Perspective

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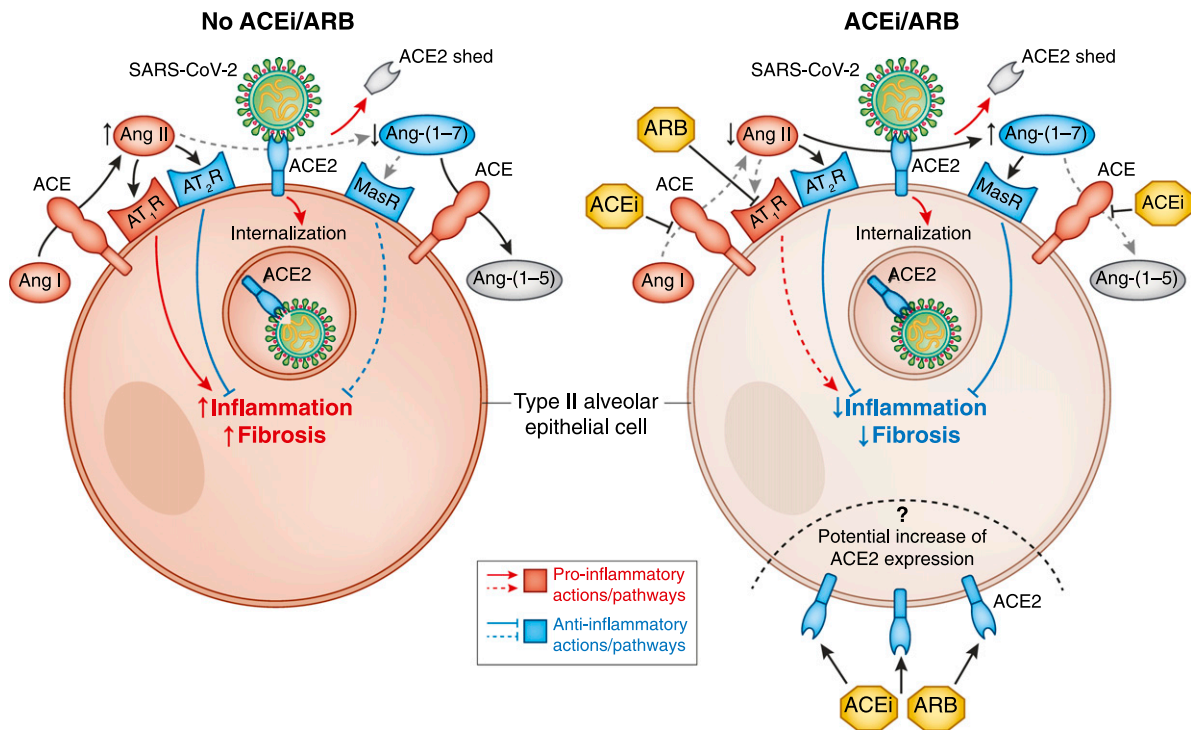
Figure 1. | **Potential effect of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced alterations to renin-angiotensin system pathways.** SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2)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

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