

## Review Article

# The Effects of Different Classes of Antihypertensive Drugs on Patients with COVID-19 and Hypertension: A Mini-Review

Farnoosh Nozari  and Nasrin Hamidizadeh 

*Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

Correspondence should be addressed to Nasrin Hamidizadeh; [n.hamidizadeh.mdrc@gmail.com](mailto:n.hamidizadeh.mdrc@gmail.com)

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Hypertension is a major risk factor for cardiovascular disease. Previous studies showed that patients with hypertension are at an increased risk of developing severe COVID-19 infection. Therefore, proper blood pressure control in hypertensive patients with COVID-19 is of great importance. In this review, we discussed the effects of different classes of antihypertensive drugs on patients with hypertension and COVID-19.

## 1. Background

Hypertension is a chronic and age-related condition which leads to cardiovascular and renal complications [1]. An increase in the proportion of adults with hypertension was observed from 26.4% in 2000 to 31.1% in 2010 [2].

Effective control of blood pressure reduces the risk of stroke, heart attack, and heart failure [3]. Antihypertensive drugs comprise different classes of chemical compounds used to prevent and treat high blood pressure [4]. The most commonly prescribed antihypertensive drug classes include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, calcium channel blockers (CCBs), and beta-blockers [5].

Novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome (SARS-CoV-2), is an emerging respiratory infectious disease, which first occurred in Wuhan, the capital of Chinese province Hubei, in December 2019 [6]. COVID-19 has a wide spectrum of clinical manifestations, ranging from asymptomatic illness to severe pulmonary infections [7].

Patients with hypertension are at increased risk of developing severe COVID-19 infection [8]. Previous studies reported that up to 30% of people with COVID-19 had chronic arterial hypertension, suggesting that hypertension could play an important role in the aggravation of COVID-

19 symptoms [9]. Furthermore, hypertensive patients affected by COVID-19 had a higher mortality risk than patients without hypertension [10].

Since hypertension is one of the main risk factors for developing COVID-19, choosing the proper agent for effective control of blood pressure is crucial.

This review focuses on the effects of various available antihypertensive drugs on managing COVID-19 patients with hypertension.

*1.1. Alpha-Blockers.* Alpha-blockers are a class of drugs that reduce vascular smooth muscle contractions and cause vasodilation [5]. However, they are not used as first-line agents in treating high blood pressure [11]. Several side effects, such as orthostatic hypotension, tachycardia, increased risk of syncope, falls, and fracture, are associated with using alpha-blockers [12].

In acute respiratory distress syndrome (ARDS), various stages including hyaline membrane formation in the alveoli, interstitial widening, edema, and fibroblast proliferation were observed [13]. Analyses in the patients with ARDS and pneumonia showed that using alpha-1 adrenergic receptors was associated with a relative risk reduction of 34% for mechanical ventilation and death [14]. Since ARDS caused by COVID-19 results in the typical ARDS pathological

changes in the lungs, using alpha-blockers might be beneficial in this setting [13].

**1.2. Beta-Blockers.** Beta-blockers reduce blood pressure by inhibiting catecholamines from binding to beta-adrenergic receptors, causing vasodilation of coronary and peripheral arteries [15]. The most common side effects of beta-blockers are bradycardia, constipation, sexual dysfunction, fatigue, and bronchospasm [15]. Besides, they have shortening effects on QT interval [16].

A study conducted by Vasanthakumar suggested that using beta-blockers could offer several benefits to treat COVID-19, such as the reduction of the SARS-CoV-2 cell entry via downregulation of the angiotensin-converting enzyme 2 (ACE-2), reducing the expression of proinflammatory cytokines, and the reduction of complications, such as pulmonary embolism, ARDS, and septic shock [17].

Bauer et al. showed that beta-blockers were not associated with the severity of COVID-19 [18]. Another study suggested that treatment with beta-blockers significantly reduced the risk of serious outcomes [19]. Reynolds et al. also found a lower chance of testing positive for COVID-19 in the patients taking beta-blockers [20].

**1.3. Calcium Channel Blockers (CCBs).** CCBs are used as a first-line treatment option alone or in combination with other antihypertensive drugs in the patients with hypertension [21]. CCBs block the movement of calcium into the cells by binding to L-type voltage-gated calcium channels in various organs such as the heart and vascular smooth muscle [22]. A decrease in the intracellular concentration of calcium induces smooth muscle cell relaxation and subsequent blood pressure reduction [23]. Major adverse reactions caused using this group are headaches, flushing, palpitations, peripheral edema, hypotension, atrioventricular block, constipation, and nausea [24].

