UPDATE ALERTS

Update Alert 3: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults

We searched MEDLINE (Ovid) weekly from 7 July to 3 August 2020 using the same search strategy as described in the original review (1). We did not limit the search by language. This search update yielded 67 results (de-duplicated), and after an independent dual-review process, we identified 2 new meta-analyses and 1 reestimated meta-analysis (2–4), interim results from 1 randomized controlled trial (5), and 13 new observational studies (6–18). New Evidence

Results of 2 meta-analyses found that angiotensin-converting enzyme inhibitor (ACEI) and angiotensin-receptor blocker (ARB) use was not associated with coronavirus disease 2019 (COVID-19) disease severity (2, 3). In 1 of these meta-analyses of 9 primary studies with a total of 3936 patients with hypertension, use of ACEIs or ARBs was associated with a lower mortality in COVID-19 (2). In the other meta-analysis of 15 studies of 7410 patients with hypertension, subgroup analysis found that ARB use, but not ACEI use, was associated with lower mortality (3). A third meta-analysis reestimated data from studies included in a prior review and found that exclusion of a retracted study by Mehra and colleagues did not change the prior review's finding of a lack of association with ACEI and ARB use and COVID-19 mortality (4, 19).

In addition, interim findings from an ongoing randomized controlled trial (started in 2018) on the use of ramipril among patients with aortic stenosis treated with transcatheter aortic valve replacement found that the use of ramipril was not associated with the incidence or severity of COVID-19 (20). To our knowledge, this is the first study to report findings from a randomized controlled trial on the association between ACEI use and COVID-19.

We also identified 13 new observational studies (6–18). One of these observational studies that was based on analysis of insurance data in Korea addressed our first key question regarding the use of ACEIs and ARBs and COVID-19 risk, finding that increased adherence to ACEI and ARB treatment was associated with a lower incidence of COVID-19 (10). Twelve studies addressed our second key question about ACEI and ARB use and COVID-19 disease severity, and 11 of these studies found a lack of association with ACEIs or ARBs and more severe disease (6–9, 11–13, 15–18). Moreover, 3 of these 11 studies found that use of ACEIs or ARBs was associated with less severe COVID-19 illness (11, 16, 18). The exception was a French study of 149 patients hospitalized with severe COVID-19 illness (defined by an oxygen saturation of 94% or less while the patient was breathing ambient air or receiving oxygen support), 44 of whom were receiving ACEIs or ARBs (14). This study found that ACEI and ARB use was associated with a higher risk for acute kidney injury. However, this study did not examine whether ACEI or ARB use was independently associated with respiratory failure or death.

Overall, inclusion of 17 studies from this search update does not change the certainty of evidence rating we reported in the original article for key questions 1 or 2. Although there is a signal toward improved outcomes among patients with COVID-19 who continue use of ACEIs or ARBs, the benefits and harms of initiating ACEIs or ARBs (that is, new users) in COVID-19 treatment remains unclear. Citation Update

A study by Bean and colleagues that was included in our original manuscript as a preprint has now been published (20).

Also of note, we attempted to register our review protocol with PROSPERO, but registration was not accepted given the stage of our review at the time. We followed standard methods and reporting guidelines for systematic reviews (21, 22). We have posted a copy of our protocol to OSF (https://osf.io/qm6h9/).

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