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

Matthew A. Sparks[1], *Andrew South*[2], *Paul Welling*[3], *J. Matt Luther*[4], *Jordana Cohen*[5], *James Brian Byrd*[6], *Louise M. Burrell*[7], *Daniel Batlle*[8], *Laurie Tomlinson*[9], *Vivek Bhalla*[10], *Michelle N. Rheault*[11], *María José Soler*[12], *Sundar Swaminathan*[13] and *Swapnil Hiremath*[14]

CJASN 15: 714–716, 2020. doi: https://doi.org/10.2215/CJN.03530320

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Matthew A. Sparks, Division of Nephrology, Duke University Medical Center, MSRB2, Room 1013, Durham, NC 27710. Email: matthew.sparks@duke.edu

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 (1,2). 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 prolyloligopeptidase is the main enzyme that metabolizes angiotensin II to angiotensin (1–7), the presence of ACE2 protein in type II pneumocytes seems important for virus entry (4) (Figure 1). Many concerned physicians and patients are conflicted about how to address ACEis/ARBs *vis-à-vis* COVID-19. As concerned physicians and scientists working in this area, we summarize the evidence and call for greater understanding and systematic data gathering rather than hasty decision making on the basis of incomplete or inaccurate information or unjustified extrapolations. The current scientific and clinical questions are as follows. Is there a link between hypertension and increased risk of viral infection in humans? Are patients on ACEis/ARBs at increased risk of infection or severity of disease? Does modulation of these drugs (starting, stopping, or continuing) lead to better or worse outcomes in COVID-19?

A hypothesized relationship between hypertension and COVID-19 mortality is not supported at this time by robust data. It is known that increasing age strongly correlates with hypertension and has been associated with higher mortality from COVID-19. However, none of the reports have adjusted for age or provided age-stratified data for the hypertension and mortality association to understand if this is a robust finding (5).

Some animal studies have demonstrated increased cardiac ACE2 mRNA levels (among other organs, such as kidney vasculature) and activity after ACEi or ARB therapy (6,7). However, others have not shown enhanced ACE2 levels after ACEi or ARB treatment (8). Moreover, data in humans have not consistently shown increased ACE2 levels, and good-quality data are lacking because full-length ACE2 anchored to cells is not easily measurable (9). Moreover, the clinical significance of this biology in COVID-19 infection is uncertain. Thus, these data do not provide sufficient evidence linking RAS inhibitors to upregulation of ACE2 in humans and subsequent SARS-CoV-2 infection.