Zhang et al. reported that CCBs could inhibit SARS-CoV-2 replication after entry in vitro. Furthermore, amlodipine besylate reduced the mortality rate in hypertensive patients [25]. Another study suggested that nifedipine and amlodipine significantly reduced the death rate and the risk of intubation and mechanical ventilation in elderly patients with COVID-19 [26]. Regarding the mortality rate and the length of hospital and intensive care unit (ICU) stay, Nouri-Vaskeh et al. found no significant differences in the administration of losartan or amlodipine in COVID-19 patients with primary hypertension [27].

**1.4. ACE Inhibitors and ARBs.** Renin-angiotensin-aldosterone system (RAAS) inhibitors, including ACE inhibitors and ARBs, are among the most commonly prescribed drugs to treat high blood pressure [28]. ACE inhibitors play a role to lower blood pressure by blocking the angiotensin-converting enzyme, which leads to a decrease in angiotensin II production and vasodilation. The action mechanism of ARBs is blocking the binding of angiotensin II to the angiotensin-1 (AT1) receptors [5]. The most important adverse effects of this

group are hyperkalemia, renal dysfunction, cough, and first-dose hypotension [29]. However, it is debatable whether it is safe to use ACE inhibitors and ARBs in hypertensive patients with COVID-19 [30]. On the one hand, ACE inhibitors and ARBs might upregulate ACE-2 expression, a cellular receptor for SARS-CoV-2. On the other hand, these drugs were shown to play a protective role in acute lung injury [31].

In this section, we reviewed studies that discussed the effects of ACE inhibitors and ARBs on the patients with hypertension in the context of the COVID-19 pandemic (Tables 1 and 2).

**1.4.1. Studies with Beneficial Effects.** Data showing the beneficial effects of ACE inhibitors and ARBs in the treatment of hypertension during the COVID-19 pandemic are rising.

Several studies indicated that angiotensin II plays a crucial role in organ damage and production of various proinflammatory cytokines such as interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  [28]. Furthermore, there is a positive association between elevated angiotensin II levels and lung injury in COVID-19 patients [32]. Therefore, the blockage of RAAS might be beneficial to prevent end-organ damage and inflammatory storm in COVID-19.

SARS-CoV-2 binds to endothelial and alveolar type 2 epithelial cells that express ACE-2 to a high degree, penetrates the cells via the activation of proteases such as transmembrane protease serine subtype 2 (TMPRSS2), infects these cells, and downregulates the expression of ACE-2 and thereby the ACE-2/Ang (1-7)/Mas-receptors (MasR) signaling pathway [33].

ACE-2 is an enzyme which breaks down angiotensin II into angiotensin 1-7 (Ang 1-7) [34]. Ang (1-7) exerts various effects, such as reducing the formation of myofibroblasts, collagen synthesis, and pulmonary fibrosis via MasR signaling pathways that have shown vasodilatory, anti-inflammatory, antiproliferative, and antifibrotic properties. This pathway also reduces the harmful effects of ACE-1-Ang II-AT1 receptor axis and at the same time enhances the ACE-2 activity. As a result, ACE-2 captures the S-proteins of SARS-CoV-2 in the plasma and thus prevents the virus from binding to lung cells [33, 35].

Although ACE-2 expression decreases after infection by SARS-CoV-2, numerous studies suggested that ACE inhibitors and ARBs increase the expression of ACE-2 and the plasma levels of Ang (1-7) [35]. It is noteworthy that no clinical data on the effects of ARBs and ACE inhibitors on ACE-2 expression in the lungs are available in either animal or human models [36].

As mentioned earlier, the dysregulation of RAAS due to the increased angiotensin II and decreased ACE-2 can lead to a severe inflammatory response. ACE inhibitors and ARBs may have a beneficial role in preventing these harmful effects by reducing angiotensin II and upregulating ACE-2 [28].

