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RESEARCH ARTICLE

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Association of renin-angiotensin-aldosterone system inhibitors with mortality and testing positive of COVID-19: Meta-analysis

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Abstract

Some have hypothesized that the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) may modify susceptibility to coronavirus disease-2019 (COVID-19) in humans. Thus, we conducted two meta-analyses to investigate the effect of ACEI and ARB on mortality and susceptibility to COVID-19. Pubmed and EMBASE were searched through June 2020 to identify clinical trials that investigated the testing positive and in-hospital mortality rates for COVID-19 for those who were treated with ACEI and/or ARB and for those who were not treated with ACEI or ARB. The first analysis investigated the testing positive rate of COVID-19. The second analysis investigated the in-hospital mortality rate for patients with COVID-19. Three eligible studies for the first analysis and 14 eligible studies for the second analysis were identified. The first analysis demonstrated that the use of ACEI or ARB did not affect the testing positive rates (odds ratio [OR] [confidence interval [CI]] = 0.96 [0.88–1.04]; $p = .69$, OR [CI] = 0.99 [0.91–1.08]; $p = 0.35$, respectively). The second analysis showed that the use of ACEI and/or ARB did not affect in-hospital mortality (risk ratio [RR] 95% [CI]] = 0.88 [0.64–1.20], $p = 0.42$). The subgroup analysis by limiting studies of patients with hypertension showed ACEI and/or ARB use was associated with a significant reduction of in-hospital mortality compared with no ACEI or ARB use (RR [CI] = 0.66 [0.49-0.89], $p = 0.004$). Our analysis demonstrated that ACEI and/or ARB use was associated neither with testing positive rates of COVID-19 nor with mortality of COVID-19 patients.

KEYWORDS

ACEI, ARB, COVID-19

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease-2019 (COVID-19), can infect host cells by means of interaction with membrane-bound angiotensin-converting enzyme 2 (ACE2) on respiratory epithelium.[1] ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) are considered first-choice drugs for patients with hypertension, heart failure, and chronic kidney disease, but also increase the expression of ACE2.[2] Therefore, some have hypothesized that their use may modify susceptibility to infection with SARS-CoV-2 in humans. On the contrary, ACE2 expression is downregulated following SARS-1 infection, resulting in disproportionate activation of the renin-angiotensin-aldosterone system and exacerbated pneumonia progression.[3] However, there is no consensus as to whether their use might increase or reduce of severity

TABLE 1 Study profile and outcomes for the first analysis

Author	Country	Total number (*n*)	ACEI/ARB (*n*)	No ACEI/ARB (*n*)	Testing positive (OR [95% CI])	
					ACEI	ARB
Mancia[10]	Italy	37,031	6,272	30,759	0.96 [0.87–1.07]	0.95 [0.86–1.05]
Mehta[11]	United States	18,472	2,285	16,187	0.89 [0.72–1.10]	1.09 [0.87–1.37]
Reynolds[12]	United States	3,384	1,692	1,692	1.00 [0.84–1.21]	1.07 [0.90–2.27]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; OR, odds ratio.

or susceptibility for SARS-CoV-2 infection. Although several meta-analyses were conducted to assess the outcome of ACEI/ARB use on patients with COVID-19,[4–6] a large observational study using databases in Asia, Europe, and North America which was included in these meta-analyses, was retracted from a peer-reviewed journal.[7] Therefore, investigation of the effect of ACEI/ARB use on patients with COVID-19 is still warranted, hence we conducted two meta-analyses to compare mortality and susceptibility of SARS-CoV-2 infection between patients treated and those not treated with ACEI and/or ARB.

2 | METHODS

All observational studies that investigated the testing positive and in-hospital mortality rates for COVID-19 for those who were treated with ACEI or/and ARB and for those not treated with ACEI or ARB were identified using a two-level strategy. First, databases including Pubmed and EMBASE were searched through June 18, 2020. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Search terms included "angiotensin," "ACE," "ARB," "RAAS," and "COVID-19 or coronavirus." We did not apply language limitations. Two independent and blinded authors (Yujiro Yokoyama and Toshiki Kuno[8]) reviewed the search results separately to select the studies based on present inclusion and exclusion criteria. Disagreements were resolved by consensus. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9]

We conducted two independent analyses. The first analysis investigated the testing positive rate of COVID-19 (positive number/all tested number) for those who were on ACEI and/or ARB and for those who were not on ACEI or ARB. The second analysis investigated in-hospital mortality for patients with COVID-19 treated with ACEI and/or ARB and those not treated with ACEI or ARB. Included studies met the following criteria: the study design was an observational study, the study population included patients with COVID-19, enrolled patients were divided into the ACEI/ARB and no ACEI/ARB groups.

