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Good or bad: Application of RAAS inhibitors in COVID-19 patients with cardiovascular comorbidities

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Abstract

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The coronavirus disease 2019 (COVID-19) pandemic is caused by a newly emerged coronavirus (CoV) called Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). COVID-19 patients with cardiovascular disease (CVD) comorbidities have significantly increased morbidity and mortality. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 blockers (ARBs) improve CVD outcomes; however, there is concern that they may worsen the prognosis of CVD patients that become infected with SARS-CoV-2 because the virus uses the ACE2 receptor to bind to and subsequently infect host cells. Thus, some health care providers and media sources have questioned the continued use of ACE inhibitors and ARBs. In this brief review, we discuss the effect of ACE inhibitor-induced bradykinin on the cardiovascular system, on the renin–angiotensin–aldosterone system (RAAS) regulation in COVID-19 patients, and analyze recent clinical studies regarding patients treated with RAAS inhibitors. We propose that the application of RAAS inhibitors for COVID-19 patients with CVDs may be beneficial rather than harmful.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a newly recognized infectious disease caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). Since the outbreak in December 2019, it spreaded rapidly and eventually caused an ongoing worldwide pandemic. According to the World Health Organization (WHO), as of June 22, 2020, SARS-CoV-2 has infected over 8,000,000 people and resulted in more than 460,000 deaths. The lack of effective anti-viral therapy and rapid emergence of COVID-19 have placed frontline physicians in a difficult position of battling an unknown disease with unproven conventional therapies. Thus, it is important to fully and correctly...
understand COVID-19 pathophysiology to effectively treat patients in order to minimize morbidity and mortality. Published literature indicates that the highest risk of death is in patients with previous heart disease and other cardiovascular comorbidities (De Rosa et al., 2020).

Renin-angiotensin-aldosterone system (RAAS) inhibitors, which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 blockers (ARBs) are widely used for treatment of hypertension, heart failure and coronary heart disease. SARS-CoV-2 can bind to the angiotensin-converting enzyme 2 (ACE2) as a receptor to facilitate cell fusion and entry which suggests a direct interaction between SARS-CoV-2 and the RAAS which may compromise normal RAAS function.

Hypertension in patients who develop COVID-19 is a common occurrence. In a study including 1099 confirmed COVID-19 patients from 552 hospitals in China, 23.7% of these patients had hypertension (Guan, et al., 2020). In another study, cerebrovascular disease was observed in 22% of 32 non-survivors from 52 patients in the intensive care unit (Yang et al., 2020b). Additionally, Zhang et al. reported that hypertension was the most common comorbidity of severe COVID-19 patients, present in 30% of the hospitalized individuals (Zhang et al., 2020a). ACE inhibitors and ARBs are first-line treatments for patients with hypertension. A recent review demonstrated that application of ACE inhibitors or ARBs could significantly upregulate ACE2 expression and enhance its activity, thus raising a valid concern that these treatments may facilitate the infectivity of SARS-CoV-2 (South, Diz, & Chappell, 2020). In addition, ACE inhibitors can lead to increased activation of the kallikrein-bradykinin system. Elevated bradykinin expression can induce airway hyperresponsiveness and pulmonary edema which could potentially lead to the deterioration of COVID-19 patients (Aztatzi-Aguilar, Uribe-Ramirez, Arias-Montano, Barbier, & De Vizcaya-Ruiz, 2015; Cao et al., 2020). Based on these concerns, some researchers have suggested that ACE inhibitors and ARBs should be discontinued in COVID-19 patients with hypertension (Diaz, 2020; Esler & Esler, 2020; Fang, Karakiulakis, & Roth, 2020).

Conversely, COVID-19 can induce severe cardiac injury (Shi et al., 2020a), which would benefit from the treatment with RAAs inhibitors. COVID-19-induced cytokine storm and increased RAAS activation might enhance the inflammation in the lungs and other organs (C. Chen, Li, Hang, & Wang, 2020b; Romero, Orias, & Weir, 2015). Therefore, there is an urgent need to develop guidelines for the use of these drugs during SARS-CoV-2 infection. In this review, we discuss the effects of ACE inhibitors on bradykinin-induced signaling in the cardiovascular system, the roles of RAAS activation in the COVID-19-induced cytokine storm and lung inflammation, and examine recent clinical outcomes observed with RAAs inhibitors in COVID-19 patients.

