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Review article

The therapy with RAS inhibitors during the COVID-19 pandemic

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COVID-19 is a disease caused by the novel coronavirus first identified in Wuhan, China. The global number of confirmed cases of COVID-19 has surpassed 28,285,700 with mortality that appears higher than for seasonal influenza. About 20% of COVID-19 patients have experienced cardiac involvement and myocardial infarction in patients infected with SARS-CoV-2 had a worse prognosis. Furthermore, the widespread use of antiviral drugs can be linked to a worsening of heart function. Arrhythmias and hypertension have also been reported in patients with Covid-19. On the other hand, previous cardiac diseases are present in 30% of patients infected with SARS-CoV-2. There is uncertainty in the use of ace inhibitors and angiotensin II (Ang II) antagonists in the COVID-19 era.

The mechanism of action of SARS-CoV-2 has been elucidated. It has been demonstrated that angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for the new coronavirus SARS-CoV-2 and it is required for host cell entry and subsequent viral replication. The effect of the SARS-CoV-2 infection is the downregulation of ACE2 that may contribute to the severity of lung pathologies as well as the cardiac function.

ACE2, a homolog of ACE, is a monocarboxypeptidase that converts Ang II into angiotensin 1–7 (Ang 1–7) that with its vasodilatory, antifibrotic, antihypertrophic effects counterbalances the negative effects of Ang II. On the other hand, angiotensin-converting enzyme inhibitors (ACEi) and AT1R blockers have been shown to upregulate the expression of ACE2. Based on the mechanism of action of SAR-CoV-2, the use of renin angiotensin system (RAS) inhibitors was questioned although all scientific societies did not recommend discontinuation when clinically recommended. The BRACE CORONA, a phase 4, randomized study tested two strategies: temporarily stopping the ACE inhibitor/angiotensin receptor blockers (ARB) for 30 days versus continuing ACE inhibitors/ARBs in patients who were taking these medications chronically and were hospitalized with a confirmed diagnosis of COVID-19 was also discussed.

Therefore, the goal of this review is to summarize recent laboratory and clinical investigations concerning the use of ACEi and ARBs during the COVID-19 pandemic. The available data, based also on a randomized trial, suggest that ACEIs or ARBs, when clinically indicated, should be regularly used in the COVID-19 era.

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Introduction

There is great concern about a new virus that has infected 28,285,700 people and killed 911,255 of them. In December 2019 in Wuhan, Hubei, China, a series of viral pneumonia cases occurred from an unknown cause, later discovered after a deep sequencing analysis from lower respiratory tract samples and identified as an infection of a novel coronavirus called 2019 novel coronavirus (SARS-CoV-2) responsible for COVID-19 disease. Viral pneumonia cases have been reported in Wuhan, in patients who had come into contact with the local fish market. The Chinese health authority released a report on 31 December 2019, and the fish market has been closed.

Data from the outbreak in Wuhan, China, show a 10.5% death rate among people with COVID-19 who also have cardiovascular disease, 7.3% for those with diabetes, 6.3% for those with respiratory disease, 6% for those with high blood pressure, and 5.6% for those with cancer.[1]

The pandemic is characterized by a very quick transmission with an exponential rate of increase as an infected person spreads the disease to two or three others.[2]

Acute cardiovascular complications of COVID 19

The mortality of COVID-19 is higher than that of seasonal influenza suggesting alternative methods of toxicity of the SARS-CoV-2 virus. A certain percentage of COVID-19 patients have experienced cardiac involvement.[1] Myocardial infarction or elevated troponin level patients infected with coronavirus had a worse prognosis.[3] Furthermore, the widespread use of antiviral drugs (in about 90% of COVID-19 patients) can be linked to a worsening of heart function.[3]

