Cardiovascular Pharmacology in the Time of COVID-19: A Focus on Angiotensin-Converting Enzyme 2

Leo F. Buckley, PharmD, Judy W. M. Cheng, PharmD, MPH,*† and Akshay Desai, MD, MPH‡*

Abstract: Coronavirus disease-2019 (COVID-19) has emerged as a pandemic affecting millions of adults. Severe acute respiratory syndrome coronavirus-2019 (SARS-CoV-2), the causative virus of COVID-19, infects host cells through angiotensin-converting enzyme 2 (ACE2). Preclinical models suggest that ACE2 upregulation confers protective effects in acute lung injury. In addition, renin–angiotensin aldosterone system inhibitors reduce adverse atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease outcomes, but may increase ACE2 levels. We review current knowledge of the role of ACE2 in cardiovascular physiology and SARS-CoV-2 virology, as well as clinical data to inform the management of patients with or at risk for COVID-19 who require renin–angiotensin–aldosterone system inhibitor therapy.

Key Words: angiotensin converting enzyme 2, coronavirus disease-2019, severe acute respiratory syndrome coronavirus-2019, renin–angiotensin–aldosterone system, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonist

(*J Cardiovasc Pharmacol*™ 2020;00:1–4)

The severe acute respiratory syndrome-coronavirus-2 [SARS-CoV-2; previously known as novel coronavirus-2019 (nCoV-19)] causes coronavirus disease-2019 (COVID-19). At the time of publication (April 30, 2020), the COVID-19 pandemic has led to 3,090,445 cases and 217,769 deaths across 209 countries according to World Health Organization data.[1] Older patients with COVID-19, those with underlying pulmonary disease, and those with hypertension, diabetes, or established cardiovascular disease have a worse prognosis than their counterparts without these comorbidities.[2–8]

SARS-CoV-2 infects host cells by binding to human angiotensin-converting enzyme-2 (ACE2),[9–11] a membrane-bound enzyme expressed in the lungs, heart, and kidneys (among many other organs).[12,13] Within the heart, pericytes express the greatest levels of ACE2, although cardiomyocytes and endothelial cells also express ACE2.[14] ACE2 catalyzes the conversion of angiotensin-I and angiotensin-II to angiotensin-(1-9) and angiotensin-(1-7), respectively.[15] Angiotensin-II promotes increased sympathetic tone, sodium and water retention, fibrosis and inflammation through the angiotensin type 1 receptor, whereas angiotensin (1-7) counteracts these effects by binding to the Mas receptor (Fig. 1).[15]

It has been proposed that renin–angiotensin–aldosterone system (RAAS) inhibitors predispose to SARS-CoV-19 infection and worsen outcomes after COVID-19 by upregulating ACE2 expression.[16] Angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor type 1 blockers (ARBs) and mineralocorticoid receptor antagonists increase heart, vascular, and kidney ACE2 expression and activity in animals.[17–21] Chronic treatment with an ACE inhibitor for 6 months was associated with increased plasma angiotensin-(1-7) level and angiotensin-II to angiotensin-(1-7) ratio, whereas no such association was observed in the immediate period after acute ACE inhibitor treatment.[22,23] Spironolactone treatment increased ACE2 activity and mRNA in human monocyte-derived macrophages from patients with heart failure.[21]

Yet others support the hypothesis that RAAS inhibitors and ACE2 counteract angiotensin-II-mediated pulmonary injury in respiratory viral illness.[24,25] These beneficial effects could be attributable to angiotensin-(1-7) binding to the Mas receptor, which promotes anti-inflammatory signaling.[15] In one study of acid aspiration and sepsis lung injury, ACE2 knockout mice and mice pretreated with recombinant human ACE2 had attenuated lung damage.[26] In the same models, treatment of ACE2 knockout mice with an angiotensin type 1 receptor blocker also protected against lung injury.[26] Administration of recombinant human ACE2 beginning one day before respiratory syncytial virus infection decreased pulmonary immune cell infiltration and attenuated histologic lung injury in mice.[27] Recombinant human ACE2 increased angiotensin-(1-7) and decreased angiotensin-II concentrations in patients with acute respiratory distress syndrome, but was stopped early for futility with no significant difference in the partial pressure of arterial oxygen to fraction of inspired oxygen ratio.[28] These data suggest that ACE2 modulation may protect against lung damage from acute respiratory distress syndrome, but do not address whether ACE2 modulation may salvage lung function after the initial lung insult. Moreover, it is unclear whether the hypothetical benefits of ACE2-mediated lung protection outweigh the theorized ACE2-mediated increase in SARS-CoV-2 entry.

