Letter to the Editor

Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19

Running Title: Angiotensin Receptor and COVID-19

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Highlight

Intravenous infusions of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in experimental animals increase the numbers of angiotensin-converting enzyme 2 (ACE2) receptors in the cardiopulmonary circulation. ACE2 receptors serve as binding sites for SARS-CoV-2 virions in the lungs. Patients who take ACEIs and ARBS may be at increased risk of severe disease outcomes due to SARS-CoV-2 infections.

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Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are highly recommended medications for patients with cardiovascular diseases, such as refractory hypertension, coronary artery disease, heart failure, and post-myocardial infarction status.[1, 2] ACEIs and ARBs are also recommended for the management of cardiovascular diseases in elderly patients, and in patients with diabetes and renal insufficiency.[3]

Intravenous infusions of ACEIs and ARBs in experimental animals increase the numbers of angiotensin converting enzyme 2 (ACE2) receptors in the cardiopulmonary circulation.[4] Patients taking ACEIs or ARBs chronically for cardiovascular diseases are assumed to have increased numbers of ACE2 receptors throughout their cardiopulmonary circulations as observed in experimental animal models.

ACE2 receptors serve as binding sites for the anchoring spike (S) proteins on the exterior surfaces of beta coronaviruses.[5] The beta coronavirus SARS-CoV causes the severe acute respiratory syndrome (SARS). The phylogenetically related beta coronavirus, SARS-Cov-2, causes the novel coronavirus disease (nCoV-2019) or COVID-19.[5] S proteins anchor both beta coronaviruses to ACE2 receptors in the lower respiratory tract of infected patients in order to gain entry into the lungs. Viral pneumonia and potentially fatal respiratory failure may result in susceptible persons after 10-14 days.[5]

Since patients treated with ACEIs and ARBS will have increased numbers of ACE2 receptors in their lungs for coronavirus S proteins to bind to, they may be at increased risk of severe disease outcomes due to SARS-CoV-2 infections. Patients treated with ACEIs and ARBs for cardiovascular diseases should avoid crowds, mass events, ocean cruises, prolonged air

travel, and all persons with respiratory illnesses during the current COVID-19 outbreak in order to reduce their risks of infection.

This warning is supported by a recent descriptive analysis of 1,099 patients with laboratory-confirmed COVID-19 infections treated in China during the reporting period, December 11, 2019, to January 29, 2020.[6] In this study, Guan et al reported more severe disease outcomes in patients with hypertension, coronary artery disease, diabetes, and chronic renal disease (**Table 1**).[6] Severe outcomes included intensive care unit (ICU) admission, mechanical ventilation, and death.[6] All patients with the diagnoses noted met the recommended indications for treatment with ACEIs or ARBs. The results of this study demonstrated that patients with COVID-19 infections, and most likely treated with ACEIs or ARBs, suffered more severe disease outcomes.[6] Future case-control studies in patients with COVID-19 infections are recommended to further confirm chronic therapy with ACEIs or ARBs as a risk factor for more severe disease outcomes.

Elderly patients, who often have comorbidities including cardiovascular diseases, hypertension, diabetes, and chronic kidney disease, are more likely to be taking ACEIs or ARBs; and are at greater risks of contracting symptomatic and even fatal COVID-19 infections than children. Two mechanisms may protect children from COVID-19 infections: (1) cross-protective antibodies from multiple upper respiratory tract infections caused by the common cold-causing alpha coronaviruses, and (2) fewer ACE2 receptors in their lower respiratory tracts to attract the binding S proteins of the beta coronaviruses. These immunological and molecular observations support the clinical observations of infrequent COVID-19 infections in children compared to more frequent COVID-19 infections in elderly patients, especially those with comorbid conditions.

In addition to elderly status with comorbidities, treatment of hypertension and other cardiovascular disorders with ACEIs or ARBs appears to be a risk factor for more severe disease outcomes including ICU admission, mechanical ventilation, and death, in patients with COVID-19 infections. This conclusion is supported by the results a recent Chinese study of over 1,000 patients with COVID-19 infections that reported more severe disease outcomes in patients with hypertension, coronary artery disease, diabetes, and chronic renal disease meeting all criteria for treatment with ACEIs or ARBs.[6]

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Table 1. **The Clinical Characteristics of Study Patients with COVID-19 Infections and Coexisting Disorders Stratified According to Disease Severity and Primary End-Point (N = 1,099).[6]**

Coexisting disorder	All patients N = 1,099 No. (%)	Non-severe disease N = 926 No. (%)	Severe disease N = 173 No. (%)	Primary end-point reached* N = 67 No. (%)	Primary end-point not reached* N = 1,032 No. (%)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	25 (35.8)	141 (13.7)
Coronary artery disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Chronic kidney disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)

***Primary end-points included intensive care unit admission, mechanical ventilation, or death.**