Original Article

Renin-Angiotensin-Aldosterone System Inhibitors and Risks of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

A Systematic Review and Meta-Analysis

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Abstract—The viral spike coat protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) engages the human ACE (angiotensin-converting enzyme) 2 cell surface receptor to infect the host cells. Thus, concerns arose regarding theoretically higher risk for coronavirus disease-19 (COVID-19) in patients taking ACE inhibitors/angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]). We systematically assessed case-population and cohort studies from MEDLINE (Ovid), Cochrane Database of Systematic Reviews PubMed, Embase, medRXIV, the World Health Organization database of COVID-19 publications, and ClinicalTrials.gov through June 1, 2020, with planned ongoing surveillance. We rated the certainty of evidence according to Cochrane methods and the GRADE approach. After pooling the adjusted odds ratios from the included studies, no significant increase was noted in the risk of SARS-CoV-2 infection by the use of ACE inhibitors (adjusted odds ratio, 0.95 [95% CI, 0.86–1.05]) or ARBs (adjusted odds ratio, 1.05 [95% CI, 0.97–1.14]). However, the random-effects meta-regression revealed that age may modify the SARS-CoV-2 infection risk in subjects with the use of ARBs (coefficient, −0.006 [95% CI, −0.016 to 0.004]), that is, the use of ARBs, as opposed to ACE inhibitors, specifically augmented the risk of SARS-CoV-2 infection in younger subjects (<60 years old). The use of ACE inhibitors might not increase the susceptibility of SARS-CoV-2 infection, severity of disease, and mortality in case-population and cohort studies. Additionally, we discovered for the first time that the use of ARBs, as opposed to ACE inhibitors, specifically augmented the risk of SARS-CoV-2 infection in younger subjects, without obvious effects on COVID-19 outcomes. (***Hypertension*. 2020;76:00-00. DOI: 10.1161/HYPERTENSIONAHA.120.15989.)**

● Data Supplement

Key Words: angiotensin-converting enzyme2 ■ coronavirus disease ■ diabetes mellitus ■ meta-analysis ■ severe acute respiratory syndrome coronavirus 2

The coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global public health crisis problem.[1] Since December 2019, COVID-19 spread rapidly to 187 countries, leading to >8.5 million cases with over 456 000 fatalities.[2] SARS-CoV-2 is transmitted from human to human through respiratory droplets or close contact, and studies suggested that SARS-CoV-2 is more transmissible than pandemic influenza A virus subtype H1N1, SARS, and Middle East respiratory syndrome.[3]

In clinical studies, the most common comorbidities among patients with COVID-19 are hypertension, diabetes mellitus, and cardiovascular diseases.[4] Patients with such comorbidities are often prescribed with RAASi (renin-angiotensin-system inhibitors) including ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blockers (ARBs). Given SARS-CoV-2 enters human cells by attaching to the membrane-bound ACE2 receptor,[5] concerns were raised regarding whether the use of RAASi could increase the susceptibility to SARS-CoV-2 infection since both ACE inhibitors and ARBs have been shown to up-regulate ACE2 expressions in animal models.[6]

Several large-scale studies from different countries assessed the relationship between the use of RAASi and

Received July 15, 2020; first decision July 30, 2020; revision accepted August 31, 2020.

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The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.120.15989.

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SARS-CoV-2 test positivity.[7–11] Mancia et al. found that ACE inhibitors and ARBs were more frequently taken by patients with COVID-198 than by controls because of their higher prevalence of cardiovascular disease, but there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.

The effect of RAASi on the risk of SARS-CoV-2 infection could complicate clinical patient management. A possible scenario is that in patients with hypertension a RAASi might be no longer organ-protective, and could even be potentially harmful due to the activation of ACE2 during the COVID-19 pandemic. Carefully curated and reliable data from an all-inclusive systemic review may shed light on this important concern timely when a well-designed clinical trial is not available. In this study, we aimed to clarify the association between the use of ACE inhibitors or ARBs and the risk of SARS-CoV-2 infection. The medical literature regarding the impact of the use of ACE inhibitors or ARBs on SARS-CoV-2 infection was systematically reviewed, and a meta-analysis was performed to provide comprehensive evidence of the effect of RAASi on the susceptibility to SARS-CoV-2 infection.

Methods

Data, analytic methods, and study materials are given below. Further details are available in the Data Supplement and on reasonable request from the corresponding author.

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[12] and used Cochrane methods.[13] We prospectively submitted the systematic review protocol for registration on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; CRD42020190666; Appendix pp 20–29).

