Renin-angiotensin system antagonists are associated with lower mortality in hypertensive patients with COVID-19

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Abstract
The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients with Coronavirus 2019 (COVID-19) has been controversial. We performed a meta-analysis of all published studies that reported the outcomes of ACEIs/ARBs in patients with COVID-19. We included four observational studies (3,267 patients). The use of ACEIs/ARBs was associated with a similar risk of all-cause death (OR: 0.75, 95% CI [0.36, 1.57], p = 0.45). Sensitivity analysis including only hypertensive patients demonstrated a lower risk of death with ACEIs/ARBs use (OR: 0.57, 95% CI [0.32-0.98], p = 0.04). In conclusion, hypertensive patients with COVID-19 treated with ACEIs/ARBS have a lower mortality but further research is needed.

Keywords
COVID-19, coronavirus, hypertension, Angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers

Coronavirus disease 2019 (COVID-19) has been a massive threat to healthcare worldwide. Hypertension is a common comorbidity in patients infected with COVID-19 with a reported incidence of 15-31% of patients admitted with COVID-19.¹⁻³ Hypertension is commonly treated with the renin-angiotensin system (RAS) antagonists [i.e., angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs)]. Angiotensin-converting enzyme-2 (ACE-2) is substantially increased by the use of ACEIs and ARBs.⁴ Chronic angiotensin-1 receptor (AT1R) blockade was also shown to cause ACE-2 upregulation.⁵ Coronaviruses, especially COVID-19, bind to their target cells through ACE-2,⁴ which created concern regarding the continuation of these medications in patients with COVID-19 given the possibility of worsening the infection. Major societies including Heart Failure Society of America (HFSA), American College of Cardiology (ACC), and American Heart Association (AHA) all recommend continuing RAS antagonists in the absence of data supporting this concern. Data on the outcomes of ACEIs/ARBs in patients with COVID-19 is limited; we, therefore, performed the current meta-analysis to fill that gap in the literature.

The current study was conducted according to the proposal for conducting and reporting meta-analyses of observational studies (Moose).⁶ We performed a computerized search limited to the English language through Embase, Medline, and Cochrane databases from December 2019 to May 2020 using the following search terms separately and in combination; “COVID-19,” “ACEIs,” “ARBs,” “RAS antagonists,” “angiotensin-converting enzyme inhibitors,” “angiotensin receptor blockers,” and “renin-angiotensin antagonists.” We included published studies that reported outcomes with the use of ACEIs/ARBs in patients admitted with COVID-19 infection (Figure S1). The data were extracted and confirmed by two independent investigators (MM, MG), both physicians. Bias risk of the included studies was assessed using the New-Castle Ottawa Scale for cohort studies (Table S1). Outcomes included all-cause death, the severity of illness, and length of stay (LOS). Definitions of outcomes, inclusion, and exclusion criteria per each study are shown in Table S2. Statistical analyses were conducted using the

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Review Manager software (Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Categorical variables were reported as frequencies while continuous variables as means with standard deviations (SD). Categorical variables were compared using Fisher's exact or Chi-square tests. Continuous variables were analyzed using the two-sample t-test. A two-tailed p-value of ≤0.05 was considered statistically significant. Odds ratios (ORs) and mean differences (MD) with 95% confidence intervals (CIs) were presented as summary statistics. Statistical heterogeneity was assessed by I² statistic. We used the Der-Simomian and Laird random-effects and random-effects generic inverse variance methods were used to calculate OR and MD, respectively. Potential publication bias was assessed using Egger's test by visual examination of the funnel plots (Figure S2). A sensitivity analysis was performed for all-cause death, including only patients with hypertension.\(^{3,7,8}\)

We included four observational studies (3,267 patients) (ACEIs/ARBs n = 534, no ACEIs/ARBs = 2,733).\(^{3,7–9}\) Baseline characteristics of the included studies are shown in Tables 1 and S3.

The use of ACEIs/ARBs was associated with a similar risk of all-cause death (OR: 0.75, 95% CI [0.36, 1.57], p = 0.45 I² = 62%), severity of illness (OR: 0.73, 95% CI [0.24, 2.24], p = 0.58, I² = 63%), and similar length of stay (LOS) (MD 1.7 days, 95% CI [−0.7, 4.0], p = 0.16, I² = 92%).

Three studies included only patients with hypertension (n = 1,532 patients).\(^{3,7,8}\) The fourth study included all patients on ACEIs/ARBS regardless of hypertension diagnosis. Sensitivity analysis, including only these studies demonstrated a lower risk of death with ACEIs/ARBs use (OR: 0.57, 95% CI [0.32–0.98], p = 0.04, I² = 19%).

A summary of the study results is shown in Figure 1.

**Discussion**

The current meta-analysis is the first to report the outcomes of ACEIs/ARBs in patients with COVID-19. In patients with hypertension, the use of ACEIs/ARBs appears to be associated with a significant reduction in the risk of death. Their use, however, did not affect the severity of illness or LOS in the limited studies that reported them.

Despite the theoretical risk of worsening COVID-19 with the use of ACEIs/ARBs, our analysis demonstrates that they may reduce the risk of death in hypertensive COVID-19 patients. The binding of the coronavirus spike protein to ACE-2 leads to its downregulation and subsequent excessive production of angiotensin and AT1R, contributing to lung injury.\(^{10,11}\) Although ACE-2 acts as the binding site of the COVID-19, it also
inactivates angiotensin II, serves as a negative regulator of RAS and inflammation, and promotes vasodilation.\(^\text{10}\) The use of ARBs, therefore, would block AT1R activation and negate the primary mechanism of COVID-19 mediated lung cytokine storm.\(^\text{12}\) In hypertensive patients, ARBs/ACEIs decreased the peak viral load, which is correlated with severe lung injury compared with other antihypertensive drugs.\(^\text{7}\)

Despite the limitation of pooling observational studies with selection bias and heterogeneity in our analysis, the use of ACEIs/ARBs may be associated with a mortality benefit in hypertensive patients with COVID-19. While thought to be paradoxical, ACEIs/ARBs should be continued in hypertensive COVID-19 patients. In a multivariate analysis, Mehra et al. demonstrated that the ACEIs’ use was associated with lower mortality, but ARBs’ use was not. This finding needs further investigation, given the observational nature of the study.\(^\text{13}\) Randomized trials are ongoing to investigate the role of losartan in the management of COVID-19 patients.\(^\text{14,15}\)

The use of ACEIs/ARBs is associated with a lower risk of death in hypertensive patients with COVID-19. Our study is in agreement with the HFSA/ACC/AHA in that hypertensive patients with COVID-19 should not stop using ACEIs/ARBs. Further research is needed to clarify the mortality benefit in these patients

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**Supplemental Material**
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