SPECIAL REPORT

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

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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.

Given the common use of ACE inhibitors and ARBs worldwide, guidance on the use of these drugs in patients with Covid-19 is urgently needed. Here, we highlight that the data in humans are too limited to support or refute these hypotheses and concerns. Specifically, we discuss the uncertain effects of RAAS blockers on ACE2 levels and activity in humans, and we propose an alternative hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. We also explicitly raise the concern that withdrawal of RAAS inhibitors may be harmful in certain high-risk patients with known or suspected Covid-19.

COVID-19 AND OLDER ADULTS WITH COEXISTING CONDITIONS

Initial reports[5-8] 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%[9]; however, this estimate appears to be lower than the estimated prevalence of hypertension seen with other viral infections[10] 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.

UNCERTAIN EFFECTS OF RAAS INHIBITORS ON ACE2 IN HUMANS

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 injury), the lung alveolar epithelial cells.[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 conditions[18] 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 tissue[21,26-34] 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 ARBs[25]; 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

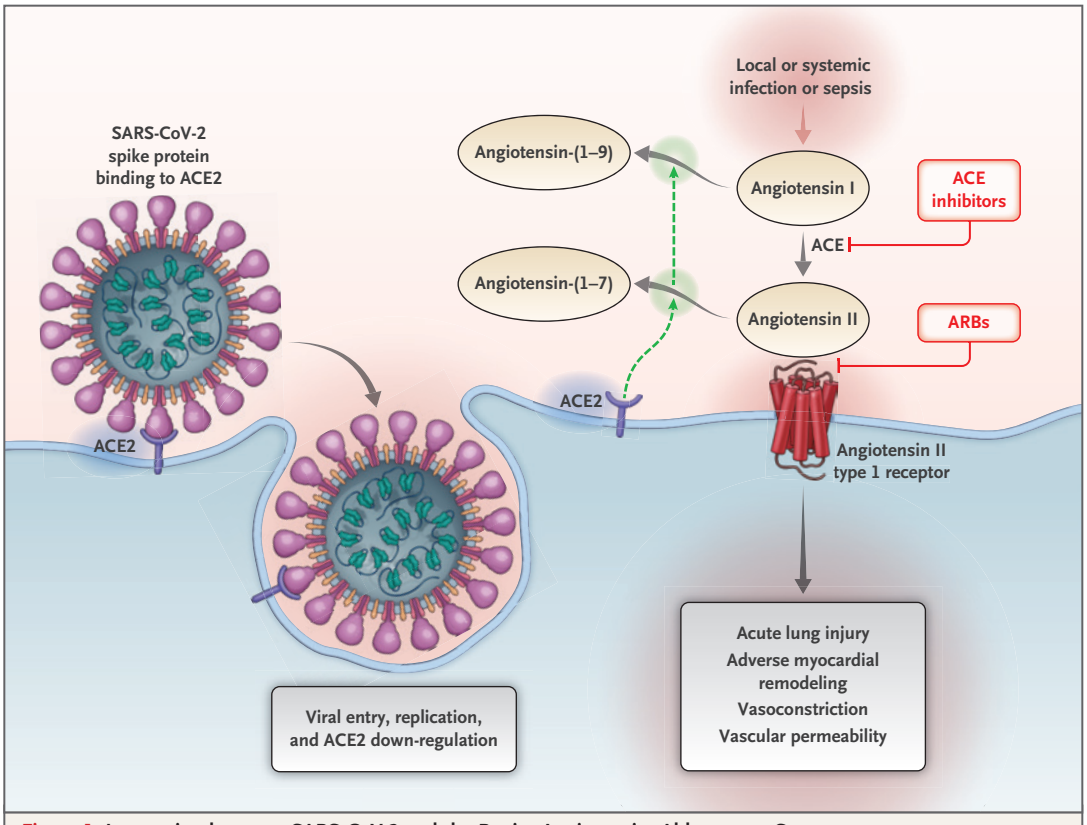

Figure 1. Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.

Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

response to therapies within a given drug class.[41] 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.[42] 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.[43,44] After the initial engagement of SARS-CoV-2 spike protein, there is subsequent down-regulation of ACE2 abundance

on cell surfaces.[45] Continued viral infection and replication contribute to reduced membrane ACE2 expression, at least in vitro in cultured cells.[46] Down-regulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial endotoxin[47] 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.[45] Other mouse models have suggested that dysregulation of ACE2 may mediate acute lung injury that is secondary to virulent strains of influenza[48,49] and respiratory syncytial virus.[50] 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.[44] Restoration of ACE2 through the administration of recombinant ACE2 appeared to reverse this devastating lung-injury process in preclinical models of other viral infections[49,50] and safely reduced angiotensin II levels in a phase 2 trial evaluating acute respiratory distress syndrome in humans.[51]

Dysregulated ACE2 may theoretically also attenuate cardioprotection in the context of myocardial involvement and abnormal pulmonary hemodynamics[52,53] in Covid-19. Markers of myocardial injury have been shown to be elevated during the disease course of Covid-19[54] and to increase rapidly with clinical deterioration and preceding death.[14] 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.[55] 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.[56] Administration of recombinant ACE2 normalizes angiotensin II levels in human explanted hearts with dilated cardiomyopathy.[57] 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,[9] and in many of these patients, active myocardial injury,[14,54,58-60] myocardial stress,[59] and cardiomyopathy[59] 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%).[59] In the Quinapril Heart Failure Trial, among patients with chronic symptomatic heart failure, withdrawal of quinapril resulted in a progressive decline in clinical status.[61] 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.[62] 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.[63] 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,[44] 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.[69]

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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