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CORRESPONDENCE

Renin–angiotensin system inhibitor use and the risk of mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials

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At the outset of the coronavirus disease 2019 (COVID-19) pandemic, a few researchers [1, 2] postulated that patients with COVID-19 who are receiving renin–angiotensin system (RAS) inhibitors might be at an increased risk for a severe course of illness. This postulation was based on the fact that angiotensin-converting enzyme 2 (ACE2) is the target receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and RAS inhibitors can upregulate the levels of ACE2 and thus facilitate the entry of SARS-CoV-2 into human host cells. Subsequently, advocates proposed the temporary discontinuation of RAS inhibitors in patients with COVID-19 [1, 2]. Nevertheless, we argued that exposure to RAS inhibitors does not consistently lead to the upregulation of the levels of ACE2 and that the ability of RAS inhibitors to upregulate ACE2 is not absolutely deleterious, since, paradoxically, the upregulation of ACE2 might protect against coronavirus-induced acute lung injury [3–5]. Therefore, the discontinuation of RAS inhibitors in patients with COVID-19 is controversial, and consideration must be given to whether the established benefits of these agents with regard to cardiovascular diseases and their potential lung-protective properties outweigh their uncertain risks [3, 6–8]. Our recent meta-analysis of observational evidence [9] asserted that patients with COVID-19 who used RAS inhibitors had a significantly lower risk of mortality than those who did not use RAS inhibitors. It is likely that residual confounding might have existed in previous observational studies; therefore, further confirmation of such an association is needed in randomized controlled trials. We conducted this meta-analysis of randomized controlled trials to validate the association between the use of RAS inhibitors and mortality in patients with COVID-19.

A systematic literature search was performed in electronic databases, including PubMed, Scopus, the Cochrane Central Register of Controlled Trials, and preprint servers (medRxiv, Research Square, SSRN) with no language restriction to identify eligible studies published prior to March 14, 2021. The search strategy was built based on the following keywords and MeSH terms: "COVID-19", "SARS-CoV-2", "randomized controlled trials", "angiotensin-converting enzyme", "ACE", "ACE inhibitor", "angiotensin receptor blocker", "ARB", "renin–angiotensin-system", "RAS inhibitor", "renin–angiotensin–aldosterone", "RAA inhibitor", and "RAAS inhibitor". The World Health Organization international clinical trial registry platform (who.int/clinical-trials-registry-platform) and the clinical trial registry of the United States (clinicaltrials.gov) were also searched to identify registered trials with reported findings. Two investigators (CSK and SSH) independently performed the literature screening to identify eligible studies. The reference lists of relevant articles were also reviewed to identify potentially eligible studies. The eligibility criteria for the inclusion of studies included a randomized controlled trial design and the comparison of mortality in patients with COVID-19 who did and did not use RAS inhibitors. We excluded studies with observational designs, nonrandomized trials, single-arm trials, and trials that did not report mortality outcomes.

The outcome of interest was all-cause mortality. Each included trial was independently evaluated by two

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Table 1 Characteristics of included trials

Study, Ref.	Country	Design	Total number of patients	Age (median/mean unless otherwise specified)	Proportion of RAS inhibitors use in the treatment group (%)	Mortality		Risk of bias
						RAS inhibitors users *n/N*; *%*)	Non-RAS inhibitors users (*n/N*; *%*)	
Lopes et al. [11]	Brazil	Randomized, open-label trial	659	RAS inhibitor users = 56 (46.1–66.1) Non-RAS inhibitor users = 55 (46.1–63.1)	ACE inhibitor = 21.0 ARB = 79.0	9/334 (2.7)	9/325 (2.8)	Some concerns
Cohen et al. [12]	Global	Randomized, open-label trial	152	RAS inhibitor users = 62 (12) Non-RAS inhibitor users = 62 (12)	ACE inhibitor = 33.3 ARB = 66.7	11/75 (14.7)	10/77 (13.0)	Some concerns
Duarte et al. [13]	Argentina	Randomized, open-label trial	72	RAS inhibitor users = 63.8 (18.7) Non-RAS inhibitor users = 60.1 (17.8)	ARB (telmisartan 80 mg twice daily for 14 days) = 100	2/38 (5.3)	4/34 (11.8)	Some concerns
Nouri-Vaskeh et al. [14]	Iran	Randomized, double-blind, controlled trial	80	RAS inhibitor users = 67.3 (14.8) Non-RAS inhibitor users = 60.1 (17.3)	ARB (losartan 25 mg twice daily for at least 14 days) = 100	2/41 (4.9)	5/39 (12.8)	Some concerns

