The Effect of Prior ACEI/ARB Treatment on COVID-19 Susceptibility and Outcome: A Systematic Review and Meta-Analysis

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Summary:

Prior treatment of ACEI/ARB does not affect susceptibility of SARS-CoV-2 infection in general community population, as well as risks of death or severe disease in COVID-19 patients. These findings are consistent across different populations and different types of drug exposure.

Abstract

There have been arguments on whether angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) treatment alters the risk of COVID-19 susceptibility and disease severity. We identified a total of 102 eligible studies for systematic review, in which 49 studies adjusting for confounders were included in the meta-analysis. We found no association between prior ACEI/ARB use and risk of SARS-CoV-2 infection in general population (adjusted OR [aOR] 1.00, 95% confidence interval [CI] 0.94-1.05). The risk of mortality (aOR 0.87, 95%CI 0.66-1.04) and severe outcomes (aOR 0.95, 95%CI 0.73-1.24) are also unchanged among COVID-19 patients taking ACEI/ARB. These findings remain consistent in subgroup analyses stratified by populations, drug exposures and in other secondary outcomes. This systematic review provides evidence-based support to current medical guidelines and position statements that ACEI/ARB should not be discontinued. Additionally, there has been no evidence for initiating ACEI/ARB regimen as prevention or treatment of COVID-19.

Keywords: COVID-19, cardiovascular disease, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, meta-analysis.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has been spreading globally, causing hundreds of thousands of deaths and affecting every aspect of human life. Individuals who are older and suffering from underlying cardiovascular and metabolic comorbidities, such as hypertension, coronary artery disease (CAD) and diabetes, are at higher risk to develop severe COVID-19 [1, 2]. The widely used medications for patients with these common comorbidities, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), have raised heated discussions recently regarding their potential effects on the susceptibility to SARS-CoV-2 and severity of COVID-19 [3-7].

ACEI and ARB are inhibitors of the renin-angiotensin system (RAS), a regulatory system that mediates vasoconstriction, blood pressure elevation, fluid and electrolyte homeostasis, and inflammation through the ACE-AngII-AT1R axis [5, 8, 9]. In animal studies, RAS inhibitors have been shown to increase the tissue expression and activity of ACE2 [10], which is the homolog for ACE and also the functional receptor for SARS-CoV-2 [11]. These findings lead to concerns that prior ACEI/ARB usage may confer increased susceptibility to SARS-CoV-2 infection [3, 5]. On the other hand, it has been shown that ACE2 can exert protective roles through the ACE2-Ang_{1-7}-Mas axis to counterbalance the over-activated ACE-AngII-AT1R axis in the pathogenesis of lung injury and cardiovascular diseases [7, 9, 10]. Diminished ACE2 activity and overactivation of ACE-AngII-AT1R axis also contribute to the progression of cardiovascular diseases and diabetic cardiovascular complication [10]. Therefore, RAS blockade by ACEI/ARB may be protective against severe COVID-19, and is being considered as a potential therapeutic for COVID-19 [3, 10].

Recently, an increasing number of retrospective studies and ongoing clinical trials are investigating the effects of ACEI/ARB on the susceptibility and disease severity of COVID-19 [6, 12]. Although it is widely accepted at this moment that prior ACEI/ARB treatment is not associated with increased susceptibility of SARS-CoV-2 infection [6, 12], whether they provide additional protection for COVID-19 patients is uncertain, particularly as many of the early studies did not adjust for important confounders [12, 13]. In addition, detailed information is lacking regarding whether the current understanding of the effects of ACEI and/or ARB on COVID-19 can be generalized to different populations and more specific clinical outcomes [13].

In this systematic review, we aim to provide a comprehensive summarization of current evidence to answer two major clinical questions: (1) Does the prior treatment of ACEI/ARB alter the susceptibility of SARS-CoV-2 infection in general population? (2) Does the prior treatment of ACEI/ARB affect risk of mortality and severe outcomes in COVID-19 patients? This information is critical to guide the evidence-based management of ACEI/ARB in patients during the COVID-19 pandemic.

Method

Search strategy and selection criteria

We followed the PRISMA statement (see Appendix) and registered the protocol of this systematic review in PROSPERO (CRD42020192898).

The eligibility criteria of study inclusion are: 1) Original research investigating the association between prior use of ACEI/ARB and COVID-19 related outcomes. 2) Eligible study designs include randomized controlled trials (RCT), non-randomized clinical trials, cohort studies, and case-control studies. 3) There were no restrictions on languages, publication status or sample size. Exclusion criteria: 1) Reviews, commentaries, in vitro studies, and other non-eligible study designs (geospatial study, etc.). 2) Studies not providing sufficient information to be included in the review after contacting corresponding authors for additional data. 3) Retracted manuscripts.

