Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The REMAP-CAP Investigators

Author and Group Information

The members of the writing committee and the collaborators appear at the end of this article.

Running Head

REMAP-CAP COVID-19 Corticosteroid Domain RCT

Keywords

Adaptive platform trial; intensive care; pneumonia; pandemic; COVID-19; hydrocortisone; corticosteroid

Revision date

August 17th, 2020

Word Count

3999

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Key Points

Question

Does intravenous hydrocortisone, administered either as a 7-day fixed dose course or restricted to when shock is clinically evident, improve 21-day organ support-free days (a composite end-point of in-hospital mortality and the duration of ICU-based respiratory or cardiovascular support) in patients with severe COVID-19?

Findings

In this Bayesian randomized clinical trial that included 403 patients and was stopped early, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support-free days within 21 days.

Meaning

Although suggestive of benefit for hydrocortisone in patients with severe COVID-19, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

Abstract

IMPORTANCE Evidence regarding corticosteroid use for severe COVID-19 is limited.

OBJECTIVE To determine whether hydrocortisone improves outcome for patients with severe COVID-19.

DESIGN, SETTING, AND PARTICIPANTS An ongoing adaptive platform trial testing multiple interventions within multiple therapeutic domains. Between March 9 and June 17th 2020, 614 adult patients with suspected or confirmed COVID-19 were enrolled and randomized within at least one domain following admission to an intensive care unit (ICU) for respiratory or cardiovascular organ support at 121 sites in 8 countries. Of these, 403 were randomized to open-label interventions within the Corticosteroid Domain. The Domain was halted after results from another trial were released. Follow-up ended August 12th, 2020.

INTERVENTIONS The Corticosteroid Domain randomized participants to a fixed 7-day course of intravenous hydrocortisone (50mg or 100mg q6h) (n=143), a shock-dependent course (50mg q6h when shock was clinically evident) (n=152), or no hydrocortisone (n=108).

MAIN OUTCOMES AND MEASURES The primary end point was organ support-free days (days alive and free of ICU-based respiratory or cardiovascular support, OSFDs) within 21 days, where patients who died were assigned –1 days. The primary analysis was a Bayesian cumulative logistic model that included all patients enrolled with severe COVID-19, adjusting for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility. Superiority was expressed as the posterior probability (%) of OR >1 (threshold for trial conclusion: >99%).

RESULTS After excluding 19 participants who withdrew consent, there were 384 patients (mean age, 60 years; 29% female) randomized to the fixed dose (n=137), shock-dependent (n=146), and no (n=101) hydrocortisone groups. The median (IQR) OSFDs were 0 (–1, 15), 0 (–1, 13) and 0 (–1, 11) days (composed of 30%, 26% and 33% mortality rates and 11.5, 9.5 and 6 median OSFDs among survivors) for the fixed dose, shock-dependent, and no hydrocortisone groups, respectively. The adjusted OR (median, 95% credible interval) and Bayesian probability of superiority (%) was 1.43 (0.91 – 2.27) and 93% for fixed dose hydrocortisone and 1.22 (0.76 – 1.94) and 80% for shock-dependent hydrocortisone compared to no hydrocortisone. Serious adverse events were reported in 4 (3%), 5 (3%) and 1 (1%) patients in the fixed dose, shock-dependent, and no hydrocortisone groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support-free days within 21 days. However, the trial was stopped early, precluding definitive conclusions.

TRIAL REGISTRATION Clinicaltrials.gov identifier: NCT02735707

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in Wuhan, China in December 2019, more than 20 million COVID-19 cases and 750,000 deaths have been reported worldwide by August 2020.[1] Though many therapies are being evaluated, strong evidence of benefit is generally lacking.[2] One class of agents that has received considerable attention is corticosteroids. Corticosteroids were reported to be beneficial in several conditions analogous to COVID-19, including sepsis, pneumonia and acute respiratory distress syndrome (ARDS).[3-5] However, other trials in these conditions, as well as in influenza and coronavirus respiratory syndromes, showed no benefit or possible harm.[3,6,7] Consequently, advice for COVID-19 has been mixed.[8] The China National Health Commission suggested hydrocortisone is appropriate,[9] the Surviving Sepsis Campaign recommended against corticosteroid use in the absence of ARDS, but suggested possible benefit in those with ARDS,[10] while the World Health Organization (WHO) initially recommended no corticosteroid treatment.[11] In practice, corticosteroids have been given variably to patients with COVID-19, and observational studies suggest both benefit and harm.[12-14] To reduce this uncertainty, several research groups launched randomized clinical trials (RCTs).

In March 2020, the REMAP-CAP investigators began randomizing patients with COVID-19 to alternative dosing strategies of the corticosteroid, hydrocortisone. Enrollment was halted on June 17th, following the announcement by the RECOVERY Collaborative Group that dexamethasone reduced mortality compared to standard of care in patients with COVID-19 receiving either invasive mechanical ventilation or supplemental oxygen.[15] This report describes the effects of hydrocortisone, in doses of similar glucocorticoid equivalency to that used in RECOVERY, in severely ill patients with COVID-19 enrolled in REMAP-CAP.

Methods

Study Design

REMAP-CAP is an ongoing, international, multicenter, open-label trial that combines features of an adaptive platform trial with a pragmatic point-of-care trial to determine best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings. A detailed description of the trial design is provided elsewhere.[16] The trial uses a novel design entitled a randomized embedded multifactorial adaptive platform (REMAP).[17] The design has 5 key features: randomization, allowing causal inference; embedding of study procedures into routine care processes, facilitating enrollment, trial efficiency, and generalizability; a multifactorial statistical model comparing multiple interventions across multiple patient subgroups; response-adaptive randomization with preferential assignment to those interventions that appear most favorable after interim analyses, and; a platform structured to permit continuous, potentially perpetual, enrollment.

The trial randomizes patients to multiple interventions within multiple domains, evaluating effectiveness within different patient strata. The term 'domain' refers to a common therapeutic area (e.g., anti-viral therapy), within which several interventions or intervention dosing strategies can be randomly assigned (including a control such as 'no anti-viral' as appropriate). All trial procedures are governed by a master, or 'core', protocol and a series of appendices that describe aspects specific to each therapeutic domain, to adaptations during a pandemic, and to region-specific trial governance and conduct. The trial's core protocol, relevant protocol appendices, and statistical analysis plans (SAPs) are provided in Supplement 1. The trial is overseen by a blinded International Trial Steering Committee (ITSC) and an unblinded independent Data and Safety Monitoring Board (DSMB)(Supplement 1). The study was approved by the relevant ethics committees at all participating sites and is conducted in accordance with Good Clinical Practice guidelines and the principles described in the Declaration of Helsinki.

