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Angiotensin-Converting Enzyme 2 and Antihypertensives (Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors) in Coronavirus Disease 2019

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, is being defined as the worst pandemic disease of modern times. Several professional health organizations have published position papers stating that there is no evidence to change the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the management of elevated blood pressure in the context of avoiding or treating COVID-19 infection. In this article, we review the evidence on the relationship between the renin-angiotensin-aldosterone system and COVID-19 infection. In agreement with current guidelines, patients with hypertension should continue taking antihypertensive medications as prescribed without interruption. Because ACEIs and ARBs are also used to retard the progression of chronic kidney disease, we suggest that these recommendations also apply to the use of these agents in chronic kidney disease. No differences generally exist between ARBs and ACEIs in terms of efficacy in decreasing blood pressure and improving other outcomes, such as all-cause mortality, cardiovascular mortality, myocardial infarction, heart failure, stroke, and end-stage renal disease. The ACEIs are associated with cough secondary to accumulation of bradykinin and angioedema, and withdrawal rates due to adverse events are lower with ARBs. Given their equal efficacy but fewer adverse events, ARBs could potentially be a more favorable treatment option in patients with COVID-19 at higher risk for severe forms of disease.

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The global public health crisis triggered by coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] is being defined as the worst pandemic disease of modern times.[2,3] According to the recent statistics from the World Health Organization, this novel coronavirus has already infected millions of people worldwide, causing over 125,000 deaths by mid April 2020, and these numbers unfortunately continue to increase.[4] Alarmingly, 15% to 20% (~10%-15% severe and ~3%-5% critical) of SARS-CoV-2—positive individuals are likely to progress toward a severe form of disease characterized by interstitial pneumonia with the potential to evolve into acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, and death.[5] The high numbers of patients requiring sub-intensive or intensive care can overwhelm many health care infrastructures, even in highly developed countries.[6]

The exponential growth of the contagion around the world has contributed to heightened speculations and concerns over whether 2 commonly used antihypertensive (anti-HTN) drugs—angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin

receptor blockers (ARBs)—also used for cardiovascular (CV) diseases (CVDs) and chronic kidney disease (CKD) may exert either deleterious or beneficial effects in patients with COVID-19 compared with other drugs used to reduce blood pressure (BP) or treat heart failure (HF).[7]

Several professional health organizations have published position papers stating that there is no evidence to change the use of ACEIs or ARBs for the management of elevated BP in the context of avoiding or treating COVID-19 infection (Table). In this article, we review the evidence on the relationship between the renin-angiotensin-aldosterone system (RAAS) and COVID-19 infection.

COVID-19 AND ACE2: ORIGIN OF THE SPECULATION

Health care professionals, physicians, researchers, and patients are actively debating the potential influence of ACEIs and ARBs on poor outcomes in patients with COVID-19 based mainly on the evidence that ACE2 is a functional receptor for coronaviruses, including SARS-CoV-2.[9] This receptor is located on the surface of type II alveolar cells and on lymphocytes, thus explaining the prevalent lung involvement (ie, interstitial pneumonia and ARDS) and lymphopenia.

Moreover, ACE2 is observed on the surface of many other cell types, such as those of the heart, kidney, liver, gastrointestinal tract (especially the esophagus, stomach, colon, ileum, and rectum), and bladder (Figure 1).[10-12]

Kuba et al[13] first showed that ACE2 is essential for SARS-CoV infection, acting as its effective host receptor in vivo. The SARS-CoV infection, through binding of viral spike (S) protein to ACE2, seems to reduce receptor expression. Injecting SARS-CoV S protein into mice induces acute lung injury (ALI) in vivo, which can be mitigated by blocking the RAAS. Wrapp et al[14] recently reported that SARS-CoV-2 binds to ACE2 with 10- to 20-fold higher affinity compared with SARS-CoV. Specifically, the S protein of SARS-CoV-2 virus binds to the catalytic domain of ACE2, inducing internalization of the virus by the cell.

