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REVIEW ARTICLE

COVID-19 and RAAS inhibitors: is there a final conclusion?

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ABSTRACT

Coronavirus disease 2019 (COVID-19), the first pandemic caused by a human infecting coronavirus, has drawn global attention from the first time it appeared in Wuhan city of China in late December 2019. Detection of the responsible viral pathogen, named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by WHO, and its possible pathogenesis lead to the forming of many hypotheses about the factors that may affect the patients' outcome.

One of the SARS-CoV-2 infection concerns was the potential role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in COVID-19 patients' morbidity and mortality. Studies demonstrated that because SARS-CoV-2 uses human ACE2 cell receptors as an entry receptor to invade the cells, there might be an association between antihypertensive drugs such as RAAS inhibitors (specifically ACEIs and ARBs) and the COVID-19 disease. Data are scarce and conflicting regarding ACEI or ARB consumption and how it influences disease outcomes, and a single conclusion has not been reached yet.

According to the literature review in our article, the most evidentially supported theory about the use of RAAS inhibitors in COVID-19 is that these medications, including ACEI/ARB, are not associated with the increased risk of infection, disease severity, and patient prognosis. However, further studies are needed to support the hypothesis.

Keywords: COVID-19; Hypertension; Renin-angiotensin-aldosterone system inhibitors

INTRODUCTION

The Coronavirus disease 2019 pandemic has spread to almost all countries (1). The disease has first appeared in Wuhan, China, as pneumonia with an unknown origin (2-5). Researches on the bronchoalveolar lavage samples demonstrated that a new member of human coronaviruses caused pneumonia (6-8). Additional studies around the causal agent of the highly contagious pneumonia revealed the fact that SARS-CoV-2 shares almost a homological sequence with SARS-CoV and MERS-CoV (7, 9-11). Entering the human body cells, SARS-CoV-2 uses the same receptor as SARS-CoV (12, 13). Under the light of all these similarities, the main COVID-19's pathology was predicted.

COVID-19 is known to be a principally respiratory illness with respiratory manifestations (14, 15). However, COVID-19 is currently considered a systemic infection with extrapulmonary involvement, and a broad spectrum of clinical manifestations has been found in patients with SARS-CoV-2 infection (16, 17). Notably, patients' presentation of the disease can differ from entirely asymptomatic to severe acute respiratory syndrome and death (18).

The COVID-19 pandemic has stunned the world due to its highly contagious viral agent, multi-organ involvement, and diverse outcomes (19). As a consis-

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tent feature, COVID-19 predilect to inflict adverse outcomes in patients with cardiovascular conditions or cardiovascular disease risk factors (20-23). According to the evidential data, COVID-19 tends to portend an increased severity and worse outcomes in patients with cardiovascular disease, including hypertension (20-22, 24, 25). Across the whole spectrum of cardiovascular diseases, pharmacotherapy is commonly used in patients with related conditions as it plays a significant role in the management of cardiovascular diseases (26, 27).

A wide range of pharmacological agents has objectively been shown to have beneficial effects on cardiovascular conditions, among which antihypertensive drugs, particularly RAAS inhibitors, are commonly prescribed (28). As a life-saving or life-prolonging intervention and quality of life enhancer, RAAS inhibitors have been shown to improve debilitating symptoms with approximately no side effects and the best choice for chronic pharmacological treatment in patients with cardiovascular conditions (29). Objective studies on the clinical outcomes of cardiovascular COVID-19 patients followed by a better understanding of COVID-19 pathophysiology and the prevalence of RAAS inhibitor usage among cardiovascular patients contributed to a significant hypothesis along with controversy; Is COVID-19 at any point associated with the use of RAAS inhibitors in cardiovascular patients?

COVID-19 pathophysiology

As the third member of the coronavirus family beside SARS-CoV and MERS-CoV, SARS-CoV-2 causes severe presentations (30, 31). Although COVID-19 is preferentially considered a respiratory disease with abnormal pulmonary presentations, SARS-CoV-2 infection can develop a diverse range of (various) non-respiratory manifestations, including cardiovascular abnormalities, neurological and hematological manifestations, liver damage, or kidney dysfunction symptoms (15). The systemic hyperinflammatory response induced by the virus is likely to be responsible for multi-organ involvement and extrapulmonary manifestations in COVID-19 patients (15). However, numerous studies have discussed the possibility of direct viral invasion by SARS-CoV-2 in non-respiratory organs, including the heart, relying on the presence of histopathological evidence (32-34). Autopsy analysis of 27 confirmed COVID-19 cases demonstrated that SARS-CoV-2 RNA was detectable in the heart, brain, liver, or kidneys other than the lungs (34). Similar data around the broad organotropism of SARS-CoV-2 preliminary support the possibility of direct viral attack and its role in the development of non-respiratory manifestations (32, 33).

