

# COVID-19, hypertension, and renin-angiotensin-aldosterone system inhibitors: Much ado about nothing or real problem to be solved?

Marijana Tadic MD, PhD<sup>1</sup>  | Cesare Cuspidi MD<sup>2,3</sup> 

<sup>1</sup>University Hospital "Dr. Dragisa Misovic - Dedinje" Department of Cardiology, Belgrade, Serbia

<sup>2</sup>University of Milan-Bicocca, Milan, Italy

<sup>3</sup>Istituto Auxologico Italiano, IRCCS, Italy

**Correspondence:** Marijana Tadic, University Hospital "Dr. Dragisa Misovic - Dedinje", Department of Cardiology, Heroja Milana Tepica 1, 11000 Belgrade, Serbia.

Email: marijana\_tadic@hotmail.com

The pandemic of coronavirus disease 2019 (COVID-19) caught the whole world unprepared. Tens of millions infected patients, close to a million victims and thousands of conducted and published studies in the last several months. However, there is still a large gap in the knowledge of how to fight and defeat this virus and it does not seem that it will be fulfilled in the near future. Studies recognized the important risk factors for the severity of COVID-19 and prediction of adverse outcome in these patients. The most cited risk factors are older age, cardiovascular diseases, hypertension, diabetes, chronic obstructive disease, and chronic kidney disease.<sup>1,2</sup>

Since investigations revealed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causative agent of COVID-19, is using angiotensin-converting enzyme 2 (ACE2) as the receptor to infect cells and replicate,<sup>3</sup> immediately started speculation about the potential negative role of the renin-angiotensin-aldosterone system (RAAS) antagonists in COVID-19 patients. This was supported by the study that reported higher prevalence of RAAS usage in COVID-19 patients with myocardial injury and adverse outcome.<sup>4</sup> However, it was an observational study with limited number of patients and could not provide information about potential causal relationship between RAAS inhibitors and higher mortality in COVID-19 patients,<sup>4</sup> but information was realized and panic spread rapidly through the world. Under the large public pressure, the majority of national and international professional societies had to publish official reassurance that RAAS inhibitors are safe in COVID-19 patients and that they should not be excluded from chronic therapy or switched to other antihypertensive medications.<sup>5,6</sup> The largest problem is that RAAS inhibitors present the most frequently proscribed medications in patients with arterial hypertension, heart failure, coronary artery disease, diabetes, and renal disease. RAAS inhibitors represent the cornerstone of therapy in many conditions, which are at the

same time the important risk factors for adverse outcome in COVID-19 patients. Even though large studies and meta-analyses denied any association between RAAS inhibitors and severity or adverse outcome in COVID-19 patients,<sup>1,8-11</sup> the initial suspicious about RAAS inhibitors is difficult to dismiss.

In the current issue of the Journal, Chen et al represented study that included 2864 COVID-19 patients, among which 57% were hypertensive, and showed that individuals with grade 2 and 3 of hypertension experienced worse outcome than participants with normal blood pressure (BP) or grade 1 of hypertension.<sup>12</sup> Previous studies investigated the influence of hypertension, without separating different subgroups according to the level of BP.<sup>1,8</sup> In the current investigation, hypertensive patients were divided into 3 groups depending of BP level and according to the European guidelines.<sup>13</sup> Interestingly, the majority of patients with grade 1 hypertension (140/90 mm Hg  $\leq$  BP < 160/100 mm Hg) were undiagnosed (63%) before admission for COVID-19. Patients with grade 2 and 3 hypertension (BP  $\geq$  160/100 mm Hg) had significantly higher mortality, prevalence of septic shock, respiratory failure, acute respiratory distress syndrome, mechanical ventilation, and admission in intensive care unit than hypertensive patients with grade 1 hypertension.<sup>12</sup> However, inflammatory markers, as well as incidence of kidney and liver injuries, were more prevalent among patients with grade 2 and 3 hypertension, which might contribute to worse outcome in these patients.<sup>12</sup>

Study demonstrated that patients who used RAAS inhibitors before hospital admission for COVID-19 had significantly better survival than those who did not take any antihypertensive drug or used some other antihypertensive medication.<sup>12</sup> The same results were obtained for hypertensive patients who started taking RAAS inhibitors after admission for COVID-19.<sup>12</sup> After adjustment, subjects with

pre-admission usage of RAAS inhibitors had lower risk of adverse clinical outcomes, including death, acute respiratory distress syndrome, respiratory failure, septic shock, mechanical ventilation, and intensive care unit admission.<sup>12</sup> Interestingly, hypertensive patients with COVID-19 who were treated with RAAS at any point (before or during hospitalization) had significantly lower risk of adverse clinical outcomes than patients who were treated with other antihypertensive medications.<sup>12</sup>