2. Comparison of SARS-CoV-2 with other coronaviruses

Human CoVs (HCoVs) belong to the Coronavirinae subfamily that are classified into 4 phylogenetic clusters: α, β, γ, and δ CoVs (Zhang et al., 2018). Among all CoVs, 7 prominent strains from the α and β subgroups can infect humans (Madjid, Safavi-Naeini, Solomon, & Vardeny, 2020). Of these 7 human-infectious CoVs, 4 (HCoV-NL63, HCoV-HKU1, HCoV-OC43 and HCoV-229E) cause self-resolving upper respiratory tract infections that are the second-most common cause (15–30%) of the common cold (Killerby et al., 2018; Su et al., 2016). Clinical manifestation vary in different strains of CoVs. HCoV-NL63, HCoV-HKU1, HCoV-OC43 and HCoV-229E mainly cause mild symptoms, but can cause organ damage in some individuals. For example, Giacomo et al. reported that HCoV-OC43 triggered fulminant myocarditis in a 51-year-old woman (Veronese et al., 2020).

Three CoVs, SARS-CoV, Middle East Respiratory Syndrome coronavirus (MERS-CoV) and SARS-CoV-2 lead to severe respiratory and systematic diseases termed SARS, MERS, and COVID-19, respectively. SARS-CoV emerged in Guangdong Province in China in 2002, the MERS-CoV epidemic began in Saudi Arabia in 2012, and SARS-CoV-2 emerged in Wuhan, China in 2019 (de Wit, van Doremalen, Falzarano, & Munster, 2016). While these three viruses can induce respiratory distress, they each have distinctive properties (Table 1). SARS-CoV-2 is most infectious, with a reproductive number (R0) estimated by the WHO of 2.0–2.5. By comparison, SARS-CoV and MERS-CoV have respective R0 estimates of 1.7–1.9 and 0.7, respectively (Petrosillo, Viceconte, Ergonul, Ippolito, & Petersen, 2020). Meanwhile, MERS-CoV and SARS-CoV infections elicit higher risk of organ damage, multi-organ failure and death than SARS-CoV-2. In contrast, SARS-CoV-2 appears to more often be associated with asymptomatic disease (Arons et al., 2020). Case reports of MERS patients reveal elevated creatinine, lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which suggest renal and liver damage (Al-Tawfiq et al., 2014; Arabi et al., 2014; Chafekar & Fielding, 2018). Patients with SARS and COVID-19 show signs multiple organ damage including effects in the heart, kidney and liver (Gu et al., 2005; Zhang et al., 2020b). The average of fatality rate is lowest in COVID-19 patients, with estimated death rates of 0.7%, 10% and 30% for COVID-19, SARS and MERS patients, respectively (Madjid et al., 2020).

The major structural proteins of CoVs are the spike protein (S), small envelope protein, matrix protein (M) and nucleocapsid protein (N). Genomic comparisons reveal that SARS-CoV-2 shares 82% nucleotide identity with SARS-CoV but is less similar to MERS-CoV (~50% nucleotide identity; Fig. 1) (Chan, et al., 2020). The 3′-terminus of the genome contains the four major structural proteins and eight accessory proteins (3a, 3b, p6, 7a, 7b, 9b and/or f14). Although SARS-CoV-2 is closely related to SARS-CoV, there are some notable differences between the two strains. For example, the 8a protein is absent in SARS-CoV-2 while present in SARS-CoV; the 8b protein in SARS-CoV-2 is 121 amino acids compared with 84 amino acids in SARS-CoV; protein 3b is much shorter in SARS-CoV-2 (22 amino acids) than in SARS-CoV (154 amino acids) (Wu et al., 2020). It remains unclear the extent to which these differences alter virulence or mortality. Both SARS-CoV and SARS-CoV-2 binds to the same surface protein (ACE2) while MERS-CoV enters host cells via binding to dipeptidyl peptidase 4 (DPP4) (Petrosillo et al., 2020). Relative to the SARS-CoV spike protein, the SARS-CoV-2 spike protein contains several amino acid changes which increase salt bridge formation and hydrophobic interactions and strengthen ACE2 binding (Ghebelayi et al., 2020). These changes may contribute to virulence and the considerably larger global spread of SARS-CoV-2 compared to SARS-CoV (Ghebelayi et al., 2020).

