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## Association of Renin-Angiotensin System Blockers With Outcomes in Patients with COVID-19



**To The Editor:** Conflicting findings have been reported regarding the safety of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) during the COVID-19 pandemic.<sup>1,2</sup> In reference to the recently published review outlining the relationship between renin-angiotensin system (RAS) and COVID-19 infection,<sup>3</sup> we present additional data regarding the association of RAS inhibitors with outcomes in patients with COVID-19.

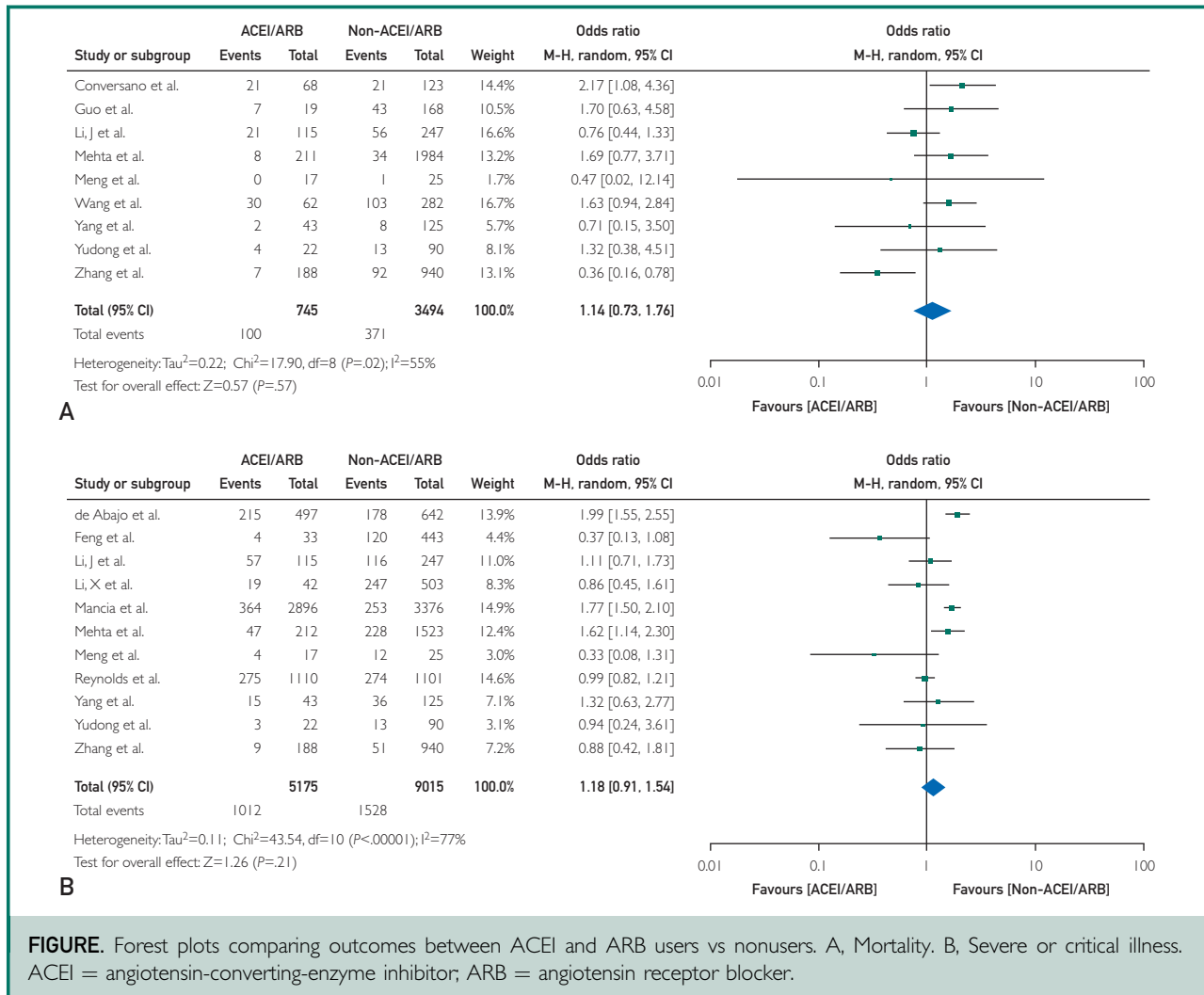
The COVID-19 pandemic, affecting more than 4.5 million people across the globe, has caused significant morbidity and mortality.<sup>4</sup> Angiotensin-converting-enzyme 2 (ACE2) has been implicated in the entry of severe acute respiratory syndrome (SARS)-Cov-2 virus into host cells.<sup>5</sup> As RAS antagonists have been suggested to upregulate ACE2 in few animal models, concerns have been raised that these drugs might be associated with increased risk of infection or severe disease from COVID-19.<sup>6,7</sup> Whether such patients on ACEIs or ARBs should continue these drugs has become a matter of debate. Accordingly, we performed a meta-analysis to study the cumulative evidence for association of the use of ACEIs and ARBs with risk of mortality and severe illness with COVID-19.

