

A Shot in the Dark! RAAS Inhibitors Cause Severe COVID-19 Infection

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Coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2), which started in Wuhan in Hubei Province of China in December 2019, has spread to all parts of the globe and continues to be a major global health concern.¹ The SARS-CoV-2 enters human cells after binding of the viral spike protein to the angiotensin-converting enzyme receptor-2(ACE2) expressed on the host alveolar cells.²

Homologue of the ACE1 receptor but with divergent physiological functions. ACE1 receptor is expressed in all tissues and is an upregulator of the renin–aldosterone–angiotensin system (RAAS). It converts angiotensin I to the vasoactive angiotensin II molecule. ACE2 is expressed on alveolar epithelial cells and endothelial cells and counterbalances the effect of ACE1. This enzyme converts angiotensin II to angiotensin (1–7) molecule, which has vasodilatory, anti-inflammatory, and cardioprotective properties.³

ACE inhibitors and angiotensin receptor blockers (RAAS inhibitors) are the drugs commonly used in treating cardiovascular diseases. It was inferred from animal studies that the use of these drugs increases the expression of ACE2 receptors and hence may increase SARS-CoV-2 entry into the human cells causing severe infection.⁴ The evidence from human studies do not support the hypothesis that RAAS inhibitors increase the expression of ACE2 receptors.⁵

The conflicting evidence and initial studies from Wuhan, China reporting severe SARS-CoV-2 infection in patients with underlying hypertension and cardiovascular disease, had raised concerns among health professionals and patients on the safety in continuing RAAS inhibitors during this pandemic.⁶ This confusion was further fueled by information from the media, leading to a change in the prescription of these medications. RAAS inhibitors are medications proven to have a mortality benefit in patients with heart failure and other cardiovascular diseases. Stoppage of RAAS inhibitors in these patients would have been detrimental.

Conversely, the ACE2 enzyme is necessary for the amelioration of lung inflammation through angiotensin (1–7) molecule. RAAS inhibitors may be useful in cardiac injury induced by COVID-19 infection.⁷ Quick research was needed to support or prove the contrary that RAAS inhibitors predispose people to severe COVID-19 infection.

Pooled meta-analysis to date has shown no association between RAAS inhibitors and COVID-19 related outcome.^{8–10} There is no data from India to date to study this relationship. One retrospective study by Reddy et al.¹¹ substantiates the evidence that the use of RAAS inhibitors is safe during the current COVID-19 pandemic.

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Ideally larger randomized controlled trials are necessary to study the causal relationship between RAAS inhibitors and COVID-19 infection—benefit, harm, or no association.

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