



Cardiovascular Disease and Use of Renin-Angiotensin System Inhibitors in COVID-19

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Abstract

There is ongoing debate on the safety of renin-angiotensin system (RAS) inhibitors in COVID-19. Recently published studies highlight a potential relationship between cardiovascular disease (CVD) and COVID-19. This article aims to summarize the evidence on the use of RAS inhibitors in CVD patients with COVID-19, focusing on safety issues of the RAS inhibitors and their relationship with COVID-19.

Key Points

Cardiovascular disease (CVD) has been reported as one of the most common comorbidities among patients with severe COVID-19

The established benefits of ACE inhibitors and ARBs in CVD outweigh the uncertain risks among patients at risk of COVID-19

As of 4 April 2020, 1,139,207 confirmed cases of novel coronavirus disease 2019 (COVID-19) have been reported worldwide [1]. Examination of the full-length genome revealed that the coronavirus responsible for COVID-19, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a β -coronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus, but in a different clade [2]. The structure of the receptor-binding gene region is very similar to that of the SARS coronavirus in which both employ the angiotensin-converting enzyme 2 (ACE2) for cell entry [2]. ACE2, a negative regulator of

the renin-angiotensin system (RAS), is a homolog of ACE, where its expression can be identified principally in the heart, kidney, and airway epithelial cells [3]. It functions as a carboxypeptidase by converting angiotensin II to angiotensin-(1–7), thereby opposing the vasoconstrictive effect of angiotensin II [4].

Currently available epidemiological studies have reported an increased prevalence of cardiovascular disease (CVD), including hypertension, among patients who developed a severe subtype of COVID-19 [5–10]. For example, the study by Guan et al. [5], which is one of the earliest analyses of the characteristics of Chinese patients with COVID-19, reported that the prevalence of coronary heart disease was more than fourfold higher among patients who developed the combined primary endpoint of admission to an intensive care unit, mechanical ventilation, or death, relative to patients with less severe outcomes. In addition, more recent studies [9, 10] that evaluated COVID-19-associated cardiac injury observed a high prevalence of hypertension (59.8–63.5%), coronary heart disease (29.3–32.7%), cardiomyopathy (15.4%) and chronic heart failure (14.6%) among COVID-19 patients complicated with cardiac injury, which is independently associated with mortality with COVID-19.

Since then, researchers tend to favor an association of CVD with the severity of COVID-19 [11, 12]. Nevertheless, interpreting such an association should be done with caution, since the validity of such an association is hampered by an unclear definition of CVD, including hypertension, adopted in these studies [5–10]. Without knowing the baseline CVD status of patients, it is hard to suggest that CVD is an added risk factor for developing severe COVID-19 infection. Moreover, the available studies originated from China,

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therefore the generalizability of such an association to the global population is limited. Patients with underlying CVD are likely to experience excessive morbidity from any cause because they have diminished circulatory reserve to meet the excessive demands on the cardiovascular system. Furthermore, since the prevalence of CVD is increased with age, age may act as a confounding factor; available studies also reported that older patients with COVID-19 tend to develop a severe course of the disease, including the development of cardiac injury [5–10]. Future studies with age-stratified analysis could shed some light on the association of CVD with the severity of COVID-19 infection.

On the other hand, some researchers have called to consider the safety of RAS inhibitors, including ACE inhibitors and angiotensin II type I receptor blockers (ARBs), among patients with COVID-19 [11, 12]. There has been speculation that patients with COVID-19 who are receiving these agents may be at increased risk for adverse outcomes, given that ACE2 is a functional receptor for SARS-CoV-2 and RAS inhibitors can increase ACE2 levels [11, 12]. However, an increased level of ACE2 upon exposure to RAS inhibitors has not been a universal finding. While some animal studies [13–18] have noticed an increased expression of ACE2 upon exposure to ACE inhibitors or ARBs, other studies reported otherwise [19, 20]. The findings from human studies [21–24] have discredited the association of levels of ACE2 with the use of ACE inhibitors and ARBs, although one study [25] did notice an increased urinary secretion of ACE2 in hypertensive patients treated with the ARB olmesartan, but not with other ACE inhibitors and ARBs. Furthermore, another study [26] demonstrated an increased gene expression for ACE2 in the small intestine of patients under ACE inhibitor/ARB treatment compared with untreated controls. In addition, the elevation of serum ACE2 was only found in patients with unsatisfactory blood pressure control utilizing ACE inhibitor therapy, as reported in a study among hypertensive subjects [27]. Therefore, the effect of RAS inhibitors on ACE2 among human subjects is mainly due to the expression of ACE2 in the plasma, kidney and gastrointestinal system, and is not the known effect, if any, of RAS inhibitors on the expression of ACE2 in human airway epithelial cells. Furthermore, increased expression of ACE2 did not correspond to increased ACE2 activity in an animal study [16], and it is not known if the biological effect on ACE2 would wane immediately upon discontinuation of ACE inhibitors and ARBs.