The REMAP-CAP investigators introduced several design adaptations for COVID-19 (see Pandemic Appendix, January 31, 2020 and subsequent updates, in Supplement 1). Specifically, all patients hospitalized with suspected or proven COVID-19 were assigned to the COVID-19 stratum. They were

further classified as clinically moderate or severe, and, depending on their moderate or severe state, were eligible for randomized assignment to alternative interventions within several COVID-19-specific domains, including anti-viral, corticosteroid, targeted immune modulation, immunoglobulin, and therapeutic anti-coagulation domains. The Corticosteroid Domain was only eligible to patients in the severe state. During the study period, the trial enrolled participants with severe COVID-19 at 121 clinical sites in Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United Kingdom, and the United States. Written or verbal informed consent, in accordance with local legislation, was obtained for all patients or from their surrogates.

Achieving a racially and ethnically diverse sample was a goal of REMAP-CAP because of evidence of disparities in outcome and treatment effectiveness in pandemic and non-pandemic pneumonia. Participants (or their surrogates) self-reported their race/ethnicity via fixed categories appropriate to their region.

Participants

Patients aged $\geq$18 years with presumed or confirmed SARS-CoV-2 infection who were admitted to an intensive care unit (ICU) for provision of respiratory or cardiovascular organ support were classified as severe and eligible for enrollment in the COVID-19 Corticosteroid Domain. An ICU could include an area of the hospital re-purposed to function as an ICU for surge capacity management. Respiratory organ support was defined as invasive or non-invasive mechanical ventilation or high flow nasal cannula if flow rate $\geq$30 L/min and FiO_2 $\geq$0.4. Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope. REMAP-CAP exclusion criteria included presumption that death is imminent with lack of commitment to full support and participation in REMAP-CAP in the prior 90 days. Additional exclusion criteria for the Corticosteroid Domain included known hypersensitivity to hydrocortisone, systemic corticosteroid use, and >36h elapsed since ICU admission. Further details regarding eligibility are listed in the Corticosteroid Domain-specific Appendix in Supplement 1 and in eAppendix 1 in Supplement 2.

Treatment Allocation

The COVID-19 Corticosteroid Domain contained fixed dose and shock-dependent hydrocortisone interventions and a standard of care with no hydrocortisone (or other corticosteroid) use. Investigators at each participating site selected a priori two or more study group assignments to which patients could be randomized, based on local equipoise. Participants were randomized to each locally available group using balanced assignment.

Procedures

The study used an open-label design, where the clinical team was provided instructions for hydrocortisone prescriptions. Hydrocortisone was supplied by each site's pharmacy. Other aspects of care were provided as per each site's standard of care. Data were collected on baseline characteristics, corticosteroid use, adverse events and outcomes by site investigators via a combination of interactive web-based response technology and electronic health record abstraction with built-in validation and logic checks. Although clinical staff were aware of their individual patient's treatment assignment, neither they nor the ITSC were provided any information about aggregate patient outcomes.

Interventions

Participants were randomized to receive a fixed dose of intravenous hydrocortisone 50mg q6 hourly for 7 days; intravenous hydrocortisone 50mg q6 hourly while in shock for up to 28 days; or no hydrocortisone. A second fixed dose regimen of 100mg q6 hourly for 7 days was being incorporated across sites when the study was halted, such that only 2 patients were assigned to that group. The rationale underlying the shock-dependent dosing strategy was that restricting hydrocortisone to the period when the patient had overt shock would maximize the risk-benefit ratio. Shock was defined as the requirement for intravenous vasopressor infusion for the treatment of shock presumed due to COVID-19 and not due to untreated hypovolemia or secondary consequences of other therapies (e.g., sedation agents). Hydrocortisone was discontinued in the shock-dependent group once shock was considered to have resolved or vasopressors had been discontinued for 24h. In all groups, systemic corticosteroid therapy was permitted if a new clinical

indication developed for which corticosteroids are an established treatment such as post-extubation stridor, bronchospasm, or anaphylaxis.

In addition to assignment to interventions in the Corticosteroid Domain, participants could be randomly assigned to other interventions within other therapeutic domains, depending on whether the site was active for that domain, patient eligibility, and consent (see Supplement 1 and www.remapcap.org for more details).

Outcomes

The primary outcome was respiratory and cardiovascular organ support-free days up to day 21, an ordinal endpoint with death within the hospital as the worst outcome (labeled –1), then the length of time free of both respiratory and cardiovascular organ support, such that the best outcome would be 21 organ support-free days. Organ support was defined using the same criteria as those for study entry. This outcome was used in a recent FDA-approved registration trial in septic shock (although up to 28 days), with a 1.5 day difference (7.5-15% relative difference) considered to be the minimal clinically important difference (MCID).[18] Secondary outcomes were in-hospital mortality, ICU and hospital length of stay, respiratory support-free days, cardiovascular support-free days, a composite outcome of progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death among those not ventilated at baseline, and the WHO ordinal scale (range: 0-8, where 0 = no illness, 1-7 = increasing level of care, and 8 = death) assessed at day 14.[19,20] This scale was used in a recent COVID-19 RCT of remdesivir, where an odds ratio of 1.32 was considered clinically important.[20]

Study Power and Sample Size

The trial is designed with no maximum sample size, given the uncertainty of the pandemic. Sample size calculations for the primary outcome were calculated using trial simulations of the adaptive design rules. If both hydrocortisone groups had effect sizes (odds ratios) of 1.75 compared to the no hydrocortisone group, there would be 90% power to determine if either group was superior to the no hydrocortisone

group with a sample size of 500 patients. If the effect was 1.5, there would be 90% power with a sample size of 1,000 patients.

Statistical Analysis

The statistical analysis plan for the COVID-19 Corticosteroid Domain was written by blinded ITSC members, posted online (www.remapcap.org) before data lock and analysis, and appears in Supplement 1). The primary analysis was generated from a Bayesian cumulative logistic model, which estimated posterior probability distributions of the 21-day organ support-free days (primary outcome) based on the evidence accumulated in the trial in terms of the observed primary outcome and assumed prior knowledge in the form of a prior distribution. Data from the United Kingdom national clinical audit on all COVID-19 ICU admissions (provided by ICNARC, London, UK) were used to inform prior distributions, including initial estimates of the effect of age on outcome. Prior distributions for treatment effects were neutral.