3. Effects of SARS-CoV-2 infection on ACE2 expression

ACE2 is a transmembrane protein that plays a central role in downregulation of RAAS (Ghebelayi et al., 2020). When co-expressed with transmembrane protease serine 2 (TMPRSS2), ACE2 acts as receptor for SARS-CoV-2 cell entry (Guzik et al., 2020). ACE2 expression is

| Nucleotide identity | SARS-CoV-2 | SARS-CoV | MERS-CoV |
|---------------------|------------|----------|----------|
| (Reference SARS-CoV-2) | 100% | 82% | 50% |
| Genome length (kb) | 29.9 | 29.7 | 30.1 |
| Spike protein (amino acids) | 1273 | 1255 | 1270 |
| Receptor | ACE2 | ACE2 | DPP4 |
| Animal reservoir | bats or Malayan pangolins probably | masked dromedary camels | |
| R0 | 2–2.5 | 1.7–1.9 | 0.7 |
| Average fatality rate | 5% | 10% | 30% |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; R0, reproductive number. Average fatality rate of SARS-CoV-2 infection is calculated according to the WHO situation report on June 22, 2020. NCBI reference sequences: NC_045512.2 (SARS-CoV-2), NC_007198.3 (SARS-CoV), NC_019843.3 (MERS-CoV).
considerably reduced after SARS-CoV and SARS-CoV-2 infection (Jung, Choi, You, & Kim, 2020). Interaction between ACE2 and the receptor binding domain (RBD) of the S1 subunit on the viral spike protein facilitates virus entrance. Endocytosis of SARS-CoV-2 along with ACE2 into endosomes reduces surface ACE2 expression (K. Wang, Gheblawi, & Oudit, 2020). Viral entry of SARS-CoV-2 subsequently upregulates ADAM metallopeptidase domain 17 (ADAM-17), which mediates ectodomain shedding of ACE2 (Patel et al., 2014). ADAM-17 activation also mediates liberation of membrane bound cytokine precursors, including IL-4 and IFN-γ which repress ACE2 mRNA expression (Wang, Gheblawi, & Oudit, 2020). SARS-CoV-2 activation of RAAS combined with reduced ACE2-mediated conversion of angiotensin II (Ang II) to Ang-(1–7) results in increased AngII accumulation. Ang II activates the angiotensin receptor type 1 receptor (AT1R) to trigger a signaling cascade whereby activation of ERK/p38 MAP kinase signaling results in upregulation of ADAM-17 to initiate a positive feedback loop that limits ACE2 expression (Patel et al., 2014). In addition, inflammation-induced lung injury leads to apoptosis of Clara cells and type II alveolar epithelial cells, which are major ACE2-expressing cell subsets. Reduced survival of these cells also contributes to the down-regulation of ACE2 (Fig. 2) (Wiener, Cao, Hinds, Ramirez, & Williams, 2007).

4. Potential benefit from kinin and bradykinin produced by ACE inhibitors

Clinical outcomes in COVID-19 patients are strongly associated with the pre-existing health status of infected patients. CVD comorbidities increase mortality of patients with COVID-19 (Shahid et al., 2020). CVD comorbidities have direct consequences upon SARS-CoV2 infection. For example, patients with abnormally high blood pressure may exhibit
increased apoptosis, not only in the heart but also in the kidney, which may be exacerbated by the additional stress of SARS-CoV2 infection (Gonzalez et al., 2003; Hamet et al., 1995). Over the course of severe COVID-19, biomarkers indicating heart injury become elevated (Mehta et al., 2020; Shi et al., 2020b). In a Washington state case series of 21 critically ill COVID-19 patients, 7 patients (33%) developed cardiomyopathy and 4 (19%) developed acute renal injury (Arentz et al., 2020). ACE2 expression in human heart might be one potential mechanism underlying heart injury during infection with SARS-CoV-2; however, SARS-CoV-2 infection-induced cytokine storm may also contribute to cardiovascular injury (Chen, Li, Chen, Feng, & Xiong, 2020a).

Tissue kallikrein produces kinin and bradykinin peptides by cleaving its substrate kininogen. In addition to its role in production of angiotensin II, ACE mediates bradykinin degradation. Thus, both kinin and bradykinin are increased with use of ACE inhibitors (Fig. 3). Increased bradykinin levels are believed to be responsible for the dry cough adverse effect observed in some patients on ACE inhibitors. Moreover, kinin and bradykinin peptides can also participate in shock and respiratory allergy. Thus, well-known side effects suggest that ACE inhibitors may aggravate lung inflammation and cause lung dysfunction during COVID-19.

