Review

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Association of ACE2 receptor and ACEIs/ARBs with disease severity in COVID-19

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SUMMARY Coronavirus disease 2019 (COVID-19) is found to be associated with various comorbidities which include cardiovascular diseases, hypertension, and diabetes. The impaired regulation of renin-angiotensin-aldosterone system (RAAS) has been seen in COVID-19 patients, but whether RAAS inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs), are responsible for worsening of clinical conditions remains unknown. Herein, we review the role of angiotensin-converting enzyme 2 (ACE2) expression in disease progression, its association with comorbidities and COVID-19, and summarize the clinical evidence for several potential directions for future research work on ACEIs/ARBs in COVID-19 patients.

Keywords COVID-19, ACE2, comorbidities, ACEIs, ARBs

1. Introduction

The recent outbreak of the coronavirus disease 2019 (COVID-19) is a serious threat to the human population all along the globe. The COVID-19 cases were first reported in December 2019, in the region of Wuhan, China, then it spread rapidly worldwide, and meanwhile, COVID-19 became a global public health emergency of utmost concern (*1*). The causative agent has been spotted as a novel enveloped RNA beta-coronavirus and has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (*2*). The clinical outcome of SARS-CoV-2 infection is mainly distinguished by respiratory tract symptoms, which include dry cough, fever, fatigue, pharyngodynia, and problems associated with pneumonia and acute respiratory distress syndrome (*3*).

Population with all age groups is vulnerable to SARS-CoV-2, but the older age population and those with other comorbidities are found to be more prone to critical outcomes. According to current knowledge, the death rate seems to be higher in patients with severe underlying diseases (*4*). This includes cardiovascular diseases, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (*5*). The causality rate in COVID-19 patients was examined to be larger in patients with underlying diseases, *i.e.* cardiovascular disease (10.5%) and hypertension (6.0%) when compared with the normal population (2.3%) (*6*). Apart from this, diabetes is another common disease that is linked to the worst outcomes in COVID-19 and is often linked to hypertension and prescribed with renin-angiotensin-aldosterone system (RAAS) inhibitors (*7*). However, the explanation behind this observation is mostly unknown.

RAAS inhibitors are commonly prescribed drugs for various indications such as hypertension, myocardial infarction, cardiac failure, kidney diseases, and complications of diabetes all over the globe (*7*). Now, the use of RAAS inhibitors is under the controversial discussion of assumptions of two hypotheses (deleterious *vs.* protective) (*8*). In the "deleterious effect" hypothesis, RAAS inhibition leads to the upregulation of angiotensin-converting enzyme 2 (ACE2) expression at the cell surface, which will promote SARS-CoV-2 entry. In the "protective effect" hypothesis, RAAS inhibition will decrease the formation of angiotensin II, which would otherwise, upon SARS-CoV-2 binding, activate angiotensin II type I receptor (AT_1R), driving inflammation and fibrosis in the lung. In response to this discussion, the Council on Hypertension of the European Society of Cardiology made the following statement, "The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) should be discontinued because of the COVID-19 infection"

(*9*). The preceding statement has been then supported by the various numbers of distinguished societies, suggesting a continuation of the current medication regimen to the hypertensive patient with COVID-19. On March 17, 2020, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology put out a joint statement commending to continue ACEIs/ARBs as prescribed and any changes in medications in the setting of COVID-19 should be done only after careful evaluation (*10*). Therefore, prompt attention is needed to answer the existing cause of disease severity in COVID-19 patients having underlying diseases that would support in making timely clinical decisions (*11,12*).

Herein, we review the role of ACE2 expression in disease progression, its association with comorbidities and COVID-19, and summarize the clinical evidence for several potential directions for future research work on ACEIs/ARBs in COVID-19 patients.

2. Expression of ACE2 receptors

ACE2, a transmembrane protein having extracellular N-terminus and an intracellular C-terminus, primarily distributed on endothelial cells. Its catalytic site, similar to that of ACE, is mainly faced to distinct vasoactive peptides that are in circulation (*13*). The action of ACE2 is regulated by its expression pattern on the cell surface and also *via* its cleavage from the cell membrane. *ACE2* genes are located on the X chromosome (*14*), and its receptors are ubiquitous. ACE2 receptor expression is broadly observed in distinct human tissues such as lung, endothelium, heart, intestine, and kidney, which indicates the entry point for viruses like SARS-CoV and SARS-CoV-2 for their infection and multiplication (*15*). However, ACE2 expression varies and depends upon various factors such as age, gender, ethnicity, and physiological state, for example, more expression of ACE2 is observed in Asian as compared to white and African-American population (*16*). This differential expression is often detrimental to the severity of the diseases (Figure 1).

