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Effect of Angiotensin Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Initiation on Organ Support-Free Days in Patients Hospitalized with COVID-19: A Randomized Clinical Trial

The REMAP-CAP Investigators*

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The members of the writing committee appear at the end of the main text and the full list of investigators and collaborators in the Supplementary Appendix.

Running Head

REMAP-CAP COVID-19 ACE2 RAS Domain RCT

Key words

Adaptive platform trial; randomized clinical trial; pneumonia; COVID-19; renin-angiotensin system; angiotensin converting enzyme inhibitors; angiotensin receptor blockers

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Key points

Question

Does initiating an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in adult patients hospitalized for COVID-19 improve organ support-free days (a composite of hospital survival and duration of intensive care respiratory or cardiovascular support)?

Findings

In this randomized clinical trial that included 779 patients, initiation of an ACE inhibitor or ARB did not improve organ support-free days. Among critically ill patients, there was a 95% probability that treatments worsened this outcome.

Meaning

Among critically ill patients, initiation of an ACE inhibitor or ARB as treatment for COVID-19 did not improve, and likely worsened, clinical outcomes.

Abstract

IMPORTANCE Over-activation of the renin-angiotensin system (RAS) may contribute to poor clinical outcomes in patients with COVID-19.

OBJECTIVE To determine whether angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) initiation improves outcomes in patients hospitalized for COVID-19.

DESIGN, SETTING, AND PARTICIPANTS In an ongoing, adaptive platform randomized clinical trial, 721 critically ill and 58 noncritically ill hospitalized adults were randomized to RAS inhibitors or control between March 16, 2021, and February 25, 2022, at 69 sites in seven countries (final follow-up date: June 1, 2022).

INTERVENTIONS Patients were randomized to receive open-label initiation of ACE inhibitor (n=257), ARB (n=248), ARB in combination with DMX-200 (a chemokine receptor-2 inhibitor; n=10), or no RAS inhibitor (control; n=264) for up to 10 days.

MAIN OUTCOMES AND MEASURES The primary outcome was organ support-free days, a composite of hospital survival and days alive without cardiovascular or respiratory organ support through 21 days. The primary analysis was a bayesian cumulative logistic model. Odds ratios (OR) >1 represent improved outcomes.

RESULTS On February 25, 2022, enrollment was discontinued due to safety concerns. Among 679 critically ill patients with available primary outcome, the median age was 56.0 years and 35.2% were female. Median (IQR) organ support-free days among critically ill patients in the ACE inhibitor group (n=231) was 10 (–1 to 16), in the ARB group (n=217) was 8 (–1 to 17), and in the control group (n=231) was 12 (0 to 17) (median adjusted odds ratio for improvement for ACE inhibitor of 0.77 [95% bayesian credible interval 0.58 to 1.06] and for ARB of 0.76 [0.56 to 1.05] compared with control). The posterior probabilities that ACE inhibitor and ARB worsened organ support-free days compared with control were 94.9% and 95.4%. Hospital survival with ACE inhibitor, ARB, and control, occurred in 166/231 (71.9%), 152/217 (70.0%), and 182/231 (78.8%) critically ill patients, respectively (posterior probabilities that ACE inhibitor and ARB worsened hospital survival compared with control were 95.3% and 98.1%).

CONCLUSIONS AND RELEVANCE In this trial, among critically ill adults with COVID-19, initiation of an ACE inhibitor or ARB did not improve, and likely worsened, clinical outcomes.

TRIAL REGISTRATION ClinicalTrials.gov number: NCT02735707

Introduction

Angiotensin converting enzyme 2 (ACE2), a central regulator of the renin-angiotensin system (RAS), is expressed in the respiratory epithelium and vascular endothelium, and is the human host receptor for the SARS-CoV-2 virus.[1,2] Disruption of ACE2 activity due to viral binding, and other mechanisms, may upregulate angiotensin II in patients with COVID-19.[3-7] Angiotensin II promotes inflammation, activates coagulation, increases capillary permeability, upregulates fibrotic responses, and causes vasoconstriction which may contribute to microcirculatory dysfunction and ventilation/perfusion mismatch.[3,8-10] These pathogenic responses characterize severe COVID-19, and therefore attenuating angiotensin II may improve outcomes. This hypothesis is supported by observational and experimental studies in COVID-19,[11,12] and other studies in acute lung injury due to SARS-CoV-1, sepsis, aspiration, and ventilator-induced lung injury.[7,13-15] Given the direct interaction between the RAS and SARS-CoV-2, attenuating angiotensin II may be particularly beneficial in COVID-19.

In an ongoing, adaptive platform trial, the effect of new initiation of a RAS inhibitor (either an angiotensin converting enzyme [ACE] inhibitor or an angiotensin receptor blocker [ARB]) on the composite of hospital survival and organ support provision through 21 days was evaluated in patients hospitalized with COVID-19 pneumonia.

Methods

Trial Design and Oversight

The ACE2 RAS Domain is one of multiple therapeutic domains in the Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial (NCT02735707). REMAP-CAP is an international, adaptive platform randomized clinical trial[16,17] evaluating treatments for severe pneumonia. Trial design details are previously reported,[18] and are available in **Supplement 1**. Patients are assessed for platform eligibility and potentially randomized to one or more interventions among available domains, organized by therapeutic areas. The trial previously reported the effects of corticosteroids, anticoagulants, antivirals, interleukin-6 receptor antagonists, convalescent plasma, and antiplatelet agents in patients with COVID-19.[19-25] The trial was approved by regional ethics committees and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written or verbal informed consent was obtained from all patients or their surrogates in accordance with local legislation.

