

VIEWPOINT

COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

What Is the Evidence?

Ankit B. Patel, MD, PhD

Renal Division, Brigham and Women's Hospital, Boston, Massachusetts.

Ashish Verma, MBBS

Renal Division, Brigham and Women's Hospital, Boston, Massachusetts.



Audio

Coronavirus disease 2019 (COVID-19) is a current pandemic infection caused by a positive-sense RNA virus named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The particularly infectious capacity of the virus, along with mortality rates ranging from 1% to above 5%, has raised concerns across the globe.¹ Older patients with comorbid conditions including pulmonary disease, cardiac disease, kidney disease, diabetes, and hypertension have been associated with even higher mortality rates, suggesting particularly susceptible populations.

The increased mortality and morbidity of COVID-19 in patients with hypertension is an association that has been observed in a number of initial epidemiological studies outlining the characteristics of the COVID-19 epidemic in China. Wu et al² found hypertension to have a hazard ratio of 1.70 for death and 1.82 for acute respiratory distress syndrome in 201 patients with COVID-19. Zhou et al³ found hypertension to have a hazard ratio of 3.05 for in-hospital mortality in 191 patients with COVID-19.

Neither of these studies^{2,3} adjusted for confounding variables and thus it remains unclear if this association is related to the pathogenesis of hypertension or another associated comorbidity or treatment. There has been a growing concern that this association with hypertension is confounded by treatment with specific antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

The link with ACEIs and ARBs is because of the known association between angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2. ACE2 has been shown⁴ to be a co-receptor for viral entry for SARS-CoV-2 with increasing evidence that it has a protracted role in the pathogenesis of COVID-19. ACE2 has a broad expression pattern in the human body with strong expression noted in the gastrointestinal system, heart, and kidney with more recent data identifying expression of ACE2 in type II alveolar cells in the lungs. The concern that ACEIs and ARBs affect the severity and mortality of COVID-19 is 2-fold. One suggestion is that ACEIs could directly inhibit ACE2; however, ACE2 functions as a carboxypeptidase and is not inhibited by clinically prescribed ACEIs.⁵

In addition, there is concern that the use of ACEIs and ARBs will increase expression of ACE2 and increase patient susceptibility to viral host cell entry and propagation. There has been considerable evidence in animal models as well as some evidence in humans showing increased expression of ACE2 in the heart, brain, and even in urine after treatment with

ARBs; however, there is limited evidence showing changes in serum or pulmonary ACE2 levels. More relevant, the significance of ACE2 expression on COVID-19 pathogenesis and mortality is not specifically known.

ACE2 primarily acts to counterbalance the effect of ACE. As ACE generates angiotensin II from angiotensin I, ACE2 generates angiotensin (1-7) from angiotensin II which, after binding to the Mas receptor broadly, shifts the balance from vasoconstriction with angiotensin II to vasodilation with Mas receptor activation in the affected vascular bed. The role this vasodilatory effect has in the pathogenesis of COVID-19 is unclear but some animal data suggest a link. ACE2 and angiotensin (1-7) have been found to be protective in a number of different lung injury models.

In an acid lung injury model in mice, ACE2 downregulation by SARS-CoV, the SARS virus responsible for the SARS outbreak in 2003, worsened lung injury that was improved by treatment with ARB. This suggested SARS-CoV exacerbates lung injury by decreasing ACE2 that is reversed by ARB treatment.⁶ Although these preclinical data suggest that increasing ACE2 expression can attenuate SARS-CoV-2-induced lung injury, there is no direct clinical evidence that has proven ACE2 to be an effective treatment for viral-induced lung injury. Of note, a preliminary trial of ACE2 infusion in 10 patients with acute respiratory distress syndrome was completed in humans but was not powered to show efficacy on pulmonary function.⁷ There is even less evidence to demonstrate that treatment with ACEIs or ARBs can decrease severity of pulmonary injury by SARS-CoV-2, though preclinical data suggest a potential mechanism of benefit.

Despite the lack of evidence, there have been advocates for both the use and cessation of ACEIs, ARBs, or both during the treatment for COVID-19 in patients with hypertension. This has prompted some individuals to solicit changes in their hypertensive medications and growing uncertainty from physicians on what should be done. Changes in antihypertensive medications would require patients to visit their pharmacy and possibly obtain blood work, which would increase their exposure and risk of infection. Antihypertensive medication changes between classes additionally require frequent dose adjustment and management of adverse effects and increases the risk of medical errors.

In response, the Council on Hypertension of the European Society of Cardiology made the following statement, "The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive

Corresponding

Author: Ankit B. Patel, MD, PhD, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (apatel38@bwh.harvard.edu).

therapy because there is no clinical or scientific evidence to suggest that treatment with ACEIs or ARBs should be discontinued because of the COVID-19 infection.”⁸ This statement has been followed by similar statements from a number of different societies suggesting patients continue their current hypertensive medication regimen. On March 17, 2020, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology put out a joint statement advocating for patients to continue ACEIs and ARBs as prescribed and that changes in medications in the setting of COVID-19 should be completed only after careful assessment.⁹

There is insufficient clinical or scientific evidence to determine how to appropriately manage hypertension in the setting of COVID-19. As such, this provides an opportunity for the research community to better outline the renin-angiotensin system and specifically ACE2 in the pathogenesis of COVID-19 while clinical data are accumulated to determine if there is a link between the use of ACEIs, ARBs, or both and COVID-19 mortality and morbidity. Until more substantial data are available to guide decision-making one way or the other, physicians should be available to listen to patients' concerns and provide reassuring advice about antihypertensive medications in the era of the COVID-19 pandemic.

ARTICLE INFORMATION

Published Online: March 24, 2020.
doi:10.1001/jama.2020.4812

Conflict of Interest Disclosures: None reported.

REFERENCES

1. 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*. Published online February 24, 2020. doi:10.1001/jama.2020.2648
2. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;S0140-6736(20)30566-3. doi:10.1016/S0140-6736(20)30566-3
4. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7
5. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J*. 2004;383(pt 1):45-51. doi:10.1042/BJ20040634
6. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-879. doi:10.1038/nm1267
7. Khan A, Benthin C, Zeno B, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Crit Care*. 2017;21(1):234.
8. European Society of Cardiology. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. Published March 13, 2020. Accessed March 20, 2020. [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang)
9. American Heart Association. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. Accessed March 20, 2020. https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp