Sound Science before Quick Judgement Regarding RAS Blockade in COVID-19

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There has been much speculation in journals as well as social and traditional media about a link between popularly used classes of drugs that inhibit the renin-angiotensin system (RAS) and novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection or coronavirus disease 2019 (COVID-19) disease severity. After examining the available evidence, we advise that inhibitors of the RAS pathway should be continued in patients with COVID-19 who are taking these drugs for evidence-based indications. The putative link between SARS-CoV-2 angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) can be rationalized by the biology of virus entry (3). The spike protein of SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter type II pneumocytes or enterocytes (and likely, other cells). Although ACE2 expression is low in lungs where prolyl oligopeptidase is the main enzyme that metabolizes angiotensin II to angiotensin (1), ACE2 expression is low in lungs where prolyloligopeptidase is the main enzyme that metabolizes angiotensin II to angiotensin (1).

The complex relationship between viral protein binding to ACE2, RAS components, and viral pathogenicity is not fully understood (Figure 1). Evidence also supports the possibility that ACEis and/or ARBs could reduce the severity of COVID-19 infection. It is also not clear if ARBs could exert preferential effects over ACEis. These questions require more rigorous studies. Severe acute respiratory distress syndrome infection is associated with decreased ACE2 expression in rodent models, and treatment with losartan reduces lung injury (10). Taken together, these gaps in knowledge highlight the urgent need to perform careful clinical and basic research on this topic.

ACEi/ARBs are the most widely used classes of antihypertensive agents, with clinically proven benefits in patients with hypertension, diabetes, heart failure, and CKD. Stopping ACEis and ARBs in asymptomatic, stable patients with heart failure, kidney disease, or hypertension will disrupt clinical care, necessitate extra visits, and increase health care utilization, thus disrupting attempts at social distancing. Preclinical studies (some animal models) actually support the idea that ACEi and/or ARB use could be protective in the setting of viral pneumonias, including coronavirus infection, but no such data are available in humans (10,11). Retrospective and observational data are still being analyzed and reported from the earliest affected regions, and new data are likely to emerge over the coming weeks to months (clinicaltrials.gov: NCT04311177 and NCT04312009). The data are coming fast and rapidly changing, and therefore, we have

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created a website, which is being updated in real time to provide a more reliable source of information (http://www.nephjc.com/news/covidace2). We believe that it is important to provide the medical community with updates as they emerge on the use of RAS inhibitors in the context of COVID-19.

We strongly suggest to the scientific community to withhold judgement on this issue due to an incomplete understanding of the risk or benefit of these medications. We believe that there is equipoise in this matter, and the only way to establish an evidence base for these decisions is to study these questions in clinical trials or thorough analysis of observational data using appropriate methodology when a trial is not ethical. Randomized clinical trials are in the planning stages at the University of Minnesota. Only through systematic and well planned and executed basic and clinical studies will we answer the scientific and clinical questions above. After reviewing the available data, our conclusion is that the link between hypertension and/or the use of RAS inhibitors (ACEis or ARBs) in patients with SARS-CoV-2 infection and COVID-19 outcomes has not been firmly established. There is no definitive evidence linking RAS inhibition with increased ACE2 expression and subsequent enhanced SARS-CoV-2 infection. Furthermore, there is preclinical data suggesting a potential benefit with RAS inhibition in SARS-CoV-1. Our recommendation is for patients to continue the use of prescribed RAS inhibitors unless there exists an evidence-based indication to discontinue these important life-saving medications.

Acknowledgments
This work was supported by NephJC, a not-for-profit organization that supports the work of NephJC and the Nephrology Social Media Collective. Dr. Hiremath, Dr. Rheault, and Dr. Sparks are on the board of directors of NephJC. They receive no monetary support. The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or CJASN. Responsibility for the information and views expressed therein lies entirely with the author(s).

Disclosures
Dr. Batlle reports nonfinancial support from Angiotensin Therapeutics Inc. In addition, Dr. Batlle is a coinventor of the patent “Active Low Molecular Weight Variants of ACE2” and has also submitted a patent on the potential use of novel angiotensin-converting enzyme 2 proteins for coronavirus infection (issued). Dr. Bhalla reports ownership stock in Pyramex, consultant fees from Maxim Integrated, and service on scientific advisory boards for Relypsa and is a coinvestigator for the Controlling and Lowering Blood Pressure With the MobiusHD-2 trial sponsored by Vascular Dynamics, Inc. outside the submitted work. Dr. Rheault reports other from Retrophin, other from Reata, other from Advicenne, and other from Genentech. Dr. Soler reports personal fees from NovoNordisk, personal fees from Janssen, nonfinancial support from

Figure 1. Potential effect of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced alterations to renin-angiotensin system pathways. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) via its spike protein and induces internalization and shedding of ACE2, leading to increased angiotensin II (Ang II) and decreased angiotensin (1–7) [Ang-(1–7)] with net increase in inflammation and fibrosis (red) relative to anti-inflammatory and antifibrotic actions (blue). In the left panel, there is no ACEi or ARB; in the right panel, ACEi and/or ARB treatment could diminish effects of Ang II and increase Ang-(1–7) effects, leading to attenuated inflammation and fibrosis. The dashed inset in the right panel represents a theoretical increase in cell membrane expression of ACE2 with ACEi and/or ARB use. AT1R, type 1 angiotensin receptor; AT2R, type 2 angiotensin receptor; MasR, Mas receptor.
Boehringer, nonfinancial support from Eli Lilly, personal fees from AstraZeneca, and nonfinancial support from Esteve during the conduct of the study. Dr. Welling reports the following disclosures unrelated to the content of the study: American Journal of Physiology scientific advisor/membership and finance committee chair. Dr. Burrell, Dr. Byrd, Dr. Cohen, Dr. Hiremath, Dr. Luther, Dr. South, Dr. Sparks, Dr. Swaminathan, and Dr. Tomlinson have nothing to disclose.

**Funding**

Dr. Battle reports grants from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) outside of the submitted work. Dr. Byrd reports grants from National Institutes of Health (NIH) and grants from Apple outside the submitted work. Dr. South reports grants from NIH, National Heart, Lung, and Blood Institute (NHLBI); other from NIH, National Heart, Lung, and Blood Institute NHLBI Loan Repayment Program (LRP); and grants from NIH, NIDDK outside of the submitted work. Dr. Sparks received a grant from Renal Research Institute outside of submitted work. Dr. Welling reports the following funding outside of the submitted work: NIDDK and Fondation Leducq. Dr. Swaminathan is supported by NIDDK grant 1RO1DK103043-01A1. Dr. Luther is supported by NIDDK grants DK117875, DK115392, and DK096994, and American Heart Association grants 16GRNT3170033 and 17SFRN33520017 outside of the submitted work. Dr. Bhalla is supported by NIDDK grants DK110385-01A1 and DK079307, and a US-Israel Binational Science Foundation grant outside of the submitted work. Dr. Cohen is supported by NHLBI grant K23-HL133843 outside of the submitted work.

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Published online ahead of print. Publication date available at www.cjasn.org.