The expression of ACE2 in the lungs is found to be declined with the progress of the age (*17*) which is more to be in men as compared to women (*17*). Reduced expression of ACE2 has been linked with clinical conditions like diabetes mellitus which may be under the effect of glycosylation (*18-20*). Also, various clinical and experimental studies show the relevance of ACE2 deficiency due to either inhibition or deletion as a causative outcome for hypertension (*21,22*). Additionally, its deficiency is linked to aggravation of hypertension as well as cardiac hypertrophy, which is stimulated by angiotensin II (*23*) which is also responsible for remodeling of defective left ventricular after myocardial infarction (*24*). Furthermore, ACE2 deficiency enables the patients more vulnerable to cardiac failure (*21*). Deletion of the heterozygote *ACE2* gene is found to be sufficient in increasing the vulnerability to cardiac diseases (*25*). Besides this, deficiency of ACE2 is found to be one of the critical factors in the pathogenesis of SARS-CoV-2 infection. The ACE2 down-regulation stimulated with the viral invasion assumed to be detrimental particularly in patients with threshold ACE2 deficiency for example in case of old age population, or having hypertension, diabetes or prior cardiovascular diseases.

Moreover, over-expression of ACE2 is found to be preventive or can reverse the heart failure conditions (*26*). Modulation of ACE2 expression is seen with some etiological factors, like 1) Environmental conditions: This mainly includes polluted air which should be considered. The ACE2 activity was increased massively about 100 fold, in experimental models after

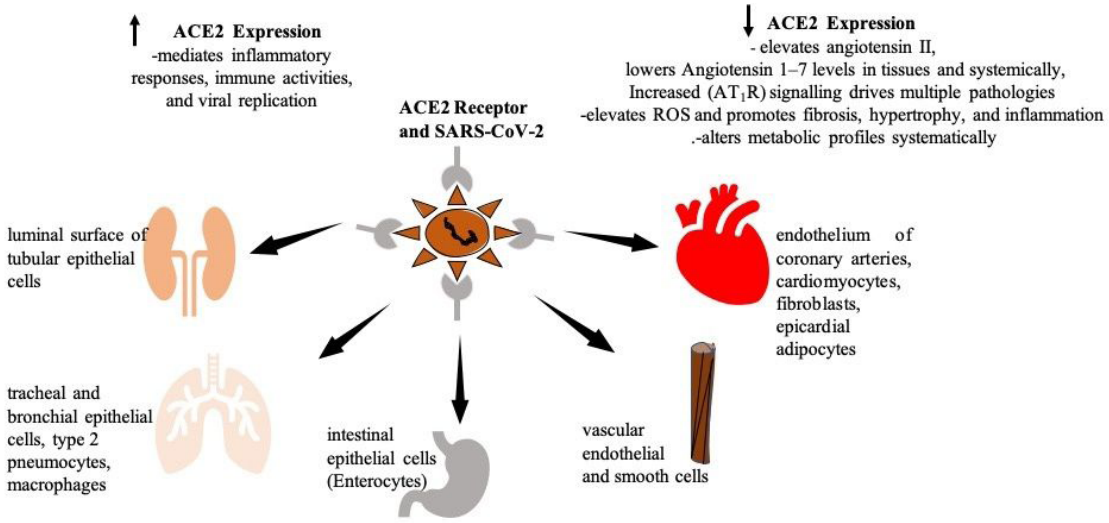

Figure 1. Expression of ACE2 receptors.