Participants

Patients aged ≥18 years hospitalized with clinically suspected or microbiologically confirmed COVID-19 pneumonia were eligible. Patients were stratified into critically ill and noncritically ill groups at enrollment. Patients receiving respiratory (high-flow nasal oxygen with flow rate ≥30 L/min and FiO_2 ≥0.4, or non-invasive or invasive mechanical ventilation) or cardiovascular (vasopressor/inotrope) organ support in an intensive care unit (ICU) were considered critically ill. All other hospitalized patients were considered noncritically ill. Critically ill patients were eligible for enrollment within 48 hours of ICU admission and

noncritically ill patients within 96 hours of hospital admission. Patients were excluded on the basis of long-term or current RAS inhibitor use or known intolerance, risk of clinically relevant hypotension or escalation of vasopressor requirements, hyperkalemia, severe renal impairment, severe renal artery stenosis, or pregnancy or breast-feeding. Detailed domain and platform eligibility are presented in **eAppendix 1** in **Supplement 2**. In view of racial and ethnic differences in outcomes during the pandemic, self-reported race and ethnicity was collected from participants or their surrogates via fixed categories appropriate to their region where approved.

Treatment Allocation

All participating sites randomized patients to control (no RAS inhibitor) and up to three active interventions, including ACE inhibitor, ARB, and, at a subset of participating sites, an ARB in combination with DMX-200. DMX-200 is an investigational oral chemokine receptor-2 antagonist targeting macrophage chemotaxis, given in combination with an ARB due to putative synergistic anti-inflammatory effects. Computerized randomization was performed centrally with balanced, fixed allocation ratios based on the number of available interventions at each site. Response adaptive randomization was not employed in this domain. Patients could also be randomized to interventions in other domains depending on availability and eligibility.

Interventions

Treatment assignments included initiation and in-hospital treatment with an enterally administered ACE inhibitor, ARB, ARB in combination with DMX-200, or control. Sites

selected from a hierarchical list of ACE inhibitors and ARBs (see **Supplement 1**) to encourage consistency in study agent while permitting flexibility based on drug availability and experience. All treatments were open-label. Initial dosing and subsequent titration were determined by the treating clinician, with guidance provided in the protocol (see **Supplement 1**). The protocol advised holding study drug for clinically-relevant hypotension or escalating vasopressor requirements, hyperkalemia, declining renal function, severe renal impairment, exposure to nephrotoxic agents, angioedema (in the ACE inhibitor group), and liver failure or hepatic transaminase elevation or other possible adverse reaction (in the combination ARB and DMX-200 group). Treatment was continued for up to 10 days or until hospital discharge, whichever came first. Patients in the control group received no RAS inhibitor absent developing a specific indication for one.

Outcome Measures

The primary outcome was organ support-free days. In this composite ordinal outcome, all deaths occurring during the index hospitalization were assigned the worst possible outcome (–1). Among survivors, respiratory and cardiovascular organ support–free days were calculated through day 21 (survivors with no organ support were assigned a score of 22). Higher scores indicate better outcomes. In REMAP-CAP, this hospital-based outcome correlates with longer-term outcomes.[26]

Prespecified secondary outcomes included hospital survival, day 90 survival, ventilator-free days, vasopressor/inotrope-free days, durations of hospital and ICU stays, World Health

Organization scale at day 14, hypotension while admitted to a ward, angioedema, change from baseline to peak creatinine, renal replacement-free days, severe adverse events, and acute kidney injury (AKI) ascertained through post-randomization days 7 and 14 using the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria for stage 2 or 3 (see **eAppendix 1** in **Supplement 2**). For the combined ARB and DMX-200 intervention, additional secondary safety outcomes included change from baseline to peak hepatic transaminases as well as occurrence of suspected unexpected serious adverse reactions. All outcomes were site reported and not adjudicated.

Statistical Analysis

This domain employed an adaptive two-stage design with an initial evaluation period given limited experience with the study treatments in critically ill patients (**eFigure 1** in **Supplement 2**). During the evaluation period, interventions were required to demonstrate an acceptable safety profile as judged by the Data and Safety Monitoring Board (DSMB), and an intermediate probability of efficacy defined as ≥50% posterior probability of a ≥20% improvement in the proportional odds ratio (OR) for organ support-free days for ACE inhibitor and ARB compared to control, or ≥30% for the combined ARB and DMX-200 intervention compared to both ARB and control to proceed to stage 2. Stage 1 was planned up to maximum sample sizes of 300 patients in each of the ACE inhibitor and ARB groups, and 200 patients in the combined ARB and DMX-200 intervention group. Graduation rules were prespecified and would be implemented in a blinded fashion. Interventions that satisfied graduation criteria would continue to the uncapped evaluative period which would enroll until platform-level adaptive stopping triggers for efficacy (posterior probability >99%

that OR >1.0 compared with control) or futility (posterior probability >95% that OR <1.2 compared with control) were reached. The futility trigger could be reached at any adaptive analysis. Interventions failing to graduate would be withdrawn in stage 1. Enrollment was closed in stage 1 for safety concerns prior to an adaptive analysis being performed.

