

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors and Coronavirus Disease 2019 (COVID-19)

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Abstract: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic. The angiotensin-converting enzyme 2 (ACE2) has been proven to be used by SARS-CoV-2 for host cell entry. Considering that angiotensin receptor blockers and ACE inhibitors (ACEIs) upregulate the expression of ACE2 in animal studies, there may be a concern about whether these drugs may increase COVID-19 susceptibility and severity. Recently, there has been a debate among clinicians about whether to continue or to stop ACEIs and angiotensin receptor blockers in the context of COVID-19. Also, some media outlets and health systems have called for the discontinuation of these drugs in the context of suspected COVID-19. This has necessitated an urgent release of guidance on the use of such medications in COVID-19 patients. To date, multiple theories relating to the pure effects of renin-angiotensin-aldosterone system (RAAS) inhibitors on COVID-19 infections have been postulated. Favorable effects include blocking the ACE2 receptors, preventing viral entry into the heart and lungs, and protecting against lung injury in COVID-19. Adverse effects include a possible retrograde feedback mechanism that upregulates ACE2 receptors. This review provides greater insight into the role of the RAAS axis in acute lung injury and the effects of RAAS inhibitors on SARS-CoVs. The hypothesis that RAAS inhibitors facilitate viral insertion and the alternative hypothesis of the beneficial role of these drugs are discussed. Up-to-date published data concerning the RAAS inhibitors and COVID-19 are summarized.

Key Words: angiotensin-converting-enzyme inhibitors, angiotensin-converting enzyme 2 receptor, angiotensin receptor blockers, COVID-19

Coronavirus disease 2019 (COVID-19) is a pandemic disease caused by a novel coronavirus called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It is an enveloped RNA virus found in wildlife and humans. It was discovered for the first time in Wuhan City, Hubei Province, China. On December 31, 2019, the disease was initially reported to the World Health

Organization.¹ The disease has a clinical spectrum ranging from asymptomatic upper respiratory tract infections to severe pneumonia linked with acute respiratory distress syndrome (ARDS).² On January 30, 2020, the World Health Organization declared the COVID-19 epidemic a global health emergency.³

The early reports from China revealed that old age, diabetes mellitus, hypertension, and cardiovascular disease were prevalent in COVID-19-infected patients, and patients with these comorbid conditions seemed to have higher case fatality rates.^{4,5} Patients with these comorbidities were admitted into intensive care units, required mechanical ventilation, and died more often than patients without these comorbidities. In a study that included 1099 patients with confirmed COVID-19 infection, many of the 173 individuals who developed severe disease had comorbidities, including hypertension (23.7%), diabetes mellitus (16.2%), coronary artery disease (5.8%), and cardiovascular diseases (2.3%).⁶ In another study, many of the 140 patients admitted to the hospital with COVID-19 infection had hypertension (30%) or diabetes mellitus (12%).⁷ In a third study done by Zhou et al, 191 confirmed COVID-19 cases in Wuhan, China were enrolled in a retrospective, multicenter cohort study that found that hypertension was associated with a hazard ratio of 3.05 for in-hospital mortality.⁸ This has raised concerns about the influence of hypertension and antihypertensive medications on the infectivity and severity of COVID-19.

ACE2 and the Renin-Angiotensin-Aldosterone System (RAAS)

Angiotensin-converting enzyme 2 (ACE2), is a type I transmembrane aminopeptidase that is mainly anchored at the apical surface

Key Points

- There is no compelling experimental or clinical evidence that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors either increase vulnerability to severe acute respiratory syndrome coronavirus 2 or aggravate coronavirus disease 2019 severity and outcomes, whereas the protective role of angiotensin-converting enzyme 2 in the lung is supported by ample evidence.
- Hypertensive patients using angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers should continue these medications during the coronavirus disease 2019 pandemic.