The information sources include: MEDLINE (via Ovid), EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), China national knowledge infrastructure (CNKI), Wanfang database, SinoMed, WHO COVID-19 database (Global literature on coronavirus disease), and Cochrane COVID-19 study register. We also hand-searched preprint servers (MedRxiv, BioRxiv, SSRN), websites of major publishers/journals, and reference lists of relevant reviews and included studies. We performed the first search on May 26, 2020 and updated the search on July 18, 2020. The search strategy was built based on terms related to COVID-19, ACEI/ARB and hypertension (see Appendix).

Two investigators (J.X. and L.S.) independently performed literature screening via Rayyan [14] and Endnote X9 to identify eligible studies. Their disagreements were resolved through discussion with a third investigator (Y.T.).

Data extraction and risk of bias assessment

The data extraction and risk of bias assessment were independently performed by two investigators (J.X. and L.S.) and cross-checked by a third investigator (Y.T.). The key components of the data extraction form include author, study design, study location, patient characteristics, event numbers, and summary estimates of effect measures, including adjusted odds ratio (aOR) and adjusted hazard ratio (aHR). We e-mailed the corresponding authors for additional necessary information.

The primary outcomes are: 1) testing positive for SARS-CoV-2 via RT-PCR, 2) COVID-19 mortality, and 3) a composite endpoint of severe illness of COVID-19, which include being categorized as severe/critical COVID-19 defined by the authors, requiring ICU admission or

mechanical ventilation. The definition for severe/critical disease by authors varied across different studies, but they are generally based on WHO or Chinese national guidelines [15, 16]. The secondary outcomes include individual components of the composite endpoint of severe illness, as well as development of complications including cardiac injury or acute kidney injury (AKI) and duration of hospitalization. Cardiac injury and acute kidney injury were defined as reported previously [17].

We used Cochrane risk-of-bias 2.0 (ROB-2) tool to assess risk of bias for RCT [18]. For observational studies, the relevant Newcastle Ottawa scale (NOS) was used according to the design as case-control or cohort study [19]. Only the data from RCT or observational studies with NOS scored 4 or above were included in the meta-analysis.

Data analysis

We used pooled odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals (95% CIs) for dichotomous outcome as summary relative effect measure. For continuous data, standard mean difference (SMD) with 95% CIs was applied, with median and inter quartile range (IQR) converted into mean and standard deviation [20]. The pooled adjusted data were included in the main analysis, and the pooled crude odds ratio were presented in the Supplementary Material. For adjusted outcomes, we calculated the logOR and standard error (SE) from original data and used generic inverse variance method to pool the results. For crude outcomes, we combined original event numbers with Mantel-Haenszel method. Random-effects model is used throughout the meta-analysis considering the potential heterogeneity across different studies. The statistical heterogeneity was assessed using the I^2 and Q statistic. For the primary outcomes, we performed pre-specified sensitivity analysis by removing (1) pre-print studies, (2) studies with NOS score ≤ 6, (3) potentially overlapping data (if several studies report cases in the same hospitals in overlapped time frame, we reserved data from the study with the largest case number), (4) study including clinically diagnosed patients without nucleic acid test results, (5) each study one by one. We also performed subgroup analyses for the primary outcomes based on study population (geographical locations, cardiovascular comorbidities, etc.) and types of drug exposure (ACEIs and ARBs). We used funnel plot and Egger's test to detect publication bias. Statistical analyses were performed using R package "meta" (version 4.13-0) [21].

Result

Study selection and characteristics

From the combination of two searches, we retrieved 4238 records from MEDLINE, EMBASE, CENTRAL and Chinese databases (CNKI, Wanfang and SinoMed), and 2082 additional records from WHO COVID-19 database and Cochrane COVID-19 study register. After removing duplications and irrelevant literatures, 554 full-text articles were assessed for eligibility. A total of 102 studies (74 published and 28 pre-print articles) were identified and 49 articles reporting adjusted outcome measures were included in the main meta-analysis (**Figure 1**).

