



LETTER TO THE EDITOR

RAAS inhibitors in COVID-19: They are not all the same!



Inibidores de RAAS na COVID-19: nem todos são iguais!

The review article authored by Gonçalves et al.¹ provided a detailed overview of the physiological mechanisms underlying the renin-angiotensin-aldosterone system (RAAS) and its potential involvement in the pathophysiology of coronavirus disease 2019 (COVID-19). The authors also discussed some of the clinical evidence supporting the use of RAAS inhibitors as a potential treatment for COVID-19, most likely due to their ability to negate the consequences of excessive angiotensin II exposure and RAAS activation in patients with COVID-19. We agree with the authors about the potential benefits of RAAS inhibitors in patients with COVID-19, and we would like to provide additional comments on the use of RAAS inhibitors in this population of patients.

The many systematic reviews and meta-analyses of observational studies investigating previous use of RAAS inhibitors in patients with COVID-19 reported not only the safety of these agents but also mortality benefits in this population of patients, including the one² reported by our team previously, which the authors also cited. Nevertheless, as also stated by the authors in their review article, the findings of the systematic review and meta-analysis of randomized trials³ reported by our team did not replicate the findings in the observational studies, where the use of RAAS inhibitors conferred insignificant mortality benefits in patients with COVID-19.

It is certainly true that the COVID-19 pandemic has created an urgent need for effective treatments. However, we believe that it is still essential for healthcare providers to prioritize evidence-based medicine rather than relying on unproven or potentially harmful therapies. Therefore, we disagree with the authors' suggestions that the urgency of the COVID-19 pandemic justifies the use of treatments that have not been thoroughly tested in randomized controlled trials, arguing that a "shortsighted vision of the concept of evidence-based medicine" may lead to a delay in the utilization of potential solutions, which could cost many lives. Furthermore, while using "yet to be proven" therapies such as RAAS inhibitors may not harm the patients, it can still divert resources and attention away from proven treatments that could save lives.

To date, as cited by the authors, only one single randomized trial⁴ has reported mortality benefits related to the use of RAAS inhibitors in patients with COVID-19. The randomized trial administered telmisartan to the study group instead of losartan, which is more widely investigated in other randomized trials. It is important to take note of the difference between telmisartan and losartan; there is evidence of partial peroxisome proliferator-activated receptor activity-gamma (PPAR γ) activity for the former, while the latter does not have this profile. Previous studies⁵ have discovered the link between the severity of COVID-19 and repression of the PPAR γ complex, suggesting the potential benefits of PPAR γ agonists, including telmisartan, in patients with COVID-19. In addition, the PPAR γ activity of telmisartan could reverse insulin resistance induced by COVID-19, which could mediate disease severity. Furthermore, the aforementioned randomized trial,⁴ which administered telmisartan, utilized a higher-than-normal dosing regimen (80 mg twice daily instead of 80 mg once daily).

Therefore, while we appreciate the efforts of Gonçalves et al.¹ to provide a comprehensive review of the potential role of RAAS inhibitors in the treatment of COVID-19, we disagree with their suggestions that evidence-based medicine should be disregarded in the face of the pandemic. Rather, we believe that future studies should focus on investigating the potential benefits of RAAS inhibitors with PPAR γ agonists, such as telmisartan, valsartan, and lisinopril rather than blindly testing any RAAS inhibitors, or administering RAAS inhibitors with higher-than-normal dosing regimens in patients with COVID-19.

Conflicts of interest

The authors have no conflicts of interest to declare.

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