# Randomized Elimination and Prolongation of ACE Inhibitors and ARBs in Coronavirus 2019 (REPLACE COVID) Trial Protocol

**Jordana B. Cohen, MD, MSCE**[1,2], **Thomas C. Hanff, MD, MPH**[2,3], **Vicente Corrales-Medina, MD, MSc**[4], **Preethi William, MD**[5], **Nicolas Renna, MD, PhD**[6], **Nelson R. Rosado-Santander, MD**[7], **Juan E. Rodriguez-Mori, MD**[8], **Jonas Spaak, MD, PhD**[9], **Jaime Andrade-Villanueva, MD**[10], **Tara I. Chang, MD, MS**[11], **Alejandro Barbagelata, MD**[12,13], **Carlos E. Alfonso, MD**[14], **Eduardo Bernales-Salas, MD**[7], **Johanna Coacalla, MD**[7], **Carlos Augusto Castro-Callirgos, MD**[8], **Karen E. Tupayachi-Venero, MD**[8], **Carola Medina, MD**[15], **Renzo Valdivia, MD**[15], **Mirko Villavicencio, MD**[15], **Charles R. Vasquez, MD**[2,16], **Michael O. Harhay, PhD, MPH**[2,17], **Jesse Chittams, MS**[2], **Tiffany Sharkoski, MPH, MBE**[3], **James Brian Byrd, MD, MS**[18], **Daniel L. Edmonston, MD**[19], **Nancy Sweitzer, MD, PhD**[5], **Julio A. Chirinos, MD, PhD**[3]

[1]Renal-Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[2]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[3]Division of Cardiovascular Medicine, Hospital of the University of Pennsylvania and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[4]Division of Infectious Diseases, University of Ottawa and The Ottawa Hospital Research Institute, Ottawa, Canada

[5]Division of Cardiology, University of Arizona, Tucson, AZ, USA

[6]Hypertension Unit, Department of Pathology, Hospital Español de Mendoza, National University of Cuyo, IMBECU-CONICET, Argentina

[7]Department of Medicine, Hospital Nacional Carlos Alberto Seguín Escobedo, EsSalud, Arequipa, Perú

[8]Department of Nephrology, Hospital Nacional Alberto Sabogal Sologuren, EsSalud, Lima, Perú

[9]Department of Clinical Sciences, Danderyd University Hospital, Karolinska Institutet, Stockholm, Sweden

---

***Corresponding Author*:** Jordana B. Cohen, 423 Guardian Drive, 831 Blockley, Philadelphia, PA 19104, jco@pennmedicine.upenn.edu, Phone: 267-588-7914, Fax: 215-615-0349, twitter: @jordy_bc.

[10]Universidad de Guadalajara, Guadalajara, Mexico

[11]Division of Nephrology, Stanford University School of Medicine, Stanford, CA, USA

[12]Universidad Católica de Buenos Aires, Buenos Aires, Argentina

[13]Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA

[14]Cardiology Division, University of Miami Miller School of Medicine, Miami, FL, USA

[15]Department of Nephrology, Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima, Perú

[16]Department of Surgery, Hospital of the University of Pennsylvania, University of Pennsylvania, Philadelphia, PA, USA

[17]Palliative and Advanced Illness Research (PAIR) Center and Pulmonary and Critical Care Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, PA, USA

[18]Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

[19]Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA

## Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for coronavirus disease-2019 (COVID-19), is associated with high incidence of multiorgan dysfunction and death. Angiotensin converting enzyme 2 (ACE2), which facilitates SARS-CoV-2 host cell entry, may be impacted by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), two commonly used antihypertensive classes. In a multicenter, international randomized controlled trial that began enrollment on March 31, 2020, we are randomizing individuals to continuation vs. withdrawal of their long-term outpatient ACEI or ARB upon hospitalization with COVID-19. The primary outcome is a hierarchical global rank score incorporating time-to-death, duration of mechanical ventilation, duration of renal replacement or vasopressor therapy, and multiorgan dysfunction severity. Approval for the study has been obtained from the Institutional Review Board of each participating institution, and all participants will provide informed consent. A data safety monitoring board has been assembled to provide independent oversight of the project.

*Clinical Trial Registration Number*: clinicaltrials.gov NCT04338009

### Keywords

## Introduction

Since its emergence in December 2019, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a devastating global health impact.[1] COVID-19 is associated with a high incidence of multiorgan dysfunction and mortality.[2, 3] Accordingly, there has been an extraordinary response by the international research community to quickly develop trials to evaluate potential disease-modifying interventions in COVID-19.

