

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

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- **1** Effect of Angiotensin Converting Enzyme Inhibitor and
- 2 Angiotensin Receptor Blocker Initiation on Organ
- **Support-Free Days in Patients Hospitalized with**
- **4** COVID-19: A Randomized Clinical Trial
- 5 The REMAP-CAP Investigators*
- 6 *Author and Group Information
- 7 The members of the writing committee appear at the end of the main text and the full list of
- 8 investigators and collaborators in the Supplementary Appendix.
- 9 Running Head
- 10 REMAP-CAP COVID-19 ACE2 RAS Domain RCT
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- 21
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23 Key points

24 Question

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

29 Findings

- 30 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%
- 32 probability that treatments worsened this outcome.

33 Meaning

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

36 **Abstract**

- IMPORTANCE Over-activation of the renin-angiotensin system (RAS) may contribute to poor
 clinical outcomes in patients with COVID-19.
- 39 **OBJECTIVE** To determine whether angiotensin converting enzyme (ACE) inhibitor or
- 40 angiotensin receptor blocker (ARB) initiation improves outcomes in patients hospitalized for
- 41 COVID-19.
- 42 **DESIGN, SETTING, AND PARTICIPANTS** In an ongoing, adaptive platform randomized clinical
- 43 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
- 45 countries (final follow-up date: June 1, 2022).
- 46 **INTERVENTIONS** Patients were randomized to receive open-label initiation of ACE inhibitor
- 47 (n=257), ARB (n=248), ARB in combination with DMX-200 (a chemokine receptor-2 inhibitor;
- 48 n=10), or no RAS inhibitor (control; n=264) for up to 10 days.
- 49 MAIN OUTCOMES AND MEASURES The primary outcome was organ support-free days, a
- 50 composite of hospital survival and days alive without cardiovascular or respiratory organ
- 51 support through 21 days. The primary analysis was a bayesian cumulative logistic model.
- 52 Odds ratios (OR) >1 represent improved outcomes.
- 53 **RESULTS** On February 25, 2022, enrollment was discontinued due to safety concerns.
- 54 Among 679 critically ill patients with available primary outcome, the median age was 56.0
- 55 years and 35.2% were female. Median (IQR) organ support-free days among critically ill
- 56 patients in the ACE inhibitor group (n=231) was 10 (-1 to 16), in the ARB group (n=217) was
- 57 8 (-1 to 17), and in the control group (n=231) was 12 (0 to 17) (median adjusted odds ratio
- 58 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
- 62 (71.9%), 152/217 (70.0%), and 182/231 (78.8%) critically ill patients, respectively (posterior
- 63 probabilities that ACE inhibitor and ARB worsened hospital survival compared with control
- 64 were 95.3% and 98.1%).

- **CONCLUSIONS AND RELEVANCE** In this trial, among critically ill adults with COVID-19,
- 66 initiation of an ACE inhibitor or ARB did not improve, and likely worsened, clinical outcomes.
- **TRIAL REGISTRATION** ClinicalTrials.gov number: NCT02735707

69 Introduction

70	Angiotensin converting enzyme 2 (ACE2), a central regulator of the renin-angiotensin system
71	(RAS), is expressed in the respiratory epithelium and vascular endothelium, and is the
72	human host receptor for the SARS-CoV-2 virus. ^{1,2} Disruption of ACE2 activity due to viral
73	binding, and other mechanisms, may upregulate angiotensin II in patients with COVID-19. ³⁻⁷
74	Angiotensin II promotes inflammation, activates coagulation, increases capillary
75	permeability, upregulates fibrotic responses, and causes vasoconstriction which may
76	contribute to microcirculatory dysfunction and ventilation/perfusion mismatch. ^{3,8-10} These
77	pathogenic responses characterize severe COVID-19, and therefore attenuating angiotensin
78	II may improve outcomes. This hypothesis is supported by observational and experimental
79	studies in COVID-19, ^{11,12} and other studies in acute lung injury due to SARS-CoV-1, sepsis,
80	aspiration, and ventilator-induced lung injury. ^{7,13-15} Given the direct interaction between the
81	RAS and SARS-CoV-2, attenuating angiotensin II may be particularly beneficial in COVID-19.
82	
83	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.