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of cells of the gastrointestinal system, heart, kidneys, blood vessels, and in type II alveolar cells of the lungs⁹ (Fig.). In addition to the membrane-bound form, there are soluble forms in the plasma and urine. ACE2 receptors are profoundly displayed in the heart and lungs. ACE2 was first discovered in 2000 as an ACE1 homolog that shares approximately 42% homology with ACE1. ACE2 is capable of producing a lung-protective factor, angiotensin 1–7, from angiotensin II. ACE2 also converts angiotensin I to angiotensin 1–9. The affinity of ACE2 is higher for angiotensin II than for angiotensin I degradation¹⁰ (Fig.). The ACE2/angiotensin 1–7 axis counterbalances the ACE1/Angiotensin II axis.¹¹ Angiotensin II causes strong vasoconstriction, proinflammatory effects, and profibrotic effects, whereas angiotensin 1–7 shows antifibrotic, antiproliferative, vasodilatory, diuretic, and natriuretic effects. The ACE2-angiotensin 1–7 axis protects the cardiovascular system against heart failure, arrhythmia, and thrombosis. It also prevents myocardial hypertrophy and reduces vascular dysfunction associated with the metabolic syndrome.¹² The equilibrium between these two opposing parts of the RAAS, at least partially, determines whether tissue injury may occur in response to stimuli, particularly in the heart and kidneys. Normally, the circulatory level of soluble ACE2 is low and its role in the lungs is minimal.¹³

SARS-CoV-2 and ACE2

Research has revealed that the ACE2 receptor is used by SARS-CoV-2 as a receptor to enter host cells¹⁴ (Fig.). Both types of SARS coronaviruses have four structural proteins: membrane, envelope, nucleocapsid, and spike proteins. Nucleocapsid, membrane, and envelope proteins play a role in viral replication, viral structure, and viral-induced host responses, among other roles.¹⁵ The spike protein, S-protein, is essential for fastening to and invading host cells. The S-protein merging with ACE2, along with proteolytic splitting of ACE2 by transmembrane serine protease 2, allows viral entry into host cells, viral replication, and cell-to-cell transmission.¹⁴ The expression of ACE2 receptors correlates with susceptibility to SARS-CoV infection *in vitro*.¹⁶ Consequently, it has been postulated that increased expression of ACE2 receptors may lead to an increased risk of infection of the lung (and possibly

other tissues) by SARS-CoV-2. ACE2 receptor is also the receptor for the SARS-CoV that was responsible for the 2002–2004 SARS epidemic; however, the SARS-CoV-2 affinity for ACE2 is 10 to 20 times higher than that of SARS-CoV, which may underlie its immense transmission ability and the differences between the two epidemics.

Pharmacology of ACEIs/ARBs and the Role of ACE2

The main pharmacological effects of ACE inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are to inhibit ACE1 and block angiotensin II type 1 receptor (AT1), respectively (Fig.). ACEIs only partially affect the production of angiotensin II from angiotensin I, because 40% of angiotensin II production does not occur in the ACE pathway.¹⁷ As a result of producing angiotensin II, ACE1 levels are in turn reduced by a negative feedback loop because of the raised angiotensin II levels. This decrease in ACE1 allows the angiotensin II to be metabolized by ACE 2 to angiotensin 1–7.¹⁸ Angiotensin 1–7 works on angiotensin II receptors to produce antifibrotic, antiproliferative, vasodilatory, diuretic, and natriuretic effects.

Angiotensin mediates its effects through two receptors. The AT1 receptor mediates the vasoconstrictive and aldosterone-stimulating effects of angiotensin II. The action of angiotensin II at the AT2 receptor tends to antagonize the pressor effects of the AT1 receptor. ARBs specifically block the action of angiotensin II at the AT1 receptor and thereby block the arteriolar contraction and sodium-retention effects of the RAAS.

Hypothesized Harmful Effects of RAAS Inhibitors in COVID-19

As mentioned above, ACE2 is used by SARS-CoV-2 as a receptor to enter host cells. Increased ACE2 expression due to upregulation leads to enhanced binding sites for SARS-CoV-2 and consequently increased liability for COVID-19 infection (Fig.). Animal models indicate that ARBs can increase the expression of messenger RNA (mRNA) or protein levels of ACE2 in animals with heart diseases¹⁹ and chronic kidney diseases such as

