Are RAAS-blocking drugs a risk factor for COVID-19?
Abstract—During the spread of the severe acute respiratory syndrome coronavirus-2, some reports of data still emerging and in need of full analysis indicate that certain groups of patients are at risk of COVID-19. This includes patients with hypertension, heart disease, diabetes mellitus, and clearly the elderly. Many of those patients are treated with renin-angiotensin system blockers. Because the ACE2 (angiotensin-converting enzyme 2) protein is the receptor that facilitates coronavirus entry into cells, the notion has been popularized that treatment with renin-angiotensin system blockers might increase the risk of developing a severe and fatal severe acute respiratory syndrome coronavirus-2 infection. The present article discusses this concept. ACE2 in its full-length form is a membrane-bound enzyme, whereas its shorter (soluble) form circulates in blood at very low levels. As a mono-carboxypeptidase, ACE2 contributes to the degradation of several substrates including angiotensins I and II. ACE (angiotensin-converting enzyme) inhibitors do not inhibit ACE2 because ACE and ACE2 are different enzymes. Although angiotensin II type 1 receptor blockers have been shown to upregulate ACE2 in experimental animals, the evidence is not always consistent and differs among the diverse angiotensin II type 1 receptor blockers and differing organs. Moreover, there are no data to support the notion that ACE inhibitor or angiotensin II type 1 receptor blocker administration facilitates coronavirus entry by increasing ACE2 expression in either animals or humans. Indeed, animal data support elevated ACE2 expression as conferring potential protective pulmonary and cardiovascular effects. In summary, based on the currently available evidence, treatment with renin-angiotensin system blockers should not be discontinued because of concerns with coronavirus infection.

Key Words: ACE inhibitor ■ angiotensin receptor blocker ■ coronavirus ■ COVID-19 ■ severe acute respiratory syndrome

Renin-Angiotensin System Blockers and the COVID-19 Pandemic
At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers
A.H. Jan Danser, Murray Epstein, Daniel Batlle

The spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has already taken on pandemic proportions, having infected >100,000 people in 100 countries.1 Although the major current focus of public health authorities is to develop a coordinated global response to prepare health systems to meet this unprecedented challenge, a corollary concern has been identified that is of particular interest to clinicians and investigators with a major interest in hypertension. Hypertension, coronary heart disease, and diabetes mellitus, particularly in elderly people, increase susceptibility to SARS-CoV-2 infection.1–3 Given that ACE2 (angiotensin-converting enzyme 2) is the receptor that allows coronavirus entry into cells, the idea has come up that preexisting use of renin-angiotensin system (RAS) blockers might increase the risk of developing a severe and fatal SARS-CoV-2 infection.2 This commentary discusses this concern and concludes that based on current evidence, there is no reason to abandon RAS blockers in patients receiving this important class of antihypertensive agents because of concerns of either increased risk of contracting SARS-CoV-2 or worsening its course.

Coronavirus and ACE2
In 2003, Li et al4 demonstrated that ACE2 is the receptor responsible for SARS coronavirus entry. Binding to the ACE2 receptor requires the surface unit of a viral spike protein (S1; Figure).5,6 Subsequent cell entry relies on priming by the serine protease TMPRSS2 (transmembrane protease, serine 2).7 Two recent reports confirmed that SARS-CoV-2 also enters the cell via this route.7,8 Importantly, SARS-CoV-2 entry into the cell could be blocked both by S-protein neutralizing antibodies and TMPRSS2 inhibitors (camostat mesylate).7 In the lung, ACE2 expression occurs in type 2 pneumocytes and macrophages. Generally, however, pulmonary ACE2 expression is
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low when compared with other organs like the intestine, testis, heart, and kidney.9–11

ACE2 and the RAS
ACE2 displays considerable homology with ACE (angiotensin-converting enzyme; 40% identity and 61% similarity) and on this basis received its name in 2000.12 As a mono-carboxypeptidase, it hydrolyzes multiple peptides, including apelin, opioids, kinins, and angiotensins. Much of the work on ACE2 has centered on the biologic effects related to the formation of angiotensin-(1–7) from angiotensin II.13,14 Unlike ACE, ACE2 does not convert angiotensin I to angiotensin II, nor do ACE inhibitors block its activity. This is not surprising because the homology does not concern the active site. ACE2 is the most potent of the 3 enzymes known to convert the vasoconstrictor angiotensin II to angiotensin-(1–7).9,15 Angiotensin-(1–7) is increasingly recognized to have organ-protective properties that oppose and counterbalance those of angiotensin II. Within the RAS, the other known target peptide for ACE2 cleavage is angiotensin I, with the subsequent formation of angiotensin-(1–9) (Figure).