The primary model adjusted for location (site, nested within country), age (categorized into 6 groups), sex, and time period (2-week epochs). The model estimated treatment effects for each intervention within each domain and pre-specified treatment-by-treatment interactions across domains. The primary analysis was conducted on all randomized patients who met severe COVID-19 criteria as of June 17, 2020, and not just those randomized within the Corticosteroid Domain. This approach allowed maximal incorporation of all information, providing the most robust estimation of the coefficients of all included covariates. Importantly, not all patients were eligible for all domains nor for all interventions within each domain (depending on site participation, baseline entry criteria, and patient or surrogate preference). Therefore, the model included covariate terms reflecting each patient's intervention and domain eligibility, such that the estimate of an intervention's effectiveness relative to any other intervention within that domain was generated from those patients that might have been randomized to either.

Because the primary model included information about assignment to interventions within domains whose evaluation is on-going, it was run by the fully unblinded Statistical Analysis Committee (Supplement 1), who conduct all protocol-specified trial update analyses and report those results to the

DSMB. For the primary analysis, the two fixed dose hydrocortisone groups were combined, such that there were 3 groups: fixed dose, shock-dependent, and no hydrocortisone. The cumulative log odds for the primary endpoint was modeled such that a parameter >0 reflects an increase in the cumulative odds for the organ support free-day outcome, which implies benefit. The model assumed proportional effects across the ordinal organ support-free days scale. This assumption was assessed by inspection of the distribution for clinically important deviations. Patients missing the primary endpoint (n=5) were ignored; there was no imputation of missing primary (or secondary) endpoint values. A patient who survived to hospital discharge was assumed to be free of organ support through 21 days (last status carried forward).

The model was fit using a Markov Chain Monte Carlo algorithm that drew iteratively (10,000 draws) from the joint posterior distribution, allowing calculation of odds ratios with their 95% credible intervals (CrI) and the probability that each Corticosteroid Domain intervention (including the no hydrocortisone group) was optimal, that either hydrocortisone group was superior to no hydrocortisone, and that the fixed dose and shock-dependent hydrocortisone groups were equivalent. An odds ratio >1 represents more survival and more days free from ICU organ support. Although this analysis was conducted in response to the disclosure of the RECOVERY trial results, it was also the first interim analysis of the COVID-19 patient cohort, which had pre-existing internal statistical triggers for trial conclusions and disclosure of results (99% probability of superiority or inferiority, defined as odds ratio >1 and <1 respectively, and 90% probability for equivalence, defined as an odds ratio between 1/1.2 and 1.2).

Analysis of the primary outcome was then repeated in a second model using only data from those patients enrolled in the Corticosteroid Domain with no adjustment for assignment to interventions in other domains. Although using less information, this analysis is more typical for a RCT. Further secondary analyses explored the effects of excluding patients who were ruled out for COVID-19 (defined as documented negative tests for SARS-CoV-2 infection and no positive tests), of excluding adjustment for site and time epoch, and of combining the fixed dose and shock dependent hydrocortisone groups.

Identical analyses were conducted to estimate the effect on mortality, except the outcome was dichotomous (alive or dead at hospital discharge). There were also 7 secondary outcome analyses (all

using the Corticosteroid Domain cohort): time to death, respiratory support-free days, cardiovascular support-free days, length of ICU stay, length of hospital stay, the WHO ordinal scale at 14 days, and progression to invasive mechanical ventilation, ECMO, or death in those not receiving invasive mechanical ventilation at enrollment. The time-to-death and length of stay outcomes were time-to-event analyses with results expressed as hazard ratios. The primary safety analysis compared the proportion of patients who developed one or more serious adverse events across groups. All analyses were pre-specified and are listed in section 15, page 12, of the COVID-19 Corticosteroid Domain SAP in Supplement 1). Data management and summaries were created using R version 3.5.2, the primary analysis was computed in R version 4.0.0 using the rstan package version 2.19.3. Additional data management and analysis was performed in R, SQL 2016, SPSS version 26, and Stata version 14.2.

Study Termination

Following a press release from the RECOVERY trial on 16th June 2020, and in response to discussions held across the participating sites, the blinded ITSC decided on 17th June, 2020 to stop enrollment of patients with COVID-19 in the Corticosteroid Domain due to a loss of equipoise. No data from the trial were reviewed prior to the decision.

Results

Participants

Between March 9th and June 17th, of 1,165 screened patients, 614 met criteria for severe COVID-19, were enrolled in REMAP-CAP, and were randomized within at least one therapeutic domain (Figure 1). Patients were recruited at 121 sites, of whom 113 (94%) were open for the Corticosteroid Domain, though 24 (21%) sites only permitted randomization to fixed or shock-dependent hydrocortisone groups (eAppendix 2 in Supplement 2). Among the 614 patients with severe COVID-19, 403 were enrolled in the Corticosteroid Domain and randomly assigned to the fixed dose (n=143), shock-dependent (n=152), and no (n=108) hydrocortisone groups. There were 24 participants (of whom 19 were in the Corticosteroid Domain) for whom either they or the local ethics board requested withdrawal of all data. The baseline characteristics of the corticosteroid study groups whose data were available (n=384) were similar across groups and typical of patients requiring ICU care for COVID-19 (Table 1 and eAppendix 2 in Supplement 2). For an additional 11 patients, of whom 5 were in the Corticosteroid Domain, follow-up data were unavailable. Thus, the final cohort available for outcome analysis comprised 576 participants in the REMAP-CAP severe COVID-19 cohort (whose data are used for covariate adjustment in the primary analysis), of whom 379 were randomized within the Corticosteroid Domain.

Intervention Fidelity

Information on corticosteroid dosing during the first week (defined as study day 1 through day 8) was available for 376 (99%) of participants in the Corticosteroid Domain. Among those assigned to the fixed dose hydrocortisone group, 97% (n=130/134) received at least one dose of hydrocortisone, an additional 1.5% (2/134) received an alternative systemic corticosteroid, and only 2 (1.5%) received no corticosteroid. The first dose of hydrocortisone was given before midnight of the first study day in 95% (124/130) of patients and the median (IQR) duration of hydrocortisone therapy was 7 (6-8) days. Among those assigned to shock-dependent dosing, 44% (62/143) received at least one dose of hydrocortisone (and 49% (70/143) received 'any' systemic corticosteroid, including hydrocortisone). Among those treated, the median (IQR) study day on which hydrocortisone was commenced was study day 1 (1-4), and

the median (IQR) duration was 3 (1-4) days of hydrocortisone and 3 (2-4) days of any systemic corticosteroid. Among those assigned to the no hydrocortisone group, 15% (15/99) received a systemic corticosteroid (6 of whom received hydrocortisone). For those receiving a corticosteroid, the median (IQR) duration was 2 (2-6) days.