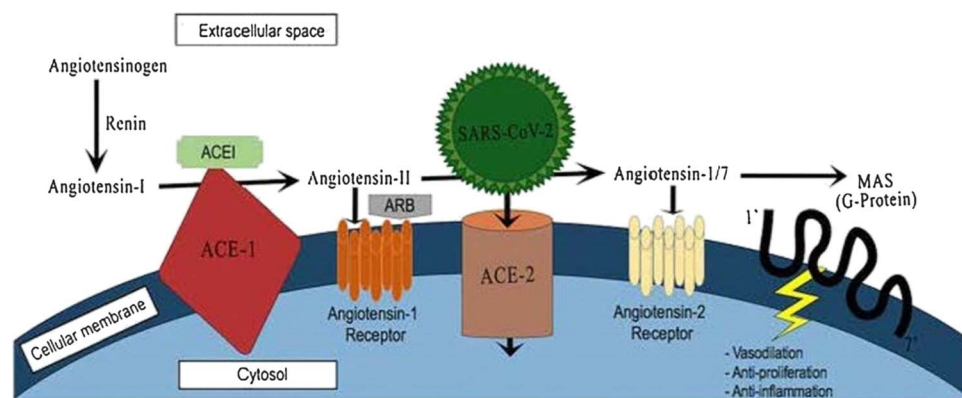


Fig. Mechanisms of action of ACEIs and ARBs and SARS-CoV-2 on the cellular RAAS receptors. Reproduced with permission from Springer Science+Business Media. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

hypertensive nephropathy and diabetic nephropathy.^{20,21} Increased ACE2 mRNA or protein levels also have been documented in the aorta of hypertensive rats.²² In another animal study, the decreased expression of ACE2 receptors and circulating angiotensin 1–9 levels in animals with late ventricular dysfunction postmyocardial infarction were prevented using enalapril, an ACEI.²³ Another animal study concluded that the expression of ACE2 is increased after telmisartan administration, an ARB.²⁴ Other animal studies have suggested that the RAAS inhibitors had no impact on ACE2 expression, however. Ramipril, valsartan, and their combination in a myocardial infarction model have shown no effect on cardiac ACE2 expression.²⁵

All of these animal models have raised concerns that patients receiving RAAS inhibitors may be more susceptible to infection with SARS-CoV-2 and become more severely ill when such an infection occurs. There is a lack of studies showing the effects of ACEIs or ARBs on the expression or activity of ACE2 receptors in the lung. In these studies, the observed effects of these drugs on ACE2 receptor expression and activity may not be comparable to humans because the doses of ACEIs and ARBs used in these animal studies were much higher than those used in humans.

In contrast to animal studies, there are few studies in humans regarding the effects of RAAS inhibitors on ACE2 expression. In a study of coronary artery disease patients who were given ACEIs intravenously, the inhibition of ACE1 with the resultant increase in angiotensin I failed to raise angiotensin 1–9 levels (Fig.). This suggests a minor function for ACE2 in the metabolism of angiotensin I, and brings into doubt whether ACEIs have any direct role in the ACE2 metabolism of angiotensin II.²⁶

In a study performed in patients with mild to moderate essential hypertension, initial treatment with captopril produced no impact on angiotensin 1–7 plasma levels; however, continuous therapy with captopril for a period of 6 months delineated an increase in angiotensin 1–7 plasma levels.²⁷

In a study performed in healthy humans, the mean duodenal mRNA expression level of ACE2 was found to be increased 1.9-fold in those given ACEI in comparison to the nontreated controls. No major variations in levels of expression were found in ARB-treated patients, however.²⁸ Cross-sectional human studies reveal that plasma ACE2 levels is patients with heart failure,²⁹ coronary artery disease,³⁰ atrial fibrillation,³¹ and aortic stenosis³² were not different whether patients did or did not receive ACEIs or ARBs.

In a Japanese cohort study, 617 hypertensive patients on ACEIs, ARBs, and calcium-channel blockers were enrolled in addition to nonhypertensive patients ($n = 101$).³³ The urinary ACE2 level was found to be higher in the olmesartan-treated group (an ARB), but not in those who took the other drugs.