Several questions about the relationship between SARS-CoV-2, ACE2, and RAAS inhibitors must be

Received for publication April 2, 2020; accepted April 7, 2020.

From the *Department of Pharmacy Services, Brigham and Women's Hospital, Boston, MA; †Department of Pharmacy Practice, MCPHS University, Boston, MA; and ‡Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.

The authors report no conflicts of interest.

Reprints: Leo F. Buckley, PharmD, Department of Pharmacy Services, Brigham and Women's Hospital, Boston, MA 02115 (e-mail: LFBuckley@bwh.harvard.edu).

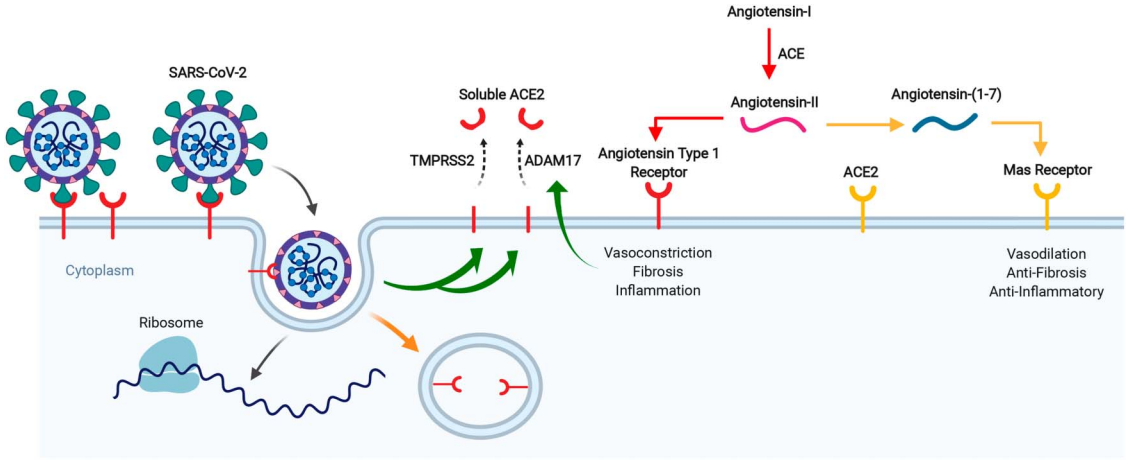

FIGURE 1. Interactions between the renin–angiotensin–aldosterone system and coronavirus Disease-2019. The complex RAAS regulates blood pressure, sodium and water retention and plays an important role in the pathogenesis of cardiovascular disease. Angiotensin-converting enzyme converts angiotensin-I to angiotensin-II, which mediates vasoconstriction, sodium and water retention and inflammation through the angiotensin type 1 receptor (red arrows). Angiotensin converting enzyme-2 (ACE2) counterbalances the angiotensin-II/angiotensin type 1 receptor pathway by converting angiotensin-II to angiotensin-(1-7), which binds the Mas receptor to mediate vasodilation and anti-inflammatory effects (yellow arrows). Importantly, the angiotensin-II/angiotensin type 1 receptor pathway leads to cleavage of membrane-bound ACE2 via ADAMS17 (green arrow). Severe acute respiratory coronavirus-2 (SARS-CoV-2) binds ACE2 and undergoes endocytosis to infect host cells. As a consequence, SARS-CoV-2 infection decreases membrane-bound ACE2 and impairs the beneficial effects of the angiotensin-(1-7)/Mas receptor axis.

answered before drawing conclusions about RAAS inhibitors and COVID-19 and to inform the design of future studies. First, there are no data to support an increase in ACE2 expression on alveolar epithelial cells during RAAS inhibition in animal models. Plasma ACE2 activity may not represent enzymatic activity at the tissue level, because angiotensin-II infusion into mice decreases myocardial ACE2 protein level and activity, but increases plasma ACE2 activity.[29] Furthermore, increased plasma ACE2 levels are associated with an adverse cardiovascular prognosis.[30]

There may be relevant differences between ACE inhibitors and ARBs, and differences within each class, with respect to their effects on circulating and tissue ACE2. In a cross-sectional analysis of adults taking various antihypertensive agents, on-treatment urinary ACE2 concentrations were increased in patients taking olmesartan, but not ACE inhibitors or other ARBs.[31] Conversely, 2 studies demonstrated higher on-treatment circulating levels of angiotensin (1-7) in patients receiving an ACE inhibitor than an ARB.[32,33] In spontaneously hypertensive rats, sacubitril-valsartan restored cardiac ACE2 mRNA expression, whereas valsartan did not.[34] Circulating angiotensin-(1-7) may not reflect ACE2 activity in patients receiving sacubitril-valsartan because neprilysin converts angiotensin-(1-9) and angiotensin-I to angiotensin-(1-7).