Literature Research

The systematic search was performed by searching all publications from January 1, 2020 to June 1, 2020, in MEDLINE (Ovid), CINAHL(Ovid), Cochrane Database of Systematic Reviews PubMed, Embase, medRXIV, Cnki.net, World Health Organization database of COVID-19 publications, and ClinicalTrials.gov to June 1, 2020, with planned ongoing surveillance that investigated the association between the use of RAASi and the risk of SARS-CoV-2 infection.

Data Extraction and Quality Assessment

Two investigators (C.-K. Chan and Y.S. Huang) who performed the literature search also independently extracted the data from the included studies using a standardized data spreadsheet. Discrepancies were resolved through consensus or referral to a third reviewer (V.-C. Wu). The following variables were extracted: author, journal, publication year, study design, geographic location, participants' details (number, study population, age, sex, and comorbidities, including hypertension, diabetes mellitus, heart failure, and chronic kidney disease), use of antihypertensive drugs, such as ACE inhibitors, ARBs, calcium-channel blockers, beta-blockers, diuretics, outcomes (including positive SARS-CoV-2 test results and disease prognosis/severity, if available). Study authors were not contacted for additional information.

The quality of the included studies was assessed independently by 2 investigators (C.-K. Chan and I.-J. Tsai) using the Newcastle–Ottawa Quality Assessment Scale scoring system for comparative nonrandomized studies corresponding with all studies design.[14] Studies with a Newcastle–Ottawa Quality Assessment Scale score of ≥7 were regarded as high quality. Two investigators (H.-C. Pan and I.-J. Tsai) independently assessed the risk of bias of each included study with the updated version of the Cochrane Risk of Bias Tool.[15] We used the GRADEpro app to rate evidence and present it in GRADE evidence profiles and summary of findings tables.[15] We formally assessed the credibility of potential effect-modifiers using GRADE guidance.[16] In addition, we included the studies extracted from the medRXIV (under peer review but also visible in PubMed) because we want to explore the whole picture of the RAASi with all available data.

Outcomes of Interests

The primary outcome was the positive SARS-CoV-2 infection. Secondary outcomes were the severe infection (including ventilator use or intensive care unit admission) or mortality of COVID-19. Crude odds ratio and the 95% CI were directly calculated when the 2 by 2 cross-table was provided in all of the included studies. In contrast, adjusted odds ratio (aOR) and the 95% CI was also extracted.

Statistical Analysis

The pooled aOR for binary outcomes (ie, SARS-CoV-2 infection) was calculated in this meta-analysis. The data from individual studies were pooled using the DerSimonian and Laird random-effect model. Inconsistency across studies was assessed using the I^2 statistics in which a value >50% indicated a substantial heterogeneity. The quantitative meta-analysis was conducted using Comprehensive Meta-Analysis version 3.3.070 (Biostat).

Results

Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the meta-analysis is shown in Figure S1 in the Data Supplement and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is shown in Appendix pp 10–12. The search strategy identified 945 studies, of which 419 articles were duplicates. A total of 491 articles were excluded after reading their titles and abstracts. The remaining 88 articles were evaluated for this meta-analysis. In total, 7 articles,[7–11,17,18] including 4 cohort studies and 3 case-control studies, were eligible for this meta-analysis according to the criteria mentioned above. The respective use of ACE inhibitors or ARBs records could be separately collected within all the 7 articles. Among them, 6 articles[7–11,17] provided the aOR of the risk of SARS-CoV-2 infection, and 4 articles[7–10] provided the aOR of the severity or mortality of COVID-19. The list of excluded studies and the reasons for exclusion are listed in Figure S1.

Patient Characteristics

The patient characteristics of the included studies are shown in Table 1, and the outcomes of included comparative studies are shown in Table 2. The 7 studies were performed in Italy, Spain, Israel, South Korea, and the United States. All of the selected studies were published in 2020 with different sample sizes that ranged from 3789 to 65 149 patients. The average or median age of 3 studies[8,9,18] was >60 years and that of 4 studies[7,10,11,17] was <60 years. Clinical outcomes were defined as the risk of SARS-CoV-2 infection and the severity/mortality of COVID-19 with crude odds ratio and aOR in all studies. The results of the quality assessment of the included studies are presented in (Table S1).