being exposed to NO_2, which concomitantly increases the binding of angiotensin II to its receptor (*27-29*). 2) Smokers: In the case of smokers, ACE2 is overexpressed on the epithelium of the lung airways, which has been observed previously in small animals, wherein exposure to smoke led to the upregulation of both the activity and the expression of ACE2 in the airways (*30,31*). Cai *et al.* recently elucidated over-expression of the *ACE2* gene in smoker groups juxtapose to non-smokers (*32*). Zhao *et al.* elicited clearly that the ACE2 is expressed in type-2 pneumocytes, wherein the genes controlling the viral multiplication and transmission are also highly expressed (*33*). Smoking has the ability to intensify the ACE2 receptor expression (*34*), active smoking and COPD leads to over-expression of ACE2 in lower airways, which to some extent may clarify the expanded threat of severity in COVID-19 patients. These observations feature the significance of withdrawal from smoking in these sub-populations, together with increased surveillance programs of these risk subgroups and rapid diagnosis would further prevent the infection from this virus (*35*). 3) Alcohol: Okuno *et al.* have detailed about the prolonged rise of the activity of serum ACE in alcoholics, and suggested that the levels of angiotensin II are increased because of incitement of ACE activity (*36,37*).

Nevertheless, during pregnancy, the ACE2 expression is markedly increased at the mRNA level (*38*). Li *et al.* showed profound expression of ACE2 in maternal-fetal interface cells. This includes perivascular cells of decidua and stromal cells, and cytotrophoblast and syncytiotrophoblast in placenta (*39*). The expression was also seen in particular types of cells in human fetal, *i.e.*, lung, liver, and heart but not seen in the kidney. This study elucidated about the widespread expression of ACE2 receptor in specific cell types of maternal-fetal interface and fetal organs which serve as an entry point for SARS-CoV-2 infection. The over-expression of ACE2 in these cells entails about the chances of placenta to be get infected by SARS-CoV-2 (*39*). Therefore, the illusion of any vertical transmission of the virus, pregnancy complication, and the placenta dysfunction or abortion due to SARS-CoV-2 must be clarified carefully with further investigation in clinical research and practice (*39*).

3. Association of ACE2 receptor in case of underlying disease or conditions in COVID-19

Various studies have given the factual basis of uses of ACE2 by the SARS-CoV and SARS-CoV-2 as a crucial cellular receptor to enable its infection. Both the viruses SARS-CoV-2 and SARS-CoV share 79% identity in nucleotide sequence (*40*). Studies have anticipated that the receptor-binding domain (RBD) of the spike glycoprotein present in both the viruses (SARS-CoV-2 and SARS-CoV) allocate almost similar conformation, and the association affinity between ACE2 and RBD was found to be much greater for SARS-CoV-2, on assessment with computer modeling and biophysical analysis (*41,42*).

Receptor binding is initiated *via* the viral spike protein, which is further processed by the TMPRSS2 protease (*43*). At this point, the spike protein associates with the extracellular domain of ACE2, which stimulates clathrin-dependent endocytosis of the complex (*43-45*). Curiously, this association is surprisingly improved in patients experiencing hypertension or coronary illness just as in diabetes or other comorbid conditions (*46-48*). After the entry of viruses, the viral RNA is discharged into the host-cell and further replicated by using the host cell's machinery to produce infectious virion which is released *via* exocytosis process. Moreover, apart from producing infectious virion, replication, and infection mechanism of SARS-CoV-2 also influences the ACE2 expression as well as its presentation. Receptor internalization leads to the decreased availability of these receptors for binding to the cell surface. The function of ACE2 is to degrade angiotensin I into angiotensin (1-7) peptides, which is responsible for lower blood pressure and vasodilation. The down-regulation of ACE2 disturbs the balance between ACE/angiotensin II and ACE2, however, the action of angiotensin II in the RAAS is increased due to the absence of antagonism, angiotensin (1-7) (*21*), shown in Figure 2. In order to know the significance of angiotensin II cleavage as a result of ACE2, there is need to understand the biological consequences of angiotensin II. Angiotensin II stimulates the release of hormone aldosterone and is a well-known vasoconstrictor. In various studies, angiotensin II has been observed for initiating a variety of adverse reactions consequences, like interstitial fibrosis, myocardial dysfunction and hypertrophy, endothelial malfunction, obesity-associated hypertension, enhanced inflammation, oxidative stress and blood coagulation (*15,21,44,49*). Moreover, angiotensin II upon binding to AT_1R exerts exacerbated pulmonary vascular permeability which results in increased hydrostatic pressure and finally pulmonary edema (*50*). In context to this, there are few experimental studies of lung injury that shows downregulation of ACE2 receptors stimulates inflammatory lesions in the tracheobronchial tree (thickening of alveolar walls, infiltrates of inflammatory cells, bleeding, edema) under the influence of angiotensin II (*51-54*). The significance of this RAAS activation as a causative factor of pulmonary edema in COVID-19 is still obscure (*29*). Nonetheless, a number of clinical observations are needed to decide whether the downregulated expression of ACE2 is a consequence of COVID-19 infection.

