Review article

Arterial Hypertension and Risk of Mortality in Patients with COVID-19 Infection

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Abstract

COVID-19 is currently a major global health concern. Among many unanswered questions related to COVID-19, some of the most debated ones are those concerning arterial hypertension. Arterial hypertension is a major risk factor for mortality worldwide and its importance has been emphasised even further in light of COVID-19. The most common antihypertensive drugs are ACE inhibitors and angiotensin II type-I receptor blockers. SARS-CoV-2 utilises the angiotensin-converting enzyme-2 (ACE2) for cell entry and therefore has a direct effect on the renin–angiotensin system (RAS). In terms of arterial hypertension and COVID-19, there are three main issues which have been the focus of extensive debates. First, is arterial hypertension a predisposing factor for COVID-19 infection? Second, does arterial hypertension affect the severity of COVID-19 infection and increase the risk of all-cause and cardiovascular mortality? And finally, how important is the interaction of COVID-19 infection and the renin–angiotensin system for clinical outcomes? Is RAS blockade beneficial or harmful? The aim of this brief review was to provide substantiated answers to these questions.

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Introduction

Infection with SARS-CoV-2 is associated with high mortality rates and it is currently the most important global health concern. The risk of severe outcomes of COVID-19 infection increases with patients' age and prevalence of comorbidities (1). Arterial hypertension is one of the most prevalent chronic conditions (2) and it is often treated with renin–angiotensin system (RAS) blockage. Angiotensin-converting-enzyme 2 (ACE2) is the pivotal receptor for SARS-CoV-2 to enter host cells (3) and as such, it provides a link between COVID-19 and RAS. The association between arterial hypertension, its treatment, the risk of SARS-CoV-2 infection and clinical outcomes of COVID-19 infection has been a concern and a matter of debate for both patients and physicians. The aim of this paper was to review our knowledge about this issue by focusing on the most important publications issued so far and by answering the following key questions. First, does arterial hypertension predispose individuals to COVID-19 infection? Second, does arterial hypertension increase the risk of all-cause and cardiovascular mortality? Third, how important is the interaction of COVID-19 infection with the renin–angiotensin system? And finally, is RAS blockade beneficial or harmful in respect to COVID-19 outcomes?

However, before discussing arterial hypertension and COVID-19 infection, it is necessary to point out some important facts about arterial hypertension, RAS and respiratory infections independent of COVID-19 infection. It is well known that people over the age of 65 have a higher risk of a lower respiratory tract infection (LRTI) as well as a higher prevalence of arterial hypertension (4,2). In addition, a beneficial effect of RAS blockade associated with LRTI was detected in terms of lower incidence and lower mortality rates (5). Based on the above, it can be concluded that arterial hypertension is not an independent risk factor for LRTI and that the use of RAS blockers decreases the incidence and improves the outcomes of LRTI (6).

Is arterial hypertension a predisposing factor for COVID-19 infection?

According to the first data collected in Lombardy in early 2020, almost 73% of patients with COVID-19 had arterial hypertension (7). At that point, arterial hypertension was often indicated as a risk factor for COVID-19, together with cardiovascular and cerebrovascular diseases, chronic kidney disease, malignancies and obesity. However, it was initially overlooked that the average age in the Lombardy group was 81. Having that in mind, it is not surprising that the prevalence of arterial hypertension was so high. Other data from the first reports from Lombardy were related to the intake of antihypertensive drugs. Almost 47% of COVID-19 patients were taking RAS blockers. This information, along with some pathophysiological considerations, aroused suspicion that drugs which block RAS could be related to the higher incidence of SARS-CoV-2 infection, more severe forms of the disease and increased mortality. To support those data, Mancia et al. analysed the data concerning 6,272 people with COVID-19, together with a control group of 30,759 subjects paired based on age and gender (8). The first important fact they discovered was that the COVID-19 patients more often had cardiovascular diseases in their medical history, especially coronary heart disease and heart failure. Moreover, they also suffered from respiratory diseases, chronic kidney disease and, to some extent, carcinomas.