The primary analysis was intention-to-treat and included all consenting patients with suspected or proven COVID-19 with available primary outcome. The primary analysis was a bayesian cumulative logistic model adjusted for age, sex, site, and enrollment time period (in 2-week intervals), and included covariates reflecting intervention and domain eligibility. Treatment effects were estimated only from patients randomized in the domain. Patients with COVID-19 enrolled into REMAP-CAP but outside of this domain did not contribute to estimates of RAS inhibitor effects, but did contribute to overall model covariate coefficient estimation.

The primary model was fit using a Markov Chain Monte Carlo algorithm with 20,000 samples from the joint posterior distribution. The model calculated posterior distributions for the proportional OR, including medians and 95% credible intervals (CrIs), and the posterior probabilities of efficacy for each intervention compared with control. The probability of harm is the complement of the probability of efficacy (i.e., posterior probability OR <1.0). Distinct treatment effects were estimated in critically ill and noncritically ill patients by nesting intervention effects in a hierarchical prior distribution centered on an overall intervention effect estimated with a neutral prior; the posterior distributions for these effects were

shrunk towards the overall estimate to an extent reflective of their similarity (dynamic borrowing).[27]

Secondary analyses were performed using bayesian logistic regression models for ordinal and dichotomous outcomes, bayesian linear models for continuous outcomes, and bayesian piecewise exponential models for time-to-event outcomes. No formal hypothesis tests were performed on secondary outcomes, and summaries of posterior distributions are provided for descriptive purposes only.

Prespecified subgroup analyses assessed treatment effect by age (<50, 50-70, or >70 years), sex, baseline invasive mechanical ventilation, estimated glomerular filtration rate (eGFR; <90, ≥90 mL/min/1.73 m^2, or unknown), and baseline vasopressor receipt. Machine learning with causal forests[28,29] estimated subgroup- and individual-level heterogeneity of treatment effects by considering all available baseline covariates in separate and pooled treatment analyses. Expected absolute risk differences were estimated for conditional average treatment effects at the levels of the individual and the subgroup (see **eAppendix 1** in **Supplement 2**).

Analysis details are provided in the Statistical Analysis Plan in **Supplement 1**. The primary and key secondary analyses were performed in R (version 4.1.3). The causal forests heterogeneity of treatment effect analyses were conducted in R (version 4.0.5) with the R package grf (version 2.1.0).

Results

Enrollment and Participant Characteristics

The first patient was enrolled in the ACE2 RAS Domain on March 16, 2021. On February 25, 2022, enrollment of critically ill patients was discontinued on advice from the DSMB due to concern for higher mortality and AKI in the ACE inhibitor and ARB groups compared to control, based on a scheduled assessment of safety data from 564 patients. Enrollment of noncritically ill patients was concurrently paused, and subsequently discontinued on June 8, 2022, by the trial steering committee due to the findings in critically ill patients and slow recruitment.

A total of 721 critically ill patients and 58 noncritically ill patients were randomized (**Figure 1**) at 69 sites in seven countries (Canada, Italy, Netherlands, New Zealand, Saudi Arabia, United Kingdom, and United States). Of these, 34 critically ill and 2 noncritically ill patients withdrew consent and outcomes were unavailable for 2 critically ill patients. Baseline characteristics were similar between groups, although some imbalances were present, including vasopressor receipt (**Table 1** and **eTable 2** in **Supplement 2**). Ramipril and losartan were the most common ACE inhibitor and ARB used, at low- or moderate-doses (see **eTable 1** in **Supplement 2** for dose classifications), for median treatment durations of 6 and 7 days in critically ill patients and 2 and 5 days in noncritically ill patients (**eTable 3** in **Supplement 2**). Among patients allocated to ACE inhibitor or ARB, 104/243 (42.8%) and 132/236 (55.9%)

did not complete the full treatment course, most commonly due to hypotension (**eTable 4** in **Supplement 2**).

Primary Outcome

Among 679 critically ill patients, the median (IQR) organ support-free days in the ACE inhibitor group (n=231) was 10 (–1 to 16), in the ARB group (n=217) was 8 (–1 to 17), and in the control group (n=231) was 12 (0 to 17) (**Figure 2**), corresponding to adjusted ORs for ACE inhibitor of 0.77 (95% CrI 0.58 to 1.06) and for ARB of 0.76 (0.56 to 1.05) compared with control (**Table 2**). The posterior probabilities that ACE inhibitor and ARB worsened organ support-free days compared with control were 94.9% and 95.4%. Results were generally consistent in sensitivity analyses, including after adjustment for potentially imbalanced variables (**eTable 5** in **Supplement 2**). There were no consistent, clinically relevant deviations from the assumption of proportional effects across the organ support-free days scale (**eFigure 2** in **Supplement 2**). Outcomes were available for only six critically ill patients randomized to the combined ARB and DMX-200 intervention (**eFigure 3** in **Supplement 2**). Among 56 noncritically ill patients, median (IQR) organ support-free days in all groups was 22 (22 to 22) (**eFigure 4** in **Supplement 2**) and posterior probabilities were inconclusive (**eTable 6** in **Supplement 2**).

