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Coronavirus Disease 2019 and Hypertension: The Role of Angiotensin-Converting Enzyme 2 and the Renin-Angiotensin System



Daniel L. Edmonston, Andrew M. South, Matthew A. Sparks, and Jordana B. Cohen

Hypertension emerged from early reports as a potential risk factor for worse outcomes for persons with coronavirus disease 2019 (COVID-19). Among the putative links between hypertension and COVID-19 is a key counter-regulatory component of the renin-angiotensin system (RAS): angiotensin-converting enzyme 2 (ACE2). ACE2 facilitates entry of severe acute respiratory syndrome coronavirus 2, the virus responsible for COVID-19, into host cells. Because RAS inhibitors have been suggested to increase ACE2 expression, health-care providers and patients have grappled with the decision of whether to discontinue these medications during the COVID-19 pandemic. However, experimental models of analogous viral pneumonias suggest RAS inhibitors may exert protective effects against acute lung injury. We review how RAS and ACE2 biology may affect outcomes in COVID-19 through pulmonary and other systemic effects. In addition, we briefly detail the data for and against continuation of RAS inhibitors in persons with COVID-19 and summarize the current consensus recommendations from select specialty organizations.

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Key Words: Renin-angiotensin system, Angiotensin-converting enzyme 2, Angiotensin-converting enzyme inhibitor, Angiotensin receptor blocker, Coronavirus, COVID-19

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), results in a devastating, multisystem disease, which has affected millions of people worldwide.¹ This pandemic has sparked efforts to identify modifiable risk factors and investigate putative treatments. With the first wave of observational data, hypertension quickly emerged as a key comorbidity potentially associated with increased COVID-19 mortality.^{1,2} Identification of angiotensin-converting enzyme 2 (ACE2) as the primary SARS-CoV-2-binding site led to further concern that

angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase SARS-CoV-2 infection and COVID-19 mortality risk.^{3,4} Select experimental studies have shown that ACE inhibitors and ARBs increase ACE2 expression in certain tissues.⁵⁻⁷ However, data continue to emerge, which either temper or refute these early concerns.^{8,9} In addition, these concerns contrast with prior experimental data, which suggest a protective role for these renin-angiotensin system (RAS) inhibitors against acute lung injury and inflammation in select viral pneumonias including SARS-CoV, the virus responsible for the SARS outbreak of 2003. Informed decisions to continue or discontinue ACE inhibitor or ARB therapy during COVID-19 hinge on ongoing research to understand the roles of ACE2 and the RAS in pulmonary biology and well-designed clinical trials targeting this patient population.

We review RAS biology and how this classic mediator of hypertension may also both hold the key to SARS-CoV-2 entry into pneumocytes and potentially modulate subsequent lung injury. We also briefly review the competing data regarding the effect of RAS inhibition in COVID-19; identify key unmet needs and the studies designed to address them; and summarize consensus recommendations regarding the use of RAS inhibition in COVID-19.

CARDIOVASCULAR AND IMMUNOMODULATORY EFFECTS OF ACE2

The RAS is a crucial regulator of numerous physiologic functions, including fluid and electrolyte balance, perfusion, and inflammatory response. The 2 predominant RAS axes, the ACE/angiotensin (Ang) II/type 1 Ang II receptor (AT₁R) pathway and the counter-regulatory ACE2/Ang-(1-7)/Mas receptor (MasR) pathway, are co-expressed in most tissues.¹⁰ ACE exists in membrane-bound and soluble forms and converts Ang I into Ang II that acts via the AT₁R and AT₂R, whereas ACE2 is

From Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, NC (D.L.E., M.A.S.); Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (D.L.E.); Renal Section, Durham VA Health Care System, Durham, NC (D.L.E., M.A.S.); Section of Nephrology, Department of Pediatrics, Brenner Children's Hospital, Wake Forest School of Medicine, Winston Salem, NC (A.M.S.); Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC (A.M.S.); Department of Surgery-Hypertension and Vascular Research, Wake Forest School of Medicine, Winston Salem, NC (A.M.S.); Cardiovascular Sciences Center, Wake Forest School of Medicine, Winston Salem, NC (A.M.S.); Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (J.B.C.); Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (J.B.C.).

Financial Disclosure: The authors declare that they have no relevant financial interests.