In brief, the RAAS is the central regulatory system for BP control.[15] In addition, RAAS activation plays a crucial pathogenic role in HTN through hemodynamic actions and cytokines and intracellular signaling pathways, which ultimately promote many adverse cellular processes implicated in systemic damage.[15] In the RAAS, angiotensin (Ang) I is converted to Ang II by ACE. Angiotensin II mediates vasoconstrictive,

TABLE. Professional Societies' Recommendations Following the Statements on the Issue[a]		
Professional society	Date of publication	
European Society of Hypertension	March 12, 2020	☑
European Society of Cardiology Council on Hypertension	March 13, 2020	☑
Hypertension Canada	March 13, 2020	☑
Canadian Cardiovascular Society	March 15, 2020	☑ ☑
The Renal Association, United Kingdom	March 15, 2020	☑
International Society of Hypertension	March 16, 2020	☑
American College of Physicians	March 16, 2020	☑
Spanish Society of Hypertension	March 16, 2020	☑
American Heart Association	March 17, 2020	☑
Heart Failure Society of America	March 17, 2020	☑
American College of Cardiology	March 17, 2020	☑
European Renal Association, European Dialysis and Transplant Association	March 17, 2020	☑
High Blood Pressure Research Council of Australia	March 18, 2020	☑

[a]All the professional societies recommended continuing angiotensin receptor blockers and angiotensin-converting enzyme inhibitors. The Canadian Cardiovascular Society also recommended continuing angiotensin receptor neprilysin inhibitors.
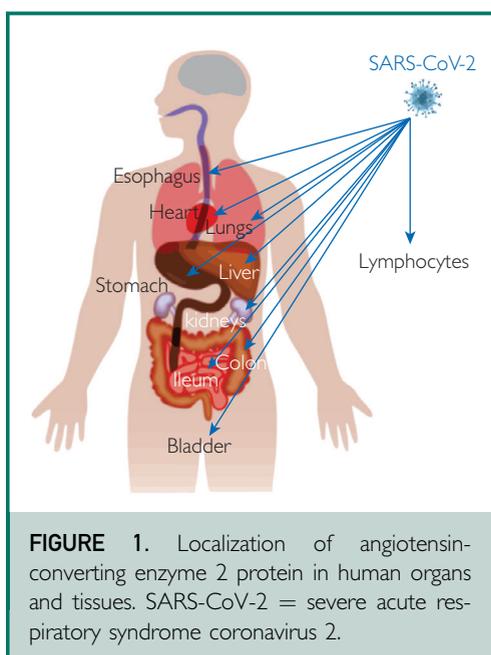Adapted from NephJC.[8] Used with permission.

FIGURE 1. Localization of angiotensin-converting enzyme 2 protein in human organs and tissues. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