Researches demonstrated that similar to SARS-CoV, SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor and the type 2 transmembrane serine protease (TMPRSS2) as an entry receptor for human cell invasion (35-40). However, some studies suggest that due to higher transmissibility than SARS-CoV, it is likely that SARS-CoV-2 may also use other cell surface attachment factors for entering the human cells, including sialic-acid-containing glycoproteins and gangliosides (41).

According to studies around COVID-19 pathophysiology, early in infection, SARS-CoV-2 spike (S) protein binds to the ACE2 receptor of the target cells, such as nasal and bronchial epithelial cells and pneumocytes (38). It is said that coronavirus entry into host cells is mediated by TMPRSS2, present in the host cell, promoting viral uptake by cleaving ACE2 and activating the SARS-CoV-2 spike protein (38). Similar to influenza and other respiratory viral diseases, when SARS-CoV-2 infects and kills T lymphocyte cells, a profound decrease in lymphocyte numbers (Lymphopenia) may occur in COVID-19 patients (21).

Additionally, the impaired lymphopoiesis and increased lymphocyte apoptosis subsequent to the viral inflammatory response, which is consists of an initiate and adaptive immune response, also result in decreased lymphocyte count in individuals with COVID-19 (42, 43). Furthermore, the acceleration in viral replication compromises the epithelial-endothelial barrier integrity in the later stages of the infection (44, 45). SARS-CoV-2 also accentuates the inflammatory response and triggers an influx of monocytes and neutrophils by invading pulmonary capillary endothelial cells (44, 45). Interstitial mononuclear inflammatory infiltrates and pulmonary edema filling the alveolar spaces followed by hyaline membrane formation contribute to the early phase of acute respiratory distress syndrome (ARDS) (46). Bradykinin-dependent lung angioedema and high levels of proinflammatory cytokines may also contribute to the disease (44, 45). Collectively, disruption of endothelial barrier, alveolar-capillary oxygen transmission dysfunc-

tion, and impaired oxygen diffusion capacity seems to be the main features of COVID-19 infection (47).

COVID-19 and cardiovascular comorbidities

A study by Chen et al. have demonstrated that relying on the ACE2 mRNA expression in different human organs, ACE2 receptors are highly expressed in the gastrointestinal tract, testis, and kidney (48). Although quantitative reverse transcription PCR in the lungs of 12 autopsy cases with COVID-19 detected the SARS-CoV-2 RNA at high concentrations, the lung does not seem to have the highest expression of the main receptor for the virus entry (49). Analyses show that the human heart has a higher amount of ACE2 receptor expression than the respiratory system turning it to another susceptible target organ for direct SARS-CoV-2 invasion and tissue damage (48, 49). Additionally, cardiovascular tissue damage, whether caused by a direct viral invasion or due to endothelial damage, hyperactive immune responses, and ACE2 pathways maladaptation, might contribute to cardiovascular dysfunction symptoms (50).

Cardiovascular disease (CVD) was common comorbidity in SARS or MERS patients (51-54). A considerable number of reports on clinical characteristics of confirmed cases with COVID-19 have also described similar findings (51, 54, 55). Initial reports from China demonstrated that CVD and its risk factors, particularly hypertension and diabetes mellitus, were common comorbidities among COVID-19 patients (56-60). Further evaluations showed that the prevalence of preexisting comorbidity is higher in critically ill patients (22, 57). A multicenter cohort of a total of 191 COVID-19 hospitalized patients reported the prevalence of preexisting hypertension and CVD, 30% and 24% respectively (48% of total 191 involved cases had any comorbidity) (22). Studies also declare that a hazard mortality rate exists among COVID-19 patients with preexisting hypertensive disease (61-63). Zhou et al. report a mortality rate of 3.05, with a total of 191 COVID-19 patients (22). However, it remains to be studied whether this high death ratio is associated with hypertension pathogenesis itself or to the associated comorbidity or pharmacological treatment.

The role of antihypertensive drugs

Antihypertensive drugs are used to control and manage blood pressure in patients with hypertension (64, 65). A variety of different medications are indicated in patients with hypertensive disorders, among which RAAS inhibitors including angiotensin AT1-receptor blockers (ARBs) or Renin-angiotensin system blockade with angiotensin-converting enzyme inhibitors (ACEIs) have been at the center of considerable debate (66). These medications are commonly prescribed for individuals with hypertension with high effectiveness and approximately no adverse reactions or serious complications (28). Nevertheless, the question is, “Are ACEI/ARB medications still safe and effective during the COVID-19 infection?”.

