BRIEF COMMUNICATION

Use of RAAS Inhibitors and Risk of Clinical Deterioration in COVID-19: Results From an Italian Cohort of 133 Hypertensives

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BACKGROUND
The effect of chronic use of renin–angiotensin–aldosterone system (RAAS) inhibitors on the severity of COVID-19 infection is still unclear in patients with hypertension. We aimed to investigate the association between chronic use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and COVID-19-related outcomes in hypertensive patients.

METHODS
A single-center study was conducted on 133 consecutive hypertensive subjects presenting to the emergency department with acute respiratory symptoms and/or fever who were diagnosed with COVID-19 infection between 9 and 31 March 2020.

RESULTS
All patients were grouped according to their chronic antihypertensive medications (ACEIs, $N = 40$; ARBs, $N = 42$; not on RAAS inhibitors, $N = 51$). There was no statistical difference between ACEIs and ARBs groups in terms of hospital admission rate, oxygen therapy, and need for noninvasive ventilation. Patients chronically treated with RAAS inhibitors showed a significantly lower rate of admission to semi-intensive/intensive care units, when compared with the non-RAAS population (odds ratio (OR) 0.25, confidence interval (CI) 95% 0.09–0.66, $P = 0.006$). Similarly, the risk of mortality was lower in the former group, although not reaching statistical significance (OR 0.56, CI 95% 0.17–1.83, $P = 0.341$).

CONCLUSIONS
Our data suggest that chronic use of RAAS inhibitors does not negatively affect clinical course of COVID-19 in hypertensive patients. Further studies are needed to confirm this finding and determine whether RAAS inhibitors may have a protective effect on COVID-19-related morbidity and mortality.

Keywords: ACEIs/ARBs; blood pressure; COVID-19 infection; hypertension; hypertensive patients; mortality; SARS-COV-2

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Coronavirus disease 19 (COVID-19) pandemic has affected more than 3 million people.[1] It has been hypothesized that chronic use of renin–angiotensin–aldosterone system (RAAS) inhibitors may worsen disease outcome in patients with hypertension.[2] Indeed, a defined receptor-binding domain of COVID-19 spike specifically recognizes angiotensin-converting enzyme 2 (ACE2)-receptor. ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) determine upregulation of ACE2-receptors in cardiopulmonary circulation, making patients taking these drugs potentially more susceptible to increased severity.[3] Conversely, ACEIs and ARBs may act protectively

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by inhibiting RAAS hyperactivation and respiratory injury progression as a consequence of ACE2-receptors downregulation occurring after COVID-19 infection.[4] However, these hypotheses are based on experimental animal models and *in vitro* studies, while clinical data are scant. For this reason, a number of scientific societies have recently taken a clear position opposing the discontinuation of ACEIs and ARBs in COVID-19 patients.[5]

The aim of the current study was to investigate whether the chronic use of ACEIs and ARBs affects COVID-19-related outcomes in hypertensive patients.

METHODS

Study population and protocol

This is a single-center retrospective study including all consecutive hypertensive subjects who presented to the emergency department (ED) with acute respiratory symptoms/fever, and were diagnosed with COVID-19 infection between 9 and 31 March 2020. We considered as hypertensives all the subjects undergoing chronic treatment with blood pressure lowering agents. Diagnosis of COVID-19 was made by semi-quantitative real-time reverse transcription polymerase chain reaction on nasopharyngeal swab. Criteria for hospital admission of COVID-19 positive patients were established by local protocols and remained unchanged throughout the observation period. These included 1 or more of the following: (i) respiratory failure, (ii) body temperature <35 °C, (iii) presence of comorbidities, (iv) CURB-65 (confusion, uremia, respiratory rate, blood pressure, and age ≥65 years) score ≥2, (v) respiratory alkalosis, and (vi) high levels of procalcitonin.

Patients' demographics and clinical characteristics were collected by medical records and entered into an anonymous database. Data included age, gender, body mass index, active smoking, duration of COVID-19-related symptoms prior to admission, as well as detailed medical history including previous cardiovascular events (myocardial infarction/stroke/decompensated heart failure), Chronic Obstructive Pulmonar Disease, diabetes, and active cancer. Main clinical outcomes included hospitalization (immediate or delayed within 7 days after discharge from the ED), need for oxygen therapy, noninvasive ventilation, admission to semi-intensive/intensive care units (s-ICU/ICU, based on PaO_2/FiO_2 ratio <250, and need for invasive or noninvasive ventilation), and death. Additional analyses were performed after grouping patients taking ACEIs and ARBs and comparing their clinical outcomes with those of hypertensives who were not on RAAS inhibitors. The study was approved by the local Research Ethic Committee.