87

88 Methods

89 Trial Design and Oversight

90	The ACE2 RAS Domain is one of multiple therapeutic domains in the Randomized,
91	Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia
92	(REMAP-CAP) trial (NCT02735707). REMAP-CAP is an international, adaptive platform
93	randomized clinical trial ^{16,17} evaluating treatments for severe pneumonia. Trial design
94	details are previously reported, ¹⁸ and are available in Supplement 1 . Patients are assessed
95	for platform eligibility and potentially randomized to one or more interventions among
96	available domains, organized by therapeutic areas. The trial previously reported the effects
97	of corticosteroids, anticoagulants, antivirals, interleukin-6 receptor antagonists,
98	convalescent plasma, and antiplatelet agents in patients with COVID-19. ¹⁹⁻²⁵ The trial was
99	approved by regional ethics committees and conducted in accordance with Good Clinical
100	Practice guidelines and the Declaration of Helsinki. Written or verbal informed consent was
101	obtained from all patients or their surrogates in accordance with local legislation.
102	
102	Particinants

103 Participants

Patients aged \geq 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 \geq 30 L/min and FiO₂ \geq 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

111 noncritically ill patients within 96 hours of hospital admission. Patients were excluded on 112 the basis of long-term or current RAS inhibitor use or known intolerance, risk of clinically 113 relevant hypotension or escalation of vasopressor requirements, hyperkalemia, severe renal 114 impairment, severe renal artery stenosis, or pregnancy or breast-feeding. Detailed domain 115 and platform eligibility are presented in eAppendix 1 in Supplement 2. In view of racial and 116 ethnic differences in outcomes during the pandemic, self-reported race and ethnicity was 117 collected from participants or their surrogates via fixed categories appropriate to their 118 region where approved.

119

120 Treatment Allocation

121 All participating sites randomized patients to control (no RAS inhibitor) and up to three 122 active interventions, including ACE inhibitor, ARB, and, at a subset of participating sites, an 123 ARB in combination with DMX-200. DMX-200 is an investigational oral chemokine receptor-124 2 antagonist targeting macrophage chemotaxis, given in combination with an ARB due to 125 putative synergistic anti-inflammatory effects. Computerized randomization was performed 126 centrally with balanced, fixed allocation ratios based on the number of available 127 interventions at each site. Response adaptive randomization was not employed in this 128 domain. Patients could also be randomized to interventions in other domains depending on 129 availability and eligibility.

130

131 Interventions

132 Treatment assignments included initiation and in-hospital treatment with an enterally

administered ACE inhibitor, ARB, ARB in combination with DMX-200, or control. Sites

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

146 Outcome Measures

147 The primary outcome was organ support-free days. In this composite ordinal outcome, all

148 deaths occurring during the index hospitalization were assigned the worst possible outcome

- 149 (-1). Among survivors, respiratory and cardiovascular organ support–free days were
- 150 calculated through day 21 (survivors with no organ support were assigned a score of 22).
- 151 Higher scores indicate better outcomes. In REMAP-CAP, this hospital-based outcome
- 152 correlates with longer-term outcomes.²⁶

153

154 Prespecified secondary outcomes included hospital survival, day 90 survival, ventilator-free

days, vasopressor/inotrope-free days, durations of hospital and ICU stays, World Health

