

## Original Article

# Effect of ACE Inhibitors, ARBs, and Other Antihypertensive Drugs on Hypertensive Patients with COVID-19 Infection

Syedpouzhia Shojaei<sup>1</sup>, Sara Nooraen<sup>2</sup>, Zahra Soroureddin<sup>3</sup>, Meghdad Sedaghat<sup>4</sup>, Padideh Ansar<sup>5</sup>, Sadaf Rassouli<sup>6</sup>, Mehdi Goudarzi<sup>7</sup>, Mehrdad Haghighi<sup>8\*</sup>

<sup>1</sup>Anesthesia and Critical Care Department, Critical Care Quality Improvement Research Center, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>School of Medicine, Iran University of Medical Science, Tehran, Iran

<sup>3</sup>Cardiovascular division, Imam Hossein hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

<sup>4</sup>Department of Internal Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

<sup>5</sup>Anesthesia and Critical Care Department, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>6</sup>Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>7</sup>Infection Disease and Tropical Medicine Research Center, Shahid Beheshti University of Medical Science, Tehran, Iran

<sup>8</sup>Department of Infectious Diseases, Imam Hossein Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

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## Abstract

**Background:** To investigate differences in disease severity and outcomes among COVID-19 patients with a history of hypertension using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and other antihypertensive drugs.

**Materials and Methods:** Based on drug exposure, 153 hypertensive patients with COVID-19 were divided into three groups: angiotensin-converting enzyme inhibitor group, angiotensin receptor blocker group, and other antihypertensive drugs group. The outcomes, laboratory and clinical results, were compared.

**Results:** The frequency of ICU admission among patients in the angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, and other antihypertensive drug groups was 25.5%, 27.8%, and 23.2%, respectively. The intubation frequency was 23.6%, 27.8%, and 30.4%, respectively. The longest hospital stay was observed in the angiotensin-converting enzyme inhibitor group, but the difference was not significant ( $P > 0.05$ ). The mortality rates were highest in the other antihypertensive drug groups.

**Conclusion:** Patients with COVID-19 who consume angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have lower mortality rates compared to patients consuming other antihypertensive drugs.

**Keywords:** COVID-19, SARS-CoV-2, Angiotensin-converting enzyme 2, Angiotensin receptor blockers, Angiotensin-converting enzyme inhibitors, Antihypertensive drugs, Outcomes

\*Corresponding Author: Mehrdad Haghighi, Department of Infectious diseases, Imam Hossein hospital, Shahid Beheshti University of medical science, Tehran, Iran. Email: mehrdad\_pana@yahoo.com

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## Introduction

Three types of coronaviruses, including COVID-19,

severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome, have emerged over the past two decades<sup>1-4</sup>. Angiotensin-converting enzyme (ACE) 2 is supposed to be responsible for the conversion of

angiotensin(ANG) II to angiotensin<sup>5-8</sup>. Accordingly, ACE2 is reported to play a key role in coronavirus disease<sup>9,10</sup>.

Increased blood pressure and vasoconstriction result from ANG II binding to the ANG II type 1 receptor (AT1R). Furthermore, to increase sodium retention, ANG II stimulates aldosterone secretion from the adrenal cortex. Through ACE1, discovered in 1956, ANG II can be produced from ANG I<sup>1</sup>. In a prothrombotic action, ANG I can be cleaved to ANG (1-9) by ACE2.

Blood pressure homeostatic regulation, stability of body fluids and electrolytes, and vascular resistance are the main activities of the renin-angiotensin system (RAS), which also plays a crucial role in various medical conditions. RAS complexity results from its systemic features and tissue-specificity, which mediate various biological mechanisms and molecules, such as the alternative ANG II receptor, ANG III, ANG IV, the angiotensin type 2 receptor (AT2R), and the Mas-related G-protein-coupled receptor<sup>12</sup>. The two principal pathways, including ACE-ANG II-AT1R and ACE2-ANG (1-7), are considered to represent the RAS signaling<sup>13</sup>. To promote the ACE2-ANG (1-7) axis and mitigate the ACE-ANG II-AT1R axis, various therapeutic agents, such as angiotensin-converting enzyme inhibitors (ACEi), AT1R blockers, mineralocorticoid receptor blockers, pioglitazone, and ibuprofen, have been used<sup>14,15</sup>.

