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Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19

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Dear 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 enter host cells after binding with angiotensin-converting enzyme 2 (ACE2); an overexpression of this enzyme has been described in hypertension, diabetes, 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 favourable impact on COVID-19 outcomes[1].

To date, clinical data about the role of RASIs in COVID-19 are lacking but they 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 ten Italian hospitals from February 22nd to April 4th 2020.

Study population consisted of 311 patients with hypertension; they were significantly older, had a higher BMI and Charlson comorbidity index with a higher prevalence of cardiovascular (CV) comorbidities, chronic obstructive pulmonary disease (COPD) and diabetes and a higher sequential organ failure assessment (SOFA) score on admission than patients without hypertension (Table). 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 (IQR 4-10) from admission.

In the group of patients with hypertension, at multivariate Cox regression analysis adjusted for age, gender, presence of CV comorbidities and COPD, the independent predictors of in-hospital mortality were: SOFA score on admission (aHR 1.32, 95% CI 1.20-1.45; p<0.001) and age (aHR 1.05, 95% CI 1.03-1.07; p<0.001). Whereas, the chronic use of RASIs (aHR 0.97, 95% CI 0.68-1.39; p=0.88) 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.

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Conflict of interest

All the authors declare no conflict of interest related to the content of the present study.

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Table 1. Characteristics of study population

	All patients (n=609)	Hypertension (n=311)	No hypertension (n=298)	p
Age, years– median (IQR)	68 (55-80)	76 (67-83)	57 (47-68)	<0.001
Males – n°(%)	410 (68)	225 (72)	185 (63)	0.007
BMI – median (IQR)	25 (23-28)	27 (24-31)	25 (23-27)	<0.001
History of smoking – n°(%)	106 (17)	80 (26)	26 (9)	<0.001
Influenza vaccination – n°(%)[a]	85/283 (30)	53/127 (42)	32/156 (20)	0.02
Charslon index – median (IQR)	3 (1-5)	5 (3-6)	1 (0-3)	<0.001
Comorbidities				
Diabetes – n°(%)	100 (16)	74 (24)	26 (9)	<0.001
CVD – n°(%)	165 (27)	131 (42)	34 (11)	<0.001
COPD – n°(%)	68 (11)	49 (16)	19 (6)	<0.001
Immunosuppression – n°(%)	22 (4)	13 (4)	9 (3)	0.44
Symptoms on admission				
BT >= 38°C – n°(%)	264 (46)	133 (46)	131 (45.5)	0.60
Cough – n°(%)	349 (57)	157 (50)	192 (64)	0.001
Dyspnoea – n°(%)	253 (41)	138 (44)	115 (39)	0.14
SOFA score – median (IQR)	2 (1-3)	2 (1-4)	1 (1-2)	<0.001
Antihypertensive treatment[b]				
None – n°(%)		60 (19)		
ACEIs – n°(%)		99 (32)		
ARBs – n°(%)		76 (24.5)		
Others – n°(%)		76 (24.5)		
DNR – n°(%)	114 (19)	83 (27)	31 (10)	<0.001
In-hospital mortality – n°(%)	174 (29)	131 (42)	43 (14)	<0.001

Abbreviations: IQR, interquartile range; BMI, body mass index; CVD, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; BT, body temperature; SOFA, sequential organ failure assessment; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; DNR, do not resuscitate indication.

[a]Data about previous influenza vaccination were available for 283/609 patients.

[b]Data about anti-hypertensive medications were collected only for patients with a previous diagnosis of hypertension.