Despite the potential adverse effect of dry cough on respiratory tract, the kallikrein/kinin system (KKS) has many positive functions which may ameliorate CVD (Fig. 3). In experimental models, the expression of human tissue kallikrein caused significant reduction of blood pressure in fructose-induced hypertension rats, but did not affect blood pressure of non-fructose-fed normal rats (Yao, Yin, Shen, Chao, & Chao, 2007). Accumulating evidence indicates that the KKS is capable of exerting organ protection apart from its blood pressure-lowering effect. An in vivo study showed that the infusion of kinin improved renal function of hypertensive rats and lowered the corresponding increase in capase-3 activity (Chao et al., 2007). Recombinant adeno-associated virus (rAAV) mediated human tissue kallikrein exerted a protective effect on myocardial apoptosis in spontaneous hypertensive rats (SHRs), specifically by modulating the activity of caspase-3 through the B2 receptor (Yan, Wang, & Wang, 2009). Tissue kallikrein not only reduced blood pressure, but also attenuated remodeling of the myocardium, large blood vessels and kidney (Wang et al., 2004). In addition, tissue kallikrein efficiently protected against diabetic nephropathy and chronic renal failure (Tu et al., 2008; Yuan et al., 2007; Zhao et al., 2003). It has also been suggested that tissue kallikrein prevents apoptosis and ventricular remodeling after myocardial infarction (Yao et al., 2007).

In summary, bradykinin may improve blood pressure regulation and provide organ protection in hypertensive patients. Since organ injury often determines mortality in hypertensive patients infected with SARS-CoV-2, we hypothesize that the ‘by product’ of increased bradykinin levels induced by ACE inhibition may provide more benefit than harm in CVD-comorbid COVID-19 patients.

5. RAAS activation in SARS-CoV-2-induced cytokine storm

Many studies have demonstrated that Ang II–induced hypertension and the accompanying vascular inflammation result in organ damage (Chen et al., 2017; Chen et al., 2019; Gonzalez et al., 2015; Yang et al., 2018). IL-6 plays an important role in mediating heart damage. Genetic disruption of Il6 markedly attenuates the cardiac injury and inflammation induced by Ang II, which suggests that IL-6 acts downstream of the Ang II effector (Chen et al., 2017; Chen et al., 2019; Gonzalez et al., 2015; Yang et al., 2018). Ang II also induces the production of other pro-inflammatory cytokines, such as TNF-α and IL-1β (Guo et al., 2011). Several studies suggest that Ang II not only acts as a vasoactive peptide that regulates blood pressure but also works as an inflammatory cytokine causing cardiovascular remodeling (Gibbons, Pratt, & Dzau, 1992; Griendling, Minieri, Ollerenshaw, & Alexander, 1994; Sadoshima & Izumo, 1993). During the immune response activated by SARS-CoV-2, a cytokine storm is often observed. In severe cases,
serum levels of pro-inflammatory cytokines including IL-6, IL-2R, and IL-1β are elevated (Huang et al., 2020; Qiu et al., 2020; Xu et al., 2020). Increased markers of this cytokine storm, such as serum IL-6, predict poor outcome in patients with severe COVID-19 (Cao, 2020). COVID-19 patients also have elevated Ang II levels which are positively associated to viral load and lung injury (Liu et al., 2020). Thus, SARS-CoV-2 infection dysregulates Ang II, over-activates the immune response and augments the cytokine storm that causes organ damage. The inhibition or the blockade of RAAS may be helpful to attenuate the inflammatory storm and prevent end-organ damage.

