

Title: *Reply: Use of statins in patients with COVID-19*

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We are grateful for the comments of Kow, et al. [1] addressing our recent commentary in the *Journal* [2]. As they mentioned, there is controversy whether statin therapy might increase mortality if used for the treatment of acute respiratory distress syndrome (ARDS). We agree that prospective trials are needed to determine if statins are indeed helpful or harmful in the setting of COVID-19 associated ARDS.

An interesting issue cited by Kow, et al., was that, in an animal model, statins have been shown to increase the expression of the angiotensin-converting enzyme 2 (ACE2) receptor [3,4], which is the functional receptor for cell entry of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Notably, ACE2 receptors are expressed in numerous tissues including, but not limited to, nasal epithelium, tongue, oral mucosa, lung (alveolar type II epithelial cells), esophagus, stomach, colon, gallbladder, bile duct, liver, myocardium, kidney, bladder, brain, cornea, conjunctiva and endothelium [5-8]. Accordingly, the diversified location of the ACE2 receptors may in part explain the various clinical manifestations and organ system pathologies seen with COVID-19, including the infectivity and asymptomatic transmissibility of the virus [9].

Therefore, since statin use is so widespread and the drugs are commonly prescribed at high doses, particularly for patients with many of the comorbidities associated with COVID-19, such as cardiovascular disease, diabetes, obesity, and hypertension, it might have a deleterious effect on some manifestations of the disease, by increasing ACE2 receptor expression. For example, might high-dose statin therapy lead to an increase in asymptomatic nasal, oral or intestinal virus transmissibility in COVID-19? On the other hand, the immunomodulatory and endothelial protective properties of statins may be beneficial in the treatment of COVID-19 [8,10]. As such, prospective trials should be done to determine if the risks of statin therapy outweigh the benefits in the context of COVID-19 illness. Until those data are obtained, clinicians should not consider changing their statin prescribing patterns, except perhaps in the primary prevention of cardiovascular disease, particularly in the older population, where their use is controversial [11].

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