JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

Writing Committee for the REMAP-CAP Investigators

IMPORTANCE Overactivation 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 non–critically ill hospitalized adults were randomized to receive an RAS inhibitor or control between March 16, 2021, and February 25, 2022, at 69 sites in 7 countries (final follow-up on June 1, 2022).

INTERVENTIONS Patients were randomized to receive open-label initiation of an 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 (ORs) greater than 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 data, the median age was 56 years and 239 participants (35.2%) were women. Median (IQR) organ support–free days among critically ill patients was 10 (–1 to 16) in the ACE inhibitor group (n = 231), 8 (–1 to 17) in the ARB group (n = 217), and 12 (0 to 17) in the control group (n = 231) (median adjusted odds ratios of 0.77 [95% bayesian credible interval, 0.58-1.06] for improvement for ACE inhibitor and 0.76 [95% credible interval, 0.56-1.05] for ARB compared with control). The posterior probabilities that ACE inhibitors and ARBs worsened organ support–free days compared with control were 94.9% and 95.4%, respectively. Hospital survival occurred in 166 of 231 critically ill participants (71.9%) in the ACE inhibitor group, 152 of 217 (70.0%) in the ARB group, and 182 of 231 (78.8%) in the control group (posterior probabilities that ACE inhibitor and ARB worsened hospital survival compared with control were 95.3% and 98.1%, respectively).

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 Identifier: NCT02735707

Visual Abstract

Editorial page 1155

Related article page 1170

Supplemental content

Author/Group Information: The REMAP-CAP authors appear at the end of the article and the full list of investigators and collaborators in Supplement 3.

Corresponding Authors: Patrick R. Lawler, MD, MPH, Toronto General Hospital, RFE3-410, 190 Elizabeth St, Toronto, ON, Canada M5G2C4 (Patrick.Lawler@uhn.ca); Lennie P. G. Derde, MD, PhD, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands (L.P.G.Derde@umcutrecht.nl).

JAMA. 2023;329(14):1183-1196. doi:10.1001/jama.2023.4480

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 that 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 an RAS inhibitor (either an ACE inhibitor or an angiotensin receptor blocker [ARB]) on the composite outcome of hospital survival and organ support provision through 21 days was evaluated in patients hospitalized with COVID-19 pneumonia.

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.

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 have been previously published[18] and are available in Supplement 1. Patients are assessed for platform eligibility and potentially randomized to receive 1 or more interventions among available domains, organized by therapeutic areas. The trial previously reported the effects of corticosteroids, anticoagulants, antivirals, IL-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 18 years or older hospitalized with clinically suspected or microbiologically confirmed COVID-19 pneumonia were eligible for inclusion (**Figure 1**). Patients were stratified into critically ill and non-critically ill groups at enrollment. Patients receiving respiratory (high-flow nasal oxygen with flow rate ≥30 L/min and fraction of inspired oxygen ≥0.4 or noninvasive 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 non-critically ill. Critically ill patients were eligible for enrollment within 48 hours of ICU admission and non-critically ill patients were eligible 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 kidney impairment, severe renal artery stenosis, or pregnancy or breastfeeding. 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 were collected from participants or their surrogates via fixed categories appropriate to their region at approving sites.

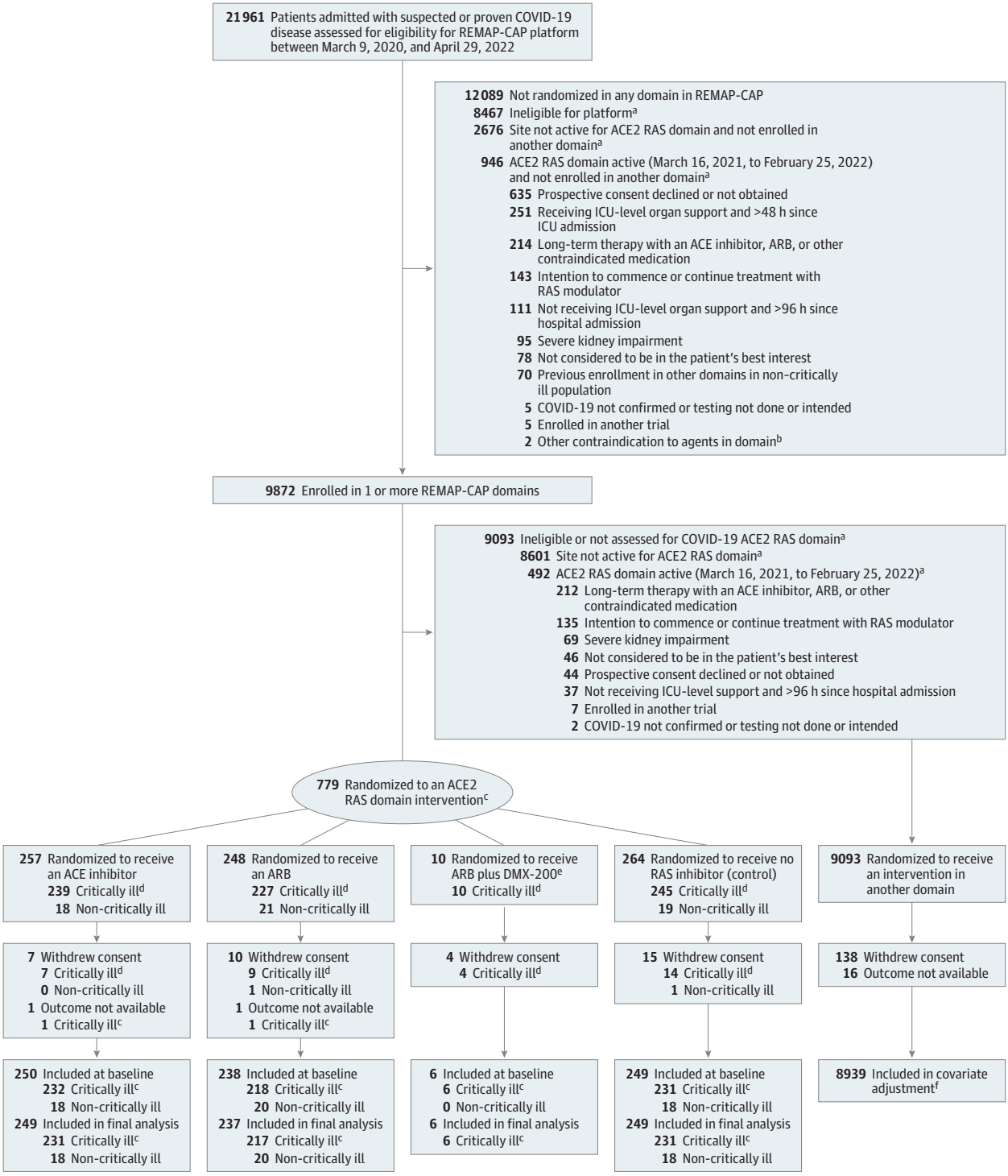
Treatment Randomization

All participating sites randomized patients to receive control (no RAS inhibitor) and up to 3 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 randomization ratios based on the number of available interventions at each site. Response-adaptive randomization was not used in this domain. Patients could also be randomized to receive interventions in other domains depending on availability and eligibility.

Interventions

Treatment assignments included initiation of and in-hospital treatment with an enterally administered ACE inhibitor, ARB, ARB in combination with DMX-200, or control (no initiation of an RAS inhibitor). Sites selected from a hierarchical list of ACE inhibitors and ARBs (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

Figure 1. Flow of Participants in a Study of the Effect of Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB)



[a] Could meet >1 exclusion criterion (Supplement 1).

[b] Concern for clinically relevant hypotension or escalation of vasopressor requirements, hyperkalemia, severe renal artery stenosis, pregnancy or breastfeeding, and, for ARB and DMX-200, severe liver disease or alanine transaminase or aspartate transaminase >5 times the upper limit of normal, known viral hepatitis, or hypersensitivity to repagermanium.

[c] Via centralized computer program with balanced assignment based on the number of interventions per site.

[d] Receiving respiratory or cardiovascular organ support.

[e] Available later than ACE inhibitor and ARB interventions at a subset of sites.

