Editor's Note

Renin-Angiotensin-Aldosterone Inhibitors and Susceptibility to and Severity of COVID-19

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The biological mechanisms by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus that causes coronavirus disease 2019 (COVID-19), enters human cells have been identified in detail.[1] The key viral protein involved in cell entry is the spike (S) protein located on the surface of the virus particle. Two host-cell proteins, angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine S2 (TMPRSS2), are also critical for cell entry. The viral S protein binds to ACE2, which serves as the cell membrane receptor for SARS-CoV-2, but only after the S protein has been "primed" by the action of the serine protease TMPRSS2. Thus, the host enzymes, ACE2 and TMPRSS2, act in concert to facilitate viral entry, setting the stage for the development of COVID-19.

Related article

Angiotensin-converting enzyme (ACE) and ACE2 are distinct enzymes, and their actions lead to opposing physiological effects. While ACE converts angiotensin I to angiotensin II, which is a potent vasoconstrictor, ACE2 catalyzes the hydrolysis of angiotensin II to angiotensin (1-7), which is a vasodilator. In this way, the physiological action of ACE2 counters the physiological action of ACE.

Early in the COVID-19 pandemic, physicians observed that patients with hypertension who developed the illness tended to have more severe disease and worse outcomes than patients without hypertension. The hypothesis was proposed that some drugs commonly used to treat hypertension may both increase susceptibility to disease and predispose to more severe illness. Specifically, experiments in animal models suggested that ACE inhibitors and angiotensin receptor blockers (ACEI/ARBs) upregulate ACE2 in cell membranes.[2] By providing more membrane receptors for viral entry into cells, it was proposed that upregulation of ACE2 may enhance both susceptibility to SARS-CoV-2 infection and the severity of the illness. This idea led to recommendations that ACEI/ARBs be discontinued in patients with or at risk for COVID-19.

In this issue of *JAMA*, Fosbøl et al[3] provide convincing evidence that ACEI/ARB therapy is not associated with increased susceptibility to SARS-CoV-2 infection or increased severity of COVID-19. Using administrative registries that capture health data for the entire country of Denmark, the authors studied a retrospective cohort of 4480 patients with COVID-19 and found that the 30-day mortality rate did not differ significantly between patients receiving ACEI/ARB therapy (n = 895) vs those not receiving ACEI/ARB therapy (n = 3585) (18.1% vs 7.3%, respectively; adjusted hazard ratio, 0.83 [95% CI, 0.67-1.03]). The authors also conducted a nested case-control analysis within a cohort of 494 170 patients with hypertension, and concluded that among patients with pre-existing hypertension, those receiving ACEI/ARBs did not have a significantly higher risk of acquiring COVID-19 than patients receiving other antihypertensive medications (hazard ratio, 1.05 [95% CI, 0.80-1.36]). These results extend those of previous studies[4-7] by including patients from an entire country and by examining both susceptibility and severity of illness in the same large database.

Even if ACEI/ARBs do upregulate ACE2 receptors, the absence of upregulation of TMPRSS2 may obviate enhanced viral entry into cells. Also, given the fact that ACE2 counters the physiological action of ACE, ACE2 upregulation may have beneficial effects on pulmonary inflammation in the setting of COVID-19 pneumonia, thereby improving clinical outcome.

The study by Fosbøl et al,[3] together with previous studies in other patient populations, should lay to rest concerns about the use of ACEI/ARBs in patients with or at risk for COVID-19. When there is a clinical indication for their use, ACEI/ARBs should not be discontinued in patients with COVID-19, unless the drugs cannot be tolerated due to hemodynamic instability.

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