Several studies reported that COVID-19 patients with hypertension using ACE inhibitors/ARBs had a lower mortality rate, the risk of ICU admission, maximal viral load,

TABLE 1: Studies that showed neutral effects of ACEIs/ARBs on COVID-19 in hypertensive patients.

| Study                | Country | Drug group   | Number of cases | Findings   |
|----------------------|---------|--|-----------------|--|
| Gao et al. [57]      | China   | RAAS inhibitors group  | 183             | No harm  |
|                      |         | Non-RAAS inhibitors group  | 527             |  |
| Ran et al. [58]      | China   | ARBs group   | 100             | No increase in the risk of adverse events                        |
|                      |         | Other antihypertensive drugs   | 813             |  |
| Mustafic et al. [59] | France  | Hypertensive patients with ACEIs or ARBs use                             | 946             | No difference in outcome   |
|                      |         | Hypertensive patients without ACEI/ARB use                               | 2035            |  |
| Haroon et al. [60]   | UK      | RAAS inhibitor group   | 29518           | No association with all-cause mortality                          |
|                      |         | CCBs group   | 18895           |  |
| Li et al. [63]       | China   | Total patients with hypertension   | 362             | No association with the severity or mortality                    |
|                      |         | ACEI/ARBs group  | 115             |  |
| Liu et al. [64]      | China   | ACEIs/ARBs group   | 74              | No influence on increasing the severe form of COVID-19 infection |
|                      |         | CCBs group   | 83              |  |
| Hu et al. [61]       | China   | ACEIs/ARBs group   | 65              | No influence on the severity and clinical outcome                |
|                      |         | Non-ACEIs/ARBs group   | 84              |  |
| Wang et al. [65]     | China   | Hypertensive patients taking ACEIs/ARBs                                  | 315             | No increased risk of developing severe COVID-19                  |
|                      |         | Nonhypertensive patients   | 308             |  |
| Kim et al. [62]      | Korea   | ACEIs/ARBs group   | 331             | No association with COVID-19 severity                            |
|                      |         | Non-ACEIs/ARBs group   | 1580            |  |
| Sardu et al. [66]    | Italy   | ACEIs/ARBs group   | 45              | No influence on the prognosis                                    |
|                      |         | CCBs group   | 17              |  |
| Khera et al. [67]    | USA     | Hypertensive patients with the use of at least one antihypertensive drug | 2263            | No association with the risk of hospitalization or mortality     |
| An et al. [68]       | USA     | ACEIs/ARBs group   | 8351            | No increased likelihood of COVID-19 infection                    |
|                      |         | Other groups   | 8547            |  |

TABLE 2: Studies that showed beneficial effects of ACEIs/ARBs on COVID-19 in hypertensive patients.

| Study                        | Country    | Drug groups   | Number of cases | Findings  |
|------------------------------|------------|---|-----------------|---|
| Guo et al. [31]              | China      | Hypertensive patients in ACEIs/ARBs and non-ACEIs/ARBs treatment groups | 3936            | Lower mortality rate  |
| Megaly et al. [42]           | USA        | ACEIs/ARBs group  | 534             | Lower mortality rate  |
|                              |            | Non-ACEIs/ARBs group  | 2733            |   |
| Salah et al. [46]            | USA, Italy | Total patients with hypertension  | 16101           | Lower mortality rate  |
|                              |            | Patients taking ACEIs or ARBs   | 7816            |   |
| Wang et al. [47]             | China      | ACEIs/ARBs group  | 8104            | Lower risk of mortality and ventilatory support                   |
|                              |            | Non-ACEIs/ARBs group  | 8203            |   |
| Zhang et al. [50]            | China      | ACEIs/ARBs group  | 188             | Lower mortality rate  |
|                              |            | Non-ACEIs/ARBs group  | 940             |   |
| Negreira-Caamaño et al. [45] | Spain      | Previous treatment with ACEIs/ARBs                                      | 392             | Lower mortality rate  |
|                              |            | No previous treatment with ACEIs/ARBs                                   | 153             |   |
| Desai et al. [39]            | Italy      | Total patients  | 575             | Reduced mortality rate in chronic ACEIs users                     |
|                              |            | ACEIs or ARBs users   | 154             |   |
| Bae et al. [37]              | Korea      | RAAS inhibitors users   | 1076            | Lower risk of ICU admission                                       |
|                              |            | Never-users of RAAS inhibitors  | 298             |   |
| Yang et al. [49]             | China      | ACEIs/ARBs group  | 43              | Lower concentrations of hs-CRP and procalcitonin                  |
|                              |            | Non-ACEIs/ARBs group  | 83              |   |
|                              |            | Controls  | 125             |   |
| Meng et al. [43]             | China      | ACEIs/ARBs group  | 17              | Decreased IL-6 levels and peak viral load                         |
|                              |            | Non-ACEIs/ARBs group  | 25              |   |
| Barochiner et al. [38]       | Argentina  | Hypertensive patients taking ACEIs or ARBs                              | 8328            | Lower risk of death, admission to ICU, and mechanical ventilation |
|                              |            | Under other or no treatment   | 8983            |   |
| Lam et al. [41]              | USA        | Hypertensive patients   | 614             | Lower ICU admission rate and mortality rate                       |
| Meng et al. [44]             | China      | Hypertensive patients in ACEIs/ARBs group                               | 73              | Improved clinical outcome such as lower death rate                |
|                              |            | Non-ACEIs/ARBs group  | 186             |   |