Secondary Outcomes

None of the 15 secondary outcomes were improved with ACE inhibitor or ARB compared with control (**Table 2** and **eTables 6**, **7**, and **8** in **Supplement 2**). Among critically ill patients in the ACE inhibitor, ARB, and control groups, hospital survival occurred in 166/231 (71.9%), 152/217 (70.0%), and 182/231 (78.8%), respectively, corresponding to adjusted ORs for ACE inhibitor of 0.70 (95% CrI 0.44 to 1.06) and for ARB of 0.62 (0.39 to 0.98) compared with control. The posterior probabilities that ACE inhibitor and ARB worsened hospital survival compared with control were 95.3% and 98.1%. The probability was high that ACE inhibitor and ARB reduced survival through 90 days (**Figure 3**). Among noncritically ill patients, one death occurred (in the ACE inhibitor group).

Among critically ill patients, vasopressor therapy was newly initiated in 69/188 (36.7%), 86/188 (45.7%), and 69/203 (34.0%) in the ACE inhibitor, ARB, and control groups, respectively. The posterior probabilities were 94.0% and 99.7% that vasopressor-free days, a composite of death and vasopressor receipt, was worsened with ACE inhibitor and ARB. Median (IQR) relative change from baseline to peak creatinine was 1.11 (1.00 to 1.25), 1.15 (1.00 to 1.42), and 1.11 (1.00 to 1.30), respectively (**eFigure 5** in **Supplement 2**). The occurrence of KDIGO stage ≥2 AKI within 14 days following randomization was 7.2%, 14.4%, and 7.5%, respectively. Among noncritically ill patients, vasopressor receipt and AKI were infrequent (**eTables 6** and **8** in **Supplement 2**). Evaluation of secondary outcomes in the combined ARB and DMX-200 arm was limited by low enrollment.

Serious adverse events were reported in 2/232 (0.9%), 5/218 (2.3%), 0/6 (0.0%), and 4/231 (1.7%) critically ill patients in the ACE inhibitor, ARB, combined DMX-200 and ARB, and control groups, respectively, and in one noncritically ill patient (in the ACE inhibitor group; **eTable 9** in **Supplement 2**).

Subgroup Analyses

In subgroup analyses, treatment effects among critically ill patients did not meaningfully vary by age, sex, mechanical ventilation receipt, or baseline eGFR (**eFigures 6** and **7** in **Supplement 2**). Among patients receiving vasopressors at enrollment, OR for organ support-free days with ACE inhibitor compared with control was 0.54 (95% CrI 0.30 to 0.97), versus 0.90 (0.66 to 1.25) among patients not receiving vasopressors. ARB treatment effect did not differ by baseline vasopressor receipt. In causal forest analyses considering whether there was evidence of heterogeneous treatment effects across all available baseline variables (**eTable 10** in **Supplement 2**), subgroup conditional average treatment effects were similar for ACE inhibitor and ARB (**eFigure 8** in **Supplement 2**). No subgroup showed strong evidence of heterogeneity (**eFigure 8** in **Supplement 2**). Point estimates of expected conditional average treatment effects at the individual level consistently favored worsened hospital survival for both treatments versus control, but with 95% confidence intervals that included null for the majority (>70%) of patients (**Figure 3**).

Discussion

In this domain of an overarching platform trial, among critically ill patients hospitalized for COVID-19, there was a 95% probability that ACE inhibitor or ARB initiation worsened organ support-free days, primarily due to differences in hospital survival. The domain was terminated due to safety concerns, and findings are inconclusive for noncritically ill patients and in the combined ARB and DMX-200 arm.

RAS activation may contribute to poor clinical outcomes in patients with acute hypoxemic respiratory failure,[30-34] including COVID-19.[3,8,35-37] Angiotensin II is upregulated in COVID-19 and other severe respiratory infections, proportional to severity.[38,39] Inhibition of angiotensin II with ACE inhibitors or ARBs improves respiratory and other organ failure in animal models of SARS-CoV-2 infection,[12] SARS-CoV-1 infection,[7] sepsis,[40-45] aspiration,[15] and ventilator-induced lung injury.[42,46-52] Observational studies suggest more favorable outcomes among existing users of ACE inhibitors and ARBs who develop COVID-19 and other respiratory infections compared with non-users.[11,13,14,53-55] However, animal models inconsistently correlate with human host response,[56] and observational studies are at risk for bias.[57]

Analyses suggest that there was a high probability that inhibiting angiotensin II, either by reducing its production (ACE inhibitors) or blocking its effect (ARBs), worsened outcomes among critically ill patients. In prespecified subgroup and causal forest heterogeneity of treatment effect analyses, there was no evidence that any subgroup benefited based on these analyses. Although a trend towards lower hospital survival was observed for some

higher risk subgroups, there was no clear evidence of differential effect by baseline characteristics to support a mechanistic hypothesis. Among secondary outcomes, vasopressor receipt and AKI were more frequent with ARB, although less clearly so with ACE inhibitor.