For the 102 studies included in the systematic review, there is one RCT, which is an unspecified interim analysis of an on-going RCT initiated before the COVID-19 pandemic evaluating ramipril in treating post-aortic-valve-replacement patients [22]. No RCTs designed to evaluate the effect of prior ACEI/ARB on COVID-19 has been published. All the other included studies are observational studies, reported in either cohort or case-control styles. Most studies are based directly on original hospital medical records, and 52 of them are single-centered observational studies. These hospital-based studies covered a moderate number of participants per study (median 175, interquartile range 75-659). There are also 17 studies using data from nation- or region-level registries, or from medical insurance databases. The locations of the included studies span Asia, Europe, and North America. Countries with the most publications are China (n=29), US (n=17), and Italy (n=12). Over half of the studies enrolled patients with cardiovascular and metabolic comorbidities. **Table S1** summarizes the main characteristics of all the included studies.

Most observational studies have adequate inclusion and exclusion criteria and clear definition of exposures and outcomes. However, less than half (49/102) of the studies provided results after adjustment for major confounders including age, gender and underlying comorbidities. Most observational studies scored 5-7 in Newcastle-Ottawa Scale and the only RCT study is subjected to high risk of bias assessed by ROB-2 (**Table S2)**. The RCT was included in the main analysis despite its high risk of bias.

ACEI/ARB and the risk of SARS-CoV-2 infection

The outcome of SARS-CoV-2 infection is available in 24 studies comparing prior ACEI/ARB users versus non-users (23 observational studies and 1 RCT), of which 16 studies providing adjusted measures (aOR or aHR) were included in the meta-analysis (**Table 1**). Prior use of ACEI/ARB is not associated with altered risk of testing positive for SARS-CoV-2 (aOR 1.00, 95%CI 0.94-1.05), nor is the case when ACEI and ARB are evaluated separately (**Figure 2** and **Figure S3A-B**). The pooled measures of aHR are consistent with that of aOR. The publication bias is not significant evaluated by

Egger regression test and the funnel plot (**Figure 2**, **Figure S1A-B**). On the contrary, the crude OR combined from all 24 studies showed significantly elevated risk of COVID-19 infection (OR 1.13, 95%CI 1.05-1.22, **Figure S2A**), indicating that unadjusted confounders of age, gender or underlying comorbidities may affect the accuracy of risk estimate of SARS-CoV-2 susceptibility. Subgroup analysis of the adjusted studies showed similar insignificant association in general community population, patients with cardiovascular comorbidities, and in population from different geographical regions (**Table S3-4**), although a slight elevated risk of infection was observed in Asian studies (aOR 1.17, 95% CI 1.01-1.34). Similar results were obtained from sensitivity analysis excluding pre-print studies, studies scored 6 or below in NOS and omitting each single study (**Figure S4-5 and S8**), and there are no potentially overlapping studies.

ACEI/ARB and COVID-19 mortality

Next, we sought to analyze the effects of ACEI/ARB on the mortality among COVID-19 patients. Fifty-two studies reported mortality outcome, and the meta-analysis of 20 studies with proper adjustment did not show altered risk for COVID-19 mortality in patients treated with ACEI/ARB measured by aOR (0.87, 95% CI 0.66-1.14) and aHR (0.86, 95% CI 0.66-1.13) (**Figure 3 and Table 2**). Pooled OR directly from crude event numbers reported in 44 studies yielded similar results (OR 1.06, 95% CI 0.85-1.31) **(Figure S2B**). The results are also consistent when ACEIs and ARBs are evaluated separately (**Figure S3C-D**) and in patients stratified by study location (**Table S3**). Results were unchanged in sensitivity analysis (**Figure S4-8**).

Notably, we observed a protective effect for ACEI/ARB in the subgroup of COVID-19 patients with cardiovascular diseases (crude OR 0.76, 95%CI 0.60-0.96), but this effect is no longer significant after adjustment (aOR 0.79, 95%CI 0.45-1.40) (**Table S4**).

ACEI/ARB and severe outcomes of COVID-19

A total of 65 studies reported the composite endpoint of severe outcomes, with 24 of them provided analysis after adjustment for potential confounders (**Figure 4 and Table 3**). Although ACEI/ARB seemed to associate with increased risk of severe outcomes of COVID-19 by pooling crude data (crude OR 1.28, 95% CI 1.06-1.54) (**Figure S2C**), the effects of ACEI/ARB remained insignificant in the adjusted studies (aOR 0.95, 95% CI 0.73-1.24) (**Figure 4**). The conclusion is not altered in subgroup analysis evaluating ACEI and ARB separately (**Figure S3E-F**) and stratifying by location or cardiovascular comorbidities **(Table S3-4)**, as well as in sensitivity analysis as described above (**Figure S4-8**).

