Original Article

Association between Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers and Mortality in Patients with Hypertension Hospitalized with COVID-19

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Abstract

Background: *Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are common hypertension medications. We aimed to investigate the association between treatment with ACEIs/ARBs and disease severity and mortality in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19).*

Methods: *Information from the medical records of 180 hospitalized patients diagnosed with COVID-19 infection admitted in 2020 to Loghman Hakim Hospital, Tehran, Iran, was collected. Clinical histories, drug therapies, radiological findings, hospital courses, and outcomes were analyzed in all the patients. The demographic and clinical characteristics of the patients were also analyzed, and the percentage of patients with hypertension taking ACEIs/ARBs was compared between survivors and nonsurvivors.*

Results: *The study population consisted of 180 patients at mean±SD age of 67.76±18.72 years. Hypertension was reported in 72 patients (40.0%). Patients with hypertension were older than those without it (mean±SD age =72.35±12.09 y). Among those with hypertension, death occurred in 33 patients (45.8%), of whom 60.6% were men. Fifty-three patients (73.6%) with hypertension were on ACEIs/ARBs. The ACEIs/ARBs group had a significantly lower mortality rate than the non-ACEIs/ARBs group (37.7% vs 68.4%; OR: 0.192; 95% CI: 0.05–0.68; P=0.011).*

Conclusion: *This single-center study found no harmful effects associated with ACEIs/ARBs treatment. Patients on ACEIs/ARBs had a lower rate of mortality and disease severity than the non-ACEIs/ARBs group. Our study supports the current guideline to continue ACEIs/ARBs in patients with hypertension.*

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Keywords: *COVID-19; Angiotensin-converting enzyme inhibitors; Angiotensin receptor antagonists; Hypertension*

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic began in December 2019 in Wuhan, in the Chinese province of Hubei. This newly diagnosed infectious respiratory disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with pneumonia and could have minor to severe symptoms and even lead to severe respiratory failure and multiple organ failure. Several studies have revealed higher risks of disease severity and complications in patients with hypertension or cardiovascular disease.[1]

Patients with hypertension or cardiovascular disease are commonly treated with angiotensin-converting enzyme inhibitors (ACEIs) such as captopril and enalapril, as well as angiotensin II receptor blockers (ARBs) such as losartan and valsartan, both of which block the renin-angiotensin system (RAS) and increase the expression of angiotensin-converting enzyme 2 (ACE2).[2] The SARS-CoV-2 virus binds to its target cells through ACE2, which is expressed by many organs like epithelial cells in the lungs, intestines, kidneys, and blood vessels.[3, 4] The increased expression of ACE2 may render patients susceptible to COVID-19 infection or more severe presentations. On the other hand, ACEI and ARBs are known to modulate the neurohormonal system and, thus, reduce inflammation, prevent tissue fibrosis, and even lower the rate of death in patients with acute respiratory distress syndrome (ARDS).[5] Further, ACE2 is known for its protective effects on severe acute lung injury and ARDS.[6] Since the beginning of the COVID-19 pandemic, physicians have been concerned about the effects of these drugs on the severity and mortality of patients with COVID-19 and pondered whether to replace or continue their prescription. While ACEIs/ARBs may increase ACE2 expression and susceptibility to SARS-COV-2 infection and disease severity, they could confer protection against lung injury.

In this study, we investigated the association between treatments with ACEIs/ARBs in 180 patients diagnosed with COVID-19 infection and disease severity, mortality, and need for mechanical ventilation.

Methods

In this retrospective study, we collected information from the medical records of 285 patients hospitalized in Loghman Hakim Hospital with signs or symptoms suspicious of COVID-19 infection. These patients were hospitalized between March and May 2020 due to their disease severity, general conditions, or low oxygen saturation levels (≤93% in room air). A total of 180 patients with a clinical diagnosis of COVID-19 infection as confirmed by positive nasopharyngeal and oropharyngeal reverse transcription-polymerase chain reaction (RT-PCR) tests and lung computed tomography scans with typical COVID-19 pneumonia patterns were included in the study.