Primary Outcome

Primary outcomes are presented in Table 2 and Figure 2. The median (IQR) organ support-free days were 0 (–1, 15), 0 (–1, 13) and 0 (–1, 11) for the fixed dose, shock-dependent, and no hydrocortisone groups. Relative to the no hydrocortisone group, the median (95% CrI) adjusted odds ratios from the primary model were 1.43 (0.91 - 2.27) and 1.22 (0.76 - 1.94) for the fixed dose and shock-dependent groups, yielding 93% and 80% probabilities of superiority. There were no clinically relevant deviations from the assumption of proportional effects across the organ support free-day scale, with the two treatment groups having observed benefit across the entire range (Figure 2b). In the pre-specified secondary analysis of the primary outcome using only data from participants in the Corticosteroid Domain and not adjusting for intervention assignment in other domains, the median (95% CrI) adjusted odds ratios were 1.45 (0.93 - 2.30) and 1.24 (0.80 - 1.95) for the fixed dose and shock-dependent groups, yielding 95% and 83% probabilities of superiority. Estimates when excluding those who were ruled out for COVID-19, when dropping site and time from the model, and when combining the fixed dose and shock-dependent groups are shown in eTables 1 and 2 in Supplement 2.

In-hospital Mortality and Other Secondary Outcomes

The primary mortality analyses and secondary outcomes are presented in Table 3. The in-hospital mortality rates were 30% (n=41/137), 26% (n=37/141), and 33% (n=33/99) in the fixed dose, shock-dependent, and no hydrocortisone groups. Relative to the no hydrocortisone group, the median (95% CrI) adjusted odds ratios from the primary model were 1.03 (0.53 – 1.95) and 1.10 (0.58 – 2.11) (where a value >1 represents benefit) for the fixed dose and shock-dependent hydrocortisone groups, yielding 54% and 62% Bayesian posterior probabilities of superiority. Results from secondary analyses of in-hospital mortality using only data from the Corticosteroid Domain are presented in eTable 2 and 3 in Supplement

2. Other secondary outcome analyses are presented in Table 3. Full model results of all outcome analyses are provided in eAppendices 3 and 4 in Supplement 2.

Adverse Events

Serious adverse event rates are presented in Table 3 and eAppendix 4 in Supplement 2. There were 10 (2.5%) patients who incurred a serious adverse event (none incurred >1), 9 of whom were in the fixed dose and shock dependent hydrocortisone groups. Two events (severe neuromyopathy and fungemia) occurred in the fixed dose hydrocortisone group and were considered by the site investigator as possibly related to study group assignment. The other events, none of which were considered related, were single cases of pneumonia, pulmonary embolism, elevated serum troponin, post-operative hemorrhage, intracranial hemorrhage, thrombocytopenia, ventricular tachycardia, and hypoglycemia.

Discussion

The principal finding from this study was a 93% probability of benefit of a fixed duration of hydrocortisone compared to no hydrocortisone. The finding was robust to sensitivity analyses, and the probability of benefit was similar as measured by several secondary outcomes. However, the study was stopped early, the probability of benefit with hydrocortisone did not trigger the internal statistical trigger for a trial conclusion of superiority, and no strategy was determined to be optimal.

REMAP-CAP is designed to test numerous interventions for pandemic and non-pandemic pneumonia over time. The design has internal statistical triggers for stopping particular study questions, but external factors, such as lack of equipoise following new evidence, can also trigger termination of a portion of the trial. This analysis was prompted by the loss of equipoise following announcement that dexamethasone reduced mortality in the RECOVERY trial.[18] Coincidentally, this analysis was also the first interim of the severe COVID-19 cohort: had any internal threshold been triggered, the results would have been released regardless of RECOVERY. However, had RECOVERY not prompted cessation, the internal action would simply be to generate updated randomization proportions and continue enrollment.

Given the findings from contemporaneous trials, the findings might generally be considered supportive of corticosteroid use in this patient population.[15,21] For example, the benefit reported in RECOVERY was in patients similar to those enrolled in REMAP-CAP using a corticosteroid, dexamethasone, with a similar glucocorticoid effect to that of the fixed dose hydrocortisone course in REMAP-CAP. As such, it seems reasonable that either dexamethasone or hydrocortisone might be beneficial. In turn, it seems further plausible that the primary benefit is exerted through glucocorticoid, rather than mineralocorticoid effects, given dexamethasone's lack of mineralocorticoid activity. Systemic corticosteroids have well-described side-effects. In this open-label trial, serious adverse events were rare, precluding statistical inference. However, they were reported more commonly in the two hydrocortisone groups.

The findings regarding the shock-dependent hydrocortisone group are less clear. In this group, physicians only administer hydrocortisone when the patient is in shock. Thus, if corticosteroids are beneficial for COVID-19 through mechanisms other than mitigation of shock, this group is effectively undertreated, and

one would anticipate less average benefit. In contrast, if the benefits of corticosteroids largely accrue to those in shock, avoidance of unnecessary corticosteroid therapy in those not in shock might improve the safety profile of corticosteroid therapy. This question remains unresolved.

Strengths of the study include the pragmatic and international design, rendering findings likely generalizable at least to other resource-rich settings around the world. In addition, all analyses were specified prior to unblinding results, and results were robust to sensitivity analyses. An advantage of using a Bayesian approach is that any data, including data following unplanned cessation in enrollment, can be analyzed and quantified as posterior probabilities, which is arguably more useful, and is more quantitative, than a frequentist finding of failure to reject a null hypothesis possibly because of lack of power.[22,23] The platform trial design allows efficient enrollment into multiple therapeutic domains simultaneously. One concern could have been potential confounding because of treatment-by-treatment interactions. However, the results were similar with and without adjustment for other treatment assignments.

Limitations

The study has several limitations. First, the results are presented before reaching any pre-specified internal trigger. Nonetheless, to our knowledge, this trial represents the largest randomized data on hydrocortisone in this patient population. Second, the study used an open-label design, although clinician and patient awareness of study assignment likely had minimal effect on the primary outcome. Third, 15% of the no hydrocortisone group received systemic corticosteroids, although typically only for a short period. This usage is similar to that in RECOVERY[18] and may often have been unavoidable (e.g., to treat post-extubation stridor). Nonetheless, it could have biased the results towards smaller effect sizes than would have been observed had corticosteroid use been lower in the no hydrocortisone group.