For secondary outcomes, we analyzed the single components of severe disease (severe disease of COVID-19 defined by each included study, ICU admission, and mechanical ventilation) and complications of cardiac and renal injury, and the results are similar to the composite endpoint (**Table S5**). Additionally, we evaluated the association between ACEI/ARB usage and hospitalization time of COVID-19. The effects are neutral as shown in the meta-analysis of hospital length of stay and the time from disease onset to hospital discharge (**Figure S9**).

Discussion

The use of ACEI/ARB in the setting of COVID-19 pandemic is one of the clinical questions gaining enormous public and academic attention, given the large amount of relevant population it reaches and the intrinsic pathogenic interplay between RAS, cardiovascular diseases and COVID-19. In this review, we summarized the evidences of effects of ACEI/ARB on SARS-CoV-2 infection and COVID-19 disease severity from 102 studies, which is, to our knowledge, the largest number of studies included in a systemic review of this topic to date. We confirmed that prior treatment of ACEI/ARB does not alter risk of SARS-CoV-2 infection, nor does it confer risks or protection for COVID-19 patients to death and severe disease. The results are overall consistent in different population stratified by the co-existing cardiovascular comorbidities and geographical location, and in both types of RAS inhibitors. In accordance with most clinical guidelines and position statements, there is no evidence to withdraw or switch treatment strategies for patients with indications of ACEI/ARB during COVID-19 pandemic.

Crude clinical observations may suggest higher percentage of ACEI/ARB users in those with more severe disease, and in COVID-19 patients compared with the community population. However, this association may be confounded by the fact that increased age and pre-existing hypertension are associated with both ACEI/ARB use and severe COVID-19. Indeed, as pointed out by many original studies, the "association" between prior ACEI/ARB treatment and severe COVID-19 (**Figure S2C**) is no longer significant when evaluating only on data adjusted for age, gender, and other factors (**Figure 4**).

While the concerns for ACEI/ARB use in COVID-19 patients arose, other voices supported ACEI and ARB as candidates for COVID-19 treatment, given that RAS inhibition may counter-balance the effects of ACE2 depletion and mitigate lung injury caused by RAS overactivation. Indeed, several recent reviews have summarized evidences of the protective effects of ACEI/ARB in hypertensive population [23, 24] but not in general COVID-19 patients [25, 26] based on early retrospective studies. However, the majority of these early retrospective studies on ACEI/ARB and COVID-19 were performed without adjustment of age, gender, comorbidities, or concurrent use of

other medications (**Table S1-2**), which may also be potential confounders for this association [13]. Interestingly, our analysis combining crude OR for mortality in COVID-19 patients with pre-existing cardiovascular diseases (mainly hypertension) (**Table S4**) is in agreement with the protective trend observed in early meta-analysis [23, 24]. However, we cannot detect the "protective" effect of ACEI/ARB in these patients when evaluating data after adjustment of confounders.

There are several possible explanations to the diminished protective effects of ACEI/ARB in hypertensive COVID-19 patients after adjustment: 1) The protective trend of ACEI/ARB shown in unadjusted studies is probably due to confounding bias rather than true protective effects. For example, the hypertensive patients who took ACEI/ARB are probably more accessible to medical resources or more compliant to treatments, and thus have better controlled blood pressure and other related cardiovascular and metabolic conditions. Another specific point to be mentioned is that the first line recommendation for elder hypertensive patients in the Chinese guideline is calcium channel blocker (CCB) rather than ACEI/ARB [27], and therefore patients taking ACEI/ARB are younger than those taking CCBs, presenting as a protective effect of the drugs if age is not adjusted. 2) It may also be that ACEI/ARB is truly protective for COVID-19 patients with hypertension, but the confounders are over-adjusted, or the protective effect is moderate and more studies are needed to achieve statistical significance. Currently, no further judgement can be made based on retrospective observational studies. The only RCT included in this review also points to a neutral effect of ACEI/ARB. Despite the large number of studies published and included in this review, the inherited limitations of retrospective design still prompt RCTs to confirm whether ACEI/ARB indeed has any protective effects on the disease severity of COVID-19.