Support: J.B.C. is supported by K23-HL133843 from the National Heart, Lung, and Blood Institute; A.M.S. is supported by R01-HL146818 and L40-HL148910 from the National Heart, Lung, and Blood Institute. The funding sources had no involvement in the preparation of this article.

Address correspondence to Jordana B. Cohen, MD, MSCE, 423 Guardian Drive, 831 Blockley, Philadelphia, PA, 19104. E-mail: jco@penntmedicine.upenn.edu

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1548-5595/\$36.00

<https://doi.org/10.1053/j.ackd.2020.07.002>

predominately membrane bound and converts Ang II into Ang-(1-7), which acts via the MasR.¹¹ Homeostasis between these pathways is critical for normal physiology, but in pathologic conditions, ACE/Ang II upregulation and/or ACE2/Ang-(1-7) downregulation propagates disease.^{11,12}

The RAS has several effects on the cardiovascular system and target organs including the kidney and brain. Experimental models of acquired or genetic ACE2 deficiency associate with several deleterious structural and functional abnormalities attributed to unopposed Ang II as well as reduced Ang-(1-7), including decreased cardiac contractility, cardiac hypoperfusion, myocardial dysfunction, impaired kidney function, and albuminuria.¹³⁻¹⁵ In the vasculature, Ang II acts on the AT₁R, resulting in diminished nitric oxide and vasoconstriction.¹⁶ In the kidneys, Ang II promotes sodium and fluid retention, which in combination with vasoconstriction raises blood pressure. On the other hand, Ang-(1-7) activation of the MasR results in part in the release of prostaglandin E₂, bradykinin, and nitric oxide to decrease blood pressure via natriuresis, diuresis, and vasodilation.^{11,16} In the brain, the ACE2/Ang-(1-7) pathway reduces sympathetic activity and increases nitric oxide synthase and nitric oxide levels, further promoting vasodilation and blood pressure decline.^{17,18}

In addition to its effects on the vasculature, Ang-(1-7) counteracts the proinflammatory and profibrotic effects of Ang II in the heart and kidneys.^{19,20} In animal models, unopposed Ang II in the setting of diminished ACE2 upregulated inflammatory cytokines interferon- γ , interleukin-6, and monocyte chemoattractant protein-1 and increased phosphorylation of extracellular signal-regulated protein kinase (ERK)1/2 and c-Jun N-terminal kinase (JNK)1/2 signaling pathways.²¹ Furthermore, AT₁R activation by Ang II has prothrombotic effects, including enhanced platelet activation and impaired fibrinolysis, resulting in hypercoagulability.^{22,23} Ang II also stimulates plasminogen activator inhibitor-1, further promoting thrombus production.²⁴ The prothrombotic effects of Ang II are downregulated by ACE2-mediated conversion into Ang-(1-7) and subsequent Ang-(1-7) signaling via MasR. Dysregulation of this pathway may contribute to the hypercoagulability and endothelial dysfunction observed in COVID-19.^{25,26}

ACE2 EFFECTS ON PULMONARY BIOLOGY

There has been increasing interest in the RAS, and ACE2/Ang-(1-7) in particular, during the COVID-19 pandemic, given that the SARS-CoV-2 spike protein binds to ACE2 to infect epithelial cells in the lung, most notably type II alveolar epithelial cells, which was the same mechanism observed with SARS-CoV.^{27,28}

In the lungs, the RAS regulates pulmonary vascular tone, alveolo-capillary integrity, and inflammatory response. Alveolar epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, and resident immune cells (i.e. alveolar macrophages) express both RAS pathways, although ACE/Ang II expression is generally much greater than ACE2/Ang-(1-7).^{10,29-32} Lung injury upregulates and stimulates *de novo* ACE/Ang II expression and, notably, ACE2/Ang-(1-7) suppression, which in turn propagates injury.^{29,30,33-35} As with SARS-CoV, evidence suggests that SARS-CoV-2 downregulates ACE2 via endocytosis and shedding and thus could potentially shift the RAS toward ACE/Ang II.³⁶⁻³⁹