[f] The primary analysis in the RAS domain is estimated from a model that adjusts for patient factors and randomization to other interventions; all patients enrolled in the COVID-19 cohort with consent and follow-up are included. The final estimate of an intervention's effectiveness relative to any other in that domain is generated from patients who could have been randomized to either.

the protocol (Supplement 1). The protocol advised discontinuing the study drug in patients with clinically-relevant hypotension or escalating vasopressor requirements, hyperkalemia, declining kidney function, severe kidney 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 occurred 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 that occurred 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, survival at 90 days, ventilator-free days, vasopressor-/inotrope-free days, duration of hospital and ICU stays, World Health Organization COVID-19 severity scale score at day 14, hypotension while admitted to a hospital ward, angioedema, change from baseline to peak creatinine, kidney replacement-free days, severe adverse events, and acute kidney injury (AKI) ascertained through postrandomization days 7 and 14 using the modified Kidney Disease Improving Global Outcomes criteria for stage 2 or 3 kidney injury (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 2-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 and an intermediate probability of efficacy, defined as at least 50% posterior probability of at least 20% improvement in the proportional odds ratio (OR) for organ support-free days for ACE inhibitor and ARB initiation compared with control or at least 30% for the combined ARB and DMX-200 intervention compared with 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% of OR >1.0 compared with control) or futility (posterior probability >95% of 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 an intention-to-treat analysis 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 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 in 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 (ie, posterior probability OR <1.0). Distinct treatment effects were estimated in critically ill and non-critically 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 toward 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. Sensitivity and other secondary analyses were performed by investigators blinded to ongoing interventions and did not include adjustment for treatment assignment in ongoing domains.

Prespecified subgroup analyses assessed treatment effect by age (<50, 50-70, or >70 y), sex, baseline invasive mechanical ventilation status, estimated glomerular filtration rate (<90 mL/min/1.73 m^2, ≥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 using R, version 4.1.3 (R Foundation). The causal forests heterogeneity of treatment effect analyses were conducted using R, version 4.0.5, with the R package grf, version 2.1.0.

Table 1. Characteristics of Critically Ill Participants at Baseline[a]

Characteristic	Median (IQR) [total No.]		
	ACE inhibitor (n = 232)	ARB (n = 218)	Control (n = 231)
Age, y	55.0 (43.0-66.0)	55.5 (44.0-63.0)	56.0 (44.0-65.0)
Women, No. (%)	82 (35.3)	66 (30.3)	91 (39.4)
Men, No. (%)	150 (64.7)	152 (69.7)	140 (60.6)
Race and ethnicity, No./total No. (%)[b]			
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 or multiple races or ethnicities	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	30.3 (26.4-36.9) [210]	30.1 (27.2-37.2) [200]	30.5 (27.3-35.8) [213]
APACHE II score[c]	11.0 (6.0-17.0) [231]	10.0 (7.0-14.0) [217]	10.0 (6.0-16.0) [230]
Clinical Frailty Scale score[d]	2.0 (2.0-3.0) [228]	2.0 (2.0-3.0) [215]	2.0 (2.0-3.0) [229]
Confirmed SARS-CoV-2 infection, No./total (%)[e]	202/207 (97.6)	189/191 (99.0)	198/199 (99.5)
Preexisting condition, No./total No. (%)[f]			
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 from hospital admission, median (IQR), d	2.0 (1.1-3.7)	2.0 (1.1-3.9)	2.1 (1.1-3.8)
Time to enrollment from ICU admission, h	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)
Noninvasive 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
Pao_2/FiO_2[g]	122.0 (88.0-158.0) [225]	112.0 (83.5-151.0) [215]	121.0 (91.0-154.8) [222]
Systolic blood pressure, mm Hg	126.0 (114.0-144.0) [227]	128.0 (115.0-145.0) [215]	130.0 (115.0-144.2) [228]
Vasopressor support, No. (%)	43 (18.6)	30 (13.8)	28 (12.1)
Extended Cardiovascular SOFA score[h]	0.0 (0.0-0.0) [230]	0.0 (0.0-0.0) [217]	0.0 (0.0-0.0) [229]

(continued)

Table 1. Characteristics of Critically Ill Participants at Baseline[a] (continued)

Characteristic	Median (IQR) [total No.]		
	ACE inhibitor (n = 232)	ARB (n = 218)	Control (n = 231)
Laboratory values[i]			
C-reactive protein, µg/mL	92.0 (34.0-157.0) [205]	76.0 (37.0-146.0) [187]	91.5 (37.8-162.8) [186]
Lactate, mmol/L	1.3 (1.0-1.9) [201]	1.3 (1.0-1.7) [197]	1.3 (1.0-1.6) [211]
Creatinine, mg/dL	0.8 (0.6-1.0) [231]	0.7 (0.6-0.9) [217]	0.7 (0.6-0.9) [228]
eGFR, min/min/1.73 m^2	100.8 (86.0-113.7) [231]	103.5 (92.4-113.4) [217]	102.9 (92.8-115.9) [228]
Potassium, mmol/L	4.3 (4.1-4.6) [222]	4.2 (4.0-4.5) [210]	4.2 (3.9-4.5) [219]
Concomitant therapies, No./total No. (%)[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)

Abbreviations: ACE, angiotensin-converting enzyme; APACHE, Acute Physiology and Chronic Health Evaluation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; Pao_2, partial pressure of oxygen.

SI conversion: To convert creatinine to µmol/L, multiply by 88.4.

[a] Due to the small sample size (n = 6), data on patients randomized to the ARB and DMX-200 group are not presented. Percentages may not sum to 100 because of rounding.

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

[c] Measures illness severity based on age, medical history, and physiologic variables (range, 0-71; higher scores indicate increasing severity).

[d] A global measure of fitness and frailty (range, 1 [very fit] to 9 [terminally ill]).

[e] SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction testing. Patients were eligible for enrollment if COVID-19 testing had been performed and results confirmed SARS-CoV-2 or if testing had not been performed but was intended to occur. After enrollment, SARS-CoV-2 was not confirmed in 8 patients, either due to negative test results or the absence of testing. These patients were included in the intention-to-treat analysis.

[f] 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 (1.5 mg/dL) or greater for men or 100 µmol/L (1.1 mg/dL) or greater for women 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.

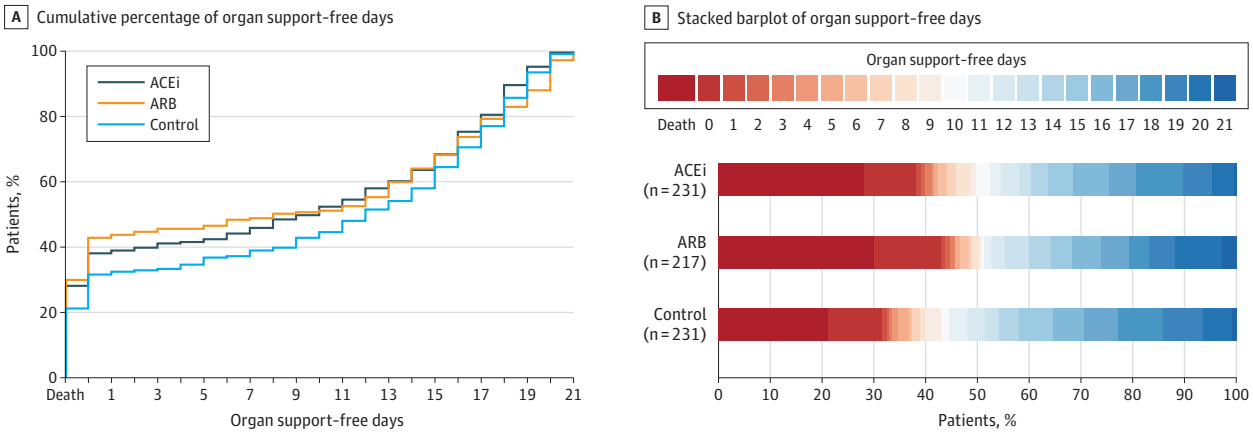
[g] A normal Pao_2/FiO_2 ratio is ≥400.

[h] The Extended Cardiovascular Sequential Organ Failure Assessment (SOFA) score reflects criteria for blood pressure and inotropic or vasoactive support, with higher scores indicating worse cardiovascular organ failure.

[i] Laboratory results were available when captured for clinical care.

