**Article summary and commentary**

**Article title: Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with Covid-19 diagnosis and mortality**

Fosbøl EL, Butt JH, Østergaard L, et al. JAMA. 2020;324(2):168-177.

**SUMMARY:**

* SARS-CoV-2 enters cells via the ACE2 enzyme. As a result, there has been interest in how ACE inhibitors might affect the incidence and severity of COVID-19. The dominant theory is that such inhibition would increase the chances of infection and severe disease, because long-term use of ACE inhibitors (ACEIs) upregulates the ACE2 enzyme (thus providing more targets for SARS-CoV-2 to enter cells). The initially reported Chinese clinical experience indicated that people taking ACE inhibitors had poorer outcomes, but this finding was criticized because of severe confounding with hypertension.
* This study had 2 main questions: (1) in patients with a COVID-19 diagnosis, is ACEI use associated with greater all-cause mortality or more severe disease, and (2) is the incidence of COVID-19 higher in people taking ACEIs or angiotensin receptor blockers (ARBs), after adjustment for known confounders, such as age and comorbidities.
* To address these questions, the authors examine several large existing national data sets from Denmark, specifically national data on hospitalizations, filled pharmacy prescriptions, and procedures.
* To answer the first question, the authors identified all the people in Denmark from February through May of 2020 with a diagnosis of COVID-19. They then divided them into those taking and not taking ACEIs/ARBs. They identified 895 patients with COVID-19 who were taking ACEIs/ARBs and 3,585 who were not.
* The authors then conducted a fairly standard Cox regression analysis, adjusting for age and comorbidities, and found that the hazard ratio (HR) for death was <1 (0.83 CI crosses 1; *P* = .17); therefore, if anything, there was a small indication that ACEIs/ARBs might be beneficial. For the outcome of serious COVID-19, the HR was also nonsignificant at 1.04.
* For the second question, the authors used a nested case-control design, in which they identified patients with COVID-19 and hypertension, and control individuals with hypertension but not COVID-19. Among the patients with COVID-19, 86% used ACEIs/ARBs, but 85% of the control individuals also used ACEIs/ARBs. The adjusted HR was 1.05 (not close to significant). The authors performed several subgroup analyses examining much older patients, and comparing men vs women. No significant associations were observed.
* Because these are not RCT data, the study is not definitive, but it is the third rigorous study that has examined these questions and not demonstrated any negative effects in terms of COVID-19 incidence or severity among patients taking ACEIs/ARBs. The American College of Emergency Physicians, along with other cardiovascular medicine societies, recommends that patients continue use of these medications throughout the pandemic.

**PMID:** [32558877](http://www.ncbi.nlm.nih.gov/pubmed/32558877)

**FULL ARTICLE:** <https://jamanetwork.com/journals/jama/fullarticle/2767669>

**EDITOR’S COMMENTARY:** This is a well-conducted, large administrative database study of Danish people with hypertension and COVID-19 that does not demonstrate any meaningful association between ACEI/ARB use and either adverse outcomes in patients with COVID-19 or the chance of contracting COVID-19 among patients with hypertension.

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