2.5%]; difference, 0.6%; 95% CI, −4.4% to 3.2%; $p > .999$). There was 1 fatal bleed in each arm. All bleeding events and associated BARC classification are detailed in Table 3.

The central coordinating center was specifically informed about cessation of therapy in 8 participants in the intervention group; 2 due to bleeding, 1 due to thrombosis, 1 due to clinical deterioration, 3 as the patient withdrew consent for the intervention, and 1 at discharge for unspecified reasons. As a pragmatic trial, therapy could be started or stopped by both participants and their physicians during the 28 days so true discontinuation rates may be higher than this.

4 | DISCUSSION

C19-ACS is the first study to test an ACS treatment regimen in patients hospitalized with COVID-19 and a risk factor for coronary disease. The trial was terminated early and found no significant evidence that the therapy reduced mortality. However, there was moderate evidence that patients were more likely to improve each day and have a shorter hospital stay. Overall, bleeding was uncommon, and although the study had limited power to detect a difference, it was similar between the arms.

This study enrolled a broad group of patients with COVID-19 with easily identifiable risk factors to a well-established therapy that may overlap in pathology.

Since the initiation of this trial, multiple randomized trials testing the individual components of the ACS therapeutic regimen in patients with COVID-19 have been reported.

Antiplatelet monotherapy has not been found to be effective in reducing mortality across a wide range of patient groups from the critically unwell (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]) [16], those hospitalized (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) [17], to those in the community (Activated Clotting Time [ACT]) [18]. However, and consistent with RECOVERY, this study found modest evidence that therapy reduced the median length of stay by 1 day. Although major bleeding events were low, there was a significant difference between the arms in RECOVERY (1.6% vs 1%) [17].

There has, however, been modest evidence that therapeutic anticoagulation with low molecular weight or intravenous heparin reduces the need for organ support in hospitalized but not critically unwell patients (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC]/Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE [ACTIV-4a]/REMAP-CAP) [12]. However, the Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label

TABLE 3 Bleeding end points.

Bleeding Academic Research Consortium bleeding level	Intervention *N* = 159	Control *N* = 160
5 (fatal)	1 (0.6%)	1 (0.6%)
4 (CABG-related)	0 (0%)	0 (0%)
3 (overt with Hb drop)	2 (1.3%)	3 (1.9%)
3B (Hb drop, ≥5 g/dL)	1	2
3A (Hb drop, 3-5 g/dL)	1	1
1 (not actionable) or 2 (overt and actionable)	10 (6.3%)	5 (3.1%)

Hb, hemoglobin; CABG, coronary artery bypass graft.

Randomized Controlled Trial (INSPIRATION) study found no benefit to intermediate-dose anticoagulation over prophylactic dose, but this regimen did not include antiplatelet agents and only recruited patients requiring intensive care unit treatment [19]. Limited benefits in some end points were found in a trial of rivaroxaban in hospitalized patients (Medically Ill hospitalized Patients for COVID-19 THrombosis Extended ProphyLaxis with rivaroxaban ThErapy [MICHELLE]) [20].

Neither the INSPIRATION-S study recruiting "critically ill" patients with COVID-19 nor the Statin and aspirin as adjuvant therapy in hospitalised patients with SARS-CoV-2 infection: a randomised clinical (RESIST) trial in those only hospitalized, found benefit with atorvastatin [21,22].

The results of C19-ACS are broadly compatible with the findings of these trials, with modest evidence that it increased the probability of clinical improvement and reduced hospital stay. The RECOVERY trials show us that the efficacy of therapy can be dependent on the patient's clinical status [23]. For dexamethasone, little efficacy was found in those with the mildest disease. Conversely, there is a possibility that there comes a point where the clinical state has deteriorated such that no therapy could work. This trial recruited in-hospital patients receiving ward-level care, and they may have been toward the milder end of the spectrum. Nevertheless, a fifth of patients were in ITU within 1 day of recruitment. Many of these trials recruiting critically unwell patients were neutral.

Unusually for an infectious disease, the risk factors for severe COVID-19 disease mirrored those for coronary disease. Furthermore, there was a nearly 4-fold increase in mortality in patients with coronary disease [24], and imaging of survivors of severe disease showed that approximately 20% suffered myocardial infarction [8]. Many patients with coronary artery disease are undiagnosed [19], underlying the importance of enrolling those with risk factors, as occurred with the pragmatic recruitment strategy for C19-ACS. This regimen is known to be an effective treatment for ACS [11], so the finding of clinical improvement and low and similar rates of bleeding shows promise.