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Data on 138 hospitalized COVID-19 patients reported that 16.7% of patients developed arrhythmia and 7.2% experienced acute cardiac injury.[4] In this retrospective, single-center case series of the 138 patients, they reported that 36 patients (26.1%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome (61.1%), arrhythmia (44.4%), and shock (30.6%). Of the 138 patients, 64 (46.4%) had one or more coexisting medical conditions. Hypertension (31.2%), diabetes (10.1%), cardiovascular disease (14.5%), and malignancy (7.2%) were the most common coexisting conditions. Compared with patients who did not receive ICU care ($n = 102$), patients who required ICU care ($n = 36$) were significantly older [median age, 66 years (IQR, 57–78) vs 51 years (IQR, 37–62); $P < 0.001$] and were more likely to have underlying comorbidities, including hypertension (58.3% vs 21.6%), diabetes (22.2% vs 5.9%), cardiovascular disease (25.0% vs 10.8%]), and cerebrovascular disease (16.7% vs 1.0%).[4]

Moreover, Huang *et al.* reported the data of 41 admitted hospital patients with laboratory-confirmed infection. Most of the infected patients were men [30 of 41 (73%)]; less than half had underlying diseases (32%), including diabetes (20%), hypertension (15%), and cardiovascular disease (15%). The median age was 49 years. Dyspnea developed in 22 (55%) of 40 patients. All 41 patients had pneumonia with abnormal findings on chest CT. Hypersensitive troponin I (hs-cTnI) was increased (>28 pg/ml) substantially in five patients (12%), in whom the diagnosis of virus-related cardiac injury was made. Four of these five patients with myocardial injury were admitted to the ICU. Blood-pressure levels were significantly higher in patients treated in the ICU than in those not treated in the ICU (mean systolic blood pressure 145 mmHg versus 122 mmHg; $P < 0.001$).[5]

Additionally, data by Shi *et al.* on 416 hospitalized COVID-19 patients have also shown that 19.7% of patients developed cardiac injury.[6] Of these 416 patients, 44 (10.6%) and 22 (5.3%) had coronary heart disease and cerebrovascular disease, respectively.[6]

A systematic analysis of 637 MERS-CoV cases suggests that, also, in this case, cardiac diseases were present in about 30%.[7]

A recent meta-analysis by Zou *et al.* including 2224 patients has shown an incidence of cardiac injury of 24.4% and that the incidence was similar between patients from China and other parts of the world. The primary outcome of all-cause mortality in hospitalized COVID-19 patients with cardiac injury was 72.6% (307/423 patients) compared with a mortality rate of 14.5% (171/1181 patients) in patients without cardiac injury (odds ratio [OR] = 17.32, 95% CI 9.21–32.57, $I^2 = 66\%$, $Z = 8.85$, $P < 0.00001$). Patients with cardiac injury were found to be older (SMD = 2.13, 95% CI 0.98–3.28, $I^2 = 96\%$, $Z = 3.63$, $P = 0.0003$) and consisted of fewer females (OR = 0.68, 95% CI 0.40–1.17, $I^2 = 48\%$, $Z = 1.39$, $P = 0.17$). Predictors of cardiac injury in hospitalized COVID-19 patients included a history of HTN (OR = 3.83, 95% CI 1.77–8.26, $I^2 = 73\%$, $Z = 3.42$, $P = 0.0006$) and chronic obstructive pulmonary disease (OR = 5.03, 95% CI 1.91–13.29, $I^2 = 0\%$, $Z = 3.26$, $P = 0.001$).[8]

Finally, SARS-CoV-2 may induce overwhelming inflammation by directly activating the p38 MAPK pathway,[9] and activation of MAPKK in T lymphocytes in patients with acute coronary syndromes (ACS) has been reported.[10] Therefore, patients with ACS infected with SARS-CoV-2 often have a poor prognosis.[11] In patients with ACS, the cardiac functional reserve can be reduced owing to myocardial ischemia or necrosis.[11]

A recent metanalysis from our group demonstrated that cardiovascular complications were registered in 14% of cases during hospitalization for COVID-19, and might contribute to adverse clinical events and mortality, together with preexisting cardiovascular comorbidities and risk factors.[12]