As a potential factor in the infectivity of individuals, the interaction between the virus SARS-CoV-2 and RAAS caused several concerns about the use of RAAS inhibitors and its possible correlation to the action of ACE2 and the virulence of the disease (43). As mentioned above, studies demonstrated that SARS-CoV-2 is capable of binding to ACE2 cell receptors, causing not only a direct viral invasion to cardiac and lung cells but significant deregulation of RAAS and subsequent downregulation effect of ACE2, which contributes to the accumulation of angiotensin II with proinflammatory effect (38).

Some believe that the ACE2 deactivation might have harmful effects on the development and progression of respiratory failure (43). Studies have demonstrated that the use of RAAS inhibitors, particularly ACEI and/or ARB, may increase the expression of ACE2 receptor in the respiratory tract and patient susceptibility to viral host cell entry and dissemination, leading to severe life-threatening COVID-19 complications (67-69). The use of these drugs in animal models can lead to an upregulation effect of ACE2 receptors in the myocardium and lung cells, enhancing SARS-CoV-2 virulence through facilitating the viral entry into the host cells (43, 70). Although this hypothesis is not supported with evidential data in any aspect, it resulted in the discontinuation of ACEIs/ARB’s usage prophylactically in patients with suspected COVID-19 (71).

In contrast, some researchers represent the theory of ACEI/ARB usage being beneficial in COVID-19 patients. It is suggested that since ACE2 primarily counterpoises ACE’s effect, it can act as a vasodilator, antioxidant, and anti-inflammatory, where increased (72-75). ACE2 acts to generate Ang (1-7), which leads to a vasodilatory effect that is believed

Table 1. Studies which demonstrated positive association between COVID-19 and the use of RAAS inhibitors

Study first author	Date of publication	Objectives	Total patient number	Study detail	Results	Conclusion
Katherine W Lam[85]	2020 Jul 23	To investigate the effects of ACEI/ARB usage in hospitalized patients with preexisting hypertension.	614	• No significant difference in mortality and intensive care unit (ICU) admission rate between non-ACEi/ARB and ACEi/ARB groups • Lower ICU admission rate in patients with continued ACEI/ARB treatment.	Continued ACEI/ARB use is associated with better clinical outcomes in hypertensive COVID-19 patients
Yasushi Matsuzaw[86]	2020 Aug 21	To investigate the relation between ACEI/ARB's use and clinical manifestation and prognosis.	151	• No significant difference in mortality and ICU admission rate and the incidence of mechanical ventilation, primary composite outcomes and severe pneumonia between non-ACEi/ARB and ACEi/ARB groups	An association between ACEI/ARB use and a lower occurrence of mental confusion were noted. Thus, the use of ACEI/ARB in hypertensive COVID-19 patients may prevent COVID-19 induced confusion.
Juan Meng[87]	2020 March 31	To investigate the association between the use of RAAS inhibitors and clinical outcomes.	417	ACEI/ARBs: • Attenuated the inflammatory response. • Decreased Th1/Th2 cytokine ratios and inflammatory cytokine production in patients with chronic heart failure. •Benefit the immune system by avoiding peripheral T cell depletion	This study suggests that the use of RAAS inhibitors improves clinical outcomes.
Yun Feng[88]	2020 Apr 10	Comparison of the clinical characteristics (and outcome) of patients with COVID-19 from three different cities in China.	476	In this study, the use of antihypertensives in patients with COVID-19 was evaluated for the first time. The proportion of patients taking antihypertensives was higher in the moderate group. There were more patients taking ACEI/ARB in the moderate group. More case studies are needed in the future to further extend our preliminary conclusion. The mechanism and relationship between antihypertensives and the severity of COVID-19 remain to be studied.	The study demonstrated that the initial/continued use of RAAS inhibitors might be associated with reduced severity.

to be associated with SARS-CoV-2 pathogenesis according to some animal models, and these two agents may eventually be protective in lung injury models (71, 72, 76-79) (Table 1).

Meanwhile, several studies around the effects of ACEI/ARB usage in COVID-19 patients and its relation with patients' outcome demonstrated that current use of these medications is not associated with increased risk of COVID-19 severe complications requiring hospital admission, intensive care unit, or those that may lead to death (80) (Table 2). Collectively, RAAS inhibitors may be potential drugs for COVID-19 treatment in patients with preexisting hypertension due to their anti-inflammatory effects, particularly in critical COVID-19 patients.