Early in the COVID-19 pandemic, several reports described hypertension as a risk factor for SARS-CoV-2 infection and severity.[4] Angiotensin converting enzyme 2 (ACE2), a key counterregulatory component of the renin angiotensin system (Figure 1), plays an important role in hypertension pathophysiology and also facilitates SARS-CoV-2 host cell entry.[5] ACE2 activity and expression have been implicated as potential contributors to SARS-CoV-2 infection and severity.[4] Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), two of the most commonly used antihypertensive classes,[6] may increase ACE2 expression.[4] Consequently, it was speculated that ACEIs and ARBs could worsen the risk of COVID-19 and COVID-19-related adverse outcomes,[7–10] resulting in widespread media coverage and possibly in empiric discontinuation of these medications. However, there is also evidence suggesting that that ACE2 overexpression ameliorates lung injury associated with COVID-19,[11, 12] and thus ACEIs and ARBs could reduce adverse outcomes in patients with this infection.[4] Thus, it remains unclear whether ACEIs and ARBs are beneficial or harmful in patients with COVID-19.

Given the high prevalence of ACEI and ARB use in the general population and the potential for harm by inappropriate discontinuation of these medications due to their cardio- and reno-protective effects,[6] it is critical to better understand the appropriate acute management of patients with COVID-19 who use ACEIs and ARBs for the long-term management of chronic conditions. Thus, we aimed to perform a randomized controlled trial to evaluate the effect of continuation compared with discontinuation of ACEIs and ARBs on hospitalization-related outcomes in patients admitted with COVID-19. We developed a hierarchical composite endpoint of outcomes with public health, clinical, and patient-centered significance using a global rank score.

## Methods and Analysis

### Overview of the trial design

Figure 2 illustrates the study structure and design. The Randomized Elimination or ProLongation of ACEIs and ARBs in CoronaVIrus Disease 2019 trial (REPLACE COVID: NCT04338009) is a prospective randomized open-label blinded endpoint (PROBE) trial[13] of continuation vs. discontinuation of ACEI/ARB therapy in patients admitted to the hospital with COVID-19. The primary endpoint is a novel hierarchical global rank score including time-to-death, duration of mechanical ventilation, duration of renal replacement therapy or vasopressor therapy, and measures of multiorgan dysfunction.

Participants are being recruited upon admission to the hospital with COVID-19 at participating centers in the United States, Canada, Argentina, Peru, and Sweden (Figure 3). The trial was approved by the Institutional Review Board or the Ethics Committee of each participating center, or via reliance agreements with the Institutional Review Board at the University of Pennsylvania, which is serving as the central Institutional Review Board. All participating subjects provided informed consent either in written form or electronically. Enrollment started on March 31, 2020 and will continue until 152 participants have been enrolled.

Participants are randomized to continuation or withdrawal of their outpatient ACEI or ARB for the duration of their hospitalization. Candidates are excluded if they have a major contraindication to either continuing or withdrawing their ACEI or ARB. Participants are followed until the end of their hospitalization and are contacted 28 days following discharge to assess for any changes in their clinical status after discharge.

### Hypothesis

Based on currently available information, there is clinical equipoise regarding the effect of continuation vs. discontinuation of ACEIs and ARBs in the setting of COVID-19. In some experimental models, ACEIs and ARBs increase ACE2 expression in several organs.[14–17] This could potentially lead to increased SARS-CoV-2 virulence, increasing the risk of multiorgan dysfunction and death. However, these findings are not consistent across studies, [18–20] and have not been corroborated in humans.[21, 22] Alternatively, animal models of SARS-CoV-1 infection (a virus highly related to SARS-CoV-2) suggest that overexpression of ACE2 protects against lung injury associated with these infections.[11, 12] Thus, ACEIs and ARBs may improve mechanisms of host defense or hyperinflammation, ultimately reducing organ injury and providing direct renal and cardiac protective benefits.[12] Observational studies evaluating the association of ACEI and ARB use with COVID-19-related outcomes have demonstrated mixed results. These studies are highly prone to confounding by indication for continuation or withdrawal of these medications based on severity of presentation.[23] Additionally, these studies have not fully addressed important issues with immortal time bias and collider bias.[24] A randomized controlled trial is necessary to adequately address these important limitations.