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

165 Statistical Analysis

166 This domain employed an adaptive two-stage design with an initial evaluation period given 167 limited experience with the study treatments in critically ill patients (eFigure 1 in 168 **Supplement 2**). During the evaluation period, interventions were required to demonstrate an 169 acceptable safety profile as judged by the Data and Safety Monitoring Board (DSMB), and an 170 intermediate probability of efficacy defined as \geq 50% posterior probability of a \geq 20% improvement in the proportional odds ratio (OR) for organ support-free days for ACE 171 172 inhibitor and ARB compared to control, or \geq 30% for the combined ARB and DMX-200 173 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, 174 175 and 200 patients in the combined ARB and DMX-200 intervention group. Graduation rules 176 were prespecified and would be implemented in a blinded fashion. Interventions that 177 satisfied graduation criteria would continue to the uncapped evaluative period which would 178 enroll until platform-level adaptive stopping triggers for efficacy (posterior probability >99%

179	that OR >1.0 compared with control) or futility (posterior probability >95% that OR <1.2
180	compared with control) were reached. The futility trigger could be reached at any adaptive
181	analysis. Interventions failing to graduate would be withdrawn in stage 1. Enrollment was
182	closed in stage 1 for safety concerns prior to an adaptive analysis being performed.
183	
184	The primary analysis was intention-to-treat and included all consenting patients with
185	suspected or proven COVID-19 with available primary outcome. The primary analysis was a
186	bayesian cumulative logistic model adjusted for age, sex, site, and enrollment time period (in
187	2-week intervals), and included covariates reflecting intervention and domain eligibility.
188	Treatment effects were estimated only from patients randomized in the domain. Patients
189	with COVID-19 enrolled into REMAP-CAP but outside of this domain did not contribute to
190	estimates of RAS inhibitor effects, but did contribute to overall model covariate coefficient
191	estimation.

193	The primary model was fit using a Markov Chain Monte Carlo algorithm with 20,000 samples
194	from the joint posterior distribution. The model calculated posterior distributions for the
195	proportional OR, including medians and 95% credible intervals (CrIs), and the posterior
196	probabilities of efficacy for each intervention compared with control. The probability of harm
197	is the complement of the probability of efficacy (i.e., posterior probability OR <1.0). Distinct
198	treatment effects were estimated in critically ill and noncritically ill patients by nesting
199	intervention effects in a hierarchical prior distribution centered on an overall intervention
200	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

203

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

209

210 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,

212 ≥90 mL/min/1.73 m², or unknown), and baseline vasopressor receipt. Machine learning with

causal forests^{28,29} estimated subgroup- and individual-level heterogeneity of treatment

214 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

217 Supplement 2).

218

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).

223

224 **Results**

225 Enrollment and Participant Characteristics

226

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.

235	A total of 721 critically ill patients and 58 noncritically ill patients were randomized (Figure
236	1) at 69 sites in seven countries (Canada, Italy, Netherlands, New Zealand, Saudi Arabia,
237	United Kingdom, and United States). Of these, 34 critically ill and 2 noncritically ill patients
238	withdrew consent and outcomes were unavailable for 2 critically ill patients. Baseline
239	characteristics were similar between groups, although some imbalances were present,
240	including vasopressor receipt (Table 1 and eTable 2 in Supplement 2). Ramipril and losartan
241	were the most common ACE inhibitor and ARB used, at low- or moderate-doses (see eTable
242	1 in Supplement 2 for dose classifications), for median treatment durations of 6 and 7 days
243	in critically ill patients and 2 and 5 days in noncritically ill patients (eTable 3 in Supplement
244	2). Among patients allocated to ACE inhibitor or ARB, 104/243 (42.8%) and 132/236 (55.9%)