Disease severity was defined as the need for mechanical ventilation, intensive care unit (ICU) admission, or death during the hospital course. Patients with unstable hemodynamics, decreased levels of consciousness, respiratory distress or failure, septic shock, or multiple organ dysfunctions were admitted to the ICU and considered to have severe disease. Hypertension was defined as a past history of antihypertensive drug use due to a persistent systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg and greater for at least 1 month before and until the day of admission or persistent high blood pressure (as defined above) in the hospital course. Patients with no previous history of hypertension or drug treatment were excluded from the hypertension group. Patients with hypertension who received ACEIs/ARBs before or during the hospital course were defined as the ACEIs/ARBs group, while those with hypertension who did not receive ACEIs/ARBs were defined as the non-ACEIs/ARBs group.

In keeping with the guidelines of the European Society of Cardiology (ESC) to continue treatment with ACEIs/ARBs in COVID-19 infection, we maintained the patients' usual antihypertensive therapy.[7] Patients who were diagnosed with hypertension during the hospital course were treated with either of the first-line antihypertensive therapies as indicated clinically according to the guidelines.[8]

All the statistical analyses were performed with SPSS, version 25 (IBM, Armonk, NY, USA). Continuous variables were presented as the mean±the standard deviation (SD), and categorical variables were expressed as numbers and percentages (%). Statistical differences between the groups were analyzed using the Mann–Whitney *U* test, the Fisher exact test, the χ^2 test, or logistic regression. A 2-sided α of less than 0.05 was considered statistically significant.

Associations between the patients' characteristics, ACEIs/ARBs use, disease severity, and mortality were measured independently; thereafter, analyses were adjusted for age, sex, and other comorbidities with logistic regression modeling.

Results

The medical records and outcomes of 180 hospitalized patients with COVID-19 pneumonia were analyzed. The mean±SD age was 61.76±18.72 years, and men accounted for 63.3% (n=114) of the entire study population. Fifty-eight percent of the patients were 60 years old or older.[9] The rate of in-hospital mortality was 39.4% (n=71), with men comprising 67.6% of this rate. The mean±SD hospital stay was 5.93±4.59 days among survivors and 3.90±4.06 days among nonsurvivors (Table 1).

Hypertension was reported in 72 patients (40.0%), of

Table 1. Demographics and clinical conditions in patients with COVID-19 pneumonia*

	Total	Survivors	Nonsurvivors	OR	95%CI for OR	P
Patients	180	109 (60.6)	71 (39.4)	-	-	-
Age (y)	61.76±18.72	56.82±18.67	69.35±16.12	-	-	<0.001
Age distribution						0.001
<60 y	76 (42.2)	57 (52.3)	19 (26.8)	0.33	0.18-0.64	
≥60 y	104 (57.8)	52 (47.7)	52 (73.2)	3.00	1.60-5.70	
Sex						0.337
Male	114 (63.3)	66 (60.6)	48 (67.6)	1.36	0.73-2.55	
Female	66 (36.7)	43 (39.5)	23 (32.4)	0.76	0.39-1.38	
ICU admission	89 (49.4)	18 (16.5)	71 (100)	-	-	<0.001
Hospital admission (d)	5.97±4.55	5.93±4.59	3.90±4.06	1.00	0.94-1.07	0.883
Intubation	79 (43.9)	8 (7.3)	71 (100)	-	-	<0.001
Diabetes	64 (35.6)	35 (32.1)	29 (49.9)	1.46	0.79-2.71	0.231
Cerebrovascular accident	7 (3.9)	3 (2.8)	4 (5.6)	2.11	0.46-9.72	0.328
CKD	9 (5.0)	4 (3.7)	5 (7.0)	1.99	0.51-7.67	0.310
Malignancy	4 (2.2)	2 (1.8)	2 (2.8)	1.55	0.21-11.27	0.662
COPD	8 (4.4)	6 (5.5)	2 (2.8)	0.50	0.10-2.54	0.392
Asthma	5 (2.8)	4 (3.7)	1 (1.4)	0.37	0.04-3.43	0.367
Hypothyroidism	4 (2.2)	1 (0.9)	3 (4.2)	4.77	0.49-46.74	0.141
Rheumatoid arthritis	2 (1.1)	1 (0.9)	1 (1.4)	1.54	0.10-25.10	0.759
Smoking	14 (7.8)	11 (10.1)	3 (4.2)	0.39	0.11-1.46	0.151
Opium addiction	20 (11.1)	13 (11.9)	7 (9.9)	0.81	0.31-2.13	0.666
Alcohol addiction	8 (4.4)	4 (3.7)	4 (5.6)	1.57	0.38-6.48	0.532
BPH	7 (3.9)	2 (1.8)	5 (7.0)	4.05	0.76-21.49	0.077
Parkinson	2 (1.1)	0	2 (2.8)	-	-	0.078
Alzheimer	3 (1.7)	1 (0.9)	2 (2.8)	3.13	0.28-35.18	0.331
Hypertension	72 (40.0)	39 (35.8)	33 (46.5)	1.56	0.89-2.87	0.152
HLP	10 (5.6)	5 (4.6)	5 (7.0)	1.58	0.44-5.65	0.482
IHD	22 (12.2)	10 (9.2)	12 (16.9)	2.01	0.82-4.95	0.122
CABG	3 (1.7)	2 (1.8)	1 (1.4)	0.76	0.07-8.59	0.827
HF	3 (1.7)	2 (1.8)	1 (1.4)	0.76	0.07-8.59	0.827
Structural heart disease	4 (2.2)	2 (1.8)	2 (2.8)	1.55	0.21-11.27	0.662
High CRP (>6 mg/L)	111 (62.0)	68 (62.4)	43 (60.5)	0.67	0.27-1.78	0.301
BMI (kg/m^2)	27.12±5.93	28.15±5.13	26.23±7.29	0.95	0.88-1.02	0.174