ACE2 plays an important role in the regulation of angiotensin signaling. The generation of Ang II is well understood. Liver-derived angiotensinogen (ATG) is cleaved by renin into Ang I, which is further processed by ACE to Ang II, and is converted by ACE2 into Ang-(1–7). Ang-(1–7) is generally considered CVD-protective; it counters the action of Ang II through a G protein-coupled receptor (GCRK), MAS. Previous studies demonstrated that both SARS-CoV-2 and SARS-CoV (which caused the SARS epidemic in 2003) spike proteins (S proteins) bind to the extracellular domain of ACE2. SARS-CoV-2 uses ACE2, abundantly expressed in pulmonary epithelium, kidney and heart, for intracellular entry (Fig. 3). After infection by SARS-CoV-2, ACE2 expression is reduced (Crackower et al., 2002; Imai et al., 2005; Kuba et al., 2005). Animal models of infection with SARS-CoV showed that ACE2 downregulation resulted in pro-inflammatory responses, including lung injury and cardiac contractility impairment (Crackower et al., 2002; Imai et al., 2005; Kuba et al., 2005). If SARS-CoV-2 infections progress similarly to SARS-CoV, the virus may deteriorate a patient’s condition via two mechanisms. First, lower ACE2 expression decreases the degradation of Ang II. Overabundance of Ang II has multiple deleterious cardiovascular consequences including elevating blood pressure, cardiomyocyte apoptosis, cardiac infiltration by macrophages and secretion of pro-inflammatory cytokines. Second, less ACE2 reduces the formation Ang-(1–7) and its CVD-protective vasodilatory, anti-inflammatory, anti-fibrillatory and anti-proliferative effects (Lelis, Freitas, Machado, Crespo, & Santos, 2019; Patel, Zhong, Grant, & Oudit, 2016). In particular, Ang-(1–7) can diminish IL-6, TNF-α, macrophage infiltration, vascular cell adhesion protein 1 (VCAM-1) and increase nitric oxide release. Together, these effects increase the survival of cardiomyocytes during inflammation (Simoese Silva, Silveira, Ferreira, & Teixeira, 2013). Moreover, Ang-(1–7) promotes resolution of vascular inflammation in vivo by decreasing VCAM-1, IL-6 and MCP-1 (Zhang et al., 2015). Decreased levels of ACE2 may lead to a deficiency of Ang-(1–7) production and contribute to tissue damage in COVID-19. Although ACE inhibitors and ARBs do not directly affect ACE2, they can indirectly lead to increased ACE2 activity and Ang-(1–7) expression (Hanff, Harhay, Brown, Cohen, & Mohareb, 2020). A study by Ferrario and co-workers showed that ACE inhibitor caused a 2.5-fold rise of plasma Ang-(1–7) concentrations and an approximately 25% increase of ACE2 expression in the left ventricle (Ferrario et al., 2005). Thus, the usage of ACE inhibitors and ARBs may have a potential benefit in preventing COVID-19-triggered organ damage via its upregulation of Ang-(1–7) and depletion of Ang II.

In conclusion, dysregulation of RAAS due to increased Ang II and decreased ACE2 can lead to a harmful inflammatory response and worsening of elevated blood pressure. ACE inhibitors and ARBs may have a potential role in preventing the harmful effects by directly countering Ang II and upregulating ACE2.

6. Pulmonary consequences induced by dysregulation of RAAS in COVID-19

Acute respiratory distress syndrome (ARDS) is a common and devastating development in patients with COVID-19. ARDS is characterized by high permeability pulmonary edema, severe hypoxemia, and acute respiratory distress (Wosten-van Asperen et al., 2011). Diffuse alveolar damage and an acute inflammation response characterized by high vascular permeability, increased vascular tone and fibroblast activation play a central role in ARDS pathophysiology (Marshall et al., 2002). Local RAAS signaling occurs in the lung as lung fibroblasts, alveolar macrophages and epithelial cells are capable of synthesizing RAAS components (Wosten-van Asperen et al., 2011). Considerable evidence suggests that dysregulation of RAAS and increased Ang II levels induce ARDS symptoms, including hypoxemia, vasoplegia and ventilation/perfusion ratio (V/Q) mismatching (Evans, McCurdy, Weiner, Zaku, & Chow, 2019; Guazzi, Melzi, Marenzi, & Agostoni, 1999; Kaparianos & Argyropoulou, 2011).

Previous findings suggest that increased ACE expression or activity may exacerbate inflammation in subjects with COVID-19. Pulmonary capillary beds are a large reservoir of endothelial-bound ACE (Orfanos et al., 2000). ACE activity is considerably elevated in the bronchoalveolar lavage fluid (BALF) of patients with ARDS (Idell et al., 1987). A polymorphic insert that reduces ACE expression and activity is associated with reduced ARDS severity (Marshall et al., 2002). ACE expression activates macrophage function and stimulates interleukin (IL) formation (Shen et al., 2007). COVID-19 is associated with an increased proportion of mononuclear phagocytes which are regulated by the RAAS (Merad & Martin, 2020). In addition, alveolar macrophages are associated with tissue repair and fibrosis generation in COVID-19 patients (Ramachandran et al., 2019). Lastly, ACE inhibitors decrease oxygen free radical production generated by lung alveolar macrophages (Suzuki et al., 1999).

