Title: **Cardiac drugs and outcome in COVID-19: *Reply***

Format: Letter to the Editor, *QJM*

Words: 397

References: 8

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Conflicts of Interest: None

Acknowledgements: None

We appreciate the comments of Mishra and colleagues [1] regarding our recent correspondence appearing in the *Journal* [2]. Although we discussed a hypothetical basis of how renin-angiotensin-aldosterone system (RAAS) blockers, specifically angiotensin receptor blockers (ARBs), and statins may promote acute respiratory distress syndrome (ARDS) and death in COVID-19 patients, the jury is still out as to how this translates clinically [3]. However, these drugs are widely used in the treatment of the common morbidities associated with severe COVID-19 disease, which raises the possibility that they are in part related to the severity of COVID-19 in some patients.

Respectfully, we disagree with Mishra and colleagues, and do not advocate the discontinuation of RAAS-blocker therapy while waiting for further studies, as that might lead to harm by increasing blood pressure or congestive heart failure in some patients. Importantly, the WHO, CDC, nor any professional societies have advocated replacing these drugs with other anti-hypertensive medications in patients with COVID-19. On the other hand, we agree and strongly advise that investigators reporting retrospective data on COVID-19 patients not only report comorbid conditions, but the drugs used in the treatment of the conditions as well. Moreover, it is important to specify whether the RAAS-blocker is an ARB or an angiotensin-converting enzyme (ACE)-inhibitor, since ARBs increase the expression of ACE2, the functional receptor for the SARS-coronavirus 2, whereas ACE-inhibitors do not [3]. Ideally, prospective studies should be done assessing the safety of ARBs and statins in the stages of the COVID-19 illness and in various populations.

Other concepts also need investigation. If ARBs do indeed increase ACE2 expression resulting in enhanced viral entry, might treatment with these drugs prolong asymptomatic viral shedding, since ACE2 receptors are present in both the upper respiratory tract and colonic epithelia [4,5]? Furthermore, if statins do increase the activation of the inflammasome pathway in ARDS, leading to triggering an increase in the inflammatory cytokine, IL-18 [6], might this cytokine in part fuel myocardial inflammation [7]? Notably, myocardial injury is significantly associated with mortality in COVID-19 [8].

In summary, clinicians need adequate retrospective and prospective data to determine if the drugs used in the treatment of the comorbidities commonly seen in patients with COVID-19 are in part related to adverse outcomes. Until such data are available,

clinicians should not routinely discontinue these medications based on theory and limited retrospective data. Finally, absence of evidence is not evidence of absence.

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