Given the perception of ACE2 as a receptor on the surface of SARS-CoV membranes, there has been controversy over the effectiveness of these drugs against viral infection. Pharmacological treatment strategies are also challenging since multiple disorders, such as high blood pressure and diabetes, 16 accompany COVID-19. The potent adverse effects of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs or Sartans) involved in the RAS pathway on COVID-19 have generated many hypotheses, especially on social media.

For patients with severe heart or renal failure, RAS inhibitors are prescribed, and self-discontinuation of such drugs can have irreversible consequences for these patients, leading to more susceptibility to COVID-19<sup>17,18</sup>. However, unlike other

antihypertensive drugs, the benefits of ACEi/ARBs are presumably more conspicuous. Accumulating studies have proposed that postoperative temporary discontinuation of antihypertensive medications, such as ARBs within 2 days or ACEi within 14 days, is associated with a high mortality rate within 30 days, even though there is no published data on the nonpermanent discontinuation of RAS inhibitors and mortality rates in COVID-19 patients<sup>19,20</sup>.

Due to contradictory information and a lack of human studies on the possible effects of ACEi and EBR drugs on the prognosis of patients with COVID-19, this study aims to investigate the effects of these drugs on the course and prognosis of hospitalized patients.

## Methods

**Patients and study design:** This is a cross-sectional study of patients with COVID-19 infection admitted to Emam Hossein Hospital of Shahid Beheshti University of Medical Science, Tehran, Iran. They were accepted from February 20, 2020, to May 21, 2020.

**Inclusion criteria:** Based on the protocol released by the World Health Organization, only confirmed cases of COVID-19 diagnosed by positive nasopharyngeal swab specimens and tested by at least two real-time reverse transcriptase polymerase chain reaction assays, or by a positive bronchial computed tomography scan, were included in this study<sup>21</sup>.

According to drug exposure, patients who consumed ACEi, ARBs, or other antihypertensive agents within 7 days or more before the onset of infection were divided into three groups: the ACEi group, the ARBs group, and the other antihypertensive agents group ( $\beta$ -blockers, thiazides, calcium channel blockers).

**Ethical approval:** The research was ethically confirmed by the Ethics Committee of the Shahid Beheshti University of Medical Sciences in Tehran, Iran (IR.SBMU.MSP.REC.1401.636). Informed consent was waived due to the retrospective nature of this study.

**Data collection:** Demographic data, including age, sex, and clinical manifestations of COVID-19 infection (fever, myalgia, loss of consciousness, dyspnea, chest pain, dry or productive cough, diarrhea), as well as core body temperature, oxygen saturation, pulse rate, and respiratory rate at the time of admission, were analyzed.

In addition, initial and final, laboratory results [polymerase chain reaction, white blood cells (WBCs), neutrophils, lymphocyte, platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), total Bilirubin, urea, sodium (Na), potassium (K), troponin, vein blood gases including pH, PCO<sub>2</sub>, HCO<sub>3</sub>, bronchial radiology reports, medications for COVID-19 were all recorded from the electronic health system. All data were documented and reserved in private. The length of hospital admission, intensive care unit (ICU) admission, intubation, side effects of drugs, death, or discharge were recorded as outcomes.

**Statistical analysis:** Continuous and categorical data were represented as median (interquartile range [IQR]) and percentage (%), respectively. U-test and one-way ANOVA were used for continuous data, while the chi-square test was used for categorical data. A *p*-value < 0.05 was considered a statistically significant difference. SPSS version 25 (IBM) was used.

## Results

**Demographic characteristics:** A total of 153 subjects were selected, including 78 males (50.1%) and 75 (49.9%) females. The average age of COVID-19 patients was 70.88 years, with a minimum age of 40 and a maximum age of 94. Most patients had diabetes (86, 56.2%) (Table 1).