Statistical analysis

Continuous variables were presented by mean and SD, while binary variables by proportions. Comparisons across groups were made using analysis of variance and Fisher's exact tests, respectively. *P* values were reported at their nominal value. The Benjamini–Hochberg procedure was performed to take account of multiple testing with a 30% false discovery rate. Uni- and multivariable logistic regressions were performed with a predefined covariate set, which included age, gender, body mass index, days with duration of symptoms prior to admission (days), previous cardiovascular events, diabetes, and cancer, further to the use of ACEI/ARBs. All statistical analyses were performed using Stata 16 (StataCorp LLC, College Station, TX).

RESULTS

Patients' characteristics

A total of 133 hypertensive patients referred to ED and diagnosed with COVID-19 were enrolled throughout the study period. Among these, 40 (30%) were chronically using ACEIs, 42 (32%) ARBs, and 51 (38%) other blood pressure lowering medications. Among those treated with ACEIs, 70% were taking ramipril, whereas olmesartan was used in more than 50% of patients treated with ARBs (see Supplementary Table S1 online). The mean follow-up was 15.8 ± 8.6 days. The general characteristics of the 3 groups are summarized in Table 1. No significant differences were observed for all demographics and clinical parameters, except for the history of chronic heart failure, which was more frequently observed in hypertensive patients not on RAAS inhibitors (31%; $P = 0.007$).

Use of RAAS inhibitors and clinical outcome

At univariate analysis, the 3 groups had similar rates of hospital admission, as well as a comparable need for oxygen therapy and noninvasive ventilation during the hospital stay. The rate of admission to s-ICU/ICU was lower among patients treated with ACEI (23%) or ARBs (29%) as compared with hypertensive patients who were not on RAAS inhibitors (49%). The death rate was also similar between patients on ACEI and ARBs (20% and 17%, respectively), but lower than that observed in the third group (35%).

Odds ratios (ORs) for hospitalization, admission to s-ICU/ICU, need for oxygen therapy, noninvasive ventilation, and death are shown in Table 2. Similar rates of hospital admission and oxygen therapy were observed in the 2 groups (RAAS vs. not on RAAS). Nevertheless, patients chronically treated with RAAS inhibitors showed a lower risk of admission to s-ICU/ICU (OR 0.36, confidence interval (CI) 95% 0.17–0.75, $P = 0.007$). This finding remained significant even at multivariate analysis after adjusting for age, gender, body mass index, days with symptoms prior to admission, previous cardiovascular events, diabetes, and cancer (OR 0.25, CI 95% 0.09–0.66, $P = 0.006$). Despite a crude OR of 0.41 (CI 95%, 0.18–0.92, $P = 0.030$) the difference in death rate between patients treated or not with RAAS inhibitors was not confirmed as statistically significant in the fully adjusted model (OR 0.56, CI 95% 0.17–1.83, $P = 0.341$).

DISCUSSION

The present study shows that chronic assumption of ACEIs/ARBs did not worsen the clinical outcomes of

Table 1. Characteristics of the study population

	ACEI (*N* = 40)	ARB (*N* = 42)	Not on RAAS inhibitors (*N* = 51)	*P*
Age, years (mean, SD)	73.1 (11.5)	69.0 (13.4)	76.2 (11.9)	0.023[a]
Gender, male (*N*, %)	28 (70)	31 (74)	27 (53)	0.088
Body mass index (mean, SD)	27.5 (5.3)	28.0 (5.5)	26.1 (4.0)	0.180
Length of stay, days (mean, SD)	9.1 (5.4)	8.5 (4.5)	11.0 (9.1)	0.423
Symptom duration before admission, days (mean, SD)	7.3 (4.9)	7.6 (2.7)	6.4 (4.5)	0.317
Active smokers (*N*, %)	1 (3)	1 (3)	1 (2)	0.999
Blood pressure on ED admission (mean, SD)				
Systolic	140.0 (22.0)	141.8 (20.0)	135.5 (28.7)	0.466
Diastolic	79.1 (15.2)	81.9 (14.1)	80.3 (17.6)	0.748
Previous cardiovascular events (*N*, %)	16 (40)	13 (31)	27 (53)	0.099
History of chronic heart failure (*N*, %)	4 (10)	4 (10)	16 (31)	0.007
Diabetes (*N*, %)	12 (30)	8 (19)	14 (28)	0.507
Active cancer (*N*, %)	9 (23)	5 (12)	7 (14)	0.436
Chronic obstructive pulmonary disease (*N*, %)	4 (10)	3 (7)	7 (14)	0.584
Hospital admission (*N*, %)	39 (98)	36 (86)	48 (96)	0.116
Admission to ICU/s-ICU (*N*, %)	9 (23)	12 (29)	25 (49)	0.022[a]
Oxygen therapy (*N*, %)	30 (75)	31 (74)	44 (86)	0.261
Noninvasive ventilation (*N*, %)	13 (33)	14 (33)	21 (41)	0.652
Death (*N*, %)	8 (20)	7 (17)	18 (35)	0.093

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ED, emergency department; ICU, intensive care unit; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation; s-ICU, semi-intensive care unit.
[a]After Benjamini–Hochberg procedure no statistical significance was found at false discovery rate of 30%.