### Participants

Patients are eligible for inclusion in the REPLACE COVID trial if they are age 18 years or older at the time of their index hospitalization with a clinical presentation consistent with COVID-19. Individuals are excluded if they have negative SARS-CoV-2 testing (among persons under investigation based on clinical suspicion) or clinical contraindications to continuing or withdrawing ACEI or ARB therapy including (1) systolic blood pressure <100 mmHg; (2) systolic blood pressure >180 mmHg or >160 if unable to substitute the ACEI or ARB with another antihypertensive class; (3) diastolic blood pressure >110 mmHg; (4) history of heart failure with unknown left ventricular ejection fraction (LVEF) or known LVEF <40%; (5) serum potassium >5 mEq/L; (6) known pregnancy or breast feeding; (7) estimated glomerular filtration rate <30 mL/min/1.73m$^2$; (8) acute kidney injury defined as 100% increase in creatinine (to a creatinine >2 mg/dL) compared to the most recent

creatinine in the past six months, if available; (9) urine protein-to-creatinine ratio >3 g/g or >3 g/24-hours within the past year; or (10) ongoing treatment with aliskiren or sacubitril-valsartan. Prisoners are also excluded from the trial. Potential participants are typically approached in the first 48-hours of admission unless they develop COVID-19 during an admission for another cause.

### Intervention

The randomized intervention is the continuation compared with discontinuation of ACEI or ARB therapy (at the dose previously prescribed for patients during their routine care) for the duration of the hospitalization. Among participants randomized to continue these agents, clinicians are encouraged to continue the randomized treatment but are permitted to change the dose of ACEI or ARB or to discontinue these medications if a compelling clinical reason is identified, such as hypotension, hyperkalemia, or significant acute kidney injury. If a participant is prescribed both an ACEI and an ARB prior to admission (anticipated to be rare), that individual will be randomized to continuation of one or both medications, at the clinician's discretion, or discontinuation of *both* medications. In all participants randomized to discontinuation, treating clinicians are reminded about the medication discontinuation upon discharge and are prompted to consider reinitiating the medication at that time, if clinically appropriate.

### Randomization and Blinding

Participants are randomized after providing informed consent either in writing or electronically. We are performing stratified blocked randomization with randomly permuted blocks based on site, sex, and age, given the strong impact of these factors on outcomes in COVID-19.[3] Each block contains an equal number of allocations to each arm. When the patient is randomized, the study team communicates the randomized treatment strategy to the primary clinician and any relevant consultants.

As in other PROBE trials,[13] treatment allocation is open, with blinding incorporated instead at the level of endpoint adjudication. A clinician panel at each site is appointed to perform blinded adjudications of the outcome events. Adjudications are performed using a standardized approach to masking patient records so that the clinicians are fully blinded to the randomization arm but are able to assess other key aspects of the participants' hospitalizations.

### Primary Outcome

The primary endpoint of the trial is a hierarchical global rank score, illustrated in Figure 4. The global rank score is a nonparametric ranked outcome that will be determined at the time of discharge or death. The hierarchical endpoint approach has been used in several randomized controlled trials to facilitate evaluation of composite outcomes of binary and continuous findings accounting for both the importance of and appropriate censorship for death.[25–29] An important benefit of the hierarchical endpoint is that it provides substantially higher statistical power for any given sample size compared to other commonly used approaches, such as 28-day ventilator-free days, time-to-death, and the World Health Organization COVID-19 ordinal endpoint.[30–34] The outcome of each patient in the

REPLACE COVID trial is ranked against all other participants from worst to best by increasing values of (1) days to death during the hospitalization (ordered lowest to highest); followed by (2) days on invasive mechanical ventilation or extracorporeal membrane oxygenation (ordered highest to lowest); followed by (3) days on renal replacement therapy or inotropic/vasopressor therapy (ordered highest to lowest); followed by (4) area under the curve of a modified Sequential Organ Failure Assessment (SOFA) score.

The modified SOFA score includes the cardiac, respiratory, coagulation and renal domains of the SOFA score (Supplemental Table S1). A modified SOFA score is used, rather than the full SOFA score, as the last tier of the global rank score. This decision confers several advantages: (1) the cardiac, renal, respiratory and coagulation systems are those most likely impacted by our randomized intervention;[5, 14–17, 35] (2) these SOFA components can be easily and reliably adjudicated using electronic health record review, minimizing workload on the clinical team and maximizing the pragmatic nature of the trial; (3) the nervous system (Glasgow comma scale) and liver (serum bilirubin) components of the SOFA score are not acquired daily on a routine basis in hospitalized patients in non-ICU settings. For the respiratory component of the SOFA score, we are applying a modified score used in settings where arterial oxygen saturation is not consistently available,[36] which uses peripheral capillary oxygen saturation instead of arterial oxygen saturation. Use of the modified SOFA score allows all patients in the trial to be compared, even when no major adverse events occur. We will weight the modified SOFA score to account for duration of hospitalization.

