UPDATE ALERTS

Update Alert 8: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults

In update alert 7, we summarized the state of the evidence for the 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 and whether these medications are effective in the treatment of COVID-19 (1). Given our high confidence in evidence indicating that use of ACEIs or ARBs does not increase the risk for SARS-CoV-2 infection, we retired this key question from our living review. In this update alert, we provide a summary of results from 2 clinical trials addressing the question of whether continuing ACEIs or ARBs in the treatment of COVID-19 is associated with worse outcomes. We also provide an update on completed and in-progress clinical trials on the effectiveness of ACEIs or ARBs in the treatment of COVID-19 and results of our literature surveillance from 23 November 2020 to 4 April 2021 using the same search strategy as described in the original review (2).

KEY QUESTION 2: IS USE OF ACEIS AND ARBS ASSOCIATED WITH MORE SEVERE COVID-19 ILLNESS?

Because of high confidence based on 78 studies (77 observational studies and 1 randomized controlled trial) in the finding that ACEI or ARB use is not associated with COVID-19 severity, we ended our routine literature surveillance for this key question but planned to report on the findings of 3 in-progress clinic trials. Results are now available for 2 trials that compared COVID-19 severity and mortality in adults who continued or discontinued ACEI or ARB treatment once COVID-19 was diagnosed; the third trial was suspended because of challenges with funding and a low incidence of COVID-19 at the study site (3–5).

In the REPLACE COVID (Randomized Elimination or ProLongation of ACEIs and ARBs in COronaVIrus Disease 2019) trial, a randomized, open-label multicenter trial of 152 adults, continuation of ACEIs or ARBs did not result in more severe disease as measured by a composite outcome incorporating time to death, duration of mechanical ventilation, time on renal replacement or vasopressor therapy, and multiorgan dysfunction (6). Similarly, the BRACE-CORONA (Blockers of Angiotensin Receptor and Angiotensin-Converting Enzyme inhibitors suspension in hospitalized patients with coronavirus infection) trial done in Brazil of 659 adults with mild to moderate COVID-19 found no significant difference in days alive and out of the hospital in the ACEI or ARB continuation group compared with the discontinuation group (7). These findings support our conclusion that use of ACEIs or ARBs before COVID-19 illness is not associated with increased severity. Because we consider these findings to be stable (meaning that future studies are likely to have the same results), we will retire this key question from our living review.

KEY QUESTION 3: WHAT ARE THE BENEFITS AND HARMS OF INITIATING ACEI OR ARB TREATMENT FOR PATIENTS WITH COVID-19?

We identified published results of 1 study in our search—a single-group, open-label trial on the safety of losartan initiation among 34 adults at the University of Kansas Hospital—finding that use of losartan in the intervention group was associated with a lower incidence of adverse events (defined as any untoward medical occurrence in a person during the study) compared with external, nonrandomized controls (8). This study was not designed to evaluate the effectiveness of losartan in COVID-19 treatment. We previously identified 5 planned or in-progress clinical trials evaluating ACEI or ARB initiation in COVID-19 treatment (**Supplement** Table) (9–13). Three of these trials remain in progress (9–11). Two are complete, but results are not published yet (11,12). We will monitor these trials for updates monthly and provide a brief status update in the fall of 2021. When results are available, we will provide an updated evidence synthesis.

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