Most patients had a history of ARBs (106, 69.3%), followed by beta blockers (58, 37.9%), CCBs (32, 20.9%), ACEi (18, 11.8%), spironolactone (8, 5.2%), and hydrochlorothiazide (3, 2%).

Dyspnea (98, 64.1%) and fever (85, 55.6%) were the most frequent symptoms. Moreover, 108 (70.6%) patients had a positive bronchial CT scan for COVID-19, and 79 (51.6%) had a positive SARS-CoV-2 PCR. Most patients were treated with hydroxychloroquine (Table 1).

### Comparison of laboratory results of the three groups

**Outcomes of the three groups:** The mean length of hospital stay in the ARBs group was (7.2±2.1) days (2-20 days), (7.3±2.9) days (4-12 days) in the ACEi group, and (7.3±3.9) days (2-20 days) in the other

antihypertensive drugs group. The mean length of ICU admission in ARBs was (4.7±2.9) days (1-11 days) in the ARBs group, (3.0±1.4) days (2-4 days) in the ACEi group, and (4.3±2.1) days (2-6 days) in the other antihypertensive drugs group. The differences in admission length ( $F=0.08$ ,  $P>0.05$ ), ICU admission length ( $F=0.1$ ,  $P>0.05$ ), and intubation parameters among the three groups were not significant ( $F=0.1$ ,  $P>0.05$ ).

The frequency of ICU admission among ARBs, ACEi, and other antihypertensive drugs was 27 (25.5%), 5 (27.8%), and 16 (23.2%), respectively ( $\chi^2 =$ ,  $P$ ). The frequency of intubation of the ARBs, ACEi, and other antihypertensive drugs group was 19 (17.9%), 2 (11.1%), and 12 (17.4%), respectively ( $\chi^2 =$ ,  $P$ ). According to our analysis, the mean intubation duration in ARBs, ACEi, and other antihypertensive drugs was 6 days. Mortality in the ARBs, ACEi, and other antihypertensive drugs group was 25 (23.6%), 5 (27.8%), and 21 (30.4%), respectively ( $\chi^2 =$ ,  $P$ ).

## Discussion

In patients with COVID-19 infection treated with three antihypertensive drugs, the study revealed that ARBs were more frequently used. In patients with COVID-19, other antihypertensive medications, such as beta-blockers, calcium-channel blockers, and diuretics, were also used.

Diabetes mellitus patients were more prone to COVID-19 (56.2%), followed by cardiovascular diseases (35.9%) and chronic kidney disease (17.6%). It has been proven that the prevalence of COVID-19 is higher in people with underlying cardiovascular diseases, such as high blood pressure, heart disease, and severe renal failure, and they use antihypertensive drugs more frequently. Some studies conducted by Chinese researchers also confirm that less healthy individuals are more susceptible to COVID-19 infection<sup>22-26</sup>.

It has been reported that patients consuming ARBs alone or combined with other drugs are at high risk of COVID-19, which can amplify the ACE2 activity. However, ACEi works solely through two protective mechanisms: reducing ACE2m on cell membranes and promoting ACE2p in the plasma. Therefore, ACEi might be an appropriate treatment option for patients with high blood pressure. These findings are derived

from various trials evaluating antihypertensive drugs for COVID-19<sup>27</sup>. Further clinical trials are still needed to support these results.