4. Role of ACEIs and ARBs in COVID-19

Obstruction of the RAAS is evinced to be favorable

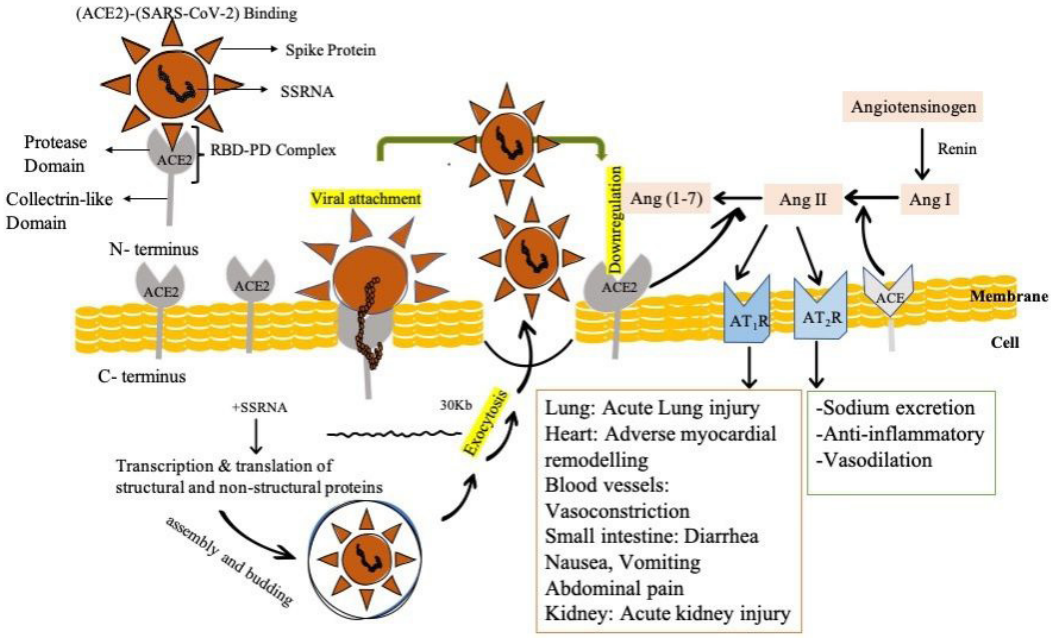

Figure 2. SARS-CoV-2 infection and its relation with renin angiotensin aldosterone system (RAAS). ACE2: angiotensin-converting enzyme 2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RBD: receptor binding domain; SSRNA: single stranded ribonucleic acid; Ang I: angiotensin I; Ang II: angiotensin II; Ang (1-7): angiotensin (1-7); AT_1R: angiotensin II type 1 receptor; AT_2R: angiotensin II type 2 receptor; ACE: angiotensin-converting enzyme.

in the restoration of kidney and cardiac function in the patients with clinical conditions such as kidney diseases, cardiac failure, and post-myocardial infarction (*55,56*). The two agents, ARBs and ACEIs are considered first-choice drugs in hypertension, heart failure, post-myocardial infarction, and chronic kidney disease and also increases the expression of ACE2 (*57*). ACEIs consist of a particular class of antihypertensive medication which is mainly marked for cardiac failure, post-myocardial infarction, asymptomatic left ventricular dysfunction, diabetic nephropathy, and proteinuria. ACEIs leads to vasodilation by reducing the production of angiotensin II (*58,59*). Furthermore, the activity of ACEIs is found to be high in the lungs due to the profound expression of ACE (*51*). So, during lung associated complications, administration of ACEIs leads in the augmented release of bradykinin in the lungs, which are mostly deteriorated by ACEIs. This may sensitize the airways and increases the cough reflex (*60,61*).