[j] Within 48 hours of randomization.

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



A, Curves that increase more gradually are more favorable. B, See eFigure 1 in Supplement 2 for the primary outcome distribution for the 6 critically ill patients randomized to the combined ARB and DMX-200 intervention and eFigure 2 in Supplement 2 for the 56 non–critically ill patients. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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 data and safety monitoring board due to concern for higher mortality and AKI in the ACE inhibitor and ARB groups compared with the control group based on a scheduled assessment of safety data from 564 patients. Enrollment of non-critically 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 non-critically ill patients were randomized (Figure 1) at 69 sites in 7 countries (Canada, Italy, Netherlands, New Zealand, Saudi Arabia, United Kingdom, and US). Of these individuals, 34 critically ill and 2 non-critically ill patients withdrew consent, and outcomes were unavailable for 2 critically ill patients. Baseline characteristics were similar between the groups, although some imbalances were present, including vasopressor receipt (**Table 1** and eTable 2 in Supplement 2). Ramipril was the most common ACE inhibitor and losartan was the most common ARB used, at low or moderate doses (see eTable 1 in Supplement 2 for dose classifications), for median treatment durations of 6 days for ACE inhibitors and 7 days for ARBs in critically ill patients and 2 days for ACE inhibitors and 5 days for ARBs in non-critically ill patients (eTable 3 in Supplement 2). Among patients randomized to receive an ACE inhibitor or ARB, 104 of 243 (42.8%) in the ACE inhibitor group and 132 of 236 (55.9%) in the ARB group did not complete the full treatment course, commonly due to hypotension (eTable 4 in Supplement 2).

Primary Outcome

Among 679 critically ill patients, the median (IQR) number of organ support-free days was 10 (-1 to 16) in the ACE inhibitor group (n = 231), 8 (-1 to 17) in the ARB group (n = 217), and 12 (0 to 17) in the control group (n = 231) (**Figure 2**), corresponding to adjusted ORs of 0.77 (95% CrI, 0.58-1.06) for ACE inhibitors and 0.76 (95% CrI, 0.56-1.05) for ARBs compared with control (**Table 2**). The posterior probabilities that treatment worsened organ support-free days compared with control were 94.9% for ACE inhibitors and 95.4% for ARBs. Results were generally consistent in sensitivity analyses, including after adjustment for potentially imbalanced baseline variables (eTable 5 in Supplement 2). There were no consistent, clinically relevant deviations from the assumption of proportional effects across the scale of organ support-free days (eFigure 2 in Supplement 2). Outcomes were available for only 6 critically ill patients randomized to the combined ARB and DMX-200 intervention (eFigure 3 in Supplement 2). Among 56 non-critically ill patients, the median (IQR) number of organ support-free days in all groups was 22 (22-22) (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 treatment compared with control (Table 2 and eTables 6, 7, and 8 in Supplement 2). Among critically ill patients, hospital survival occurred in 166 of 231 patients (71.9%) in the ACE inhibitor group, 152 of 217 (70.0%) in the ARB group, and 182 of 231 (78.8%) in the control group, corresponding to adjusted ORs of 0.70 (95% CrI, 0.44-1.06) for ACE inhibitors and 0.62 (95% CrI, 0.39-0.98) for ARBs compared with control. The posterior probabilities that ACE inhibitor and ARB initiation worsened hospital survival, compared with control, were 95.3% and 98.1%, respectively. The probability was high that ACE inhibitor and ARB initiation reduced survival through 90 days (**Figure 3**). Among non-critically ill patients, 1 death occurred (in the ACE inhibitor group).

Among critically ill patients, vasopressor therapy was newly initiated in 69 of 188 patients (36.7%) in the ACE inhibitor group, 86 of 188 (45.7%) in the ARB group, and 69

Table 2. Primary and Select Secondary Outcomes in Critically Ill Patients[a]

Outcome	Median (IQR)			ACE inhibitor vs control			ARB vs control		
	Control (n = 231)	ACE inhibitor (n = 231)	ARB (n = 217)	Adjusted odds ratio (95% CrI)[b]	Probability of efficacy[c]	Probability of harm[c]	Adjusted odds ratio (95% CrI)[d]	Probability of efficacy[b]	Probability of harm[b]
Primary outcome									
Organ support-free days[e,f]	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./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-d survival[g]				0.70 (0.49 to 1.02)	3.1	96.9	0.67 (0.46 to 0.96)	1.4	98.6
KDIGO AKI stage 2 or higher by day 14[h]	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
KDIGO AKI stage 3 by day 14[i]	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
Vasopressor-/inotrope-free days[d]	28 (7.5 to 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

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CrI, credible interval; KDIGO, Kidney Disease Improving Global Outcomes.

[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 group (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 are reported in footnotes in eTable 7 in Supplement 2.

[b] 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 eligibility, randomization within each domain, and time epochs. Odds ratios for the remaining outcomes are adjusted for age and sex. Odds ratios >1 correspond with treatment benefit and <1 correspond 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.

[c] The probabilities of efficacy and harm of ACE inhibitor or ARB relative to the control group were computed from the posterior distributions.

[d] This composite outcome included mortality and, among survivors, the number of days alive without vasopressor use 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 receiving them at enrollment) after randomization.

[e] The primary outcome was organ support–free days, evaluated using an ordinal scale that combined in-hospital death and the number of days without 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 15 (8-18) for the ACE inhibitor group; 15 (6-18) for the ARB group, and 15 (9-18) for the control group.

[f] Dynamic borrowing of information on treatment effect from non–critically 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.

[g] Time-to-event outcome. The effect estimates are median hazard ratios. Hazard ratios greater than 1 indicate benefit and less than 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 was164 of 231 (71.0%) in the ACE inhibitor group, 151 of 217 (69.6%) in the ARB group, and 179 of 231 (77.5%) in the control group.

[h] AKI was defined using the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria as either stage 2 or higher (serum creatinine increase by 2-2.9 times from baseline, with baseline defined as time of enrollment) or as stage 3 (serum creatinine increase by ≥3 times from baseline, increase in serum creatinine by ≥0.5 mg/dL [44 mmol/L] to ≥4 mg/dL [353.6 μmol/L], or new initiation of kidney replacement therapy). An odds ratio <1 indicates treatment benefit, whereas an odds ratio >1 indicates treatment harm.

[i] Need for kidney replacement therapy among patients meeting criteria for KDIGO stage 3 AKI by day 14: 4 of 223 (1.8%) in the ACE inhibitor group, 10 of 208 (4.8%) in the ARB group, and 4 of 212 (1.9%) in the control group. The occurrence of incident AKI at 7 days is reported in eTable 7 in Supplement 2.

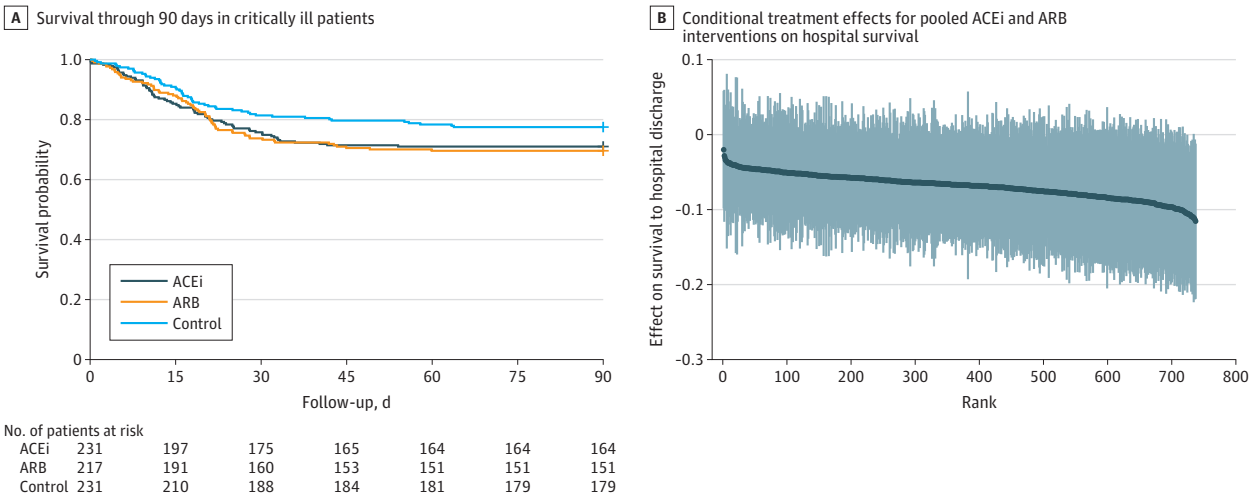
of 203 (34.0%) in the control group. The posterior probabilities that vasopressor-free days, a composite of death and vasopressor receipt, was worsened with ACE inhibitor initiation was 94.0% and ARB initiation of 99.7%. Median (IQR) ratio of peak to baseline creatinine was 1.11 (1.00-1.25) in the ACE inhibitor group, 1.15 (1.00-1.42) in the ARB group, and 1.11 (1.00-1.30) in the control group (eFigure 5 in Supplement 2). The occurrence of Kidney Disease Improving Global Outcomes stage 2 or higher AKI within 14 days following randomization was 7.2% in the ACE inhibitor group, 14.4% in the ARB group, and 7.5% in the control group. Among non-critically 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 group was limited by low enrollment.