Recent large investigation showed high prevalence of hypertension among COVID-19 patients (55%), but hypertension was not an independent predictor associated with mortality in these patients.<sup>1</sup> Findings showed that diabetes, chronic obstructive pulmonary disease, and chronic kidney disease were independent predictors.<sup>1</sup> Angiotensin-converting enzyme inhibitors (ACEI) were not related with mortality in COVID-19 patients.<sup>1</sup> UK study performed in 1439 COVID-19 patients demonstrated that hypertension, together with male sex, diabetes, greater BMI and smoking, was independently associated with corona virus infection.<sup>7</sup> Use of RAAS inhibitors was not associated with the risk of COVID-19 infection.<sup>7</sup>

Italian study that included 6272 COVID-19 patients revealed the presence of hypertension in 58% of all patients.<sup>8</sup> After multivariable adjustment, RAAS inhibitors did not have significant association with the risk of COVID-19, which was also confirmed for calcium-channel blockers, beta-blockers, and diuretics.<sup>8</sup> However, the authors did not investigate the influence of hypertension and RAAS inhibitors on outcome.<sup>8</sup> Meta-analysis that involved 3936 hypertensive COVID-19 patients showed that RAAS inhibitors were not associated with COVID-19 disease severity, but with lower mortality.<sup>9</sup> Another meta-analysis that included 17 311 COVID-19-infected hypertensive patients showed that RAAS inhibitors were associated with 16% reduced risk of the composite outcome (death, admission to intensive care unit, mechanical ventilation requirement or progression to severe, or critical pneumonia).<sup>10</sup> However, Salah et al did not show any impact of RAAS inhibitors on outcome in 16 101 COVID-19 patients with concomitant hypertension included in this meta-analysis.<sup>11</sup>

The novel finding from the current study was a difference in inflammatory and cardiac biomarkers, parameters of liver, and kidney function between COVID-19 patients with different levels of hypertension.<sup>12</sup> All parameters were significantly higher among patients with hypertension grade 2 and 3 than those with grade 1.<sup>12</sup> Interestingly, inflammatory and cardiac biomarkers (hs-CRP and creatine kinase MB), as well as prevalence of kidney, liver, and myocardial injuries, were higher in grade 2 than in grade 3 hypertension.<sup>12</sup> Nevertheless, there was no difference in coagulation profiles between 3 groups of COVID-19-infected hypertensive patients or between normotensive and hypertensive COVID-19 patients.<sup>12</sup> One should consider the potential influence of these parameters on the interaction between BP and severity/outcome in COVID-19 patients in the current study. Indeed, the multivariable regression analysis demonstrated that age, cardiac injury, acute renal injury, neutrophil, lymphocyte, hs-CRP, chronic obstructive pulmonary disease, and hypertension  $\geq$  grade 2 were independently associated with adverse outcome in hypertensive COVID-19 patients.<sup>12</sup> The importance of

laboratory parameters, and particularly inflammation, cardiac, and renal injuries, has been previously reported as important predictors of adverse outcome in the population of COVID-19 patients.<sup>12</sup>

The interesting point of this study was evaluation of effect of RAAS inhibitors that were used before and after admission. COVID-19 patients who continuously used RAAS, before and after hospital admission, had the best survival and those who used other antihypertensive medications had the worst survival.<sup>12</sup> Furthermore, participants who started usage of RAAS inhibitors after admission had better survival than those who were switched from RAAS inhibitors to other antihypertensive medications.<sup>12</sup> This emphasized the importance of RAAS inhibitors in treatment of hypertension in COVID-19 patients and confirmed the recommendations of various professional societies that RAAS inhibitors should not be excluded from antihypertensive therapy or switched to another medication because it might be related to increased risk of adverse outcome. Additionally, study underlined the importance of BP control in COVID-19 patients because individuals with normal BP and grade 1 hypertension had significantly better outcome than patients with grade 2 and 3 hypertension.<sup>12</sup>

This investigation revealed some limitations that deserve to be mentioned and further discussed. The large percentage of hypertensive patients was undiagnosed and untreated before admission for COVID-19. The prevalence of undiagnosed patients gradually decreased from patients with grade 1 to grade 3 hypertension. Data regarding usage of other antihypertensive classes remained unknown, and their influence on outcome could not be investigated. The authors reported better outcome in COVID-19 patients treated with RAAS inhibitors in comparison to patients treated with all other antihypertensive classes combined into one group. One should emphasize that majority of patients were treated with traditional Chinese medicines, which is the important part of Chinese tradition and lifestyle. Unfortunately, the influence of this therapy is difficult to estimate and this could significantly interfere the relationship between hypertension, antihypertensive medications, and COVID-19 outcome. The authors did not include any parameter of obesity, which is significantly associated with COVID-19 infection and mortality.<sup>14</sup> The lack of body mass index, as the basic parameter of obesity, is very important limitation that did not allow evaluation of overweight and obesity on outcome in hypertensive COVID-19 patients.<sup>12</sup> However, one must acknowledge that obesity in Chinese population is significantly less prevalent than in Western countries.

