Review

Classical and Counter-Regulatory Renin–Angiotensin System: Potential Key Roles in COVID-19 Pathophysiology

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ABSTRACT

In the current COVID-19 pandemic, severe acute respiratory syndrome coronavirus 2 uses angiotensin-converting enzyme-2 (ACE-2) receptors for cell entry, leading to ACE-2 dysfunction and downregulation, which disturb the balance between the classical and counter-regulatory renin–angiotensin system (RAS) in favor of the classical RAS. RAS dysregulation is one of the major characteristics of several cardiovascular diseases; thus, adjustment of this system is the main therapeutic target. RAS inhibitors—particularly angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs)—are commonly used for treatment of hypertension and cardiovascular disease. Patients with cardiovascular diseases are the group most commonly seen among those with COVID-19 comorbidity. At the beginning of this pandemic, a dilemma occurred regarding the use of ACEIs and ARBs, potentially aggravating cardiovascular and pulmonary dysfunction in COVID-19 patients. Urgent clinical trials from different countries and hospitals reported that there is no association between RAS inhibitor treatment and COVID-19 infection or comorbidity complication. Nevertheless, the disturbance of the RAS that is associated with COVID-19...
infection and the potential treatment targeting this area have yet to be resolved. In this review, the link between the dysregulation of classical RAS and counter-regulatory RAS activities in COVID-19 patients with cardiovascular metabolic diseases is investigated. In addition, the latest findings based on ACEI and ARB administration and ACE-2 availability in relation to COVID-19, which may provide a better understanding of the RAS contribution to COVID-19 pathology, are discussed, as they are of the utmost importance amid the current pandemic.

Per the World Health Organization’s update of January 6, 2021, there have been 84,780,171 confirmed cases of COVID-19 and 1,853,525 deaths worldwide. 10 ACE-2 depletion—associated with SARS-CoV-2 infection and the resulting accumulation of angiotensin II (Ang II)—worsens any preexisting cardiovascular disease, along with RAS dysregulation, leading to severe cases and deaths. 11 Regardless, the potential role of the RAS in COVID-19 patients either with or without cardiovascular diseases cannot be overlooked, and a reasonable understanding of the crosstalk between COVID-19 and the RAS is almost essential for the ideal management of patients with cardiometabolic diseases. In the following review, we describe the imbalance of the classical RAS and counter-regulatory RAS axes in COVID-19 patients with cardiovascular metabolic diseases and discuss the latest findings based on angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II type 1 receptor blocker (ARB) administration and ACE-2 availability in relation to COVID-19.

RAS

Classical axis: ACE/Ang II/angiotensin II type 1 receptor (AT1R)

The RAS plays a pivotal role in the pathophysiology of cardiovascular diseases. Renin (angiotensinogenase) is secreted by the kidney, stimulating angiotensinogen to release angiotensin I (Ang I) peptide. Ang I is then converted to Ang II by ACE, which is expressed in high volumes by endothelial and epithelial cells in the vasculature, kidneys, heart, and lungs. 12 Ang II is the major vasoactive peptide, playing a crucial role during normal or pathophysiologic conditions. 13

The binding of Ang II to AT1R is common throughout the cardiovascular system and induces systemic vasoconstriction, proinflammatory and profibrotic effects, and aldosterone secretion. 13 Activation of the ACE/Ang II/AT1R axis induces apoptosis in alveolar epithelial cells, 14 promotes ventilator-induced lung injury, 15 increases lung microvascular permeability, 16 stimulates proinflammatory cytokine release, and promotes macrophage and neutrophil chemotaxis associated with lung injuries. 17 Moreover, the activation of the ACE/Ang II/AT1R axis stimulates both the adaptive and innate immune proinflammatory responses, leading to inflammation, autoimmune dysfunction, and cardiovascular damage. 18,19

Counter-regulatory axes

ACE-2/Angiotensin 1-7 (Ang 1-7) Mas receptor (MasR).

Ang 1-7 is produced by cleavage of Ang I and II by nephrilysin and ACE-2, respectively. 20 The RAS regulatory effect of Ang 1-7 is imparted by its binding to the MasR. Ang 1-7 has been reported to play a protective role in cardiovascular diseases through its central control of blood pressure 21 and by serving as an important neuromodulator in the central nervous system to control cardiovascular function and counteract Ang II effects. 22 Ang 1-7 might also act as a local synergistic regulator of kinin-induced vasodilation via inhibiting the generation of ACE and nitric oxide. 23

During vascular inflammation, Ang 1-7 decreases monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), nuclear factor kappa-B, vascular cell adhesion protein 1, reactive oxygen species levels, and apoptosis. 24 Furthermore, activation of angiotensin II type 2 receptor (AT2R) via Ang 1-7 stimulation prevents inflammation and cardiac hypertrophy, as well as reducing vascular remodeling and alveolar septum thickness, which—in a rat with chronic lung disease—protects the heart and lungs from damage. 25

Ang 1-7 can also be a source of another counter-regulatory renin—angiotensin pathway when produced from Ang II by ACE-2 and then transformed to alamandine. 26 Alternatively, Ang II can be transformed to angiotensin A (Ang A) by aspartate decarboxylase. Ang A can be converted to alamandine by ACE-2. Recently discovered as part of RAS regulation, alamandine—via binding to Mas-related G protein—coupled receptor member D (MrgD)—promotes antihypertensive and cardioprotective effects similar to those of Ang 1-7. 27,28