In an early pandemic trial of 162 hospitalized patients with COVID-19 but excluding those admitted to an ICU, telmisartan improved survival and reduced inflammatory biomarkers compared to control;[58] however, enrollment was prematurely terminated, limiting inference. In a more recent trial of 205 patients, oxygenation and survival were not improved with losartan compared to placebo, although hypotension and AKI occurred more frequently.[59] A recent meta-analysis of smaller and incomplete trials observed no survival benefit with RAS inhibitor initiation for COVID-19, and hypotension and AKI appeared more frequent in severely ill patients.[60] The CLARITY trial, which included lower risk patients, did not observe a benefit of telmisartan initiation in hospitalized patients with COVID-19.[61] The current trial had the largest sample size to date, and included the highest proportion of critically ill patients, who are at greatest risk of hypotension and AKI, which may explain the more evident harm signal. Importantly, prior randomized clinical trials evaluating continuation compared to discontinuation of RAS inhibitors in less severely ill patients hospitalized for COVID-19 suggest their continuation is safe[62] – although there is uncertainty among more severely ill patients.[63,64]

Strengths of this trial include its pragmatic evaluation of candidate repurposed, widely-available treatments in diverse international settings. Consistency of treatment effects

across both ACE inhibitor and ARB supports inference across shared mechanisms of action. The application of a two-stage design with graduation rules permitted efficient evaluation of early candidate treatments. Finally, the application of forest-based techniques suited to high-dimensional data permitted a broad evaluation of potentially clinically important effect modifiers, and may overcome some of the limitations of conventional subgroup analyses.

Limitations

The trial has several limitations. First, the protocol was pragmatic and agents and dose equivalents varied; nevertheless, 89% of patients in each group received the same agent and dose equivalents were consistently low-to-moderate. Second, approximately 1 in 20 randomized patients withdrew consent and were excluded from this analysis. However, the frequency was similar across groups, and similar to other acute care trials where patients often lack capacity to provide consent at the time of enrollment. Third, some potentially relevant baseline characteristics (e.g., vasopressor receipt) were imbalanced: These imbalances may have had a modest influence on treatment effect estimates. Fourth, this trial evaluated new RAS antagonist initiation specifically as treatment for COVID-19, and not the separate question of whether to continue or discontinue existing therapy. Fifth, the trial was terminated for safety concerns after enrollment of only a modest sample size: Although this may leave uncertainty about precise treatment effects, the likelihood of meaningful clinical benefit is low. Finally, due to being available later and offered only at a subset of sites, enrollment into the combined ARB and DMX-200 arm was low at the time of closure of enrollment.

Conclusions

In conclusion, in this trial, in critically ill adults with COVID-19, initiation of ACE inhibitor or ARB did not improve, and likely worsened, clinical outcomes.

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To be generated from author contribution forms.

Access to data statement:

Dr. Lawler had full access to all the data relative to this domain. Dr. Lewis had full access to all the data required for the primary analyses. Together, Drs. Lawler and Lewis take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures

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The REMAP-CAP Investigators

See attachment 'REMAP-CAP Investigators'.

Data Sharing Statement

Data Sharing Statement: See Supplement 4

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Summary of Supplements

Supplement 1. Trial Protocol and SAP Documents

- Table of Contents
- Brief introduction to explain the protocol structure given modular nature of ongoing platform trial
- REMAP-CAP Core Protocol (Version 3.0, July 10th, 2019, the Original Version - predating any COVID-19 screening and inclusion)
- Pandemic Appendix to Core (PAtC) protocol (Final Version 2.0, May 18th, 2020 including summary of changes from version 1.1 and Original Version 1.1, February 12th, 2020)
- REMAP-COVID Core Protocol (Version 1.0, March 27th, 2020)
- Statistical Analysis Appendix to the Core Protocol (Version 3.0, August 24th, 2019 - the Original Version predating any Covid-19 screening and inclusion)
- ACE2 RAS Domain Specific Appendix (Versions 1 and 2, November 8th, 2020, and October 14th, 2021)
- Statistical Analysis Plan for the ACE2 RAS Domain analysis (Version 1.2, August 4th, 2022)

Supplement 2.

The REMAP-CAP Investigators

eAppendix 1 – Supplementary Methods

eAppendix 2 –Supplementary Results

Supplemental Tables and Figures

eTable 1 Study Drug Intensity Dose Equivalents for Retrospective Categorization

eTable 2 Noncritically Ill Participant Characteristics at Baseline

eTable 3 Study Drug Intensity Dose Equivalents

Supplement 3. Non-author collaborators

Supplement 4. Data sharing Agreement

Figure Legends

Figure 1. Screening, Randomization, and Follow-up of Participants in the REMAP-CAP COVID-19 ACE2 RAS Domain Randomized Clinical Trial

REMAP-CAP is a platform trial with a single master protocol (**Supplement 1**) evaluating multiple treatments. The trial applied eligibility criteria at the platform level and at the domain level: Patients had to be eligible for both the platform and domain to be randomized. A "domain" refers to a common therapeutic area within which several interventions or intervention dosing strategies could be randomly assigned. Participating sites selected at least 2 of up to 4 possible interventions in this domain (including control).

Footnotes:

[a] Patients could meet more than 1 ineligibility criterion. Full details are provided in **Supplement 1**.

[b] Other contraindications to ACE2 RAS agents included: concern for clinically relevant hypotension or escalation of vasopressor requirements; hyperkalemia; known severe renal artery stenosis; known or suspected pregnancy or breastfeeding; and for the combined ARB and DMX-200 intervention, known severe liver disease or an ALT or AST that is more than five times the upper limit of normal, known viral hepatitis, or hypersensitivity to repagermanium.