Effect of ARBs and ACE inhibitors on the Risk of SARS-CoV-2 Infection

Together, 14 921 users of ACE inhibitors and 149 163 nonusers were included. In the eligible studies, 2756 users of ACE inhibitors had a positive SARS-CoV-2 test result among a total of 22 114 patients of SARS-CoV-2 infection. On the other

Table 1. Characteristics of Included Comparative Studies

Author	Country (City)	Study Design	Study Status	Study Period	Age, y	Men, %	HTN/DM/Heart Failure/CKD Prevalence, %	Patient Sample Size	ACE Inhibitors/ ARBs Cases	No ACE Inhibitors/ARBs Cases
de Abajo et al[9]	Spain (Madrid)	Population-based case-control study	Published (original article)	March 1 to March 24, 2020	69.1±15.4	61	50/20.1/3.8/5.3	12 529	4221 (ACE inhibitors: 2432; ARBs: 1860)	8308 (no ACE inhibitors: 10 097; no ARBs: 10 669)
Chodick et al[11]	Israel	Cross-sectional real-world data	Published (brief report)	N/A	37.3	47.4	11.2/5.2/0.5/6.4	14 520	975 (ACE inhibitors: 388; ARBs: 603)	13 545 (no ACE inhibitors: 14 132; no ARBs: 13 917)
Huh et al[17]	South Korea	Case-control study using a nationwide database	Unpublished (original article; medRXIV)	The last date of data entry was April 8, 2020	48.3	49.4	32.8/27.6/ N/A /10.8	65 149	ACE inhibitors: 653; ARBs: 10 045	no ACE inhibitors: 64 496; no ARBs: 55 104
Mancia et al[8]	Italy (Lombardy)	Population-based case-control study	Published (original article)	February 21 to March 11, 2020	68±13	63.1	51.2/10.9/2.9/3	37 031	ACE inhibitors: 8071; ARBs: 7304	no ACE inhibitors: 28 960; no ARBs: 29 727
Mehta et al[10]	United States (OH and FL)	Retrospective cohort	Published (original article)	March 8 to April 12, 2020	49±21	40	39.6/18.8/10.2/ N/A	18 472	2285 (ACE inhibitors: 1322; ARBs: 982)	16 187 (no ACE inhibitors: 17 150; no ARBs: 17 490)
Rentsch et al[18]	United States	Retrospective cohort	Unpublished (original article; medRXIV)	February 8 to March 30, 2020	median 65.7 (IR, 60.5–70.7)	90.2	65/37.8/ N/A /14.8	3789	1532 (ACE inhibitors: 1011; ARBs: 563)	2257 (ACE inhibitors: 2778; ARBs: 3226)
Reynolds et al[7]	United States (NY)	Population-based cohort	Published (original article)	March 1 to April 15, 2020	Median 49 (IR, 34–63)	41.5	34.6/18/6.2/9.6	12 594	2319 (ACE inhibitors: 1044; ARBs: 1328)	10 275 (no ACE inhibitors: 11 550; no ARBs: 11 266)

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; HTN, hypertension; and N/A, not applicable.

hand, 22 685 users of ARBs and 141 399 nonusers were included. In the eligible studies, 3352 users of ARBs had a positive SARS-CoV-2 test result among a total of 22 114 patients of SARS-CoV-2 infection. The initial crude results showed that either the users of ACE inhibitors or ARBs had higher risks of SARS-CoV-2 infection than nonusers (crude odds ratio, 1.21 [95% CI, 1.01–1.45] for ACE inhibitors; crude odds ratio, 1.25 [95% CI, 0.99–1.57] for ARBs), but with a substantial heterogeneity (both I^2 statistics >75%; Figure S2).

After adjusting for possible confounders, the risk of SARS-CoV-2 infection in the users of ACE inhibitors was similar to that of nonusers (aOR, 0.95 [95 % CI, 0.86–1.05]; I^2 statistics=34.7%). Although the risk of SARS-CoV-2 infection in the users of ARBs was numerically slightly higher than that of the nonusers, no statistically significant difference was noted (aOR, 1.05 [95 % CI, 0.97–1.14]; I^2 statistics=34.9%; Figure 1). It was noted that the heterogeneity substantially decreased when we pooled the aORs. Additionally, the sensitivity analysis revealed that the results were not altered when removing anyone's study (data not shown).

Effect Modification of Age

We first separated the included studies by the mean or median age of 60 years. The results showed that either the older users of ACE inhibitors or older users of ARBs had similar risks of SARS-CoV-2 infection than those of the nonusers. The younger users of ACE inhibitors also had similar risk of SARS-CoV-2 infection than that of the nonusers. Noticeably, the result indicated that the users of ARBs <60-year-old had a mild but statistically higher risk of SARS-CoV-2 infection than that of nonusers (aOR, 1.09 [95% CI, 1.01–1.18]; I^2 statistics=0%; Figure 2). Furthermore, we conducted a meta-regression analysis by treating the continuous mean or median age as an effect modifier. The result also suggested that the age did not modify the effect of ACE inhibitors on risks of SARS-CoV-2 infection (coefficient, –0.006 [95% CI, –0.016 to 0.004]; Table S2 and Figure 3A). However, the result showed age significantly modified the effect of ARBs on risks of SARS-CoV-2 infection (coefficient, –0.006 [95% CI, –0.012 to 0.0002]; P=0.042; Table S2 and Figure 3B).