Since ACE is detectable in the entire alveolar capillary network of human lung, conversion from Ang I to Ang II can rapidly occur in the pulmonary circulation (Metzger, Franke, Bohle, Ahlenc-Gelas, & Danilov, 2011). Excessive Ang II can lead to significant effects during COVID-19-induced ARDS through several mechanisms. Ang II-induced vasconstriction in the pulmonary circulation can cause low blood flow, V/Q mismatching and hypoxemia (Zhang & Baker, 2017). Ang II-induced vascular permeability and vasoconstriction can result in pulmonary edema (Yamamoto et al., 1997). Ang II can also induce endothelial expression of IL-8, E-selectin, P-selectin, CC-chemokine ligand-5 (CCL5) and CCL2 which increase pulmonary leukocyte recruitment and retention (Bernstein et al., 2018). Moreover, Ang II induces nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in vascular smooth muscle cells and endothelial cells to increase reactive oxygen species (ROS) and cause vascular injury (Bernstein et al., 2018). In addition, Ang II reduces alveolar epithelial cell survival by accelerating cellular apoptosis with an EC50 of just 10 nM (Wang et al., 1999). Epithelial apoptosis is linked to subsequent fibrotic responses (Shetty et al., 2017).

Prolonged hyperinflammation in ARDS or COVID-19 can cause progressive tissue damage. Unchecked inflammation can induce a state of dysregulated tissue repair and lung fibrosis. Lung fibrosis thickens alveolar walls, reduces lung compliance, obliterates alveolar air spaces and impairs gas exchange. Ang II is implicated in tissue repair or, when in excess, lung fibrosis (Uhal, Li, Piasceki, & Molina-Molina, 2012). Actin through the actinogenins II receptor type 1 (AT1R), Ang II activates p38 and p42/44 MAPK, induces DNA synthesis and fibroblast proliferation (Konigshoff et al., 2007; Marshall, McNulty, & Laurent, 2000a; Marshall, Puddicombe, Cookson, & Laurent, 2000b). Furthermore, Ang II activates fibroblasts synthesis and deposition of extracellular matrix (ECM) including type I collagen that thickens alveolar walls and reduces lung compliance (Uhal et al., 2012). Finally, during the severe ARDS or COVID-19, patients often suffer from septic shock. Prolonged Ang II signaling induces AT1R phosphorylation and desensitization which is a major cause of the vascular hyporesponsiveness that leads to pulmonary vasoplegia (Levy et al., 2018). Together, this data suggests that Ang II may be a potential therapeutic target for the treatment many vascular pathophysiologies of COVID-19.

ACE2 is an indispensable regulator in the RAAS that counteracts ACE and Ang II. Lower ACE2 has deleterious cardiovascular consequences and also worsens lung functional decline. Compared to WT mice, Ace2-deficient mice had impaired lung function and higher mortality in sepsis-induced lung injury (Imai et al., 2005). Severe lung failure in
Ace2-deficient mice could be rescued by inactivation of ACE and AT1R blockade (Imai et al., 2005). ARBs can prevent downregulation of ACE2 during LPS-induced ARDS, suggesting that RAAS inhibitors may also protect against lung damage in patients with SARS (Wosten-van Asperen et al., 2011). Furthermore, downregulation of ACE2 can lead to elevated activation of ACE and Ang II (Li et al., 2008; Simoese Silva et al., 2013), which can exacerbate the physiological progression of ARDS in COVID-19. Thus, despite acting as the receptor for SARS-CoV-2, ACE2 activity is likely protective during COVID-19 disease progression.

In conclusion, elevation of ACE and Ang II and down-regulation of ACE2 can exacerbate SARS-CoV-2 induced ARDS. Drugs that target ACE and Ang II, ACE inhibitors and ARBs, may play an important role in abrogating the inflammatory response, vasoconstriction and V/Q mismatching that causes clinical deterioration in patients with COVID-19.

7. Clinical outcomes of RAAS inhibitor treatment in COVID-19 patients

Animal models and clinical experience suggest both beneficial and deleterious effects of ACE inhibitors and ARBs in patients suffering from COVID-19. This uncertainty raises concerns regarding the overall effect of RAAS inhibitors after SARS-CoV-2 infection (Sriram & Insel, 2020). Such concerns should not be ignored. Examination of clinical outcomes of RAAS inhibitor application in COVID-19 patients should be a top priority (Zhou et al., 2013).