Moreover, ARBs act on the RAAS pathway through effective blocking of AT_1R and was initially developed for the treatment of hypertension. ARBs display pleiotropic defending effects as it is helpful in directly reducing the endothelial injury, organ fibrosis and inflammation, maintain mitochondrial activity, energy metabolism, and insulin sensitivity. It also protects the excessive metabolism of lipids and harmonize the coagulation processes (*62,63*). All these processes are the clinical features that are observed in a recovered patient with acute critical disorders (*62,63*). Because of these facts, ARBs are widely prescribed as first- line antihypertensives treatment options as well as for the treatment of other diseases like cardiovascular diseases, diabetes and kidney disease. Moreover, ARBs have the ability to decrease inflammation and debilitated epithelial and endothelium of various organs, which has been seen in various viral infections where ARBs protect the integrity of lung endothelial barrier directly that occurred due to acute injury (*64*). There is also considerable clinical evidence that shows straight consequences of ARB medication, which protects the lung from severe injury linked to sepsis, pneumonia sepsis, and influenza and reduces the mortality (*64*).

COVID-19 patients with hypertension, diabetes, and cardiovascular diseases (among other underlying disease conditions that are often treated with these agents) have been reported to have the highest case fatality rates (*6,65*). The ACEIs/ARBs treatment which has the ability to induce exacerbated ACE2 expression, a receptor for SARS-CoV-2 entry in COVID-19 patients, assumes to be having a controversial action because of reducing inflammatory responses in context to pathogen and at the same facilitating the virus entry (*66*). Moreover, the major concern is about ACEIs and ARBs treatment, which increases the severity as well as the mortality of COVID-19 patients by 2-fold. One assumption is that ACEIs could straight inhibit ACE2; however, ACE2 functions as a carboxypeptidase and is not hindered by clinically recommended ACEIs (*67*). Moreover, the topic is controversial and debatable, with a limited number of clinical evidence, shown in Table 1, which mostly suggest continuation of these medications till date.

Table 1. Studies showing use of ACEIs/ARBs in COVID-19

Authors	Hypothesis/Aim	Patient enrolled	Results/Outcome	Conclusion/ recommendation on use or not use of ACEIs or ARBs	Limitation
Bean *et al.*, 2020 (*68*)	"To evaluate the association between treatment with ACEI or ARB and disease severity in COVID-19 patients".	Multicentre retrospective study -cohort of 205 acute inpatients with COVID-19, 53 patients out of 205 patients reached the primary endpoint and out of this only 9 patients were taking ARBs.	Individuals diagnosed with hypertension had a similar likelihood of developing severe disease as those that were not diagnosed with hypertension.	Recommended for use of ARB and ACEIs	Relatively small sample taken from a single UK centre over a short follow-up.
Guo *et al.*, 2020 (*69*)	"To evaluate the association of underlying cardiovascular disease and myocardial injury with fatal outcomes in patients with COVID-19".	Single-centre, retrospective, observational study of 187 patients, 66 (35.3%) had underlying cardiovascular disease including hypertension, coronary heart disease, and cardiomyopathy, and 52 (27.8%) exhibited myocardial injury as indicated by elevated Troponin T levels.	The mortality rates of patients with and without use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was 36.8% (7 of 19) and 25.6% (43 of 168).	Recommended for use of ARB and ACEIs in COVID-19 patients	Limited number of patients, the mortality of those treated with or without use of ACEIs/ARBs did not show a significant difference in outcome. -a larger cohort study is needed for further verification.
Li *et al.*, 2020 (*70*)	"To investigate the association between ACEIs/ARBs and severity of illness and mortality in patients with hypertension hospitalized for COVID-19 infection".	Retrospective, single-centre case series of the 1178 hospitalized patients with COVID-19 infections -362 patients with hypertension and of whom 115 were taking ACEIs/ARBs.	Data provide some reassurance that ACEIs/ ARBs are not associated with the progression or outcome of COVID-19 hospitalizations in patients with hypertension.	Data support current guidelines and societal recommendations for treating hypertension during the COVID-19 pandemic.	Enrolment of small number of patients with hypertension taking ACEIs/ARBs who were hospitalized with COVID-19. -biasness in maintenance of ACEIs/ ARBs treatment at baseline.
Liu *et al.*, 2020 (*71*)	"To investigate any difference in disease severity between COVID-19 patients with hypertension comorbidity".	Multicentre retrospective study, -clinical data of 511 COVID-19 patients -Patients were categorized into six sub-groups of hypertension comorbidity based on treatment using one of anti-hypertension drugs (ACEI, ARB, CCB, BB, thiazide), or none.	Elderly (age > 65) COVID-19 patients with hypertension comorbidity who were taking ARB anti-hypertension drugs may be less likely to develop severe lung disease compared to patients who were not taking anti-hypertension drugs.	Data support various society guidelines to continue current treatment of chronic disease conditions with either ACEIs/ARBs during the COVID-19 pandemic.	Limited number of sample. -lack of statistical difference between Contol and studied population
Mehta *et al.*, 2020 (*72*)	"To clarify the potential association of use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) with testing positive for coronavirus disease 2019 (COVID-19)".	Retrospective prospective, observational study, -Includes 18,472 patients who underwent COVID-19 testing, 2,285 (12.4%) were taking ACEIs or ARBs.	Taking either an ACEI or ARB was not associated with an increase in the likelihood of testing positive for SARS-CoV-2 infection (overlap propensity score-weighted odds ratio, 0.97; 95% CI, 0.81-1.15).	These data support various society guidelines to continue current treatment of chronic disease conditions with either ACEI or ARB during the COVID-19 pandemic.	The data did not include information on duration of ACEI or ARB use before or after testing. Limited to particular races/ ethnicities.