Subgroup Analysis of Other Characteristics

In addition to age, we also investigated the possible effect modification of other characteristics, including the proportions of male sex, the existence of hypertension, diabetes mellitus, heart failure, or chronic kidney disease. The results showed that these characteristics did not modify the effect of ACE inhibitors on the risk of SARS-CoV-2 infection. Regarding the impact of the use of ARBs, it was shown that the proportion of hypertension patients might play a role

Table 2. Outcomes of Included Comparative Studies

Author	Crude Odds Ratio of SARS-CoV-2 Infection	Adjust Odds Ratio of SARS-CoV-2 Infection	Adjust Odds Ratio of Risk of Severe SARS-CoV-2	Severity and Mortality Outcome	Confounding Factors	Reference	Definition of Severe Infection
de Abajo et al[9]	Yes	Yes	Yes	Yes	Adjusted for the age, sex, history of DM, dyslipidemia, ischemic heart disease, heart failure, atrial fibrillation, thromboembolic disease, cerebrovascular accident, chronic obstructive pulmonary disease, asthma, cancer, and CKD	Patients without RAASi anti-HTN drugs	Mortality and ICU admission
Chodick et al[11]	Yes	Yes	No	No	Adjusted for age, sex, HTN, DM, BMI, and heart failure status	Patients without ACE inhibitors or ARBs usage	N/A
Huh et al[17]	Yes	Yes	No	No	Adjusting for comorbidities and other concomitant medications	Patients without ACE inhibitors or ARBs usage	N/A
Mancia et al[8]	Yes	Yes	Yes	Yes	Adjust for drugs (anti-HTN and OHA and other drugs) and coexisting conditions (cardiovascular, respiratory, kidney disease and cancer)	Patients without ACE inhibitors or ARBs usage	Critical or fatal infection (assisted ventilation or mortality)
Mehta et al[10]	Yes	Yes	Yes	Yes	Propensity score match	Patients without ACE inhibitors or ARBs usage	ICU admission
Rentsch et al[18]	Yes	No	No	No	N/A	Patients without ACE inhibitors or ARBs usage	N/A
Reynolds et al[7]	Yes	Yes	Yes	Yes	Adjusted for demographics and comorbidities	Patients without ACE inhibitors or ARBs usage	Severe illness (intensive care, mechanical ventilation, or mortality)

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; N/A, not applicable; OHA, oral hypoglycemic agents; RAASi, renin-angiotensin-aldosterone system inhibitors; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

in the association between the use of ARBs and the risk of SARS-CoV-2 infection (coefficient, −0.007 [95% CI, −0.013 to −0.001]; *P*=0.028; Table S2).

Effect of ARBs and ACE Inhibitors on Severe COVID-19

The overall analysis included 4 articles.[7–10] The risk associated with the use of ACE inhibitors or ARBs versus the risk of severe COVID-19 or mortality was estimated via aOR. The results demonstrated that the risks of severe COVID-19 or mortality in either the users of ACE inhibitors (aOR, 1.00 [95 % CI, 0.80–1.26]) or the users of ARBs was similar with those nonusers (aOR, 0.99 [95 % CI, 0.83–1.18]; Figure 4). In the subgroup analysis, we did not see the effect of the use of ACE inhibitors or ARBs on the outcomes of COVID-19 in older and younger subjects (Figure S5 and Figure S6).

Risk of Bias and Publication Bias

The risks of bias should be addressed as low to moderate in these observational study designs (Table 1). As seen in Figure S3 and Figure S4, the funnel plots showed symmetrical distribution of the adjusted odds ratios, which suggested an absence of publication bias among the included studies. The Egger tests also confirmed the absence of publication bias among the included studies for the use of ACE inhibitors (*P*=0.545) and the use of ARBs (*P*=0.265).

Discussion

The systematic review findings of the 7 high-quality studies (with comparative data on the controls) on SARS-COV-2 infection provide the best available evidence proving that therapy with ACE inhibitors or ARBs is not associated with an increase of positive SARS-CoV-2 test result and the severity of COVID-19 disease or overall population mortality as a whole in case-population and cohort studies. However, we also showed for the first time that the usage of ARBs, as opposed to ACE inhibitors, specifically augmented the adjusted odds ratio of SARS-CoV-2 infection in younger subjects (<60 years old); thus, we demonstrated that ACE inhibitors and ARBs might lead to different susceptibility to SARS-CoV-2 infection in various individual groups.