Combining all of these studies, the upregulation of ACE2 receptors was noted only in animal studies using various ARBs or ACEIs at doses higher than typically used in humans. Such results also suggest that results from animal models may not be applicable in humans. Also, it must be noted that the biologic

relevance of ACE2 differs according to tissue and the clinical state. As mentioned before, there is a lack of studies showing the effects of these RAAS inhibitors on the lung-specific expression of ACE2. The levels of the soluble forms of ACE2 in plasma and urine do not constitute a strong indicator of the membrane-bound form, as the latter is normally shed out of the membrane.³⁴ As a result, there is no convincing evidence that the ARBs/ACE-enhanced ACE2 increment can enhance human susceptibility to SARS-CoV-2 (Table 1).

Potential Benefits of RAAS Inhibitors in COVID-19

Following the initial binding of the S-protein of SARS-CoV-2, there is downregulation of the membrane-bound ACE2.³⁵ This downregulation of ACE2 receptor activity in the lungs leads to unopposed accumulation of angiotensin II, the substrate for ACE2 (Fig.). Accumulated angiotensin II leads to increased neutrophil accumulation, increased vascular permeability, and exacerbated pulmonary edema, and eventually leads to ARDS.³⁶ Consequently, by reducing angiotensin II levels, ACEIs and ARBs may protect against lung injury in individuals with COVID-19.

In mice studies, Kuba et al noted that after infection with SARS-CoV occurs and ARDS ensues, the downregulation of ACE2 occurs and is accompanied by unopposed accumulation of angiotensin II.³⁵ Angiotensin II then leads to increased pulmonary vascular permeability and pulmonary edema. Injection of the SARS-CoV spike protein in mice substantially reduces lung ACE2 protein levels (downregulated the ACE2 expression in the lung) with consequent acute lung injury. The study delineated that losartan, an ARB, can mitigate the severity of SARS-CoV-induced acute lung injury in both a pretreatment study and a more clinically related postinfection study.³⁵ Noting that the structure of the S-protein of both types of SARS viruses is almost identical, SARS-CoV-2 infection also may downregulate the ACE2 expression in the lung.¹¹ In this situation, ARBs may prove useful to mitigate the severity of acute lung injury caused by SARS-CoV-2.

Imai et al used a mouse model of acute lung injury/ARDS triggered by acid aspiration to demonstrate that expression of ACE2 is downregulated in response to toxic stimuli.³⁷ This downregulation of ACE2 resulted in reduced oxygenation and enhanced inflammation, leading to acid-induced acute lung injury.³⁷ Treatment with AT1 blockers before acid-incited ARDS revealed a notable reduction in lung injury, which confirmed the function of the AT1 receptors in the physiological response. Exogenous ACE2 administration also has been shown to rescue acid aspiration-induced acute lung injury.³⁷ In *in vitro* human research, low ACE2 expression was noted to be linked to a more severe form of lung injury.³⁸

In concordance with the results of these studies, the result of a small human study performed in Wuhan, China revealed that the serum angiotensin II level was significantly high in a total of 12 patients infected with COVID-19. Also, it showed that

Table 1. Hypothesized harmful effects of RAAS inhibitors in COVID-19**Summary of Animal Studies**

- ARBs can increase the expression of messenger RNA or protein levels of ACE2 in those heart diseases and chronic kidney diseases (hypertensive nephropathy and diabetic nephropathy) and in hypertensive rats.¹⁹⁻²²
- The decline in the expression of ACE2 receptors and circulating angiotensin 1–9 levels in animals with late ventricular dysfunction postmyocardial infarction were prevented using enalapril, an ACEI.²³
- The expression of ACE2 is increased after telmisartan administration, an ARB.²⁴
- The RAAS inhibitors had no impact on ACE2 expression. Ramipril, valsartan, and their combination in a myocardial infarction model have shown no effect on cardiac ACE2 expression.²⁵

Summary of Human Studies

- Patients with coronary artery disease who were given ACEIs intravenously, inhibition of ACE1 with the resultant increase in angiotensin I failed to raise angiotensin 1–9 levels (Fig.). This suggests a minor function for ACE2 in the metabolism of angiotensin I and casts doubt on whether ACEIs have any direct role in the ACE2 metabolism of angiotensin II.²⁶
- In patients with mild to moderate essential hypertension, initial treatment with captopril revealed no impact on angiotensin 1–7 plasma levels; however, continuous therapy with captopril for a period of 6 mo delineated an increase in angiotensin 1–7 plasma levels.²⁷
- The mean duodenal mRNA expression level of ACE2 was found to be increased 1.9-fold in those given ACEIs in comparison with the nontreated controls. No major variations in levels of expression have been found in ARB-treated patients, however.²⁸
- Plasma ACE2 levels in patients with heart failure,²⁹ coronary artery disease,³⁰ atrial fibrillation,³¹ and aortic stenosis³² were not different if the patients did or did not receive ACEIs or ARBs.
- In a Japanese cohort study, which enrolled 617 hypertensive patients on ACEIs, ARBs, CCBs in addition to nonhypertensive patients of 101 subjects,³³ the urinary ACE2 level was found to be higher in the olmesartan-treated group (an ARB), but not in those who took the other drugs when compared.

