Evidence That Renin-Angiotensin System Inhibitors Should Not Be Discontinued Due to the COVID-19 Pandemic

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The severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) that has caused the current coronavirus disease 2019 (COVID-19) pandemic has now spread to over 3 million people in >185 countries and territories accounting for >200 000 deaths worldwide. Experience thus far indicates that, in addition to age, comorbidities, such as cardiovascular disease (chiefly ischemic heart disease, atrial fibrillation, and stroke), hypertension, diabetes mellitus, and chronic respiratory disease, elevate the risk of mortality among SARS-Cov-2 infected individuals.[1,2] Hypertension not only predisposes to more severe SARS-Cov-2 disease, but widespread antihypertensive treatment with blockers of the renin-angiotensin system (RAS) has been questioned due to the possible facilitation of SARS-Cov-2 infection.

The RAS plays an important role in facilitating SARS-Cov-2 infection, especially in the lungs. Ang (Angiotensin) II, the major effector peptide of the RAS, is formed by renin enzymatic action on angiotensinogen to produce the decapeptide Ang I, which is enzymatically cleaved by ACE (Ang-converting enzyme) to the octapeptide Ang II, the principal effector peptide of the RAS.[3] Ang II activates the AT_1R (Ang type-1 receptor), inducing untoward effects including vasoconstriction, antinatriuresis, and aldosterone secretion (leading to hypertension), as well as inflammation and fibrosis in many target organs, including the lung. Opposing AT_1R-mediated detrimental actions, the so-called protective arm of the RAS is composed of the AT_2R and the ACE-2, Ang (1–7), *Mas* receptor pathway. ACE-2, a monocarboxypeptidase, predominantly cleaves Ang II forming the heptapeptide Ang (1–7), which in turn activates the *Mas* receptor that helps counterbalance Ang II actions via AT_1Rs, including inflammation.[3] Although ACE-2 is a structural homolog of ACE, ACE-2 is not inhibited by ACE inhibitors. Paradoxically, ACE-2 serves not only as a counterregulatory enzyme in the RAS but also as a receptor for SARS-Cov-2.[4] ACE-2 is anchored in the plasma membranes of epithelial cells, including pulmonary alveolar cells.[4] The spike protein of SARS-Cov-2 binds to the extracellular domain of ACE-2, triggering cellular internalization of both SARS-Cov-2 and ACE-2. Cellular entry of SARS-Cov-2 is facilitated by the cellular serine protease TMPRSS2, which primes the viral spike protein for ACE-2 binding.[4] Following cellular internalization, the resulting downregulation of ACE-2 on the plasma membrane theoretically could downregulate this component of the protective arm of the RAS, leading to increased inflammation stimulated by unopposed actions of Ang II via AT_1Rs.[4]

Because ACE inhibitors and Ang receptor blockers (ARBs) may increase the amount of ACE-2 formation, theoretically increasing the risk of SARS-Cov-2 entry into epithelial cells inducing inflammation, the question has been raised whether these drugs should be discontinued during the COVID-19 pandemic.[5] In response, many scientific organizations and journals issued statements cautioning against discontinuation of these agents due to lack of evidence of harm and because discontinuation would predictably lead to uncontrolled blood pressure with its own cardiovascular disease risks. However, no direct evidence from patients with COVID-19, either taking or not taking these agents, was yet available upon which to base a recommendation with confidence.

In the current issue of *Hypertension*, Yang et al[6] provide one of the first reports of the effect of ACE inhibitors and ARBs on clinical outcomes in patients with COVID-19 and hypertension. This is a retrospective, single-site cohort study from Wuhan, China, comparing clinical outcomes among 126 patients with COVID-19 with preexisting hypertension, 43 of whom were taking either ACE inhibitors or ARBs and 83 of whom were not taking these agents, and 125 age- and sex-matched COVID-19 control patients without hypertension. The study showed that ACE inhibitor or ARB therapy did not impose an increased risk of morbidity or mortality for SARS-Cov-2 infection. Indeed, the study showed a nonsignificant trend toward marginally lower critical illness and death rates in patients taking RAS inhibitors compared to those taking other antihypertensive agents. The study also demonstrated a statistically significant reduction in circulating inflammatory biomarkers, procalcitonin, and hsCRP (highly sensitive C-reactive protein), but not IL (interleukin)-6, in the RAS blocker group compared with controls.[6] Although this was a retrospective cohort study with all of the biases inherent in such studies, the results provide an initial level of confidence that ACE inhibitors and ARBs can be safely continued in patients with COVID-19. Nevertheless, these findings

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required confirmation from other cohort studies and optimally from randomized clinical trials.

At least 2 other retrospective cohort studies from China are currently available comparing severity of illness and mortality rates from COVID-19 in patients with hypertension who were taking or not taking ACE inhibitors or ARBs.[7,8] In a single-center study (1178 hospitalized patients with COVID-19 362 with hypertension and 115 taking ACE inhibitors or ARBs), the percentage of patients taking RAS inhibitors did not differ between those with severe and nonsevere infections, nor between survivors and nonsurvivors.[7] A multicenter, cohort study addressing a similar question in patients with COVID-19 was recently published.[8] Adults with hypertension and COVID-19 using ACE inhibitors or ARBs (N=188) were compared with 940 adults with hypertension and COVID-19 taking antihypertensive drug therapy other than RAS blocking agents and 2302 patients with COVID-19 without hypertension. Risk for 28-day all-cause mortality was lower in the ACE inhibitor/ARB group than the control group (adjusted hazard ratio, 0.42 [95% CI, 0.19–0.92]; *P*=0.03) and in a matched subgroup analysis (adjusted hazard ratio, 0.30 [95% CI, 0.12–0.70]; *P*=0.01).

Two additional recent studies respectively from northern Italy and New York provided further evidence on the use of antihypertensive medication and COVID-19.[9,10] The large sample size of these 2 studies allowed comparisons for all major classes of antihypertensive drugs, including ACE inhibitors and ARBs. The Italian study used a case-control design and included 6272 patients with COVID-19 and 30 759 controls matched for age, sex, and municipality of residence.[9] After adjustment for drugs and coexisting conditions, the odds ratios for the use of ACE inhibitors and ARBs were 0.96 (95% CI, 0.87–1.07) and 0.95 (95% CI, 0.86–1.05), respectively, among all case patients and 0.91 (95% CI, 0.69–1.21) and 0.83 (95% CI, 0.63–1.10), respectively, among severely ill or deceased patients.[9] The New York study contrasted patients who tested positive for COVID-19 (n=5894) with those who tested negative (n=6700).[10] None of the major classes of antihypertensive drugs were associated with a positive test or severity of illness.[10]

Taking together, the data of these 5 studies from different ethnicities,[6–10] although retrospective, lend substantial support for the recently published recommendations to continue ACE inhibitor or ARB treatment in patients with hypertension and COVID-19.

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Disclosures

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