Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pharmacology & Therapeutics 215 (2020) 107628

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

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

James Jiqi Wang [a], Matthew L. Edin [b], Darryl C. Zeldin [b], Chenze Li [a], Dao Wen Wang [a], Chen Chen [a,*]

[a] Division of Cardiology, Department of Internal Medicine and Hubei Key Laboratory of Genetics and Molecular Mechanisms of Cardiological Disorders, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[b] Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA

ARTICLE INFO

Available online 9 July 2020

Keywords:
Hypertension
RAAS inhibitors
COVID-19
Bradykinin
Inflammation

ABSTRACT

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.

Contents

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

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Ave., Wuhan 430030, China.

https://doi.org/10.1016/j.pharmthera.2020.107628

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 phylogenic clusters: α, β, γ, and δ CoVs (Zhang et al., 2018). Among all CoVs, 7 prominant 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 (R_0) estimated by the WHO of 2.0–2.5. By comparison, SARS-CoV and MERS-CoV have respective R_0 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, kindey 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).

Table 1
Comparison of coronaviruses known to cause severe viral pneumonia.

	SARS-CoV-2	SARS-CoV	MERS-CoV
Nucleotide identity (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 palm civets	dromedary camels
R_0	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, R_0, 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_004718.3 (SARS-CoV), NC_019843.3 (MERS-CoV).

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, 8b, 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 (Gheblawi et al., 2020). These changes may contribute to virulence and the considerably larger global spread of SARS-CoV-2 compared to SARS-CoV (Gheblawi et al., 2020).

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

ACE2 is a transmembrane protein that plays a central role in down-regulation of RAAS (Gheblawi 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

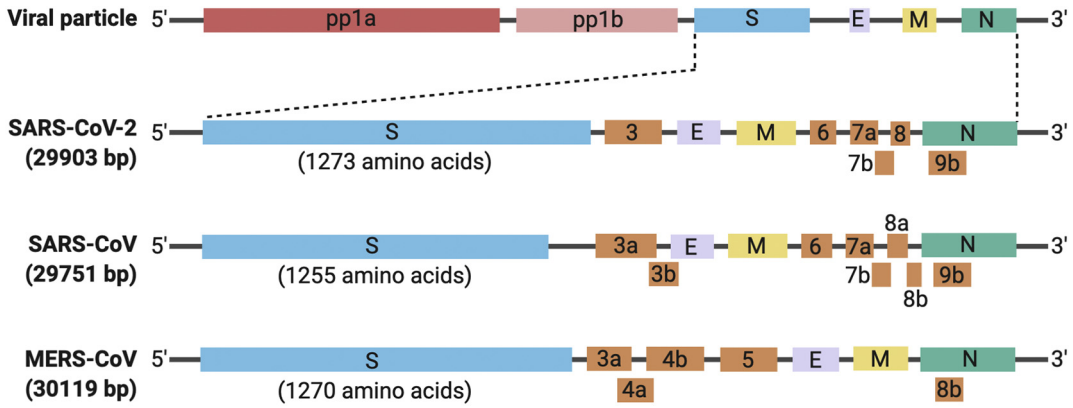

Fig. 1. Genomic structure of SARS-CoV-2, SARS-CoV and MERS-CoV. The genomic structures of SARS-CoV-2, SARS-CoV and MERS-CoV each contain two long polypeptides represented as pp1a (red box) and pp1b (pink box) and four structural proteins (spike protein, S, light blue box; envelope protein, E, light purple box; membrane protein, M, yellow box; nucleocapsid protein, N, green box), and accessory proteins (orange boxes). The different lengths of the genomes and spike proteins are marked for each strain. NCBI reference sequences: NC_045512.2 (SARS-CoV-2), NC_004718.3 (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