There is lack of data regarding the percentage of treated hypertension patients before admission.<sup>12</sup> Considering the fact that the percentage of treated hypertensive patients, as well as the distribution of antihypertensive classes, is significantly different in China from Western world, the obtained results may not be applicable to other countries with different lifestyle, diagnostic, and therapeutic approach.

There are several important take-home messages from the current research. First, hypertensive patients, particularly undiagnosed, are very prevalent among COVID-19 subjects. Second, BP control and prompt diagnose of hypertension are necessary in all

COVID-19 patients. Third, antihypertensive therapy should include RAAS inhibitors and should be initiated as soon as hypertension is diagnosed. This investigation does not recommend the exclusion or switching RAAS inhibitors to another antihypertensive medication. Nevertheless, future longitudinal studies are necessary to investigate the effect of hypertension and its treatment on outcome in COVID-19 patients.

#### CONFLICT OF INTEREST

The authors have nothing to disclose.

#### AUTHOR CONTRIBUTIONS

Marijana Tadic contributed to writing the article. Cesare Cuspidi contributed to detailed review with constructive remarks that substantially changed the article.

#### ORCID

Marijana Tadic  <https://orcid.org/0000-0002-6235-5152>

Cesare Cuspidi  <https://orcid.org/0000-0002-7689-478X>

#### REFERENCES

1. Iaccarino G, Grassi G, Borghi C, et al. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of hypertension. *Hypertension*. 2020;76(2):366-372.
2. Tadic M, Cuspidi C, Mancia G, Dell'Oro R, Grassi G. COVID-19, hypertension and cardiovascular diseases: Should we change the therapy? *Pharmacol Res*. 2020;158:104906.
3. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med*. 2020;46:586-590.
4. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with Coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):1-8.
5. ESH Update on COVID-19, 2020. <https://www.eshonline.org/spotlights/eshstatement-on-covid-19-2/>
6. BSH & BCS Joint Statement on ACEi or ARB in Relation to COVID-19, 2020. <https://www.britishcardiosocietysociety.org/news/ACEi-or-ARB-and-COVID-19>
7. Raisi-Estabragh Z, McCracken C, Ardissino M, et al. Renin-angiotensin-aldosterone system blockers are not associated with coronavirus disease 2019 (COVID-19) hospitalization: study of 1,439 UK Biobank Cases. *Front Cardiovasc Med*. 2020;7:138.
8. Mancia G, Rea F, Ludergrani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of covid-19. *N Engl J Med*. 2020;382(25):2431-2440.
9. Guo X, Zhu Y, Hong Y. Decreased mortality of COVID-19 with renin-angiotensin-aldosterone system inhibitors therapy in patients with hypertension: a meta-analysis. *Hypertension*. 2020;76(2):e13-e14.
10. Barochiner J, Martínez R. Use of inhibitors of the renin-angiotensin system in hypertensive patients and COVID-19 severity: A systematic review and meta-analysis [published online ahead of print, 2020 Aug 7]. *J Clin Pharm Ther*. 2020; <https://doi.org/10.1111/jcpt.13246>
11. Salah HM, Calcaterra G, Mehta JL. Renin-angiotensin system blockade and mortality in patients with hypertension and COVID-19 infection [published online ahead of print, 2020 Aug 4]. *J Cardiovasc Pharmacol Ther*. 2020; <https://doi.org/10.1177/1074248420947628>
12. Chen R, Yang J, Gao X, et al. Influence of blood pressure control and application of renin angiotensin-aldosterone system inhibitors on the outcomes in COVID-19 patients with hypertension. *J Clin Hypertens (Greenwich)*. 2020.
13. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018;36:1953-2041.
14. Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization [published online ahead of print, 2020 Aug 12]. *Ann Intern Med*. 2020; <https://doi.org/10.7326/M20-3742>

**How to cite this article:** Tadic M, Cuspidi C. COVID-19, hypertension, and renin-angiotensin-aldosterone system inhibitors: Much ado about nothing or real problem to be solved? *J Clin Hypertens*. 2020;22:1984-1986. <https://doi.org/10.1111/jch.14045>