There are controversies in using ACEi or ARBs for

**Table 1.** Demographic characteristics (n=153).

| Items                     | n   | %    |
|---------------------------|-----|------|
| <b>Medical history</b>    |     |      |
| Cardiovascular disease    | 55  | 35.9 |
| Diabetes mellitus         | 86  | 56.2 |
| Lung diseases             | 5   | 3.3  |
| Gastrointestinal bleeding | 2   | 1.3  |
| Chronic kidney disease    | 27  | 17.6 |
| Cancer                    | 1   | 0.7  |
| Hyperlipidemia            | 12  | 7.8  |
| Cerebrovascular accident  | 16  | 10.5 |
| Alzheimer                 | 3   | 2    |
| CABG                      | 6   | 3.9  |
| Negres disease            | 1   | 0.7  |
| BPH                       | 2   | 1.3  |
| Parkinson                 | 3   | 2    |
| Hypothyroid               | 4   | 2.6  |
| Asthma                    | 2   | 1.3  |
| ESRD                      | 2   | 1.3  |
| <b>Drug history</b>       |     |      |
| HCTZ                      | 3   | 2.0  |
| B blocker                 | 58  | 37.9 |
| Spironolactone            | 8   | 5.2  |
| ARBs                      | 106 | 69.3 |
| ACEi                      | 18  | 11.8 |
| CCBs                      | 32  | 20.9 |
| ASA                       | 93  | 60.8 |
| Clopidogrel               | 1   | 0.7  |
| B blocker                 | 2   | 1.3  |
| Anti-coagulants           | 34  | 22.2 |
| Statins                   | 73  | 47.7 |

| Items                      | n   | %    |
|----------------------------|-----|------|
| Insulin                    | 30  | 19.6 |
| Anti-diabetes              | 57  | 37.3 |
| <b>Symptoms</b>            |     |      |
| Fever                      | 85  | 55.6 |
| Tiredness                  | 50  | 32.7 |
| Aches pains                | 51  | 33.3 |
| Dry cough                  | 69  | 45.1 |
| Productive cough           | 14  | 9.2  |
| Chilling                   | 34  | 22.2 |
| LOC                        | 18  | 11.8 |
| Chest pain                 | 15  | 9.8  |
| Dyspnea                    | 98  | 64.1 |
| Diarrhea                   | 8   | 5.2  |
| <b>Diagnosis</b>           |     |      |
| Positive bronchial CT scan | 108 | 70.6 |
| SARS-Cov-2 PCR             | 79  | 51.6 |
| <b>Treatments</b>          |     |      |
| Interferon                 | 18  | 11.8 |
| Hydroxychloroquine         | 113 | 73.9 |
| Antibiotics                | 55  | 35.9 |
| Ribavirin                  | 2   | 1.3  |
| Kaletra                    | 62  | 40.5 |

CABG: coronary artery bypass grafting; BPH: benign prostatic hyperplasia; ESRD: end-stage renal disease; HCTZ: hydrochlorothiazide; ARBs: angiotensin receptor blockers; ACEi: angiotensin-converting-enzyme inhibitors; CCBs: calcium channel blockers; ASA: acetylsalicylic acid (aspirin); LOC: loss of consciousness

treating patients with COVID-19, as a study explained, there is no significant difference between recovered and dead patients after using such drugs, which suggests using RAS inhibitors may not result in a better prognosis<sup>28</sup>. It is not clear whether this study is reliable enough due to a limited number of patients (n=22). In another trial, the infected cases with hypertension receiving ACEi or ARBs were compared to their counterparts not receiving such medicines, and the result showed that the former group had an extremely low mortality rate, and they also experienced a lower proportion of severe illnesses. In

the present study, the highest mortality rate was observed in the group using other blood pressure medications. The highest rate of ICU admission was observed in ACEi users, followed by ARBs and other blood pressure medications. Furthermore, the hospital stay was longest in the ARBs group, followed by the group taking other blood pressure medications, and finally the ACEi group. A prior study also reported lower levels of C-reactive protein and procalcitonin, indicating the anti-inflammatory activity of ACEi and ARBs<sup>29</sup>.