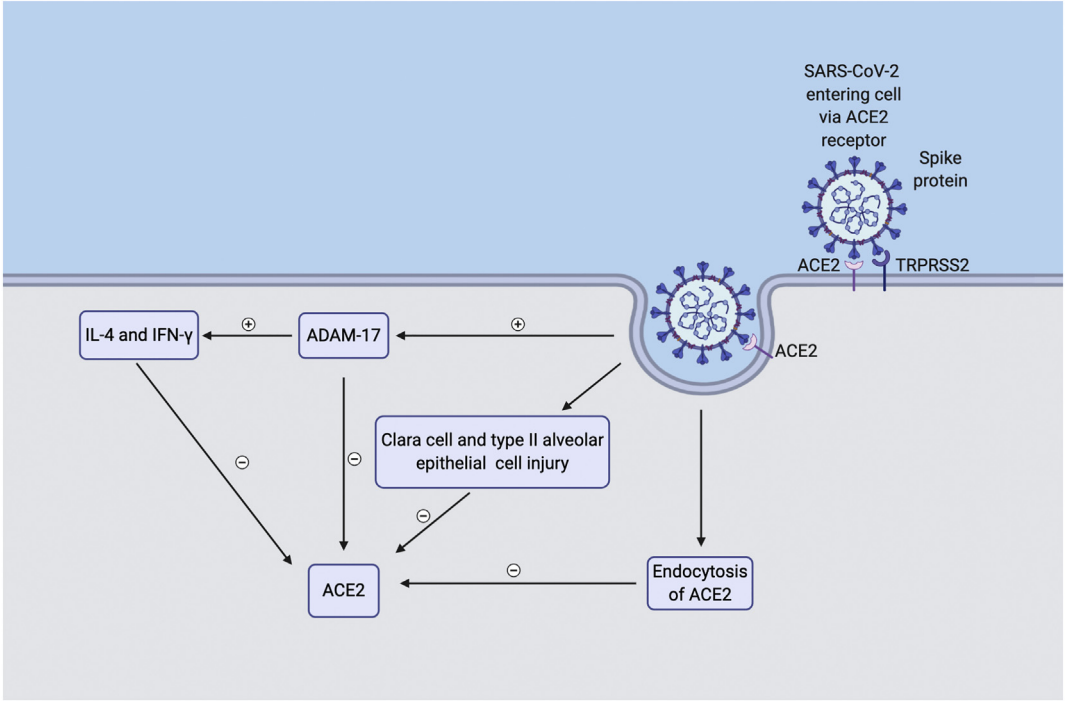

Fig. 2. Mechanism of ACE2 desensitization after infection of SARS-CoV-2. Endocytosis of SARS-CoV-2 along with ACE2 causes reduction of surface ACE2. Infection of SARS-CoV-2 leads to upregulation of ADAM metallopeptidase domain 17 (ADAM-17), which mediates ectodomain shedding of ACE2. ADAM-17 also causes subsequent liberation of membrane bound cytokine precursors IL-4 and IFN-γ, which repress *ACE2* mRNA transcription.