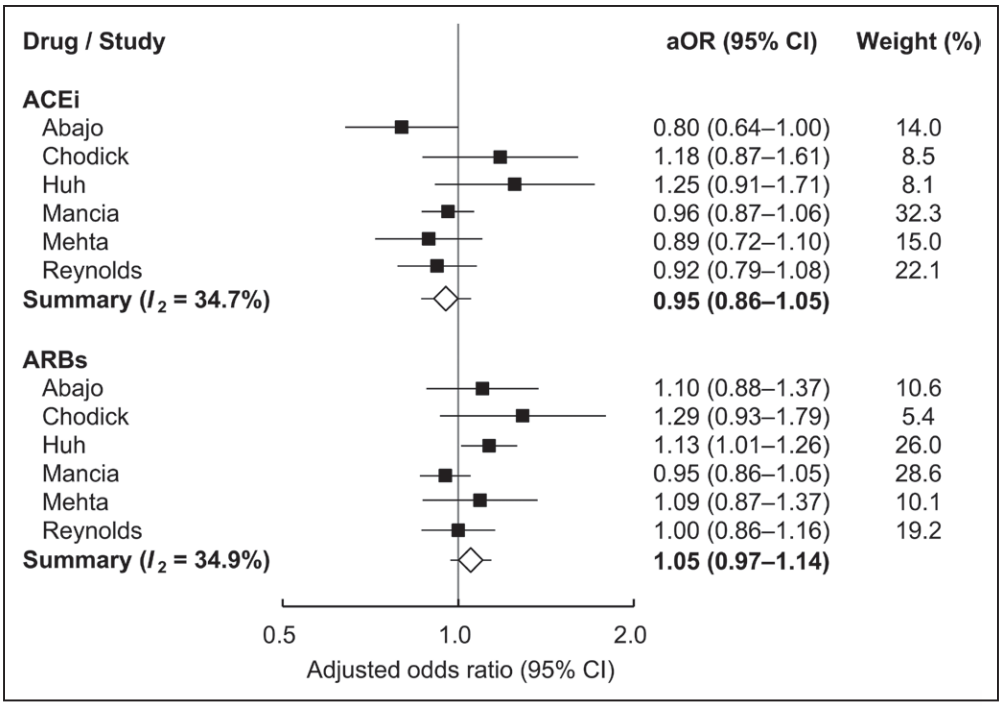

Figure 1. The forest plot showing the association between the use of ACE (angiotensin-converting enzyme) inhibitors or the use of angiotensin receptor blockers (ARBs) and the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by pooling the adjusted odds ratios (aOR).

The higher susceptibility to SARS-CoV-2 infection via the usage of ARBs seems more obvious in younger subjects, whereas the usage of ACE inhibitors with the younger subjects did not show increased risk of SARS-CoV-2 infection. For younger subjects who require RAASi therapy, caution needs to be executed regarding ARBs prescribed during the COVID-19 era, as ARBs might aggravate their risk of SARS-CoV-2 infection.

Although the study is observational in nature, this finding was identified from multiple population-based, case-control studies with stringent meta-analysis methodology, and consistent across different populations, sex, and patients with various comorbidities.

Use of RAASi and SARS-CoV-2 Susceptibility

Given that ACE2 is the receptor that allows coronavirus entry into cells, pretreatment with RAASi, such as ACE inhibitors or ARBs, might modulate SARS-CoV-2 infection or compound organ damage. There is no solid data to support the notion that ACE inhibitors or ARBs administration facilitates coronavirus entry by increasing ACE2 expression in either animals or humans. Nonetheless, preclinical analysis showed inconsistent findings regarding the effects of RAASi on ACE2 expression.[19] ACE inhibitors could decrease[20] or not affect the activity of ACE2,[21] whereas ARBs have been shown to augment ACE2 expression more consistently at both the mRNA and protein level.[19,22] The increased levels of angiotensin II occurring after ARBs treatment, but not after ACE inhibitors, would impose an increased substrate load on ACE2, thus leading to its upregulation[23]; as manifested in patients with hypertension who had been treated with olmesartan (an ARB) their urinary level of ACE2 was shown higher than those treated with ACE inhibitors and other antihypertensives.[24]