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

247

248 **Primary Outcome**

249	Among 679 critically ill patients, the median (IQR) organ support-free days in the ACE
250	inhibitor group (n=231) was 10 (–1 to 16), in the ARB group (n=217) was 8 (–1 to 17), and in
251	the control group (n=231) was 12 (0 to 17) (Figure 2), corresponding to adjusted ORs for ACE
252	inhibitor of 0.77 (95% CrI 0.58 to 1.06) and for ARB of 0.76 (0.56 to 1.05) compared with
253	control (Table 2). The posterior probabilities that ACE inhibitor and ARB worsened organ
254	support-free days compared with control were 94.9% and 95.4%. Results were generally
255	consistent in sensitivity analyses, including after adjustment for potentially imbalanced
256	variables (eTable 5 in Supplement 2). There were no consistent, clinically relevant
257	deviations from the assumption of proportional effects across the organ support-free days
258	scale (eFigure 2 in Supplement 2). Outcomes were available for only six critically ill patients
259	randomized to the combined ARB and DMX-200 intervention (eFigure 3 in Supplement 2).
260	Among 56 noncritically ill patients, median (IQR) organ support-free days in all groups was
261	22 (22 to 22) (eFigure 4 in Supplement 2) and posterior probabilities were inconclusive
262	(eTable 6 in Supplement 2).

263

264 Secondary Outcomes

265	None of the 15 secondary outcomes were improved with ACE inhibitor or ARB compared
266	with control (Table 2 and eTables 6, 7, and 8 in Supplement 2). Among critically ill patients
267	in the ACE inhibitor, ARB, and control groups, hospital survival occurred in 166/231 (71.9%),
268	152/217 (70.0%), and 182/231 (78.8%), respectively, corresponding to adjusted ORs for ACE
269	inhibitor of 0.70 (95% CrI 0.44 to 1.06) and for ARB of 0.62 (0.39 to 0.98) compared with
270	control. The posterior probabilities that ACE inhibitor and ARB worsened hospital survival
271	compared with control were 95.3% and 98.1%. The probability was high that ACE inhibitor
272	and ARB reduced survival through 90 days (Figure 3). Among noncritically ill patients, one
273	death occurred (in the ACE inhibitor group).
274	
275	Among critically ill patients, vasopressor therapy was newly initiated in 69/188 (36.7%),
276	86/188 (45.7%), and 69/203 (34.0%) in the ACE inhibitor, ARB, and control groups,
277	respectively. The posterior probabilities were 94.0% and 99.7% that vasopressor-free days, a
278	composite of death and vasopressor receipt, was worsened with ACE inhibitor and ARB.
279	Median (IQR) relative change from baseline to peak creatinine was 1.11 (1.00 to 1.25), 1.15
280	(1.00 to 1.42), and 1.11 (1.00 to 1.30), respectively (eFigure 5 in Supplement 2). The
281	occurrence of KDIGO stage \geq 2 AKI within 14 days following randomization was 7.2%, 14.4%,
282	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.

289	eTable 9 in Supplement 2).
288	control groups, respectively, and in one noncritically ill patient (in the ACE inhibitor group;
287	(1.7%) critically ill patients in the ACE inhibitor, ARB, combined DMX-200 and ARB, and
286	Serious adverse events were reported in 2/232 (0.9%), 5/218 (2.3%), 0/6 (0.0%), and 4/231

291 Subgroup Analyses

292 In subgroup analyses, treatment effects among critically ill patients did not meaningfully 293 vary by age, sex, mechanical ventilation receipt, or baseline eGFR (eFigures 6 and 7 in 294 Supplement 2). Among patients receiving vasopressors at enrollment, OR for organ support-295 free days with ACE inhibitor compared with control was 0.54 (95% Crl 0.30 to 0.97), versus 296 0.90 (0.66 to 1.25) among patients not receiving vasopressors. ARB treatment effect did not 297 differ by baseline vasopressor receipt. In causal forest analyses considering whether there 298 was evidence of heterogeneous treatment effects across all available baseline variables 299 (eTable 10 in Supplement 2), subgroup conditional average treatment effects were similar 300 for ACE inhibitor and ARB (eFigure 8 in Supplement 2). No subgroup showed strong 301 evidence of heterogeneity (eFigure 8 in Supplement 2). Point estimates of expected 302 conditional average treatment effects at the individual level consistently favored worsened 303 hospital survival for both treatments versus control, but with 95% confidence intervals that 304 included null for the majority (>70%) of patients (Figure 3).