The role of ACE2 in coronavirus infection is still controversial. Although ACE2 is a prerequisite for infectivity of SARS-CoV, the presence of other co-factors seems to be important for efficient cellular infection, since SARS-CoV was also identified in cell types lacking ACE2 expression [28]. In addition, the upregulation of ACE2 is not entirely harmful, since, paradoxically, an increased level of ACE2

might protect against coronavirus-induced lung injury [29]. Binding of the coronavirus spike protein to ACE2 leads to ACE2 downregulation, which in turn results in excessive production of angiotensin II [30]. As angiotensin II increases pulmonary vascular permeability, it could produce lung injury and impair lung function [30, 31]. Coincidentally, a study that investigated the clinical and biochemical parameters of patients with COVID-19 observed that levels of angiotensin II were higher compared with healthy controls [32]. Moreover, angiotensin II levels were linearly associated with lung injury, supporting the hypothesis that angiotensin II is responsible for lung injury in COVID-19. As previously mentioned, the clinical course of COVID-19 can be complicated by cardiac injury manifested by increased biomarkers, which portends a worse prognosis, and ACE2 plays a significant role in myocardial recovery response [9, 10, 33]. Indeed, in some of the heart samples from patients who died from SARS, the presence of viral RNA was identified, which was associated with reduced ACE2 protein expression [34].

The safety issue of ACE inhibitors and ARBs has since created great concerns on social media sites, but emerging data are reassuring. A retrospective observational study [35] published in the Chinese language reported that the use of ACE inhibitors or ARBs did not differ significantly between patients who recovered and patients who died from COVID-19, suggesting that the use of RAS inhibitors may not result in worse prognosis, although a conclusion on the safe use of RAS inhibitors could not be firmly drawn from this study due to the limited number of patients receiving RAS inhibitors ($n = 22$). However, another recent retrospective study [36] reported that COVID-19 patients with underlying hypertension taking ACE inhibitors/ARBs had a much lower proportion of critical disease (9.3% vs. 22.9%; $p = 0.061$) and a lower mortality rate (4.7% vs. 13.3%; $p = 0.283$) than their hypertensive counterparts not receiving an ACE inhibitor/ARB. Furthermore, patients taking ACE inhibitors/ARBs had significantly lower levels of C-reactive protein and procalcitonin when compared with patients not receiving an ACE inhibitor/ARB, suggesting a potential anti-inflammatory function in COVID-19.

RAS inhibitors could be indicated for chronic heart failure or chronic kidney disease, in which self-discontinuation of these agents without prior consultation with physicians may lead to decompensation within days to weeks, further compromising cardiopulmonary reserve in patients at risk of COVID-19 [37, 38]. The benefits that are specific to ACE inhibitors/ARBs may not be recapitulated by other antihypertensive agents for these diseases. While no data have been reported on the effect of temporary discontinuation of RAS inhibitors on mortality among patients with COVID-19, the shreds of evidence extrapolated from other patient settings suggest harm, in which studies from the Veterans Affairs Healthcare System showed that non-resumption of ARBs

Table 1 Position statements of selected major cardiovascular societies on the use of renin-angiotensin system inhibitors in the context of COVID-19 [41]

Society	Position statement	Date, website
European Society of Hypertension	“The currently available data on COVID-19 infections do not support a differential use of RAS blockers (ACEI or ARBs) in COVID-19 patients”	12 March 2020 https://www.eshonline.org/spotlights/esh-statement-on-covid-19/
European Society of Cardiology	“... strongly recommend 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 ACEi or ARBs should be discontinued because of the COVID-19 infection”	13 March 2020 https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang
Canadian Cardiovascular Society, Canadian Heart Failure Society	“The Canadian Cardiovascular Society and the Canadian Heart Failure Society strongly discourage the discontinuation of guideline-directed medical therapy (GDMT) involving Angiotensin-Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARB) or Angiotensin Receptor Neprilysin Inhibitors (ARNi) in hypertensive or heart failure patients as a result of the COVID-19 pandemic”	15 March 2020 https://www.ccs.ca/images/Images_2020/CCS_CHFS_state_ment_regarding_COVID_EN.pdf
International Society of Hypertension	“... there is no good evidence to change the use of ACE-inhibitors or ARBs for the management of raised blood pressure in the context of avoiding or treating COVID-19 infection”	16 March 2020 https://fsh-world.com/news/a/A-statement-from-the-International-Society-of-Hypertension-on-COVID-19/
American Heart Association, Heart Failure Society of America, American College of Cardiology	“... recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease”	17 March 2020 https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19

within 2 days, or ACE inhibitors within 14 days, after surgery was associated with higher 30-day mortality rates [39, 40]. The risk of fall in the elderly population from abruptly stopping long-term medication (e.g. ACE inhibitors) could result in significant adverse consequences by increasing the risk of fractures and bleeding.

In conclusion, although CVD has been reported as one of the most common comorbidities among patients with severe COVID-19, the association of CVD with the severity of COVID-19 has yet to be confirmed, since, thus far, there is no biological connection between CVD and viral replication. In addition, the established benefits of ACE inhibitors and ARBs in CVD outweigh the uncertain risks among patients at risk of COVID-19 since available evidence demonstrated no direct pathological relationship between RAS blockade and COVID-19. Therefore, we echo the position statements (Table 1) of some of the major cardiovascular societies [41] to discourage the discontinuation of ACE inhibitors or ARBs in patients with COVID-19. Such statements should provide reassurance to clinicians who would like to continue using ACE inhibitors and ARBs among patients at risk of COVID-19. Furthermore, an ongoing clinical trial of COVID-19-infected patients receiving an ACE inhibitor/ARB randomized to either an alternative antihypertensive medication or continuation of the ACE inhibitor/ARB therapy may provide a definitive answer to this debate [42].

Compliance with Ethical Standards

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Conflict of interest Chia Siang Kow, Syed Tabish Razi Zaidi, and Syed Shahzad Hasan declare that they have no potential conflicts of interest that might be relevant to this manuscript.

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