Conclusions

Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80%

probabilities of superiority with regard to the odds of improvement in organ support-free days within 21 days. However, the trial was stopped early, precluding definitive conclusions.

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To be generated from author contribution forms.

Conflict of Interest Disclosures

See submitted ICMJE forms for declared potential conflict of interests.

Funding/Support

The Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1 (#602525), the Australian National Health and Medical Research Council (#APP1101719), the New Zealand Health Research Council (#16/631), and the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant (#158584), the UK National Institute for Health Research (NIHR) and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (CTN 2014-012), the UPMC Learning While Doing Program, the Breast Cancer Research Foundation, the French Ministry of Health (PHRC-20-0147), and the Minderoo Foundation.

Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study has 4 regional non-profit sponsors (Monash University, Melbourne, Australia (Australasian sponsor); Utrecht Medical Center, Utrecht, the Netherlands (European sponsor); St. Michael's Hospital, Canada (Canadian sponsor), and; GCAR, San Francisco, USA (US sponsor)). Several authors are employees of these organizations. However, beyond the declared author contributions, the sponsors had no additional role.

The REMAP-CAP Investigators

See attachment 'REMAP-CAP Investigators'.

Data Sharing Statement

See Data Sharing Statement in Supplement 3.

Acknowledgement

We are grateful to the NIHR Clinical Research Network (UK), UPMC Health System Health Services Division (US), and the Direction de la Recherche Clinique et de l'Innovation de l'AP-HP (France) for their support of participant recruitment. ACG is funded by an NIHR Research Professorship (RP-2015-06-18). DCA had full access to all Corticosteroid Domain data and all baseline data in the study; RJL had full access to all data required for the primary analyses. Together, they take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Johns Hopkins University of Medicine Coronavirus Resource Center. https://coronavirus.jhu.edu/. Published 2020. Accessed July 30, 2020.

2. Siemieniuk RA-O, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. 2020;370:m2980. doi:10.1136/bmj.m2980

3. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev.* 2019;12:CD002243.

4. Ewald H, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection. *Cochrane Database Syst Rev.* 2015(4):CD006150.

5. Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ.* 2020;192(27):E756-E767.

6. Lansbury LE, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Shen Lim W. Corticosteroids as Adjunctive Therapy in the Treatment of Influenza: An Updated Cochrane Systematic Review and Meta-analysis. *Crit Care Med.* 2020;48(2):e98-e106.

7. Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. *Leukemia.* 2020;34(6):1503-1511.

8. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395(10223):473-475.

9. China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). http://kjfy.meetingchina.org/msite/news/show/cn/3337.html. Published 2020. Updated March 4, 2020. Accessed August 3, 2020, 2020.

10. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med.* 2020;48(6):e440-e469.

11. The World Health Organization. The WHO Clinical Management of COVID-19 Interim Guidance. https://www.who.int/publications/i/item/clinical-management-of-covid-19. Updated 27 May 2020. Accessed August 3, 2020, 2020.

12. Chopra A, Chieng HC, Austin A, et al. Corticosteroid Administration Is Associated With Improved Outcome in Patients With Severe Acute Respiratory Syndrome Coronavirus 2-Related Acute Respiratory Distress Syndrome. *Crit Care Explor.* 2020;2(6):e0143.

13. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis.* 2020. doi: https://doi.org/10.1093/cid/ciaa601.

14. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology.* 2020. doi: https://doi.org/10.1053/j.gastro.2020.05.032.

15. The RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with COVID-19 - Preliminary Report. New Engl J Med. 2020. doi: 10.1056/NEJMoa2021436.

16. Angus DC, Berry S, Lewis RJ, et al. The Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) Study: Rationale and Design. *Annals of the American Thoracic Society*. 2020. doi: https://doi.org/10.1513/AnnalsATS.202003-192SD

17. Angus DC. Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems? *JAMA.* 2015;314(8):767-768.

18. Laterre PF, Berry SM, Blemings A, et al. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. *JAMA.* 2019;322(15):1476-1485.

19. The WHO Clinical Characterization and Management Committee. A minimal common outcome measure set for COVID-19 clinical research. *The Lancet Infectious Diseases*. 2020. doi: https://doi.org/10.1016/S1473-3099(20)30483-7

20. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *N Engl J Med*. 2020. doi: 10.1056/NEJMoa2007764

21. The WHO REACT Group. Prospective Meta-analysis of Randomized Trials of Corticosteroids for Severe COVID-19. JAMA. 2020; forthcoming.

22. Bittl John A, He Y. Bayesian Analysis: A Practical Approach to Interpret Clinical Trials and Create Clinical Practice Guidelines. *Circulation: Cardiovascular Quality and Outcomes.* 2017;10(8):e003563.

23. Quintana M, Viele K, Lewis RJ. Bayesian Analysis: Using Prior Information to Interpret the Results of Clinical Trials. *JAMA.* 2017;318(16):1605-1606.

Summary of Supplements

Supplement 1. Trial Protocol and SAP Documents

Supplement 2.

eAppendix 1. Enrollment criteria

eAppendix 2. Site Participation in the Corticosteroid Domain

eTable 1. Secondary Analyses of Primary Outcome (Organ Support-free Days), restricted to participants enrolled in Corticosteroid Domain

eTable 2. Secondary Analyses of Primary Outcome and of Mortality with Fixed Dose and Shock-dependent Hydrocortisone Groups Combined

