

EDITORIAL



## COVID-19 and inhibitors of the renin–angiotensin–aldosterone system

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), main cause of coronavirus disease 2019 (COVID-19), uses the aminopeptidase angiotensin-converting enzyme 2 (ACE2) for entry into the host cell. ACE2, part of the renin–angiotensin–aldosterone system (RAAS), is abundantly expressed in heart, lungs, and other tissues. ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARBs) are considered first-choice drugs in hypertension, post–myocardial infarction states, heart failure, and chronic kidney disease. Multicenter study has revealed that hypertension, coronary artery disease, and diabetes are the most frequent comorbidities in severe COVID-19 patients than nonsevere illness [1,2].

Various preclinical and clinical studies have speculated that ACEI and/or ARBs could theoretically worsen outcomes via increasing the ACE2 expression for SARS-CoV-2 entry into the host cell [3,4]. These speculated discoveries have stimulated discussions about whether ACEI and ARBs may potentially treat COVID-19 or, conversely, worsen disease [5,6] while arguments need aroused potential concerns.

This hypothesis gained traction via social media and medical press. For instance, COVID-19 patients with hypertension and diabetes could be at increased risk of severe coronavirus symptoms [7] and are four times as likely to die [8] if they are taking one of these drugs, prior to coronavirus exposure. Anxiety among physicians and patients has been profound because ACEI and ARBs are the most widely prescribed drugs globally for treatment of hypertension, heart disease, and chronic kidney disease, and also increase the expression of ACE2 [9,10]. In this regard, clinicians are weighing the alleged harm of continuing these medications in patients for whom ACE inhibitors and ARBs have known benefit against the harm to their cardiovascular and kidney health associated with discontinuing them.

In this rapidly evolving setting, many observational studies [11–16] with the looming possibility of confounding and largest meta-analysis [17–19] were conducted in different populations with different designs to assess whether ACEI and/or ARBs are indeed harmful in the context of the COVID-19

epidemic. Importantly, message obtained from all of these observational studies and meta-analysis was consistent because none of these provide evidence to support the hypothesis that neither ACEI nor ARBs were associated with the increased risk for SARS-CoV-2 infection, severe illness, or death [11–16]. Secondary analysis involving hypertension patients also did not show harm between these drugs and severe COVID-19. Additionally, several other smaller studies conducted in the United Kingdom and China also revealed same conclusion [20–22].

Unexpectedly, Francisco et al. [11] and Mehra et al. [12] revealed that the use of either ACEI and/or ARBs or statins may be associated with a lower risk of in-hospital death than non-use, but neither of the other studies revealed such effect. Other studies have also suggested that the use of RAAS inhibitors might confer protective effects against complications and death in patients with COVID-19 versus other antihypertensive drugs, although these studies were not restricted to patients with diabetes [21,22]. These outcomes may be due to the absence of a randomized trial and unmeasured confounding, and should not be regarded as evidence to prescribe these drugs in COVID-19 patients.

Taken together, several professional societies and experts have put forward their guidance with one voice that COVID-19 patients should not discontinue ACEI or ARB therapy during the COVID-19 pandemic [23,24] because complications due to the indiscriminate discontinuation of these drugs could have far more serious consequences than many of the surmised adverse effects. In short, we would strongly encourage hypertensive patients to continue with RAAS inhibitor pharmacotherapy during the COVID-19 pandemic.

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## Declaration of interest

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## References

- Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020;323(13):1239–1242.
- South AM, Diz DI, Chappell MCCOVID-19. ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol*. 2020;318(5):H1084–H1090.
- Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *J Travel Med*. 2020;27. DOI:10.1093/jtm/taaa041
- Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.
- Sunden-Cullberg J. Chronic use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers is high among intensive care unit patients with non-COVID-19 sepsis but carries a moderately increased risk of death. *Hypertension*. 2020;75(6):e15–16. (Dallas, Tex.: 1979).
- Blanchard S Medicines taken by 6.6 million people with high blood pressure and diabetes could raise the risk of deadly coronavirus symptoms, scientists claim. *Daily Mail*; 2020 March 13. Available from: <https://www.dailymail.co.uk/news/article-8108735/Medicines-high-blood-pressure-diabetes-worsen-coronavirus-symptoms.html> (Accessed October 16, 2019).
- Kendrick M. Perhaps 4X more likely to die of COVID-19 if take ACE inhibitors (reduce blood pressure). *VitaminDWiki*; 2020 March 22. Available from: <https://vitaminwiki.com/Perhaps+4X+more+likely+to+die+of+COVID-19+if+take+ACE+inhibitors+%28reduce+blood+pressure%29+-+March+2020>
- Soler MJ, Barrios C, Oliva R, et al. Pharmacologic modulation of ACE2 expression. *Curr Hypertens Rep*. 2008;10(5):410.
- Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;111(20):2605–2610.
- de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet*. 2020;395(10238):1705–1714. .
- Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in COVID-19. *N Engl J Med*. 2020;382:e102(1) - e102(7).
- Mancia G, Rea F, Ludergnani M, et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med*. 2020;382:2431–2440.
- Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med*. 2020;382:2441–2448.
- Yang G, Tan Z, Zhou L, et al. Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. *Hypertension*. 2020;76(1):51–58. .
- Conversano A, Melillo F, Napolano A, et al. RAAs inhibitors and outcome in patients with SARS-CoV-2 pneumonia. A case series study. *Hypertension*. 2020;76:e10–e12.
- Baral R, White M, Vassiliou VS. Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. *Curr Atheroscler Rep*. 2020;22(10):1–9.
- 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. *J Clin Pharm Ther*. 2020;45:1244–1252.
- Beressa TB, Sahilu T, Deyno S. Effect of renin-angiotensin-aldosterone system inhibitors on outcomes of COVID-19 patients with hypertension: systematic review and meta-analysis. *medRxiv*. 2020 Aug 12.
- Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect*. 2020;9(1):757–760.
- Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126(12):1671–1681.
- Li J, Wang X, Chen J, et al. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol*. 2020;5(7):825–830.
- Vaduganathan M, Vardeny O, Michel T, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382(17):1653–1659.
- American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19; 2020 March 17. [cited 2020 Aug 12]. Available from: <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>