[c] Participants were randomized via a centralized computer program to each intervention with balanced assignment based on number of interventions available per site.

[d] Critically ill patients were categorized as such if they were receiving at least one of the following organ supports in an intensive care unit: high flow nasal cannula oxygenation, invasive or non-invasive mechanical ventilation, or vasopressor or inotropic infusion. All other patients were considered noncritically ill.

[e] The combined ARB and DMX-200 intervention was available later than the ACE inhibitor and ARB interventions, and was only available at a subset of sites, contributing to low recruitment by the time of overall domain enrollment closure.

[f] The primary analysis in the ACE2 RAS domain is estimated from a model that adjusts for patient factors and for assignment to other interventions; all patients enrolled in the COVID-19 cohort for whom there is consent and follow-up are included. The final estimate of an ACE2 RAS domain intervention's effectiveness relative to any other within that domain is generated from those patients that might have been randomized to either. In contrast to the analyses of organ support-free days (the primary outcome) and its component hospital survival (a secondary outcome), which were performed by an independent unblinded statistical analysis committee, sensitivity and other secondary analyses were performed by investigators blinded to ongoing interventions and therefore did not include adjustment for treatment assignment in ongoing domains.

Figure 2. Primary Outcome in Critically Ill Patients – Organ Support-Free Days Up to Day 21

The **upper panel** displays the distributions of organ support-free days (days alive and free of respiratory or cardiovascular organ support in an intensive care unit) up to day 21. The ordinal scale includes in-hospital death (the worst possible outcome, truncated at 90 days), and a score of 0 to 21 (the numbers of days alive without organ support) by randomization group as the cumulative proportion (y axis) for each trial group by day (x axis), with death listed first. Curves that rise more slowly are more favorable. The difference in the height of the two curves at any point represents the difference in the cumulative probability of having a value for days without organ support of less than or equal to that point on the x axis. The **lower panel** displays organ support-free days as horizontally stacked proportions by trial group. Red represents worse values and blue represents better values, the deepest red is death and deepest blue is alive without organ support at 21 days. The primary outcome

distribution for the six critically ill patients randomized to the combined ARB and DMX-200 intervention is shown in **eFigure 1** in **Supplement 2**, and for 56 noncritically ill patients in **eFigure 2** in **Supplement 2**.

Figure 3. (Upper Panel) Survival through 90 Days in Critically Ill Patients. (Lower Panel) Individual Conditional Treatment Effects for Pooled ACE Inhibitor and ARB Intervention Effect on Hospital Survival.

The **upper panel** displays Kaplan-Meier curve of 90-day all-cause survival in critically ill patients. Patients that do not die within 90 days are censored at day 90 with no event. The **lower panel** displays ranked estimated individual-level conditional average treatment effect on hospital survival for all patients. From the final causal forest on hospital survival pooling both ACE inhibitor and ARB, treatment effect in tree terminal leaves with each individual's control and intervention neighbors are combined to give an estimate of individual-level treatment effect conditional on their baseline covariates. Ranked absolute risk difference estimate with its 95% confidence interval is shown for each.

Figure 1. Screening, Randomization, and Follow-up of Participants in the REMAP-CAP COVID-19 ACE2 RAS Domain Randomized Clinical Trial

Figure 2. Primary Outcome in Critically Ill Patients – Organ Support-Free Days Up to Day 21

Figure 3. (Upper Panel) Survival through 90 Days in Critically Ill Patients. (Lower Panel) Individual Conditional Treatment Effects for Pooled ACE Inhibitor and ARB Intervention Effect on Hospital Survival

Table 1. Critically Ill Participant Characteristics at Baseline[a]

	ACE inhibitor (n = 232)	ARB (n = 218)	Control (n = 231)
Age in years, median (IQR)	55.0 (43.0-66.0)	55.5 (44.0-63.0)	56.0 (44.0-65.0)
Female sex, No. (%)	82 (35.3)	66 (30.3)	91 (39.4)
Male sex, No. (%)	150 (64.7)	152 (69.7)	140 (60.6)
Race / Ethnicity[b], No./total (%)			
Asian	7/146 (4.8)	7/142 (4.9)	8/140 (5.7)
Black	6/146 (4.1)	11/142 (7.7)	9/140 (6.4)
Mixed	0/146 (0.0)	3/142 (2.1)	2/140 (1.4)
White	126/146 (86.3)	114/142 (80.3)	114/140 (81.4)
Other	7/146 (4.8)	7/142 (4.9)	7/140 (5.0)
Body-mass index[c], median (IQR)	30.3 (26.4-36.9) (n=210)	30.1 (27.2-37.2) (n=200)	30.5 (27.3-35.8) (n=213)
APACHE II score[d], median (IQR)	11.0 (6.0-17.0) (n=231)	10.0 (7.0-14.0) (n=217)	10.0 (6.0-16.0) (n=230)
Clinical Frailty Score[e], median (IQR)	2.0 (2.0-3.0) (n=228)	2.0 (2.0-3.0) (n=215)	2.0 (2.0-3.0) (n=229)
Confirmed SARS-CoV-2 infection[f], No./total (%)	202/207 (97.6)	189/191 (99.0)	198/199 (99.5)
Pre-existing condition[g], No./total (%)			
Diabetes	35/231 (15.2)	31 (14.2)	29 (12.6)
Respiratory disease	45/230 (19.6)	43/217 (19.8)	51/229 (22.3)
Kidney disease	7/205 (3.4)	2/209 (1.0)	2/213 (0.9)
Severe cardiovascular disease	9/231 (3.9)	9 (4.1)	5/228 (2.2)
Any immunosuppressive condition	12/230 (5.2)	13/217 (6.0)	15/229 (6.6)
Time to enrollment, median (IQR)			
From hospital admission, days	2.0 (1.1-3.7)	2.0 (1.1-3.9)	2.1 (1.1-3.8)
From ICU admission, hours	17.7 (8.9-27.0) (n=231)	16.9 (7.3-23.4)	16.2 (6.5-23.8)
Acute respiratory support, No. (%)			
Invasive mechanical ventilation	73/231 (31.6)	62 (28.4)	66 (28.6)
Non-invasive ventilation only	91/231 (39.4)	83 (38.1)	85 (36.8)
High-flow nasal cannula	68/231 (29.4)	73 (33.5)	81 (35.1)
None / supplemental oxygen	0/231 (0.0)	0 (0.0)	0 (0.0)