proinflammatory, and pro-oxidative effects through agonism at Ang II type 1 receptor (AT$_1$R).[16] Angiotensin-converting enzyme 2 converts Ang II to Ang 1-7, which finally binds to Mas receptor (MasR) and mediates many beneficial actions, including vasodilation and anti-inflammatory, antioxidant, and antiapoptotic effects.[16] Thus, the ACE2/Ang 1-7/MasR axis has opposite actions to the ACE/AngII/AT$_1$R axis (Figure 2).
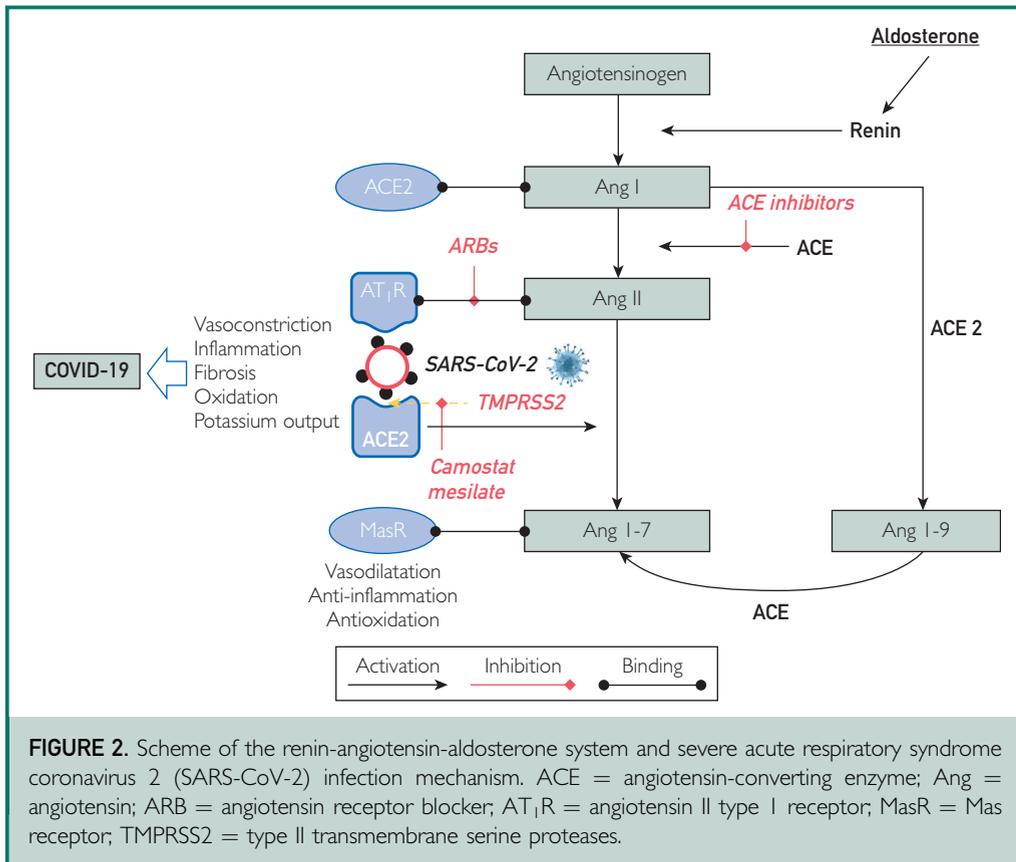
Angiotensin-converting enzyme 2, a homologue of ACE, is an integral cell membrane protein with a catalytic domain on the extracellular surface exposed to vasoactive peptides.[17] It is a monocarboxypeptidase whose major role is converting Ang II to Ang 1-7,[17] with vasodilatory and antifibrotic actions[18] when it activates MasR.[19] Moreover, ACE2 also converts Ang I to Ang 1-9, which can be further converted by ACE into Ang 1-7. Thus, ACE2 limits the adverse vasoconstrictor and profibrotic effects of Ang II through its degradation and by counteracting its actions through the formation of Ang 1-7. The high expression of ACE2 in heart, type II alveolar cells, capillary endothelium,[20] and enterocytes[21] demonstrates its essential role in the CV and immune systems,[21] being principally involved in heart

function and the development of HTN and complications of diabetes mellitus (DM).

As previously discussed, SARS-CoV-2 penetrates the cell through ACE2 but also necessitates type II transmembrane serine proteases (TMPRSS2) for effective priming of viral S protein. The binding of coronavirus S protein to ACE2 triggers a conformational change in the S protein, allowing for proteolytic digestion by TMPRSS2, which enables viral and cell membrane fusion.[22] This was recently confirmed by the evidence that camostat mesylate, a protease TMPRSS2 inhibitor, blocks viral entry and may be a promising drug for SARS-CoV-2 infection.[22,23] Because ACE2 is a functional receptor for SARS-CoV-2, many health care professionals have begun to reconsider the safety and effects of anti-HTN therapy with ACEIs or ARBs in patients during the COVID-19 outbreak; and despite statements by medical organizations, they began to question whether patients with COVID-19 and HTN maintained on ACEIs or ARBs to decrease BP values (or for conditions such as CVD and CKD) should change to another anti-HTN pharmacological agent.[24] Such considerations contributed to the current controversy.

