The coronavirus disease 2019 (COVID-19) has been a mild disease in most patients. However, initial reports suggest that hypertension, diabetes, and cardiovascular diseases are common comorbidities in such patients, and mortality tended to be high.\(^4\) Angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) are widely used for hypertension, diabetic nephropathy, heart failure, and postmyocardial infarction. The apprehension of nephrologists, cardiologists, and all physicians on the use of ACE inhibitors/ARBs in the population who are at risk of COVID-19 is valid.

ACE and ACE2, both belonging to dipeptidyl carboxypeptidases family, have different physiological functions. ACE catalyzes angiotensin I to angiotensin II, which binds to angiotensin receptor II type 1 receptor (ATR1). ACE inhibitors block ACE and ARBs block ATR1. ACE2 is predominantly present on the epithelial cells of the lung, kidney, heart, intestine, and blood vessels. ACE2 majorly catalyzes the conversion of angiotensin II to angiotensin 1–7, and its minor action is on conversion of angiotensin 1 to angiotensin 1–9. ACE2 exists in two forms: (1) structural transmembrane protein with extracellular domain which binds to spike protein of SARS-CoV-2 and (2) the soluble form that represents the circulating ACE2 which catalyzes angiotensin II and I. ACE2 physiologically encounters renin-angiotensin-aldosterone system (RAAS) and exerts its vasodilatory effects on the cardiovascular system by deactivating angiotensin II.\(^2\)

Association of coronavirus action with the renin angiotensin system pathway has been streamlined in Figure 1. The SARS-CoV-2 virus enters the lung through ACE 2, replicates, and further downregulates the ACE 2 enzyme (dotted line). The physiological function of ACE 2 is to degrade angiotensin II into angiotensin 1–7. Downregulation of the ACE 2 enzyme by virus leads to an increase in Angiotensin II, which causes systemic injury. The upregulation of RAAS pathway is a hypothesis in SARS-CoV-2 injury. ACEi block ACE enzyme and ARBs block ATR1 thereby potentially blocking this upregulated pathway. RAAS (renin angiotensin aldosterone system) SARS-CoV-2 (Severe acute respiratory syndrome- Coronavirus 2), ACE2 (soluble angiotensin-converting enzyme2), ACEi (Angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptors blockers), ATR1 (angiotensin II receptors)

\[\text{Figure 1: RAAS and COVID-19 cascade. The SARS-Cov-2 virus enters the lung through ACE 2, replicates, and further downregulates the ACE 2 enzyme (dotted line). The physiological function of ACE 2 is to degrade angiotensin II into angiotensin 1–7. Downregulation of the ACE 2 enzyme by virus leads to an increase in Angiotensin II, which causes systemic injury. The upregulation of RAAS pathway is a hypothesis in SARS-CoV-2 injury. ACEi block ACE enzyme and ARBs block ATR1 thereby potentially blocking this upregulated pathway. RAAS (renin angiotensin aldosterone system) SARS-CoV-2 (Severe acute respiratory syndrome- Coronavirus 2), ACE2 (soluble angiotensin-converting enzyme2), ACEi (Angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptors blockers), ATR1 (angiotensin II receptors)\]

The role of ACE2 in contributing to the cardioprotective effect of angiotensin 1–7 was demonstrated by Loot et al.,\(^4\) who showed that long-term infusions of angiotensin 1–7 reversed cardiac dysfunction in animals after myocardial infarction. In addition, Ferrario et al. showed that the ACE inhibitors/ARBs increased cardiac ACE2 gene expression and cardiac ACE2 activity.\(^5,6\) Contrary to it, recent animal studies showed no effect of ACE inhibitors/ARBs over cardiac ACE2 activity.\(^7\)

Likewise, human studies of ACE inhibitors/ARBs have shown conflicting results. ACE2 is always a molecule of research for heart failure from two decades. Increased levels of soluble ACE2 have been observed in heart failure and myocardial infarction.\(^8\) Increased urinary ACE2 levels by olmesartan has revealed additional renoprotective effect of olmesartan in a longitudinal cohort study.\(^9\) On
the contrary, some studies have shown no relation of ACE inhibitors with ACE2 levels.\textsuperscript{[10]}

There is a complex relationship between SARS-CoV-2 virus and ACE inhibitors/ARBs. Theoretically, upregulation of ACE2 level by ACE inhibitors/ARBs aids the entry of virus inside cell and potentially exacerbates injury.\textsuperscript{[11]} In this COVID-19 pandemic, the recent study by Liu et al.\textsuperscript{[12]} showed that angiotensin II levels were higher and linearly associated with viral load and lung injury in COVID-19 pneumonia patients. Conversely, ACE inhibitors/ARBs inhibit production and attachment of angiotensin II, prevent vasoconstrictor effects of angiotensin II, and might be beneficial in these patients.

The COVID-19 and RAAS cascade have been discussed in various large platforms, and to lessen the confusion, American, European, and Canadian guidelines on hypertension and heart failure discourage the discontinuation of ACE inhibitors/ARBs in the population already on these drugs.\textsuperscript{[13]}

The biological plausibility of ACE inhibitors/ARBs with COVID-19 is controversial and unproven. Sudden discontinuation of ACE inhibitors/ARBs in the population already on these drugs would precipitate heart failure and can cause rebound hypertension, thereby leading to increased morbidity and mortality. Thus, the key learning point is to continue these drugs till further evidence.

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Conflicts of interest
There are no conflicts of interest.

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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. 2020 Feb 24. doi: 10.1001/jama.2020.2648. [Epub ahead of print] PubMed PMID:32091533.
2. Danilczyk U, Eriksdotter U, Oudit GY, Penninger JM. Physiological roles of angiotensin-converting enzyme 2. Cell Mol Life Sci 2004;61:2714-9.
3. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.
4. Loot AE, Roks AJ, Henning RH, Tio RA, Suurmeijer AJ, Boomsma F, et al. Angiotensin-(1-7) attenuates the development of heart failure after myocardial infarction in rats. Circulation 2002;105:1548-50.
5. Ferrari CM, Jessup MJ, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605-10.
6. Sukumar V, Veeravedu PT, Gurusamy N, Lakshmanan AP, Yagamagi K, Ma M, et al. Olmesartan attenuates the development of heart failure after experimental autoimmune myocarditis in rats through the modulation of ANG I-7 mas receptor. Mol Cell Endocrinol 2012;351:208-19.
7. Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK, Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in experimental myocardial infarction: Implications for future therapeutic directions. Clin Sci (Lond) 2012;133:649-58.
8. Epelman S, Shrestha K, Troughton RW, Francis GS, Sen S, Klein AL, et al. Soluble angiotensin-converting enzyme 2 in human heart failure: Relation with myocardial function and clinical outcomes. J Card Fail 2009;15:565-71.
9. Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, 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.
10. Campbell DJ, Zeitz CJ, Esler MD, Horowitz JD. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. J Hypertens 2004;22:1971-6.
11. Sommerstein R, Gräni C. Rapid response: Re: Preventing a Covid 19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid 19. BMJ 2020;368:m810.doi: https://doi.org/10.1136/bmj.m810 (Published 28 February 2020).
12. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-74.
13. Bavishi C, Maddux TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin-Angiotensin System Blockers. JAMA Cardiol. 2020 Apr 3. doi: 10.1001/jamacardio.2020.1282. [Epub ahead of print] PubMed PMID: 32242890.

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