ACE2/Ang 1-9/AT2R. It was demonstrated in the rat model that angiotensin 1-9 (Ang 1-9) has a cardioprotective effect resulting from the activation of AT2R, improving endothelial function, fibrosis, oxidative stress, collagen deposition, 29 and cardiac hypertrophy, 30 and protecting against cardiac ischemia/reperfusion injury. 31 It was further reported that Ang 1-9 ameliorates pulmonary arterial hypertension via AT2R by decreasing apoptosis and plasmatic proinflammatory response, 32 and normalizes the plasma expression of intercellular adhesion molecule 1. 33

19. Des essais cliniques urgents issus de différents pays et hôpitaux ont montré qu’il n’y avait pas d’association entre le traitement par inhibiteurs du SRA et les complications liées à l’infection par la COVID-19 ou aux comorbidités. Néanmoins, la perturbation du SRA qui est associée à l’infection par la COVID-19 et le traitement potentiel dans ce champ restent à résoudre. Dans la présente revue, le lien entre la dysrégulation du SRA traditionnel et les activités contre-régulatrices du SRA chez les patients atteints de la COVID-19 qui ont des maladies cardiovasculaires métaboliques est étudié. De plus, nous nous penchons sur les plus récentes conclusions fondées sur l’administration des IECA et des ARA et la disponibilité de l’ECA2 en relation avec la COVID-19 pour offrir une meilleure compréhension de la contribution du SRA à la pathologie de la COVID-19, puisqu’ils sont de la plus haute importance dans le contexte de l’actuelle pandémie.
cytokines, such as TNF-α, MCP-1, IL-1β, and IL-6. Indepen-
dently of MasR or AT2R, Ang 1-9 protects against hyper-
tension and cardiovascular damage by decreasing the
inflammation in deoxycorticosterone acetate-salt rat test
subjects. It was suggested that the Ang 1-9/AT2R axis has a
protective effect in vasculature, preventing the heart and kid-
neys in patients with heart failure and/or hypertension from
adverse cardiovascular remodeling.

It has been observed in vivo that selective activation of
AT2 receptors attenuates the progression of pulmonary hyper-
tension and inhibits cardiopulmonary fibrosis. It has also
been identified that the stimulation of AT2R using a selective
agonist, compound 21 (C21), attenuates the progression of
lung fibrosis and pulmonary hypertension in an experimental
model of a bleomycin-induced lung injury while attenuating
pulmonary inflammation in a model of acute lung injury.

Classical and Counter-Regulatory RAS Axes
Interplay in Cardiometabolic and Pulmonary
Diseases During SARS-CoV-2 Infection

During pathophysiologic conditions, the ACE/Ang II/
AT1R axis is highly activated, yet it may be counter-regulated
by the activation of the ACE-2/Ang 1-7/MasR and ACE-2/
Ang 1-9/AT2R axes. Pharmacologic inhibition of the ACE/
Ang II/AT1R axis using ACEIs or ARBs induced the upregu-
lation of ACE-2 expression. It was found that ACE-2 inhib-
its the Ang II/AT1R axis via degradation of Ang I to Ang 1-9
and Ang II into Ang 1-7, which are active biologically through
their receptors AT2 and MAS, respectively, and act as anti-
inflammatory vasodilators, and anti-fibrotic and anti-prolifer-
ative peptides. It was demonstrated that the SARS virus
outbreak in 2003 was accompanied by a decrease in ACE-2
expression in the heart, which is posited by some to be the
possible cause of the myocardial dysfunction and inflamma-
tion observed in COVID-19 patients.

During COVID-19 infection, the virus uses ACE-2 for cell
entry, potentially disturbing RAS-induced homeostasis, while
potentially also affecting the activity of the counter-regulatory
RAS system dependent on ACE-2 availability. This action
could, in turn, exaggerate the effects of COVID-19 infection,
in terms of RAS homeostasis leading to cardiovascular and
pulmonary complications.

Recently, it was reported that ACE-2 overexpression
counter-regulates the inflammatory responses due to RAS acti-
vation, by maintaining the balance between the ACE-2/Ang
1-7/MasR and ACE/Ang II/AT1R axes associated with pro-
tective effects against lipopolysaccharide-induced acute lung
injury in the mice model, as well as inhibiting the inflamma-
tory response and oxidative stress. More recently, it was
reported that the Ang 1-7/MasR axis mediates its anti-inflam-
matory effects in a murine model of asthma through Src-
mediated epidermal growth factor receptor transactivation.

In some COVID-19 cases, the immune response to the
viral infection intensified due to the up-regulation of the
ACE/Ang II/AT1R axis, accompanied by ACE-2 depletion,
which increases the production of proinflammatory cytokines,
leading to cytokine storm syndrome, which is associated with
severe cases and death. Most of the deleterious effects fol-
lowing ACE/Ang II/AT1R axis activation that are associated with
lung injuries, such as acute respiratory distress syndrome
(ARDS) and ventilator-induced lung injury, are prevented
using RAS inhibitors (ACEIs and ARBs) or RAS regulators
(AT2R agonist [C21], recombinant soluble human ACE-2
[rhACE-2], Ang 1-7, and MasR agonists; Fig. 1).

