UPDATE ALERTS

Update Alert 9: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults

In Update Alerts 7 and 8, we summarized the state of the evidence for 2 key questions of this systematic review: whether angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) increase the risk for SARS-CoV-2 infection or worse outcomes (1, 2). In both cases, we have high confidence in the evidence indicating that these medications are not associated with increased risk for infection or severe disease. Because we consider these findings to be stable, we retired the key question about risk for SARS-CoV-2 infection in February 2021 and retired the key question about disease severity in June 2021.

In this update alert, we summarize available evidence about our third key question: the benefits and harms of initiating an ACEI or ARB in adults with COVID-19 who were not previously receiving these medications. In Update Alert 8, we provided an overview of in-progress trials but did not identify any completed studies. In an updated literature search from 5 April to 22 November 2021 using the same search strategy as our original review (3), we identified 277 potentially relevant articles and included 4 completed trials with published results (**Supplement Table 1**) (4–7). We used the same methods for study selection, data extraction, quality assessment, and evidence synthesis as we described in our original review (3).

Three inpatient trials evaluated ARB initiation. Specific interventions were 80 mg of telmisartan twice daily for 14 days compared with standard care, 12.5 mg of losartan twice daily for 10 days compared with standard care, and 25 mg of losartan daily for at least 14 days compared with 5 mg of amlodipine. In the trial of telmisartan, done among 158 adults in Argentina, 30-day mortality risk was lower with telmisartan than with usual care (relative risk, 0.19 [95% CI, 0.06 to 0.57]) (4). However, we have methodological concerns about this trial (rated high risk of bias) because of differences between groups at baseline as well as changes in study end points and some secondary outcomes during the study period (**Supplement Table 2**). The other 2 trials of losartan, one of 31 hospitalized adults with mild to moderate hypoxia done in the United States and the other of 80 hospitalized adults with hypertension in Iran, did not identify a mortality benefit (5, 6). In the U.S. study, the need for intensive care was also similar between the intervention and comparison groups (1 of 16 [6%] versus 2 of 15 [13%], respectively) (5). In addition to the inconsistency in the direction of effect across studies, all studies were small (fewer than 200 participants) and had low event rates, making results imprecise. This evidence is insufficient to determine the benefits and harms of initiating ACEIs or ARBs among adults hospitalized with COVID-19 (**Supplement Table 3**).

We identified 1 trial done in the outpatient setting of 117 adults in the United States who tested positive for SARS-CoV-2 (7). This trial found that 25 mg of losartan twice daily for 10 days compared with placebo did not result in a lower risk for hospitalization. The absolute difference in all-cause hospitalization between groups was −3.5%, favoring the placebo (7). Although well conducted (rated low risk of bias), this trial was small, with low event rates. This evidence is insufficient to determine the effects of initiating ACEIs or ARBs among nonhospitalized adults with COVID-19 (**Supplement Table 3**).

Given the numerous deficiencies of the existing evidence base, additional evidence is needed to determine the benefits and harms of initiating ACEIs or ARBs for COVID-19. We also note that these trials were all completed by the fall of 2020 and have unclear applicability to patients contemporaneously diagnosed with COVID-19, who may have different disease trajectories based on vaccine status, infection with different SARS-CoV-2 variants, or general improvements in COVID-19 care over time.

Several clinical trials are in progress, including 3 large trials (estimated sample size >1000), and an updated list is presented in **Supplement Table 4** (8–18). We will monitor these trials for updates monthly and anticipate providing a final update alert in the summer of 2022 when more results are available.

Katherine Mackey, MD, MPP
Devan Kansagara, MD, MCR
Kathryn Vela, MLIS, AHIP
VA Portland Health Care System, Portland, Oregon

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Corresponding Author: Katherine Mackey, MD, MPP, VA Portland Health Care System, 3710 SW US Veterans Hospital Road, Portland, OR 97239; e-mail, Katherine.Mackey@va.gov.

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