ACE2 is a membrane-bound enzyme, and its (soluble) levels in blood are very low.9,15 Cleavage of its membrane-anchor (shedding) by a disintegrin and metalloprotease 17 (ADAM17) (Figure) underlies its occurrence in body fluids. AT1 (angiotensin II, via its type 1) receptor, upregulates ADAM17, thus increasing soluble ACE2 levels.16 In urine, soluble ACE2 levels can be significant and likely originate from shedding from the proximal tubular membrane. In pathological states, shedding of ACE2 is often increased, resulting in elevated soluble ACE2 levels in blood, urine, and other body fluids.17,18 Indeed, a doubling of soluble ACE2 has been reported in cerebrospinal fluid of hypertensive patients.16 However, given that by far the majority of ACE2 is membrane-bound, even a doubling is unlikely to significantly alter the amount of membrane-bound ACE2. For instance, if 2% of ACE2 occurs in a soluble form, doubling would increase this to 4%, while still 96% of ACE2 is membrane-bound. Theoretically, RAS blockade might (partly) reverse this, thus returning the percent of membrane-bound ACE2 to 97–98. This is unlikely to seriously affect SARS-CoV-2 entry, which depends on membrane-bound (full-length) ACE2.

What Are the Effects of RAS Blockers on ACE2?
This is really at the crux of the question and the prevailing confusion and panic that we are witnessing in the medical community after the word came out that ACE2 is the receptor for SARS-CoV-2. Part of the confusion in social media and the public in general stands because, at times, ACE inhibitors are confused with ACE2 inhibitors. Those are 2 different enzymes with 2 different active sites and any effect of ACE inhibitors on ACE2 activity must therefore be an indirect one, via their respective substrates. This is unlikely to have any relationship with SARS-CoV-2 binding. There are, however, limited reports that ACE inhibitors affect the expression of ACE2 in the heart and the kidney.19 AT1 receptor blockers (ARBs) alter ACE2 expression more consistently in several studies, both at the mRNA and protein level.19–21 Upregulation has been best documented in cardiac tissue and in the renal vasculature. Yet, even here, results are diverse, required high doses, and often differed per ARB and per organ. Given the relationship with ADAM17, a clear distinction should be made between membrane-bound and soluble ACE2 because an

Figure. The carboxypeptidase ACE2 (angiotensin-converting enzyme 2) converts Ang II (angiotensin II) to Ang-(1–7) and Ang I to Ang-(1–9) (A), yet is not blocked by ACE (angiotensin-converting enzyme) inhibitors, which prevent the conversion of Ang I to Ang II. ACE2 also binds and internalizes SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2; B), after priming by the serine protease TMPRSS2 (transmembrane protease, serine 2). Shedding of membrane-bound ACE2 by a disintegrin and metalloprotease 17 (ADAM17) results in the occurrence of soluble (s) ACE2, which can no longer mediate SARS-CoV-2 entry and which might even prevent such entry by keeping the virus in solution. AT1R (Ang II, via its type 1 receptor) upregulates ADAM17, and AT1R blockers (ARBs) would prevent this.
increase in soluble ACE2, if anything, might imply a decrease in membrane-bound ACE2. Because measuring membrane-bound ACE2 in vivo is technically challenging, most publications from humans have reported levels of ACE2 activity in blood that reflect the soluble ACE2 protein circulating at very low levels.22 If ARBs as a drug class would truly upregulate membrane-bound ACE2, it is reasonable to first assume that this is because of AT1 receptor blockade. In agreement with this assumption, angiotensin II acutely induced ACE2 internalization via its AT1 receptor in ACE2-transfected neuroblastoma cells.23 ACE inhibitors should then have the same directional effect as ARBs, although for these drugs there is very limited data showing upregulation of ACE2. Esler and Esler24 suggested that the difference is due to the increased levels of angiotensin II occurring after ARB treatment (but not ACE inhibition): high angiotensin II levels would impose an increased substrate load on the enzyme, thus requiring its upregulation. Here it should be stressed that the carboxypeptidase ACE2 has multiple substrates and that an alteration in the level of one of these substrates (angiotensin II, occurring at fmol/mL levels, i.e., many orders of magnitude below the actual ACE2 concentration!) cannot possibly make a meaningful difference in its substrate load.