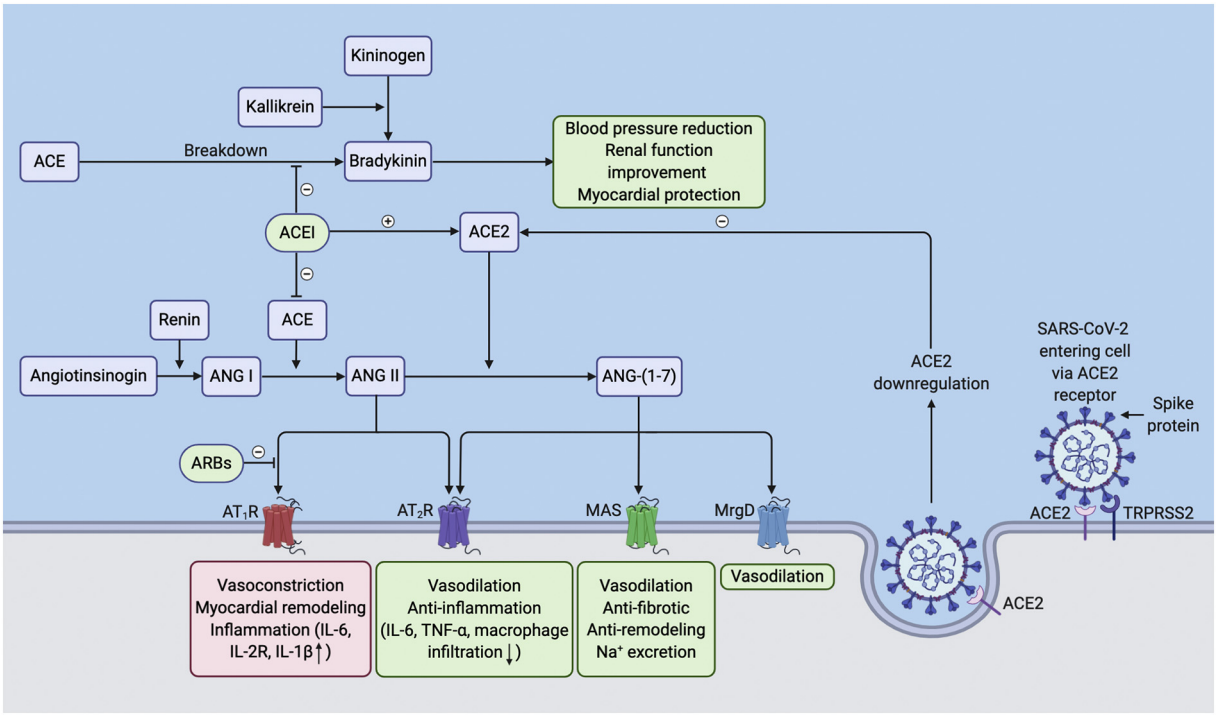

Fig. 3. Relationship between viral entry of SARS-CoV-2 and the renin-angiotensin-aldosterone system. Angiotensin-converting enzyme (ACE) converts angiotensin I (Ang I) to Ang II, which activates angiotensin type 1 receptor (AT_1R) and angiotensin type 2 receptor (AT_2R). ACE also mediates breakdown of bradykinin. ACE2 cleaves Ang II into Ang-(1–7), which activates AT_2R, MAS receptor, and MAS-related G protein-coupled receptor (MrgD receptor) to induce protective effects. SARS-CoV-2 spike protein binds ACE2 to facilitate endocytosis. Viral endocytosis reduces ACE2 expression which results in Ang II accumulation and increased vasoconstriction, inflammatory responses and myocardial injury. Other abbreviations: ACE inhibitor, ACEI; and ARB, angiotensin-receptor blocker.

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-lowing 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; Qin 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 blockage 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 (GRCR), 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-proliferatory 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, Alhenc-Gelas, & Danilov, 2011). Excessive Ang II can lead to significant effects during COVID-19-induced ARDS through several mechanisms. Ang II-induced vasoconstriction 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 EC_{50} 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, Piasecki, & Molina-Molina, 2012). Acting through the angiotensin II receptor type 1 (AT1R), Ang II activates p38 and p42/44 MAPK, induces DNA synthesis and fibroblast proliferation (Konigshoff et al., 2007; Marshall, McAnulty, & 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 treatement 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 blockage (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/ARBs 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 statisticaly 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 RAAS inhibitors	Number of patients given ACE inhibitors	Number of patients given ARBs	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	N Engl J Med. 2020;382(25):2431–2440
6885	2263	1453	722	731	Yes (for ACE inhibitors)	America	medRxiv. 2020:2020.05.17.20104943
2877	850	183	–	–	Neutral	China	European Heart Journal. 2020;41:2058–2066

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 breakdown 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.

Funding

This work was supported by grants from the National Natural Science Foundation of China (91839302, 81630010, and 81790624) and Tongji Hospital Clinical Research Flagship Program (2019CR207). This research is supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01 ES025034 to DCZ). No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

Acknowledgments

We thank all our colleagues from the Division of Cardiology, Tongji Hospital, as well as all the medical staff fighting against COVID-19, for their tremendous efforts.

References

Al-Tawfiq, J. A., Hinedi, K., Ghandour, J., Khairalla, H., Musleh, S., Ujayli, A., & Memish, Z. A. (2014). Middle East respiratory syndrome coronavirus: A case-control study of hospitalized patients. *Clinical Infectious Diseases 59*, 160–165.

Arabi, Y. M., Arifi, A. A., Balkhy, H. H., Najm, H., Aldawood, A. S., Ghabashi, A., ... Al Raiy, B. (2014). Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Annals of Internal Medicine 160*, 389–397.

Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F. X., Chong, M., & Lee, M. (2020 Mar 19). Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA 323*(16), 1612–1614. https://doi.org/10.1001/jama.2020.4326.

Arons, M. M., Hatfield, K. M., Reddy, S. C., Kimball, A., James, A., Jacobs, J. R., ... Team, C. C. -I. (2020). Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *The New England Journal of Medicine 382*, 2081–2090.

Aztatzi-Aguilar, O. G., Uribe-Ramirez, M., Arias-Montano, J. A., Barbier, O., & De Vizcaya-Ruiz, A. (2015). Acute and subchronic exposure to air particulate matter induces expression of angiotensin and bradykinin-related genes in the lungs and heart: Angiotensin-II type-I receptor as a molecular target of particulate matter exposure. *Particle and Fibre Toxicology 12*, 17.

Bavishi, C., Maddox, T. M., & Messerli, F. H. (2020). Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. *JAMA Cardiology*. https://doi.org/10.1001/jamacardio.2020.1282 (Online ahead of print).