Acid aspiration-induced acute lung injury resulted in ACE-dependent increased Ang II concentrations in lung and plasma associated with reduced ACE2 expression.³⁴ In a rat acute respiratory distress syndrome (ARDS) model, a combination of lipopolysaccharide and mechanical ventilation decreased the ACE2/ACE activity and Ang-(1-7)/Ang II concentration ratios in bronchoalveolar lavage fluid.²⁹ Patients with ARDS had elevated plasma Ang II levels⁴⁰; in addition, prior ACE inhibitor and ARB use, as well as ACE genotype, were associated with improved mortality in patients with ARDS.^{41,42} Ang II binds to AT₁R to increase pulmonary vascular permeability, induce alveolar epithelial cell apoptosis and fibroblast differentiation, and promote immune cell migration, activation, differentiation, and cytokine release.^{30,34,43-45} Indeed, cytokine release by activated type II alveolar epithelial cells and alveolar macrophages is mediated in part through ERK1/2 and p38 mitogen-activated protein kinase signaling cascades, which are regulated by AT₁R and MasR.⁴⁵⁻⁴⁷

The ACE2/Ang-(1-7) pathway mitigates acute lung injury/ARDS. The binding of the SARS-CoV spike protein to ACE2 downregulated ACE2 expression, increased Ang II lung concentration, and enhanced AT₁R-mediated acute lung injury, including increased lung elastance and pulmonary edema.³⁶ Furthermore, ACE2 deficiency worsened lung elastance, pulmonary vascular permeability and pulmonary edema, inflammatory cell infiltration, and hyaline membrane formation and decreased oxygenation in several acute lung injury models; catalytically active recombinant human ACE2 improved these lung measures and reduced lung Ang II concentration.³⁴ In a phase II clinical trial, recombinant human ACE2 caused a sustained decrease in plasma Ang II and a sustained increase in Ang-(1-7).⁴⁰

The beneficial effects of the ACE2/Ang-(1-7) pathway in acute lung injury extend beyond Ang II metabolism; Ang-(1-7) binding to MasR, and to a lesser extent Ang II binding to AT₂R, also exerts a protective effect.⁴⁸ In several rodent models of acute lung injury, Ang-(1-7) infusion (peptide

CLINICAL SUMMARY

- ACE2 facilitates SARS-CoV-2 host-cell entry and may be upregulated by RAS blockade.
- Despite their potentially deleterious interaction with ACE2, RAS blockers may be helpful to protect against acute lung injury.
- While we await trial evidence to determine the safety and efficacy of RAS blockade in COVID-19, international organizations recommend continuing these medications unless otherwise contraindicated.

and cyclized) reduced pulmonary vascular resistance and edema, increased PaO₂, blocked increased tumor necrosis factor α , increased bronchoalveolar lavage fluid ACE2/ACE activity and Ang-(1-7)/Ang II concentration ratios, and protected against alveolo-capillary barrier failure and neutrophil invasion.^{29,49} Intriguingly, Ang-(1-7) restored systemic blood pressure and reduced right ventricle pressure load and, in part, mediated beneficial ARB effects.⁴⁹ The RAS plays a significant role in acute and chronic lung injury, including SARS, and given ACE2's role as the SARS-CoV-2 binding site, the RAS likely plays a role in COVID-19 pathophysiology, although confirmatory clinical and experimental data are needed.

THE CASE AGAINST RAS INHIBITION IN COVID-19

SARS-CoV-2 cellular entry via ACE2 is dependent on priming of the SARS-CoV-2 spike protein by type II transmembrane serine proteases.^{3,39} In addition, SARS-CoV-2 binds to ACE2 with a higher affinity than SARS-CoV.⁵⁰ Therefore, any process which increases ACE2 expression theoretically could increase the likelihood of viral binding, cellular infection, and thus increase the risk of worse outcomes in patients with COVID-19 (Fig 1).

RAS inhibitors may increase cell surface ACE2 levels and expression.⁵⁻⁷ ACE2 interacts with the AT₁R on the cellular surface; however, Ang II binding to AT₁R interrupts this AT₁R-ACE2 interaction and promotes increased ACE2

internalization.⁵¹ In experimental models, RAS inhibitors can decrease this effect and subsequently decrease ACE2 internalization, which can explain the increased ACE2 expression observed in certain animal models. However, this association has multiple caveats, most important of which are the lack of evidence of this phenomenon in human studies and the absence of specific experimental evidence of ACE inhibitor or ARB-induced changes in ACE2 expression in the lungs.^{52,53} Although this putative effect of RAS inhibition on ACE2 expression could in theory facilitate viral entry into pneumocytes and other cellular targets of SARS-CoV-2, whether this action truly increases susceptibility to SARS-CoV-2 infection and subsequent development of COVID-19 in humans remains unclear.

