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EDITORIAL COMMENTARY

Angiotensin-converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use and COVID-19: Time to Change Practice or Keep Gathering Data?

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To the Editor—Since the emergence of the coronavirus disease 2019 (COVID-19) pandemic, there has been intensive research dedicated to elucidating the pathogenesis of the virus as well as the risk factors that portend poor outcomes in this disease. Case series from early on in the pandemic showed that several risk factors including diabetes, coronary artery disease, and hypertension were more common in those suffering with severe forms of COVID-19 [1]. It is now known that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, enters human cells via binding of the viral spike protein to the angiotensin-converting enzyme 2 (ACE2) [2]. This mechanism of entry, in combination with the findings of the previously mentioned risk factors, raised concerns that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) could increase both the susceptibility and severity of SARS-CoV-2 infection. Soon thereafter, members of both the healthcare community and the medical press began to call for the discontinuation of these drug classes both preemptively and in the setting of COVID-19 infection. While this mechanism of increased susceptibility to COVID-19 was biologically plausible, many jumped to conclusions about discontinuing these agents prior to the performance of rigorous human studies.

Multiple studies since the beginning of the outbreak have returned with conflicting results of the effects of ACEI or ARB use on outcomes with COVID-19. This particular conundrum has come to the light of science in a short period of time with significant implications for public health. Inevitably, the studies have relied on available data that have been retrospective and with marked limitations. A large study out of New York City of >5800 patients showed no positive association of ACEIs and ARBs for either a positive test result or severe illness [3]. An international, multicenter study that included electronic records from 169 hospitals in 11 countries on 3 continents again confirmed that advanced age (>65 years), heart failure, coronary disease, and hypertension (among other factors) increased risk for in-hospital mortality with COVID-19, but ACEI/ARB therapy showed no harm [4]. It is important to note, however, that the aforementioned study was recently retracted due to concerns about the quality of the data. In contrast to these findings, early studies out of China suggested that ARB therapy may improve clinical outcomes in COVID-19 infection [5, 6]. A separate study out of the United Kingdom also suggested that there may be a trend toward beneficial effects of ACEI/ARB therapy [7].

The study by Oussalah and colleagues in this issue of *Clinical Infectious Diseases* is unique in that it focuses on patients with "severe COVID" disease and found that chronic ACEI and ARB use was associated with an increased risk of acute kidney injury, as well as a signal for a dosage effect. The authors also showed a potential interaction between ACEI/ARB use with the occurrence of acute respiratory failure. While this was a well-designed retrospective cohort study, it faces all the limitations that challenged the previous observational studies that were mentioned. Also, the study was limited by a relatively small sample size, and this may in part be due to the focus on the "severe COVID" disease population. Nevertheless, the study adds high-quality retrospective data and, importantly, provides an elegant analysis that identified potential groups of patients who may be at higher risk of poor outcomes in the setting of COVID-19. It is evident that randomized controlled trials must be conducted before we can establish a cause-and-effect relationship.

At this relatively early stage of the pandemic, the accumulation of data, though substantial, has yet to change practice recommendations [8, 9]. One might conclude that the currently

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limited knowledge in the matter has provided more questions than answers. Nevertheless, studies like the one commented here are worthy investments as they enhance medical understanding of the disease, which may impact clinical decision-making in the near future.

Note

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