Bernstein, K. E., Khan, Z., Giani, J. F., Cao, D. Y., Bernstein, E. A., & Shen, X. Z. (2018). Angiotensin-converting enzyme in innate and adaptive immunity. *Nature Reviews. Nephrology 14*, 325–336.

Cao, X. (2020). COVID-19: Immunopathology and its implications for therapy. *Nature Reviews. Immunology 20*, 269–270.

Cao, X., Wang, M., Li, J., Luo, Y., Li, R., Yan, X., & Zhang, H. (2020). Fine particulate matter increases airway hyperresponsiveness through kallikrein-bradykinin pathway. *Ecotoxicology and Environmental Safety 195*, 110491.

Chafekar, A., & Fielding, B. C. (2018). MERS-CoV: Understanding the latest human coronavirus threat. *Viruses 10*.

Chan, J. F., Kok, K. H., Zhu, Z., Chu, H., To, K. K, Yuan, S., & Yuen, K. Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections 9*, 221–236.

Chao, J., Li, H. J., Yao, Y. Y., Shen, B., Gao, L., Bledsoe, G., & Chao, L. (2007). Kinin infusion prevents renal inflammation, apoptosis, and fibrosis via inhibition of oxidative stress and mitogen-activated protein kinase activity. *Hypertension 49*, 490–497.

Chen, F., Chen, D., Zhang, Y., Jin, L., Zhang, H., Wan, M., ... Ye, J. (2017). Interleukin-6 deficiency attenuates angiotensin II-induced cardiac pathogenesis with increased myocyte hypertrophy. *Biochemical and Biophysical Research Communications 494*, 534–541.

Chen, D., Li, Z., Bao, P., Chen, M., Zhang, M., Yan, F., ... Ye, J. (2019). Nrf2 deficiency aggravates angiotensin II-induced cardiac injury by increasing hypertrophy and enhancing IL-6/STAT3-dependent inflammation. *Biochimica et Biophysica Acta - Molecular Basis of Disease 1865*, 1253–1264.

Chen, L., Li, X., Chen, M., Feng, Y., & Xiong, C. (2020a). The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovascular Research 116*, 1097–1100.

Chen, C., Li, H., Hang, W., & Wang, D. W. (2020b). Cardiac injuries in coronavirus disease 2019 (COVID-19). *Journal of Molecular and Cellular Cardiology 145*, 25–29.

Crackower, M. A., Sarao, R., Oudit, G. Y., Yagil, C., Kozieradzki, I., Scanga, S. E., ... Penninger, J. M. (2002). Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature 417*, 822–828.

De Rosa, S., Spaccarotella, C., Basso, C., Calabro, M. P., Curcio, A., Filardi, P. P., ... Societa Italiana di, C., & the, C. C. U. A. i. g. (2020). Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *European Heart Journal 41*, 2083–2088.

de Wit, E., van Doremalen, N., Falzarano, D., & Munster, V. J. (2016). SARS and MERS: Recent insights into emerging coronaviruses. *Nature Reviews. Microbiology 14*, 523–534.

Diaz, J. H. (2020). Hypothesis: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *Journal of Travel Medicine 27*.

Esler, M., & Esler, D. (2020). Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *Journal of Hypertension 38*, 781–782.

Evans, A., McCurdy, M. T., Weiner, M., Zaku, B., & Chow, J. H. (2019). Use of angiotensin II for post cardiopulmonary bypass Vasoplegic syndrome. *The Annals of Thoracic Surgery 108*, e5–e7.

Fang, L., Karakiulakis, G., & Roth, M. (2020). Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet Respiratory Medicine 8*, e21.

Ferrario, C. M., Jessup, J., Chappell, M. C., Averill, D. B., Brosnihan, K. B., Tallant, E. A., ... Gallagher, P. E. (2005). Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation 111*, 2605–2610.

Gao, C., Cai, Y., Zhang, K., Zhou, L., Zhang, Y., Zhang, X., ... Li, F. (2020). Association of hypertension and antihypertensive treatment with COVID-19 mortality: A retrospective observational study. *European Heart Journal 41*, 2058–2066.

Gheblawi, M., Wang, K., Viveiros, A., Nguyen, Q., Zhong, J. C., Turner, A. J., ... Oudit, G. Y. (2020). Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20th anniversary of the discovery of ACE2. *Circulation Research 126*, 1456–1474.