305

306

307 **Discussion**

308	In this domain of an overarching platform trial, among critically ill patients hospitalized for
309	COVID-19, there was a 95% probability that ACE inhibitor or ARB initiation worsened organ
310	support-free days, primarily due to differences in hospital survival. The domain was
311	terminated due to safety concerns, and findings are inconclusive for noncritically ill patients
312	and in the combined ARB and DMX-200 arm.
313	
314	RAS activation may contribute to poor clinical outcomes in patients with acute hypoxemic
315	respiratory failure, ³⁰⁻³⁴ including COVID-19. ^{3,8,35-37} Angiotensin II is upregulated in COVID-19
316	and other severe respiratory infections, proportional to severity. ^{38,39} Inhibition of
317	angiotensin II with ACE inhibitors or ARBs improves respiratory and other organ failure in
318	animal models of SARS-CoV-2 infection, ¹² SARS-CoV-1 infection, ⁷ sepsis, ⁴⁰⁻⁴⁵ aspiration, ¹⁵
319	and ventilator-induced lung injury. ^{42,46-52} Observational studies suggest more favorable
320	outcomes among existing users of ACE inhibitors and ARBs who develop COVID-19 and
321	other respiratory infections compared with non-users. ^{11,13,14,53-55} However, animal models
322	inconsistently correlate with human host response, 56 and observational studies are at risk
323	for bias. ⁵⁷

324

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

331 characteristics to support a mechanistic hypothesis. Among secondary outcomes,

vasopressor receipt and AKI were more frequent with ARB, although less clearly so with ACEinhibitor.

334

335	In an early pandemic trial of 162 hospitalized patients with COVID-19 but excluding those
336	admitted to an ICU, telmisartan improved survival and reduced inflammatory biomarkers
337	compared to control; ⁵⁸ however, enrollment was prematurely terminated, limiting
338	inference. In a more recent trial of 205 patients, oxygenation and survival were not
339	improved with losartan compared to placebo, although hypotension and AKI occurred more
340	frequently. ⁵⁹ A recent meta-analysis of smaller and incomplete trials observed no survival
341	benefit with RAS inhibitor initiation for COVID-19, and hypotension and AKI appeared more
342	frequent in severely ill patients. ⁶⁰ The CLARITY trial, which included lower risk patients, did
343	not observe a benefit of telmisartan initiation in hospitalized patients with COVID-19. ⁶¹ The
344	current trial had the largest sample size to date, and included the highest proportion of
345	critically ill patients, who are at greatest risk of hypotension and AKI, which may explain the
346	more evident harm signal. Importantly, prior randomized clinical trials evaluating
347	continuation compared to discontinuation of RAS inhibitors in less severely ill patients
348	hospitalized for COVID-19 suggest their continuation is safe ⁶² – although there is uncertainty
349	among more severely ill patients. ^{63,64}
350	

351 Strengths of this trial include its pragmatic evaluation of candidate repurposed, widely-352 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.

359 **Limitations**

360 The trial has several limitations. First, the protocol was pragmatic and agents and dose 361 equivalents varied; nevertheless, 89% of patients in each group received the same agent 362 and dose equivalents were consistently low-to-moderate. Second, approximately 1 in 20 363 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 364 365 often lack capacity to provide consent at the time of enrollment. Third, some potentially 366 relevant baseline characteristics (e.g., vasopressor receipt) were imbalanced: These 367 imbalances may have had a modest influence on treatment effect estimates. Fourth, this 368 trial evaluated new RAS antagonist initiation specifically as treatment for COVID-19, and not 369 the separate question of whether to continue or discontinue existing therapy. Fifth, the trial 370 was terminated for safety concerns after enrollment of only a modest sample size: Although 371 this may leave uncertainty about precise treatment effects, the likelihood of meaningful 372 clinical benefit is low. Finally, due to being available later and offered only at a subset of 373 sites, enrollment into the combined ARB and DMX-200 arm was low at the time of closure of 374 enrollment.