*Data are presented as mean±SD or n (%)
OR, Odds ratio; CI, confidence interval for OR; SD, Standard deviation; ICU, Intensive care unit; CKD, Chronic kidney disease; COPD, Chronic obstructive lung disease; BPH, Benign prostate hyperplasia; HLP, Hyperlipidemia; IHD, Ischemic heart disease; CABG, Coronary artery bypass graft; HF, Heart failure; CRP, C-reactive protein; BMI, Body mass index

Table 2. Characteristics of the hypertension group compared with the non-hypertension group in patients with COVID-19*

	Patients Infected with COVID-19			OR (95%CI)	P
	Total	Hypertension	Non-Hypertension		
Patients	180	72 (40.0)	108 (60.0)	-	-
Age (y)	61.76±18.7	72.35±12.09	54.70±19.06	NA	-
Age distribution					<0.001
<60 y	76 (42.2)	9 (12.5)	67 (62.0)	0.87 (0.04-0.19)	-
≥60 y	104 (57.8)	63 (87.5)	41 (38.0)	11.43 (5.14-25.44)	-
Sex					<0.001
Male	114 (63.3)	33 (45.8)	81 (75.0)	0.28 (0.15-0.53)	-
Female	66 (36.7)	39 (54.2)	27 (25.0)	3.54 (1.88-6.70)	-
ICU admission	89 (49.4)	39 (54.2)	50 (46.3)	1.37 (0.75-2.49)	0.301
Hospital admission (d)	5.97±4.55	6.07±4.19	5.90±4.79	1.008 (0.95-1.08)	0.804
Intubation	79 (43.9)	34 (47.2)	45 (41.7)	1.25 (0.69-2.28)	0.462
Diabetes	64 (35.6)	40 (55.6)	24 (22.2)	4.38 (2.29-8.38)	<0.001
Cerebrovascular accident	7 (3.9)	4 (5.6)	3 (2.8)	2.05 (0.45-9.49)	0.354
CKD	9 (5.0)	6 (8.3)	3 (2.8)	3.18 (0.77-13.16)	0.110
Malignancy	4 (2.2)	1 (1.4)	3 (2.8)	0.49 (0.05-4.86)	0.544
COPD	8 (4.4)	4 (5.6)	4 (3.7)	1.52 (0.37-6.32)	0.557
Asthma	5 (2.8)	2 (2.8)	3 (2.8)	1.00 (0.16-6.14)	1.000
Hypothyroidism	4 (2.2)	3 (4.2)	1 (0.9)	4.65 (0.47-45.63)	0.187
RA	2 (1.1)	1 (1.4)	1 (0.9)	1.51 (0.09-24.49)	0.773
Smoking	14 (7.8)	3 (4.2)	11 (10.2)	0.38 (0.10-1.42)	0.153
Opium addiction	20 (11.1)	3 (4.2)	17 (15.7)	0.23 (0.07-0.83)	0.024
Alcohol addiction	8 (4.4)	0 (0.0)	8 (7.4)	1.72 (1.51-1.95)	0.018
BPH	7 (3.9)	3 (4.2)	4 (3.7)	1.13 (0.25-5.29)	0.875
Parkinson	2 (1.1)	2 (2.8)	0 (0.0)	2.54 (2.12-3.05)	0.082
Alzheimer	3 (1.7)	3 (4.2)	0 (0.0)	2.57 (2.13-3.08)	0.032
HLP	10 (5.6)	9 (12.5)	1 (0.9)	15.29 (1.89-123.50)	0.001
IHD	22 (12.2)	17 (23.6)	5 (4.6)	6.37 (2.23-18.19)	<0.001
CABG	3 (1.7)	2 (2.8)	1 (0.9)	3.057 (0.27-34.36)	0.342
HF	3 (1.7)	2 (2.8)	1 (0.9)	3.057 (0.27-34.36)	0.342
Structural heart disease	4 (2.2)	1 (1.4)	3 (2.8)	0.49 (0.11-4.83)	0.536
High CRP (>6 mg/L)	111 (61.7)	50 (69.4)	61 (82.2)	1.33 (0.51-3.47)	0.557