ACE2-independent factors also influence SARS-CoV-2 infection and COVID-19 severity. For example, SARS-CoV-2 entry seems to require TMPRSS2, a serine protease expressed on ACE2-expressing cells.[11] Host genetics and comorbidities likely play a role in susceptibility to SARS-CoV-2 infection and outcome, as suggested by the high prevalence of advanced age, and cardiac and pulmonary comorbidities among patients with COVID-19.

Randomized clinical trials provide the only opportunity to answer to questions in a rigorous manner. Two ongoing trials will compare losartan, an ARB, against placebo or an active comparator in hospitalized patients and outpatients with COVID-19 (clinicaltrials.gov NCT04311177, NCT04312009 and NCT04328012). Another clinical trial will compare continuing ACE inhibitor or ARB therapy and switching to an alternative agent in patients with hypertension, but without COVID-19 (NCT04329195). Epidemiologic studies should be performed to estimate the association of RAAS inhibitor use to risk of COVID-19 in patients with hypertension, heart failure or chronic kidney disease.

Withdrawal of RAAS inhibition increases the risk of decompensation in patients with heart failure and adverse physiological changes occur shortly after RAAS inhibitor withdrawal. Plasma angiotensin II, aldosterone, cortisol, and norepinephrine levels increase to pretreatment levels within 4-days of ACE inhibitor cessation in patients with heart failure and New York Heart Association functional class III or IV symptoms.[35] After a mean 15 days without ACE inhibitor therapy, left ventricular end-diastolic and end-systolic volumes return to pretreatment values in patients with heart failure with reduced ejection fraction.[36] Worsening symptoms and decreased exercise tolerance occurs within 4–6 weeks of ACE inhibitor withdrawal.[37] Even among patients with recovery of left ventricular function and reversal of left ventricular remodeling, withdrawal of neurohormonal blockade increases the risk of clinical relapse or subclinical adverse left ventricular remodeling.[38] Discontinuing ACE inhibitor or ARB therapy in patients with progression of chronic kidney disease was associated with an increased risk of cardiovascular disease over a 5-year period.[39]

In March 2020, the American College of Cardiology, American Heart Association, Heart Failure Society of America and European Society of Cardiology issued recommendations against discontinuing RAAS inhibitors during the COVID-19 pandemic.[40,41] Clinicians should consider the risk of COVID-19 exposure when caring for patients with hypertension, heart failure, acute myocardial infarction, and diabetic nephropathy. Clinicians should reinforce preventative measures for those patients who must leave their homes to provide blood samples for electrolyte and renal function monitoring with RAAS inhibitors.[42]

In summary, we have limited preclinical and clinical evidence of the effects of RAAS inhibitors on COVID-19. Clinicians should continue to use RAAS inhibitors during the COVID-19 pandemic according to current standards of care. Scientists must focus on addressing several knowledge gaps to inform clinical management of COVID-19, particularly among those patients with underlying pulmonary and cardiovascular disease.