Hypertensive COVID-19 patients

Numerous studies have focused on the patients' characteristics and/or agent dosing and treatment duration and how these factors may affect the outcomes in confirmed COVID-19 cases who underwent treatment with RAAS inhibitors. Li et al. have recently investigated whether the use of RAAS inhibitors in hypertensive COVID-19 patients aggravates the severity of the disease by a comparative study of computed tomography images (81).

The study analyzed 47 cases with confirmed laboratory nucleic acid assay of pharyngeal swab samples for COVID-19 hospitalized in Huoshenshan Hospital in Wuhan, Hubei Province, between February 18 and March 31, 2020 (81). Patients with hypertensive disorders were divided into two main groups based on individual long-term use of specific drug classes recorded in their medical records (81). Group A with long-term use of ACE inhibitors or/and ARBs and group B with chronic users of other antihypertensive drugs (group members were randomly selected and matched by age, sex, and underlying diseases) (81).

Patients were stratified into mild, normal, severe, and critical diseases using the "diagnosis and treatment of pneumonia infected by coronavirus disease 2019 (trial version 7)" criteria after collecting clinical histories, laboratory test results, and epidemiological histories (81, 82). Series of CT and laboratory examinations were performed for each included patient. Characteristics of the included patients in the study were compared in age, sex, laboratory results, time from chest CT examination to onset, and chest

CT score (81).

The results demonstrated that hypertensive COVID-19 patients with chronic use of ACE inhibitors and/or ARBs were not significantly different in the clinical characteristics or the results of routine blood, myocardial enzyme, liver function, renal function test, or chest CT pneumonia findings and did not develop severe complications compared with those who were taking other antihypertensive drugs (81).

On the other hand, a recent study noted that due to the hypothesis involving the entry mechanism of SARS-CoV-2 to the lung and the RAAS imbalance in favor of the proinflammatory effects of Ang II stimulating AT1 receptors, the clinical trials described using ACEi/ARBs have to be interpreted depending on the disease stage and severity, highlighting the start time of patients' prescription concerning the time of COVID-19 diagnosis as well as the administered daily dosage and duration of treatment (83).

In summary of guidelinepublished by European Society of Cardiology regarding the use of ACEIs/ARBs in patients with COVID-19, discontinuation of these medications is not recommended in patients with indications. They concluded that interrupting RAAS inhibitors in COVID-19 patients has no clinical benefit and is recommended to be continued for individuals with an indication of RAAS inhibitors usage (84).

Some studies have been shown in Tables 1 and 2 (85-92).

Table 2. Studies which demonstrated no association between COVID-19 and the use of RAAS inhibitors

Study first author	Date of publication	Study detail			Conclusion
		Objectives	Total patient number	Results	
Juan Simon Rico-Mesa[89]	2020 April 14	To examine whether the use of ACEI contributes to poor prognosis.	Review article	There is no association between patients clinical outcomes and use of ACEI/ARBs in COVID-19 patients	Continuing the use of ACEI/ARBs in COVID-19 patients is strongly recommended.
Peng Zhang[90]	2020 Apr 17	To define the association between hospitalized COVID-19 patients with hypertension and mortality rate.	1128	inpatient use of ACEI/ARB was associated with lower risk of mortality Among hospitalized patients with hypertensive COVID-19 compared with ACEI/ARB nonusers.	In-hospital association of ACEI/ARB use with an increased mortality risk of hypertensive COVID-19 patients seems unlikely.
Sara Tedeschi[91]	2020 Apr 27	To investigate the impact of long-term RAAS inhibitor treatment on in-hospital mortality.	311	The chronic use of RAAS inhibitors were not associated with outcomes.	Despite of finding no significant relevance the study recommends patients to continue their current hypertensive medication.
Chinonyerem O. Iheanacho[92]	2021 Mar 24	Effects of RAAS inhibitors on the risk of COVID-19 and its prognosis.	Systematic review	Nosignificant association between exposure to RAAS susceptibility to COVID-19	Evidence does not suggest higher risks for SARS-CoV-2 infection or poor disease prognosis in the use of RAAS inhibitors
Lopes RD[93]	2021	ACEI and ARBs in patients hospitalized with COVID-19	659 patients		No difference in outcome in patients with continue or discontinue of ACEIs or ARBs

CONCLUSION

According to the literature review in our article, the most evidentially supported theory about the use of RAAS inhibitors in COVID-19 is that these medications, including ACEI/ARB, are not associated with the increased risk of infection, disease severity, and patient prognosis. However, further studies are needed to support the hypothesis.

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