VIEWPOINT

Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already surpassed the combined mortality inflicted by the severe acute respiratory syndrome (SARS) epidemic of 2002 and 2003 and the Middle East respiratory syndrome (MERS) epidemic of 2013. The pandemic is spreading at an exponential rate, with millions of people across the globe at risk of contracting SARS-CoV-2. Initial reports suggest that hypertension, diabetes, and cardiovascular diseases were the most frequent comorbidities in affected patients, and case fatality rates tended to be high in these individuals. In the largest Chinese study to date,[1] which included 44 672 confirmed cases, preexisting comorbidities that had high mortality rates included cardiovascular disease (10.5%), diabetes (7.3%), and hypertension (6.0%). Patients with such comorbidities are commonly treated with renin angiotensin system blockers, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). However, the use of ACEIs/ARBs in patients with COVID-19 or at risk of COVID-19 infection is currently a subject of intense debate. Below, we outline the mechanisms by which ACEIs/ARBs may be of benefit in those with COVID-19, what the current recommendations are for their use in infected patients, and suggested areas for further research.

SARS-CoV-2 uses the angiotensin-converting enzyme (ACE) 2 receptor for entry into target cells. ACE2 is predominantly expressed by epithelial cells of the lung, intestine, kidney, heart, and blood vessels. Both ACE and ACE2 belong to the ACE family of dipeptidyl carboxydipeptidases and exert distinct physiological functions. ACE cleaves angiotensin I to angiotensin II, which in turn binds and activates angiotensin II receptor type 1. This activation leads to vasoconstrictive, proinflammatory, and pro-oxidative effects. In contrast, ACE2 also degrades angiotensin II to angiotensin 1-7 and angiotensin I to angiotensin 1-9. When angiotensin 1-9 binds to the Mas receptor, it leads to anti-inflammatory, antioxidative, and vasodilatory effects. It is important to note that 2 forms of ACE2 exists: a structural transmembrane protein with extracellular domain that serves as a receptor for spike protein of SARS-CoV-2 and a soluble form that represents the circulating ACE2. Understanding the relationship between SARS-CoV-2 and membranous and soluble ACE2 may help us better understand the adaptive or maladaptive processes operative in COVID-19 infection.

Animal (mice) studies have shown that expression of ACE2 is substantially increased in patients treated with ACEIs/ARBs.[2,3] Similar to these observations, higher urinary ACE2 levels were seen in patients with hypertension treated with the ARB olmesartan. In another study,[4] circulating ACE2 levels were increased in patients with diabetes treated with ACEIs. Based on these observations, some experts have speculated that use of ACEIs/ARBs leading to increased expression of ACE2 could potentially facilitate infection with COVID-19.

A recent study by Liu et al[5] showed that serum angiotensin II levels in patients with COVID-19 pneumonia was significantly higher compared with healthy individuals and were linearly associated with viral load and lung injury. Based on this, it can be postulated that SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity, skewing the ACE/ACE2 balance to a state of heightened angiotensin II activity leading to pulmonary vasoconstriction and inflammatory and oxidative organ damage, which increases the risk for acute lung injury (ALI). Conceivably, renin angiotensin system modulation, either by ACEIs/ARBs or recombinant ACE2, leading to increased expression of ACE2 may help mitigate some of these deleterious effects of angiotensin II. It is also postulated that increased levels of soluble form of ACE2 may act as a competitive interceptor of SARS-CoV-2 and slow virus entry into the cells and protect from lung injury.[6] Presently, to our knowledge, there are no clinical data on the utility of initiating ACEI/ARB therapy in treating patients with COVID-19. There is some evidence that ACEIs/ARBs may be beneficial in patients with ALI or acute respiratory distress syndrome (ARDS). In a meta-analysis of 37 studies,[7] ACEIs and ARBs were associated with reduced risk of pneumonia and pneumonia-related mortality compared with control treatment. In a small double-blind, placebo-controlled randomized clinical trial of 61 patients,[8] those randomized to receive enalaprilat (up to 10 mg intravenously over 24 hours following a regimen based on blood pressure) had numerically higher ventilator-free days (12.3 vs 8.7 days; $P = .18$) and days alive outside the intensive care unit (8.9 vs 4.9 days; $P = .09$) compared with those randomized to placebo. The trial did not complete its intended sample size owing to slow enrollment. In a retrospective cohort study from Korea with 132 patients with ARDS,[9] patients taking ACEIs/ARBs showed better survival compared with controls, albeit several confounding factors could have influenced the results. In a subgroup of patients with severe COVID-19, hyperinflammation and cytokine storm syndrome led to acute respiratory failure from ARDS. What drives such intense hyperinflammation is not yet known; however, through upregulation of ACE2, ACEIs/ARBs can exert anti-inflammatory and antioxidative effects, which may be beneficial in preventing ALI and ARDS.[10] Based on the pathophysiology of SARS-CoV-2 infection and pleiotropic effects of ACEIs/ARBs, these agents may have a

Table. Recommendations on the Use of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in Patients With Coronavirus Disease 2019 (COVID-19)

