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Angiotensin-Converting Enzyme Inhibitors vs Angiotensin II Receptor Blockers: A Comparison of Outcomes in Patients with Coronavirus Disease 2019 (COVID-19)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes membrane-bound angiotensin-converting enzyme 2 (ACE2) as a functional receptor to gain entry into host cells. An early finding of the COVID-19 pandemic was the high mortality observed in

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patients with hypertension, diabetes and coronary heart disease,[1] raising concerns with regard to the potential for increased risk of SARS-CoV-2 infection and adverse outcomes in patients taking either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). These concerns largely stemmed from the possible upregulation of ACE2 expression by these medications, although literature exists to both support and refute this notion.[2,3] Observational studies in COVID-19 patients have since shown no association between the use of either ACEIs or ARBs and testing positive for SARS-CoV-2.[4,5] Whether a differential impact of ACEIs compared with ARBs on outcomes in COVID-19 exists remains uncertain. We sought to report on the association of ACEIs compared with ARBs on the risk of hospital admission, intensive care unit (ICU) admission, and need for mechanical ventilation in patients diagnosed with COVID-19.

The data that support the findings of this study are available from the corresponding author upon request. A retrospective cohort analysis of an observational, institutional review board-approved registry of all patients who were tested for COVID-19 in the Cleveland Clinic Health System between March 8, 2020 and May 8, 2020 was conducted. Data regarding baseline characteristics, medications, test results, use of ACEI or ARB, and outcomes were extracted from EPIC electronic medical record system. Subjects recorded as being on both an ACEI and an ARB were excluded from the analysis. In order to account for the heterogeneity in the medical co-morbidities among patients taking ACEI and ARB, an overlap propensity-score weighting was performed, as previously published.[4] The primary outcome of interest was a head-to-head comparison of incidence of a severe disease process as assessed by hospital admission, ICU admission and requirement for mechanical ventilation in COVID-19 patients who were on ACEI vs ARB. All statistical analyses were performed using SAS version 9.4 (SAS Institute). P values were 2-sided, with a significance threshold of 0.05.

The data set consisted of 39,042 patients tested for SARS-CoV-2. A total of 117 patients were tested multiple times for COVID-19. Data regarding only the index test was used for analysis in such cases to avoid duplication. The mean (SD) age was 65 (14) years, 2,758 (51%) were male, and 3,867 (72%) were white. Among all tested patients, 3,094 (58%) were taking ACEIs and 2,277 (42%) were taking ARBs. Among these 5,371 tested patients, 381 (7.1%) tested positive (219 on ACEIs and 162 on ARBs). After overlap propensity-score weighting, the test positivity rate was 7.0% in ACEIs compared with 7.4% in ARBs group (overlap propensity score–weighted odds ratio [OR], 0.95; 95% confidence interval [CI], 0.77–1.17) (Figure). Among patients with positive test results, overlap propensity-score weighting demonstrated the following: 58% taking ACEIs (vs 59% taking ARBs) were admitted to the hospital (OR, 0.95; 95% CI, 0.62–1.45); 22% taking ACEIs (vs 19% taking ARBs) were admitted to an ICU (OR, 1.15; 95% CI, 0.69–1.92); and 12% taking ACEIs (vs 11% taking ARBs) required mechanical ventilation (OR, 1.12; 95% CI, 0.59–2.15) (Figure). A total of 21 deaths (5.6%) occurred. Fifteen of 219 patients (6.9%) were taking an ACEI and 6 of 162 (3.7%) were taking an ARB.

This study did not show a difference in the rates of hospitalization, ICU admission, and need for mechanical ventilation between patients taking ACEIs vs ARBs. Although both classes of medications act on the renin-angiotensin-aldosterone system, their mechanisms of action

differ. Both of these medications, in theory, could enhance viral entry into the respiratory epithelial cell. Interestingly, angiotensin II has previously been studied for its prothrombotic and proinflammatory role in patients with hypertension.[6] It is also increasingly becoming clear that patients with severe COVID-19 experience coagulopathy with increased thromboembolic events. This raises a question regarding the possible differential effects of the two agents in patients with severe COVID-19. The differential effects of ACEIs vs ARBs on bradykinin levels via their interaction with the prekallikrein/kallikrein (PKK) system may be another driver of their differential outcomes in COVID-19 patients. Higher bradykinin levels lead to increased nitric oxide and prostaglandin levels, inhibiting platelet activation and release of von Willebrand factor, which may play a role in COVID-19 coagulopathy.[7] At the same time, prior studies have shown a possible vasoprotective role of bradykinin in mediating endothelium-mediated vasodilation,[8] making such estimates conjectural. Although our study did not show any difference in the odds of testing positive for COVID-19, hospital and ICU admission, and subsequent need for mechanical ventilation, it underscores the need for a much-needed randomized controlled trial to address any differential effects on clinical outcomes in COVID-19 between the two drug classes.