In the early discussions of RAS inhibitors and COVID-19, there are many speculations on the potential difference of ACEI and ARB in COVID-19. It has been proposed that ARB warrant more attention to SARS-CoV-2 infection based on findings that ARB but not ACEI increases ACE2 activity in animal models [28]. Besides, ARBs directly block AT1R but not AngII, and the accumulation of physiological AngII may result in the production of protective peptide Ang_{1-7} by ACE2. Therefore, some deduced that ARBs are more favorable as a treatment strategy for COVID-19 [29]. In this review, we concluded that neither drug has effects on susceptibility or severe disease of COVID-19 when evaluated individually (**Figure S3**), and there is thus no considerable difference between these two drugs. Another related research update worth mentioning is that treatment of ACEI/ARB does not affect ACE2 level in human plasma [30]. Recent animal studies also confirmed that ACEI/ARB does not alter ACE2 expression in pulmonary tissues [31, 32]. These results indicate that there are still gaps between theoretical deduction and real-world clinical conditions, which must be connected by evidence-based medicine.

Our study has several limitations. First, almost all included studies are retrospective observational studies. Second, the definition and criteria of "prior use" of ACEI/ARB is not consistent across studies. Third, we did not address ACEI/ARB continuation versus discontinuation during hospitalization, as the number of studies providing this information is limited at this stage.

Conclusion

In conclusion, this review comprehensively summarized the best available evidence that ACEI/ARB should not be discontinued in context of COVID-19 pandemic due to concerns for increased risk of COVID-19 susceptibility or severity. There is currently no evidence for initiating short-term ACEI/ARB as prevention or treatment for COVID-19. This review also provides rationale for evaluating potential protective effect of ACEI/ARB in hypertensive COVID-19 patients with prospective and well-controlled interventional trials.

Notes

Author Contributions

JX, YT, LS, BC and SZ conceived the study. LS designed protocol for literature retrieval. JX, LS, and YT performed article screening, data extraction and statistical analysis. YT and LS wrote the first manuscript with input from JX. BC, SZ, GF, XG, YC and RT provided critical revision to the manuscript.

Declaration of Interest

We declare no competing interest.

Disclaimer

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Table 1. Use of ACEIs or ARBs and the risk of receiving a positive test result for SARS-CoV-2 infection

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
Amat-Santos, I.[22]	Spain	Patients with aortic stenosis successfully treated with transcatheter aortic valve replacement	ACEI	50	52	Randomization was performed	1.15 (0.351, 3.768)*
Chodick, G.[33]	Israel	General population tested for SARS-CoV-2	ACEI	388	14132	Age, sex, BMI, and medical history (HTN, DM, HF)	1.18 (0.87, 1.61)
			ARB	603	13917		1.29 (0.93, 1.79)
de Abajo, F.[34]	Spain	COVID-19 patients and matched population control	ACEI/ARB	4221	8308	Age, sex, and medical history (DM, dyslipidemia, IHD, HF, COPD, asthma, cancer, CKD, etc.).	0.92 (0.76, 1.12)
			ACEI	2432	10097		0.80 (0.64, 1.00)
			ARB	1789	10740		1.10 (0.88, 1.37)
Fosbol, E.[35]	Denmark	COVID-19 patients with HTN and matched HTN control	ACEI/ARB	5370	911	Age, sex, and medical history (COPD, DM, cancer, MI, and CBVD).	1.05 (0.80, 1.36)
			ACEI	N.A.	N.A.		0.85 (0.70, 1.01)
			ARB	N.A.	N.A.		1.15 (0.96, 1.37)
Gnavi, R.[36]	Italy	General population with history of IHD, CBVD, HF, or DM.	ACEI/ARB	568	458	Age and sex. Medical history is similar.	0.95 (0.68, 1.34)
			ACEI	327	699		0.92 (0.64, 1.32)
			ARB	254	772		1.03 (0.70, 1.50)
Huh, K.[37]	Korea	General population tested for SARS-CoV-2	ACEI	653	64496	Age, sex, region of residence, comorbidities, healthcare utilization, and medications.	1.25 (0.91, 1.71)
			ARB	10045	55104		1.13 (1.01, 1.26)