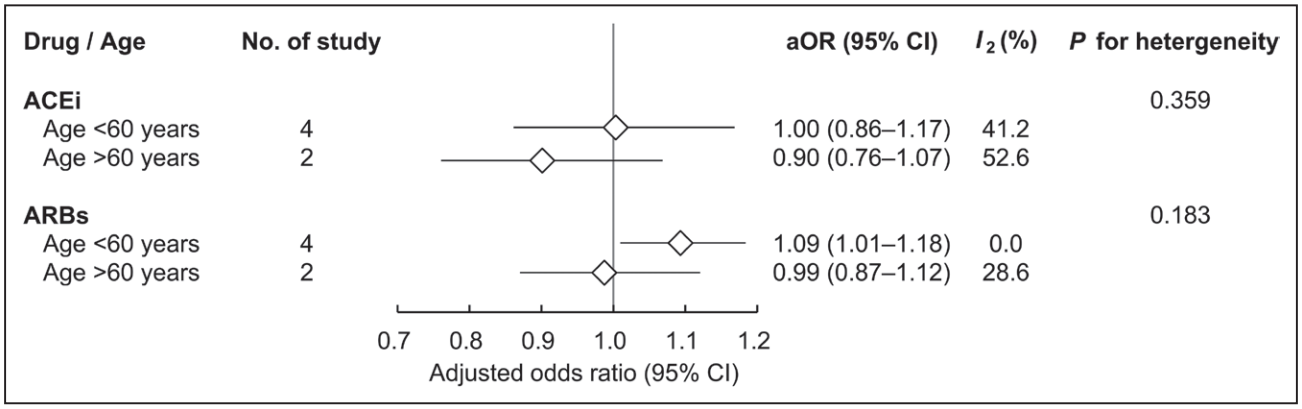

Figure 2. The forest plot showing the association between the use of ACE (angiotensin-converting enzyme) inhibitors or the use of angiotensin receptor blockers (ARBs) and the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection stratified by the mean or median age of 60 y. aOR indicates adjusted odds ratio.

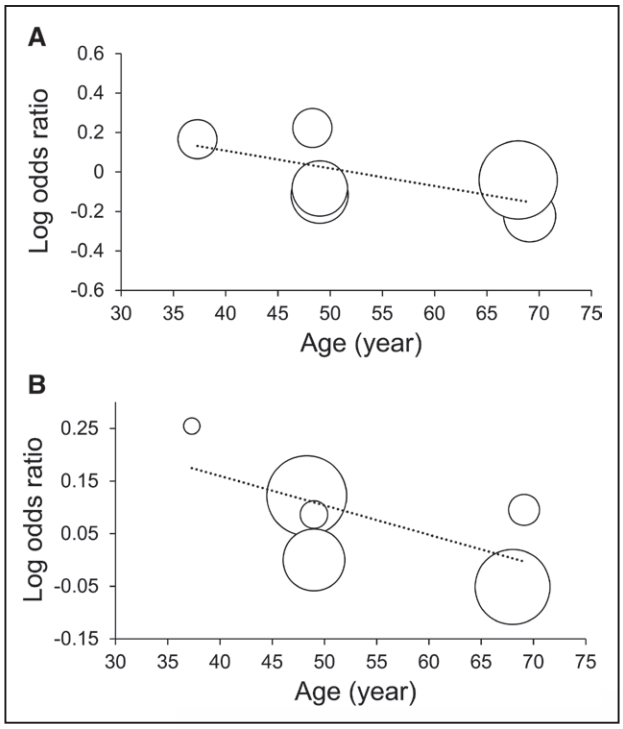

Figure 3. The meta-regression bubble plot showing the effect modification of continuous age in the association between the use of ACE (angiotensin-converting enzyme) inhibitors (**A**) or the use of angiotensin receptor blockers (ARBs; **B**) and the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Our finding intriguingly suggests that the effects on ACE2 should not be assumed uniform across various subcategories of RAASi, especially regarding their respective relationship in affecting SARS-CoV-2 infection susceptibility.

Intriguingly, a recently geospatial study from the United States showed that the use of ARBs (compared with no-use), but not the use of ACE inhibitors, was associated with a higher COVID-19 confirmed case rate, but they did not conduct sub-analysis with different age groups. They suggest that long-term use of ARBs might facilitate SARS-CoV-2 entry and increase infectivity.[25] This article was not included in this meta-analysis because it did not provide the use of RAASi information in the COVID-19 negative cases and no SARS-CoV-2 test–negative controls.

Comorbidities and the Use of RAASi and SARS-CoV-2 Infection

Hypertension as the most frequently coexisting comorbidity in patients with COVID-19 increases susceptibility to SARS-CoV-2 infection, particularly, in elderly individuals.[26,27] However, from our meta-regression (included no patients with hypertension) adjusted with recorded status of lower hypertension prevalence, the use of ARBs was linked to more SARS-CoV-2 infection (Table S2). Speculation arose that the susceptibility might be based on the use of antihypertensives rather than the comorbidity caused by high blood pressure. Age has consistently been reported to be a common risk attributing to COVID-19 infection and its related mortality. Older patients usually have more significant comorbidities, higher prevalence of hypertension, or use multiple drugs, in which there are already higher risks of SARS-CoV-2 infection, and thus masking off the clear effect of infection susceptibility attributed to ARBs alone. *ACE2* gene is located on the X chromosome, and there is a possibility that the dosage effect of sex chromosome may impact ACE2 activity due to escape from X-inactivation.[28] However, our analysis did not show the sex difference contributed to the detrimental effect of RAASi. Diabetes mellitus[29] or patients with underlying cardiovascular diseases, especially high prevalence of heart failure,[30] is associated with a higher risk of severity and fatality of COVID-19. However, our meta-regression did not show this comorbidity integrated the effect of ACE inhibitors or ARBs.