In summary, we selected a hierarchical global rank score due to its ability to incorporate biomarkers and important clinical events into a combined, readily interpretable, and reproducible metric.[26, 27] Our proposed global rank score incorporates patient-centered factors and health-resource utilization, while better resolving the time course of COVID-19-related events and with higher statistical power for any given sample size compared to incorporating each individual factor.[30–34]

### Secondary Outcomes

Secondary endpoints are (1) time to all-cause death; (2) length of hospital stay; (3) length of intensive care unit stay, invasive mechanical ventilation, or extracorporeal membrane oxygenation; and (4) area under the curve of the modified SOFA score, weighted to account for death and duration of hospitalization. Exploratory endpoints include (1) intensive care unit admission or respiratory failure requiring mechanical ventilation; (2) hypotension requiring vasopressors, inotropes, or mechanical hemodynamic support such as a ventricular assist device or intra-aortic balloon pump; (3) number of 28-day ventilator-free days; (4) maximal change in NT-proB-type natriuretic peptide from baseline (when available); (5) change in serum creatinine between baseline and discharge or time of death; (6) acute kidney injury during hospitalization (defined as Kidney Disease Improving Global Outcomes stage 2 or higher).[37] Additional exploratory outcomes will be ascertained by a follow-up call 28-days after discharge from the index hospitalization and will include (1) readmissions, (2) major adverse cardiac events, (3) functional status, and (4) quality of life.

**Statistical Analysis Plan**

The global rank score is a nonparametric ranked outcome.[25–27] The primary analyses will be performed on an intent-to-treat basis using the total number of subjects randomized. Initial descriptive estimates of all measures will be generated for study participants by randomization arm. Primary assessment of the treatment effect will be performed using the non-parametric Wilcoxon rank sum test. This will be followed by a more comprehensive linear regression analysis allowing for assessments of the treatment effect while controlling for effects of age, sex, race/ethnicity, history of pre-existing heart failure, history of pre-existing chronic lung disease, and ACEI vs. ARB therapy at baseline.[3, 38–40] We will utilize non-parametric methods or consider distribution-stabilizing transformations, as appropriate. The models will include data from participants who drop out.[41–43] Model assumptions will be examined (e.g., QQ plots to assess normally distributed residuals for valid Wald tests). Secondary and exploratory time-to-event outcomes will be evaluated using Cox proportional hazards models. The proportional hazards assumption will be assessed via weighted versions of Kaplan-Meier curves using log-log plots and graphical displays based on the Schoenfeld and scaled Schoenfeld residuals, and violations of the proportional hazards assumption will be addressed with a time-interaction term.[44] In exploratory analyses, we will assess for effect modification by sex, age,[3, 38] race,[39] presence of pre-existing heart failure or left ventricular dysfunction, baseline ACEI vs. ARB therapy,[40] chronic kidney disease, diabetes, and BMI.

We will make every possible effort to minimize missing data and ensure final assessments for participants opting to discontinue study participation. Missing data, however, is an inevitable problem in any study. The mechanism for missingness will be evaluated prior to implementing methodology intended to minimize bias from missing data, such as multiple imputation.[45] We anticipate that <5% of randomized subjects will have missing data in the components required to compute the study outcomes.

There is a possibility of systematic bias in the outcomes for those who withdraw from the study or cross over treatment arms. In participants randomized to continuation of these drugs, clinicians will be encouraged to continue the randomized treatment but will be allowed to change the dose of ACEI/ARB or discontinue these medications if compelling clinical reasons are identified. As noted above, in participants randomized to discontinuation, treating clinicians will be reminded about the medication discontinuation upon discharge and will be prompted to consider reinitiating the medication at that time if appropriate, per the clinician's discretion. Sensitivity analyses will be performed on a modified intent-to-treat basis, including only data obtained during the period of time in which participants remain on the randomized treatment strategy.

In order to summarize the SOFA score over the course of the hospitalization, we will calculate the Area Under the Curve of the modified SOFA (AUC SOFA) from daily measurements. The AUC SOFA will be ranked from highest to lowest so that lower ranks represent worse outcomes in alignment with the rest of the global rank score.

### Sample Size

Assuming feasible distributions of patients across each of the primary endpoint hierarchies based on the available published evidence at the time of trial inception,[1–3] we performed 10,000 Monte Carlo simulations of rank distributions of 152 patients, and determined that there will be >80% power to observe a minimal significant difference of 30% in rank scores between the treatment arms, allowing for interim analyses at 50% and 75% of enrollment. [46, 47] Regarding secondary endpoints, we will have 90% power to detect a 2 day difference in length of ICU stay and length of hospital stay assuming a standard deviation of 2 days based on data from initial reports of these outcomes in COVID-19.[1–3, 32] Power calculations were performed using python and PASS16.[48]

### Data Management

The University of Pennsylvania is the Data Coordinating Center (DCC) for the study. The DCC is overseeing randomization, data entry, and data safety monitoring board (DSMB) meetings. The data are being collected using *ad hoc* electronic case report forms. Data capture and storage are being performed within the framework of the Research Electronic Data Capture (REDCap) project.