Accumulated clinical data demonstrates that hypertension is associated with higher mortality in patients with COVID-19, SARS and Middle East Respiratory Syndrome (MERS) (Wang et al., 2020; Zhou et al., 2020). Guidance on management of high blood pressure is required for this special situation. A jointly published statement by American Heart Association (AHA), the American College of Cardiology (ACC) and the Heart Failure Society of America strongly recommended continuation of ACE inhibitor/ARBs (Zhang, Zhu, et al., 2020b). Although we have illustrated that ACE inhibitors/ARBs can theoretically benefit COVID-19 patients with hypertension, further evidence regarding the effect of ACE inhibitor/ARB usage is indispensable. Several clinical studies based on the application RAAS inhibitors in COVID-19 patients with hypertension were carried out in the past few months (Table 2).

A large-scale study included 1128 hospitalized patients with hypertension and COVID-19 infection from nine hospitals in Hubei Province, China (Zhang, Dong, et al., 2020a). During the 28-day follow up, all-cause mortality of patients in the ACE inhibitor/ARB group was significantly lower than in the non-ACE inhibitor/ARB group (3.7% [7/188] versus 9.8% [92/940]). In addition, incidence of disseminated intravascular coagulation (0.0% in ACE inhibitor/ARB group versus 2.3% in non-ACE inhibitor/ARB group) and septic shock (3.2% in ACE inhibitor/ARB group versus 8.0% in non-ACE inhibitor/ARB group) were also lower. The findings in this multi-center, retrospective cohort study provide compelling evidence for potential beneficial effects in ACE inhibitors and ARBs, and supports continuous usage of these drugs in hypertensive COVID-19 patients. A more recent retrospective study by Yang et al. in April 2020 reported similar observations (Yang et al., 2020a). Hypertensive COVID-19 patients using ACE inhibitors/ARBs had lower proportion of critically ill patients (9.3% versus 22.9%) and mortality rate (4.7% versus 13.3%) than hypertensive COVID-19 patients that were not on ACE inhibitors/ARBs.

Jung et al. reported a nationwide cohort study on the use of RAAS inhibitors in COVID-19-related outcomes in South Korea (Jung et al., 2020). Among the 5179 confirmed SARS-CoV-2 patients, RAAS inhibitor use did not alter mortality (adjusted OR, 0.88; 95% CI, 0.53–1.44; p = .60) (Jung et al., 2020). Among hospitalized COVID-19 patients with hypertension, in-hospital mortality was lower (9%) in patients given RAAS inhibitors than those not treated with RAAS inhibitors (13%) although this difference was not statistically significant (p = .14) (Jung et al., 2020). Multivariate analysis that adjusted for baseline co-morbidities revealed no independent association between RAAS inhibitor use and risk mortality among hypertensive COVID-19 patients (adjusted OR, 0.71; 95% CI, 0.40–1.26; p = .25) (Jung et al., 2020). Similarly, Mancia et al. retrospectively examined 6272 patients and found no association between RAAS inhibitor use and susceptibility or evolution of COVID-19 (Mancia, Rea, Ludergnani, Apolone, & Corrao, 2020). Adjusted OR for risk of SARS-CoV-2 infection was 0.96 (95% CI, 0.87–1.07) for ACE inhibitors and 0.95 (95% CI, 0.86–1.05) for ARBs, while the risk of severe COVID-19 or death was 0.91 (95% CI, 0.69 to 1.21) for ACE inhibitors and 0.83 (95% CI, 0.63 to 1.10) for ARBs (Mancia et al., 2020). These data suggest that treatment with ACE inhibitors/ARBs did not increase the likelihood of SARS-CoV-2 infection or the risk of death in patients with COVID-19.

Gao et al. retrospectively analyzed 850 hospitalized COVID-19 patients with hypertension and found no significant difference in mortality between RAAS inhibitor-treated (183 patients, 2.2% mortality) and non-RAAS inhibitor-treated subjects (527 patients; 3.6% mortality; p = .774) (Gao et al., 2020). Further meta-analysis including three additional studies in China revealed a lower risk of mortality associated with RAAS inhibitor treated vs non-RAAS inhibitor treated hypertensive patients (relative risk 0.65; 95% CI, 0.45–0.94, p = .02) (Gao et al., 2020).