Table 1. Studies showing use of ACEIs/ARBs in COVID-19 (continued)

Authors	Hypothesis/Aim	Patient enrolled	Results/Outcome	Conclusion/ recommendation on use or not use of ACEIs or ARBs	Limitation
Meng *et al.*, 2020 (*73*)	"To evaluate the ability of RAAS inhibitors to protect against COVID-19 in patients with hypertension".	Single-centre, retrospective study. -42 patients receiving antihypertensive therapy were included and were divided: the ACEI/ARB group (17 patients) included patients treated with ACEI or ARB drugs, and the non-ACEI/ARB group (25 patients) included patients treated with other antihypertensive drugs, including calcium channel blockers (CCBs), β-blockers and diuretics.	First clinical evidence demonstrating that RAAS inhibitors improve the clinical outcomes of COVID-19 patients with hypertension.	Data support various society guidelines to continue current treatment of chronic disease conditions with either ACEIs/ ARBs during the COVID-19 pandemic.	Small sample size and selection bias.
Shi *et al.*, 2020 (*74*)	To explore the association between cardiac injury and mortality in patients with COVID-19.	The study population included 416 patients hospitalized with confirmed COVID-19: 82 patients (19.7%) with cardiac injury and 334 patients (80.3%) without cardiac injury.	ACEIs/ARBs was not included in the study.	Study demonstrates the statistically significant association between cardiac injury and mortality in patients with COVID-19. However, the mechanism of cardiac injury among these patients with COVID-19 was not revealed.	Larger populations and multiple centres are warranted to further confirm the outcomes of cardiac injury in COVID-19. Disease is not study to look into role of ARBS/ACEIS in COVID-19.
Wei *et al.*, 2020. (*75*)	"To explore the prevalence and immediate clinical implications of acute myocardial injury in a cohort of patients with COVID-19".	Single-centre, observational study -101 Covid-19 patients.	Explanations was hypothetical, and did not provide any clue to justify alteration of ACEIs/ARBs treatment in patients with COVID-19	Not specified	Limited with a small sample size, unable to draw definitive conclusions and acknowledge the existence of selection bias as complete documentation of exposure history and laboratory testing was not available for every patient, and echocardiography was only performed for clinical expediency.
Yang *et al.*, 2020 (*66*)	"To evaluate the correlation of ARBs/ACEIs usage with the pathogenesis of COVID-19 patients with pre-existing hypertension".	Retrospective, single-center study. -126 COVID-19 patients allocated to ARBs/ ACEIs group (n = 43) and non-ARBs/ ACEIs group (n = 83) according to their antihypertensive medication.	Within the hypertension group, patients on ARBs/ACEIs had a much lower proportion of critical patients and a lower death rate than those on non-ARBs/ACEIs medications, although these differences failed to reach statistical significance.	Finding of the study support the use of ARBs/ACEIs in COVID-19 patients with pre-existing hypertension.	Interpretation of findings was limited by the sample size and selection bias.