375

376 **Conclusions**

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

Article Information 379

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465 Author contributions

466 To be generated from author contribution forms.

467 Access to data statement:

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

471

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513

514 The REMAP-CAP Investigators

515 See attachment 'REMAP-CAP Investigators'.

516

517 Data Sharing Statement

518 Data Sharing Statement: See Supplement 4

519

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700			
701	Summary of Supplements		
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703	Supplement 1. Trial Protocol and SAP Documents		
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707	• <u>REMAP-CAP Core Protocol</u> (Version 3.0, July 10 th , 2019, the Original Version -		
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712	• <u>REMAP-COVID Core Protocol</u> (Version 1.0, March 27 th , 2020)		
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736	the Non-critically III Population
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741	eFigure 2. Evaluation of Proportional Effects Assumption among Critically III Patients
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749	Logistic Model for Hospital Survival
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751	Survival
752	References
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754	Supplement 3. Non-author collaborators
755	

- 756 Supplement 4. Data sharing Agreement
- 757

758 Figure Legends

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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

763 multiple treatments. The trial applied eligibility criteria at the platform level and at the

764 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
- 766 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.
- 784 [†]The primary analysis in the ACE2 RAS domain is estimated from a model that adjusts for patient 785 factors and for assignment to other interventions; all patients enrolled in the COVID-19 cohort for 786 whom there is consent and follow-up are included. The final estimate of an ACE2 RAS domain 787 intervention's effectiveness relative to any other within that domain is generated from those patients 788 that might have been randomized to either. In contrast to the analyses of organ support-free days (the 789 primary outcome) and its component hospital survival (a secondary outcome), which were performed 790 by an independent unblinded statistical analysis committee, sensitivity and other secondary analyses 791 were performed by investigators blinded to ongoing interventions and therefore did not include

adjustment for treatment assignment in ongoing domains.

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Figure 2. Primary Outcome in Critically III 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

- 800 group as the cumulative proportion (y axis) for each trial group by day (x axis), with death 801 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
- 804 **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
- 806 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

809 **eFigure 2** in **Supplement 2**.

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812 Figure 3. (Upper Panel) Survival through 90 Days in Critically III Patients. (Lower Panel)

Individual Conditional Treatment Effects for Pooled ACE Inhibitor and ARB Intervention
 Effect on Hospital Survival.

815 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

817 **Iower panel** displays ranked estimated individual-level conditional average treatment effect

818 on hospital survival for all patients. From the final causal forest on hospital survival pooling

819 both ACE inhibitor and ARB, treatment effect in tree terminal leaves with each individual's

820 control and intervention neighbors are combined to give an estimate of individual-level

treatment effect conditional on their baseline covariates. Ranked absolute risk difference

822 estimate with its 95% confidence interval is shown for each.

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826 827	Figure 1. Screening, Randomization, and Follow-up of Participants in the REMAP-CAP COVID-19 ACE2 RAS Domain Randomized Clinical Trial
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834	Figure 2. Primary Outcome in Critically III Patients – Organ Support-Free Days Up to Day 21			
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836				
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838	Figure 3. (Upper Panel) Survival through 90 Days in Critically Ill Patients. (Lower Panel) Individual
839	Conditional Treatment Effects for Pooled ACE Inhibitor and ARB Intervention Effect on Hospital
840	Survival
Q/I1	