Moreover, the vast majority of protective peptides are
dependent on ACE-2 enzyme activity, with this enzymatic
pathway representing an endogenous negative regulator of
RAS activation. SARS-CoV-2 enters cells via an interaction
with ACE-2, which is highly expressed in coronary endothelial
cells, cardiomyocytes, and cardiac fibroblasts. Further-
more, ACE-2 has been recognized as a major RAS regulator,
able to alleviate the deleterious effects mediated by Ang II and
AT1R. Current studies on angiotensin peptides such as Ang
1-7, angiotensin 2-8, Ang 1-9, angiotensin 3-7, and angioten-
sin 3-8 are vital in counteracting the deleterious effects of Ang
II. Interestingly, in the midst of ACE-2 deficiency, protec-
tive Ang 1-7 can be produced independently of ACE-2, either
from Ang I via neprilisin, thimet olligopeptidase, or prolyl oll-
igopeptidase, or it can be produced from Ang-II via prolyl car-
boxypeptidase, or prolyl olligopeptidase, favoring a tilt toward
the protective Ang1-7/MasR axis (Fig. 1).

Additionally, it has been strongly suggested that ACE-2
deficiency resulting from SARS-CoV-2 binding leads to an
increase in bradykinin and des-Arg₉-bradykinin levels, which
in turn causes difficulties seen during COVID-19 infection,
such as pulmonary edema, pneumonia, and respiratory fail-
ure. Thimet olligopeptidase and prolyl carboxypeptidase are
defined to be expressed in endothelial cells and to contribute
to the metabolism of bradykinin and des-Arg₉-bradykinin,
respectively. Moreover, in addition to the ability of prolyl olligopepti-
dase to produce antifibrotic and anti-inflammatory Ang 1-7,
it can convert thymosin β4 to N-acetyl-β-aspartyl-lysyl-
proline (AC-SDKP), which provides an anti-inflammatory
and antifibrotic effect in lung and cardiovascular diseases.
Activation of the ACE2 compensatory pathways during
COVID-19 infection could potentially do the following: (i)
cause an increase in Ang 1-7 production from accumulated
Ang I and Ang II, in order to reconcile the RAS balance; (ii)
result in the degradation of bradykinin and des-Argα-bradyki-
nin via the actions of thimet olligopeptidase and prolyl car-
boxypeptidase, respectively, for the purpose of managing or
alleviating pulmonary edema and respiratory failure; and (iii)
support Ang 1-7 function by increasing AC-SDKP produc-
tion and reducing Ang-II accumulation.

Cardiometabolic and Pulmonary Diseases During
COVID-19 Infection

COVID-19 has an acutely harmful effect on patients with
cardiovascular diseases. The volume of severe cases and high
mortality rates noted in COVID-19 patients are closely corre-
lated with cardiovascular metabolic comorbidities, such as
hypertension, cardiovascular diseases, and diabetes. COVID-
19 can aggravate any damage to the heart and signifi-
cantly increase the incidence of acute cardiac injury in inten-
sive care unit/severe patients. Additionally, elevated levels of
creatine kinase and lactate dehydrogenase have been reported
in COVID-19 patients. Wang et al. also found arrhyth-
mia and elevated hypersensitive troponin I in 138 COVID-
19 patients at Zhongnan Hospital in Wuhan, which might
be due to SARS-CoV-2 infection—induced lung failure, cytokine storm, or decreased oxygenation. According to available clinical data from China, 2.5% to 15% of COVID-19 patients also have cardiovascular diseases, and 15% to 30% also have hypertension. These values are variable across countries, and in Italy, according to recent clinical data, the percentage of patients with COVID-19 who also have hypertension (46%-52%), cardiovascular disease (19%-24%), and hypercholesterolemia (16%-20%) is much higher. All these clinical features share a common disorder of RAS activity, wherein the classical RAS is highly activated, leading to an increase in Ang II and upregulation of the ACE/Ang II/AT1R axis.

A recent study by Osman et al. exemplified that RAS components were modulated by SARS-CoV-2 in 44 COVID-19 patients. ACE-2 expression was decreased in the blood cells and Ang I and Ang II were increased in the plasma. At the same time, the Ang 1-7 level, which is supposed to be low, was not significantly changed compared to that in the control samples, where it could be explained by the activation of ACE-2 independent of Ang 1-7 production pathways as a result of Ang I accumulation. That was not, however, enough to prevent the detrimental effects of Ang II accumulation.

In order to counteract the deleterious effect of Ang II, the RAS is regulated either endogenously by negative feedback to reduce renin secretion or stimulation of AT2R, or exogenously by using ARBs, renin inhibitors, and ACEIs, which are the main drugs used to treat hypertension and vascular diseases.

