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Letter to the Editor

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Keep Taking Your ACE Inhibitors and ARBs During the COVID 19 Pandemic

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The information conveyed by James Diaz, M.D. in a recent letter to the editor "Hypothesis: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19" 1 is inaccurate, misleading and potentially harmful to individuals taking angiotensin system blocking antihypertensive medicines.

Diaz cites only one article 2 that investigated the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) on ACE2. Moreover, he incorrectly cites this article 2 as indicating that both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) increase angiotensin-converting enzyme 2 (ACE2) in animal models: "*Intravenous infusions of ACEIs and ARBs in experimental animals increase the numbers of angiotensin converting enzyme 2 (ACE2) receptors in the cardiopulmonary circulation.*" He then amplifies this misinterpretation by extrapolating it to all tissues in humans: "*Patients taking ACEIs or ARBs … are assumed to have increased numbers of ACE2 receptors throughout their cardiopulmonary circulations …" "… 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.*"

Ferrario et al., 2005 [2] administered drugs to a single (Lewis) strain of rats for 12 days in drinking water, not intravenously. They measured mRNA for ACE2 and ACE2-mediated metabolism of ^{125}I-angiotensin II in the rats' left ventricle. The largest increase in left ventricular ACE2 mRNA was caused by lisinopril, without any increase in ACE2-mediated metabolism of ^{125}I-angiotensin II. Losartan caused a smaller increase in left

ventricular ACE2 mRNA, while increasing ACE2-mediated metabolism of ^{125}I-angiotensin II. Co-administration of lisinopril and losartan to the rats did not alter ACE2 mRNA, but increased ACE2-mediated metabolism of ^{125}I-angiotensin II. Measurement of enzymatic activity used a very low substrate concentration, <10 nmolar, which could indicate an altered Km of the ACE2 for its substrate, versus an increase in ACE2 protein.

So, based upon an ambiguous observation of alterations in left ventricular ACE2 mRNA and enzymatic activity in a single strain of rats, Diaz has aroused concern that persons taking ACE inhibitors and ARBs to control their hypertension may be at greater risk from SARS-CoV-2 infection. This is an indefensible speculation with the potential to harm to hypertensive individuals who may eschew these medications, increasing their risk of cardiovascular morbidity.

More disconcerting is the misinterpretation of the report by Guan et al. 2020. [3] They do not provide any information in their report regarding patient use of antihypertensive medications, let alone whether or not they were taking ACE inhibitors or ARBS. The report by Guan et al., 2020 [3] is completely irrelevant to the issue of whether ACE inhibitors or ARBs increase or decrease the risk of morbidity and mortality from SARS-CoV-2 infection.

The American College of Cardiology, American Heart Association and the Heart Failure Society of America have advised patients who are taking ACE inhibitors and ARBs to continue doing so in the face of the current corona virus pandemic https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19

References

1. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *J Travel Med* 2020.
2. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; **111**(20): 2605-10.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine* 2020.