Among other complications of this multiorgan disease, COVID-19 may increase the risk for acute kidney injury (AKI); in studies of critically ill persons with COVID-19, the rate of AKI ranges from 19 to 39%.⁵⁴⁻⁵⁶ However, AKI estimates for all hospitalized patients vary substantially and the incidence of AKI in outpatients with COVID-19 remains unknown.^{1,2,56-58} Through impairment of the autoregulatory response to changes in kidney perfusion,^{59,60} ACE inhibitors or ARBs could theoretically increase the risk of AKI in highly susceptible individuals. However, aside from the demonstrated risks of dual therapy,⁶¹ neither ACE inhibitors nor ARBs clearly increase AKI risk in randomized studies of other at-risk

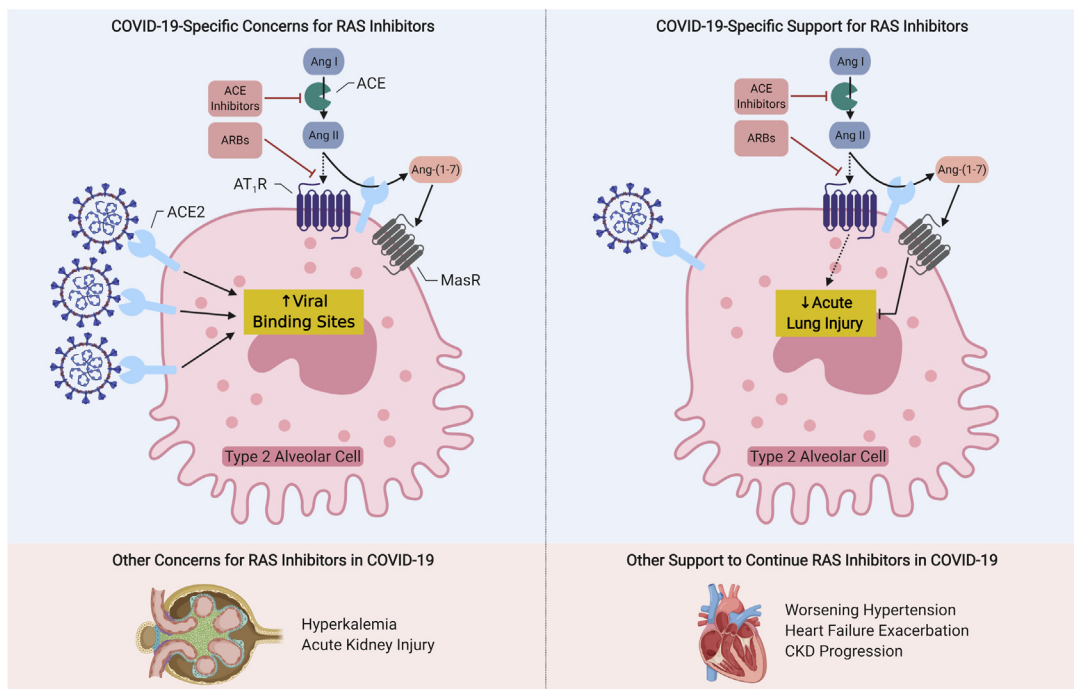


Figure 1. Putative helpful and harmful actions of RAS inhibition in COVID-19. The top-left panel depicts the potential for increased ACE2 expression leading to increased SARS-CoV-2 binding sites. The bottom-left panel lists other potential adverse effects from RAS inhibition in persons with COVID-19 outside of increased viral binding sites. The top-right panel depicts the potential for decreased acute lung injury from the shift from ACE/Ang II/AT₁R to ACE2/Ang-(1-7)/MasR predominance. The bottom-right panel lists adverse effects of RAS discontinuation in persons with COVID-19. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE, angiotensin-converting enzyme; Ang, angiotensin; ARB, angiotensin receptor blocker; MasR, Mas receptor; RAS, renin-angiotensin system. (Figure 1 was created with the assistance of [BioRender.com](https://www.biorender.com).)