There is evidence that the coagulopathy in COVID-19 illness is distinct from those in other critical illnesses. As compared with other causes of sepsis, higher fibrinogen and D-dimer levels and only minor changes in platelet count are seen with COVID-19 [25]. However, the differences are not limited to the coagulation pathway and also include direct endothelial cell dysfunction (perhaps via the ACE-2 receptor) and pulmonary vascular constriction (particularly in the setting of hypoxia) [26–28]. Furthermore, pulmonary thrombosis is likely to be important, with autopsy studies showing almost 10 times the rate of pulmonary thrombus in COVID-19 compared with influenza [29].

The benefit of the C19-ACS regimen may therefore reflect a systemic prothrombotic illness in which both antiplatelet-responsive atherosclerotic and anticoagulant-responsive thrombosis are therapeutic targets. Multiple mechanisms of cardiac injury occur in COVID-19, and it is possible that the broader range of interventions seen in the ACS bundle treats a larger spectrum of potential insults that may be occurring in the same patient. Our data provide the impetus for further investigations of antithrombotic therapies in patients with COVID-19 infection.

4.1 | Limitations

This trial was underpowered for the primary outcome of mortality as it was terminated early due to an inadequate recruitment rate.

We were aware of a bias against recruiting to the study due to safety concerns about bleeding. This may have resulted in selecting a patient population with a lower risk of bleeding. The incidence of major bleeding was low, and similar to the 1% seen in the RECOVERY-aspirin trial. However, as a pragmatic trial, not all participants received all the trial medications due to individual contraindications. Due to the nature of the pandemic, data for exposure to trial medications were based on issued prescriptions and participant phone calls rather than pill counts. Not all patients would have completely adhered to the trial medications throughout the 28 days. These 2 factors will reduce the reported incidence of bleeding.

Furthermore, the study was underpowered to detect small absolute differences in the incidence of major bleeding and the common use of prophylactic heparin in medical inpatients in the control arm, and the continuation of existing antiplatelet and anticoagulant therapy may have reduced any differences between the arms resulting from the therapy.

We aimed to enroll a broad range of patients with minimal exclusion criteria. Enrolling patients on the basis of biomarkers, such as D-dimer, may have selected patients in whom therapy was more likely to be successful. However, other trials enrolling with such a strategy for anticoagulation have had variable results. The Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID) trial of therapeutic dose heparin found a reduction in mortality, although this was a small study and a secondary end point [30]. Conversely, the Anticoagulation Coronavirus (ACTION) trial found no benefit of higher doses of rivaroxaban (15-20 mg) despite enrolling those with raised D-dimer levels [31].

As with many other trials repurposing existing therapies for COVID-19, this trial was open-label. This may have introduced bias. However, it might be expected to act in the converse direction, with the addition of therapies requiring a longer stay to assess tolerability and with the participant's responsible clinicians more likely to report bleeds if they are known to be on additional antiplatelet or anticoagulant therapy.

5 | CONCLUSION

The C19-ACS trial was underpowered to determine whether an ACS treatment regimen improved survival in patients hospitalized for COVID-19 with risk factors for coronary disease. However, there was moderate evidence that it accelerated clinical improvement and reduced the median length of hospital stay. This merits further evaluation in a larger trial.

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AUTHOR CONTRIBUTIONS

P.K. was the chief investigator for C19-ACS. D.P.F., P.K., C.C., A.M., and M.S.-S. formed the C19-ACS Committee. M.S.S., M.S., and V.C. formed the Statistical Analysis Protocol working group. The Trial Steering Committee comprised of G.Y.H.L., P.K., A.J.C., M.T., W.G., G. C., V.C., A.S.M.B., A.M., D.P.F., M.S.-S., M.S., G.S.C., R.A.-L., and C.C. The DMC was formed by N.M., M.J.L., and S.J.C. Principal investigators at UK sites were M.K., R.M., J.S., S.N., and N.R. Principal investigators at Brazil sites were D.C., P.P., D.d.A.N., R.E., G.B., and R.M.-M. Patient recruitment was overseen by A.M., C.C., G.K., M.M., K.M., and P.P. The imperial clinical trials unit provided support via A.M. and M.D. The manuscript was prepared by P.K., C.C., and M.S.-S. with contributions from all authors.

DECLARATION OF COMPETING INTERESTS

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DATA SHARING STATEMENT

The data collected in the study, including anonymized individual patient data and a data dictionary defining each field in the data set, will be made available to others on reasonable request to the corresponding author.

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and registered) have been explained. All authors had full access to the data.

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SUPPLEMENTARY MATERIAL

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