Taken together, there is evidence from animal studies that ARBs may upregulate membrane-bound ACE2, whereas ACE inhibitors may not. The current data, however, are often conflicting and vary between ARBs and tissue (eg, heart versus kidney). Even if the reported upregulation of tissue ACE2 by ARBs in animal studies and generally with high doses could be extrapolated to humans, this would not establish that it is sufficient to facilitate SARS-CoV-2 entry.

We like to point out that a potentially beneficial pulmonary effect of ARBs needs to be considered as well. During acute lung injury, alveolar ACE2 appears to be downregulated.25,26 This would decrease angiotensin II metabolism, thus resulting in higher local levels of this peptide, which increases alveolar permeability and fosters lung injury. In this context, one can speculate that having increased ACE2 expression by preexisting ARBs treatment may actually be protective in the course of SARS-CoV-2 infection.

**Risks of Abandoning RAS Treatment in Corona Patients**

It is not clear how hypertension was coded in the recent SARS-CoV-2 report—we can only speculate that it might be based on the use of hypertension medication rather than actual blood pressure measurement. To truly address whether patients with hypertension are more likely to get serious and fatal SARS-CoV-2 infections, a prospective cohort study with incidence rates of SARS-CoV-2 infection in a cohort of patients with hypertension and patients without hypertension is required, with similar exposure history. Instead, what has been reported is history of hypertension versus not, in SARS-CoV-2 patients, without any adjustment (eg, for age). The use of RAS blockers as a causal link is an assumption that lacks evidence, as discussed here. We therefore strongly recommend that patients who are taking ACE inhibitors or ARBs for high blood pressure, heart failure, or other medical indications should not withdraw their current treatment regimens unless they are specifically advised to do so by their physician or healthcare provider. There is an additional caveat. Any resulting destabilizing of blood pressure control in hypertension, which might possibly occur with medication changes, would carry unacceptable risks of precipitating strokes and heart attacks, risks which clearly are not just hypothetical. Simply discontinuing antihypertensive agents is strongly discouraged and should not be an option, considering the widespread use of RAS blockers throughout the world. In particular, Asian people seem to be more prone to cough, and therefore, ARBs may be preferable.27

**Next Steps**

The available clinical database from the pandemic to date is insufficient to provide sufficient detail on the variables of interest: hypertension diagnosis and the antihypertensive drugs prescribed to test the hypotheses proposed and provide certainty. Hence such information is desperately needed.

Although no therapy is currently established for SARS-CoV-2 patients, the field is moving rapidly with potential approaches being considered. Those include broad spectrum antivirals such as favipiravir and remdesivir;28,29 ADAM17 inhibition with camostat mesylate,7 and ADAM17 upregulation. A more specific approach might be using soluble recombinant ACE2 protein to intercept the virus from binding to the full-length ACE2 anchored in the cell plasma membrane.6 These approaches make the most sense for the treatment of patients with high risk for acute respiratory distress syndrome. For preventive purposes, the goal, of course, is the development of a SARS-CoV-2 vaccine.