*Data are presented as mean±SD or n (%)

OR, Odds ratio; CI, confidence interval for OR; SD, Standard deviation; ICU, Intensive care unit; CKD, Chronic kidney disease; COPD, Chronic obstructive lung disease; RA, Rheumatoid arthritis; BPH, Benign prostate hyperplasia; HLP, Hyperlipidemia; IHD, Ischemic heart disease; CABG, Coronary artery bypass graft; HF, Heart failure; CRP, C-reactive protein

Table 3. Characteristics and clinical outcomes of patients with hypertension and COVID-19*

	Patients with Hypertension			OR (95%CI)	P
	Total	Survivors	Nonsurvivors		
Patients	72	39 (54.2)	33 (45.8)	-	-
Age (y)	72.35±12.09	70.00±10.86	75.12±13.02	-	0.015
Age distribution					0.929
<60 y	9 (12.5)	5 (12.8)	4 (12.1)	0.94 (0.23-3.82)	
≥60 y	63 (87.5)	34 (87.2)	29 (87.9)	1.06 (0.26-4.35)	
Sex					0.022
Male	33 (45.8)	13 (33.3)	20 (60.6)	3.08 (1.17-8.08)	
Female	39 (54.2)	26 (66.7)	13 (39.4)	0.33 (0.12-0.85)	
ICU admission	39 (54.2)	6 (15.4)	33 (100)	-	<0.001
Hospital admission (d)	6.07±4.19	6.33±4.00	5.76±4.44	0.97 (0.86-1.08)	0.443
Intubation	34 (47.2)	1 (2.6)	33 (100)	-	<0.001
Diabetes	40 (55.6)	23 (59.0)	17 (51.5)	0.74 (0.29-1.88)	0.526
Cerebrovascular accident	4 (5.6)	3 (7.7)	1 (3.0)	0.38 (0.04-3.79)	0.406
CKD	6 (8.3)	3 (7.7)	3 (9.1)	1.20 (0.23-6.39)	0.831
Malignancy	1 (1.4)	1 (2.6)	0	-	0.354
COPD	4 (5.6)	4 (10.3)	0	-	0.058
Asthma	2 (2.8)	2 (5.1)	0	-	0.187
Hypothyroidism	3 (4.2)	1 (2.6)	2 (6.1)	2.45 (0.21-28.3)	0.459
RA	1 (1.4)	0	1 (3.0)	-	0.274
Smoking	3 (4.2)	1 (2.6)	2 (6.1)	2.45 (0.21-28.3)	0.459
Opium addiction	3 (4.2)	0	3 (9.1)	-	0.054
Alcohol addiction	0	0	0	-	-
BPH	3 (4.2)	1 (2.6)	2 (6.1)	2.45 (0.21-28.32)	0.473
Parkinson	2 (2.8)	0	2 (6.1)	-	0.119
Alzheimer	3 (4.2)	1 (2.6)	2 (6.1)	2.45 (0.21-28.32)	0.459
HLP	9 (12.5)	4 (10.3)	5 (15.2)	1.56 (0.38-6.37)	0.531
IHD	17 (23.6)	8 (20.5)	9 (27.3)	1.45 (0.48-4.33)	0.501
CABG	2 (2.8)	2 (5.1)	0	-	0.187
HF	2 (2.8)	1 (2.6)	1 (3.0)	1.19 (0.07-19.7)	0.905
Structural heart disease	1 (1.4)	1 (2.6)	0	-	0.354
Medications					0.025
ACEIs/ARBs	53 (73.6)	33 (84.6)	20 (60.6)	0.28 (0.09-0.85)	-
Non-ACEIs/ARBs	19 (26.4)	6 (15.4)	13 (39.4)	3.57 (1.17-10.91)	-
Adjusted	-	-	-	0.19 (0.05-0.68)	0.011
High CRP (>6 mg/L)	50 (69.4)	31 (79.5)	19 (57.6)	0.09 (0.01-0.77)	0.028