USE OF ARBS OR ACEIS IN PATIENTS AT HIGH RISK FOR SEVERE COVID-19: DELETERIOUS OR BENEFICIAL?

It has been hypothesized that increased levels of ACE2 may facilitate COVID-19 infection such that administering ARBs or ACEIs might increase the risk of severe and fatal COVID-19.[25-27] As discussed later in this section, this premise is based in part on the findings in some, but not all, studies that ARBs and ACEIs may increase ACE2 levels. According to the most recent studies on COVID-19, it seems that HTN is one of the most important factors associated with poor prognosis at an early stage of COVID-19 infection.[28-33] However, HTN has also been found to be associated with decreased baseline levels of ACE2 expression. Unfortunately, most of these early COVID-19 studies have not been adjusted for age or other comorbidities. The last report on the

FIGURE 2. Scheme of the renin-angiotensin-aldosterone system and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection mechanism. ACE = angiotensin-converting enzyme; Ang = angiotensin; ARB = angiotensin receptor blocker; AT_1R = angiotensin II type 1 receptor; MasR = Mas receptor; TMPRSS2 = type II transmembrane serine proteases.

characteristics of deceased COVID-19—positive patients in Italy officially released on March 20, 2020, by the Italian Ministry of Health through the National Institute of Health (Istituto Superiore di Sanità) showed that the most common concurrent medical comorbidities observed were arterial HTN (73.8%; 355 of 481), DM (33.9%; 163 of 481), ischemic cardiopathy (30.1%; 145 of 481), and atrial fibrillation (22%; 106 of 481).[34] Before hospitalization, 36% (173 of 481) of patients with fatal COVID-19 were taking ACEIs, and 16% (77 of 481) were taking ARBs (odds ratio, 2.26; 95% CI, 1.66-3.09; P<.001). Nevertheless, these numbers are preliminary and may not precisely reflect adjusted differences in risk. It is virtually impossible to precisely identify all medical therapies before admission from medical records.[34] Moreover, patients with elevated BP on admission may be noted to have a history of chronic HTN in their medical record, and such coding

may reflect provider biases from the current infectious illness. The median age of SARS-CoV-2—positive patients who died was 78.5 years (median, 80 years; range, 31-103 years; interquartile range, 73 to 85 years). Because HTN prevalence increases in parallel with aging, this pattern may represent the expected prevalence for the given age group. Therefore, although the number of fatal COVID-19—positive patients treated with ACEIs was more than twice the number of those treated with ARBs, one cannot definitely conclude risks or benefits of these therapies due to confounding variables of age, HTN, and impact of yet-unidentified comorbidities on outcome with the COVID-19 pandemic.

In a recent study in which potential drugs targeting SARS-CoV-2 were evaluated, the authors reported that ARBs (eg, irbesartan) may associate with some human coronavirus-associated host proteins in the human interactome.[35] Irbesartan targets the

SLC10A1 gene (solute carrier family 10 member 1), which interacts with the *C11orf74* gene, a potential transcriptional repressor that interacts with the nonstructural protein 10 of SARS-CoV and participates in CoV replication fidelity.[36]

Crackower et al[37] reported that disruption of ACE2 results in increased Ang II levels and impaired cardiac function, whereas other authors reported that ACE2 overexpression reduced left ventricular hypertrophy and myocardial fibrosis in HTN rats.[38] Lower cardiac ACE2 concentrations are observed in HTN,[38,39] CVD associated with DM,[40] and Ang II—induced cardiac dysfunction,[41] suggesting that augmenting ACE2 could have beneficial therapeutic effects on the CV system. In numerous studies performed in animal models, ACEIs and ARBs may increase ACE2 expression or levels,[42-46] although other authors failed to observe such increases.[47,48] Importantly, no studies have reported an increase in circulating ACE2 levels or expression thus far,[49,50] and increased expression would not necessarily imply increased risk of infection or disease severity.