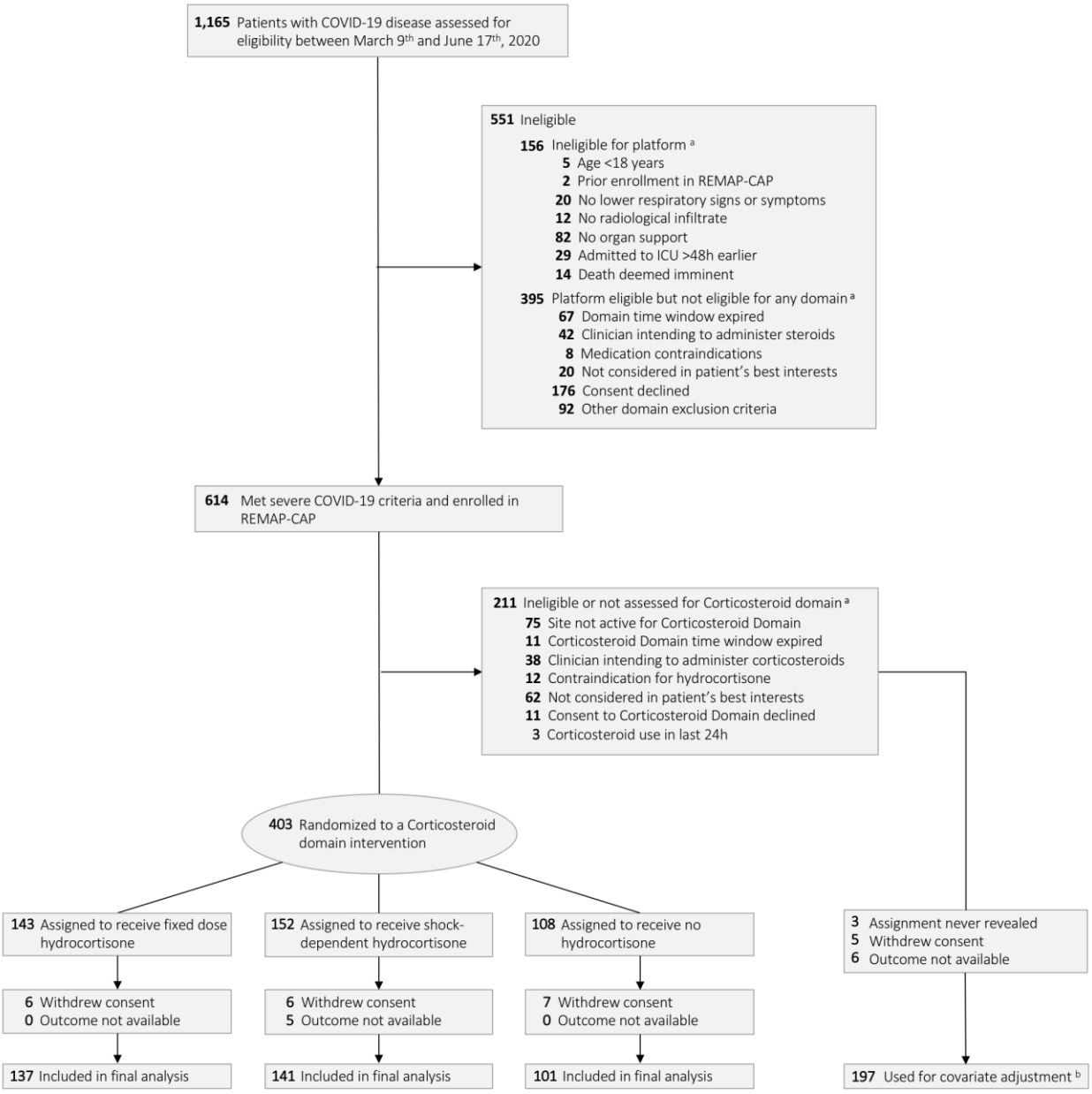
eTable 3. Secondary Analyses of In-hospital Mortality

eAppendix 3. Technical Report from the Statistical Analysis Committee for SAP Outcome Analyses 15.1-4.

eAppendix 4. Technical Report from Berry Consultants for SAP Outcome Analyses 15.5-20.

Supplement 3. Data Sharing Statement

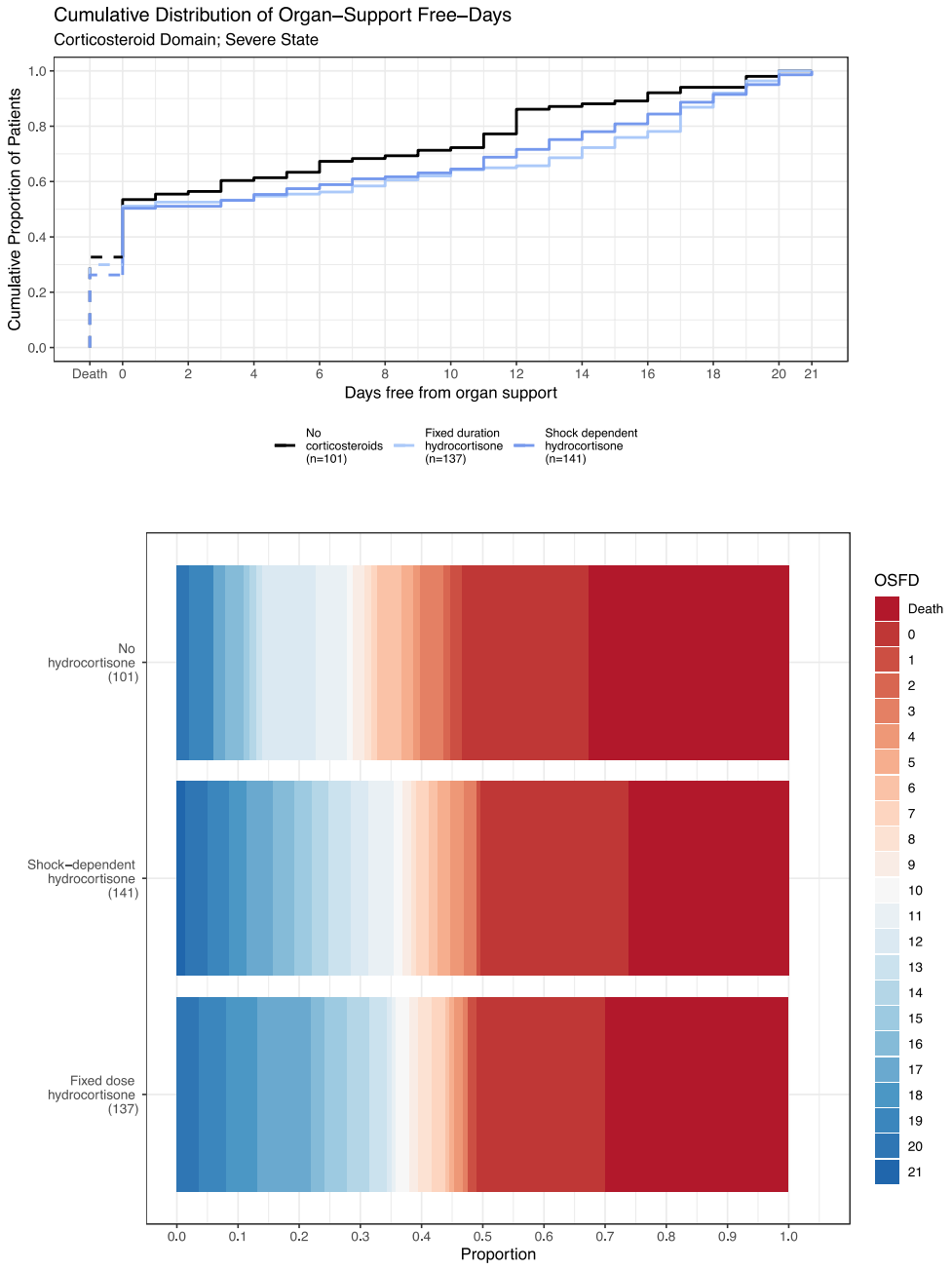
Figure 1. **Screening, Randomization, and Follow-up of Participants in the REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial**



[a] Patients could meet more than 1 ineligibility criterion.