The upregulation of ACE2 receptors was noted only in animal studies using the comparatively increased doses of various ARBs and one ACEI; however, there is a lack of studies showing the effects of ACEIs or ARBs on the expression or activity of ACE2 receptors in the lung, and the levels of the soluble forms of ACE2 in plasma and urine do not constitute a strong indicator of the membrane-bound form, as the latter is normally shed out of the membrane. There is no convincing evidence, however, that the ARBs/ACE-enhanced ACE2 increment can enhance human susceptibility to SARS-CoV-2. ACE, angiotensin-converting enzyme; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; mRNA, messenger RNA; RAAS, renin-angiotensin-aldosterone system.

the angiotensin II level was in a linear correlation with viral capacity and lung damage.³⁹ These findings lead us to propose that ARBs may have a positive role in COVID-19 by reducing angiotensin II levels (Table 2).

New Data

A large case-control study has been performed in Italy. The study compared 6272 people with established COVID-19 infection between February 21 and March 11, 2020, with a control group of 30,759 people who were comparable in sex, age, and the city of residency who did not have COVID-19 infection. The use of ACEIs and ARBs was more common among case-patients than among controls. Using multivariate conditional logistic regression analysis, the likelihood of SARS-CoV-2 infection was not associated with either ACEIs or ARBs. Further analysis also showed no relation between these drugs and the severity of COVID-19, when matching subjects with severe or fatal infections with paired controls.⁴⁰

A case-population study of 1139 adult cases was conducted in Madrid, Spain, in patients who were 18 years or older diagnosed as having COVID-19 using polymerase chain reaction and required hospitalization between March 1 and March 24, 2020, in any of seven hospitals in Madrid. To give an aggregate of 11,390 matched controls, the patients were each thoughtfully paired with 10 population controls using data from 2018. The study measured the hospitalization rates of polymerase chain reaction–confirmed COVID-19 patients using RAAS inhibitors versus other antihypertensive drugs. It delineated that compared with other antihypertensive medications, the use of RAAS inhibitors was not shown to be correlated with an augmented risk of hospital admission because of COVID-19 or an expanded risk

of serious complications from COVID-19 requiring intensive care unit admission or leading to fatal consequences.⁴¹

A large database study has been conducted that enrolled 8910 hospitalized patients in 11 countries of three continents. The covered patients were those who had been diagnosed as having COVID-19, who were admitted to the hospital between December 20, 2019 and March 15, 2020, and who had either died in the hospital or had lived until discharge. In concordance with the results of the previously mentioned Italian study, this study delineated that neither ACEIs nor ARBs were correlated with an expanded risk of in-hospital mortality. An additional interpretation limited to hypertensive patients (those for whom RAAS inhibitors would be indicated) also did not reveal an adverse correlation.⁴²

Another study was conducted at the New York University Langone Health system using data from electronic health records. A total of 12,594 patients were enrolled who were tested for COVID-19 between March 2020 and April 15, 2020. The study aimed to assess whether previous treatment with either ARBs, ACEIs, calcium-channel blockers, β -blockers, or thiazide diuretics has an impact on the likelihood that a COVID-19 test will become positive or negative. In addition, it measured the relation between previous treatment with these medications and the likelihood that positively tested patients will develop severe illness, which is defined as the admission to an intensive care unit, the need for mechanical ventilation, or even death. A total of 5894 (46.8%) patients tested positive for COVID-19, 1002 of whom (17.0%) had severe illness. The study revealed that 4357 (34.6%) patients had a history of hypertension, 2573 of whom (59.1%) tested positive, and 634 (24.6%) patients had severe illness. The study concluded that none of these drugs was found to increase the