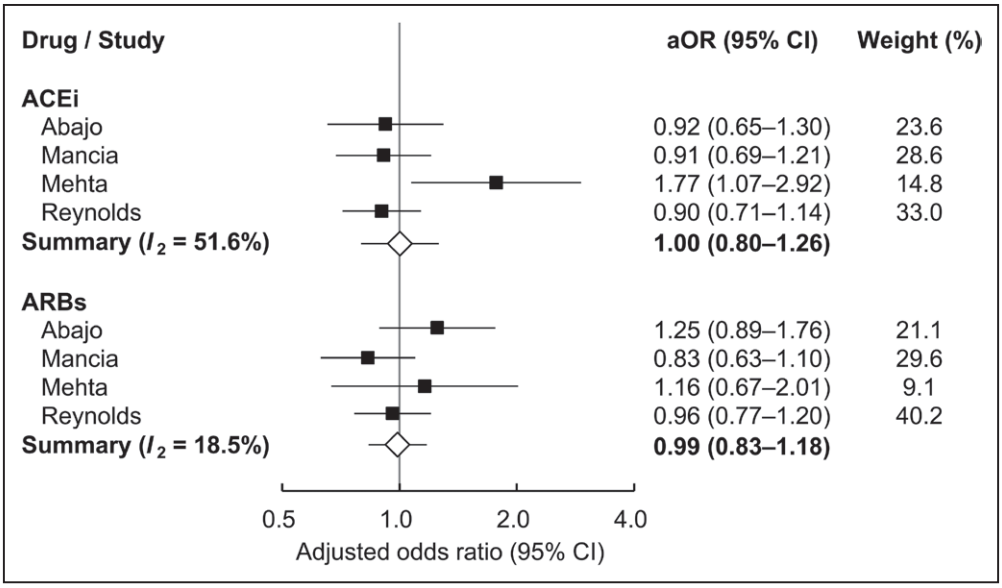

Figure 4. The forest plot showing the association between the use of ACE (angiotensin-converting enzyme) inhibitors or the use of angiotensin receptor blockers (ARBs) and the risk of severe or mortality of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. aOR indicates adjusted odds ratio.

Use of RAASi and COVID-19 Related Patients' Outcomes

Our meta-analysis on the aORs of various secondary end points, that is, the severity of COVID-19 (including admission to intensive unit, respirator usage, or mortality) revealed that the users of RAASi had similar secondary end point outcomes as compared to those of the nonusers. We also did not see the influence of the outcomes among various age subgroups of various users of RAASi which further confirms the safety of using RAASi during this era of COVID-19 pandemic. Interestingly, some data suggested that hypertensive COVID-19 patients receiving ACE inhibitors/ARBs treatment were found to have a lower rate of disease severity[31] or similar risk as non–ACE inhibitors/ARBs usage in patients with COVID-19,[32] a trend toward reduced blood levels of Interleukin-6 and reduced viral load and increased counts of cytotoxic T cells.[33] Some animal data supported elevated ACE2 expression could confer potential protective pulmonary and cardiovascular effects[34] and argue the biologic plausibility, thus suggesting that ARBs may be helpful in managing COVID-19.[18]

Possible induction of ACE2 in lungs by RAASi would augment soluble ACE2 and may have a beneficial effect of having protection from membrane-anchored ACE2-mediated injury with SARS-CoV-2.[35] In addition, Liu et al[36] showed that the level of angiotensin II in patients with SARS-CoV-2 infection was strongly associated with viral load and lung injury which was suggesting that COVID-19 could cause the imbalanced RAAS and drugs of ACE inhibitors and ARBs balancing RAAS may have the potential benefit on the lung protection in COVID-19. There still remains a lot we do not know about COVID-19 versus ACE inhibitors/ARBs/RAASi. Increased ACE2 expression by preexisting RAASi treatment may affect the virus susceptibility in certain sub-population, but could eventually be protective in the course of SARS-CoV-2 infection.