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
Khawaja, A.[38]	UK	General population	ACEI	33827	372966	Age, sex, ethnicity, anti-HTN medication and HTN comorbidity status.	1.17 (0.90, 1.52)
			ARB	17402	389391		1.00 (0.70, 1.42)
Kolin, D.[39]	UK	General population tested for SARS-CoV-2 (participants of UK Biobank)	ACEI	86	1388	Age, sex, BMI, BP, and co-morbidities (DM, angina, MI).	1.32 (0.95, 1.84)*
			ARB	30	1444		1.37 (0.94, 1.98)*
Mancia, G.[40]	Italy	General population	ACEI	8071	28960	Age, sex, drugs, and medical history (CVD, CKD, cancer, respiratory disease)	0.96 (0.87, 1.07)
			ARB	7304	29727		0.95 (0.86, 1.05)
Mehta. N.[41]	US	General population tested for SARS-CoV-2	ACEI/ARB	2,285	16187	Age, sex, and medical history (HTN, DM, CHD, HF, and COPD).	0.97 (0.81, 1.15)
			ACEI	1,322	17150		0.89 (0.72, 1.10)
			ARB	982	17490		1.09 (0.87, 1.37)
Morales, D.[42]	Spain, US	General population with HTN	ACEI/ARB	363785	248915	Age, gender, race, prior conditions, drug exposures, and procedures.	1.10 (0.92, 1.32)*
			ACEI	268711	248915		1.08 (0.89, 1.31)*
			ARB	92485	248915		1.16 (0.89, 1.50)*
Raisi-Estabragh, Z.[43]	UK	General population tested for SARS-CoV-2	ACEI/ARB	312	1162	Age, sex, ethnicity, BMI, medical history (DM, HTN, high cholesterol, MI), and smoking.	0.956 (0.695, 1.316)
Rentsch, C.[44]	US	General population tested for SARS-CoV-2	ACEI/ARB	1532	2,257	Age, sex, race, BMI, residence type, medical history (CKD, COPD, DM, HTN), alcohol	0.98 (0.78, 1.23)
			ACEI	1011	2,778		N.A.

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
			ARB	563	3,226	use, smoking, NSAID, baseline vital signs.	N.A.
Reynolds, H.[45]	US	General population	ACEI	1,044	1,044	Age, sex, ethnicity, BMI, medical history (HTN, MI, HF, DM, CKD, asthma, COPD), medication, and smoking.	0.92 (0.79, 1.08)
			ARB	1,137	1,137		1.00 (0.86, 1.15)
Son, M.[46]	Korea	General population with HTN who were also tested for SARS-CoV-2	ACEI/ARB	2147	700	DM, dyslipidemia, MI, stroke, liver disease, cancer, COPD, asthma, dialysis, and immuno-compromised status.	1.161 (0.958, 1.407)
			ACEI	145	2,702		0.927 (0.639, 1.344)
			ARB	2048	799		1.140 (0.950, 1.369)
Yan, H.[47]	China	COVID-19 patients matched with general population	ACEI	560	48,717	Age, sex, and BMI.	0.65 (0.26, 1.57)
			ARB	7538	41,739		0.24 (0.17, 0.34)

* Adjust Hazard Ratio (aHR) is marked with star (*). Otherwise, it is adjusted odds ratio (aOR).

[$] Abbreviations: BMI (body weight index), BP (blood pressure), CBVD (cerebrovascular disease), coronary heart disease, CKD (chronic kidney disease), COPD (chronic obstructive pulmonary disease), CVD (cardiovascular disease), DM (diabetes mellitus), HTN (hypertension), HF (heart failure), IHD (ischemic heart disease), MI (myocardial infarction), NSAID (non-steroid anti-inflammation drug),

Table 2. Use of ACEIs and ARBs and the risk of mortality[†] for COVID-19 patients

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
Andrea, C.[48]	Italy	COVID-19	ACEI/ARB	69	122	Age, HTN, and DM.	0.75 (0.36, 1.56)*
Cannata, F.[49]	Italy	COVID-19	ACEI/ARB	56	224	Age, BMI, body temperature, eGFR, medical history (DM, COPD, HF, malignancy), vitals and laboratory values on admission.	0.05 (0.01, 0.54)
Felice, C.[50]	Italy	COVID-19 with HTN and taking anti-HTN medication	ACEI/ARB	82	51	Age, sex, BMI, days with symptoms, CVD, DM and cancer.	0.56 (0.17, 1.83)
Fosbol, E.[35]	Denmark	COVID-19 (including clinical diagnosis)	ACEI/ARB	895	3585	Age, sex, education, medical history (MI, HF, CKD, stroke, peripheral artery disease, AF, DM, COPD, malignancy), use of anti-HTN, lipid-lowering, and anticoagulation drugs.	0.83 (0.67, 1.03)
			ACEI	377	3585		0.98 (0.71, 1.35)
			ARB	630	3585		0.80 (0.6, 1.09)
Gao, C.[51]	China	COVID-19 with HTN and	ACEI/ARB	183	527	Age, sex, medical history (DM, MI, PCI/CABG, CKD, HF,	0.85 (0.28, 2.58)*