PaO_2 / FiO_2, median (IQR)[h]	122.0 (88.0-158.0) (n=225)	112.0 (83.5-151.0) (n=215)	121.0 (91.0-154.8) (n=222)
Systolic blood pressure, mmHg	126.0 (114.0-144.0) (n=227)	128.0 (115.0-145.0) (n=215)	130.0 (115.0-144.2) (n=228)
Vasopressor support, No. (%)	43 (18.6)	30 (13.8)	28 (12.1)
Extended Cardiovascular SOFA score, median (IQR)[i]	0.0 (0.0-0.0) (n=230)	0.0 (0.0-0.0) (n=217)	0.0 (0.0-0.0) (n=229)
Median laboratory values (IQR)[i]			
C-reactive protein, µg/mL	92.0 (34.0-157.0) (n=205)	76.0 (37.0-146.0) (n=187)	91.5 (37.8-162.8) (n=186)
Lactate, mmol/L	1.3 (1.0-1.9) (n=201)	1.3 (1.0-1.7) (n=197)	1.3 (1.0-1.6) (n=211)
Creatinine, mg/dL	0.8 (0.6-1.0) (n=231)	0.7 (0.6-0.9) (n=217)	0.7 (0.6-0.9) (n=228)
eGFR, min/min/1.73m^2	100.8 (86.0-113.7) (n=231)	103.5 (92.4-113.4) (n=217)	102.9 (92.8-115.9) (n=228)
Potassium, mmol/L	4.3 (4.1-4.6) (n=222)	4.2 (4.0-4.5) (n=210)	4.2 (3.9-4.5) (n=219)
Concomitant therapies, No./total (%)[j]			
Remdesivir	34/228 (14.9)	34/217 (15.7)	39/230 (17.0)
Corticosteroids	226/228 (99.1)	214/217 (98.6)	226/230 (98.3)
Tocilizumab or sarilumab	173/228 (75.9)	165/217 (76.0)	183/230 (79.6)
Baricitinib	2/228 (0.9)	6/217 (2.8)	9/230 (3.9)
Antiviral monoclonal antibody	1/228 (0.4)	2/217 (0.9)	2/230 (0.9)

Percentages may not sum to 100 because of rounding. SD denotes standard deviation; ACE, angiotensin converting enzyme; APACHE, Acute Physiology and Chronic Health Evaluation; ARB, angiotensin receptor blocker; IQR, interquartile range; eGFR, estimated glomerular filtration rate; PaO_2/FiO_2, ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2).

[a] Due to the small sample size (n=6), data on patients randomized to the combined ARB and DMX-200 arm are not presented.

[b] Data collection was not approved in Canada and continental Europe. 'Other' includes 'declined' and 'other ethnic group'. Participants (or their surrogates) self-reported their race/ ethnicity via fixed categories appropriate to their region. “Declined” does not simply represent missing data. A patient may decline to provide their race at the time of registration or the person performing the registration may decline to ask the patient to clarify race at the time of registration.

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

[d] This score measures illness severity based on age, medical history, and physiologic variables. Scores range from 0 to 71, with higher number representing increasing severity.

[e] The Clinical Frailty Score is a global measure of fitness and frailty, with increasing scores – ranging from 1 (very fit) to 9 (terminally ill) – reflecting worse fitness and increasing frailty.

[f] SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test. Patients were eligible for enrollment if COVID-19 testing had been performed and confirmed the presence of SARS-CoV-2, or if testing had not yet been performed but was intended to occur. Following enrollment, in eight patients, SARS-CoV-2 was not confirmed, either due to negative test results or the absence of testing. These patients are nevertheless included in the intention-to-treat analysis.

[g] Kidney disease was determined from the most recent stable serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was

defined as a creatinine level of 130 µmol/L or greater (1.5 mg/dL) for males or 100 µmol/L or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of immunosuppressive disease.

[h] A normal PaO_2/FiO_2 ratio is ≥400.

[i] Extended Cardiovascular SOFA Score reflects criteria for blood pressure and inotropic or vasoactive support, with higher scores indicating worse cardiovascular organ failure.