**Myocardial injuries**

Ang 1-7 acts as an antiarrhythmic component in rat cardiac injury-reperfusion, which contributes to the alleviation of reversible and/or irreversible ischemia-reperfusion injury. activates the sodium pump, hyperpolarizes the heart cell, and re-establishes impulse conduction. Moreover, alamandine via the MrgD receptor stimulates the adenosine monophosphate–activated protein kinase pathway to alleviate cardiac hypertrophy that is induced by Ang II in alamandine-treated cardiomyocytes from a C57BL/6 mouse model. In the transverse aortic constriction mouse model, the oral administration of alamandine for 2 weeks prevented vascular remodelling and attenuated vascular wall fibrosis. In addition, alamandine was able to elevate MrgD receptor expression and attenuate AT1R expression induced by transverse aortic constriction.
In the case of COVID-19, acute cardiac injury, ischemic stroke, acute coronary syndromes, myocarditis, arrhythmias, and heart failure were reported in hospitalized patients. High expression of ACE-2 in heart tissue, cytokine storm, and viral infection—associated hypoxemia are the main potential causes of COVID-19-associated myocardial injury. Recently, it was found that SARS-CoV-2 infected the cardiomyocytes in an engineered human heart tissue model of COVID-19 with severe myocarditis, leading to contractile deficits, cytokine production, and cell death. Moreover, critically ill COVID-19 patients showed intense inflammatory syndrome and cardiac complications such as arrhythmia and myocarditis after 1 week of the infection, whereas deceased patients showed acute cardiac injury, type I respiratory failure, heart failure, and acute kidney injury. Acute cardiac injury and heart failure were especially common among these COVID-19 cases.

Increasing interleukin, leukocyte, and neutrophil levels in patients with myocardial injury was correlated with the severity of inflammation during COVID-19. As a result, the administration of alamandine may have therapeutic potential through antifibrotic and anti-inflammatory effects, to compensate for the effect of ACE-2 deficiency in cardiovascular diseases during COVID-19 infection. Additionally, ARBs—telmisartan and olmesartan—demonstrated an anti-inflammatory effect in an experimental rat model of autoimmune myocarditis via the reduction of TNF-α, interferon gamma, IL-1β, IL-6 proinflammatory cytokines, and increasing anti-inflammatory cytokine IL-10 associated with less myocardial fibrosis.

Blood thrombosis and embolism

Disseminated intravascular coagulation and pulmonary embolisms were detected in COVID-19 patients. Furthermore, increasing D-dimer and fibrinogen levels in COVID-19 patients indicates thrombotic formation, and the endothelial damage produced by SARS-CoV-2 infection promotes the coagulation process that leads to the microthrombi formation. They can travel through blood vessels to different internal organs, resulting in pulmonary embolisms in addition to heart, kidney, and liver ischemic injuries. Moreover, frequent activation of the coagulation process—referred to as COVID-19 coagulopathy—leads to poor outcomes and high mortality rates. The elevation of proinflammatory cytokines and chemokines during COVID-19 inhibits anticoagulation pathways, thus promoting thrombin formation. Recently, high levels of Ang II were detected in COVID-19 patients, possibly contributing to the thrombosis seen in COVID-19 patients, whereas Ang 1-7 is posited to have an antithrombotic effect similar to that of losartan, mediating the antithrombotic effect of captopril in addition to that of losartan.

Obesity and diabetes

In obese individuals, dysfunctional adipose tissue secretes proinflammatory cytokines in the circulatory system, contributing to obesity-related chronic inflammation. SARS-CoV-2 entry via the expression of ACE-2 on adipose tissue could direct adipocytes to produce more proinflammatory cytokines, therefore contributing to the immune dysfunction seen during COVID-19 infection. In addition, IL-6 was identified as being more elevated in COVID-19 patients who also have diabetes—particularly compared to nondiabetic patients—putting them at risk of forming a deadly uncontrollable cytokine storm due to the damage of islets and pancreatic injury caused by SARS-CoV-2 entry. Moreover, diabetes increases the risk of death in COVID-19 patients fourfold, compared to the risk in COVID-19 patients without diabetes. In a Korean cohort observational study of 1082 COVID-19 patients, diabetes mellitus was found to be a risk factor for COVID-19 severity and mortality.

The activation of the RAS plays a crucial role in inflammation, with the bulk of this system’s proinflammatory function being due to Ang II and, more specifically, mediation by AT1R. AT1R, present in most cells, is stimulated by Ang II and activates targeted cells, as well as downstream signaling pathways associated with tissue injury and the inflammatory microenvironment, including fibrosis, oxidative stress, calcium mobilization, adaptive immune cell recruitment, neutrophils and monocyte adhesion, cytokines and chemokines expression, synthesis, and release. It was demonstrated that most of these effects are negatively regulated by the ACE-2/Ang 1-7/MasR axis, which serves as a beneficial anti-inflammatory axis in several inflammatory conditions associated with RAS activation and adipokine dysregulation, such as obesity, type 2 diabetes, and cardiovascular diseases. In a model of high-fat, diet-induced obesity, ACE-2 deficiency worsens epicardial adipose tissue inflammation, cardiac dysfunction, myocardial lipotoxicity, and cardiac insulin resistance. In obese patients, the administration of Ang 1-7 improved insulin-stimulated, endothelium-dependent vasodilation and blunted the vasoconstrictor effect of endothelin-1, which may counteract the hemodynamic abnormalities of human obesity.

Lung injuries

It has been reported that up to 20% of COVID-19 patients suffer from respiratory diseases such as ARDS that are characterized by severe hypoxia, accumulation of inflammatory cells, and increased vascular permeability-dependent pulmonary edema. ACE/Ang II/AT1R activation and/or expression is significantly upregulated in patients with sepsis, one of the most common causes of ARDS. Furthermore, pneumonia that is closely associated with infections such as SARS coronavirus or human influenza viruses is a predisposing factor for ARDS.