[b] The primary analysis of alternative interventions within the Corticosteroid Domain is estimated from a model that adjusts for patient factors and for assignment to interventions in other domains. To obtain the most reliable estimation of the effect of these patient factors and of other interventions on the primary outcome, all patients enrolled in the severe COVID-19 cohort (for whom there is consent and follow-up) are included. Importantly, however, the model also factors eligibility for the Corticosteroid Domain and its interventions, such that the final estimate of a Corticosteroid Domain intervention's effectiveness relative to any other within that domain is generated from those patients that might have been randomized to either.

Figure 2. **Organ Support-free Days**



The upper panel displays the distributions of organ support-free days (see Methods for definition) by study group as the cumulative proportion (y axis) for each study group by day (x axis), with death listed first. Curves that rise more slowly are more favorable. The lower panel displays organ support-free days as horizontally stacked proportions by study group. Red represents worse values and blue represents better values. The median (95% credible interval) adjusted odds ratios from the primary analysis, using a Bayesian cumulative logistic model, were 1.43 (0.91 - 2.27) and 1.22 (0.76 - 1.94) for the fixed course and shock-dependent hydrocortisone groups compared to the no hydrocortisone group, yielding 93% and 80% probabilities of superiority over the no hydrocortisone group.

Table 1. Participant Characteristics at Baseline

Characteristic	No. (%) of participants [a]		
	Fixed Dose [b] Hydrocortisone (N=137)	Shock-dependent Hydrocortisone (N=146)	No Hydrocortisone (N=101)
Age – mean (SD), years	60.4 (11.6)	59.5 (12.7)	59.9 (14.6)
Sex – Male	98 (71.5)	103 (70.6)	72 (71.3)
Female	39 (28.5)	43 (29.5)	29 (28.7)
Body mass index - mean (SD), kg/m^2	30.9 (7.3) (n=135)	30.7 (7.4) (n=141)	29.7 (7.5) (n=100)
Race/Ethnicity [c] - White – n/N (%)	79/111 (71.2)	80/105 (76.2)	45/79 (57.0)
Asian – n/N (%)	18/111 (16.2)	11/105 (10.5)	22/79 (27.9)
Black – n/N (%)	4/111 (3.6)	7/105 (6.7)	4/79 (5.1)
Mixed – n/N (%)	4/111 (3.6)	0/105 (0.0)	2/79 (2.5)
Other [c] – n/N (%)	6/111 (5.4)	7/105 (6.7)	6/79 (7.6)
Confirmed SARS-CoV2 infection [d] – n/N (%)	109/134 (81.3)	87/125 (69.6)	79/100 (79.0)
Pre-existing conditions – n/N (%)			
Diabetes mellitus	50/129 (38.8)	39/144 (27.1)	30/98 (30.6)
Respiratory disease¤	27/127 (21.3)	28/144 (19.4)	20/98 (20.4)
Asthma/COPD	21/137 (15.3)	25/144 (17.4)	16/100 (16.0)
Other	7/127 (5.5)	4/144 (2.8)	4/95 (4.2)
Kidney disease	13/128 (10.2)	11/127 (8.7)	8/92 (8.7)
Severe cardiovascular disease	9/136 (6.6)	13/140 (9.3)	6/99 (6.1)
Immunosuppressive disease	7/127 (5.5)	9/144 (6.3)	2/95 (2.1)
Chronic immunosuppressive therapy	8/137 (5.8)	7/144 (4.9) (n=142)	6/100 (6.0)
Time to enrollment - median (IQR)			
From hospital admission - days	1.2 (0.8 – 2.6)	1.0 (0.7 – 2.8)	1.1 (0.7 – 2.0)
From ICU admission - hours	15.1 (7.5 – 19.8)	12.3 (5.4 – 18.8)	13.5 (8.1 – 17.5)
Acute respiratory support			
None/supplemental oxygen only	0 (0.0)	1 (0.7)	0 (0.0)
High flow nasal cannula	17 (12.4)	23 (15.8)	16 (15.8)
Non-invasive ventilation only	33 (24.1)	49 (33.6)	32 (31.7)
Invasive mechanical ventilation	87 (63.5)	73 (50.0)	53 (52.5)
ECMO – n/N (%)	1/137 (0.7)	0/143 (0.0)	2/99 (2.0)
Vasopressor support	56 (40.9)	47 (32.2)	30 (29.7)
APACHE II score [e] - median (IQR)	18 (10 - 23) (n=123)	17 (12 – 24) (n=130)	15 (12 - 21) (n=94)
Glasgow Coma Scale [f] - mean (SD)	13 (4) (n=131)	13 (4) (n=133)	14 (3) (n=98)
Acute physiology and laboratory values [g]			
PaO_2/FiO_2 – mean (SD)	149 (83) (n=130)	137 (74) (n=142)	138 (78) (n=96)
Creatinine - median (IQR), mg/dL	0.9 (0.7 - 1.2) (n=136)	0.9 (0.7 - 1.3) (n=143)	0.8 (0.6 – 1.2) (n=98)
Lactate – median (IQR), mmol/L	1.2 (0.9 - 1.5) (n=124)	1.1 (0.9 - 1.6) (n=124)	1.1 (0.8 - 1.5) (n=88)
Platelets - mean (SD), $x10^9/L$	254 (117) (n=135)	259 (112) (n=143)	259 (112) (n=98)
Bilirubin - median (IQR), mg/dL	0.1 (0.1 - 0.2) (n=129)	0.1 (0.1 – 0.2) (n=134)	0.1 (0.1 – 0.2) (n=93)

Abbreviations: SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

[a] Unless otherwise indicated. Percentages may not sum to 100 because of rounding.

[b] Fixed dose combines those assigned to 50mg (n=135) or 100mg (n=2) IV q6h for 7d.

[c] Data collection not approved in Canada and continental Europe. 'Other' includes 'declined' and 'multiple'.

[d] Infection confirmed by respiratory tract PCR test.