### Data Safety Monitoring Board

A DSMB has been assembled to provide independent oversight of the project. The DSMB is responsible for assessing: (1) baseline comparability between groups; (2) participant accrual rate and retention; (3) data quality with special emphasis on eligibility data; and (4) patient safety. The DSMB will make recommendations regarding study continuation, protocol modification, and review of additional data. The DSMB will review planned interim analyses performed when the study reaches 50% and 75% of enrollment. The DSMB will also review new and emerging data related to the proposed trial that would potentially affect the continuation of the trial.

### Ethics and Protection of Human Subjects

All subjects will be adults able to give informed consent or in whom informed consent can be obtained by a legally authorized representative. Subjects will be enrolled regardless of sex, race, or ethnicity, aiming to assure adequate representation of women and African Americans. Vulnerable populations such as children, pregnant women, and prisoners will not be enrolled. The risks to study participants are related to the clinical equipoise itself: it is possible that one strategy is better than the other, but at the moment this clinical equipoise is not solvable based on clinical grounds or intuition. Furthermore, after the initial randomized strategy, our trial allows for altering the course of therapy based on clinical grounds that clearly favor one strategy based on clinical assessment as per the treating clinician (such as hypotension, which would prompt discontinuation of ACEIs/ARBs among patients randomized to continued therapy, or pre-discharge reinitiation of these medications for compelling indications, particularly in the setting of heart failure with a reduced ejection fraction).

The cardiovascular risk of short-term ACEI or ARB withdrawal is generally minimal. Even in higher risk groups, such as patients with moderately decompensated heart failure (NYHA

class II to III), heart failure decompensation is not observed until 4–6 weeks following ACEI/ARB withdrawal.[49] This time course far exceeds the typical duration of COVID-19 hospitalization. However, to ensure an even higher safety threshold, we created an additional exclusion criterion for patients with a LVEF < 40%. Patients with heart failure and moderately reduced ejection fraction (LVEF 40–50%) should be even less likely to decompensate from ACEI/ARB withdrawal. Furthermore, we are reminding treating clinicians of the potential need to reinitiate therapy at the time of hospital discharge. In patients without heart failure, including those with resistant hypertension, short-term withdrawal of antihypertensive medications is safe and well-tolerated.[50] To ensure an additional margin of safety for this group, we created additional exclusion criteria for patients with a baseline systolic blood pressure >180 mmHg or >160 if unable to substitute another drug class in place of ACEIs or ARBs, and for diastolic blood pressure 110 mmHg.

In order to minimize exposure of the study staff to COVID-19, many sites are using electronic informed consent forms. When electronic informed consent is performed, potential participants receive the consent form via email and provide consent attestation using a deidentified participant number via an electronic REDCap survey. The informed consent process is performed via phone or video conferencing. The study intervention and potential associated risks are explained to study participants verbally, and they have adequate time to ask questions. No study interventions are initiated until the study team receives either the signed informed consent form or attestation documenting the participants' agreement to participate. Participants either receive a copy of the signed document via email or a REDCap attestation verification email once they agree to participate.

### Regulatory Standards

Because the REPLACE COVID trial is not aimed at obtaining regulatory approval of a novel drug, a labeled approved indication, or repurposing of existing drugs, this trial was formally determined by the Investigational New Drug support unit at the University of Pennsylvania to not require a US Food and Drug Administration Investigational New Drug application.

### Current Progress

As of July 23, 2020, the study has enrolled 103 of the planned 152 participants across nine sites in the United States, Canada, Peru, Argentina, and Sweden.

### Trial registration

The trial was registered at clinicaltrials.gov (NCT04338009)

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

## References

1. Dong E, Du H and Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020.

2. Wu Z and McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.

3. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966. [PubMed: 32444366]

4. Sparks MA, Hiremath S, South A, et al. "The Coronavirus Conundrum: ACE2 and Hypertension Edition" NephJC http://www.nephjc.com/news/covidace2. Accessed 13 Apr 2020 2020.

5. 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.

6. Gu Q, Burt VL, Dillon CF and Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. Circulation. 2012;126:2105–14. [PubMed: 23091084]

7. Fang L, Karakiulakis G and Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8:e21. [PubMed: 32171062]

8. Sommerstein R and Gräni C. Rapid response to: Preventing a covid-19 pandemic. BMJ. 2020;368:m810. [PubMed: 32111649]

9. Esler M and Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38:781–782. [PubMed: 32195824]

10. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med. 2020;27.

11. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436:112–6. [PubMed: 16001071]

12. 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;11:875–9. [PubMed: 16007097]

13. Smith DH, Neutel JM, Lacourciere Y and Kempthorne-Rawson J. Prospective, randomized, open-label, blinded-endpoint (PROBE) designed trials yield the same results as double-blind, placebo-controlled trials with respect to ABPM measurements. J Hypertens. 2003;21:1291–8. [PubMed: 12817175]

14. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI and Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111:2605–10. [PubMed: 15897343]

15. Ocaranza MP, Godoy I, Jalil JE, et al. Enalapril attenuates downregulation of Angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. Hypertension. 2006;48:572–8. [PubMed: 16908757]

16. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB and Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension. 2004;43:970–6. [PubMed: 15007027]

17. Soler MJ, Ye M, Wysocki J, William J, Lloveras J and Batlle D. Localization of ACE2 in the renal vasculature: amplification by angiotensin II type 1 receptor blockade using telmisartan. Am J Physiol Renal Physiol. 2009;296:F398–405. [PubMed: 19004932]

18. Burrell LM, Risvanis J, Kubota E, et al. Myocardial infarction increases ACE2 expression in rat and humans. Eur Heart J. 2005;26:369–75; discussion 322–4. [PubMed: 15671045]

19. Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK and Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in experimental myocardial

infarction: implications for future therapeutic directions. Clin Sci (Lond). 2012;123:649–58. [PubMed: 22715807]

20. Wysocki J, Lores E, Ye M, Soler MJ and Batlle D. Kidney and Lung ACE2 Expression after an ACE Inhibitor or an Ang II Receptor Blocker: Implications for COVID-19. J Am Soc Nephrol. 2020.

21. Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E and Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. Europace. 2017;19:1280–1287. [PubMed: 27738071]

22. Ramchand J, Patel SK, Srivastava PM, Farouque O and Burrell LM. Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. PLoS One. 2018;13:e0198144. [PubMed: 29897923]

23. Hanff TC, Harhay MO, Brown TS, Cohen JB and Mohareb AM. Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic Investigations. Clin Infect Dis. 2020.

24. Cohen JB, Hanff TC, South AM, Sparks MA, Hiremath S, Bress AP, Byrd JB and Chirinos JA. Response by Cohen et al. to Letter Regarding Article, "Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19". Circ Res. 2020;126:e140–e141. [PubMed: 32496917]

25. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular Outcomes With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure: The CAT-HF Trial. J Am Coll Cardiol. 2017;69:1577–1587. [PubMed: 28335841]

26. Margulies KB, Hernandez AF, Redfield MM, et al. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA. 2016;316:500–8. [PubMed: 27483064]

27. Felker GM and Maisel AS. A global rank end point for clinical trials in acute heart failure. Circ Heart Fail. 2010;3:643–6. [PubMed: 20841546]

28. Wilson FP, Reese PP, Shashaty MG, Ellenberg SS, Gitelman Y, Bansal AD, Urbani R, Feldman HI and Fuchs B. A trial of in-hospital, electronic alerts for acute kidney injury: design and rationale. Clin Trials. 2014;11:521–9. [PubMed: 25023200]

29. Wilson FP, Shashaty M, Testani J, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet. 2015;385:1966–74. [PubMed: 25726515]

30. O'Brien PC. Procedures for comparing samples with multiple endpoints. Biometrics. 1984;40:1079–87. [PubMed: 6534410]

31. Harhay MN, Hill AS, Wang W, et al. Measures of Global Health Status on Dialysis Signal Early Rehospitalization Risk after Kidney Transplantation. PLoS One. 2016;11:e0156532. [PubMed: 27257680]

32. Hozo SP, Djulbegovic B and Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. [PubMed: 15840177]

33. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020.

34. Peterson RL, Vock DM, Babiker A, Powers JH 3rd, Hunsberger S, Angus B, Paez A, Neaton JD and group IF-Is. Comparison of an ordinal endpoint to time-to-event, longitudinal, and binary endpoints for use in evaluating treatments for severe influenza requiring hospitalization. Contemp Clin Trials Commun. 2019;15:100401. [PubMed: 31312748]

35. Senchenkova EY, Russell J, Esmon CT and Granger DN. Roles of Coagulation and fibrinolysis in angiotensin II-enhanced microvascular thrombosis. Microcirculation. 2014;21:401–7. [PubMed: 24495184]

36. Grissom CK, Brown SM, Kuttler KG, Boltax JP, Jones J, Jephson AR and Orme JF Jr. A modified sequential organ failure assessment score for critical care triage. Disaster Med Public Health Prep. 2010;4:277–84. [PubMed: 21149228]

37. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2.