An experimental investigation on a mouse model

for myocardial infarction revealed that decreased ACE2 expression can be modulated by enalapril, an ACEi. Another ACEi, ramipril, showed no specific

impact on ACE2 expression. Other antihypertensive

**Table 2.** Laboratory result

| Variables                | ARBs              | ACEi | Other drugs | U/F | P |
|--------------------------|-------------------|------|-------------|-----|---|
| Hb (unit?)               |                   |      |             |     |   |
| PLT (unit?)              |                   |      |             |     |   |
| AST (unit?)              |                   |      |             |     |   |
| ALT (unit?)              |                   |      |             |     |   |
| CPK (unit?)              |                   |      |             |     |   |
| LDH (unit?)              |                   |      |             |     |   |
| Total bilirubin (unit?)  |                   |      |             |     |   |
| Urea (unit?)             |                   |      |             |     |   |
| Cr (unit?)               |                   |      |             |     |   |
| Na (unit?)               |                   |      |             |     |   |
| K (unit?)                |                   |      |             |     |   |
| SBP (unit?)              |                   |      |             |     |   |
| DBP (unit?)              |                   |      |             |     |   |
| PR (unit?)               |                   |      |             |     |   |
| Temperature (unit?)      | 36.6 ± 0.397      |      |             |     |   |
| Respiratory rate         | 15.38 ± 1.347     |      |             |     |   |
| SaO <sub>2</sub> (unit?) | 94.27 ± 3.895     |      |             |     |   |
| WBC (unit?)              | 10.25 ± 6.613     |      |             |     |   |
| Lymph (%)                | 15.34 ± 9.858     |      |             |     |   |
| Neut (%)                 | 76.77 ± 11.297    |      |             |     |   |
| Troponin (unit?)         | 485.66 ± 2328.662 |      |             |     |   |
| pH                       | 7.37 ± 0.082      |      |             |     |   |
| PCO <sub>2</sub> (unit?) | 41.82 ± 8.942     |      |             |     |   |
| HCO <sub>3</sub> (unit?) | 24.68 ± 4.457     |      |             |     |   |

Hb: hemoglobin; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; Cr: creatinine; Na: sodium; K: potassium; SBP: systolic blood pressure; DBP: diastolic blood pressure; PR: pulse rate; WBC: white blood cell; Lymph: lymphocyte; Neut: neutrophil.

drugs, such as losartan and olmesartan, considered ATR1 blockers, promoted the expression of *ACE2* gene. Some coronavirus-associated studies found a more undoubtedly essential proper treatment mechanism<sup>30-32</sup>. Some studies elucidated the association between drugs for cardiac disorders and coronavirus. A survey of 78 hypertension cases aged 65 or older found no association between cardiovascular drugs and chronic types of infection. Still, the severity of COVID-19 was lower in those who had previously been treated with cardiovascular drugs<sup>33</sup>. In another study, no correlation between illness severity and ACEi or ARBs was found either<sup>34</sup>. Some other factors, such as age, are considered risk factors for infection. COVID-19 mortality rates have been reported as less than 0.4% in the younger generation, 1.3% in adults aged 50 to 59 years, 3.6% in adults aged 60 to 69 years, 80% in adults aged 70 to 79 years, and 14.8% in adults aged 80 years and above<sup>35</sup>. The result is similar to the mean age of patients in the current study (70.88 years). Since this infection tends to occur in older people who have been diagnosed with hypertension, diabetes, or renal disorders and usually use ACEi and ARBs<sup>36</sup>, it can be a reason for the high mortality among patients with these conditions. Accordingly, we cannot firmly approve an association between receiving ACEi and ARB and the severity of COVID-19.

## Conclusion

In this study, mortality among patients on ACEi and ARBs is lower, but the difference is not significant. ACE and ARB are not associated with worse or better clinical outcomes. Generally, it cannot be concluded that ACEi and ARBs affect mortality, hospitalization duration, ICU admission, or patient condition in COVID-19. Discontinuation of these drugs or replacement may have many disadvantages. ACEi and ARBs may play an important role in improving patients' condition with COVID-19, and this should be studied further in much larger volumes.

This study has some limitations. First, the patient volume is relatively small, and perhaps more samples

would yield more significant results. The second problem is that the number of patients in each group was not equal, which may increase the error rate. This study reports a small number of COVID-19 patients with high blood pressure. To achieve more significant results, multicenter studies with larger subgroup volumes and longer follow-up are needed.

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## Conflict of interest

The authors further declare that they have no conflict of interest.

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