Table 2. Potential benefits of RAAS inhibitors in COVID-19**Summary of Animal Studies**

- Infection with SARS-CoV results in the downregulation of ACE2 receptors accompanied by unopposed accumulation of angiotensin II. Angiotensin II then leads to increased pulmonary vascular permeability and pulmonary edema. Losartan, an ARB, can mitigate the severity of SARS-CoV–induced acute lung injury in both a pretreatment study and in a more clinically related postinfection study.³⁵
- The expression of ACE2 is downregulated in response to noxious stimuli. This downregulation of ACE2 resulted in reduced oxygenation and enhanced inflammation, leading to acid-induced acute lung injury.³⁷ Treatment with AT1 blockers before acid-incited ARDS revealed a notable reduction in lung injury.
- In in vitro human research, low ACE2 expression was noted to be linked to a more severe form of lung injury.³⁸

Summary of Human Studies

- A small human study revealed that the serum angiotensin II level was significantly higher in a total of 12 patients infected with COVID-19. Angiotensin II level also was found to be in a linear correlation with viral capacity and lung damage.³⁹

Animal studies revealed that the expression of ACE2 is downregulated by SARS-CoV infection, and this downregulation is associated with a more severe form of lung injury. SARS-CoV-induced acute lung injury could be mitigated by using ARBs. The human study also revealed that ARBs may have a positive role in COVID-19 by reducing angiotensin II levels. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; SARS-CoV, severe acute respiratory syndrome-coronavirus; RAAS, renin-angiotensin-aldosterone system.

likelihood of a positive COVID-19 test. Also, none of these medications was associated with a substantial increase in the risk of severe illness among patients with positive tests.⁴³

Similar conclusions were achieved by Mehta and colleagues in a cohort study of 18,472 patients who had been tested for COVID-19 infection in the Cleveland Clinic Health System in Ohio and Florida. Overlap propensity score weighting revealed no correlation between the use of ACEIs or ARBs and the likelihood of a positive test (odds ratio 0.97, 95% confidence interval 0.81–1.15).⁴⁴

A retrospective, multicenter study was conducted in Hubei Province, China, including 1128 patients with a history of hypertension, 188 patients (17%) of whom received an ACEI/ARB drug during hospitalization.⁴⁵ The study concluded that inpatient use of ACEI/ARB was found to be associated with a lower risk of all-cause mortality in comparison with those who do not use these drugs. Although analysis of the study needs to consider the potential for residual confounders, in-hospital use of ACEI/ARB is unlikely to be associated with an increased mortality rate.

Official Statements

Before the results of the previous large COVID-19 studies, the Council on Hypertension of the European Society of Cardiology, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology navigated the uncertainty about whether to continue or discontinue the use of RAAS inhibitors in COVID-19, and have spoken with one voice in advising that ACEI or ARB therapy should be continued during the COVID-19 pandemic, as there is no convincing evidence that they can increase susceptibility to infection, severe illness, or death.^{46–48}

Conclusions

The controversy regarding the use of ACEIs and ARBs in COVID-19 came after finding that the COVID-19 virus binds to the ACE2 receptor to gain host cell entry. Many studies, mainly animal studies, proposed that ACEIs and ARBs may increase the expression of ACE2, which has raised concerns

that the use of these drugs may increase the susceptibility for contracting SARS-CoV-2. Other studies showed that these drugs may play a protective role against lung injury in COVID-19 patients, however. To date, there is no compelling experimental or clinical evidence that ARBs and ACEIs either increase vulnerability to SARS-CoV-2 or aggravate COVID-19 severity and outcomes, whereas the protective role of ACE2 in the lung is supported by ample evidence. In this regard, several professional societies have released statements and agreed upon the continuation of ACEIs/ARBs during the COVID-19 outbreak. Results from newly published studies have contributed to diminishing the speculation about the safety of RAAS inhibitors during the COVID-19 pandemic. Large-scale clinical studies with convincing evidence are needed to navigate the uncertainty regarding whether ACEIs and ARBs have favorable, harmful, or neutral effects regarding the susceptibility to SARS-CoV-2 and the severity and outcomes of COVID-19.

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