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Clinical Impact of Renin-angiotensin System Inhibitors on In-hospital Mortality of Patients With Hypertension Hospitalized for Coronavirus Disease 2019

To the Editor—We read with interest the article from Haffn et al, indicating key clinical research priorities to clarify the role of renin-angiotensin system (RAS) inhibition in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–associated coronavirus disease 2019 (COVID-19) [1].

Initial epidemiological studies have associated the presence of hypertension with a more severe disease and higher mortality rates [2, 3]. Nevertheless, it is unclear if this association is related to the pathogenesis of hypertension or to advanced age, coexisting comorbidities, or antihypertensive treatment [4]. SARS-CoV-2 enters host cells after binding with angiotensin-converting enzyme 2 (ACE2); an overexpression of this enzyme has been described in hypertension, diabetes, and cardiovascular diseases, and in animal models of pharmacologic RAS blockade [1, 5]. Although the significance of ACE2 expression on COVID-19 pathogenesis and mortality is not specifically known, it has been hypothesized that overexpression may increase the risk of severe and fatal COVID-19 but also that RAS inhibition may mitigate clinical course, by interfering with the negative effects of angiotensin II on ACE2 downregulation in infected patients. Consequently, it has been proposed that either the use or avoidance/withdrawal of RAS inhibitors (RASIs) could have a favorable impact on COVID-19 outcomes [1].

To date, clinical data about the role of RASIs in COVID-19 are lacking but are urgently needed, especially in Italy where the outbreak of COVID-19 is particularly heavy among elderly people [6], many of whom are prescribed RASIs to treat hypertension.

To investigate whether chronic treatment with RASIs has an impact on in-hospital mortality, we selected patients with hypertension from a cohort of prospectively enrolled adults with a microbiologically confirmed diagnosis of COVID-19, hospitalized in 10 Italian hospitals from 22 February to 4 April 2020.

The study population consisted of 311 patients with hypertension. They were significantly older; had a higher body

Table 1. Characteristics of the Study Population

Characteristic	All patients (N = 609)	Hypertension (n = 311)	No Hypertension (n = 298)	*P* Value
Age, y, median (IQR)	68 (55–80)	76 (67–83)	57 (47–68)	<.001
Male sex	410 (68)	225 (72)	185 (63)	.007
BMI, kg/m^2, median (IQR)	25 (23–28)	27 (24–31)	25 (23–27)	<.001
History of smoking	106 (17)	80 (26)	26 (9)	<.001
Influenza vaccination[a]	85/283 (30)	53/127 (42)	32/156 (20)	.02
Charlson index, median (IQR)	3 (1–5)	5 (3–6)	1 (0–3)	<.001
Comorbidities				
Diabetes	100 (16)	74 (24)	26 (9)	<.001
CVD	165 (27)	131 (42)	34 (11)	<.001
COPD	68 (11)	49 (16)	19 (6)	<.001
Immunosuppression	22 (4)	13 (4)	9 (3)	.44
Symptoms on admission				
Temperature ≥38°C	264 (46)	133 (46)	131 (45.5)	.60
Cough	349 (57)	157 (50)	192 (64)	.001
Dyspnea	253 (41)	138 (44)	115 (39)	.14
SOFA score, median (IQR)	2 (1–3)	2 (1–4)	1 (1–2)	<.001
Antihypertensive treatment[b]				
None	…	60 (19)	…	
ACEIs	…	99 (32)	…	
ARBs	…	76 (24.5)	…	
Others	…	76 (24.5)	…	
DNR	114 (19)	83 (27)	31 (10)	<.001
In-hospital mortality	174 (29)	131 (42)	43 (14)	<.001

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DNR, do not resuscitate indication; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

[a]Data about previous influenza vaccination were available for 283 of 609 patients.
[b]Data about antihypertensive medications were collected only for patients with a previous diagnosis of hypertension.

mass index; had a Charlson comorbidity index with a higher prevalence of cardiovascular (CV) comorbidities, chronic obstructive pulmonary disease (COPD), and diabetes; and had a higher Sequential Organ Failure Assessment (SOFA) score on admission compared with patients without hypertension (Table 1). Patients receiving antihypertensive drugs other than RASIs had a higher Charlson comorbidity index, with a higher prevalence of COPD and CV comorbidities.

Overall in-hospital mortality was 29% (179/609); among the 311 patients with hypertension, 131 (42%) died in-hospital, after a median of 6 days (interquartile range, 4–10 days) from admission.

In the group of patients with hypertension, in multivariate Cox regression analysis adjusted for age, sex, presence of CV comorbidities, and COPD, the independent predictors of in-hospital mortality were SOFA score on admission (adjusted hazard ratio [aHR], 1.32; 95% confidence interval [CI], 1.20–1.45; $P < .001$) and age (aHR, 1.05; 95% CI, 1.03–1.07; $P < .001$), whereas the chronic use of RASIs (aHR, 0.97; 95% CI, .68–1.39; $P = .88$) was not associated with outcome.

Our study population consists of aged patients with multiple comorbidities, from a hospital-based cohort with a probable selection bias for sicker cases, so in-hospital mortality is very high. Nevertheless, our findings support the statements of several scientific societies that recommend patients to continue their current hypertensive medication regimen, waiting for the results of randomized controlled trials addressing the impact of RASIs on COVID-19 morbidity and mortality.

Notes

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