Among critically ill patients, serious adverse events were reported in 2 of 232 patients (0.9%) in the ACE inhibitor group, 5 of 218 (2.3%) in the ARB group, 0 of 6 (0.0%) in the combined DMX-200 and ARB group, and 4 of 231 (1.7%) in the control group; there was 1 serious adverse event among non-critically ill patients (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 estimated glomerular filtration rate (eFigures 6 and 7 in Supplement 2). Among patients receiving vasopressors at enrollment, the OR for organ support-free days with an ACE inhibitor compared with control was 0.54 (95% CrI, 0.30-0.97) vs 0.90 (95% CrI, 0.66-1.25) 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

Figure 3. Survival Through 90 Days in Critically Ill Patients and Treatment Effects on Hospital Survival



A, Patients who did not die within 90 days are censored at day 90 with no event. B, Ranked estimated individual-level conditional average treatment effect on hospital survival for all patients is shown. From the final causal forest on hospital survival pooling both angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) interventions, 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% CI is shown for each.

effects across all available baseline variables (eTable 10 in Supplement 2), subgroup conditional average treatment effects were similar for ACE inhibitor and ARB use (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 vs control, but with 95% CIs 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 non-critically ill patients and those in the combined ARB and DMX-200 treatment group.

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 nonusers.[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 toward lower hospital survival was observed with treatment 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 initiation, although less clearly so with ACE inhibitor initiation.

In an early pandemic trial of 162 hospitalized patients with COVID-19 excluding those admitted to an ICU, telmisartan improved survival and reduced inflammatory biomarkers compared with control[58]; however, enrollment was prematurely terminated, limiting inference. In a 2022 trial of 205 patients, oxygenation and survival were not improved with losartan compared with placebo, although hypotension and AKI occurred more frequently with losartan.[59] A 2022 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 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, previous randomized clinical trials evaluating continuation compared with 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 initiation supports inference across shared mechanisms of action. The application of a 2-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

This 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 in which patients often lack capacity to provide consent at the time of enrollment. Third, some potentially relevant baseline characteristics (eg, 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. Sixth, due to being available later and offered only at a subset of sites, enrollment in the combined ARB and DMX-200 group was low at the time of closure of enrollment.

Conclusions

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.

ARTICLE INFORMATION

Accepted for Publication: March 7, 2023.

Authors/Writing Committee for REMAP-CAP: Patrick R. Lawler, MD, MPH; Lennie P. G. Derde, MD, PhD; Frank L. van de Veerdonk, MD, PhD; Bryan J. McVerry, MD; David T. Huang, MD, MPH; Lindsay R. Berry, PhD; Elizabeth Lorenzi, PhD; Roland van Kimmenade, MD, PhD; Frank Gommans, MD, PhD; Muthiah Vaduganathan, MD, MPH; David E. Leaf, MD, MMSc; Rebecca M. Baron, MD; Edy Y. Kim, MD, PhD; Claudia Frankfurter, MD; Slava Epelman, MD, PhD; Yvonne Kwan, BScPhm, ACPR; Richard Grieve, PhD; Stephen O'Neill, PhD; Zia Sadique, PhD; Michael Puskarich, MD, MS; John C. Marshall, MD; Alisa M. Higgins, PhD; Paul R. Mouncey, MSc; Kathryn M. Rowan, PhD; Farah Al-Beidh, PhD; Djillali Annane, MD, PhD; Yaseen M. Arabi, MD; Carly Au; Abi Beane, PhD; Wilma van Bentum-Puijk, MSc; Marc J. M. Bonten, MD, PhD; Charlotte A. Bradbury, MD, PhD; Frank M. Brunkhorst, MD, PhD; Aidan Burrell, MBBS, PhD; Adrian Buzgau, MSc; Meredith Buxton; Maurizio Cecconi, MD; Allen C. Cheng, MBBS, PhD; Matthew Cove, MBBS; Michelle A. Detry, PhD; Lise J. Estcourt, MBBCh, PhD; Justin Ezekowitz, MBBCh, MSc; Mark Fitzgerald, PhD; David Gattas, MD, PhD; Lucas C. Godoy, MD; Herman Goossens, PhD; Rashan Haniffa, PhD; David A. Harrison, PhD; Thomas Hills, MBBS, PhD; Christopher M. Horvat, MD; Nao Ichihara, MD, MPH, PhD; Francois Lamontagne, MD; Kelsey M. Linstrum, MS; Daniel F. McAuley, MD; Anna McGlothlin, PhD; Shay P. McGuinness, MD; Zoe McQuilten, MD, PhD; Srinivas Murthy, MD; Alistair D. Nichol, MD, PhD; David R. J. Owen, MBBS, PhD; Rachael L. Parke, PhD; Jane C. Parker, BN; Katrina M. Pollock, MBBS, PhD; Luis Felipe Reyes, MD, PhD; Hiroki Saito, MD, MPH; Marlene S. Santos, MD, MSHS; Christina T. Saunders, PhD; Christopher W. Seymour, MD, MSc; Manu Shankar-Hari, MD, PhD; Vanessa Singh; Alexis F. Turgeon, MD, MSc; Anne M. Turner, MPH; Ryan Zarychanski, MD, MSc; Cameron Green, MSc; Roger J. Lewis, MD, PhD; Derek C. Angus, MD, MPH; Scott Berry, PhD; Anthony C. Gordon, MBBS, MD; Colin J. McArthur, MD; Steve A. Webb, MD, PhD.