Table 1. Statements From Select Professional Societies Regarding the Use of RAS Inhibitors During COVID-19

Society	Statement Summary
American College of Physicians	<ul style="list-style-type: none"> • There is no evidence linking antihypertensive agents to COVID-19 disease severity. • ARBs have possible benefits for use as SARS-CoV-2 treatments. • Discontinuing or changing antihypertensive therapy without medical indication and supervision could lead to adverse effects and may be harmful.
American Heart Association, Heart Failure Society of America, and American College of Cardiology	<ul style="list-style-type: none"> • There are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACE inhibitor or ARB medications. • Recommend continuation of RAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease. • In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation.
American Society of Pediatric Nephrology	<ul style="list-style-type: none"> • Strongly recommends that patients continue to take their ACE inhibitors and ARBs, until new evidence to the contrary becomes available. • Appropriate medical management continues to be provided to patients on these medications who test positive for SARS-CoV-2 and those who have COVID-19, including discontinuation of ACE inhibitors and ARBs when medically indicated.
European Society of Cardiology Council on Hypertension	<ul style="list-style-type: none"> • Strongly recommend that physicians and patients should continue treatment with their usual antihypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACE inhibitors or ARBs should be discontinued because of the COVID-19 infection.
International Society of Hypertension	<ul style="list-style-type: none"> • There are no clinical data in humans to show that ACE inhibitors or ARBs either improve or worsen susceptibility to COVID-19 infection nor do they affect the outcomes of those infected. • Strongly recommend that the routine use of ACE inhibitors or ARBs to treat raised blood pressure should continue and should not be influenced by concerns about COVID-19 infection.
National Institutes of Health	<ul style="list-style-type: none"> • Persons with COVID-19 who are prescribed ACE inhibitors or ARBs for cardiovascular disease (or other indications) should continue these medications. • The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19 outside of the setting of a clinical trial.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; RAS, renin-angiotensin system.

The position statements from each professional society have been summarized; edits to the statements were made only to truncate length and standardize the abbreviations used. Statements are current through May 1, 2020.

populations.⁶² Moreover, no study has directly demonstrated an association between RAS inhibition and the risk of AKI in patients with COVID-19.⁵⁸

THE CASE FOR RAS INHIBITION IN COVID-19

Despite the theoretical increase in ACE2 binding sites, RAS blockade could improve clinical outcomes in persons infected with SARS-CoV-2. This rationale is supported by preclinical studies in which losartan, an ARB, attenuated lung injury in a nonviral mouse model of SARS-CoV spike protein-enhanced acid-induced lung injury.³⁶ In this

study, either infection with SARS-CoV or the use of spike protein combined with an acid-inhalation model substantially reduced ACE2 levels and increased Ang II levels in the lung. Thus, the overarching hypothesis is that viral infection diminishes ACE2 protein and activity, leading to Ang II accumulation and reduced Ang-(1-7).

The aforementioned upregulation of ACE/Ang II and concomitant suppression of ACE2/Ang-(1-7) likely propagate lung injury during SARS-CoV-2 infection.^{29,30,33-35} This increased Ang II/Ang-(1-7) ratio leads to vasoconstriction of the pulmonary vasculature, further

reducing pulmonary blood flow to the already-damaged lung parenchyma in the face of hypoxemia from the viral pneumonia. The predominance of Ang II intensifies the immune response, which may further contribute to lung injury.⁶³ However, whether AT₁R universally stimulates inflammation and fibrosis remains unclear: specific deletion of AT₁Rs on both macrophages and T-cells in mice suggests that activation of AT₁Rs on these immune cell lineages limits rather than propagates inflammation and organ injury in kidney models.^{64,65} How AT₁R signaling of macrophages and T-cells contributes to lung injury during SARS-CoV-2 infection remains unknown.

Although the benefits of RAS inhibition in COVID-19 remain unclear, we may be able to extrapolate from the use of RAS inhibition in other types of viral infections. For example, in a mouse model of H7N9 influenza, viral infection also decreased ACE2 levels (with resultant increased Ang II).⁶⁶ ACE2 knockout mice had worse outcomes after viral infection; in contrast, losartan mitigated lung injury in wild-type mice with influenza infection similar to the effect seen in the SARS-CoV model.⁶⁶ Moreover, respiratory syncytial virus models demonstrate similar improvements with RAS inhibition.⁶⁷ These data in other analogous viral infections provide a favorable precedent for the use of RAS inhibition in COVID-19.