A comprehensive search in electronic databases (MEDLINE and EMBASE) was performed for studies published between November 1, 2019, and May 31, 2020. The following key terms were used for search in different combinations: *coronavirus 2019, COVID-19, SARS-Cov-2, renin-angiotensin system, angiotensin-converting-enzyme, angiotensin-converting-enzyme inhibitors, ACEI, angiotensin receptor blockers, ARB, and outcomes*. Inclusion criteria were studies published in peer-reviewed journals and reporting outcomes based on use of ACEIs or ARBs in COVID-19. Two reviewers (A.G. and A.R.) screened the study titles and abstracts, followed by full manuscript evaluation. From individual studies, we collected baseline characteristics of patients including proportion of patients with hypertension and those taking ACEIs or ARBs. The primary outcome was in-hospital mortality. Secondary outcome was severe or critical illness—need for intensive care unit, invasive

mechanical ventilation, or mortality—as defined per individual study protocol. We used the Cochrane review manager 5.3 for statistical analysis. Random-effects model with Mantel-Haenszel method was used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs) for each end point. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>8</sup>

After initial screening and full text review, 15 studies were identified to report outcomes based on use of ACEIs or ARBs in patients with confirmed COVID-19.<sup>1,2,5,9-20</sup> One study was excluded because of retraction by the authors.<sup>10</sup> Thus, a total of 14,882 COVID-19–positive patients (n=5323 ACEI/ARB, n=9559 non-ACEI/ARB) among 14 studies were included. Compared with patients not on RAS inhibitors, patients using RAS inhibitors had similar risks for mortality (OR 1.14 [0.73-1.76];  $P=.57$ ) and severe illness (1.18 [0.91-1.54];  $P=0.21$ ) (Figure). In subanalyses restricted to patients with hypertension, use of ACEIs and ARBs was associated with significantly lower mortality (0.64 [0.45-0.89]), whereas the trend of severe or critical illness (0.76 [0.52-1.12]) remained nonsignificant compared with non-ACEI and ARB users (Supplemental Figure, available online at <http://www.mayoclinicproceedings.org>).

Currently available data from observational studies have shown contrasting findings regarding the relationship between the use of ACEIs and ARBs and outcomes in patients with COVID-19. In this context, our meta-analysis, including >14,000 patients, reconciles the findings of existing studies and shows that use of ACEIs and ARBs is not associated with



increased risk of mortality or severe illness among a broad patient population with COVID-19. Although hypothesis generating, our finding of reduced mortality associated with use of ACEIs and ARBs in patients with hypertension is concordant with few other retrospective studies.<sup>1,18</sup> Of relevance, recent studies have suggested a lower SARS-CoV-2 viral load and inflammatory marker levels in hypertensive patients taking ACEIs or ARBs compared with other antihypertensive medications.<sup>14,18</sup> Our findings have important implications for the management of patients with COVID-19 and cardiovascular

disease; SARS-CoV-2-mediated downregulation of ACE2 and immune dysregulation with endothelial dysfunction, myocardial injury, and prothrombotic state might account for worse outcomes in these patients.<sup>21</sup> Although the role of ACE2 as cellular receptor for SARS-CoV-2 entry into host cells is proven, human studies have been inconclusive with respect to the effect of RAS inhibitors on ACE2 levels.<sup>22</sup> Furthermore, contradictory to the speculation that RAS inhibitor-mediated ACE2 upregulation might increase risk of infection, ACE2 expression has

been suggested to protect against severe lung injury in these patients.<sup>23</sup>

There are several limitations to our study. First, our pooled analyses were based on observational studies that have inherent risk of bias, owing to confounding variables. Patients taking ACEIs or ARBs have increased burden of other comorbidities that might make them more prone to fatality. However, despite this potential bias, we observed no association of use of ACEIs or ARBs with increased risk of mortality or severe illness. Second, ascertainment of drug data is limited in individual

retrospective studies. It remains unknown whether continuation or withdrawal of these drugs during hospitalization influenced outcomes in patients admitted with COVID-19.

In conclusion, our study provides reassurance that there is no increased risk of mortality or severe illness in patients using ACEIs and ARBs compared with nonusers. In patients with hypertension, use of ACEs and ARBs might be associated with reduced mortality; however, these findings need to be confirmed in prospective randomized controlled trials.

#### SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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In reply— Association of Renin-Angiotensin System Blockers with Outcomes in Patients With COVID-19



**To The Editor:** Current guidelines and health professional recommendations endorse the continuation of both antihypertensives angiotensin-