investigators (CSK and SSH) who also extracted the study characteristics. The data collected included author (s), trial design, country, patient age, proportion of patients using RAS inhibitors, and mortality outcomes. Furthermore, to evaluate potential bias in the reports of randomized trials, two investigators (CSK and SSH) assessed the risk of bias in the included trials with a standardized method, namely, version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [10]. Essentially, RoB 2 is structured into a fixed set of domains of bias, including different aspects of the trial design, conduct, and reporting. The random effects model was utilized for the meta-analysis to estimate the pooled odds ratio with 95% confidence intervals. Subsequently, the heterogeneity between studies was examined using the I^2 statistic and the χ^2 test, with cutoff values of 50% and $P < 0.10$, respectively. The meta-analysis was performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Our systematic literature search returned 878 titles, of which 440 were unique (titles retrieved after removing duplications). Four randomized controlled trials [11–14] were included after screening, with a total of 488 patients who were randomized to the use of RAS inhibitors during hospitalization for COVID-19 and 475 patients who were randomized to the control group and did not receive RAS inhibitors during hospitalization for COVID-19. Specifically, two trials [11, 12] investigated the continued use of RAS inhibitors versus the discontinuation of RAS inhibitors, while the other two trials [13, 14] evaluated the effect of the de novo introduction of RAS inhibitors (telmisartan and losartan, respectively) versus standard care and amlodipine, respectively, among patients hospitalized for COVID-19. Three of the included randomized trials in the meta-analysis were from Brazil [11], Argentina [13], and Iran [14], whereas the remaining randomized trial [12] was an international multicenter study performed in seven countries. Details of the included studies and the overall risk of bias assessed by RoB 2 are depicted in Table 1. In terms of the risk of bias, all the included trials had some concerns with regard to the overall risk of bias; the trials by Lopes et al. [11], Cohen et al. [12], and Duarte et al. [13] had some concerns over the risk of bias in the domain of "deviations from intended interventions" because of their open-label trial design, whereas the trial by Nouri-Vakesh et al. [14] had some concerns over the risk of bias in the domain of "selection of the reported results" due to the possibility that the trial was not anlyzed as pre-specified.

The meta-analysis revealed no difference in the risk of mortality between patients with COVID-19 who did and did not use RAS inhibitors; the estimated effect measure

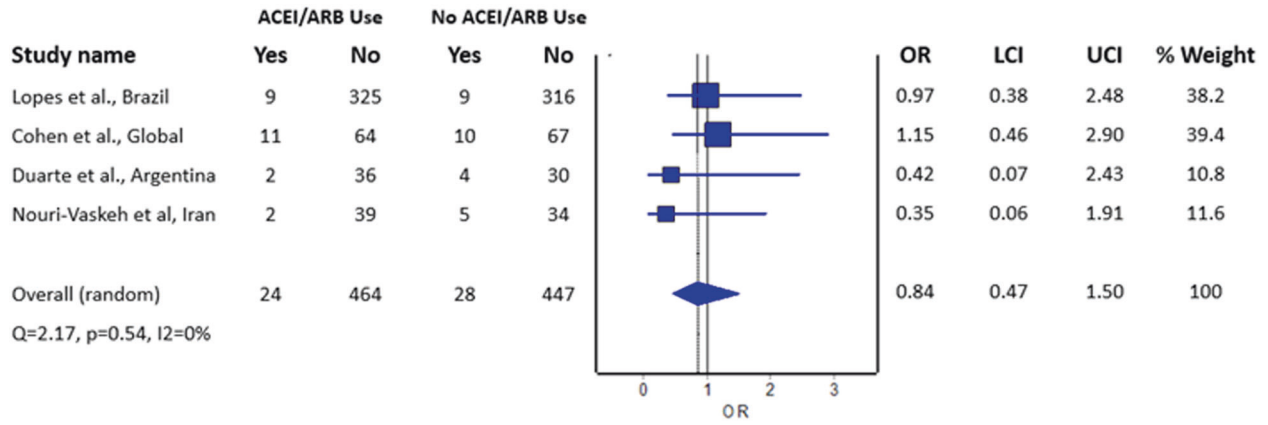

Fig. 1 Pooled odds ratio for mortality in RAS inhibitor users compared to nonusers hospitalized with COVID-19

indicated no benefit with the use of RAS inhibitors with regard to mortality (Fig. 1; pooled odds ratio = 0.84; 95% confidence interval 0.47–1.50, $n = 963$), where there was inadequate evidence to refute the model hypothesis of "no significant difference" given the current sample size. Of note, these findings conflict with those of our previous meta-analysis [9] of observational studies, in which the use of RAS inhibitors was found to be associated with reduced mortality. The findings seem to suggest that while the downregulation of ACE2 upon the entry of SARS-CoV-2 into host cells can occur [15], it may not adequately explain for the underlying mechanism of mortality in patients with COVID-19 tested in the included studies. In addition, because individual RAS inhibitors have different effects on ACE2 expression, it may be difficult to determine the effect in trials that included patients who received any type of RAS inhibitor. Thus far, only the trial by Duarte et al. [13] and the trial by Nouri-Vakesh et al. [14] assessed the use of a single RAS inhibitor (telmisartan and losartan, respectively), although they reported no benefit with regard to mortality. Regardless of the absence of mortality benefits, the findings from our meta-analysis, for the first time, indicate the safety of RAS inhibitors among patients with COVID-19.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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