The angiotensin-converting enzyme 2 and the SARS-CoV-2 infection

Angiotensin-converting enzyme 2 (ACE2) is a type I transmembrane protein with an extracellular N-terminal domain containing the catalytic site and an intracellular C-terminal tail. ACE2 (or ACE homolog) was discovered as a zinc metalloproteinase by two different groups in 2000.[13]

ACE2 was initially identified from human heart failure (HF) and lymphoma cDNA libraries[13,14] and was later shown to serve as a receptor for the SARS-CoV-2.[15,16]

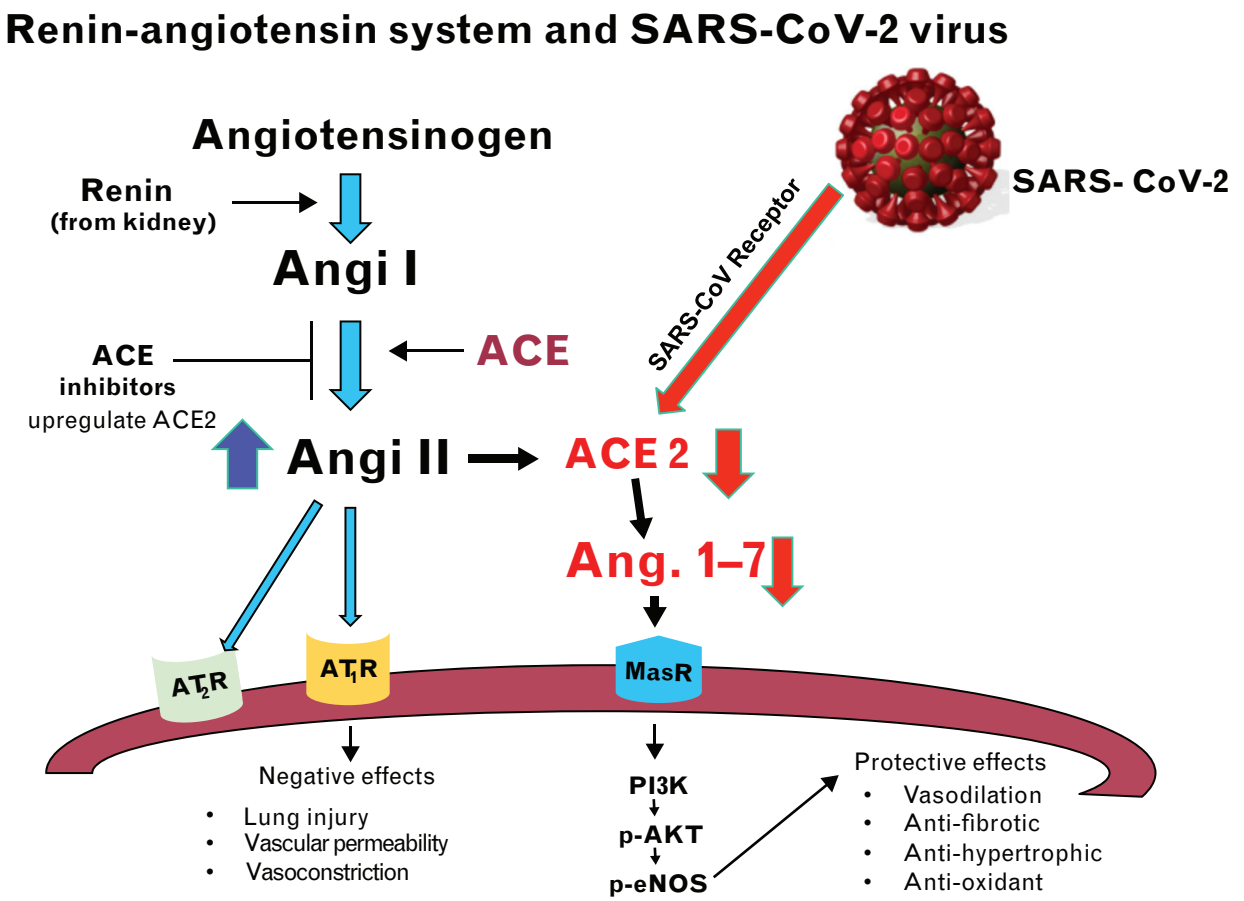
It has been shown that a specific region of SARS-CoV-2, called SARS-CoV-1 spike protein (S1) interacts with ACE2, leading to fusion with the host cell membrane.[15,17]