Ageing and ARDS are known to be lung fibrosis risk factors, with the 2 being identified together in the vast majority of COVID-19 cases. During the inflammatory phase of ARDS, matrix metalloproteinases are produced to contribute to lung injury and fibroproliferation. This process is followed by the production of IL-6, TNF-α, and vascular endothelial growth factor, which are implicated in the ARDS conversion to fibrosis. Most COVID-19 patients with ARDS die due to the development of pulmonary fibrosis, which typically occurs in the first to third week of infection, and it is in most of the tissues of deceased patients. Therefore, the importance of anti-fibrotic intervention to counteract early-onset ARDS has been raised.

The ACE-2/Ang 1-7/MasR axis protects against lung fibrosis by inhibiting Ang II-induced apoptotic
| Study | Study type | Race or population | Mean age, y | Sex | Sample size | Presence of comorbidity |
|-------|------------|--------------------|-------------|-----|-------------|------------------------|
| Mancusi et al. | Observational study (accession no.: NCT04331574) | Italian | 67.9 ± 15.6 | Male, 62% | 1498 | Hypertension, HF |
| Iaccarino et al. | Observational study (accession no.: NCT04331574) | Italian | 66.5 ± 0.4 | Male, 65% | 1591 | Hypertension, DM, COPD, CAD, HF, obesity, CKD |
| Semenzato et al. | Retrospective cohort | French | 49 ± 31 | Male, 42.3% | 2 million | Only hypertension without cardiovascular or respiratory diseases |
| Russo et al. | Observational, retrospective | Italian | 54 ± 17 | Male, 55% | 351 | Hypertension, AF, dyslipidemia, DM, CAD, COPD, CKD |
| Genet et al. | Observational retrospective | French | 86.3 ± 8 | Male, 33% | 201 | Hypertension, dementia, cancer, stroke, HF, AF, CAD, COPD, DM, depression, anemia, malnutrition |
| Zhong et al. | Retrospective observational | Chinese | 66.3 ± 10.6 | Male, 44.4% | 126 | DM, CAD, COPD, CVD, malignant tumours, chronic hepatorenal disease |
| Palazzuoli et al. | Retrospective observational cohort | Italian | 69 ± 9 | Male, 63.8% | 781 | Hypertension, DM, OLD, HF, CAD |
| de Castelnuovo et al. | Retrospective observational (accession no: NCT04318418) | Italian | 67 ± 12 | Male, 61.7% | 4069 | Hypertension, HHD, DM, cancer, CKD, CPD |
| Negreira-Camañno et al. | Observational cohort | Spanish | 76.5 ± 12.3 | Male, 51.9% | 545 | Hypertension, DM, obesity, lung disease, COPD, asthma, OSAS, HF, reduced LVEF, IHD, AF, CKD, cancer |
| Reynolds et al. | Observational | Black, 15%; White, 46.5%; Asian, 8.8%; other, 29.6% | 49 ± 15 | Male, 41.5% | 12,594 | Hypertension, HF, DM, MI, CKD, OLD |
| Bauer et al. | Observational | Black, 11%; White, 53%; unknown, 31%; other, 5% | 54.7 ± 22.5 | Male, 37% | 1449 | Hypertension, chronic respiratory disease, DM, arterial disease, HF, CKD, cancer, CLD |
| Meng et al. | Retrospective observational | Chinese | 62 ± 7 | Male, 57.1% | 42 | Hypertension, hypothyroidism, DM, cancer, atrioventricular block, Sjogren's syndrome, CHD |
| Soleimani et al. | Retrospective observational | Iranian | 66.4 ± 12.9 | Male, 58.7% | 254 | Hypertension, cardiac disease, DM, CKD, CVD, chronic lung disease, malignancy |
| Matsuzawa et al. | Retrospective observational | Japanese | 60 ± 19 | Male, 59.6% | 151 | Hypertension, DM, COPD, CKD, HF, stroke |
| Gao et al. | Retrospective observational | Chinese | 58 ± 17 | Male, 51% | 2877 | Hypertension, DM, MA, MI, peripheral vascular disease, HF, renal failure, stroke, COPD, pneumonia, asthma, cancer, OSAS |
| Vila-Corcoles et al. | Retrospective observational | Spanish | 70 ± 20 | Male, 40.5% | 205 | Hypertension, neurologic, rheumatic, renal, liver, respiratory, cardiac diseases, AF, cancer, hypercholesterolemia, DM |
| Desai et al. | Retrospective observational | Italian | 64.8 ± 14.5 | Male, 66% | 575 | Hypertension, respiratory, and cardiovascular diseases, DM, malignancy |
| Zhang et al. | Retrospective observational | Chinese | 62 ± 7 | Male, 53.5% | 1128 | Hypertension, DM, CHD, CLD, chronic renal diseases, CVD, COPD |

(continued)
resistance of lung fibroblasts via the MAPK/nuclear factor kappa-B pathway and activating the B-cell lymphoma-2 (BCL-2)-associated X protein/caspase-dependent mitochondrial apoptotic pathway. \(^{116,117}\) Interestingly, recent in silico studies noted that the combination of losartan—an ARB—with imatinib\(^{118}\) or C21\(^{119}\) has the potential to alleviate ARDS during COVID-19 infection.

