

.gov number, NCT04366050) — may provide clearer insight regarding the effect of ACE inhibitors or ARBs in patients with Covid-19.

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**TO THE EDITOR:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE 2 (ACE2) receptor to enter human cells.<sup>1</sup> ACE2 expression may be up-regulated by ACE inhibitors and ARBs. These observations have led to speculation regarding potential harmful effects of ACE inhibitors and ARBs.

Recent observational studies have shown no association between mortality from Covid-19 and

ACE inhibitors and ARBs, after adjustment for a range of potential confounders. However, they have not shown an association between the duration of the underlying diseases or the duration of the ACE inhibitor or ARB treatment and mortality from Covid-19. This lack of an association is particularly important for several reasons. First, ACE2 activity is correlated with the duration of diabetes.<sup>2</sup> Second, in a recent study,<sup>3</sup> the adjusted effects of angiotensin blockade on the incidence of influenza varied nonlinearly, with a higher risk of influenza among patients who received treatment for 0.5 years to less than 1.5 years with ACE inhibitors (adjusted hazard ratio, 1.07; 95% CI, 0.97 to 1.17) and ARBs (adjusted hazard ratio, 1.15; 95% CI, 0.98 to 1.35) than among those who had not received these agents. Third, the spike protein of SARS-CoV-2 is primed by the transmembrane protease, serine 2 (TMPRSS2),<sup>1</sup> the expression of which has also been reported to be associated with disease duration.<sup>4</sup> Therefore, can the authors report the effects according to the duration of underlying conditions, according to the duration of treatment with ACE inhibitors, ARBs, and other inhibitors of the renin–angiotensin–aldosterone system (RAAS), or according to both durations?

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