Table 1. Critically III Participant Characteristics at Baseline ^a				
	ACE inhibitor	ARB	Control	
	(n = 232)	(n = 218)	(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	30.3 (26.4-36.9)	30.1 (27.2-37.2)	30.5 (27.3-35.8)	
(IQR)	(n=210)	(n=200)	(n=213)	
APACHE II score ^d , median	11.0 (6.0-17.0)	10.0 (7.0-14.0)	10.0 (6.0-16.0)	
(IQR)	(n=231)	(n=217)	(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	202/207 (97.6)	189/191 (99.0)	198/199 (99.5)	
infection', No./total (%)	(0.10)	(
Pre-existing condition ⁸ ,				
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,	126.0 (114.0-144.0)	128.0 (115.0-145.0)	130.0 (115.0-144.2)
mmHg	(n=227)	(n=215)	(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)	76.0 (37.0-146.0)	91.5 (37.8-162.8)
	(n=205)	(n=187)	(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)
$eGER min/min/1.73m^2$	100.8 (86.0-113.7)	103.5 (92.4-113.4)	102.9 (92.8-115.9)
	(n=231)	(n=217)	(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 (%) ⁱ			
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	1/228 (0.4)	2/217 (0.0)	2/220 (0.0)
antibody	1/220 (0.4)	2/217 (0.9)	2/230 (0.9)

844 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;

PaO₂/FiO₂, ratio of arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen
(FiO₂).

^a Due to the small sample size (n=6), data on patients randomized to the combined ARB and DMX200 arm are not presented.

^b Data collection was not approved in Canada and continental Europe. 'Other' includes 'declined' and

852 '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

854 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

862 were eligible for enrollment if COVID-19 testing had been performed and confirmed the presence of

863 SARS-CoV-2, or if testing had not yet been performed but was intended to occur. Following

864 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.

866 ^g Kidney disease was determined from the most recent stable serum creatinine level prior to this

867 hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was

- 868 defined as a creatinine level of 130 μmol/L or greater (1.5 mg/dL) for males or 100 μmol/L or greater
- 869 (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New
- 870 York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent
- 871 chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of
- 872 immunosuppressive disease.
- 873 ^h A normal PaO_2/FiO_2 ratio is \geq 400.
- ⁱ Extended Cardiovascular SOFA Score reflects criteria for blood pressure and inotropic or vasoactive
- support, with higher scores indicating worse cardiovascular organ failure.
- ^jLaboratory results available when captured for clinical care.
- 877 ^k Within 48hr of randomization.

REMAP-CAP COVID-19 ACE2 RAS Domain RCT

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

ACE denotes angiotensin converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CrI, credible interval; IQR, interquartile range; (DIGO, Kidney Disease Improving Global Outcomes; no., number. 879 878

^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 880

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 881

are shown in eFigure 1 in Supplement 2, and descriptive data on secondary outcomes is reported in footnotes to eTable 7 in Supplement 2. 882

cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. The conditional median (IQR) organ support-^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 883 884

free days for patients who survived hospitalization was: control, 15 (9 to 18); ACE inhibitor, 15 (8 to 18); ARB, 15 (6 to 18)

885 886

^b Dynamic borrowing of information on treatment effect from noncritically ill patients was permitted. Results from a sensitivity analysis assuming 887

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%), 888 889
 - and control (179/231, 77.5%) 890
- ^e Acute kidney injury was defined using the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria as either stage >2 (serum creatinine 891
- 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 893 892
 - benefit, whereas an odds ratio >1 indicates treatment harm. 894
- 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, 4/223 895
 - (1.8%); ARB arm, 10/208 (4.8%). The occurrence of incident AKI at 7 days is reported in eTable 7 in Supplement 2.
- 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 ^g This composite outcome included mortality and, among survivors, the number of days alive without vasopressor through day 28. Among critically ill vasopressors (after not been on them at enrollment) after randomization. 896 897 898 898
- domain ineligibility, randomization within each domain and time epochs. Odds ratios for the remaining outcomes are adjusted for age and sex. Odds ratios ^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), 900 901
- >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. 903 902
 - The probabilities of efficacy and harm of ACE inhibitor or ARB relative to the control group were computed from the posterior distributions. 904







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Rank

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Effect on survival to hospital discharge

-0.3