In clinical practice, RAASi are typically used to treat cardiovascular diseases, diabetes mellitus, and chronic kidney disease. On the contrary, discontinuing these agents could lead to the risk that they may not be resumed after the intervention and lead to withdrawal effect.[37]

Simply suspending or abandoning antihypertensive agents is strongly dissuaded and should not be a choice, considering the widespread use of RAASi worldwide. Our results further scientifically coincide and confirm the mainstream recommendations of various medical societies, which suggest not to discontinue medication in patients who have a reliance on these drugs.[31] Their therapeutic benefit, most likely, outweighs any potential risk of being predisposed to SARS-CoV-2 infection.

Study Limitations

There are still many potential study limitations to be discussed. First, the available clinical database from the pandemic to date is still insufficient and heterogeneous, for example, race and screening policy of COVID-19 to provide sufficient detail on all the variables of interest. These factors might account for some of the residual statistical heterogeneity seen for some outcomes, in light of our results, the albeit I^2 is commonly inflated in meta-analyses of observational data.[33]

However, the evidence we presented was based on 7 large methodologically sound observational studies. Second, some drug indications among those with the use of ACE inhibitors/ARBs were not elucidated, which could confound the risk. The use of RAASi may indicate a subgroup of patients who are especially vulnerable to the virus. In such a case, the use of ARBs is not a cause, but a marker of risk. Third, further studies are required to define the mechanisms through which RAASi modulate ACE2 and exert beneficial or harmful effects among patients with COVID-19. However, caution should be admonished regarding these associations because of potential unmeasured confounding interactions given the observational design of the studies and the small numbers of patients in the secondary investigative analysis. Fourth, although we revealed higher susceptibility to SARS-CoV-2 infection for younger patients taking ARBs, we do not imply to withdraw RAASi during COVID-19 pandemic period, as the second end point of COVID-19 outcomes showed no difference among the users of RAASi versus nonusers. Fifth, we included the studies extracted from the medRXIV which were the unpublished articles before certification by peer review to explore the whole picture of the RAASi with all available data.

Perspectives

Our comprehensive systematic review provided the best available information on treatment with RAASi and was not associated with a higher likelihood of a positive test for SARS- CoV-2 infection, disease severity, or mortality. However, in younger subjects, the use of ARBs could increase the risk of SARS-CoV-2 infection. Nonetheless, when international collaborative and well-conducted studies, including randomized trials, of different RAASi usage strategies and susceptibility of COVID-19, are potentially unethical regardless of the challenges, this systematic appraisal of the currently best available evidence could be considered to inform interim guidance.

Acknowledgments

We thank the staff of the Second Core Lab in the Department of Medical Research at National Taiwan University Hospital for technical assistance. This study was supported by Taiwan National Science Council (grants NSC 101-2314-B-002-132-MY3, NSC100-2314-B-002-119, NSC 101-2314-B-002-085-MY3, Ministry of Science and Technology [MOST] 104-2314-B-002 -125 -MY3), NTUH 100-N1776, 101-M1953, 102-S2097 and MOST of the Republic of China (Taiwan; grant number, MOST 106-2321-B-182-002 and MOST 109-2314-B-002-174-MY3). We thank Eric B. Chueh, BA, MBA, of Case Western Reserve University, Cleveland, OH, for English editing.

Sources of Funding

None.

Disclosures

None.

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Novelty and Significance

What Is New?

- The results of our meta-analysis, based on case-population studies and cohort studies, support the theory that treatment with RAASi (renin-angiotensin-aldosterone system inhibitors), especially ACE (angiotensin-converting enzyme) inhibitors, was not associated with a higher likelihood of a positive test for severe acute respiratory syndrome coronavirus 2 infection, disease severity, or mortality. However, the younger subjects with angiotensin receptor blockers (ARBs) treatment might have increased risk of severe acute respiratory syndrome coronavirus 2 infection with ARBs treatment.

What Is Relevant?

- Severe acute respiratory syndrome coronavirus 2 engages the human angiotensin-converting enzyme2 cell surface receptor to infect the host cells. Thus, concerns arose regarding theoretically higher risk for coronavirus disease 2019 (COVID-19) in patients taking ACE inhibitors/ARBs.

Summary

To the best of our knowledge, our study is the first meta-analysis to holistically evaluate whether independent the use of ACE inhibitors or ARBs is associated with increased risk of severe acute respiratory syndrome coronavirus 2 infection or not. The use of either ACE inhibitors or ARBs treatment was not associated with an increased risk of positive severe acute respiratory syndrome coronavirus 2 test for the population as a whole; however, we showed for the first time that the use of ARBs, as opposed to ACE inhibitors, specifically augmented the risk of severe acute respiratory syndrome coronavirus 2 infection in younger subjects. In addition, the use of either ACE inhibitors or ARBs treatment did not aggravate disease severity or mortality of COVID-19 in the whole population and subgroup analysis in our study.