Increasing evidence has recently demonstrated the existence of local angiotensin systems in the alveolar endothelial cells of the lung.\(^{120}\) Ang II induces collagen deposition, nucleotide-binding oligomerization, domain-like receptor pyrin domain containing 3 (NLRP3) inflammasome activation, and oxidative stress that promotes pulmonary fibrosis.\(^{121,122}\) These effects were inhibited by ACE-2/Ang II-1/7/MasR, which decreases lung fibroblast migration and lung fibrosis.\(^{122}\) The expression and activity of ACE-2 are severely downregulated in both human and experimental lung fibrosis, suggesting that ACE-2 protects against lung fibrogenesis by limiting the local accumulation of the Ang II as a profibrotic peptide.\(^{122}\)

Many COVID-19 patients have endothelial damage—induced inflammation, detected by increased production of inflammatory cytokines and chemokines such as TNF-\(\alpha\), interferon gamma (IFN-\(\gamma\)), IL-2, IL-6, and IL-8.\(^{82,89,124}\) IL-6 acts as a crucial mediator of cytokine storm syndrome, resulting in lung damage and disseminated intravascular coagulation.\(^{125,126}\) Moreover, coronaviruses promote NLRP3, increasing the release of IL-18 and IFN-\(\gamma\). IFN-\(\gamma\) mediates acute lung injury and activates macrophages to release IL-18, IL-6, IL-8, IL-1, and MCP-1, which contribute to alveolar epithelial damage and acute lung injury.\(^{125,126}\)

Ang II—induced acute lung injury was found to be attenuated by calcitriol/vitamin D receptor signals, reducing the expression of Ang II in endothelial cells and suppressing the Ang II-Tie-2-myosin light-chain kinase pathway in the acute lung injury mouse model.\(^{127}\) In a randomized clinical trial of 76 COVID-19 patients, all of whom were treated with a high dose of calcifediol, the severity of the disease decreased, as determined by a reduction of admissions to the intensive care unit.\(^{128}\) As Ang II is known to be elevated in patients with ARDS,\(^{55}\) the most severe form of lung injury, it can be assumed that calcifediol can be converted to the active vitamin D3 (calcitriol), which blocks the Ang II inflammatory effect and alleviates ARDS in COVID-19 patients. To verify the discovery of calcifediol-induced effects and their exact mechanisms, more clinical trials with larger numbers of test subjects are required.

### ACE-2 Expression and COVID-19

Due to the propensity for patients under ACEI and ARB treatment to present with an upregulation of ACE-2, it was initially suggested that their conditions could be exacerbated by COVID-19. If this suggestion is correct, it renders a huge population of people under RAS inhibitor treatment at high risk, leading to a debate about the use of this medication. However, the upregulation of ACE-2 in cardiac diseases such as myocardial infarction was considered to be a negative regulatory action in response to the increase of the activity of the ACE/Ang II/AT1R axis. Moreover, that upregulation was suggested to be part of ACE-2 involvement in the inflammatory response during myocardial infarction rather than being an ACEI or ARB direct effect.\(^{129}\)

Interestingly, a high level of expression of ACE-2 in cardiovascular disorders is unlikely to be a risk factor for or responsible for COVID-19 severity. To the best of our knowledge, men/boys are at higher risk of COVID-19 compared to women/girls, but the level of ACE-2 expression was shown to be higher in Asian women/girls compared to Asian men/boys.\(^{130}\) Moreover, the ACE-2 expression level in type-2 diabetic patients tends to decrease as the disease progresses. At the same time, patients with most cardiovascular diseases and those with type-2 diabetes need intensive care once they have...
Table 2. Continued summary of clinical studies and trials associated with hypertension and ACEI/ARB administration in relation to COVID-19 infection