*Data are presented as mean±SD or n (%)

OR, Odds ratio; CI, 95% confidence interval for OR; SD, Standard deviation; ICU, Intensive care unit; CKD, Chronic kidney disease; COPD, Chronic obstructive disease; RA, Rheumatoid arthritis; BPH, Benign prostate hyperplasia; HLP, Hyperlipidemia; IHD, Ischemic heart disease; CABG, Coronary artery bypass graft; HF, Heart failure; ACEIs, Angiotensin-converting-enzyme inhibitors; ARBs, Angiotensin II receptor blockers; CRP, C-reactive protein

Table 4. ACEIs/ARBs and non-ACEIs/ARBs therapy, characteristics, and comorbid conditions in patients with hypertension*

	ACEIs/ARBs	Non-ACEIs/ARBs	OR (95%CI)	Total	P
Patients	53 (73.6)	19 (26.4)	-	72 (100)	-
Age (y)	72.36±12.20	72.32±12.11	-	72.35±12.09	0.954
Age distribution					
<60 y	7 (13.2)	2 (10.5)	1.29 (0.24-6.85)	9 (132.5)	0.762
≥60 y	46 (86.8)	17 (89.5)	0.77 (0.15-4.09)	63 (87.5)	
Nonsurvivor	20 (37.7)	13 (68.4)	0.28 (0.09-0.85)	33 (45.8)	0.025
ICU admission	25 (47.2)	14 (73.7)	0.32 (0.10-1.01)	39 (54.2)	0.047
Hospital admission (d)	6.38±4.49	5.21±3.12	1.08 (0.93-1.25)	6.07±4.19	0.415
Intubation	21 (39.6)	13 (68.4)	0.30 (0.10-0.92)	34 (47.2)	0.035
Diabetes	29 (54.7)	11 (57.9)	0.88 (0.31-2.53)	40 (55.6)	0.811
Cerebrovascular accident	1 (1.9)	3 (15.8)	0.11 (0.01-1.06)	4 (5.6)	0.024
Cardiovascular disease	14 (26.4)	5 (26.3)	1.01 (0.31-3.30)	19 (26.4)	0.993
CKD	4 (7.6)	2 (10.5)	0.69 (0.12-4.13)	6 (8.3)	0.688
High CRP (>6 mg/L)	36 (67.9)	14 (73.7)	0.86 (0.15-4.76)	50 (69.4)	0.860

*Data are presented as mean±SD or n (%)
ACEIs, Angiotensin-converting-enzyme inhibitors; ARBs, Angiotensin II receptor blockers; OR, Odds ratio; CI, 95% Confidence interval for OR; SD, Standard deviation; ICU, Intensive care unit; CKD, Chronic kidney disease; CRP, C-reactive protein

whom 45.8% were men. Patients with hypertension were older than those without it (mean±SD age: 72.35±12.09 y vs 54.70±19.06 y). Sixty-three patients (87.5%) with hypertension were 60 years old or older. Among those suffering from hypertension, 53 patients (73.6%) were on ACEIs/ARBs. During the hospital course, 33 patients (45.8%) with hypertension died. Nonsurvivors were older (75.12±13.02 y vs 70±10.86 y) and were more likely to be male (n=20 [61%]; odds ratio [OR]: 3.08; 95% confidence interval [CI]: 1.17–8.08; P=0.022). Other comorbidities such as diabetes, cerebrovascular disease, chronic kidney disease, and coronary artery diseases were not significantly different between the 2 groups. No significant associations between hypertension and mortality rates or disease severity were found, likely due to the sample size and the selection method. ACEIs/ARBs were the most common drugs used by the patients (73.6%) (Table 2 & Table 3).

