

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Joint HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19

BIYKEM BOZKURT, MD, PhD, President, HFSA, RICHARD KOVACS, MD, FACC, President, ACC, AND BOB HARRINGTON, MD, FAHA, President, AHA

*The following joint statement from the ACC, American Heart Association and Heart Failure Society of America addresses using renin angiotensin aldosterone system (RAAS) antagonists in COVID-19. "The continued highest standard of care for cardiovascular disease patients diagnosed with COVID-19 is top priority, but there are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACE-I or ARB medications," said Richard J. Kovacs, MD, FACC. "We urge urgent, additional research that can guide us to optimal care for the millions of people worldwide with cardiovascular disease and who may contract COVID-19. These recommendations will be adjusted as needed to correspond with the latest research."

Patients with underlying cardiovascular diseases appear to have an increased risk for adverse outcomes with coronavirus disease 2019 (COVID-19). Although the clinical manifestations of COVID-19 are dominated by respiratory symptoms, some patients also may have severe cardiovascular damage. Angiotensin converting enzyme 2 (ACE2) receptors have been shown to be the entry point into human cells for SARS-CoV-2, the virus that causes COVID-19. In a few experimental studies with animal models, both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to upregulate ACE2 expression in the heart. Though these have not been shown in human studies, or in the setting of COVID-19, such potential upregulation of ACE2 by ACE inhibitors or ARBs has resulted in a speculation of potential increased risk for COVID-19 infection in patients with background treatment of these medications.

ACE2 is a homolog of angiotensin converting enzyme (ACE). ACE2 negatively regulates the renin angiotensin system by converting Angiotensin II to vasodilatory Angiotensin 1-7, diminishing and opposing the vasoconstrictor effect of angiotensin II. ACE2, ACE, angiotensin II and other renin angiotensin aldosterone system (RAAS) system interactions are quite complex, and at times, paradoxical. Furthermore, tissue expression of ACE2 differ in heart, kidneys and lungs of healthy patients, cardiovascular disease patients, and coronavirus-infected patients, and its role in the setting of COVID-19 infection in patients with cardiovascular disease is unclear. Furthermore, in experimental studies, both ACE inhibitors and ARBs have been shown to reduce severe lung injury in certain viral pneumonias, and it has been speculated that these agents could be beneficial in COVID-19.

Currently there are no experimental or clinical data demonstrating beneficial or adverse outcomes with background use of ACE inhibitors, ARBs or other RAAS antagonists in COVID-19 or among COVID-19 patients with a history of cardiovascular disease treated with such agents. The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease. In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation. Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.

These theoretical concerns and findings of cardiovascular involvement with COVID-19 deserve much more detailed research, and quickly. As further research and developments related to this issue evolve, we will update these recommendations as needed.

Further reading

- Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020 Feb 28. https://doi.org/10.1056/NEJMoa2002032.
- Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
- Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020;395:565–74. https://doi.org/10.1016/S0140-6736(20)30251-8.
- Hoffmann M, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020 Mar 4. https://doi.org/10.1016/j. cell.2020.02.052. pii: S0092-8674(20)30229-4.
- Ferrario CM, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005 May 24;111(20):2605–10. Epub 2005 May 16.
- Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirusinduced lung injury. Nature Medicine August 2005;11(8):875–9. https://doi.org/10.1038/nm1267. PMID 16007097.
- Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature July 2005;436(7047):112–6.
- Zheng Y, Ma Y, Zhang J, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020. https://doi.org/10.1038/ s41569-020-0360-5.