The second important piece of data concerned the association between RAS blockers and COVID-19 infection – no significant correlation of RAS blockers with COVID-19 infection was detected in the study, neither with regard to the severity of the clinical features of COVID-19 infection nor with regard to age or gender. In relation to COVID-19 in this group of subjects, RAS blockers had the same status as all other

classes of antihypertensive drugs. The final conclusion was that the observed relationship between arterial hypertension and COVID-19 infection was blurred by the influence of age and comorbidity. A number of other studies have confirmed that the prevalence of arterial hypertension in COVID-19 patients does not differ significantly from the prevalence in the general population (9).

Does arterial hypertension affect the severity of COVID-19 infection and increase mortality?

A number of researchers have noticed that patients with more severe forms of COVID-19 infection suffer from arterial hypertension significantly more frequently (Table 1). By analysing a group of patients from Wuhan, China, Shi et al. found that COVID-19 mortality was significantly higher in patients with myocardial damage and that arterial hypertension was also much more common among them (10). In a retrospective study by Wu et al., patients with hypertension were more likely to have increased oxygen demand, myocardial injury and a greater risk of developing severe COVID-19, suggesting that hypertension might play an important role in COVID-19 (11). These findings are consistent with the idea that hypertension cases involve an increased risk of comorbidity, infection and multiple organ function damage (12,13). In a multicentre retrospective cohort study of 1,833 COVID-19 patients, Mubarik et al. found that the prevalence of hypertension was 40.5% and that patients with hypertension were more likely to have severe COVID-19 illness than patients without hypertension (14). Evidence from a meta-analysis which included 24 observational studies with 99,918 COVID-19 patients suggested that hypertension was independently associated with a significantly increased risk of critical COVID-19 and in-hospital mortality of COVID-19 (15). Guan et al. detected a higher risk of severe COVID-19 in older individuals and those with underlying health conditions such as arterial hypertension (16). Gao et al. observed that mortality was much higher in patients with uncontrolled hypertension compared to those who achieved target blood pressure values (17). They also noticed that mortality was significantly lower in patients treated with RAS blockers.

Interesting results were obtained from the HOPE COVID-19 registry (Italy, Spain, Germany), where out of 5,937 patients with COVID-19 infection, 48.8% had arterial hypertension and 70.3% were treated with RAS blockers (18). As in the Lombardy group, the patients with COVID-19 infection more frequently had comorbidities associated with an increased risk of death. Over 40 days of follow-up, a significantly higher mortality rate was noticed among patients with arterial hypertension (29.6% vs 11.3%; $p<0.001$). Based on this finding, the authors expected that the increased mortality in COVID-19 infection could be related to arterial hypertension. However, when data was analysed in more detail using the multivariate Cox regression analysis, the authors found that the age over 65, respiratory infections and sepsis were independent predictors of mortality. A very important finding derived from their analysis was the fact that the use of RAS blockers had a protective effect on mortality, consistent with the findings by Gao et al. (17). Sheppari et al. have recently published an interesting finding concerning a group of patients with stage 1 uncontrolled arterial hypertension that there were no differences in mortality compared to the patients with controlled hypertension (19). They did not observe any associations between the control of arterial hypertension and COVID-19 infection or the need for hospitalisation. They concluded that the association between arterial hypertension control and mortality could be explained by advanced atherosclerosis and pre-existing target organ damage. The authors pointed out a probable key problem associated with arterial hypertension and COVID-19 infection, and that is the issue of irregular medical check-ups. Additionally, it should not be forgotten that the immune system in patients with arterial hypertension is already promoted and as such, it might represent the mechanisms through which arterial hypertension could be associated with severe forms of COVID-19 infection. This is an area which requires further research.