REFERENCES

1. *Coronavirus Disease*. 2019. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed April 30, 2020.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020;323:1061–1069.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395:507–513.
5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020. doi:10.1016/S2213-2600(20)30079-5 [epub ahead of print].
6. 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;6736:1–9.
7. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. *N Engl J Med.* 2020. doi:10.1056/NEJMoa2004500 [epub ahead of print].
8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA.* 2020. doi:10.1001/jama.2020.4683 [epub ahead of print].
9. Chen Y, Guo Y, Pan Y, et al. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun.* 2020. doi:10.1016/j.bbrc.2020.02.071 [epub ahead of print].
10. Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2. *Science.* 2020. doi:10.1126/science.abb2762.
11. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor article SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181:1–10.
12. Zou X, Chen K, Zou J, et al. The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. *Front Med.* 2020:1–8. doi:10.1007/S11684-020-0754-0.
13. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004;203:631–637.
14. Chen L, Li X, Chen M, et al. The ACE2 expression in human heart indicates New potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res.* 2020;116:1097–1100.
15. Ocaranza MP, Riquelme JA, Garcia L, et al. Counter-regulatory renin-angiotensin system in cardiovascular disease. *Nat Rev Cardiol.* 2020;17:116–129.
16. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir.* 2020;2600:30116.
17. Ferrario CM, Jessup J, Gallagher PE, et al. Effects of renin-angiotensin system blockade on renal angiotensin-(1-7) forming enzymes and receptors. *Kidney Int.* 2005;68:2189–2196.
18. Ishiyama Y, Gallagher PE, Averill DB, et al. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension.* 2004;43:970–976.
19. Igase M, Strawn WB, Gallagher PE, et al. Angiotensin II at1 receptors regulate ACE2 and angiotensin-(1-7) expression in the aorta of spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol.* 2005;289:H1013–H1019.
20. Karram T, Abbasi A, Keidar S, et al. Effects of spironolactone and eprosartan on cardiac remodeling and angiotensin-converting enzyme isoforms in rats with experimental heart failure. *Am J Physiol Heart Circ Physiol.* 2005;289:H1351–H1358.
21. Keidar S, Gamliel-Lazarovich A, Kaplan M, et al. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. *Circ Res.* 2005;97:946–953.
22. Luque M, Martin P, Martell N, et al. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. *J Hypertens.* 1996;14:799–805.
23. Campbell D, Zeitz C, Esler M, et al. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. *J Hypertens.* 2004;22:1971–1976.
24. *Two Generic Drugs Being Tested in U.S. In Race to Find Coronavirus Treatments—Reuters*. Available at: https://www.reuters.com/article/us-health-coronavirus-usa-treatments/two-generic-drugs-being-tested-in-u-s-in-race-to-find-coronavirus-treatments-idUSKBN2161QQ. Accessed March 21, 2020.
25. Vaduganathan M, Vardeny O, Michel T, et al. Renin–angiotensin–aldosterone system inhibitors in patients with covid-19. *N Engl J Med.* 2020;382:1653–1659.
26. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature.* 2005;436:112–116.
27. Gu H, Xie Z, Li T, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. *Sci Rep.* 2016;6:19840.
28. 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;21:234.
29. Patel V, Clarke N, Wang Z, et al. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. *J Mol Cell Cardiol.* 2014;66:167–176.
30. Wang K, Gheblawi M, Oudit GY. Angiotensin converting enzyme 2: a double-edged sword. *Circulation.* 2020.120.047049.
31. Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. *Am J Hypertens.* 2015;28:15–21.
32. Pavo N, Wurm R, Goliasch G, et al. Renin-angiotensin system fingerprints of heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2016;68:2912–2914.
33. Basu R, Poglitsch M, Yogasundaram H, et al. Roles of angiotensin peptides and recombinant human ACE2 in heart failure. *J Am Coll Cardiol.* 2017;69:805–819.
34. Zhao Y, Ma R, Yu X, et al. AHU377+Valsartan (LCZ696) modulates renin–angiotensin system (RAS) in the cardiac of female spontaneously hypertensive rats compared with valsartan. *J Cardiovasc Pharmacol Ther.* 2019;24:450–459.
35. Nicholls MG, Ikram H, Espiner EA, et al. Hemodynamic and hormonal responses during captopril therapy for heart failure: acute, chronic and withdrawal studies. *Am J Cardiol.* 1982;49:1497–1501.
36. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. *Circulation.* 1992;86:431–438.

37. Pflugfelder PW, Baird G, Tonkon MJ, et al. The Quinapril Heart Failure Trial Investigators. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawl in chronic heart failure: a double-blind, placebo-controlled study of quinapril. *J Am Coll Cardiol.* 1993;22:1557–1563.
38. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2018; 393:61–73.
39. Qiao Y, Shin J-I, Chan TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med.* 2020:e200193.
40. *COVID-19 and Cardiology—European Society of Cardiology*. Available at: https://www.escardio.org/Education/COVID-19-and-Cardiology. Accessed March 21, 2020.
41. *Patients Taking ACE-I and ARBs Who Contract COVID-19 Should Continue Treatment, unless Otherwise Advised by Their Physician—Heart Failure Society of America*. Available at: https://www.hfsa.org/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician/. Accessed March 21, 2020.
42. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *JAMA.* 2020. doi:10.1001/jama.2020.4812 [epub ahead of print].