S1 contains the receptor-binding domain and directly binds to the peptidase domain of ACE2 to gain entry into host cells.[15,18]

In humans, ACE2 was highly expressed on lung alveolar epithelial cells and small intestinal epithelial cells, consistently with potential routes of viral transmission of SARS-CoV-2, as both respiratory and gastrointestinal systems share interfaces with the external environment. This epithelial expression, together with its presence in vascular endothelium, also provides a first step in understanding the pathogenesis of the main SARS disease manifestations, in particular in the lung.[19]

ACE2 is a homolog of ACE and converts angiotensin II (Ang II) into angiotensin 1–7 (Ang 1–7) which, by its actions on the Mas receptor, opposes the molecular and cellular effects of Ang II (Fig. 1). While Ang II promotes vasoconstriction, inflammation, salt and water

Fig. 1



Angiotensin-converting enzyme 2 (ACE2), a homolog of ACE, is a monocarboxypeptidase that converts angiotensin II into angiotensin 1–7 (Ang 1–7) that with vasodilatory, antifibrotic, antihypertrophic effects counterbalances the negative effects of angiotensin II. ACE2 is widely expressed in cardiomyocytes, cardiofibroblasts, lung alveolar epithelial cells of type II and coronary endothelial cells. Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for the new coronavirus SARS-CoV-2 and it is required for host cell entry and subsequent viral replication. SARS-CoV infection downregulates ACE2 decreasing Ang 1–7 (Red Arrows), which in turn results in excessive production of angiotensin II (Blue arrow) by the related enzyme ACE. On the other hand, ACE inhibitors upregulate ACE2.

reabsorption, and oxidative stress, Ang 1–7 activation counter-regulates Ang II/AT1R-mediated effects and also stimulates cardiac contractility mediated by the phosphatidylinositol 3-kinase (PI3K)–Akt–endothelial nitric oxide synthase pathway (Fig. 1).[20] ACE2 is an essential regulator of cardiac function and ACE2 knockout mice showed reduced systolic function.[21] The decrease in systolic function was both sex- and time-dependent, with more severe abnormalities in male than in female mice, and a more pronounced phenotype in older animals.[21]

Therefore, ACE2 is the cellular receptor for the new coronavirus SARS-CoV-2[22] and is required for host cell entry and subsequent viral replication. Overexpression of human ACE2 enhanced disease severity in a mouse model of SARS-CoV infection, demonstrating that viral entry into cells is a critical step.[23] angiotensin-converting enzyme inhibitors (ACEi) and AT1R blockers have been shown to upregulate the expression of ACE2 or prevent the loss of ACE2.[24] Overexpression of human ACE2 enhanced disease severity in a mouse model of SARS-CoV infection, demonstrating that viral entry into cells is a critical step.[23] On the other hand, ACE2 is protective of severe acute lung failure.[25]

SARS-CoV infection downregulates ACE2 then contributing to the severity of lung pathologies.

Thus, for SARS-CoV pathogenesis, ACE2 is not only the entry receptor of the virus but also protects from a lung injury, therefore SARS-CoV became highly lethal because the virus deregulates a lung-protective pathway[26] and the virus-induced downregulation of ACE2 may also reduce the left ventricular function.