Affiliations of Authors/Writing Committee for REMAP-CAP: Peter Munk Cardiac Centre at University Health Network, Toronto, Canada (Lawler, Frankfurter, Epelman, Kwan, Godoy); McGill University Health Centre, Montreal, QC, Canada (Lawler); University Medical Center Utrecht, Utrecht, Netherlands (Derde, van Bentum-Puijk, Bonten); Radboud University Medical Centre, Nijmegen, Netherlands (van de Veerdonk, van Kimmenade, Gommans); University of Pittsburgh, Pittsburgh, Pennsylvania (McVerry, Huang, Linstrum, Seymour, Angus); Berry Consultants, Austin, Texas (L. R. Berry, Lorenzi, Detry, Fitzgerald, McGlothlin, Saunders, Lewis, S. Berry); Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Vaduganathan, Leaf, Baron, Kim); London School of Hygiene and Tropical Medicine, London, United Kingdom (Grieve, O'Neill, Sadique); University of Minnesota, Minneapolis (Puskarich); St Michael's Hospital Unity Health, Toronto, Canada (Marshall, Santos); Monash University, Melbourne, Australia (Higgins, Burrell, Buzgau, Cheng, McGuinness, McQuilten, Nichol, Parker, Singh, Green, Webb); Intensive Care National Audit & Research Centre (ICNARC), London, United Kingdom (Mouncey, Rowan, Au, Harrison); Imperial College London, London, United Kingdom (Al-Beidh, Pollock, Gordon); Hospital Raymond Poincaré (Assistance Publique Hôpitaux de Paris), Garches, France (Annane); Université Versailles SQY - Université Paris Saclay, Montigny-le-Bretonneux, France (Annane); King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia (Arabi); University of Oxford, Oxford, England (Beane); University of Bristol, Bristol, United Kingdom (Bradbury); Jena University Hospital, Jena, Germany (Brunkhorst); Global Coalition for Adaptive Research, Larkspur, California (Buxton); Humanitas University, Milan, Italy (Cecconi); Yong Loo Lin School of Medicine, National University Singapore, Singapore (Cove); NHS Blood and Transplant, Oxford, United Kingdom (Estcourt); University of Alberta, Calgary, Canada (Ezekowitz); The George Institute for Global Health, Sydney, Australia (Gattas); University of Antwerp, Wilrijk, Belgium (Goossens); University of Oxford, Bangkok, Thailand (Haniffa); National Intensive Care Surveillance (NICST), Colombo, Sri Lanka (Haniffa); Medical Research Institute of New Zealand (MRINZ), Wellington, New Zealand (Hills, Turner); UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania (Horvat); The University of Tokyo, Japan (Ichihara); Université de Sherbrooke, Sherbrooke, Canada (Lamontagne); Queen's University Belfast, Belfast, Northern Ireland (McAuley); Royal Victoria Hospital, Belfast, Northern Ireland (McAuley); Auckland City Hospital, Auckland, New Zealand (McGuinness, Parke, McArthur); University of British Columbia, Vancouver, Canada (Murthy); University College Dublin, Dublin, Ireland (Nichol); Department of Brain Sciences, Imperial College London, London, United Kingdom (Owen); UK Dementia Research Institute of Imperial College London, London, United Kingdom (Owen); University of Auckland, Auckland, New Zealand (Parke); Universidad de La Sabana, Chia, Colombia (Reyes); Clinica Universidad de La Sabana, Chia, Colombia (Reyes); St Marianna University School of Medicine, Yokohama City Seibu Hospital, Yokohama, Japan (Saito); Associate Editor, *JAMA* (Seymour); The University of Edinburgh, Edinburgh, United Kingdom (Shankar-Hari); Université Laval, Québec City, Canada (Turgeon); CHU de Québec-Université Laval Research Center, Québec City, Canada (Turgeon); University of Manitoba, Winnipeg, Canada (Zarychanski); Harbor-UCLA Medical Center, Torrance, California (Lewis); Statistical Editor, *JAMA* (Lewis); Senior Editor, *JAMA* (Angus); Imperial College Healthcare NHS Trust, St Mary's Hospital, London, United Kingdom (Gordon); St John of God Hospital, Subiaco, Australia (Webb).

Author Contributions: Dr Lawler had full access to all the data relative to this domain and Dr Lewis had full access to all the data required for the primary analyses. Drs Lawler and Lewis take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Gordon, McArthur, and Webb contributed equally as co–senior authors.
Concept and design: Lawler, Derde, van de Veerdonk, McVerry, Huang, L. Berry, Lorenzi, van Kimmenade, Gommans, Vaduganathan, Leaf, Baron, Kim, Frankfurter, Epelman, Kwan, Rowan, Brunkhorst, Cheng, Ezekowitz, Gattas, Goossens, Hills, Lamontagne, Linstrum, McAuley, Murthy, Nichol, Owen, Parke, Parker, Pollock, Reyes, Seymour, Shankar-Hari, Turgeon, Zarychanski, Green, Lewis, Angus, S. Berry, Gordon, McArthur, Webb.
Acquisition, analysis, or interpretation of data: Lawler, Derde, van de Veerdonk, McVerry, Huang, L. Berry, Lorenzi, van Kimmenade, Gommans, Vaduganathan, Leaf, Baron, Grieve, O'Neill, Sadique, Puskarich, Marshall, Higgins, Mouncey, Rowan, Al-Beidh, Annane, Arabi, Au, Beane, Bentum-Puijk, Bonten, Bradbury, Burrell, Buzgau, Buxton, Cecconi, Cheng, Cove, Detry, Estcourt, Ezekowitz, Fitzgerald, Godoy, Haniffa, Harrison, Hills, Horvat, Ichihara, Lamontagne, Linstrum, McAuley, McGlothlin, McGuinness, McQuilten, Nichol, Parker, Reyes, Saito, Santos, Saunders, Shankar-Hari, Singh, Turgeon, Turner, Zarychanski, Green, Lewis, Angus, S. Berry, Gordon, McArthur, Webb.
Drafting of the manuscript: Lawler, van de Veerdonk, McVerry, Huang, Frankfurter, Grieve, O'Neill, Sadique, Al-Beidh, Bentum-Puijk, Buzgau, Cecconi, McAuley, McQuilten, Owen, Parke, Pollock, Santos, Seymour, S. Berry, McArthur.
Critical revision of the manuscript for important intellectual content: Derde, van de Veerdonk, McVerry, Huang, L. Berry, Lorenzi, van Kimmenade, Gommans, Vaduganathan, Leaf, Baron, Kim, Epelman, Kwan, O'Neill, Sadique, Puskarich, Marshall, Higgins, Mouncey, Rowan, Annane, Arabi, Au, Beane, Bonten, Bradbury, Brunkhorst, Burrell, Buxton, Cecconi, Cheng, Cove, Detry, Estcourt, Ezekowitz, Fitzgerald, Gattas, Godoy, Goossens, Haniffa, Harrison, Hills, Horvat, Ichihara, Lamontagne, Linstrum, McAuley, McGlothlin, McGuinness, Murthy, Nichol, Parker, Reyes, Saito, Saunders, Shankar-Hari, Singh, Turgeon, Turner, Zarychanski, Green, Lewis, Angus, S. Berry, Gordon, McArthur, Webb.
Statistical analysis: L. Berry, Lorenzi, Leaf, Grieve, O'Neill, Sadique, Detry, Fitzgerald, McGlothlin, Saunders, Lewis, S. Berry, McArthur.
Obtained funding: Derde, van Kimmenade, Gommans, Marshall, Higgins, Rowan, Annane, Beane, Bonten, Burrell, Buxton, Cheng, Cove, Goossens, Hills, Ichihara, McAuley, McGuinness, Murthy, Nichol, Reyes, Turgeon, Angus, Gordon, McArthur, Webb.
Administrative, technical, or material support: Derde, Huang, Gommans, Kim, Frankfurter, Marshall, Higgins, Mouncey, Rowan, Al-Beidh, Arabi, Au, Beane, Bentum-Puijk, Brunkhorst, Buzgau, Buxton, Cove, Estcourt, Harrison, Horvat, Ichihara, Linstrum, McAuley, McGuinness, McQuilten, Nichol, Parker, Saito, Santos, Seymour, Shankar-Hari, Singh, Turner, Green, Gordon, McArthur, Webb.
Supervision: Derde, McVerry, van Kimmenade, Leaf, Kim, Grieve, Mouncey, Rowan, Arabi, Bonten, Buxton, Ezekowitz, Hills, McAuley, Murthy, Reyes, Seymour, Zarychanski, Lewis, Angus, Gordon, Webb.
Other - International steering group member: Cheng.