Gibbons, G. H., Pratt, R. E., & Dzau, V. J. (1992). Vascular smooth muscle cell hypertrophy vs. hyperplasia. Autocrine transforming growth factor-beta 1 expression determines growth response to angiotensin II. *The Journal of Clinical Investigation 90*, 456–461.

Gonzalez, A., Fortuno, M. A., Querejeta, R., Ravassa, S., Lopez, B., Lopez, N., & Diez, J. (2003). Cardiomyocyte apoptosis in hypertensive cardiomyopathy. *Cardiovascular Research 59*, 549–562.

Gonzalez, G. E., Rhaleb, N. E., D'Ambrosio, M. A., Nakagawa, P., Liu, Y., Leung, P., ... Carretero, O. A. (2015). Deletion of interleukin-6 prevents cardiac inflammation, fibrosis and dysfunction without affecting blood pressure in angiotensin II-high salt-induced hypertension. *Journal of Hypertension 33*, 144–152.

Griendling, K. K., Minieri, C. A., Ollerenshaw, J. D., & Alexander, R. W. (1994). Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circulation Research 74*, 1141–1148.

Gu, J., Gong, E., Zhang, B., Zheng, J., Gao, Z., Zhong, Y., ... Leong, A. S. (2005). Multiple organ infection and the pathogenesis of SARS. *The Journal of Experimental Medicine 202*, 415–424.

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... China Medical Treatment Expert Group for, C (2020). Clinical characteristics of coronavirus disease 2019 in China. *The New England Journal of Medicine 382*, 1708–1720.

Guazzi, M., Melzi, G., Marenzi, G. C., & Agostoni, P. (1999). Angiotensin-converting enzyme inhibition facilitates alveolar-capillary gas transfer and improves ventilation-perfusion coupling in patients with left ventricular dysfunction. *Clinical Pharmacology and Therapeutics 65*, 319–327.

Guo, F., Chen, X. L., Wang, F., Liang, X., Sun, Y. X., & Wang, Y. J. (2011). Role of angiotensin II type 1 receptor in angiotensin II-induced cytokine production in macrophages. *Journal of Interferon & Cytokine Research 31*, 351–361.

Guzik, T. J., Mohiddin, S. A., Dimarco, A., Patel, V., Savvatis, K., Marelli-Berg, F. M., ... McInnes, I. B. (2020). COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. *Cardiovascular Research*. https://doi.org/10.1093/cvr/cvaa106 (Online ahead of print).

Hamet, P., Richard, L., Dam, T. V., Teiger, E., Orlov, S. N., Gaboury, L., ... Tremblay, J. (1995). Apoptosis in target organs of hypertension. *Hypertension 26*, 642–648.

Hanff, T. C., Harhay, M. O., Brown, T. S., Cohen, J. B., & Mohareb, A. M. (2020). Is there an association between COVID-19 mortality and the renin-angiotensin system-a call for epidemiologic investigations. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciaa329 (Online ahead of print).

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet 395*, 497–506.

Idell, S., Kueppers, F., Lippmann, M., Rosen, H., Niederman, M., & Fein, A. (1987). Angiotensin converting enzyme in bronchoalveolar lavage in ARDS. *Chest 91*, 52–56.

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., ... Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature 436*, 112–116.

Jung, S. Y., Choi, J. C., You, S. H., & Kim, W. Y. (2020). Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: A nationwide population-based cohort study. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciaa624 (Online ahead of print).

Kaparianos, A., & Argyropoulou, E. (2011). Local renin-angiotensin II systems, angiotensin-converting enzyme and its homologue ACE2: Their potential role in the pathogenesis of chronic obstructive pulmonary diseases, pulmonary hypertension and acute respiratory distress syndrome. *Current Medicinal Chemistry 18*, 3506–3515.

Khera, R., Clark, C., Lu, Y., Guo, Y., Ren, S., Truax, B., ... Krumholz, H. M. (2020). Association of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with the risk of hospitalization and death in hypertensive patients with coronavirus disease-19. *medRxiv*. https://doi.org/10.1101/2020.05.17.20104943 (2020.2005.2017.20104943; Preprint).

Killerby, M. E., Biggs, H. M., Haynes, A., Dahl, R. M., Mustaquim, D., Gerber, S. I., & Watson, J. T. (2018). Human coronavirus circulation in the United States 2014-2017. *Journal of Clinical Virology 101*, 52–56.

