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Title: Cardiac drugs and outcome in COVID - 19

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We read with much interest the article “Are certain drugs associated with enhanced mortality in COVID -19” by Goldstein et al your esteemed Journal. Authors have discussed the theoretical basis of angiotensin receptor blockers, statins in worsening outcome of COVID – 19 patients.(1) We believe that this topic is rapidly evolving and requires further evidence and discussion for understanding the multiple factors which contribute to the pathogenesis and outcome. We have the following comments.

Goldstein et al. have discussed that ARB’s facilitate viral entry by increasing the expression of ACE 2 receptors resulting in greater disease severity. Cao et al have compared the genetic analysis of COVID -19 receptor ACE -2 in different populations. They have shown that the expression level and pattern of ACE-2 receptors is different in different tissue and different populations. (2) Even though they have shown that the East Asian population has a higher expression of the same, surprisingly reported mortality in this population has not been high compared to certain other countries. (3)

Zheng et al have reported that patients with cardiovascular diseases have increased ACE- 2 as compared to individuals. As it is expressed in the heart and is involved in counteracting the effects of angiotensin II, its levels are elevated in hypertension, congestive heart failure, atherosclerosis, coronary artery disease due to activation of training angiotensin system.(4) They also have mentioned that renin – angiotensin- aldosterone system inhibitors can also increase ACE-2 levels, hence any antihypertensive agent including ARBs, ACE inhibitors could possibly worsen the outcome in patients with COVID -19.(4) In animal models Administration of aldosterone has also shown to downregulate ACE 2 mRNA levels. Hence

possibly its antagonists could also increase ACE-2 levels.(5) Similarly, in the animal model binding of SARS-CoV spike protein to ACE 2 has been soon to cause downregulation of ACE 2, resulting in an increase in angiotensin II and worsening lung injury. Recombinant ACE 2 and Losartan is shown to reduce lung injury in such case. (6) Surprisingly randomized controlled trials of losartan for patients with COVID -19 are being held in both hospitalized and non-hospitalized patients. (6,7)

We agree with the authors that increase expression of ACE 2 receptor potentially increases viral entry and disease severity, however the data regarding only ARB's causing the same might not be enough.(6,8) While awaiting further studies it would be prudent to discontinue ACE inhibitors, ARB's, and other RAAS antagonist on clinical ground as per the treating physician's discretion.(9)

Though at present there is not enough evidence of any potential benefit or harm of most prescribed medications including the ARBs, ACEi, Statins, Antiviral agents we strongly agree with the authors that meticulous and detailed reporting of medications of COVID -19 affected patients is crucial in order to further understand the multifaceted interaction of the virus, medications, and clinical outcome.

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