Deshotels et al[51] investigated the compensatory reduction of ACE2 expression and activity in response to Ang II—mediated HTN. Elevated levels of Ang II decreased ACE2 activity on the cell surface via an AT_1R-dependent internalization mechanism.[51] Moreover, in vitro treatment of HEK293T cells with Ang II enhanced ACE2 ubiquitination also mediated by AT_1R, which ultimately stimulates ACE2 lysosomal degradation (which might prevent interaction of the SARS-Co-V2 with ACE2 catalytic site).[51] This is reported to be prevented by the AT_1R antagonist losartan, which may block internalization, proteolytic degradation, and ubiquitination of ACE2.[51] As such, this latter pathway represents another mechanism by which ACEIs or ARBs could prevent COVID-19 viral entry. If the viral protein interaction with ACE2 is reduced in the presence of stabilized ACE2-AT_1R complexes, then ARBs could prove beneficial by stabilizing ACE2-AT_1R interaction and preventing viral

protein—ACE2 interaction and internalization. Based on this mechanism of action, Gurwitz[52] recently suggested ARBs (losartan and telmisartan) as a tentative therapy for patients with COVID-19 before the development of ALI/acute respiratory failure. However, it remains unknown whether preventing ACE2 internalization would be effective at attenuating infections by SARS coronaviruses, and further studies are urgently needed to clarify this mechanism.

Interestingly, Liu et al[53] reported that serum Ang II levels were significantly higher in COVID-19—infected individuals than in noninfected individuals and were linearly associated with viral load and lung damage. It is suspected that Ang II, via pulmonary vasoconstriction leading to decreased flow and ventilation/perfusion mismatch and via increased vascular permeability and its proinflammatory and pro-oxidative properties, may induce or perpetuate ARDS in a variety of pathologic disorders.[54] The findings by Liu et al[53] support the hypothesis that elevated levels of Ang II may foster ARDS in patients with COVID-19. Nevertheless, this study has important limitations because it was performed in a limited sample and, as such, requires confirmation.[53]

The role of RAAS peptides in ALI has also been investigated in other patients with ARDS (diagnosed within 24 hours) by using a targeted metabolomics approach.[55] Concentrations of Ang I were significantly higher in nonsurvivors at study entry and at 72 hours, whereas ARDS survival was associated with lower Ang I levels but higher Ang 1-9 concentrations (a precursor to Ang 1-7). Survivors showed a significantly higher average Ang 1-9/Ang I and Ang 1-7/Ang I ratios, which suggests that ACE2 activity is higher in survivors than in nonsurvivors.[55] Therefore, ACE2 activities seem to be reduced in patients who succumb to ARDS.

Farther downstream, high levels of Ang II, which may be due to attenuated ACE2, such as that potentially caused by the SARS-CoV-2 interaction with ACE2, stimulate increased production of aldosterone. Aldosterone, in turn, increases ACE activity, inducing further production of Ang II,

leading to a potentially vicious cycle that perpetuates ARDS.[56] Moreover, aldosterone decreases expression of the MasR, minimizing the antagonizing benefits of any Ang 1-7 produced by ACE2. As such, aldosterone receptor blockers or aldosterone synthase inhibitors may have a potential role in COVID-19 therapy; however, careful evaluation of any influence on corticosteroid synthesis and signaling is required.[56]

Because SARS-CoV-2 invades alveolar epithelial cells, respiratory symptoms are often the most common reported and are reported to be more severe in patients with CVD.[24] This might be associated with higher ACE2 levels, which has been suggested to be increased in patients maintained on RAAS inhibitors.[24] However, in a study conducted in rats by Xie et al,[57] ACE2 expression dramatically decreased with age in both sexes, whereas older male rats also had lower ACE2 concentrations than did older female rats. Whether such altered profiles of ACE2 are similarly observed in humans, or ACE2 expression is altered in disease, requires further investigation.