Our study has several limitations, including the potential for bias given the observational nature of the analysis. The majority of our cohort was white, which limits the external validity of our findings, especially given the differential expression of ACE2 receptor among different ethnicities.

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References:

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062. [PubMed: 32171076]
2. Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. Am J Physiol Heart Circ Physiol. 2008;295:H2373–2379. [PubMed: 18849338]
3. Hamming I, van Goor H, Turner AJ, Rushworth CA, Michaud AA, Corvol P, Navis G. Differential regulation of renal angiotensin-converting enzyme (ACE) and ACE2 during ACE inhibition and dietary sodium restriction in healthy rats. Exp Physiol. 2008;93:631–638. [PubMed: 18192334]
4. Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, Carmona-Rubio AE, Jacob M, Procop GW, Harrington S, Milinovich A, Svensson LG, Jehi L, Young JB, Chung MK. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.1855
5. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med. 2020;382:2431–2440. [PubMed: 32356627]
6. Celi A, Cianchetti S, Dell'Omo G, Pedrinelli R. Angiotensin II, tissue factor and the thrombotic paradox of hypertension. Expert Rev Cardiovasc Ther. 2010;8:1723–1729. [PubMed: 21108554]

7. Maier CL, Truong AD, Auld SC, Polly DM, Tanksley C-L, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? Lancet. 2020;395:1758–1759. [PubMed: 32464112]

8. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation. 1997;95:1115–1118. [PubMed: 9054837]

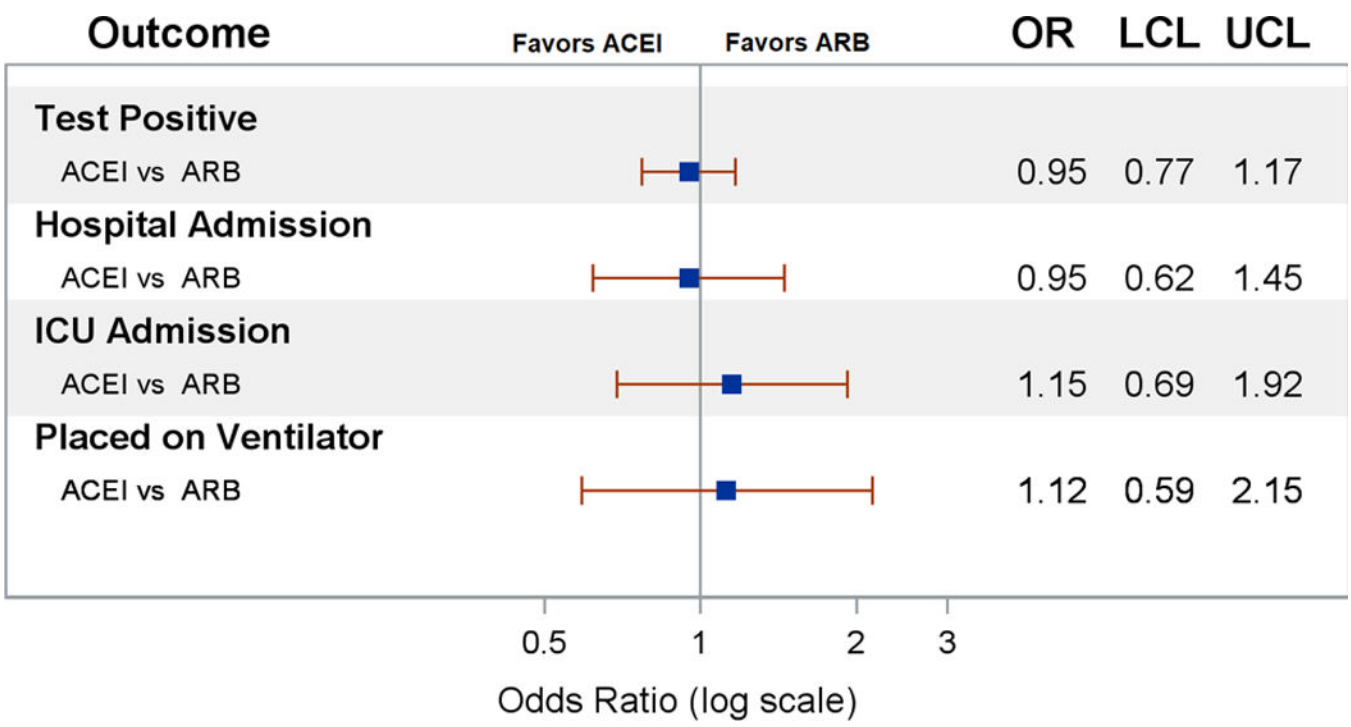

Figure:

Comparison of ACEIs vs ARBs for incidence of hospital admission, ICU admission and requirement for mechanical ventilation in patients with SARS-CoV-2 (primary outcome) and testing positive for SARS-CoV-2 (secondary outcome): overlap propensity-score weighted–analysis ORs with 95% CIs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.