Odds ratios (ORs) for testing positive and hazard ratios (HRs) or risk ratios (RRs) for in-hospital mortality were extracted or calculated from each study. The Review Manager (RevMan) Version 5.3 (Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark) was used to combine ORs for the first analysis and HRs/RRs for the second analysis in the random-effects model.

For the second analysis, the subgroup analysis was conducted by restricting studies which only investigated the patients with hypertension and the sensitivity analysis was performed by removing the outcome without adjustment methods.

3 | RESULT

Our search identified three eligible studies for the first analysis[10–12] and 14 eligible studies for the second analysis[11,13–25] (Figure S1). Characteristics and outcomes of the studies are summarized in Tables 1 and 2. The first analysis showed that the testing positive rates were similar for those treated with ACEI and those not treated with ACEI (OR [95% confidence interval [CI]] = 0.96 [0.88–1.04], $p = 0.69$; Figure 1) and for those treated with ARB and those not treated with ARB (OR [95% CI] = 0.99 [0.91–1.08], $p = 0.35$; Figure 2).

The second analysis demonstrated that in-hospital mortality for patients with positive COVID-19 testing was similar between for those on ACEI and/or ARB and those not on ACEI or ARB (RR [95% [CI]] = 0.88 [0.64-1.20], $p = 0.42$; Figure 3). However, the sensitivity analysis by removing the outcome without adjustment methods showed that ACEI and/or ARB use was associated with a significant reduction of in-hospital mortality compared with no ACEI or ARB use (RR [CI] = 0.59 [0.35-0.98], $p = 0.04$; Figure S2). Similarly, the subgroup analysis by restricting studies which investigated only patients with hypertension showed that ACEI and/or ARB use was associated with a significant reduction of in-hospital mortality compared with no use of ACEI or ARB (RR [CI] = 0.66 [0.49–0.89], $p = .004$; Figure 4). The sensitivity analysis by removing the outcome without adjustment methods also showed that ACEI and/or ARB use was associated with a significant reduction of in-hospital mortality compared with no use of ACEI or ARB in patients with hypertension (RR [CI] = 0.63 [0.39–0.99], $p = 0.04$; Figures S2 and S3).

TABLE 2 Study profile and outcomes for the second analysis

Author	Country	Total number (*n*)	ACEI/ ARB (*n*)	no ACEI/ ARB (*n*)	In-hospital mortality (RR/HR [95% CI]) ACEI/ARB
Cannata[13]	Italy	280	56	224	0.05 [0.01–0.54][a]
Conversano[14]	Italy	96	68	28	0.5 [0.2–1.2]
Gao[15]	China	710	183	527	0.93 [0.31–2.84][a]
Guo[16]	China	187	19	168	1.72 [0.89–3.31]
Hu[17]	China	149	65	84	3.86 [0.16–93.31]
Jung[18]	Korea	1,954	377	1,577	0.87 [0.54–1.41][a]
Li[19]	China	362	115	247	0.81 [0.51–1.26]
Mehta[11]	USA	1,705	211	1,494	1.67 [0.78–3.55]
Meng[20]	China	42	17	25	0.48 [0.02–11.16]
Richardson[21]	USA	1,366	413	953	1.18 [0.99–1.41]
Tadeschi[22]	Italy	311	N/A	N/A	0.97 [0.68–1.39][a]
Yang[23]	China	126	43	83	0.35 [0.08–1.51]
Zhang[24]	China	1,128	174	348	0.37 [0.15–0.89][a]
Zhou[25]	China	2,718	906	1,812	0.32 [0.15–0.66][a]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensinogen receptor blocker; CI, confidence interval; HR, hazard ratio; N/A, not available; RR, risk ratio.
[a]Adjusted RR or HR.

4 | DISCUSSION

The first meta-analysis assessed the susceptibility to COVID-19 for those who were on ACEI or ARB and showed that the use of ACEI/ARB did not affect the susceptibility to COVID-19. In the second meta-analysis, we observed that the use of ACEI and/or ARB was not associated with a change in in-hospital mortality for patients who were diagnosed with COVID-19. When restricting studies with hypertensive patients only, the use of ACEI and/or ARB was associated with a significant reduction in in-hospital mortality compared with no use of ACEI or ARB.

There has been a debate on whether ACEI/ARB should be continued or discontinued for those who were previously treated with ACEI/ARB. Our results support continuous use of the medications regardless of prior history of hypertension, since a protective effect of ACEI/ARB on patients with COVID-19 has been reported, including reduced severity of COVID-19 pneumonia by preserving hypoxic vasoconstriction, limited deterioration of renal function, and protection against myocardial injury.[26] Cannata et al.[13] reported that COVID-19 patients who continued ACEI/ARB had lower all-cause mortality compared with those who discontinued ACEI/ARB at the time of hospitalization. In addition, our findings might suggest a potential benefit of initiation of ACEI/ARB for patients with hypertension who were not previously treated with ACEI/ARB.

