UPDATE ALERTS

Update Alert 10: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults

This living systematic review has addressed 3 key questions about COVID-19 and the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs): whether these medications increase susceptibility to SARS-CoV-2, increase the likelihood of worse outcomes, and paradoxically, whether they have protective effects and could be used as COVID-19 treatment (1). In previous update alerts, we summarized high-strength evidence that antecedent use of ACEIs and ARBs is not associated with increased risk for SARS-CoV-2 infection or severe disease and retired these key questions. In this final update alert, we summarize current evidence about our third key question: the benefits and harms of initiating ACEIs or ARBs in adults with COVID-19 who were not previously receiving these medications.

In an updated literature search from 22 November 2021 to 19 December 2022 using the same search strategy as our original review, we identified 285 potentially relevant articles and included 3 additional randomized controlled trials with published results (**Supplement Table 1**), adding to 4 previously included trials (2–8). We used the same methods for study selection, data extraction, quality assessment, and evidence synthesis as we described in our original review.

In Update Alert 9, we discussed 3 small trials of ARB initiation among adults hospitalized with COVID-19 (5–7, 9). Because of study methodological concerns, inconsistency, and imprecision, we concluded that the evidence was insufficient to draw conclusions about benefits and harms. Similarly, we identified only 1 study of losartan initiation in the outpatient setting among adults with a positive SARS-CoV-2 test result, which did not find a benefit in terms of hospitalization risk (8). We also concluded that this evidence was insufficient.

The addition of 3 new trials (all rated low risk of bias) (**Supplement Table 2**) in this update alert increases the total number of participants across studies from 386 to 1392. None of the 3 new trials found ARB initiation to be beneficial. In the largest trial to date, which was done primarily in India but also included a few participants in Australia, a total of 787 adults (71% hospitalized) were randomly assigned to receive telmisartan at a starting dose of 40 mg daily versus placebo (in India) or an ARB at the discretion of the treating team versus usual care (in Australia) (2). Deaths were relatively rare (16 participants overall), and mortality was similar between groups (odds ratio, 1.74 [95% credible interval, 0.62 to 5.25]). Disease severity as measured by the World Health Organization Clinical Progression Scale, the study's primary outcome, was worse in the intervention group at day 14 but similar in both groups by day 28. Another new trial of 205 adults hospitalized with COVID-19 in the United States compared use of 50 mg of losartan twice daily to placebo for 10 days or until hospital discharge and did not find a difference between groups in 28-day mortality rates (11% in the intervention group compared with 9% in the control group) or the primary outcome—the ratio of arterial Pa_{O_2} to F_{IO_2} (3). The third new trial of 14 hospitalized adults compared 25 mg of losartan twice daily to placebo (3 participants) or 400 mg of lopinavir–100 mg of ritonavir twice daily (2 participants) for 5 to14 days and did not identify a difference in COVID-19 mortality or disease severity (4).

Among all 7 included trials (3 new trials and 4 included in Update Alert 9), 2 identified numerically higher rates of adverse events in the ARB intervention groups compared with the comparator groups (3–4). Adverse events included acute kidney injury, hypotension, and hyperkalemia, as well as cardiovascular and respiratory serious adverse events. The remaining 5 trials did not identify any difference in adverse events between groups.

In summary, on the basis of moderate-strength evidence, ARB initiation among adults with COVID-19 probably does not have a mortality benefit. Although the specific interventions varied (use of different ARBs and varying doses), results were consistent across 6 of the 7 trials with no serious methodological concerns (**Supplement Table 3**). Event rates (deaths) were low across studies, making results imprecise. A recent meta-analysis of trials of ACEIs and ARBs continuation as well as initiation among adults with COVID-19 also found no difference in all-cause mortality. This meta-analysis included 5 of the same trials included in our review, as well as results from 3 unpublished trials (10).

In addition, on the basis of moderate-strength evidence from 3 trials (including 1 trial that evaluated the need for intensive care, which could be considered a surrogate for disease severity), ARB initiation probably does not change COVID-19 severity. Other outcomes varied among studies, precluding additional conclusions. However, we note that none of the trials identified a statistically significant benefit for any outcome except for 1 trial of telmisartan initiation among hospitalized adults (5). However, as discussed in our previous update alert, we have methodological concerns about this trial (rated high risk of bias) because of differences between groups at baseline, changes in study end points, and some secondary outcomes during the study period.

Trials included participants with a mix of disease severity and generally did not stratify results, which is a limitation of the current evidence. Most trials were also completed within the first year of the pandemic, and the most recent trial was completed by the end of 2021. Because of the introduction of vaccines, presence of new SARS-CoV-2 variants, and changes in COVID-19 management over time, results may have limited applicability to adults diagnosed with COVID-19 now and in the future. Many clinical trials on ACEI or ARB treatment of COVID-19 were launched in 2020. Several of these trials were terminated early because of low enrollment, whereas others lack a recent status update on ClinicalTrials.gov (11–17). An updated list of active trials is presented in **Supplement Table 4** (18–19).

See also:

Supplement
Related article

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