In closing, we see no reason to abandon or discontinue temporarily the use of RAS blockers preventatively in SARS-CoV-2 patients.30 There are some concerns that these agents, particularly ARBs, can affect the expression of ACE2 based on animal models that, however, have not been challenged with coronavirus infection to evaluate the impact of RAS blocker therapy. Since this information is lacking, we see no rationale to panic and to alter the prescription of this critically important class of antihypertensives. Their therapeutic benefit, in our opinion, outweighs any potential risk of them predisposing to corona infection. Moreover, it is unknown whether alternative antihypertensives do not carry the same risk. Another question is what to do in infected individuals with risk to progress to end-stage renal disease. Here the decision should be based on clinical judgment and considering the pros and cons of RAS blockade in the acutely ill, such as the presence or absence of hypotension and kidney function.

**Take Home Messages**

- ACE2 (angiotensin-converting enzyme 2) is the receptor that allows coronavirus entry into cells.
- ACE2 in its full-length form is a membrane-bound enzyme, whereas its shorter (soluble) form circulates in blood at very low levels.
- ACE inhibitors do not inhibit ACE2 because ACE and ACE2 are entirely different enzymes.
- Although angiotensin II type 1 receptor blockers have been suggested to upregulate ACE2, the evidence is not fully consistent and differs per angiotensin II type 1 receptor blocker and per organ.
• There are no data supporting that ACE inhibitors or angiotensin II type 1 receptor blockers facilitate coronavirus entry by increasing ACE2 expression.
• Animal data support a potential protective pulmonary and cardiovascular effects of elevated ACE2 expression.
• Treatment with RAS blockers should not be discontinued because of concerns with coronavirus infection based on the currently available evidence.

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D. Batlle is a co-inventor of the patent Active Low Molecular Weight Variants of ACE2 and has also submitted a patent on the potential use of novel ACE2 (angiotensin-converting enzyme 2) proteins for coronavirus infection. D. Batlle is Founder of Angiotensin Therapeutics. The other authors report no conflicts.

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease 2019 (COVID-19) in the study by Xiaobo Yang and colleagues1 were cerebrovascular diseases (22%) and diabetes (22%). Another study2 included 1099 patients with confirmed COVID-19, of whom 173 had severe disease with comorbidities of hypertension (23-7%), diabetes mellitus (16-2%), coronary heart diseases (5-8%), and cerebrovascular disease (2-3%). In a third study,3 of 140 patients (5-8%), and cerebrovascular disease (16-2%), coronary heart diseases, hypertension (23-7%), diabetes mellitus (22%). Another study2 included 1099 patients with confirmed COVID-19, of whom 173 had severe disease with comorbidities of hypertension (23-7%), diabetes mellitus (16-2%), coronary heart diseases (5-8%), and cerebrovascular disease (2-3%). In a third study,3 of 140 patients who were admitted to hospital with COVID-19, 30% had hypertension and 12% had diabetes. Notably, the most frequent comorbidities reported in these three studies of patients with COVID-19 are often treated with angiotensin-converting enzyme (ACE) inhibitors; however, treatment was not assessed in either study.

Human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.4 The expression of ACE2 is substantially increased in diabetes mellitus, cerebral stroke, and hypertension, specifically in Asian populations. Summarising this information, the sensitivity of an individual might result from a combination of both therapy and ACE2 polymorphism.

We suggest that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs. Based on a PubMed search on Feb 28, 2020, we did not find any evidence to suggest that antihypertensive calcium channel blockers increased ACE2 expression or activity, therefore these could be a suitable alternative treatment in these patients.

We declare no competing interests.

Lei Fang, George Karakiulakis, *Michael Roth
michael.roth@usb.ch
Pulmonary Cell Research and Pneumology, Department of Biomedicine and Internal Medicine, University Hospital Basel, CH-4031 Basel, Switzerland (LF, MR); and Department of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece (GK)

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*Correspondence

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Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

Muthiah Vaduganathan, M.D., M.P.H., Orly Vardeny, Pharm.D., Thomas Michel, M.D., Ph.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., and Scott D. Solomon, M.D.

