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EDITORIAL COMMENT

Renin-Angiotensin System Blockade in COVID-19



Good, Bad, or Indifferent?*

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Based on the observation that patients with hypertension appear to have adverse outcomes with coronavirus disease-2019 (COVID-19) infection and the discovery that the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus, which causes COVID-19, uses a component of the renin-angiotensin system (RAS) as its route of cellular infection, there has been tremendous interest in determining the net clinical effect of RAS-blocking agents in COVID-19 patients. In just a few weeks, the cardiology community has gone from concern about using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with COVID-19 infection to optimism about potential benefits of these medications over and above their usual effects on blood pressure and cardiovascular (CV) structure and function. Explaining this transition requires a comprehensive understanding of how the SARS-CoV-2 virus interacts with components of the RAS.

As seen in [Figure 1](#), similar to what was observed with the related SARS-CoV-1 virus, the currently circulating SARS-CoV-2 virus gains entry into cells through binding of its spike protein to the enzyme ACE2. ACE2 is a mostly membrane-bound carboxypeptidase with approximately 40% homology to the

more commonly appreciated circulating ACE enzyme. ACE2 is primarily responsible for degrading angiotensin II into angiotensin 1 to 7. The ACE2 enzyme is found in lung alveolar tissue, nasopharyngeal tissue, enterocytes, nervous tissue, vascular tissue, and the kidney (1)—all points of potential viral entry for SARS-CoV-2.

The initial thinking regarding RAS-blocking agents and COVID-19 was that these drugs could have adverse effects due to up-regulation of ACE2 expression on cell surfaces leading to a greater number of potential sites of viral entry. Although ACE2 up-regulation has been seen with RAS-blocking drugs in some animal models, reassuringly, in humans there is little evidence that these medications increase ACE2 levels, at least in circulation (2,3).

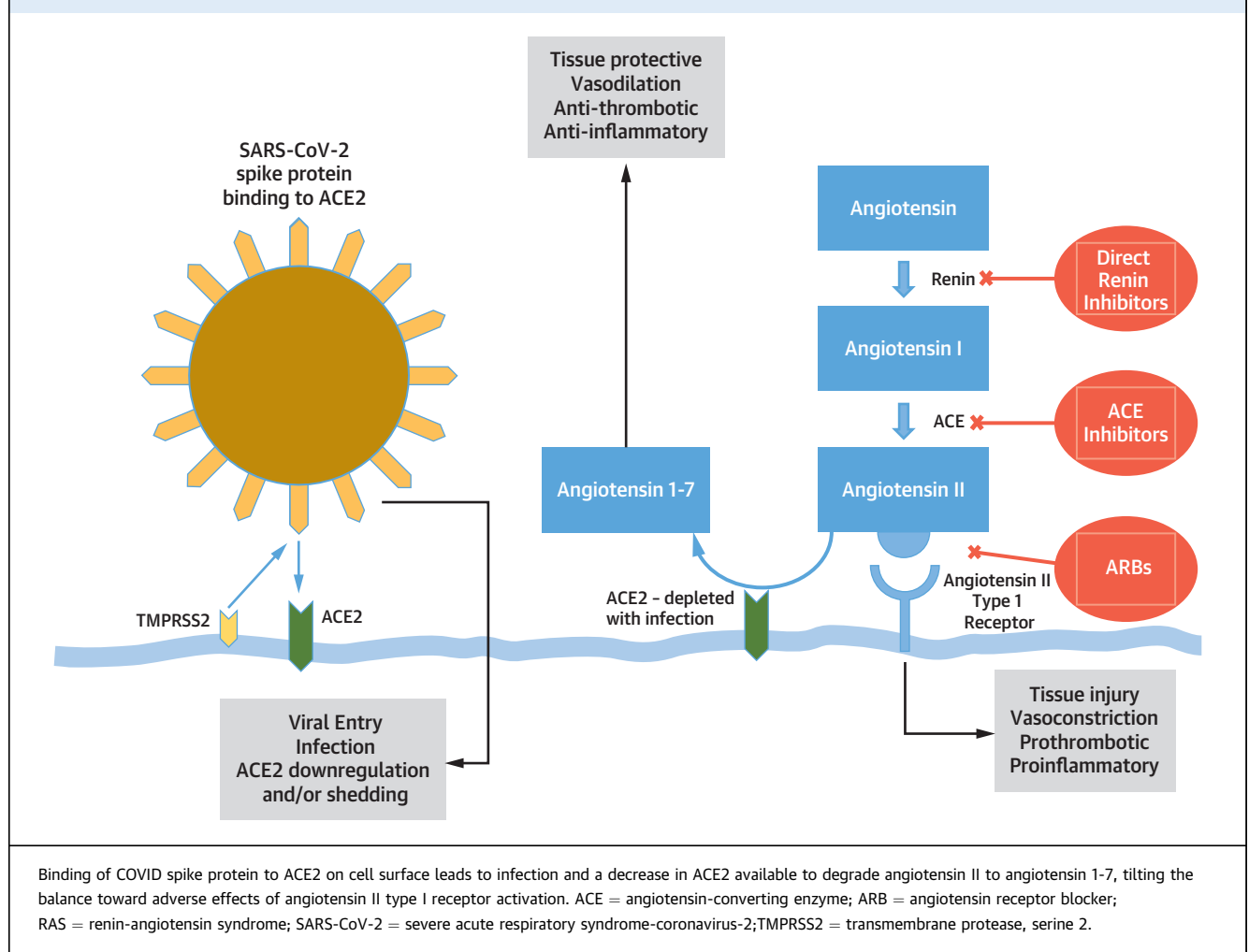
As our understanding of how SARS-CoV-2 interacts with the RAS has grown, the theory that RAS-blocking agents may actually be beneficial has emerged. This hypothesis posits that COVID infection leads to imbalance between the potentially deleterious effects of angiotensin (AT) II interacting with the AT1 receptor and the potentially beneficial effects of the RAS that are primarily mediated through Ang 1 to 7. It appears that COVID infection leads to a decrease in the amount of available ACE2 on the tissue surface. With less ACE2 available to degrade ATII, COVID-19 infection tilts the balance of power in favor of ATII-mediated vasoconstriction, cytotoxicity, and inflammation—all of which may lead to worse outcomes in COVID-19 patients. According to this model, use of RAS-blocking agents can decrease the deleterious effects of angiotensin II and restore balance to the RAS.

