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LETTER TO THE EDITOR

Response by Cohen et al to Letter Regarding Article, "Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19"

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In Response:

We read with great interest the original investigation by Zhang et al[1] and the accompanying editorial by Shah et al.[2] The study question is urgent and important, given the potential relationships among ACE (angiotensin-converting enzyme) inhibitor or ARB (angiotensin receptor blocker) use, ACE2 expression/activity, and coronavirus disease 2019 (COVID-19) severity.[3–5] We appreciate that the authors appropriately tempered their interpretation of the results based on several limitations noted in their publication and the accompanying editorial. Nonetheless, we are concerned that many readers may still overinterpret the impressive hazard ratios. Notably, exposure assignments were based only on antihypertensive medications administered at any point during hospitalization. Patients had to survive long enough, or be clinically stable enough, to achieve the exposure (ie, ACE inhibitors/ARB use). This time-dependent bias (or immortal time bias) underestimates the hazard of the exposure group,[6] which may result in a false or exaggerated apparent protective effect of ACE inhibitors/ARBs. Also, fewer patients were on ACE inhibitors/ARBs than expected (17% versus 30%–40% prevalent use[7,8]), suggesting substantial unmeasured confounding and nonsystematic exposure ascertainment: sicker patients will almost invariably be less likely to receive ACE inhibitors/ARBs during hospitalization. These limitations may explain contradictory results in observational US veteran data which did not show an association between baseline ACE inhibitors/ARB use and need for intensive care in patients with COVID-19 (unadjusted odds ratio, 1.94 [95% CI, 1.30–2.90] and adjusted odds ratio, 1.66 [95% CI, 0.94–2.93]).[9]

Based on several clinical and mechanistic considerations, we believe that there is equipoise regarding potential benefit or harm from ACE inhibitors/ARB use in patients at risk for or who have COVID-19.[3,4] The current study reinforces the urgent need for randomized controlled trial evidence to address this important issue.[2] We are currently conducting an international, multicenter, randomized controlled trial (REPLACE COVID trial [The Randomized Elimination or Prolongation of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Coronavirus Disease 2019], URL: https://www.clinicaltrials.gov. Unique identifier: NCT04338009) randomizing patients on chronic ACE inhibitors/ARBs who are hospitalized with COVID-19 to continuation versus withdrawal of their ACE inhibitors/ARB upon admission, evaluating a hierarchical outcome including death, mechanical ventilation, pressor requirement, and other markers of severity of critical illness. Another ongoing trial in Ireland (URL: https://www.clinicaltrials.gov. Unique identifier: NCT04330300) is randomizing outpatients with hypertension to continuation versus withdrawal of ACE inhibitors/ARBs, evaluating the risk of COVID-19-related hospitalization and mortality.

ARTICLE INFORMATION

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Disclosures

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