The renin–angiotensin–aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology. Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2, which have been responsible for the SARS epidemic in 2002 to 2004 and for the more recent coronavirus disease 2019 (Covid-19) pandemic, respectively, interface with the RAAS through angiotensin-converting enzyme 2 (ACE2), an enzyme that physiologically counters RAAS activation but also functions as a receptor for both SARS viruses.1,2 The interaction between the SARS viruses and ACE2 has been proposed as a potential factor in their infectivity,3,4 and there are concerns about the use of RAAS inhibitors that may alter ACE2 and whether variation in ACE2 expression may be in part responsible for disease virulence in the ongoing Covid-19 pandemic.5-8 Indeed, some media sources and health systems have recently called for the discontinuation of ACE inhibitors and angiotensin-receptor blockers (ARBs), both prophylactically and in the context of suspected Covid-19.

Initial reports5-8 have called attention to the potential overrepresentation of hypertension among patients with Covid-19. In the largest of several case series from China that have been released during the Covid-19 pandemic (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), hypertension was the most frequent coexisting condition in 1099 patients, with an estimated prevalence of 15%; however, this estimate appears to be lower than the estimated prevalence of hypertension seen with other viral infections10 and in the general population in China.11,12

Coexisting conditions, including hypertension, have consistently been reported to be more common among patients with Covid-19 who have had severe illness, been admitted to the intensive care unit, received mechanical ventilation, or died than among patients who have had mild illness. There are concerns that medical management of these coexisting conditions, including the use of RAAS inhibitors, may have contributed to the adverse health outcomes observed. However, these conditions appear to track closely with advancing age,13 which is emerging as the strongest predictor of Covid-19–related death.14 Unfortunately, reports to date have not rigorously accounted for age or other key factors that contribute to health as potential confounders in risk prediction. With other infective illnesses, coexisting conditions such as hypertension have been key prognostic determinants,10 and this also appears to be the case with Covid-19.15

It is important to note that, despite inferences
about the use of background RAAS inhibitors, specific details have been lacking in studies (Table S1). Population-based studies have estimated that only 30 to 40% of patients in China who have hypertension are treated with any antihypertensive therapy; RAAS inhibitors are used alone or in combination in 25 to 30% of these treated patients.11,12 Given such estimates, only a fraction of patients with Covid-19, at least in China, are anticipated to have been previously treated with RAAS inhibitors. Data showing patterns of use of RAAS inhibitors and associated health outcomes that rigorously account for treatment indication and illness severity among patients with Covid-19 are needed.

Tissue-specific and circulating components of the RAAS make up a complex intersecting network of regulatory and counterregulatory peptides (Fig. 1). ACE2 is a key counterregulatory enzyme that degrades angiotensin II to angiotensin-(1–7), thereby attenuating its effects on vasoconstriction, sodium retention, and fibrosis. Although angiotensin II is the primary substrate of ACE2, that enzyme also cleaves angiotensin I to angiotensin-(1–9) and participates in the hydrolysis of other peptides.16 In studies in humans, tissue samples from 15 organs have shown that ACE2 is expressed broadly, including in the heart and kidneys, as well as on the principal target cells for SARS-CoV-2 (and the site of dominant viral replication).17 Of interest, the circulating levels of soluble ACE2 are low and the functional role of ACE2 in the lungs appears to be relatively minimal under normal conditions18 but may be up-regulated in certain clinical states.

Because ACE inhibitors and ARBs have different effects on angiotensin II, the primary substrate of ACE2, the effects of these agents on ACE2 levels and activity may be anticipated to differ. Despite substantial structural homology between ACE and ACE2, their enzyme active sites are distinct. As a result, ACE inhibitors in clinical use do not directly affect ACE2 activity.19 Experimental animal models have shown mixed findings with respect to the effects of ACE inhibitors on ACE2 levels or activity in tissue.20-25 Similarly, animal models have had inconsistent findings with respect to the effects of ARBs on ACE2, with some showing that ARBs may increase messenger RNA expression or protein levels of ACE2 in tissue21,26-34 and others showing no effect.23