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
		taking anti-HTN medication				and COPD.	
Grasselli, G.[52]	Italy	Critically ill COVID-19 patients in ICU	ACEI	N.A.	N.A.	Age, sex, comorbidities (HTN, DM, COPD, malignancy, hypercholesterolemia), and medications.	1.17 (0.97, 1.42)*
			ARB	N.A.	N.A.		1.05 (0.85, 1.29)*
Iaccarino, G.[53]	Italy	COVID-19	ACEI	348	1243	Age, sex, HTN, DM, COPD, CKD, CAD, HF, β-blockers, diuretics	1.45 (0.99, 1.98)
Imam, Z.[54]	US	COVID-19	ACEI/ARB	565	740	Age, Charlson Comorbidity Index, and NSAID.	1.20 (0.86, 1.68)
Jung, C.[55]	38 countries	COVID-19 patients in ICU	ACEI	62	262	Age, sex, BMI, SOFA score, chronic HF, IHD, renal insufficiency, chronic pulmonary disease, HTN and DM.	0.32 (0.15, 0.67)
Jung, S.[56]	Korea	COVID-19	ACEI/ARB	377	1577	Age, sex, CCI, immuno-suppression, and hospital type.	0.88 (0.53, 1.44)
Khera, R.[57]	US	COVID-19 with ICU	ACEI	2360	3338	Age, sex, race, insurance type, DM, MI, HF, CKD, CCI, and anti-HTN medication.	0.97 (0.81, 1.16)*
			ARB	2224	3338		1.15 (0.95, 1.38)*
Lala, A.[58]	US	COVID-19 patients with available cTnI test results	ACEI/ARB	N.A.	N.A.	cTnI strata, demographics, race, ethnicity, medical history, BMI, CURB-65 score, and	1.05 (0.85, 1.31)

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
						statin use.	
Lopez-Otero, D.[59]	Spain	COVID-19	ACEI/ARB	N.A.	N.A.	Age, sex, BMI, health personnel, dependency status, medical history (HTN, DM, dyslipidemia, arterial disease, heart disease, AF, pneumonia, CKD, CBVD, auto-immune disease), fever, oxygen saturation < 95%, and medications.	1.20 (0.33, 4.37)
			ACEI	N.A.	N.A.		0.02 (0.01, 0.63)
			ARB	N.A.	N.A.		3.96 (1.06, 14.87)
Lorente-Ros, A.[60]	Spain	COVID-19	ACEI/ARB	N.A.	N.A.	Age, sex, MI, HTN, hematocrit, creatinine, D-dimer, CRP, and CCI.	1.033 (0.685, 1.562)*
Selcuk, M.[61]	Turkey	COVID-19 with HTN and taking anti-HTN medication	ACEI/ARB	74	39	Age, CHD, D-dimer, WBC count, creatinine, glucose, and LDH.	3.66 (1.11, 18.18)
Son, M.[46]	Korea	COVID-19 with HTN and taking anti-HTN medication	ACEI/ARB	77	25	End-stage renal disease with dialysis and CCI.	1.363 (0.513, 3.662)
			ACEI	7	95		0.260 (0.030, 2.247)
			ARB	71	31		2.132 (0.829, 5.485)
Tedeschi, S.[62]	Italy	COVID-19 with HTN	ACEI/ARB	175	136	Age, sex, CVD, and COPD.	0.97 (0.68, 1.39)*
Xu, J.[63]	China	COVID-19 with HTN and taking anti-HTN medication	ACEI/ARB	40	61	Age and sex.	0.78 (0.32, 1.93)
Zhang, P.[64]	China	COVID-19 with HTN	ACEI/ARB	188	940	Age, sex, medical history, and	0.29 (0.12, 0.69)

Author [ref]	Country	Population	Exposure	Exposed number	Unexposed number	Adjusted for[$]	aOR* (95% CI)
						in-hospital medications.	
Zhou, F.[65]	China	COVID-19 patients who have indications for ACEI/ARB treatment	ACEI/ARB	906	1812	Age, sex, disease severity, medical history and use of calcium channel blockers.	0.39 (0.26, 0.58)*
			ACEI	N.A.	N.A.		0.49 (0.20, 1.20)*
			ARB	560	2240		0.31 (0.18, 0.53)*

* Adjust Hazard Ratio (aHR) is marked with star (*). Otherwise, it is adjusted odds ratio (aOR).

[†] For mortality, no specific timing (e.g., in-hospital death, 28-day death, etc.) was set as all the studies investigated short-term mortality.