The ACEIs/ARBs group had a less frequent past history of cerebrovascular incidents than the non-ACEIs/ARBs group (1.89% vs 15.78%; OR: 0.11; 95%CI: 0.09–0.85; P=0.024). Other comorbidities like diabetes, cardiovascular disease, and chronic kidney disease were not significantly different between the 2 groups. The non-ACEIs/ARBs group had a significantly higher mortality rate than the ACEIs/ARBs group (68.4% vs 37.7%; OR: 0.28; 95%CI: 0.09–0.85; P=0.025). The mean length of hospital stay was longer among survivors and ACEIs/ARBs users than among nonsurvivors and non-ACEIs/ARBs users (6.38±4.49 d vs 5.76±4.44 d and 5.21±3.12 d). Disease severity was higher among the patients in the non-ACEIs/ARBs group as they needed more ICU care, intubation, or mechanical ventilation than among those in the other group (95% CI: 0.10–1.01; P=0.047 vs 95%CI: 0.10–0.92; P=0.035) (Table 4).

After adjustments for age, sex, diabetes, and cardiovascular, cerebrovascular, and chronic kidney diseases with logistic regression modeling, the effect of ACEIs/ARBs on mortality became more significant (OR: 0.19; 95%CI: 0.05–0.68; P=0.011).

Discussion

We analyzed the medical records of 180 hospitalized patients with COVID-19 infection. In-hospital treatment with ACEIs/ARBs was not associated with an increase in the severity or mortality of COVID-19 infection. It could be argued that it might even reduce the mortality and severity of the disease. Some previous studies have also reported no association between ACEIs/ARBs and higher mortality or disease severity.[10-12] Our findings showed that survivors stayed longer in the hospital and had a milder disease in their course of treatment as they needed less ICU care and mechanical ventilation support.

We found no association between hypertension and mortality rates, which could be due to our sample size or approach to population selection as we evaluated only patients with critical conditions in need of hospital admission.

As was hypothesized earlier, ACEIs/ARBs may help patients with COVID-19 infection by enhancing the

expression of ACE2. Indeed, ACEIs/ARBs upregulate the expression of ACE2, which binds to the SARS-CoV-2 spike protein and facilitates virus entry to the respiratory epithelial cells. The absence of statistically significant differences concerning cardiovascular morbidities in our hospitalized patients with COVID-19 divided into the ACEIs/ARBs group and the non-ACEIs/ARBs group could support the hypothesis. Some studies have found no significant associations between ACEIs/ARBs use and positive COVID-19 tests.[13, 14] Indubitably, more research is required to shed sufficient light on this relationship.

As was mentioned earlier, ACEIs/ARBs can reduce RAS activity and elevate ACE2 levels, which can be protective in ARDS. Additionally, high ACE2 levels can lower RAS activity even more.[6, 15] We found that patients on ACEIs/ARBs had a less severe infection, a lower mortality rate, and less need for ICU care or mechanical ventilation, supporting the hypothesis that these drugs lower RAS activity and confer protection against ARDS.

This study was limited by its single-center design and the small number of patients in need of hospitalization for COVID-19 infection. Accordingly, our results may not be generalizable to other populations and may differ from those reported by other studies.

Conclusion

Based on our observation and lack of any harmful evidence, patients with COVID-19 infection should continue their treatment with ACEIs/ARBs as the current ESC guideline also suggests.[7] ACEIs/ARBs may even have a protective role against disease severity and mortality. For patients without COVID-19 infection but in contact with the current pandemic environment, as they may increase the risk of infection, there is no definite evidence to change or discontinue treatment with ACEIs/ARBS.

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