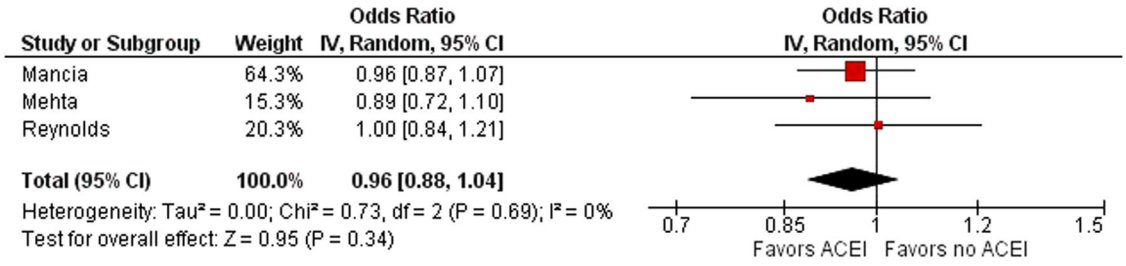

FIGURE 1 Comparisons of the testing positive rates of COVID-19 for those who were on ACEI versus for those who were not on ACEI. The left portions of the figure show the studies analyzed with their corresponding odds ratio, lower, and upper limits. The right portions of the figure show a forest plot of the data. The horizontal lines represent the values within the 95% confidence interval of the underlying effects. The vertical line indicates an odds ratio of 1. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; COVID-19, coronavirus disease-2019; OR, odds ratio; IV, inverse variance

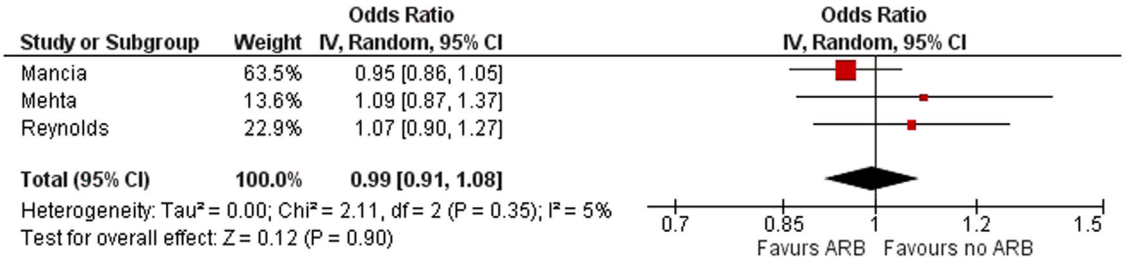

FIGURE 2 Comparisons of the testing positive rates of COVID-19 for those who were on ARB versus those who were not on ARB. The left portions of the figure show the studies analyzed with their corresponding odds ratio, lower, and upper limits. The right portions of the figure show a forest plot of the data. The horizontal lines represent the values within the 95% confidence interval of the underlying effects. The vertical line indicates an odds ratio of 1. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COVID-19, coronavirus disease-2019; CI, confidence interval; IV, inverse variance

There have been several meta-analyses reported that investigated the effect of ACEI/ARB on COVID-19 patients.[4–6] However, they included a large observational study using databases in Asia, Europe, and North America,[7] which was retracted from a peer-reviewed journal.[27] Since this observational study might have affected the outcomes of these meta-analyses, an updated meta-analysis is warranted to clarify the true effect of ACEI/ARB on COVID-19 patients.

Our study has some limitations. First, our analysis included observational studies and is subject to possible selection bias and confounding. However, the sensitivity analysis by removing the outcomes without adjustment methods for the second analysis showed the potential benefit of ACEI/ARB use compared with no use of ACEI/ARB. Therefore, the use of ACEI/ARB is less likely to have a negative impact on in-hospital mortality. Second, we could not analyze severity for COVID-19 such as the ICU admission or intubation rates, since each study used a different definition for severe disease. Similarly, we could not analyze the outcomes of ACEI and ARB separately since few studies reported these separately.

In conclusion, our analysis demonstrated that ACEI and/or ARB use was not associated with positive rates of COVID-19, and mortality in COVID-19 patients, but might exert beneficial effects on hypertensive patients with COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Yujiro Yokoyama and Toshiki Kuno had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. *Study concept and design*: Toshiki Kuno. *Data curation, drafting of the manuscript, and statistical analysis*: Yujiro Yokoyama.