In contrast to available animal models, there are few studies in humans regarding the effects of RAAS inhibition on ACE2 expression. In one study, the intravenous administration of ACE inhibitors in patients with coronary artery disease did not influence angiotensin-(1–7) production, a finding that calls into question whether ACE inhibitors have any direct effects on ACE2-directed angiotensin II metabolism.35 Similarly, in another study, among patients with hypertension, angiotensin-(1–7) levels appeared to be unaffected after initial treatment with the ACE inhibitor captopril; however, with exposure to captopril monotherapy over a period of 6 months, angiotensin-(1–7) levels increased.36 Furthermore, few studies have examined plasma ACE2 activity or urinary ACE2 levels in patients who have received long-term treatment with RAAS inhibitors. In cross-sectional studies involving patients with heart failure,37 atrial fibrillation,38 aortic stenosis,39 and coronary artery disease,40 plasma ACE2 activity was not higher among patients who were taking ACE inhibitors or ARBs than among untreated patients. In a longitudinal cohort study involving Japanese patients with hypertension, urinary ACE2 levels were higher among patients who received long-term treatment with the ARB olmesartan than among untreated control patients, but that association was not observed with the ACE inhibitor enalapril or with other ARBs (losartan, candesartan, valsartan, and telmisartan).41 Previous treatment with ACE inhibitors was associated with increased intestinal messenger RNA levels of ACE2 in one study, but that association was not observed with ARBs25; data are lacking regarding the effects of RAAS inhibitors on lung-specific expression of ACE2.

These seemingly conflicting data indicate the complexity underlying RAAS responses to pathway modulators and reinforce the concept that findings from preclinical models may not readily translate to human physiology. Such data do suggest that effects on ACE2 should not be assumed to be uniform across RAAS inhibitors or even in...
response to therapies within a given drug class. It is important to note that the plasma ACE2 level may not be a reliable indicator of the activity of the full-length membrane-bound form, in part because ACE2 is shed from the membrane, a process that appears to be separately regulated by an endogenous inhibitor. In addition to the degree of expression, the biologic relevance of ACE2 may vary according to tissue and clinical state. Unfortunately, data showing the effects of ACE inhibitors, ARBs, and other RAAS inhibitors on lung-specific expression of ACE2 in experimental animal models and in humans are lacking. Furthermore, even if RAAS inhibitors modify ACE2 levels or activity (or both) in target tissue beds, clinical data are lacking to indicate whether this would in turn facilitate greater engagement and entry of SARS-CoV-2 spike protein. Further mechanistic studies in humans are needed to better define the unique interplay between SARS-CoV-2 and the RAAS network.

**Potential for Benefit Rather Than Harm of RAAS Blockers in Covid-19**

SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently down-regulate ACE2 expression such that the enzyme is unable to exert protective effects in organs. It has been postulated but unproven that unabated angiotensin II activity may be in part responsible for organ injury in Covid-19. After the initial engagement of SARS-CoV-2 spike protein, there is subsequent down-regulation of ACE2 abundance.
Continued viral infection and replication contribute to reduced membrane ACE2 expression, at least in vitro in cultured cells. Down-regulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial endotoxin and may result in unopposed angiotensin II accumulation and local RAAS activation. Indeed, in experimental mouse models, exposure to SARS-CoV-1 spike protein induced acute lung injury, which is limited by RAAS blockade. Other mouse models have suggested that dysregulation of ACE2 may mediate acute lung injury that is secondary to virulent strains of influenza and respiratory syncytial virus. In a small study, patients with Covid-19 appeared to have elevated levels of plasma angiotensin II, which were in turn correlated with total viral load and degree of lung injury. Restoration of ACE2 through the administration of recombinant ACE2 appeared to reverse this devastating lung-injury process in preclinical models of other viral infections and safely reduced angiotensin II levels in a phase 2 trial evaluating acute respiratory distress syndrome in humans.

Dysregulated ACE2 may theoretically also attenuate cardioprotection in the context of myocardial involvement and abnormal pulmonary hemodynamics in Covid-19. Markers of myocardial injury have been shown to be elevated during the disease course of Covid-19 and to increase rapidly with clinical deterioration and preceding death. Many viruses are cardiotropic, and subclinical viral myocarditis is commonly seen in viremia associated with a wide range of infectious agents. ACE2 has a well-recognized role in myocardial recovery and injury response; in one study, ACE2 knockout in animal models contributed to adverse left ventricular remodeling in response to acute injury driven by angiotensin II. In autopsies of patients who died from SARS, 35% of heart samples showed the presence of viral RNA, which in turn was associated with reduced ACE2 protein expression. Administration of recombinant ACE2 normalizes angiotensin II levels in human explanted hearts with dilated cardiomyopathy. These hypotheses have prompted trials to test whether the provision of recombinant ACE2 protein may be beneficial in restoring balance to the RAAS network and potentially preventing organ injury (ClinicalTrials.gov number, NCT04287686). In addition, paired trials of losartan as a treatment for Covid-19 are being conducted among patients who have not previously received treatment with a RAAS inhibitor and are either hospitalized (NCT04312009) or not hospitalized (NCT04311177).