[e] Range: 0 - 71, with higher scores indicating greater severity of illness.

[f] Range: 3 - 15, with higher scores indicating greater consciousness, using values closest to randomization but prior to use of sedative agents.

[g] Value closest to randomization within prior 8h. For creatinine, lactate, platelets and bilirubin, if pre-randomization value missing, the closest value within 2h post-randomization was used.

Table 2. Primary Outcome

Outcome/Analysis	Fixed Dose Hydrocortisone (N=137)	Shock-dependent Hydrocortisone (N=141)	No Hydrocortisone (N=101)
Primary Outcome, Organ support-free days (OSFDs)			
OSFDs, median (IQR)	0 (–1 - 15)	0 (–1 - 13)	0 (–1 - 11)
Subcomponents of OSFDs			
In-hospital deaths, n (%)	41 (30)	37 (26)	33 (33)
OSFDs in survivors, median (IQR)	11.5 (0 - 17)	9.5 (0 - 16)	6 (0 - 12)
Primary Analysis of Primary Outcome, using covariate data from all COVID-19 severe state participants (n=576)			
Adjusted OR - mean (SD)	1.47 (0.35)	1.26 (0.31)	1
- median (95% CrI)	1.43 (0.91 – 2.27)	1.22 (0.76 – 1.94)	1
Probability of superiority to no hydrocortisone, %	93	80	-
Secondary Analysis of Primary Outcome, restricted to Corticosteroid Domain participants (n=379) with no adjustment for intervention assignment in other domains			
Adjusted OR - mean (SD)	1.49 (0.35)	1.28 (0.30)	1
- median (95% CrI)	1.45 (0.93 - 2.30)	1.24 (0.80 - 1.95)	1
Probability of superiority to no hydrocortisone, %	95	83	-

The primary analysis used data from all participants enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least one domain (n=576), adjusting for age, sex, time period, site, region, domain and intervention eligibility and intervention assignment (see COVID-19 Corticosteroid Domain SAP in **Supplement 1** and full report from Statistical Analysis Committee in eAppendix 3 of **Supplement 2**). The secondary analysis was restricted to participants enrolled in the Corticosteroid Domain (n=379) and did not include information on assignment to interventions other than hydrocortisone. Definitions of OSFDs and other outcomes are provided in Methods and the study protocol (see **Supplement 1**). Models are structured such that a higher OR is favorable.

Other sensitivity analyses are described in Results and provided in eTables 1 and 2 and eAppendices 3 and 4 in **Supplement 2**.

OSFD - organ support-free day; IQR - interquartile range; SD - standard deviation; CrI - credible interval; OR - odds ratio.

Table 3. Secondary Outcomes and Serious Adverse Events

Outcome/Analysis	Fixed Dose Hydrocortisone (N=137)	Shock-dependent Hydrocortisone (N=141)	No Hydrocortisone (N=101)
Primary In-hospital Mortality Model, using covariate data from all COVID-19 severe state participants (n=576)			
Adjusted OR - mean (SD)	1.08 (0.37)	1.16 (0.40)	1
- median (95% CrI)	1.03 (0.53 – 1.95)	1.10 (0.58 – 2.11)	1
Probability of superiority to no hydrocortisone, %	54	62	-
Other Secondary Outcomes, restricted to Corticosteroid Domain participants (n=379) with no adjustment for intervention assignment in other domains			
Time to death			
Adjusted HR - mean (SD)	0.97 (0.22)	1.01 (0.23)	1
- median (95% CrI)	0.94 (0.61 - 1.46)	0.98 (0.63 - 1.54)	1
Probability of superiority to no hydrocortisone, %	40	47	-
Respiratory support-free days			
Adjusted OR - mean (SD)	1.45 (0.34)	1.31 (0.30)	1
- median (95% CrI)	1.42 (0.90 - 2.24)	1.28 (0.81 - 2.00)	1
Probability of superiority to no hydrocortisone, %	94	85	-
Cardiovascular free-days			
Adjusted OR - mean (SD)	1.68 (0.40)	1.32 (0.31)	1
- median (95% CrI)	1.63 (1.03 - 2.59)	1.29 (0.81 - 2.02)	1
Probability of superiority to no hydrocortisone, %	98	86	-
Length of ICU stay			
Adjusted HR - mean (SD)	0.93 (0.14)	0.86 (0.13)	1
- median (95% CrI)	0.92 (0.68 - 1.24)	0.85 (0.62 - 1.15)	1
Probability of superiority to no hydrocortisone, %	29	14	-
Length of hospital stay			
Adjusted HR - mean (SD)	0.99 (0.16)	0.94 (0.15)	1
- median (95% CrI)	0.97 (0.72 - 1.32)	0.93 (0.69 - 1.26)	1
Probability of superiority to no hydrocortisone, %	43	31	-
WHO scale at day 14			
Adjusted OR - mean (SD)	1.33 (0.32)	1.06 (0.26)	1
- median (95% CrI)	1.29 (0.83 – 2.05)	1.03 (0.65 - 1.65)	1
Probability of superiority to no hydrocortisone, %	87	55	-
Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline (n=168)			
Free of invasive mechanical ventilation at baseline, n	50	70	48
Progression to intubation, ECMO or death, n (%)	23 (46)	42 (60)	37 (77)
Adjusted OR - mean (SD)	3.02 (1.40)	1.36 (0.59	1
- median (95% CrI)	2.74 (1.18 - 6.56)	1.24 (0.56 - 2.82)	1
Probability of superiority to no hydrocortisone, %	99	70	-
Serious Adverse Events			
Patients with ≥1 serious adverse event, n (%)	4 (3)	5 (4)	1 (1)

The primary analysis of in-hospital mortality used data from all participants enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least one domain (n=576), adjusting for age, sex, time period, site, region, domain and intervention eligibility and intervention assignment (see COVID-19 Corticosteroid Domain SAP in Supplement 1 and full report from Statistical Analysis Committee in eAppendix 3 of Supplement 2). Other analyses were restricted to participants enrolled in the Corticosteroid Domain (n=379) and did not include information on assignment to interventions other than hydrocortisone. Definitions of outcomes are provided in Methods and the study protocol (see Supplement 1). Models are structured such that a higher OR or HR is favorable. The WHO scale ranges from 0 (no disease) to 8 (death).

Other sensitivity analyses are described in Results and provided in eTables 2 and 3 and eAppendices 3 and 4 in Supplement 2.

SD - standard deviation; CrI - credible interval; OR - odds ratio; HR - hazard ratio; WHO - World Health Organization.