While these studies suggest a potential protective effect of RAAS inhibitors in treatment of COVID-19 patients, we should interpret them with extreme caution. Like all retrospective studies, these studies are limited by sample selection biases. The pool of RAAS inhibitor-treated patients likely have multiple or more severe co-morbidities and might be expected to have worse outcomes than non-RAAS inhibitor-treated patients. Confounding factors may also contribute to reduced hospitalization or mortality. For example, RAAS inhibitor-treated subjects may seek more routine or intensive medical care or have heightened awareness that leads to more diligent hygiene and/or social distancing. In addition, these findings may not replicate in other populations. Geographically and ethnically diverse cohorts and randomized,

### Table 2
Summary of clinical observational studies on the effects of RAAS inhibitors on COVID-19 patients.

| Total number of enrolled subjects | Number of patients with hypertension | Number of patients given ACE inhibitors | Number of patients given ARBs | Number of patients given RAAS inhibitors | Reduced mortality | Country | Reference |
|----------------------------------|-------------------------------------|----------------------------------------|-------------------------------|------------------------------------------|-------------------|--------|-----------|
| 3611                            | 1128                                | 188                                    | –                            | –                                        | Yes               | China  | Lancet, 2020;395:1054–1062 |
| 462                             | 126                                 | 43                                     | –                            | –                                        | Yes               | China  | Circ Res. 2020;126(12):1671–1681 |
| 5179                            |                                     | 762                                    | –                            | –                                        | Neutral           | Korea  | Clin Infect Dis. 2020;ciaa624 https://doi.org/10.1093/cid/ciaa624 |
| 6272                            |                                     | 2896                                   | 1502                          | 1394                                     | Neutral           | Italian America  | medRxiv. 2020.05.03.17.20104943 |
| 6885                            | 2263                                | 1453                                   | 722                           | 731                                      | Neutral (for ACE inhibitors) | Neutral           | China  | European Heart Journal. 2020;41:2058–2066 |
| 2877                            | 850                                 | 183                                    | –                            | –                                        | –                 | –      | –         |

RAAS, renin–angiotensin–aldosterone system; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor type 1 blocker.
controlled clinical trials are needed to better understand the specific effect of RAAS inhibitors in COVID-19 patients.

8. Outcomes of selective RAAS interventions in COVID-19 patients

Two recent studies suggest the interesting finding that, while ACE inhibitors might reduce COVID-19 morbidity, ARBs have a less pronounced effect. Khera et al. reported that of 2263 hypertensive SARS-CoV-2 patients, those treated with ACE inhibitors were 40% less likely to be hospitalized than those not treated with ACE inhibitors, while there was no reduction in hospitalization in patients treated with ARBs (Khera et al., 2020). Milne et al. analyzed gene expression of 1051 lung tissue samples and discovered that ACE inhibitor treatment was associated with significantly lower expression of the ACE2 co-receptor TMPRSS2. In contrast, TMPRSS2 expression was not altered in patients treated with ARBs (Milne, Yang, Timens, Bosse, & Sin, 2020). These data provide a potential mechanistic explanation for a protective role of ACE inhibitors, but not ARBs, in COVID-19 treatment.

9. Conclusions

Our review of the recent literature suggests potential for protective effects of continued treatment of CVD COVID-19 subjects with ACE inhibitors and/or ARBs. Specifically, (1) ACE inhibitors attenuate the deterioration of ARDS in COVID-19 patients by limiting both Ang II-dependent and Ang II-independent pro-inflammatory signaling; (2) ACE inhibitors limit breakthrough of bradykinin which attenuates hypertension and prevents ventricular apoptosis and remodeling that worsen after SARS-CoV-2 infection; and (3) ACE inhibitors suppress TMPRSS2 expression which is an essential co-receptor for SARS-CoV-2 cell entry. Based on the available evidence of clinical studies and previous animal research, we believe that there is no reason to discontinue the use of ACE inhibitors or ARB drugs in patients with COVID-19 and hypertension or other cardiovascular comorbidities. This recommendation is in accordance with the major professional societies (Bavishi, Maddox, & Messerli, 2020). Whether ACE inhibitors/ARBs provide protection in COVID-19 patients without history of CVD remains unknown. Further studies need to be conducted in order to provide a definite answer.

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Declaration of Competing Interest

The authors have declared that no competing interests exist.

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