Professional society; source	Date of release	Key statements
HFSA, ACC, and AHA; 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	March 17, 2020	"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."
ESC Council on Hypertension; https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang	March 13, 2020	"The Council on Hypertension strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection."
ESH; https://www.eshonline.org/spotlights/esh-statement-on-covid-19/	March 12, 2020	• "In stable patients with COVID-19 infections or at risk for COVID-19 infections, treatment with ACEIs and ARBs should be executed according to the recommendations in the 2018 ESC/ESH guidelines." • "The currently available data on COVID-19 infections do not a support a differential use of RAS blockers (ACEI or ARBs) in COVID-19 patients."
Hypertension Canada; https://hypertension.ca/wp-content/uploads/2020/03/2020-30-15-Hypertension-Canada-Statement-on-COVID-19-ACEi-ARB.pdf	March 13, 2020	• "However, there is no evidence that patients with hypertension or those treated with ARB or ACE inhibitor antihypertensive therapy are at higher risk of adverse outcomes from COVID-19 infection." • "We endorse patients with hypertension to continue with their current blood pressure treatment."
The Canadian Cardiovascular Society and the Canadian Heart Failure Society; https://www.ccs.ca/images/Images_2020/CCS_CHFS_statement_regarding_COVID_EN.pdf	March 15, 2020	"The Canadian Cardiovascular Society and the Canadian Heart Failure Society strongly discourage the discontinuation of guideline directed medical therapy (GDMT) involving Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARB) or Angiotensin Receptor Neprilysin Inhibitors (ARNi) in hypertensive or heart failure patients as a result of the COVID-19 pandemic."
International Society of Hypertension; https://ish-world.com/news/a/A-statement-from-the-International-Society-of-Hypertension-on-COVID-19/	March 16, 2020	"[T]here is no good evidence to change the use of ACE-inhibitors or ARBs for the management of raised blood pressure in the context of avoiding or treating COVID-19 infection."
BCS and BSH; https://www.britishcardiovascularsociety.org/news/ACEi-or-ARB-and-COVID-19	March 19, 2020	"[T]he BCS and the BSH…share the view of the European Society of Hypertension and the Renal Association that patients should continue treatment with ACEi and ARB unless specifically advised to stop by their medical team."

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BCS, British Cardiovascular Society; BSH, British Society for Heart Failure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HFSA, Heart Failure Society of America; RAAS, renin angiotensin aldosterone system.

potential role in the management of select patients with severe COVID-19.

Several professional societies have put forward their guidance regarding the use of ACEIs/ARBs in patients with COVID-19. In summary, all guidelines recommend continuing ACEIs/ARBs in patients with COVID-19 unless clinically indicated (**Table**). Furthermore, they do not suggest initiation of ACEIs/ARBs in those without another clinical indication (eg, hypertension, heart failure, diabetes), given the lack of strong evidence showing benefit of these medications in COVID-19. We agree with these recommendations, given the current state of evidence. However, the biological plausibility of salutary effects of ACEIs/ARBs in those with COVID-19 is intriguing. A multicenter, double-blind, placebo-controlled phase 2 randomized clinical trial of starting losartan in patients with COVID-19 in outpatient settings (ClinicalTrials.gov identifier: NCT04311177) and in in-patient settings (ClinicalTrials.gov identifier: NCT04312009) is currently being planned. Accordingly, further epidemiological studies and prospective trials are urgently needed to investigate if use of ACEIs/ARBs can reduce the incidence or mortality associated with COVID-19–associated ALI or ARDS, both in patients with and without additional clinical indications for ACEIs/ARBs.

ARTICLE INFORMATION

Published Online: April 3, 2020. doi:10.1001/jamacardio.2020.1282

Conflict of Interest Disclosures: Dr Maddox has received grants from the National Center for Advancing Translational Sciences, consulting fees from Creative Educational Concepts and Atheneum Partners, and honoraria and personal fees from the University of Utah, NewYork-Presbyterian, Westchester Medical Center, Sentara Heart Hospital, Henry Ford Health System, and University of California, San Diego; is the Executive Director of the Healthcare Innovation Lab at BJC HealthCare/Washington University School of Medicine in St Louis; advises Myia Labs through his institution, which receives equity compensation; and is the director of JF Maddox Foundation. Dr Messerli has received personal fees from Menarini, Medtronic, and Pfizer. No other disclosures were 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. Klimas J, Olvedy M, Ochodnicka-Mackovicova K, et al. Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal Mas receptor in spontaneously hypertensive rats. *J Cell Mol Med*. 2015;19(8):1965-1974. doi:10.1111/jcmm.12573

3. 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. doi:10.1161/CIRCULATIONAHA.104.510461

4. Soro-Paavonen A, Gordin D, Forsblom C, et al; FinnDiane Study Group. Circulating ACE2 activity is

increased in patients with type 1 diabetes and vascular complications. *J Hypertens*. 2012;30(2):375-383. doi:10.1097/HJH.0b013e32834f04b6

5. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63(3):364-374. doi:10.1007/s11427-020-1643-8

6. Batlle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? *Clin Sci (Lond)*. 2020;134(5):543-545. doi:10.1042/CS20200163

7. Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ*. 2012;345:e4260. doi:10.1136/bmj.e4260

8. Wirtz H, Hasenclever D, Schwabe K, et al. ACE inhibitor for lung protection during mechanical ventilation for acute lung injury—results of the double-blind, placebo controlled, randomised ACEmeVENT pilot study. *Am J Respir Crit Care Med*. 2017;195:A2895.

9. Kim J, Choi SM, Lee J, et al. Effect of renin-angiotensin system blockage in patients with acute respiratory distress syndrome: a retrospective case control study. *Korean J Crit Care Med*. 2017;32(2):154-163. doi:10.4266/kjccm.2016.00976

10. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436(7047):112-116. doi:10.1038/nature03712