TABLE 2: Continued.

| Study                 | Country | Drug groups                                   | Number of cases | Findings  |
|-----------------------|---------|---|-----------------|---|
| Kim et al. [40]       | Korea   | ACEIs/ARBs users                              | 682             | Lower clinical outcomes                                 |
|                       |         | Non-users of ACEIs/ARBs                       | 603             |   |
| Yuan et al. [54]      | China   | ACEIs/ARBs group                              | 196             | Protective effects                                      |
|                       |         | Uncontrolled group                            | 233             |   |
| Golpe et al. [51]     | Spain   | Hypertensive patients with hospital admission | 69              | Lower risk of hospitalization                           |
|                       |         | Outpatient management                         | 88              |   |
| Semenzato et al. [52] | France  | ACEIs/ARBs group                              | 1524250         | Lower risk of hospitalization and intubation            |
|                       |         | CCBs group                                    | 358306          |   |
| Tian et al. [55]      | China   | Discontinued ACEIs/ARBs group                 | 27              | Discontinued ACEIs/ARBs group had longer hospital stays |
|                       |         | Other antihypertensive drugs group            | 26              |   |
| Chen et al. [53]      | China   | RAAS inhibitors group                         | 355             | Protective effects on mortality                         |
|                       |         | Non-RAAS inhibitors group                     | 827             |   |

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin 6; ICU: intensive care unit; RAAS: renin-angiotensin-aldosterone system; CCBs: calcium channel blockers.

the need for mechanical ventilation, and also decreased concentrations of high sensitivity C-reactive protein (hs-CRP), procalcitonin, and IL-6. Furthermore, they showed improved clinical outcomes in this population [31, 37–50].

Two other studies concluded that using ACE inhibitors/ARBs was associated with a significantly lower risk of hospitalization in hypertensive patients infected by SARS-CoV-2 [51, 52]. Furthermore, prehospitalization and in-hospital use of ACE inhibitors and ARBs also had a protective role in treating this population [53, 54]. In Tian et al.'s study, the discontinuation of ACE inhibitors and ARBs resulted in longer hospital stays [55]. In general, ACE inhibitors and ARBs should not be discontinued in hypertensive patients during the COVID-19 pandemic [47, 56].

**1.4.2. Studies with No Adverse Effects.** Regarding the use of RAAS inhibitors in COVID-19 patients, some studies have not reported any adverse events in hypertensive patients with COVID-19 [57–59].

It was shown that there is no association between using ACE inhibitors/ARBs and the severity, mortality, clinical outcome, or poor prognosis of COVID-19 in the patients with hypertension [60–65].

Sardu et al. found no significant differences in the study endpoints including ICU admission, mechanical ventilation, cardiac injury, and deaths between patients in ACE inhibitors, ARBs, and CCBs groups [66]. Khera et al. reported that the use of ACE inhibitors and ARBs did not increase the risk of hospitalization or mortality in individuals with hypertension [67]. Furthermore, a large cohort study also found no association between using ACE inhibitors and ARBs and an increased likelihood of COVID-19 infection [68].

**1.5. Spironolactone.** Spironolactone is a pharmacological antagonist of aldosterone acting as a diuretic and an antihypertensive agent [69]. The most common side effects related to using spironolactone are lethargy, headache, ataxia, dyspepsia, nausea, vomiting, and anorexia [70].

Spironolactone is considered a safe option in COVID-19. Due to the increase in circulating ACE-2 and prevention of SARS-CoV-2 cell entry, spironolactone has a potential protective role in COVID-19 infection [71]. However, this drug has no effects on ACE-2 levels in the lungs [72]. Spironolactone can downregulate androgen-mediated TMPRSS2, which plays an important role in virus activation [71, 73, 74]. Besides, it can prevent pulmonary complications of COVID-19 through its anti-inflammatory and antiviral effects [71]. Spironolactone is effective in reducing SARS-CoV-2 infectivity, inhibit cytokine storm, and alleviate organ injury. Therefore, it can protect at all stages of COVID-19 infection [75].

**1.6. Diuretics.** Diuretics are among the most commonly prescribed agents used for the management of hypertension [4]. An association between using diuretics and several side effects including hyponatremia, hypokalemia, hypomagnesemia, acid-base changes, and hyperuricemia has been reported [76].

In contrast to other antihypertensive drugs, it was suggested that diuretics could have deleterious effects on cardiopulmonary interactions in COVID-19 patients receiving mechanical ventilation [77]. Furthermore, an association between using diuretics and a higher risk of cardiac injuries in COVID-19 has been observed [54].

**1.7. Vasodilators and Central-Acting Agents.** To date, no study was performed on the effects of vasodilators and central-acting agents on patients with hypertension and COVID-19.

**1.8. Direct Renin Inhibitors.** Direct renin inhibitors are a class of drugs used to block the effects of renin-angiotensin system [78]. Several adverse events, such as diarrhea, dizziness, fatigue, dry cough, and headache, were reported using aliskiren [79].

Oliveira et al. suggested that aliskiren could play an important role in preventing angiotensin I and II formation by direct blockade of renin and might have beneficial effects in the COVID-19 setting. However, they are associated with decreased ACE-2 expression with less infection gravity [80]. Furthermore, aliskiren was shown to be effective and safe for treating severe COVID-19 patients with hypertension [81].

## 2. Discussion

Patients with hypertension are at increased risk of severe COVID-19 infection and mortality [82]. The high prevalence of COVID-19 in the patients with preexisting hypertension raises major concerns about using antihypertensive drugs in such a population [83].

Yuan et al. reported that COVID-19 patients with hypertension taking RAAS inhibitors had a lower risk of death, ICU admissions, and septic shock, and patients who used beta-blockers, CCBs, and diuretics did not show any significant difference compared with the patients with uncontrolled blood pressure [54]. Besides, the patients in the ACE inhibitors and ARBs group had lower IL-6 levels and peak viral load than patients treated with beta-blockers, CCBs, and diuretics [43]. In a detailed meta-analysis, Ren et al. also confirmed that the mortality and severity of COVID-19 were significantly lower in the patients taking ACE inhibitors/ARBs than in controls. No association was found between using other antihypertensive drugs including CCBs, beta-blockers, and diuretics and the incidence and severity of COVID-19 [83]. However, Yan et al. suggested that antihypertensive drugs including ARBs, ACE inhibitors, CCBs, and beta-blockers, except for thiazide diuretics, might be beneficial for COVID-19 patients with hypertension [84].

In addition, previous studies have reported that the prevalence of COVID-19 infection differs between men and women [85]. A systematic review conducted by Abate et al. showed that the prevalence of COVID-19 in males and females was 55 and 45, respectively [86]. In several other studies, the rate of this infection was found to be higher in men than in women [87, 88]. Similarly, the male gender comprised the majority of hospitalized patients affected by COVID-19 [89, 90]. Moreover, among the hypertensive population with COVID-19, most patients have been reported to be males [89, 90].

Studies have suggested that the sex disparity of COVID-19-related morbidity and mortality is attributed to the differences in chromosomes and sex steroids, more engagement of men in activities such as smoking and alcohol consumption, and higher rates of comorbidities including hypertension and chronic obstructive pulmonary disease (COPD) in males [91]. According to these explanations, the gender might also affect the rate of response to hypertension treatment.

In contrast to the other studies, we investigated the effects of antihypertensive drugs on COVID-19 solely in the population of patients with hypertension. Recent data suggest that RAAS inhibitors have beneficial effects such as lower mortality and severity of COVID-19 infection in hypertensive patients [83]. Therefore, when compared to

other antihypertensive drugs, ACE inhibitors and ARBs may be better choices to treat hypertension in this population. Conversely, diuretics can be considered the least effective drug in the setting of concomitant hypertension and COVID-19.

## 3. Conclusions

Based on the available literature, it is recommended to continue using antihypertensive agents in the patients with coexisting COVID-19 and hypertension. Furthermore, RAAS inhibitors may have superior beneficial effects to treat hypertension among this population. Further clinical studies on both genders are needed to validate the findings of this review.

## Data Availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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