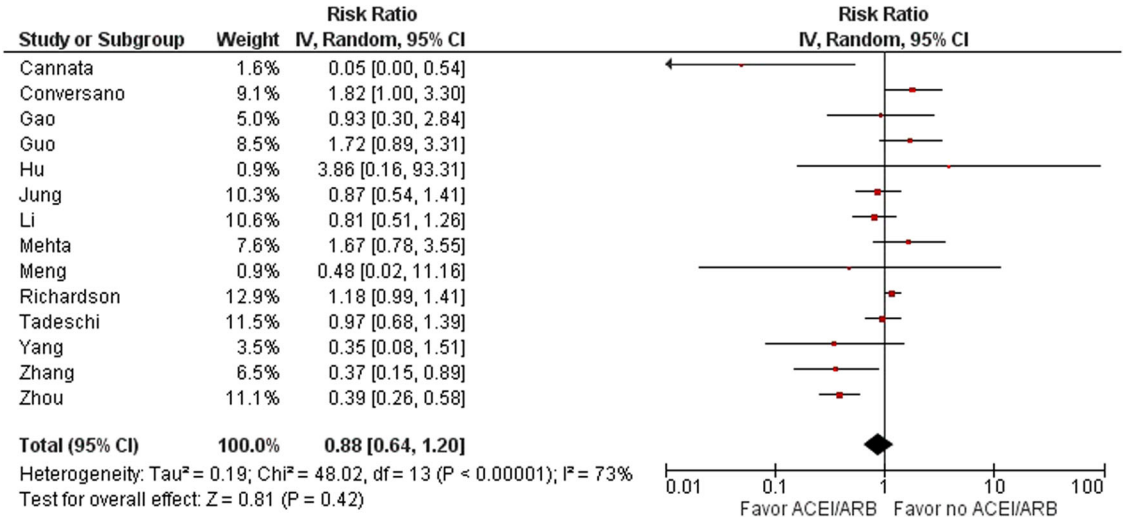

FIGURE 3 Comparisons of in-patient mortality of COVID-19 for those who were on ACEI and/or ARB and for those who were not on ACEI or ARB. The left portions of the figure show the studies analyzed with their corresponding risk ratio, lower, and upper limits. The right portions of the figure show a forest plot of the data. The horizontal lines represent the values within the 95% confidence interval of the underlying effects. The vertical line indicates a risk ratio of 1. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; COVID-19, coronavirus disease-2019; IV, inverse variance

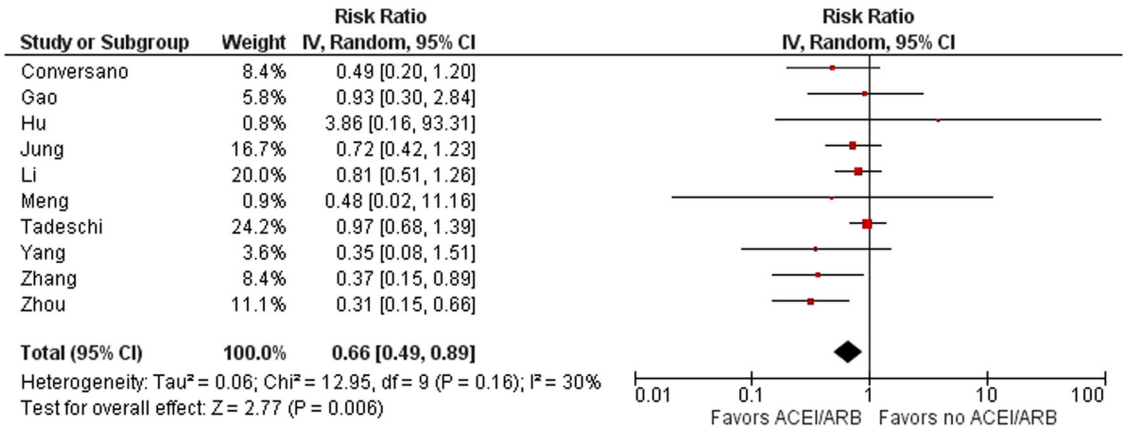

FIGURE 4 Comparisons of in-patient mortality of COVID-19 for patients with hypertension who were on ACEI and/or ARB and for patients with hypertension who were not on ACEI or ARB. The left portions of the figure show the studies analyzed with their corresponding risk ratio, lower, and upper limits. The right portions of the figure show a forest plot of the data. The horizontal lines represent the values within the 95% confidence interval of the underlying effects. The vertical line indicates a risk ratio of 1. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; COVID-19, coronavirus disease-2019; IV, inverse variance

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DATA AVAILABILITY STATEMENT

Data sharing not applicable. No new data generated given its nature of meta-analysis from published data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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