38. Xie X, Chen J, Wang X, Zhang F and Liu Y. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci. 2006;78:2166–71. [PubMed: 16303146]

39. Wright JT Jr., Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. JAMA. 2005;293:1595–608. [PubMed: 15811979]

40. Gurwitz D Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020.

41. Willan AR and Pater JL. Carryover and the two-period crossover clinical trial. Biometrics. 1986;42:593–9. [PubMed: 3567292]

42. Brown BW Jr. The crossover experiment for clinical trials. Biometrics. 1980;36:69–79. [PubMed: 7370374]

43. Grizzle JE. The Two-Period Change-over Design an Its Use in Clinical Trials. Biometrics. 1965;21:467–80. [PubMed: 14338679]

44. Therneau TM and Grambsch PM. Modeling Survival Data: Extending the Cox Model Statistics for Biology and Health New York, NY: Springer; 2001.

45. Little RJ. Modeling the drop-out mechanism in repeated-measures studies. Journal of the American Statistical Association. 1995;90:1112–1121.

46. Julious SA. Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data. Stat Med. 2004;23:1921–1986. [PubMed: 15195324]

47. O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549–56. [PubMed: 497341]

48. PASS 16 Power Analysis and Sample Size Software. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass 2018.

49. Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R and Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. The Quinapril Heart Failure Trial Investigators. J Am Coll Cardiol. 1993;22:1557–63. [PubMed: 8227822]

50. Beeftink MM, van der Sande NG, Bots ML, Doevendans PA, Blankestijn PJ, Visseren FL, Voskuil M and Spiering W. Safety of Temporary Discontinuation of Antihypertensive Medication in Patients With Difficult-to-Control Hypertension. Hypertension. 2017;69:927–932. [PubMed: 28373591]
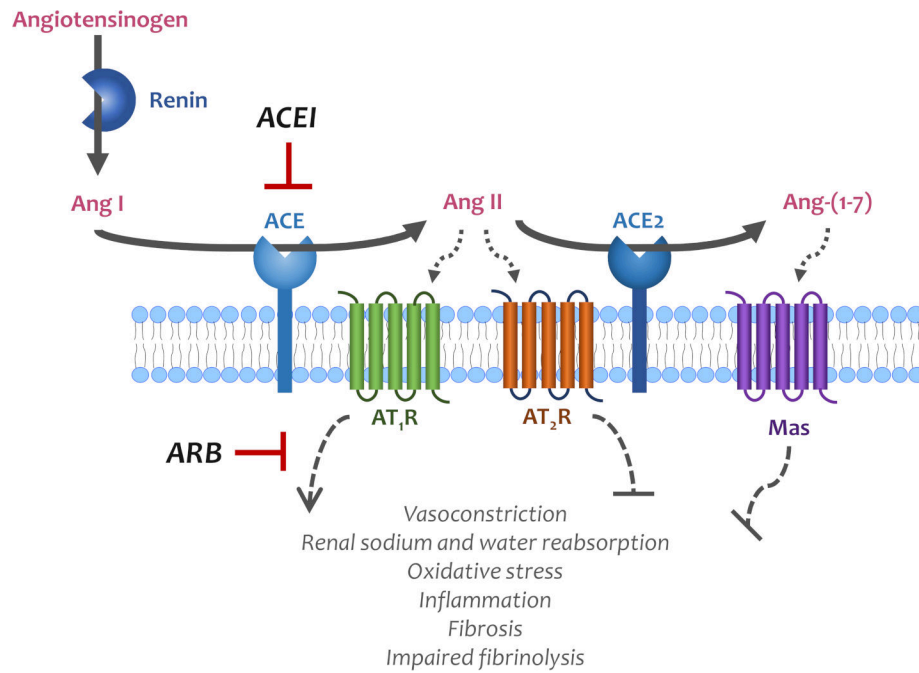
**Figure 1. The counterregulatory role of ACE2 in the renin angiotensin system**
Angiotensin converting enzyme inhibitors and angiotensin receptor blockers may increase ACE2 levels. This effect is speculated to increase the risk of SARS-CoV-2 host cell entry but may also have important anti-inflammatory effects.
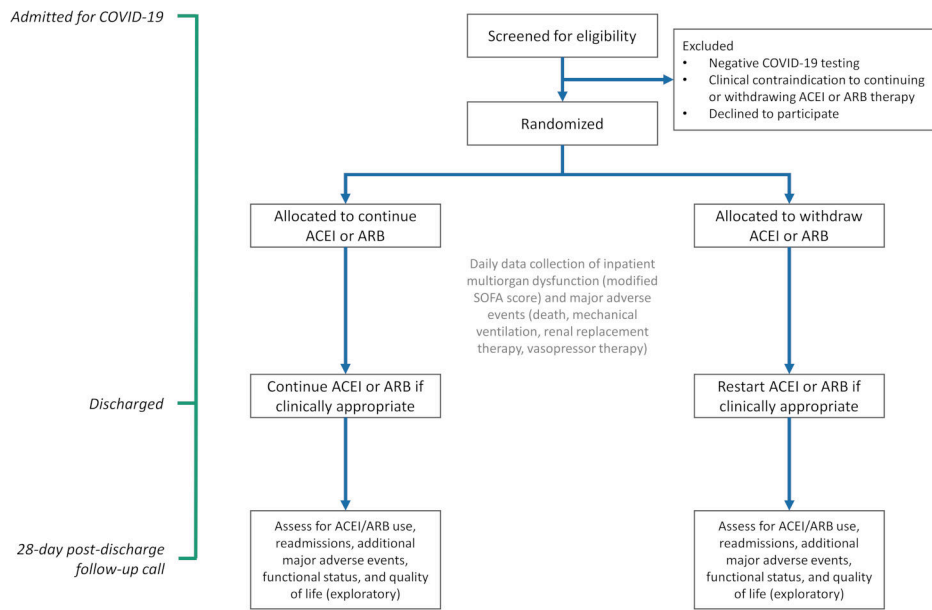
**Figure 2. Study overview and design**