Is the interaction of COVID-19 infection and RAS important for the clinical course of the disease?

Table 1. Publications related to the association between severe COVID-19 and arterial hypertension

Authors	Findings
Shi et al. [10]	Cardiac injury is a common condition among hospitalised patients with COVID-19 in Wuhan, China and it is associated with a higher risk of in-hospital mortality. A total of 82 patients (19.7%) had cardiac injury. Compared with patients without cardiac injury, these patients were older and had more comorbidities (e.g. hypertension in 49 of 82 [59.8%] vs 78 of 334 [23.4%]; P < .001).
Wu C et al. [11]	Arterial hypertension, especially poorly controlled hypertension, may play an important role in the severity of COVID-19.
Guo T et al. [12]	This retrospective single-centre case series analysed patients with COVID-19 in Wuhan, China, from 23 January 2020 to 23 February 2020. Myocardial injury is significantly associated with a fatal outcome of COVID-19, while the prognosis for patients with underlying CVD, but without myocardial injury is relatively favourable. 66 patients (35.3%) had underlying CVD, including hypertension, coronary heart disease and cardiomyopathy.
Dessie GZ et Zewotir T. [13]	Chronic comorbidities, complications and demographic variables, including acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, increased D-dimer, male gender, older age, current smoker and obesity are clinical risk factors for a fatal outcome associated with coronavirus.
Mubarik S et al. [14]	Prevalence of hypertension in 1,833 studied COVID-19 patients was 40.5%. Hypertension was associated with the severity and mortality of COVID-19 infection.
Du Y et al. [15]	Evidence from this meta-analysis suggested that hypertension was independently associated with a significantly increased risk of critical COVID-19 and in-hospital mortality of COVID-19.
Guan WJ et al. [16]	Advanced age was associated with a higher prevalence of other comorbidities such as diabetes, renal impairment, arterial hypertension and obesity, which altogether increased the proportion of hypertensive patients.

Angiotensin-converting enzyme 2 (ACE2) is a protein which has a crucial role in the entry of the COVID-19 virus into the cells. It is the key matter of debate on the benefits or dangers of RAS blockade in COVID-19 infection. Verdechia et al. labelled COVID-19 an ACE2-centric infectious disease (20). Recently, the results of a study that used human cardiomyocytes as a model for researching the entry of SARS-CoV-2 into the cells have been published. After the viral infection, there is an increase in the synthesis of ACE2, type 1 receptors for angiotensin II, but no change in the synthesis of the angiotensin-converting enzyme (ACE) (21). The same group of researchers have observed that the synthesis of ACE2 in ACE2-knockout (ACE2-KO) cardiomyocytes was almost immeasurable, and, after the infection, these cells also had a negligible quantity of SARS-CoV-2. Furthermore,

the authors treated human cardiomyocytes and human endothelial cells either only with the virus or with the virus combined with lisinopril or losartan. The amount of the virus was not increased in endothelial cells or in cardiomyocytes after the use of ACE-inhibitors or sartans and the expression of proteins (ACE2) did not significantly change after the use of these medications. This research provides an additional confirmation that ACE-inhibitors or sartans do not promote SARS-CoV-2 infection.

The hypothesis that advocated a negative role of RAS blockade in SARS-CoV-2 infection was based on the fact that RAS blockers, by inducing an enhanced ACE2 expression, facilitate the entry of the virus into the cell (22). Supporters of the opposing hypothesis, however, believe that the enhanced ACE2 expression, along with RAS blockade, facilitates increased synthesis of angiotensin 1-7, promoting its beneficial anti-inflammatory and antifibrotic effects and preventing lung injury (Figure 1) (23).