Konigshoff, M., Wilhelm, A., Jahn, A., Sedding, D., Amarie, O. V., Eul, B., ... Rose, F. (2007). The angiotensin II receptor 2 is expressed and mediates angiotensin II signaling in lung fibrosis. *American Journal of Respiratory Cell and Molecular Biology 37*, 640–650.

Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., ... Penninger, J. M. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine 11*, 875–879.

Lelis, D. F., Freitas, D. F., Machado, A. S., Crespo, T. S., & Santos, S. H. S. (2019). Angiotensin-(1-7), Adipokines and inflammation. *Metabolism 95*, 36–45.

Levy, B., Fritz, C., Tahon, E., Jacquot, A., Auchet, T., & Kimmoun, A. (2018). Vasoplegia treatments: the past, the present, and the future. *Critical Care (London, England) 22*, 52.

Li, X., Molina-Molina, M., Abdul-Hafez, A., Uhal, V., Xaubet, A., & Uhal, B. D. (2008). Angiotensin converting enzyme-2 is protective but downregulated in human and experimental lung fibrosis. *American Journal of Physiology. Lung Cellular and Molecular Physiology 295*, L178–L185.

Liu, Y., Yang, Y., Zhang, C., Huang, F., Wang, F., Yuan, J., ... Liu, L. (2020). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China. Life Sciences 63*, 364–374.

Madjid, M., Safavi-Naeini, P., Solomon, S. D., & Vardeny, O. (2020). Potential effects of coronaviruses on the cardiovascular system: A review. *JAMA Cardiology*. https://doi.org/10.1001/jamacardio.2020.1286 (Online ahead of print).

Mancia, G., Rea, F., Ludergnani, M., Apolone, G., & Corrao, G. (2020). Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *The New England Journal of Medicine 382*, 2431–2440.

Marshall, R. P., McAnulty, R. J., & Laurent, G. J. (2000a). Angiotensin II is mitogenic for human lung fibroblasts via activation of the type 1 receptor. *American Journal of Respiratory and Critical Care Medicine 161*, 1999–2004.

Marshall, R. P., Puddicombe, A., Cookson, W. O., & Laurent, G. J. (2000b). Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. *Thorax 55*, 143–146.

Marshall, R. P., Webb, S., Bellingan, G. J., Montgomery, H. E., Chaudhari, B., McAnulty, R. J., ... Laurent, G. J. (2002). Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine 166*, 646–650.

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J.Hlh Across Speciality Collaboration, U. K. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet 395*, 1033–1034.

Merad, M., & Martin, J. C. (2020). Pathological inflammation in patients with COVID-19: A key role for monocytes and macrophages. *Nature Reviews. Immunology 20*, 355–362.

Metzger, R., Franke, F. E., Bohle, R. M., Alhenc-Gelas, F., & Danilov, S. M. (2011). Heterogeneous distribution of angiotensin I-converting enzyme (CD143) in the human and rat vascular systems: Vessel, organ and species specificity. *Microvascular Research 81*, 206–215.

Milne, S., Yang, C. X., Timens, W., Bosse, Y., & Sin, D. D. (2020). SARS-CoV-2 receptor ACE2 gene expression and RAAS inhibitors. *The Lancet Respiratory Medicine 8*, e50–e51.

Orfanos, S. E., Armaganidis, A., Glynos, C., Psevdi, E., Kaltsas, P., Sarafidou, P., ... Roussos, C. (2000). Pulmonary capillary endothelium-bound angiotensin-converting enzyme activity in acute lung injury. *Circulation 102*, 2011–2018.

Patel, V. B., Clarke, N., Wang, Z., Fan, D., Parajuli, N., Basu, R., ... Oudit, G. Y. (2014). Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: A positive feedback mechanism in the RAS. *Journal of Molecular and Cellular Cardiology 66*, 167–176.

Patel, V. B., Zhong, J. C., Grant, M. B., & Oudit, G. Y. (2016). Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. *Circulation Research 118*, 1313–1326.

Petrosillo, N., Viceconte, G., Ergonul, O., Ippolito, G., & Petersen, E. (2020). COVID-19, SARS and MERS: Are they closely related? *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases 26*, 729–734.

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., ... Tian, D. S. (2020). Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciaa248 (Online ahead of print).

Ramachandran, P., Dobie, R., Wilson-Kanamori, J. R., Dora, E. F., Henderson, B. E. P., Luu, N. T., ... Henderson, N. C. (2019). Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature 575*, 512–518.

Romero, C. A., Orias, M., & Weir, M. R. (2015). Novel RAAS agonists and antagonists: Clinical applications and controversies. *Nature Reviews. Endocrinology 11*, 242–252.

