**RESEARCH LETTER**

# Decreased Mortality of COVID-19 with Renin–Angiotensin–Aldosterone System Inhibitors Therapy in Patients with Hypertension: A Meta-Analysis

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**Running Title:** RAAS Inhibitors and COVID-19

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The coronavirus disease 2019 (COVID-19) is caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), having gradually developed into a pandemic and endangered global health. As drugs for the management of hypertension, the continued use of angiotensin converting enzyme inhibitor (ACEIs) and angiotensin II receptor blockers (ARBs) which are part of renin-angiotensin-aldosterone system (RAAS) inhibitors in patients with COVID-19 has become controversial. On the one hand, animal studies have revealed that ACEIs and ARBs may up-regulate angiotensin-converting enzyme 2 (ACE2) expression which was regarded as the main host cell receptor of SARS-CoV-2.[1, 2] On the other hand, ACEIs and ARBs may be protective in acute lung injury which can be caused by down-regulation of ACE2 expression following SARS-CoV-2 infection.[3, 4] Thus, we performed a meta-analysis of the current studies to explore whether the use of ACEI/ARB was associated with disease severity and mortality in COVID-19 patients with hypertension.

A comprehensive literature search was conducted in Pubmed, Web of Science, Scopus and Embase up to 13 May 2020 using following terms: "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus" AND "ACEI" OR "ARB" OR "Renin-angiotensin system inhibitor" OR "Angiotensin-Converting Enzyme Inhibitor" OR "Angiotensin Receptor Blocker". The primary outcome was disease severity of COVID-19 (classified based on published criteria). Secondary outcome was mortality of COVID-19. Two investigators (XG and YZ) independently screened the articles and any disagreements were resolved through discussion with a third reviewer (YH). The quality of observational studies was evaluated using the Newcastle-Ottawa Scale (NOS). We used Review Manager 5.3 software to calculate odds ratio (OR) and corresponding 95% confidence interval (CI). The chi-square test (assessing the *P*-value) and the $I^2$ statistic were performed to estimate the heterogeneity. A random- or fixed-effects model was applied based on study heterogeneity. Funnel plots were conducted to assess the potential publication bias.

Finally, we included 9 studies comprising 3936 patients with hypertension and COVID-19 infection. All included observational studies were judged as high quality with a score of 8/9 or 7/9 or 6/9. Compared with non-ACEI/ARB treatment, ACEI/ARB treatment was not associated with disease severity (OR 0.71, 95 % CI 0.46–1.08, *P* 0.11, $I^2$ 59%, Fig. 1A) but was related to lower mortality of COVID-19 in patients with hypertension (OR 0.57, 95 % CI 0.38–0.84, *P* 0.004, $I^2$ 0, Fig. 1B). No significant publication bias was observed by funnel plots.

In summary, ACEI/ARB therapy did not aggravate disease severity of COVID-19. Besides, ACEI/ARB therapy can decrease the mortality of COVID-19. Current evidence suggested that RAAS inhibitors should be continued in COVID-19 patients with hypertension. Previous studies have reported that COVID-19 patients with hypertension have higher risk of more severe illness than those without hypertension.[5] In our meta-analysis, some included studies divided patients with no antihypertension drug treatment into the non-ACEI/ARB group. Thus, hypertension might be milder in the non-ACEI/ARB group, leading to underestimating the protective effect of

ACEI/ARB in COVID-19 patients. Future well-designed randomized controlled trials are needed to confirm these findings.

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**Disclosures**

None.

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## Figure legends

**Figure.** Forest plots of **A** disease severity and **B** mortality in the ACEI/ARB versus the non-ACEI/ARB groups in COVID-19 patients with hypertension