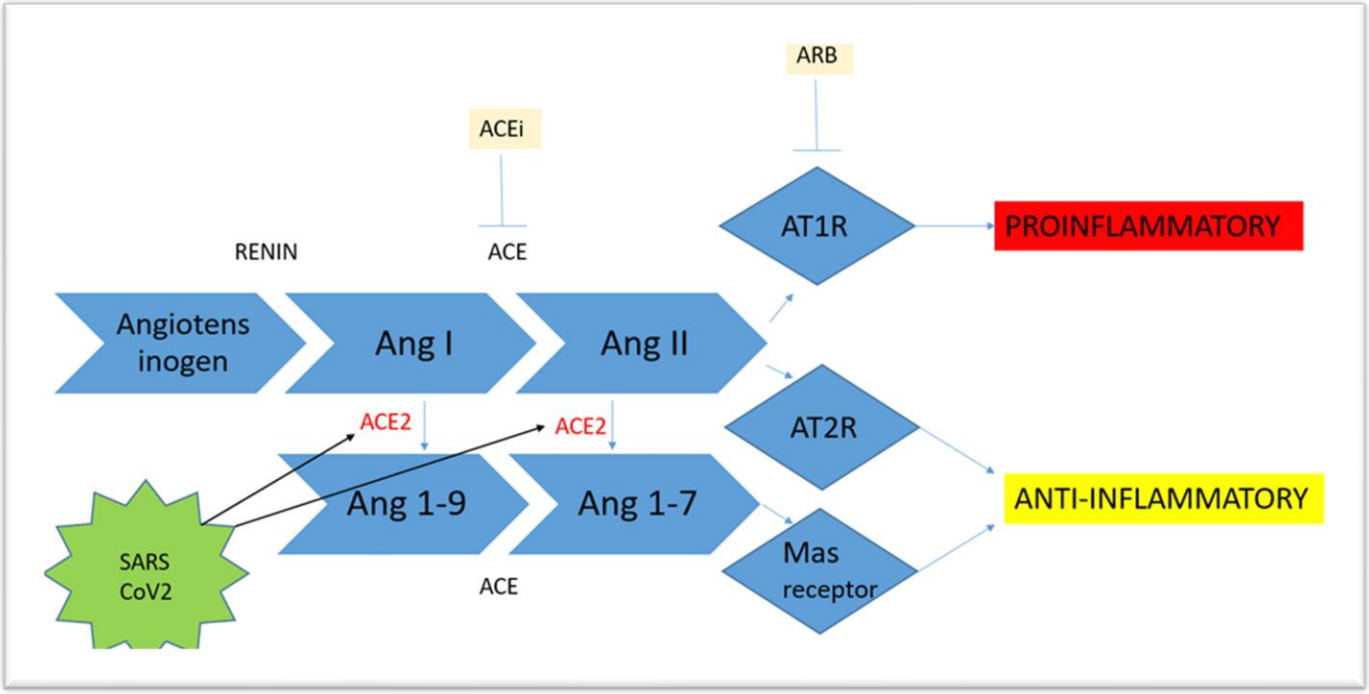

Figure 1. Association between SARS-CoV-2 and renin angiotensin system

ACE – angiotensin-converting enzyme, ACEi – angiotensin-converting enzyme inhibitor, Ang – angiotensin, ARB – angiotensin type II receptor blocker, AT1R – angiotensin II type 1 receptor, AT2R – angiotensin II type 2 receptor

It has already been mentioned that RAS blockers have a positive effect on the clinical course of pulmonary diseases without COVID-19 infection (5,24). The significance of the beneficial impact of ACE2 and angiotensin 1-7 on COVID-19 infection is evident from the fact that, among other drugs which are synthesised for the treatment of COVID-19 infection, scientists have been intensively working on recombinant ACE2 and angiotensin 1-7 (20).