Sadoshima, J., & Izumo, S. (1993). Molecular characterization of angiotensin II–induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. *Circulation Research 73*, 413–423.

Shahid, Z., Kalayanamitra, R., McClafferty, B., Kepko, D., Ramgobin, D., Patel, R., ... Jain, R. (2020). COVID-19 and older adults: What we know. *Journal of the American Geriatrics Society 68*, 926–929.

Shen, X. Z., Li, P., Weiss, D., Fuchs, S., Xiao, H. D., Adams, J. A., ... Bernstein, K. E. (2007). Mice with enhanced macrophage angiotensin-converting enzyme are resistant to melanoma. *The American Journal of Pathology 170*, 2122–2134.

Shetty, S. K., Tiwari, N., Marudamuthu, A. S., Puthusseri, B., Bhandary, Y. P., Fu, J., ... Shetty, S. (2017). p53 and miR-34a feedback promotes lung epithelial injury and pulmonary fibrosis. *The American Journal of Pathology 187*, 1016–1034.

Shi, S., Qin, M., Cai, Y., Liu, T., Shen, B., Yang, F., ... Huang, C. (2020a). Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *European Heart Journal 41*, 2070–2079.

Shi, S., Qin, M., Shen, B., Cai, Y., Liu, T., Yang, F., ... Huang, C. (2020b). Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology*. https://doi.org/10.1001/jamacardio.2020.0950 (Online ahead of print).

Simoese Silva, A. C., Silveira, K. D., Ferreira, A. J., & Teixeira, M. M. (2013). ACE2, angiotensin-(1-7) and mas receptor axis in inflammation and fibrosis. *British Journal of Pharmacology 169*, 477–492.

South, A. M., Diz, D. I., & Chappell, M. C. (2020). COVID-19, ACE2, and the cardiovascular consequences. *American Journal of Physiology. Heart and Circulatory Physiology 318*, H1084–H1090.

Sriram, K., & Insel, P. A. (2020). Risks of ACE inhibitor and ARB usage in COVID-19: Evaluating the evidence. *Clinical Pharmacology and Therapeutics*. https://doi.org/10.1002/cpt.1863 (Online ahead of print).

Su, S., Wong, G., Shi, W., Liu, J., Lai, A. C. K., Zhou, J., ... Gao, G. F. (2016). Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends in Microbiology 24*, 490–502.

Suzuki, M., Teramoto, S., Katayama, H., Ohga, E., Matsuse, T., & Ouchi, Y. (1999). Effects of angiotensin-converting enzyme (ACE) inhibitors on oxygen radical production and generation by murine lung alveolar macrophages. *The Journal of Asthma 36*, 665–670.

Tu, L., Xu, X., Wan, H., Zhou, C., Deng, J., Xu, G., ... Wang, D. W. (2008). Delivery of recombinant adeno-associated virus-mediated human tissue kallikrein for therapy of chronic renal failure in rats. *Human Gene Therapy 19*, 318–330.

Uhal, B. D., Li, X., Piasecki, C. C., & Molina-Molina, M. (2012). Angiotensin signalling in pulmonary fibrosis. *The International Journal of Biochemistry & Cell Biology 44*, 465–468.

Veronese, G., Cipriani, M., Bottiroli, M., Garascia, A., Mondino, M., Pedrotti, P., ... Ammirati, E. (2020). Fulminant myocarditis triggered by OC43 subtype coronavirus: A disease deserving evidence-based care bundles. *Journal of Cardiovascular Medicine (Hagerstown, Md.) 21*, 529–531.

Wang, R., Zagariya, A., Ibarra-Sunga, O., Gidea, C., Ang, E., Deshmukh, S., ... Uhal, B. D. (1999). Angiotensin II induces apoptosis in human and rat alveolar epithelial cells. *The American Journal of Physiology 276*, L885–L889.

Wang, T., Li, H., Zhao, C., Chen, C., Li, J., Chao, J., ... Wang, D. W. (2004). Recombinant adeno-associated virus-mediated kallikrein gene therapy reduces hypertension and attenuates its cardiovascular injuries. *Gene Therapy 11*, 1342–1350.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., & Peng, Z. (2020 Feb 7). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA 323*(11), 1061–1069.

Wang, K., Gheblawi, M., & Oudit, G. Y. (2020). Angiotensin converting enzyme 2: A double-edged sword. *Circulation*. https://doi.org/10.1161/CIRCULATIONAHA.120.047049 (Online ahead of print).