Conflict of Interest Disclosures: Dr Lawler reported receiving grants from the Heart and Stroke Foundation of Canada during the conduct of the study and personal fees from Novartis, Brigham and Women's Hospital, CorEvitas, American College of Cardiology, and McGraw-Hill Publishing outside the submitted work. Dr Derde reported receiving grants European Union FP7 grant PREPARE (602525); EU FP7-HEALTH-2013-INNOVATION-1, grant number 602525, grants from H2020 H2020 RECOVER grant agreement No 101003589, and grants from H2020 ECRAID-Base (HORIZON-Health GRANT_NUMBER: 965313) during the conduct of the study; and being a member of the International Advisory Board Sepsis Canada, the Taskforce Acute Infectious Threats of Dutch National Intensivist Society, and chair of the ESICM Education and Training Committee. Dr McVerry reported receiving grants from Translational Breast Cancer Research Consortium and UPMC Learning While Doing Program during the conduct of the study; grants from the National Heart, Lung, and Blood Institute, Bayer Pharmaceuticals, and The Pittsburgh Foundation and personal fees from Boehringer and Synairgen Research outside the submitted work. Dr L. Berry reported receiving grants from and being an employee of Berry Consultants, which receives payments for statistical analysis and design of REMAP-CAP during the conduct of the study. Dr Lorenzi reported receiving personal fees from and being an employee of Berry Consultants, which receives payments for statistical modeling and design of REMAP-CAP during the conduct of the study. Dr van Kimmenade reported receiving grants from Novartis during the conduct of the study and personal fees from Bayer outside the submitted work. Dr Gommans reported receiving grants from ZonMw (10430012010020) during the conduct of the study. Dr Vaduganathan reported receiving personal fees from Amgen, AstraZeneca, American Regent, Baxter HealthCare, Bayer AG, Boehringer Ingelheim, Cytokinetics, Relypsa, Novartis, Roche Diagnostics, Lexicon Pharmaceuticals, Galmed, Occlutech, Impulse Dynamics, Tricog Health, NovoNordisk, and Chiesi outside the submitted work. Dr Baron reported serving on an advisory board for Merck and Genentech outside the submitted work. Dr Puskarich reported receiving grants from Bill and Melinda Gates Foundation, Minnesota Partnership for Biotechnology and Medical Genomics, and the National Institutes of Health outside the submitted work and consulting and/or serving on scientific advisory boards for Opticyte, Cytovale, and Vail Scientific for development of diagnostic devices related to sepsis. Dr Marshall reported receiving grants from the Canadian Institutes of Health Research during the conduct of the study and serving as a chair of data and safety monitoring board for AM Pharma and Adrenomed. Dr Higgins reported receiving grants from National Health and Medical Research Council and grants from The Minderoo Foundation during the conduct of the study. Dr Mouncey reported receiving grants from European Union FP7: PREPARE, Horizon 2020: ECRAID-Base, Horizon 2020: RECOVER, and the UK National Institute for Health Research during the conduct of the study. Dr Rowan reported receiving grants from the European Commission and the UK National Institute for Health and Care Research during the conduct of the study. Dr Au reported receiving grants from European Union FP7 PREPARE, Horizon 2020 ECRAID-Base, RECOVER, UK National Institute for Health and Care Research, and Monash University during the conduct of the study. Dr Beane reported receiving grants from Wellcome Trust during the conduct of the study. Dr Bradbury reported receiving personal fees for advisory, speaker fees, or conference attendance from Eli Lilly, BMS Pfizer, Bayer, Amgen, Novartis, Janssen, Portola, Ablynx, and Grifols outside the submitted work. Dr Buxton reported receiving grants from Breast Cancer Research Foundation during the conduct of the study and having contracts with Amgen and Eisai outside the submitted work. Dr Cecconi reported receiving personal fees from Edwards Lifesciences, GE HealthCare, and Draeger outside the submitted work. Dr Cove reported receiving grants from National University Health System Research Office and National Medical Research Council (Integrated innovations in infectious diseases; OFLCG19May-0034) during the conduct of the study; receiving personal fees from Medtronic and Baxter outside the submitted work; and having a patent issued for removal of carbon dioxide by dialysis (US10322221B2). Dr Detry reported receiving grants from EU Prepare European Union PREPARE consortium funding for the statistical design and analysis of REMAP-CAP trial to Berry Consultants, grants from Australian National Health and Medical Research Council (#APP1101719) Australian funding for the statistical design and analysis of REMAP-CAP trial to Berry Consultants, grants from Health Research Council of New Zealand New Zealand funding for the statistical design and analysis of REMAP-CAP trial to Berry Consultants, and grants from University of Pittsburgh Medical Center (UPMC) US funding from Learning While Doing Program for the statistical design and analysis of REMAP-CAP trial to Berry Consultants during the conduct of the study. Dr Estcourt reported receiving grants from National Institute for Health and Care Research and European Union Horizon 2020 outside the submitted work. Dr Ezekowitz reported receiving grants from Bayer, Merck, Novartis, Novo Nordisk, Otsuka, Applied Therapeutics, AstraZeneca, and Boeringher Ingelheim outside the submitted work. Dr Fitzgerald reported receiving grants from PREPARE Network, European Commission Statistical design and analysis of the REMAP-CAP trial, grants from OPTIMISE-CAP, Australia Funding Statistical design and analysis of the REMAP-CAP trial, grants from REMAP-CAP, New Zealand Funding Statistical design and analysis of the REMAP-CAP trial, and grants from GCAR, United States Funding Statistical design and analysis of the REMAP-CAP trial during the conduct of the study. Dr Godoy reported receiving the Frederick Banting and Charles Best Canada Graduate Scholarship (Doctoral Research Award) from the Canadian Institutes of Health Research. Dr Haniffa reported receiving grants from Wellcome Trust, Medical Research Council/UK Research and Innovation, and Canadian Institutes of Health Research during the conduct of the study and grants from ICODA, Wellcome Trust, and National Institute for Health and Care Research outside the submitted work. Dr Harrison reported receiving grants from European Union FP7 (PREPARE) and Horizon 2020 (ECRAID-Base and RECOVER), UK National Institute

for Health and Care Research, and Monash University during the conduct of the study. Dr Hills reported receiving grants from Health Research Council of New Zealand during the conduct of the study. Dr Horvat reported receiving grants from Eunice Kennedy Shriver National Institute of Child Health and Human Development during the conduct of the study. Dr McAuley reported receiving grants from National Institute for Health and Care Research Health Technology Assessment during the conduct of the study; personal fees from Bayer, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Eli Lilly, and Vir Biotechnology and grants from Wellcome Trust , National Institute for Health and Care Research, Innovate UK, MRC, and Northern Ireland HSC Research and Development Division outside the submitted work; and having a patent for anti-inflammatory treatment issued to Queen's University Belfast for novel treatment for inflammatory disease (US8962032) and being co-director for research for the Intensive Care Society and NIHR/MRC Efficacy and Mechanism Evaluation Programme. Dr McGlothlin reported receiving grants reported receiving grants from EU Prepare European Union PREPARE consortium funding for the statistical design and analysis of REMAP-CAP trial to Berry Consultants, grants from Australian National Health and Medical Research Council (#APP1101719) Australian funding for the statistical design and analysis of REMAP-CAP trial to Berry Consultants, grants from Health Research Council of New Zealand funding for the statistical design and analysis of REMAP-CAP trial to Berry Consultants, and grants from University of Pittsburgh Medical Center (UPMC) US funding from Learning While Doing Program for the statistical design and analysis of REMAP-CAP trial to Berry Consultants during the conduct of the study. Dr Murthy reported receiving grants from the Canadian Institutes of Health Research and Health Research Foundation during the conduct of the study. Dr Nichol reported receiving grants from Health Research Board of Ireland during the conduct of the study. Dr Parke reported receiving grants from Fisher and Paykel Healthcare paid to the institution outside the submitted work. Dr Pollock reported Imperial College London receiving funding from the European Commission through the PREPARE FP7 grant (number 602525) during the conduct of the study; and grants from MRC/UKRI MRC (MR/W024977/1), Chan Zuckerberg Initiative, Trevena, Imperial, British Heart Foundation, grants from MRC/UKRI, European Commission Horizon 2020 European AIDS Vaccine Initiative 2020, and MRC/UKRI and personal fees from Sanofi Pasteur, Seqirus, and Moderna outside the submitted work. Dr Reyes reported receiving grants and personal fees from Merck and personal fees from Pfizer and GSK outside the submitted work. Dr Saunders reported receiving grants from PREPARE Network, OPTIMISE-CAP, and REMAP-CAP during the conduct of the study. Dr Seymour reported receiving grants from NIH/NIGMS during the conduct of the study and personal fees from Inotrem and Beckman Coulter outside the submitted work. Dr Shankar-Hari reported being funded by a clinician scientist fellowship (2016-16-011) from the National Institute for Health and Care Research; receiving grants from the Chief Scientists Office Scotland for time-critical precision medicine in critically ill adult patients (TRAITS Programme) and highlights industry support for TRAITS research programme (https://www.ed.ac.uk/inflammation-research/clinical-trials/traits-ci-trial). Dr Turgeon reported receiving grants from Canadian Institutes of Health Research during the conduct of the study. Dr Turner reported receiving grants from Health Research Council of New Zealand during the conduct of the study. Dr Lewis reported being the senior medical scientist at Berry Consultants, a statistical consulting firm that specializes in the design, implementation, oversight, and interpretation of bayesian adaptive and platform clinical trials. Dr Angus reported receiving grants from Breast Cancer Research Foundation and grants from the National Institutes of Health during the conduct of the study. Dr S. Berry reported being part owner of Berry Consultants, which received fees for trial design and analysis during the conduct of the study. Dr Gordon reported receiving grants from NIHR Research Professorship (RP-2015-06-18) and grants from NIHR REMAP-CAP trial during the conduct of the study and personal fees from 30 Respiratory, AstraZeneca, Janssen, and Novartis and and grants from NIHR Imperial BRC outside the submitted work. Dr McArthur reported receiving grants from Health Research Council of New Zealand during the conduct of the study. Dr Webb reported receiving grants from National Health and Medical Research Council, Medical Research Future Fund, and Minderoo Foundation during the conduct of the study. No other disclosures were reported.