| Antihypertensive drugs used (% of population) | Period of ACEI/ARB intake before COVID-19 infection | Main outcomes | Reference |
|-----------------------------------------------|---------------------------------------------------|---------------|-----------|
| ACEIs (35.4%) /ARBs (29.7%)                   | Unknown                                           | Administration of ACEIs/ARBs did not affect chance of recovery in COVID-19 patients with hypertension or heart failure | 133       |
| ACEIs (21.9%) /ARBs (19.3%)                   | Not mentioned                                     | ACEIs/ARBs did not contribute to mortality from COVID-19 | 134       |
| ACEIs (30%), ARBs (51%).                     | ≥3 mos before study conduction                    | ACEI/ARB administration lowered risk of hospitalization and intubation or death with COVID-19 compared to calcium-channel blocker administration; long-term use of ACEIs/ARBs might decrease risk of COVID-19 in hypertensive patients | 135       |
| ACEIs/ARBs (26.78%)                          | Not mentioned                                     | Most COVID-19 patients who did not require hospitalization were hypertensive patients and/or ACEI/ARB users | 136       |
| ACEIs/ARBs (31.34%)                          | ≥1 wk before the onset of infection               | ACEI/ARB administration, before onset of infection, significantly lowered mortality rate in COVID-19 patients | 137       |
| ACEIs/ARBs (29.37%)                          | Not mentioned                                     | ACEI/ARB therapy did not contribute to mortality in COVID-19 patients with hypertension | 138       |
| ACEIs (21.9%)/ ARBs (17%)                    | Not mentioned                                     | Previous use of ACEIs/ARBs reduced risk of mortality in patients hospitalized with COVID-19 infection | 139       |
| ACEIs (15.5%); ARBs (13.3%); both ACEIs and ARBs (6.4%) | Not mentioned                                   | No association between ACEI/ARB usage and severity or mortality in all COVID-19 patients | 140       |
| ACEI/ARB (30.8%)                             | ≥1 mo before hospital admission                   | ACEI/ARB administration reduced risk of death during hospitalization in COVID-19 hypertensive patients | 141       |
| ACEIs (8.3%); ARBs (10.5%); ACEIs or ARBs (18.4%) | Within 18 mos before COVID-19 diagnosis           | No association between ACEI/ARB treatment and susceptibility to or severity of COVID-19 infection | 142       |
| ACEIs/ARBs (16%)                             | Within 12 mos before COVID-19 test                | Previous use of ACEIs/ARBs had no effect on severity of COVID-19 infection | 143       |
| ACEIs/ARBs (40.5%)                           | For >1 y                                          | ACEI/ARB administration improved clinical outcomes of COVID-19 patients with hypertension | 144       |
| ARBs (48%)                                   | ≥7 d after hospital admission                     | ARB treatment did not worsen clinical outcomes during COVID-19 infection in hypertensive patients | 145       |
| ACEIs (2%); ARBs (12.6%)                     | Not mentioned                                     | ACEI/ARB treatment reduced poor outcomes in COVID-19 patients with hypertension | 146       |
| ACEIs/ARBs (6.36%)                           | Not mentioned                                     | No association between ACEI/ARB treatment and risk of mortality in COVID-19 patients | 147       |
| ACEIs (37.6%)/ARBs (16.1%)                   | Not mentioned                                     | No association between ACEI/ARB treatment and risk of COVID-19 infection in hypertensive patients | 148       |
| ACEIs (14.4%)/ARBs (12.3%)                   | Not mentioned                                     | Unlike ARBs, ACEIs reduced mortality risk in COVID-19 patients | 149       |
| ACEIs (2.75%)/ARBs (14%)                     | Not mentioned                                     | Administration of ACEIs/ARBs reduced risk of all-cause mortality in COVID-19 patients with hypertension | 150       |
| ACEIs (23.9%)/ARBs (22.2%)                   | ≥1 prescription during 2019                       | No association between ACEI/ARB treatment and risk of COVID-19 infection | 151       |
| ACEIs/ARBs (31.8%)                           | Not mentioned                                     | ACEIs/ARBs are not associated with severity or mortality of COVID-19 patients with hypertension | 152       |
| ACEIs/ARBs (50.6%)                           | Not mentioned                                     | Previous administration of ACEIs/ARBs had no association with the number of days alive and out of the hospital in mild COVID-19 | 153       |
| ACEIs/ARBs (49.3%)                           | Not mentioned                                     | ACEI/ARB administration had no effect on severity and mortality of COVID-19 | 154       |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker.
COVID-19, regardless of the ACE-2 level before the COVID-19 infection. Therefore, the severity of their cases seems to be due to the fact that they are suffering from metabolic disorders, with the balance of the RAS having already shifted toward the ACE/Ang II/AT1R axis, and alongside that, the COVID-19 infection has augmented the ACE/Ang II/AT1R axis effect, which includes vasoconstriction, hypertension, inflammation, and myocardial hypertrophy.130

**ACEI and ARB Administration During the COVID-19 Pandemic**

Various clinical studies and trials have been performed on diverse populations and ages, as well as on those with a range of comorbidities (Table 1), in order to determine the association between ACEI/ARB administration and COVID-19 infection. Most of those studies highlighted the lack of relationship of hypertension or ACEI/ARB administration with the risk of COVID-19 infection, severity, mortality, poor outcomes, and even chance of recovery. Other studies indicate that previous administration of ACEIs/ARBs lowers the risk of COVID-19 infection, as well as the severity and mortality rate (Table 2). This controversy could be attributed to the presence of several competing factors, which were overcome in some studies but not in others, thus limiting the ability to determine the exact relationship of COVID-19 with the following factors: (i) missing information about patient lifestyle, body mass index, history of smoking, dose and period of ACEI/ARB intake, and ACE-2 activity and expression; (ii) the degree of hypertension and its duration, which directly relates to heart failure and, therefore, poor outcomes; (iii) the fact that the presence of participants aged 80 years and over could cause an underestimation of the effects of antihypertensive drugs, due to the correlation between COVID-19 severity and mortality in older age patients; (iv) adherence to antihypertensive drug intake prior to, or during, COVID-19 infection, which due to the nature of retrospective studies, is not fully guaranteed and was based on drug prescriptions recorded in the databases. Furthermore, it is challenging to isolate and analyze the effects of ACEIs and ARBs independently, as they are commonly used for several comorbidities such as diabetes mellitus, hypertension, and coronary artery disease. At the same time, selection bias cannot be completely excluded, even following statistical analysis such as propensity-score matching. This consideration means that randomized, controlled trials are a necessity in order to delineate the potential effect of ACEIs/ARBs on COVID-19 patients. Avoiding the aforementioned factors could help to limit bias in future studies.