Table 2. Comparison of main clinical outcomes between hypertensive patients taking or not renin–angiotensin–aldosterone system inhibitors

	Crude OR	95% CI	*P*	Adj-OR	95% CI	*P*
Hospital admission	0.45	0.09–2.24	0.327	0.39	0.05–2.94	0.365
Oxygen therapy	0.46	0.18–1.18	0.107	0.51	0.15–1.78	0.292
Admission to ICU/s-ICU	0.36	0.17–0.75	0.007	0.25	0.09–0.66	0.006
NIV	0.70	0.34–1.44	0.336	0.58	0.21–1.60	0.296
Death	0.41	0.18–0.92	0.030	0.56	0.17–1.83	0.341

Abbreviations: Adj-OR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; NIV, noninvasive ventilation; OR, odds ratio; s-ICU, semi-intensive care unit. Multivariable logistic regressions were performed with a predefined covariate set, which included age, gender, body mass index, days with symptoms prior to admission, previous cardiovascular events, diabetes, and cancer.

COVID-19 infection in hypertensive patients. A significant lower risk of admission to s-ICU/ICU was observed in COVID-19 positive subjects chronically treated with ACEIs/ARBs as compared with other hypertensive patients, whereas the rates of hospitalization, oxygen therapy, noninvasive ventilation, and death did not differ between the 2 groups.

While highly expressed in the vascular endothelium and lung, ACE2-receptors have been shown to represent the cellular entry receptor of COVID-19.[6,7] Based on experimental animal models demonstrating an upregulation of ACE2-receptors associated with intravenous infusion of ACEIs and ARBs,[8] it has been warned that these medications might negatively impact clinical course of COVID-19 in hypertensives.[3,9] However, 2 previous studies failed to demonstrate modification in ACE2 mRNA expression and plasma ACE2 activity in rat and human cells treated with RAAS inhibitors, respectively.[10,11] Moreover, Tan *et al.* showed a protective role of ACEIs and ARBs in pneumonia prevention,[12] suggesting that RAAS may even potentially benefit COVID-19 patients.[13] High-quality randomized controlled trials are needed to further understand and resolve this conundrum.

Although the rates of noninvasive ventilation did not differ between the 2 groups, the ACEIs/ARBs treated subjects were less frequently admitted to s-ICU/ICU compared with their counterpart. This difference was maintained

even after adjusting for anthropometric and clinical factors (i.e. age, body mass index, history of previous cardiovascular diseases, and diabetes). A trend of lower mortality was observed in patients on ACEIs/ARBs when compared with other hypertensives. Although not reaching statistical significance when analyzed in a fully adjusted model, this finding might further indicate that chronic ACEIs/ARBs administration does not negatively affect clinical outcomes in COVID-19 positive hypertensives.

Similar to our data, two recent Chinese studies[14,15] reported a lower risk of COVID-19-related mortality in hypertensive subjects associated with RAAS inhibitors during hospital stay. However, results were not stratified by type of chronic treatment (i.e. ARBs vs. ACEIs). In addition, very recent reports, based on data from electronic health records, suggested that treatment with ARBs/ACEIs does not correlate to an increased susceptibility to SARS-COV-2 nor to the development of severe disease.[16–19] These evidences have been confirmed by our analysis, which focused on clinical outcome of a specific cohort of hypertensive patients referring to the ED for acute symptoms of COVID-19 infection. Specifically designed intervention studies are needed to confirm that the use of RAAS inhibitors can protect from clinical deterioration and to identify mechanisms associated with these beneficial effects (such as potential anti-inflammatory activities or protective modulatory effects on ACE2 expression).

Our study presents some important limitations. First, the retrospective design and the limited sample size, which allowed us to only make an exploratory assessment of our working hypotheses. Second, only patients testing COVID-19 positive at the ED were enrolled in this study, thus not being representative of the entire infected population. Furthermore, the potential association with other antihypertensive drugs, the prosecution of antihypertensive therapy throughout the hospital stay, and different COVID-19 specific therapeutic strategies might have been other confounding factors.

In conclusion, our data suggest that chronic use of RAAS inhibitors does not correlate with an adverse clinical course in hypertensive patients. Conversely, discontinuing such a lifesaving therapy might be potentially harmful in line with societal recommendation.[5] Further large studies are needed to confirm whether the use of RAAS inhibitors may exert a protective effect on the risk of mortality associated to COVID-19 infection.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

The authors declared no conflict of interest.

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