[j] Laboratory results available when captured for clinical care.

[k] Within 48hr of randomization.

Table 2. Primary Outcome (Organ Support-Free Days) and Select Secondary Outcomes in the Critically Ill Population[a]

Outcome	Groups			ACE Inhibitor Compared to Control			ARB Compared to Control		
	Control N= 231	ACE inhibitor N= 231	ARB N= 217	Adjusted odds ratio (95% CrI)[h]	Probability of efficacy[i]	Probability of harm[i]	Adjusted odds ratio (95% CrI)[g]	Probability of efficacy[h]	Probability of harm[h]
Primary outcome	*median no. (IQR)*				%	%		%	%
Organ support-free days[b, c]	12 (0 to 17)	10 (-1 to 16)	8 (-1 to 17)	0.77 (0.58 to 1.06)	5.1	94.9	0.76 (0.56 to 1.05)	4.6	95.4
Secondary outcomes	*no. of patients/total no. (%)*				%	%		%	%
In-hospital survival	182/231 (78.8)	166/231 (71.9)	152/217 (70.0)	0.70 (0.44 to 1.06)	4.7	95.3	0.62 (0.39 to 0.98)	1.9	98.1
90-day survival[d]	-	-	-	0.70 (0.49 to 1.02)	3.1	96.9	0.67 (0.46 to 0.96)	1.4	98.6
AKI KDIGO[e] Stage ≥ 2 by day 14	16/212 (7.5)	16/223 (7.2)	30/208 (14.4)	0.85 (0.43 to 1.69)	67.2	32.8	1.87 (1.02 to 3.48)	2.2	97.8
AKI KDIGO[e] Stage 3 by day 14[f]	12/212 (5.7)	12/223 (5.4)	23/208 (11.1)	0.87 (0.39 to 1.90)	64.2	35.8	1.78 (0.89 to 3.58)	5.4	94.6
	median no. (IQR)								
Vasopressor/inotrope-free days[g]	28 (7.5, 28)	26 (-1 to 28)	24 (-1 to 28)	0.75 (0.53 to 1.07)	6.0	94.0	0.62 (0.44 to 0.89)	0.4	99.7

ACE denotes angiotensin converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CrI, credible interval; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; no., number.

[a] Additional secondary outcomes in critically ill patients are reported in **eTable 7** in **Supplement 2**. Due to the low number of patients with available outcomes in the combined ARB and DMX-200 arm (n=6), effect estimates were not calculated in this group; rather, distributions of the primary outcome are shown in **eFigure 1** in **Supplement 2**, and descriptive data on secondary outcomes is reported in footnotes to **eTable 7** in **Supplement 2**.

[b] The primary outcome was organ support-free days, evaluated using an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. The conditional median (IQR) organ support-free days for patients who survived hospitalization was: control, 15 (9 to 18); ACE inhibitor, 15 (8 to 18); ARB, 15 (6 to 18).

[c] Dynamic borrowing of information on treatment effect from noncritically ill patients was permitted. Results from a sensitivity analysis assuming independent treatment effects between disease-severity cohorts are provided in **eTable 5** in **Supplement 2**.

[d] Time-to-event outcome. The effect estimates are median hazard ratios. Hazard ratios above 1 indicate benefit and below 1 indicate harm of ACE inhibitor or ARB relative to the control group. The No./total (%) of patients alive at 90 days in each group is: ACE inhibitor (164/231; 71.0%), ARB (151/217, 69.6%), and control (179/231, 77.5%).
[e] Acute kidney injury was defined using the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria as either stage ≥2 (serum creatinine increase 2-2.9x from baseline, with baseline defined as time of enrollment) or as stage 3 (serum creatinine increase ≥3x from baseline, or increase in serum creatinine by ≥0.5 mg/dL [44 mmol/L] to ≥4 mg/dL [353.6 µmol/L], or new initiation of renal replacement therapy). An odds ratio <1 indicates treatment benefit, whereas an odds ratio >1 indicates treatment harm.
[f] Need for renal replacement therapy among patients meeting criteria for KDIGO stage 3 by day 14: control arm, 4/212 (1.9%); ACE inhibitor arm, 4/223 (1.8%); ARB arm, 10/208 (4.8%). The occurrence of incident AKI at 7 days is reported in **eTable 7** in **Supplement 2**.
[g] This composite outcome included mortality and, among survivors, the number of days alive without vasopressor through day 28. Among critically ill patients in the ACE inhibitor, ARB, and control groups, 69/188 (36.7%), 86/188 (45.7%), and 69/203 (34.0%) patients, respectively, received new initiation of vasopressors (after not been on them at enrollment) after randomization.
[h] Values are median odds ratios. Odds ratios for organ support-free days and in-hospital survival are adjusted for age, sex, site (nested within country), domain ineligibility, randomization within each domain and time epochs. Odds ratios for the remaining outcomes are adjusted for age and sex. Odds ratios >1 corresponds with treatment benefit and <1 corresponds with treatment harm – except in the reporting of occurrence of acute kidney injury, wherein the direction of treatment effect is reversed to be consistent with the outcome description.
[i] The probabilities of efficacy and harm of ACE inhibitor or ARB relative to the control group were computed from the posterior distributions.