Funding/Support: The Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1 (#602525), the Rapid European COVID-19 Emergency Research response (RECOVER) consortium by the European Union's Horizon 2020 research and innovation programme (#101003589), the Australian National Health and Medical Research Council (#APP1101719), the Health Research Council of New Zealand (#16/631), the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant (#158584), the UK National Institute for Health and Care 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 Translational Breast Cancer Research Consortium, the French Ministry of Health (PHRC-20-0147), the Minderoo Foundation, and the Wellcome Trust Innovations Project (215522). Dr Gordon is funded by an NIHR Research Professorship (RP-2015-06-18), Dr Shankar-Hari by an NIHR Clinician Scientist Fellowship (CS-2016-16-011), and Dr Higgins is funded by an NHMRC Emerging Leadership Fellowship (GNT2008447). In the Netherlands and EU, this domain was supported by the Dutch ZonMw grant 10430012010020. Financial assistance for the DMX-200 arm was received by Dimerix Bioscience who received funding from the Australian government via the Medical Research Future Fund Targeted Translation Research Accelerator fund.

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 platform trial has several regional non-profit sponsors: Monash University, Melbourne, Australia (sponsor for Australia, India, Pakistan, Nepal, Saudi Arabia and Colombia); Medical Research Institute of New Zealand (New Zealand sponsor); Utrecht Medical Center, Utrecht, the Netherlands (European sponsor); Unity Health, Toronto, Canada (Canadian sponsor); Global Coalition for Adaptive Research, San Francisco, California (US sponsor); and St Marianna University Hospital, Japan (Japanese sponsor). Several authors are employees of these organizations. However, beyond the declared author contributions, the sponsors had no additional role. Dimerix Bioscience provided DMX-200 study drug at no cost to the investigators. The protocol was written by the investigators, with input from Dimerix Bioscience related to the combined ARB and DMX-200 intervention. The study was conducted and analyzed and the manuscript was written independently by the investigators.

Disclaimer: The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care. Dr Seymour is an Associate Editor, Dr Lewis is a Statistical Editor, and Dr Angus is Senior Editor of *JAMA* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

The REMAP-CAP Investigators: See Supplement 3.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We are very thankful to the patients who participated in this trial. We are grateful to the data and safety monitoring board and to the National Institute for Health and Care Research Clinical Research Network, UPMC Health System Health Services Division, and Unity Health for their support of participant recruitment.

REFERENCES

1. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280.e8. doi:10.1016/j.cell.2020.02.052

2. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. 2020;581(7807):215-220. doi:10.1038/s41586-020-2180-5

3. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382(17):1653-1659. doi:10.1056/NEJMsr2005760

4. Silhol F, Sarlon G, Deharo JC, Vaïsse B. Downregulation of ACE2 induces overstimulation of the renin-angiotensin system in COVID-19: should we block the renin-angiotensin system? *Hypertens Res*. 2020;43(8):854-856. doi:10.1038/s41440-020-0476-3

5. Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*. 2020;24(1):422. doi:10.1186/s13054-020-03120-0

6. Matsuzawa Y, Kimura K, Ogawa H, Tamura K. Impact of renin-angiotensin-aldosterone system inhibitors on COVID-19. *Hypertens Res*. 2022;45(7):1147-1153. doi:10.1038/s41440-022-00922-3

7. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS

coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-879. doi:10.1038/nm1267

8. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med*. 2020;46(4):586-590. doi:10.1007/s00134-020-05985-9

9. Treml B, Neu N, Kleinsasser A, et al. Recombinant angiotensin-converting enzyme 2 improves pulmonary blood flow and oxygenation in lipopolysaccharide-induced lung injury in piglets. *Crit Care Med*. 2010;38(2):596-601. doi:10.1097/CCM.0b013e3181c03009

10. Doerschug KC, Delsing AS, Schmidt GA, Ashare A. Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis. *Crit Care*. 2010;14(1):R24. doi:10.1186/cc8887

11. Baral R, Tsampasian V, Debski M, et al. Association between renin-angiotensin-aldosterone system inhibitors and clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(3):e213594. doi:10.1001/jamanetworkopen.2021.3594

12. Rysz S, Al-Saadi J, Sjöström A, et al. COVID-19 pathophysiology may be driven by an imbalance in the renin-angiotensin-aldosterone system. *Nat Commun*. 2021;12(1):2417. doi:10.1038/s41467-021-22713-z

13. Chung SC, Providencia R, Sofat R. Association between angiotensin blockade and incidence of influenza in the United Kingdom. *N Engl J Med*. 2020;383(4):397-400. doi:10.1056/NEJMc2005396

14. Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ*. 2012;345:e4260. doi:10.1136/bmj.e4260

15. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436(7047):112-116. doi:10.1038/nature03712

16. Park JJH, Detry MA, Murthy S, Guyatt G, Mills EJ. How to use and interpret the results of a platform trial: users' guide to the medical literature. *JAMA*. 2022;327(1):67-74. doi:10.1001/jama.2021.22507

17. Lawler PR, Hochman JS, Zarychanski R. What are adaptive platform clinical trials and what role may they have in cardiovascular medicine? *Circulation*. 2022;145(9):629-632. doi:10.1161/CIRCULATIONAHA.121.058113

18. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study: rationale and design. *Ann Am Thorac Soc*. 2020;17(7):879-891. doi:10.1513/AnnalsATS.202003-192SD

19. Angus DC, Derde L, Al-Beidh F, et al; Writing Committee for the REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022

20. Arabi YM, Gordon AC, Derde LPG, et al; REMAP-CAP Investigators. Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial. *Intensive Care Med*. 2021;47(8):867-886. doi:10.1007/s00134-021-06448-5

21. Gordon AC, Mouncey PR, Al-Beidh F, et al; REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384(16):1491-1502. doi:10.1056/NEJMoa2100433

22. Goligher EC, Bradbury CA, McVerry BJ, et al; REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789. doi:10.1056/NEJMoa2103417

23. Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):790-802. doi:10.1056/NEJMoa2105911

24. Estcourt LJ, Turgeon AF, McQuilten ZK, et al; Writing Committee for the REMAP-CAP Investigators. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2021;326(17):1690-1702. doi:10.1001/jama.2021.18178

25. Bradbury CA, Lawler PR, Stanworth SJ, et al; REMAP-CAP Writing Committee for the REMAP-CAP Investigators. Effect of antiplatelet therapy on survival and organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(13):1247-1259. doi:10.1001/jama.2022.2910

26. Higgins AM, Berry LR, Lorenzi E, et al; Writing Committee for the R-CAPI. Long-term (180-day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial. *JAMA*. 2023;329(1):39-51. doi:10.1001/jama.2022.23257

27. McGlothlin AE, Viele K. Bayesian hierarchical models. *JAMA*. 2018;320(22):2365-2366. doi:10.1001/jama.2018.17977

28. Nie X, Wager S. Quasi-oracle estimation of heterogeneous treatment effects. *Biometrika*. 2021;108(2):299-319. doi:10.1093/biomet/asaa076

29. Athey S, Wager S. Estimating treatment effects with causal forests: an application. *arXiv*. 2019;1902.07409. doi:10.48550/arXiv.1902.07409

30. Zhang H, Baker A. Recombinant human ACE2: acing out angiotensin II in ARDS therapy. *Crit Care*. 2017;21(1):305. doi:10.1186/s13054-017-1882-z