It has also been recently reported that recombinant ACE2 administration in mice with ARDS protects from development of ALI and severe lung disease, thus strongly suggesting that ACE2 mediates a cytoprotective role in ALI[58]; whether such effects are also observed in ARDS caused by COVID-19 is unknown at this time. Thus, extrapolating from these and previously discussed findings, one may speculate that the administration of recombinant ACE2 or its product, Ang 1-7, which directly opposes Ang II, may offer potentially beneficial effects in SARS-CoV-2–associated ARDS.[58] Moreover, specifically with SARS-CoV-2, recombinant ACE2 may serve the role as a competitive inhibitor, binding up viral particles that would otherwise bind to membrane-bound ACE2, thus decreasing viral load and protecting/increasing residual endogenous membrane-bound ACE2. Studies that directly administer recombinant ACE2 to mice in conjunction with those that use ACE2 knockout mice demonstrated that ACE2 protects murine lungs from ARDS. Such an approach in preclinical studies of ARDS specifically due to COVID-19 is especially important and timely.

CONCLUSIONS AND POTENTIAL RECOMMENDATIONS

Binding of SARS-CoV-2 to ACE2 may attenuate residual ACE2 activity, further tipping the ACE/ACE2 balance to a predominant ACE/Ang II/AT$_1$ axis signaling, in which Ang II may then foster pulmonary vasoconstriction and inflammatory and oxidative organ damage, ultimately progressing toward ALI/ARDS.[54] We speculate that RAAS dysregulation may play a central role in the pathophysiology of COVID-19–associated ALI/ARDS, but definitive studies that address this issue are needed. Whether RAAS modulation may have a beneficial effect in selected patients with severe COVID-19 at risk for ALI/ARDS is entirely unknown at the present time. Moreover, the effects of other agents that may interrupt the RAAS by inhibiting renin, such as renin inhibitors and β-blockers, would also be of interest regarding their effects on COVID-19 and attendant ALI.

In agreement with current guidelines, patients with HTN should continue taking anti-HTN medications as prescribed without interruption. Current evidence shows that RAAS inhibitors, ie, ACEIs and ARBs, significantly reduce mortality in CVD, reduce the progression of CKD, and are the cornerstone of HF and HTN treatment. Therapy with ACEIs or ARBs should be maintained or initiated, as indicated, in patients with HF, HTN, or myocardial infarction regardless of SARS-CoV-2 status. No differences exist between ARBs and ACEIs in terms of efficacy to decrease BP and improve other outcomes, such as all-cause mortality, CVD mortality, myocardial infarction, HF, stroke, and end-stage renal disease.[59] The ACEIs are associated with cough secondary to accumulation of bradykinin and angioedema, whereas withdrawal rates due to adverse events are lower with ARBs.[59] Given the equal efficacy but fewer adverse events, ARBs could potentially be a more favorable treatment option in patients

with COVID-19 at higher risk for severe forms of disease. Risk factors related to worse prognosis in patients with COVID-19 include age (>65 years), current smoker, HTN, diabetes, coronary heart disease, atrial fibrillation, chronic obstructive lung disease, CKD, cancer, and obesity (body mass index >30 [calculated as the weight in kilograms divided by the height in meters squared]). To further evaluate the role of RAAS modulation in COVID-19, data sets should be analyzed to investigate whether use of ACEIs and ARBs on admission could be associated with ALI/ARDS or survival/mortality in patients with DM, HTN, and CVD.

Finally, the potential utility of alternative therapies, such as recombinant ACE2, Ang 1-7 peptides, ang II receptor inhibitors, and, potentially, aldosterone synthase inhibitors, for preventing or mitigating ALI caused by viruses is unknown and requires consideration and investigation for a disease for which current care is entirely supportive.

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