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

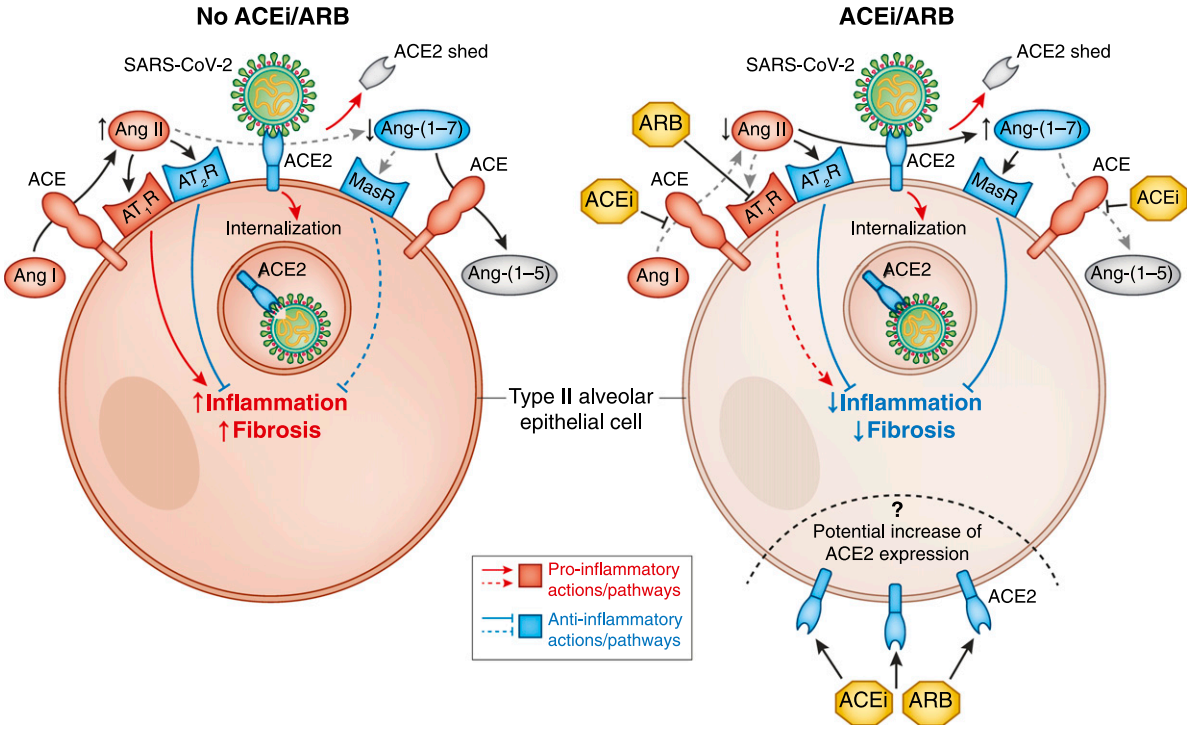

Figure 1. | Potential effect of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced alterations to renin-angiotensin system pathways. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) 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. AT_1R, type 1 angiotensin receptor; AT_2R, type 2 angiotensin receptor; MasR, Mas receptor.

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).

Dr. Batlle 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. Rheault reports grants from Goldfinch Bio 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 16GRNT31170033 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.

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 Pyrames, consultant fees from Maxim Integrated, and service on scientific advisory boards for Relypsa and is a cosite investigator 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 Novo-Nordisk, personal fees from Janssen, nonfinancial support from 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.

References

1. Sommerstein R: Rapid response: Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk factor for fatal COVID-19. *BMJ* 368: m810, 2020
2. Fang L, Karakiulakis G, Roth M: Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? [published online ahead of print March 11, 2020]. *Lancet Respir Med*
3. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M: Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 426: 450–454, 2003
4. Serfozo P, Wysocki J, Gulua G, Schulze A, Ye M, Liu P, Jin J, Bader M, Myöhänen T, García-Horsman JA, Batlle D: Ang II (angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (prolyloligopeptidase)-dependent and ACE2 (angiotensin-converting enzyme 2)-independent. *Hypertension* 75: 173–182, 2020
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study [published online ahead of print March 11, 2020]. *Lancet*
6. Ocaranza MP, Godoy I, Jalil JE, Varas M, Collantes P, Pinto M, Roman M, Ramirez C, Copaja M, Diaz-Araya G, Castro P, Lavandero S: Enalapril attenuates downregulation of Angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. *Hypertension* 48: 572–578, 2006
7. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE: Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 111: 2605–2610, 2005
8. Burrell LM, Risvanis J, Kubota E, Dean RG, MacDonald PS, Lu S, Tikellis C, Grant SL, Lew RA, Smith AI, Cooper ME, Johnston CI: Myocardial infarction increases ACE2 expression in rat and humans. *Eur Heart J* 26: 369–375, 2005
9. Ramchand J, Patel SK, Srivastava PM, Farouque O, Burrell LM: Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. *PLoS One* 13: e0198144, 2018
10. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM: A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 11: 875–879, 2005
11. Yang P, Gu H, Zhao Z, Wang W, Cao B, Lai C, Yang X, Zhang L, Duan Y, Zhang S, Chen W, Zhen W, Cai M, Penninger JM, Jiang C, Wang X: Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci Rep* 4: 7027, 2014

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

AFFILIATIONS

[1]Division of Nephrology, Department of Medicine, Duke University School of Medicine and Durham VA Health System, Durham, North Carolina
[2]Section of Nephrology, Department of Pediatrics, Department of Epidemiology & Prevention, Division of Public Health Sciences, Department of Surgery-Hypertension & Vascular Research, Wake Forest School of Medicine, Winston-Salem, North Carolina
[3]Joseph S and Esther Handler Professor, Departments of Medicine (Nephrology) and Physiology, Johns Hopkins School of Medicine, Baltimore, Maryland
[4]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Vanderbilt Hypertension Center, Nashville, Tennessee
[5]Renal-Electrolyte and Hypertension Division, Department of Medicine and Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[6]Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, Michigan
[7]Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Victoria, Australia
[8]Northwestern University Feinberg School of Medicine, Department of Medicine, Division of Nephrology, Chicago, Illinois
[9]London School of Hygiene and Tropical Medicine, London, United Kingdom
[10]Stanford Hypertension Center, Stanford University School of Medicine, Stanford, California
[11]Division of Pediatric Nephrology, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota
[12]Division of Nephrology, Hospital Universitari Vall d'Hebron, Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain
[13]Division of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, University of Virginia, Charlottesville, Virginia
[14]Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Canada