31. Lawler PR, Derde LPG, McVerry BJ, Russell JA, van de Veerdonk FL. The renin-angiotensin system in acute lung injury. *Crit Care Med*. 2022;50(9):1411-1415. doi:10.1097/CCM.0000000000005567

32. Gierhardt M, Pak O, Walmrath D, et al. Impairment of hypoxic pulmonary vasoconstriction in acute respiratory distress syndrome. *Eur Respir Rev*. 2021;30(161):210059. doi:10.1183/16000617.0059-2021

33. Ingraham NE, Barakat AG, Reilkoff R, et al. Understanding the renin-angiotensin-aldosterone-SARS-CoV axis: a comprehensive review. *Eur Respir J*. 2020;56(1):2000912. doi:10.1183/13993003.00912-2020

34. Krenn K, Tretter V, Kraft F, Ullrich R. The renin-angiotensin system as a component of biotrauma in acute respiratory distress syndrome. *Front Physiol*. 2022;12:806062. doi:10.3389/fphys.2021.806062

35. Samavati L, Uhal BD. ACE2, much more than just a receptor for SARS-COV-2. *Front Cell Infect Microbiol*. 2020;10:317. doi:10.3389/fcimb.2020.00317

36. Murakami N, Hayden R, Hills T, et al. Therapeutic advances in COVID-19. *Nat Rev Nephrol*. 2023;19(1):38-52. doi:10.1038/s41581-022-00642-4

37. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res*. 2020;126(10):1456-1474. doi:10.1161/CIRCRESAHA.120.317015

38. Reindl-Schwaighofer R, Hödlmoser S, Eskandary F, et al. ACE2 elevation in severe COVID-19. *Am J Respir Crit Care Med*. 2021;203(9):1191-1196. doi:10.1164/rccm.202101-0142LE

39. Camargo RL, Bombassaro B, Monfort-Pires M, et al. Plasma angiotensin II is increased in critical coronavirus disease 2019. *Front Cardiovasc Med*. 2022;9:847809. doi:10.3389/fcvm.2022.847809

40. Li Y, Zeng Z, Li Y, et al. Angiotensin-converting enzyme inhibition attenuates lipopolysaccharide-induced lung injury by regulating the balance between angiotensin-converting enzyme and angiotensin-converting enzyme 2 and inhibiting mitogen-activated protein kinase activation. *Shock*. 2015;43(4):395-404. doi:10.1097/SHK.0000000000000302

41. Hagiwara S, Iwasaka H, Matumoto S, Hidaka S, Noguchi T. Effects of an angiotensin-converting enzyme inhibitor on the inflammatory response in in vivo and in vitro models. *Crit Care Med*. 2009;37(2):626-633. doi:10.1097/CCM.0b013e3181958d91

42. Wösten-van Asperen RM, Lutter R, Specht PA, et al. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. *J Pathol*. 2011;225(4):618-627. doi:10.1002/path.2987

43. Wang F, Xia ZF, Chen XL, Jia YT, Wang YJ, Ma B. Angiotensin II type-1 receptor antagonist attenuates LPS-induced acute lung injury. *Cytokine*. 2009;48(3):246-253. doi:10.1016/j.cyto.2009.08.001

44. Shen L, Mo H, Cai L, et al. Losartan prevents sepsis-induced acute lung injury and decreases activation of nuclear factor kappaB and mitogen-activated protein kinases. *Shock*. 2009;31(5):500-506. doi:10.1097/SHK.0b013e318189017a

45. Salgado DR, Rocco JR, Silva E, Vincent JL. Modulation of the renin-angiotensin-aldosterone system in sepsis: a new therapeutic approach? *Expert Opin Ther Targets*. 2010;14(1):11-20. doi:10.1517/14728220903460332

46. Mao X, Krenn K, Tripp T, et al. Tidal volume-dependent activation of the renin-angiotensin system in experimental ventilator-induced lung injury. *Crit Care Med*. 2022;50(9):e696-e706. doi:10.1097/CCM.0000000000005495

47. Wösten-van Asperen RM, Lutter R, Haitsma JJ, et al. ACE mediates ventilator-induced lung injury in rats via angiotensin II but not bradykinin. *Eur Respir J*. 2008;31(2):363-371. doi:10.1183/09031936.00060207

48. Jerng JS, Hsu YC, Wu HD, et al. Role of the renin-angiotensin system in ventilator-induced lung injury: an in vivo study in a rat model. *Thorax*. 2007;62(6):527-535. doi:10.1136/thx.2006.061945

49. Yao S, Feng D, Wu Q, Li K, Wang L. Losartan attenuates ventilator-induced lung injury. *J Surg Res*. 2008;145(1):25-32. doi:10.1016/j.jss.2007.03.075

50. Jiang JS, Wang LF, Chou HC, Chen CM. Angiotensin-converting enzyme inhibitor captopril attenuates ventilator-induced lung injury in rats. *J Appl Physiol (1985)*. 2007;102(6):2098-2103. doi:10.1152/japplphysiol.00514.2006

51. Chen CM, Chou HC, Wang LF, Lang YD. Captopril decreases plasminogen activator inhibitor-1 in rats with ventilator-induced lung injury. *Crit Care Med*. 2008;36(6):1880-1885. doi:10.1097/CCM.0b013e31817c911d

52. Wösten-van Asperen RM, Lutter R, Specht PA, et al. Ventilator-induced inflammatory response in lipopolysaccharide-exposed rat lung is mediated by angiotensin-converting enzyme. *Am J Pathol*. 2010;176(5):2219-2227. doi:10.2353/ajpath.2010.090565

53. Kim J, Kim YA, Hwangbo B, et al. Effect of antihypertensive medications on sepsis-related outcomes: a population-based cohort study. *Crit Care Med*. 2019;47(5):e386-e393. doi:10.1097/CCM.0000000000003654

54. Hsu WT, Galm BP, Schrank G, et al. Effect of renin-angiotensin-aldosterone system inhibitors on short-term mortality after sepsis: a population-based cohort study. *Hypertension*. 2020;75(2):483-491. doi:10.1161/HYPERTENSIONAHA.119.13197

55. Mortensen EM, Nakashima B, Cornell J, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis*. 2012;55(11):1466-1473. doi:10.1093/cid/cis733

56. Seok J, Warren HS, Cuenca AG, et al; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2013;110(9):3507-3512. doi:10.1073/pnas.1222878110

57. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med*. 2011;26(5):546-550. doi:10.1007/s11606-010-1609-1

58. Duarte M, Pelorosso F, Nicolosi LN, et al. Telmisartan for treatment of Covid-19 patients: an open multicenter randomized clinical trial. *EClinicalMedicine*. 2021;37:100962. doi:10.1016/j.eclinm.2021.100962

59. Puskarich MA, Ingraham NE, Merck LH, et al; Angiotensin Receptor Blocker Based Lung Protective Strategies for Inpatients With COVID-19 (ALPS-IP) Investigators. Efficacy of losartan in hospitalized patients with COVID-19-induced lung injury: a randomized clinical trial. *JAMA Netw Open*. 2022;5(3):e222735. doi:10.1001/jamanetworkopen.2022.2735

60. Gnanenthiran SR, Borghi C, Burger D, et al; COVID-METARASI Consortium. Renin-angiotensin system inhibitors in patients with COVID-19: a meta-analysis of randomized controlled trials led by the International Society of Hypertension. *J Am Heart Assoc*. 2022;11(17):e026143. doi:10.1161/JAHA.122.026143

61. Jardine MJ, Kotwal SS, Bassi A, et al; CLARITY trial investigators. Angiotensin receptor blockers for the treatment of covid-19: pragmatic, adaptive, multicentre, phase 3, randomized controlled trial. *BMJ*. 2022;379:e072175. doi:10.1136/bmj-2022-072175

62. Lopes RD, Macedo AVS, de Barros E Silva PGM, et al; BRACE CORONA Investigators. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA*. 2021;325(3):254-264. doi:10.1001/jama.2020.25864

63. Bauer A, Schreinlechner M, Sappler N, et al; ACEI-COVID investigators. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomized, controlled, open-label trial. *Lancet Respir Med*. 2021;9(8):863-872. doi:10.1016/S2213-2600(21)00214-9

64. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomized, open-label trial. *Lancet Respir Med*. 2021;9(3):275-284. doi:10.1016/S2213-2600(20)30558-0