The reason why the lung is the organ most affected by the SARS-CoV-2 infection is related to the large surface area but also because 83% of the cells that express ACE2 are alveolar epithelial cells of type II.[27]

The therapy with RAS inhibitors for SARS-CoV-2 infection

It has been previously suggested that ACEI and AT1R inhibitors could be used in patients with COVID-19 pneumonia.[28,29]

However, the AT1R antagonists' losartan and olmesartan were shown to increase cardiac ACE2 expression about 3-fold following chronic treatment (28 days) after myocardial infarction induced by coronary artery ligation of rats.[30]

Therefore, the possibility to treat COVID-19 with angiotensin-receptor antagonists that increase the ACE2 (the cellular receptor of SAR-CoV-2), as Gurwitz pointed out, seems to be counter-intuitive.[31]

However, the decreased ACE2 activity leads to an increase in the ACE function with an increase in Ang II, that in turn, induces vasoconstriction, and an increase in pulmonary vascular permeability, thereby mediating increased lung pathology.[26,32] At the lung level, such dysregulation would facilitate the progression of inflammatory and hyper-coagulation processes.

The treatment with angiotensin-receptor antagonists might reduce the effects of the increased angiotensin production induced by the viral infection as well as upregulate ACE thereby increasing the protective effects of Ang 1–7.[33] Decreased expression of ACE2 is associated with cardiovascular diseases.[21,34]

The SARS-CoV-2 infection resulted in the exhaustion of ACE2, and then the ACE2/Ang /Mas receptor pathway was inhibited. Therefore, one hypothesis is that the ACEI and AT1R inhibitors could be used in patients with COVID-19 pneumonia under the condition of controlling blood pressure, and might reduce the pulmonary inflammatory response.[35]

On the other hand, caution for using renin angiotensin system (RAS) inhibitors is related to the effects of ACE inhibitor lisinopril and the angiotensin-receptor blocker losartan that significantly increased mRNA expression and the function of cardiac ACE2 (5-fold and 3-fold, respectively).[24]

The increased expression of ACE2 receptors in the virus targeted cells by the use of ACE-inhibitor/angiotensin-receptor blockers could, on the other hand, increase the risk in patients with Covid-19.[36]

There are two functional variants of ACE2: a structural transmembrane domain, which has been demonstrated as a receptor for SARS-CoV-2,[22] and a soluble form of ACE2, which circulates in small amounts in the blood.[37] In this contest, a soluble recombinant ACE2 protein could have therapeutic potential by limiting coronavirus attachment to the cell membranes, cell entry, and replication.[38] At that time, studies in animals or humans testing the therapeutic potential of soluble recombinant ACE2 proteins are not yet available.[39]

The association of hypertension and COVID-19

There is a great concern in the medical world for the association between hypertension and COVID-19. The data of the Italian Ministry of Health on 20 March showed that in a cohort of 481 patients who died with COVID-19, 74% were affected by hypertension. Early reports suggested that patients with severe COVID-19 were more likely to have a history of hypertension than those with milder disease.[40] However, not surprisingly the hypertension is a frequent finding in elderly patients. In our recent metanalysis among 77 317 hospitalized patients from 21 studies, however, hypertension was present in 36.08% (95% CI = 20.25–53.64) of all patients.[12]

It has also been suggested that patients with cardiac diseases, hypertension, or diabetes who are treated with ACE-I or angiotensin receptor blockers (ARBs) are at higher risk for severe COVID-19 infection[41] and since most of the deceased COVID-19 patients had hypertension, further consideration is needed for the use of ACEi and ARBs in these patients. The use of these drugs has been widely questioned and it has been suggested that the practice of prescribing ARBs or ACE inhibitors for the prevention of COVID-19 infection should be discouraged[36] but a cause–effect relation between the use of ACEI or ARBs and adverse events in COVID-19 cannot be established since many confounding factors could explain the worse or better outcomes for this patients. Given the frequent use of these agents worldwide, a randomized clinical trial is needed to guide the use of this medication in patients affected by COVID-19. Recently, a large number of authors have supported their use and contraindicated the interruption of treatment.[28,42,43]