**Figure 3. Geographic distribution of study sites enrolling participants in the REPLACE COVID trial**

As of July 23, 2020, 103 participants have been enrolled across sites in the United States, Canada, Peru, Argentina, and Sweden. Additional sites in the United States, Mexico, Argentina, Bolivia, and Brazil are initiating enrollment.
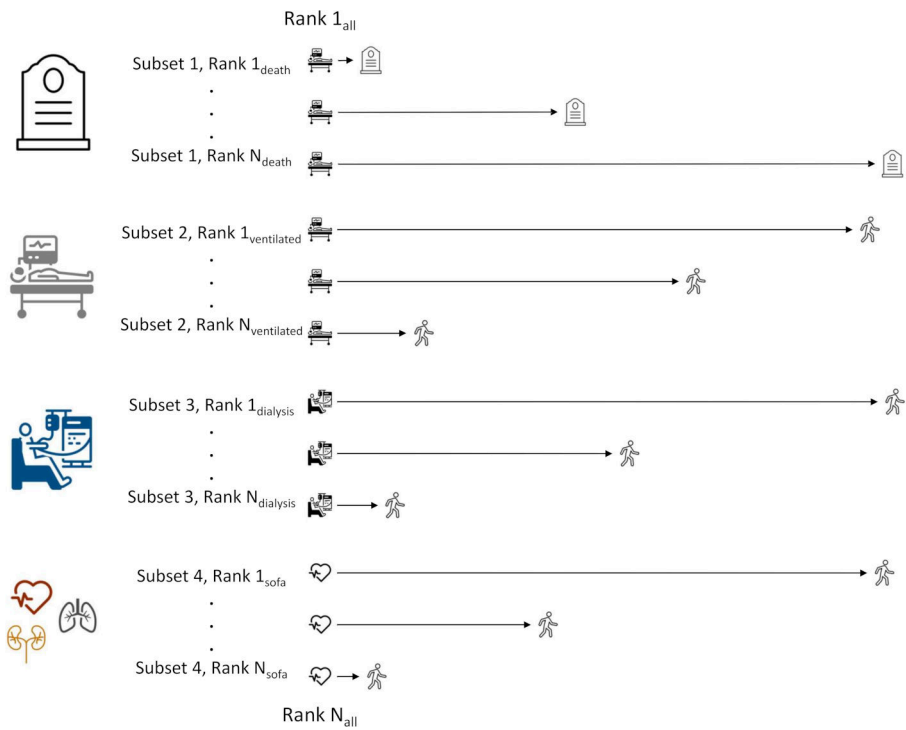
**Figure 4. The REPLACE COVID global rank score**

Subjects are ranked from worst to best outcomes by (1) days in hospital to death; (2) days on invasive mechanical ventilation or extracorporeal membrane oxygenation; (3) days on renal replacement therapy or inotropic/vasopressor therapy; and (4) area under the curve of a modified SOFA score.