The results of basic research are bringing us back to the epidemiological clinical research by Mancia et al., which proved in a group of patients with confirmed COVID-19 infection that neither ACE-inhibitors nor sartans were associated with a higher probability of COVID-19 infection (8). This was also confirmed in a meta-analysis by Kurdi et al., which involved 72,372 patients from 27 studies (25). Analysing a group of 1,002 patients with severe COVID-19 infection, Reynolds et al. concluded that RAS blockade is not associated with severe forms of COVID-19 infection (26). Those data were confirmed in the previously mentioned meta-analysis by Kurdi et al., where no association was observed between RAS blockade and severe forms of pneumonia (25). The HOPE COVID-19 registry, Zhang et al. and research by Gao et al. indicated a lower mortality rate in patients treated with RAS

blockers in comparison to those who did not receive these medications (18,27,17). Finally, the meta-analysis by Kurdi et al. also showed that the use of RAS blockers was associated with a lower mortality rate and a lower risk of admission to intensive care units (25).

Another meta-analysis was published in 2021 and it included 101,949 patients from 52 studies, 26% of whom were treated with RAS blockade (28). In this meta-analysis, the authors did not find an association between the use of RAS blockers and higher mortality. On the contrary, they found that RAS blockade has a positive effect, i.e. there were less deaths and severe complications after adjusting for all risk factors.

In an extensive observational research, Semenzato et al. noticed that patients treated with ACE-inhibitors or sartans for a very long time had a lower risk of COVID-19 infection than those treated with calcium channel blockers (29). This finding corresponds to the previously published results, according to which the use of ACE-inhibitors or sartans increases survival, i.e. reduces mortality rates in hypertensive patients with COVID-19 infection (30). The authors have not found any differences between ACE-inhibitors and sartans. However, a group of authors has recently raised an intriguing question whether sartans are the drug of choice for the treatment of arterial hypertension, and moreover, during COVID-19 infection (31).

There is obviously no hard evidence for this approach and further research is needed to either confirm or reject this premise. Nevertheless, it is a good example of how the paradigm has switched from the fear of possible danger of applying RAS blockers in patients with COVID-19 infection to completely the opposite – exploring the details of their benefits. However, as mentioned, apart from sartans that obviously precede ACE inhibitors, recombinant ACE2 and angiotensin 1-7 are potential treatment options that are currently being explored (20,32).

The real consequences of COVID-19 infection for patients with arterial hypertension

Inadequate access to medical care, either due to the fear of infection or the medical personnel's preoccupation with an enormous number of COVID-19 cases, will lead to numerous negative impacts. The real consequence of COVID-19 infection is a decline in the control of treated hypertensive patients, decline in adherence to medications, irregular blood pressure measurements and an increase in morbidity and mortality from cardiovascular, cerebrovascular and renal causes. Instead of an isolated pandemic, a syndemic, clustering COVID-19 and the excess burden of cardiovascular, cerebrovascular and kidney disease/deaths will become our harsh reality.

Conclusion

In our opinion, the answer to the first question – does arterial hypertension increase the risk of COVID-19 infection? – is most probably not, although there has been insufficient evidence so far. The answer to the second question – does arterial hypertension increase the risk of severe infections? – might be that it does, but only if arterial hypertension is not controlled well and treated properly. If it is controlled poorly, then there is a higher possibility of a fatal or more severe cytokine storm due to the chronic latent stimulation of the immune system among patients with arterial hypertension. The answer to the third question – is the risk of severe COVID-19 infection associated with the use of drugs that block RAS? – is that there is no evidence to suggest so.

Finally, are RAS blockers beneficial or harmful? According to the recent studies, which indicate that patients treated with RAS blockers might have a better prognosis, RAS blockers might be beneficial. Therefore, patients with stable arterial hypertension must continue taking RAS blockers. However, in severe COVID-19 infections accompanied by hypotension, patients must stop using RAS blockers as well as any other antihypertensive drugs.

Numerous questions related to these issues are still left unanswered. As a stimulus for further considerations, we decided to select these two questions: should we introduce RAS blockers for

lung protection in case of COVID-19 and are there really any differences between ACE-inhibitors and sartans?

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