In particular, the beneficial effects of chronic ACEi/ARB use, especially in a hypertensive cohort with COVID-19[44], has been shown and their use in hypertensive patients with COVID-19 has been associated with lower mortality.[45,46]

Besides, patients receiving ACEI or ARB therapy had a lower rate of severe diseases and a lower level of IL-6 in peripheral blood. Also, ACEI or ARB therapy increased CD3 and CD8 T cell counts in peripheral blood and decreased the peak viral load compared with other antihypertensive drugs.[47]

Moreover, in a large single-center retrospective analysis, a protective effect of prehospitalization use of RAS inhibitors on mortality in hypertensive COVID-19 patients, which might be associated with reduced inflammatory response, has been observed.[48]

These results have also been confirmed by a large cohort study including 8.3 million people by Hippisley-Cox *et al.* in which ACE inhibitors and ARBs have been associated with reduced risks of COVID-19 disease.[49]

In this setting, the Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual antihypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection.[50]

With the aim to determine whether discontinuation or maintenance of RAS inhibitors in a high-risk population of patients infected with SARS-CoV-2 increases days alive and out of the hospital, Renato D. Lopes *et al.* designed the BRACE CORONA trial.[51] In 659 patients hospitalized for COVID-19, two different strategies have been tested: suspending treatment with ACE inhibitors/ARBs for 30 days or continued use. They found no significant difference in the number of days alive/out of the hospital at 30 days among patients who stopped ACE inhibitor/ARB treatment and those who continued with therapy.[51] This study provides the first high-quality evidence to guide the treatment of RAS inhibitors in this population.

It should be pointed out, however, that the RAS inhibitors are very successful in treating especially patients with heart failure. ACEIs have been shown to reduce mortality and morbidity in patients with HF and reduced EF.[52–54] Also, the evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial has led to the recommendation that an ACE-I is given to all patients at high risk for coronary disease, whether hypertensive or not.[55] During the 4.5 years of the HOPE study, ramipril therapy reduced the risk of cardiovascular mortality by 25%, the risk of myocardial infarction by 20%, and stroke risk by 32%. Furthermore, only 16% of patients treated with this ACE inhibitor needed to undergo revascularization interventions, such as angioplasty and bypass, against 18.4% of those who received a placebo.[55] Additionally a position paper by Zhang *et al.* on the management of HF patients with concomitant COVID-19 suggests that medical therapy (including beta-blocker, ACEi, ARB or ARNI, and mineralocorticoid receptor antagonist) should be continued in chronic HF patients whenever blood pressure and hemodynamic conditions permit and considering drug interaction with COVID-19-related therapies and side effect profile.[56] There is still little evidence and the expert recommendations are mainly based on the current pandemic situation and may need to be revised based on a randomized clinical trial.

In conclusion, the mortality of COVID-19 is higher than that of seasonal influenza suggesting alternative methods of toxicity of the SARS-CoV-2 virus. In particular, the receptor used by SARS-CoV-2, ACE2, may be involved in the cardiovascular commitments of the Covid-19 disease. However, many scientific societies, including the European Council of Hypertension,[50] as well as the Italian Society of Cardiology strongly recommend that physicians and patients should continue treatment with RAS-inhibitor therapy if indicated. The only randomized study available so far is the BRACE CORONA, a phase 4, randomized study testing two strategies: temporarily stopping the ACE inhibitor/ARB for 30 days versus continuing ACE inhibitors/ARBs in patients who were taking these medications chronically and were hospitalized with a confirmed diagnosis of COVID-19.[51] This study demonstrated that there is no clinical benefit from routinely interrupting these medications in hospitalized patients with mild to moderate COVID-19.

Therefore the BRACE CORONA trial further suggests that the RAS inhibitors should generally be continued in Covid-19 infection.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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