Wiener, R. S., Cao, Y. X., Hinds, A., Ramirez, M. I., & Williams, M. C. (2007). Angiotensin converting enzyme 2 is primarily epithelial and is developmentally regulated in the mouse lung. *Journal of Cellular Biochemistry 101*, 1278–1291.

Wosten-van Asperen, R. M., Lutter, R., Specht, P. A., Moll, G. N., van Woensel, J. B., van der Loos, C. M., ... Bos, A. P. (2011). Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. *The Journal of Pathology 225*, 618–627.

Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P., ... Jiang, T. (2020). Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host & Microbe 27*, 325–328.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., ... Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine 8*, 420–422.

Yamamoto, T., Wang, L., Shimakura, K., Sanaka, M., Koike, Y., & Mineshita, S. (1997). Angiotensin II-induced pulmonary edema in a rabbit model. *Japanese Journal of Pharmacology 73*, 33–40.

Yan, J. T., Wang, T., & Wang, D. W. (2009). Recombinant adeno-associated virus-mediated human kallikrein gene therapy protects against hypertensive target organ injuries through inhibiting cell apoptosis. *Acta Pharmacologica Sinica 30*, 1253–1261.

Yang, S., Chen, D., Chen, F., Zhao, X., Zhang, Y., Li, Z., ... Ye, J. (2018). Deletion of protein kinase B2 preserves cardiac function by blocking interleukin-6-mediated injury and restores blood pressure during angiotensin II/high-salt-diet-induced hypertension. *Journal of Hypertension 36*, 834–846.

Yang, G., Tan, Z., Zhou, L., Yang, M., Peng, L., Liu, J., ... He, S. (2020a). Effects of angiotensin II receptor blockers and ACE (angiotensin-converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: A single-center retrospective study. *Hypertension 76*, 51–58.

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., ... Shang, Y. (2020b). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *The Lancet Respiratory Medicine 8*, 475–481.

Yao, Y. Y., Yin, H., Shen, B., Chao, L., & Chao, J. (2007). Tissue kallikrein infusion prevents cardiomyocyte apoptosis, inflammation and ventricular remodeling after myocardial infarction. *Regulatory Peptides 140*, 12–20.

Yuan, G., Deng, J., Wang, T., Zhao, C., Xu, X., Wang, P., ... Wang, D. W. (2007). Tissue kallikrein reverses insulin resistance and attenuates nephropathy in diabetic rats by activation of phosphatidylinositol 3-kinase/protein kinase B and adenosine 5′-monophosphate-activated protein kinase signaling pathways. *Endocrinology 148*, 2016–2026.

Zhang, H., & Baker, A. (2017). Recombinant human ACE2: Acing out angiotensin II in ARDS therapy. *Critical Care (London, England) 21*, 305.

Zhang, Y. H., Zhang, Y. H., Dong, X. F., Hao, Q. Q., Zhou, X. M., Yu, Q. T., ... Zhang, Y. (2015). ACE2 and Ang-(1-7) protect endothelial cell function and prevent early atherosclerosis by inhibiting inflammatory response. *Inflammation Research 64*, 253–260.

Zhang, S. F., Tuo, J. L., Huang, X. B., Zhu, X., Zhang, D. M., Zhou, K., ... Xu, L. (2018). Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010-2015 in Guangzhou. *PLoS One 13*, e0191789.

Zhang, J. J., Dong, X., Cao, Y. Y., Yuan, Y. D., Yang, Y. B., Yan, Y. Q., ... Gao, Y. D. (2020a). Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. https://doi.org/10.1111/all.14238 (Online ahead of print).

Zhang, P., Zhu, L., Cai, J., Lei, F., Qin, J. J., Xie, J., ... Li, H. (2020b). Association of Inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circulation Research 126*, 1671–1681.

Zhao, C., Wang, P., Xiao, X., Chao, J., Chao, L., Wang, D. W., & Zeldin, D. C. (2003). Gene therapy with human tissue kallikrein reduces hypertension and hyperinsulinemia in fructose-induced hypertensive rats. *Hypertension 42*, 1026–1033.

Zhou, G. L., Beloiartsev, A., Yu, B., Baron, D. M., Zhou, W., Niedra, R., ... Bloch, K. D. (2013). Deletion of the murine cytochrome P450 Cyp2j locus by fused BAC-mediated recombination identifies a role for Cyp2j in the pulmonary vascular response to hypoxia. *PLoS Genetics 9*, e1003950.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet 395*, 1054–1062.