OBSERVATIONAL STUDIES OF RAS INHIBITION IN COVID-19

Several observational studies have evaluated the association of ACE inhibitor and ARB therapy with the development and severity of COVID-19.^{8,9,68,69} These studies have several limitations, including confounding by indication, collider bias (conditioning on specific factors such as hospitalization or for-symptom COVID-19 testing, which may distort or induce spurious associations between ACE inhibitor or ARB use and COVID-19), time-dependent bias, or lack of accounting for multiple hypothesis testing. Accordingly, the studies show conflicting results regarding the association of ACE inhibitor and ARB therapy with COVID-19. For example, Zhang and colleagues found that ACE inhibitor or ARB therapy was associated with lower risk of mortality among individuals hospitalized with COVID-19 in Hubei Province, China⁶⁸; in contrast, Rentsch and colleagues found that ACE inhibitors and ARBs were associated with a higher risk of requiring intensive care among US veterans hospitalized with COVID-19.⁶⁹ Further research is needed to better understand the magnitude and direction of these associations.

CURRENT RECOMMENDATIONS AND FUTURE DIRECTIONS

The dizzying pace of research in the wake of the COVID-19 pandemic has yielded incomplete and conflicting data regarding the safety of RAS inhibitors for patients with COVID-19. For patients with certain comorbidities such

as heart failure and chronic kidney disease, decades of research clearly demonstrate improved survival and disease trajectory with RAS inhibitors.^{70,71} Given the stakes of the decision to continue or hold these medications, patients and providers need clear guidelines to help navigate this difficult situation. While our understanding of COVID-19 continues to evolve, [Table 1](#) summarizes the current consensus guidelines from select organizations regarding the use of RAS inhibitor therapy in persons affected by COVID-19.⁷²⁻⁷⁷ The measured and consistent responses from these organizations to continue RAS inhibitor therapy through SARS-CoV-2 infection unless otherwise directed by a health-care provider reflect the lack of high-quality data to overturn the existing indications for these medications.

Several confounding factors—both measurable and unmeasurable—underlie the clinical decision to continue, discontinue, or start RAS inhibitor therapy in the setting of COVID-19; these confounding factors limit the ability of observational studies to definitively answer this question. A growing number of clinical trials have begun enrollment that target this question in various patient populations with or at risk for COVID-19. These trials include randomized continuation vs discontinuation of existing ACE inhibitor or ARB therapy to prevent SARS-CoV-2 infection (CORONACION, NCT04330300) or improve outcomes of patients hospitalized with COVID-19 (REPLACE-COVID, NCT04338009; ACEI-COVID, NCT04353596; BRACE-CORONA, NCT04364893; Acores-2, NCT04329195; RASCOVID-19, NCT04351581). In addition, select trials randomize inpatients (COVIDMED, NCT04328012; RAMIC, NCT04366050; CAPTOCOVID, NCT04355429; NCT04312009, NCT04355936, NCT04335786, NCT04394117) and outpatients (NCT04311177) with COVID-19 to ARB or ACE inhibitor vs placebo or usual care. As these and other studies provide more-definitive evidence regarding the safety and efficacy of RAS inhibitors during COVID-19, future studies will need to expand to all stages of illness severity, consider inclusion of the pediatric population,^{78,79} investigate how other ACE2-altering processes such as smoking modify any relationship between RAS inhibition and outcomes, and determine how RAS inhibitors influence clinical outcomes when used in concert with other experimental COVID-19 therapies.

ACKNOWLEDGMENTS

The authors would like to acknowledge the extensive and expanding resources related to this topic provided by the editors of [nephjc.com](#). The authors also thank The COVID-19 and ACE2 in Cardiovascular, Lung, and Kidney Working Group for providing critical review and discussion of the literature: Matthew A. Sparks, Swapnil Hiremath, Daniel Batlle, Andrew M. South, Paul Welling, J. Matt Luther, Jordana B. Cohen, James Brian Byrd, Louise M. Burrell, Laurie Tomlinson, Vivek Bhalla, María José Soler, Sundar Swaminathan, Michelle N. Rheault, and Sundar Swaminathan. The figure was created with the assistance of [BioRender.com](#).

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