Despite the relationship between ACE-2 expression level and susceptibility to or severity of COVID-19, ARB and ACEI administration should not be discontinued, as their detrimental effect has not been confirmed, so their administration at least will protect COVID-19 patients with metabolic disorders from life-threatening consequences.130

Interestingly, in 2014, Deshotels and coworkers131 demonstrated the effect of increased Ang II level on ACE-2 downregulation during hypertension. The Ang II treatment was able to internalize ACE-2 receptor and promote ACE-2 ubiquitination through AT1R binding, and the AT1 receptor in the absence of Ang II was found to be complexed with ACE-2 to prevent ACE-2 internalization.

Moreover, the absence of AT1R or AT1R blocking by losartan was found to attenuate the Ang II–mediated ACE-2 internalization. In the same context, ACEIs prevent Ang II production and upregulate Ang 1-7, which has an anti-inflammatory effect. Hence, we posit that the use of ACEIs may protect against pulmonary injury, and ARBs—in particular, losartan—may prevent ACE-2 internalization and impede viral entry in hypertensive people with metabolic disorders.

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**Figure 2.** The effect of angiotensin (Ang) II treatment on angiotensin-converting enzyme (ACE)-2 downregulation in presence/absence of angiotensin II type 1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs). AT1R, angiotensin II type 1 receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Created with BioRender.com.

**Figure 3.** Dysregulation of classical and counter-regulatory renin–angiotensin system during COVID-19 infection. ACE, angiotensin-converting enzyme; Ang, angiotensin; AT1R, angiotensin II type 1 receptor; MasR, Mas receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Created with BioRender.com.
COVID-19. All these speculations need further investigation \(^{130,131}\) (Fig. 2).

In addition, the depletion of ACE-2 due to the SARS-CoV-2 binding in COVID-19 patients with respiratory problems increases the pulmonary injury. There is growing evidence to support the administration of ARBs and ACEIs to activate the ACE-2/Ang 1-7/MasR axis, which ameliorates the deleterious effects of ACE-2 depletion and accelerates disease recovery. \(^{130}\) Thus, targeting the counter-regulatory RAS pathways could be of interest in explaining the association between COVID-19 and cardio-metabolic diseases and could be a potential future target for treatment. Moreover, conducting randomized, controlled trials with large sample sizes is of utmost importance in order to determine the definitive effect of ACEI/ARB administration on COVID-19 infection, and the pharmacologic mechanisms behind that effect.

**COVID-19 Treatment**

The administration of several antiviral drugs that intervene with viral–host interaction has been under investigation as a possible COVID-19 treatment. \(^{132}\) For COVID-19 patients with ARDS, treatment with recombinant human ACE-2 (rhACE-2) is suggested as a possible strategy to maintain ACE-2 availability and prevent viral-AKC-2 binding in the lung tissue by saturating SARS-CoV-2 spike protein in the blood before entry into the lung. In addition, the rhACE-2 may shift the balance toward the ACE-2/Ang 1-7/MasR axis, as activity of the latter was confirmed to increase after rhACE-2 treatment. \(^{8}\)

As recommended by Rello et al. (2020), COVID-19 treatment by either antiviral, anti-inflammatory, anticoagulant, or antifibrotic agents can be personalized based on the main clinical phenotypes that occur in the patient. \(^{89}\) Ang 1-7 and Ang 1-9 can act as anti-inflammatory, anticoagulant, and antifibrotic factors, \(^{40}\) which can cover the majority of clinical phenotypes and thus potentially improve disease outcomes. In light of our hypothesis, the activation of Ang 1-7 without increasing ACE-2 activity may be a promising strategy to rebalance the RAS axes in COVID-19. For example, producing Ang 1-7 from Ang I through nephrilysin activity will promote the protective effect of Ang 1-7 without stimulating ACE-2, which is known to be a virus entry portal.

In conclusion, COVID-19 patients share clinical phenotypes similar to those found in diseases where the ACE-2/Ang 1-7/MasR axis is downregulated, indicating the pivotal role of RAS balance during SARS-CoV-2 infection.

**Conclusion and Perspectives on the Future**

The main issue related to COVID-19 infection is the severity of the cases that lead to organ failure and death. In the majority of these cases, the patient is elderly, with at least one comorbidity factor. The majority of these comorbidities are related to cardiovascular diseases and risk factors. When infected with COVID-19, patients with cardiovascular diseases are most likely to develop new cardiac injuries, or worsen their existing pathologies. The RAS—as a crucial factor in cardiovascular diseases—will be disturbed during infection. This is because of the lack of ACE-2 function caused by virus binding and because of the potential imbalance of the RAS classical pathway activation (mainly ACE/Ang II/AT1R) and the RAS counter-regulatory pathway activation (mainly ACE-2/Ang 1-7/MasR and ACE-2/Ang 1-9/AT2R; Fig. 3). Targeting the counter-regulatory pathways using agonists or stimulators, such as rhACE-2, MasR agonists, or AT2R agonists, may be of interest to boost the function of this system, or compensate for the poor ACE-2 functionality or availability, possibly due to virus binding, and, seems to be a promising therapeutic strategy for COVID-19 treatment.

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