Leaving the bench and heading to the bedside, we need to look for evidence as to which of these competing effects best fits the available data. Observational studies have consistently shown that patients with hypertension or cardiovascular disease are more likely to have severe outcomes with COVID-19

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FIGURE 1 Interaction of COVID Infection and RAS

infection (2). Although there are several potential explanations, this finding could be due to higher activation of the RAS at baseline in these patients. Overall, there is little evidence to suggest that use of RAS-blocking agents, either ACE inhibitors or ARBs, leads to adverse clinical outcomes. Observational studies from Asia, Europe, and New York demonstrate that patients on RAS-blocking agents appear to have no greater risk of infection, hospitalization, severe illness, or death compared with those on other antihypertensive agents or no antihypertensive medications at all (4-8).

Of course, observational studies may be subject to important confounding variables that can be difficult to identify. Full determination of the overall net clinical benefit or harm of RAS-blocking agents in COVID-19 requires carefully designed prospective randomized controlled clinical trials. In this light, the accompanying interim report from the RASTAVI (Renin-Angiotensin System Blockade Benefits in

Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation) trial offers a unique opportunity (9). Although patients in RAS-TAVI were recruited to answer a completely different question—the effect of ACE inhibitor (ramipril) versus placebo in patients undergoing transcatheter aortic valve implantation—the fact that this trial was conducted in Spain in the midst of the pandemic allowed the authors to examine the placebo-controlled effects of ACE inhibition on COVID-19 patients.

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As Amat-Santos et al. (8) concede in their paper in this issue of the *Journal*, the number of patients with identified COVID-19 was small, and testing was only performed in symptomatic patients based on clinical indications as interpreted by treating clinicians. It would have been ideal to screen the entire RASTAVI population for evidence of infection, but this was likely impractical at the time of this interim analysis.

These shortcomings aside, it was encouraging to see that randomization to ramipril appears to have had no effect on susceptibility to infection or mortality, and this represents the only results from a randomized population we have available at the present time.

Looking to the future, we now have a number of ongoing or planned prospective randomized clinical trials of ARB use in COVID-19 patients. One effort is examining losartan versus placebo in 2 groups of COVID patients in the United States: those who do and do not require hospitalization (10). A second group of researchers in South America are launching a study of telmisartan versus standard of care in COVID-19 patients (11).

Another interesting potential area of investigation is whether or not polymorphisms in ACE2 or other associated peptides may be partially responsible for the variable severity of clinical presentation and course with COVID-19 infection (11). No significant association was identified between variants of ACE2 or TMPRSS2 (which primes the spike protein for binding with ACE2) in a recently published Italian cohort (12), but further research is clearly needed.

Based on the limited data available to date, including this report from RASTAVI, the Heart Failure Society of America/American College of Cardiology/

American Heart Association statement remains as valid today as when it was published in the early stages of the pandemic: “recommend continuation of RAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease” (13). We eagerly await the results of the planned randomized clinical trials of ARBs in COVID patients. Given the pathophysiological complexity of COVID-19 infection, it seems unlikely to me that RAS blockade will be a “silver bullet” that has a dramatically beneficial effect on clinical outcomes. But, unlike most other therapies being evaluated for this pandemic, ARBs are widely available, inexpensive, safe, and well-tolerated (14). Even if they are shown to have only a modest clinical benefit, the overall impact could be substantial. This unfolding story certainly highlights that the RAS is much more complicated than the simple schema that we outline for our first-year medical students, and understanding it is integral not just to cardiovascular disease but other fundamental aspects of human physiology.

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