Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and COVID-19: Demonstrating the Actionability of Real-World Evidence

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Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are used by many millions of people[1] for highly prevalent conditions including hypertension, heart failure, and diabetes. It was therefore quite concerning when mechanistic considerations regarding the role of angiotensin-converting enzyme 2 (ACE2) in the pathogenesis of SARS-CoV-2[2] led to the hypotheses that these widely used, lifesaving drugs might both increase the risk of developing COVID-19 and worsen outcomes in people who developed COVID-19. These hypotheses were especially concerning because the aforementioned therapeutic indications for using ACEIs and ARBs themselves are among the most prevalent comorbidities in patients who develop COVID-19, and are associated with worse outcomes of COVID-19.[3,4] Based on these mechanistic considerations, some authors went so far as to recommend that ACEIs and ARBs be discontinued in patients with active COVID-19 infection, and that their discontinuation be considered in some people who are at high risk for developing COVID-19.[5,6] It is therefore reassuring that the recent population-based cohort study conducted by Dublin *et al.*[7] found that ACEIs and ARBs do not appear to increase the risk of developing COVID-19 or to increase the risk of hospitalization in those who develop COVID-19, and that there is no dose–response relationship between ACEI/ARB use and risk of developing COVID-19 or of being hospitalized once a person has developed COVID-19.

The study by Dublin *et al.* has numerous strengths that bolster the confidence that we can have in its conclusions. These strengths include a methodologically rigorous, clinically informed design that adjusted for a broad set of potential confounders, including diseases, dispensed prescription drugs, and several potentially important factors that are often unavailable in administrative databases such as race/ethnicity, tobacco use, and body mass index. Indeed, the study demonstrated the importance of adjusting for such factors, since ACEI/ARB use was associated with adverse outcomes in unadjusted but not in adjusted analyses, similar to prior studies evaluating this question.[8] This suggests that a less rigorous study that controlled for a narrower set of confounders might have yielded spurious associations between ACEIs/ARBs and adverse outcomes. The study was also large enough to produce reasonably narrow 95% confidence intervals that suggest that the results are statistically incompatible with even moderately strong associations. The broad inclusion criteria for the primary analyses helped to reduce the risk for selection and collider bias. Secondary analyses were restricted to patients with indications for ACEI/ARB use to help to address confounding by indication. Finally, the study examined dose–response relationships and associations with comparator antihypertensive medications (examined as control exposures) that would have helped to contextualize any positive associations that may have emerged between ACEIs/ARBs and adverse outcomes.

The results of Dublin *et al.*'s paper agree with and extend those of prior studies, conducted in Europe, that found no association between ACEI/ARB use and the development and severity of COVID-19.[9–11] Prior observational studies evaluating the association between ACEI/ARB use and the development and severity of COVID-19 had several potential weaknesses such as collider bias, the potential for misclassification of ACEI/ARB use in the absence of dispensing data, and lack of information on ACEI/ARB dose. In addressing several of the limitations of prior studies, Dublin *et al.*'s findings strengthen the existing evidence supporting current recommendations[12] to continue indicated ACEI/ARB therapy during the pandemic, even in people who develop COVID-19.

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There are potential physiologic explanations for the lack of association of ACEI/ARB use with development and severity of COVID-19 observed in the current study. Early in the pandemic, ACE2 was identified as the binding site for SARS-CoV-2. ACE2 is an important counterregulatory enzyme in the renin–angiotensin system that typically promotes vasodilation and reduces inflammation and fibrosis.[12] Evidence from prior to the pandemic suggested that ACEIs and ARBs increase ACE2 expression and activity. This upregulation of ACE2 was hypothesized to increase the risk of development and severity of COVID-19 due to an increase in the number of binding sites for SARS-CoV-2.[5,6] However, experimental data from SARS-CoV-1 suggested that an increase in ACE2 may be protective against acute lung injury due to the downstream anti-inflammatory and antifibrotic effects of ACE2.[13] These data prompted the initiation of several randomized controlled trials that are currently underway evaluating ACEIs, ARBs, and recombinant ACE2 as potential therapies for COVID-19. Furthermore, more recent data from studies in mice and humans suggest no association of ACEI or ARB use with ACE2 expression in the lung and kidneys[14] nor with circulating ACE2 levels.[15] Thus, current mechanistic evidence suggests that ACEIs and ARBs may not have any effect on the pathogenesis of COVID-19, which supports emerging population-level evidence, including the current study.

The evolving COVID-19 pandemic is merely the latest illustration of the need to combine rigorous epidemiologic methods with real-world healthcare data to address important clinical questions that cannot be feasibly addressed in randomized trials. However, in the context of the ongoing discussions on the utility and actionability of real-world evidence,[16] a few authors have questioned the validity of all nonrandomized research on the health effects of drugs and other healthcare interventions as at best hypothesis generating.[17] However, it is obvious that given, for example, the massive scale of the potential health consequences of the hypothesized adverse effect of ACEIs/ARBs on COVID-19 incidence and outcomes, and the implausibility of a randomized trial that would assign thousands community-dwelling people to continue or discontinue their ACEI/ARB to examine effects of COVID-19 incidence and outcomes, rigorous nonrandomized evidence is both crucial and actionable. Admittedly, given the potential for confounding that accompanies nonrandomized studies, multiple such studies—preferably performed in different populations and relying on different sets of assumptions—are highly desirable. Luckily, given the widespread availability of healthcare data, multiple studies on important topics like this are highly feasible, permitting examination of the consistency of findings.

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