**Maintenance of RAAS Inhibitors With Known or Suspected Covid-19**

Despite these theoretical uncertainties regarding whether pharmacologic regulation of ACE2 may influence the infectivity of SARS-CoV-2, there is clear potential for harm related to the withdrawal of RAAS inhibitors in patients in otherwise stable condition. Covid-19 is particularly severe in patients with underlying cardiovascular diseases, and in many of these patients, active myocardial injury, myocardial stress, and cardiomyopathy develop during the course of illness. RAAS inhibitors have established benefits in protecting the kidney and myocardium, and their withdrawal may risk clinical decompensation in high-risk patients.

Although rates of heart failure have been infrequently reported in epidemiologic reports from China to date, the prevalence of heart failure among critically ill patients with Covid-19 in the United States may be high (>40%). In the Quinapril Heart Failure Trial, among patients with chronic symptomatic heart failure, withdrawal of quinapril resulted in a progressive decline in clinical status. In the TRED-HF trial, among asymptomatic patients with heart failure with recovered left ventricular ejection fraction, the phased withdrawal of medical therapy (including RAAS inhibitors) resulted in rapid relapse of dilated cardiomyopathy. In addition, RAAS inhibitors are a cornerstone of therapy after myocardial infarction: maintenance of therapy in the days to weeks after the index event has been shown to reduce early mortality. Among patients with unstable clinical status, myocardial injury associated with Covid-19 may pose even higher early risks after withdrawal of RAAS inhibitors.

Withdrawal of RAAS inhibitors that are being administered for the management of hypertension may be less risky than withdrawal of RAAS inhibitors that are being administered for conditions in which they are considered guideline-
directed therapy but may be associated with other challenges. Switching from a RAAS inhibitor to another antihypertensive therapy in a stable ambulatory patient may require careful follow-up to avoid rebound increases in blood pressure. In addition, selection of dose-equivalent antihypertensive therapies may be challenging in practice and may be patient-dependent. Even small and short-lived periods of blood pressure instability after a therapeutic change have been associated with excess cardiovascular risk.64-66 This may be an especially important consideration in patients with Covid-19, which appears to result in a state of RAAS activation,64 and in settings (e.g., China) where baseline blood-pressure control is infrequently reached at the population level.11,12

The effects of withdrawing RAAS inhibitors or switching treatments are uncertain among patients with chronic kidney disease. Although reported rates of chronic kidney disease appear to be low among hospitalized patients with Covid-19 in China (1 to 3%) (Table S1), the prevalence may be higher among patients who are critically ill and among those in other geographic regions.59 Many patients have varying degrees of acute kidney injury during illness.14,67,68 For these high-risk patients, individualized treatment decisions regarding the maintenance of RAAS inhibitors that are guided by hemodynamic status, renal function, and clinical stability are recommended.

On the basis of the available evidence, we think that, despite the theoretical concerns and uncertainty regarding the effect of RAAS inhibitors on ACE2 and the way in which these drugs might affect the propensity for or severity of Covid-19, RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have Covid-19 (see text box), a position now supported by multiple specialty societies (Table S2). Although additional data may further inform the treatment of high-risk patients with Covid-19, clinicians need to be cognizant of the unintended consequences of prematurely discontinuing proven therapies in response to hypothetical concerns that may be based on incomplete experimental evidence.59

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Key Points Related to the Interplay between Covid-19 and the Renin–Angiotensin–Aldosterone System

- ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic.
- Select preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with Covid-19.
- Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19.
- Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19.
- Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes.
- Until further data are available, we think that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or with Covid-19.
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