Table 1. Studies showing use of ACEIs/ARBs in COVID-19 (continued)

Authors	Hypothesis/Aim	Patient enrolled	Results/Outcome	Conclusion/ recommendation on use or not use of ACEIs or ARBs	Limitation
Zeng *et al.*, 2020 (*76*)	"To investigate and compare the demographic characteristics, coexisting diseases, severity of pneumonia, and the effect of antihypertensive drugs (ACEI/ ARB versus non-ACEI/ARB) in COVID-19 patients with coexisting hypertension".	Retrospective, Single-centre, observational study. -included data from all patients with clinically confirmed COVID-19. A total of 274 patients, 75 with hypertension and 199 without hypertension, were included in the analysis.	Patients with hypertension who had previously taken ACEI/ARB drugs for antihypertensive treatment have an increased tendency to develop severe pneumonia after infection with SARS-COV-2 ($p = 0.064$).	Not specified	The number of patients included was small.
Zhang *et al.*, 2020 (*77*)	"To determine the association between in-hospital use of ACEI/ ARB and all-cause mortality in COVID-19 patients with hypertension".	Retrospective, multi-centre study, included 1128 adult patients with hypertension diagnosed with COVID-19, including 188 taking ACEI/ARB (ACEI/ARB group; and 940 without using ACEI/ARB (non-ACEI/ ARB group.	The detected risk for all-cause mortality was lower in the ACEI/ARB group versus the non-ACEI/ARB group (adjusted HR, 0.42; 95% CI, 0.19-0.92; $p = 0.03$).	Recommended for use of ARB and ACEIs in COVID-19	Modest sample-size who received ACEI/ARB. -few parameters were not available in all patients, and in-hospital medications might be not fully recorded.

5. Conclusion

Patients taking common hypertensive medications were not found to be at higher risk for infection with SARS-CoV-2, or to be more likely to have severe complications from COVID-19. However, this could be one of the active areas of research and proper clinical trials. The published clinical evidence is limited by various confounding factors, like small sample size, selection bias, the inappropriate association of data, time period of ACEIs or ARBs administration prior to or after testing, *etc.* Moreover, result interpretation is also subjected to a different grade of variations between countries as a result of insufficient testing of COVID-19 patients and differences in disease prevalence (*78*). Moreover, few points that need to be considered from various studies in this context are:

(1) The *ACE2* gene is subjected to a larger degree of polymorphism and significantly associated with the phenomenon of arterial hypertension which has been observed in Han Chinese men and in women of diverse races and ethnicity (*29,79*). In addition to this, ACE2 polymorphism is also linked to susceptibility to diabetes mellitus, ventricular hypertrophy cerebral stroke, septal wall thickness, and coronary artery disease mainly in the Asian population (*29*). Nonetheless, any possible association of ACE2 polymorphism with regards to differences in vulnerability to COVID-19 infection is still needed to be answered.

(2) ACE2 binds more efficiently (about > 10-20 fold) to SARS-CoV-2 than to SARS-CoV. This data, along with the other interpretation, like people of diverse races and ethnicity, with different sexes and ages were all vulnerable to SARS-CoV-2 infection, which entails that expression of ACE2 inside the human body under normal physiological condition may be sufficient enough to contract SARS-CoV-2 infection, and additional upregulation would not be the reason for increased risk or severity (*66*).

(3) The RAAS inhibitors instead of inhibiting viral replication directly; there may be chances that they display their antiviral role through an indirect effect of inflammatory responses and immune regulation (*77*). Large prospective studies are needed to validate and explore this preliminary finding for further studies that will focus on the mechanism of action of ACEIs/ARBs to control the inflammatory response.

(4) A randomized controlled clinical trial evaluating the role of ACEIs/ARBs is the need of the situation, before reaching to any interpretation regarding the likely benefit of these drugs in COVID-19 patients. Moreover, the trial will also be beneficial in the futuristic approach in tackling such a pandemic in different geographical regions. Together, these efforts may lead to finding of some new therapeutic molecule that will target ACE2 in COVID-19 patients with other comorbidities.

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