[$] Abbreviations: AF (atrial fibrillation), BMI (body weight index), CABG (coronary artery bypass grafting), CCI (Charlson Comorbidity Index), COPD (chronic obstructive pulmonary disease), CKD (chronic kidney disease), CRP (C-reactive protein), cTnI (cardiact troponin I), CVD (cardiovascular disease), DM (diabetes mellitus), eGFR (estimated glomerular filtration rate), HTN (hypertension), HF (heart failure), IHD (ischemic heart disease), ICU (intensive care unit), LDH (lactase dehydrogenase), MI (myocardial infarction), NSAID (non-steroid anti-inflammation drug), PCI (percutaneous coronary intervention), SOFA (sequential organ failure assessment), WBC (white blood cell).

Table 3. Use of ACEIs and ARBs and the risk of poor clinical outcome of COVID-19

Author [ref]	Country	Population	Outcome	Exposure	Ex #	Un #	Adjusted for	aOR* (95% CI)
Bean, D.[66]	UK	COVID-19	Death or requiring ICU admission within 21 days of symptom onset	ACEI/ARB	399	801	Age, sex, and medical history (HTN, DM, CKD, IHD, HF).	0.63 (0.47, 0.84)
Bravi, F.[67]	Italy	COVID-19 with HTN	Death or requiring ICU admission	ACEI/ARB	450	93	Age, gender, and medical history (DM, CVD, COPD, cancer and CKD).	0.87 (0.50, 1.49)
				ACEI	251	292		0.82 (0.49, 1.36)
				ARB	228	315		0.83 (0.50, 1.40)
Cheung, K.[68]	China	COVID-19	Severe pneumonia, respiratory failure, septic shock and/or MODS, ventilatory support, admission to ICU, or death	ACEI	NA.	NA.	Age, sex, medical history (DM, HTN, IHD, stroke, AF), medication, and laboratory tests.	0.14 (0.02, 0.87)
				ARB	NA.	NA.		1.86 (0.31, 9.97)
Choi, M.[69]	Korea	COVID-19	Progression to moderate or severe cases as defined in the article	ARB	16	277	Age, ECOG performance status, vitals at hospital admission, HTN, and DM.	1.60 (0.41, 6.23)
Chung, S.[70]	Korea	COVID-19 with diabetes	ARDS, septic shock, requiring ICU admission, or mortality within 28 days	ACEI/ARB	14	15	Age, sex, smoking status, and glycosylated hemoglobin level.	0.566 (0.058, 5.52)
De Spiegeleer, A.[71]	Belgium	Elderly COVID-19 patients (including clinical diagnosis)	Death within 14 days or Hospitalization ≥ 7 days	ACEI/ARB	30	124	Age, sex, functional status, DM, HTN, and diagnosis.	0.72 (0.1, 4.56)
Ebinger,	US	COVID-19	Respiratory failure	ACEI	NA.	NA.	Age and sex.	0.57 (0.17, 1.85)

Author [ref]	Country	Population	Outcome	Exposure	Ex #	Un #	Adjusted for	aOR* (95% CI)
J.[72]			(intubation)	ARB	NA.	NA.		1.38 (0.56, 3.42)
Felice, C.[50]	Italy	COVID-19 with HTN and taking anti-HTN medication	Requiring oxygen therapy	ACEI/ARB	82	51	Age, sex, BMI, days with symptoms, previous cardiovascular events, DM and cancer.	0.51 (0.15, 1.78)
Fosbol, E.[35]	Denmark	COVID-19	Death or severe disease (SARS or requiring ICU admission)	ACEI/ARB	895	3585	Age, sex, education, medical history (MI, HF, CKD, stroke, peripheral artery disease, AF, DM, COPD, malignancy), use of anti-HTN, lipid-lowering, and anticoagulation drugs.	1.04 (0.89, 1.23)*
				ACEI	377	3585		1.15 (0.89, 1.49)*
				ARB	630	3585		0.90 (0.71, 1.14)*
Golpe, R.[73]	Spain	COVID-19 with HTN	Hospitalization because of severe COVID-19	ACEI	32	125	Age, sex, medical history (DM, dyslipidaemia, CVD, chronic HF, CHD, etc.), and medications.	0.29 (0.08, 1.04)
				ARB	89	68		0.29 (0.1, 0.88)
Jung, S.[56]	Korea	COVID-19	Requiring mechanical ventilation	ACEI/ARB	377	1577	Age, sex, CCI, immuno-suppression, hospital type.	1.03 (0.5, 2.13)
Khera, R.[57]	US	COVID-19 with HTN	Requiring hospital admission	ACEI	722	810	Age, sex, race, insurance type, DM, MI, HF, CKD, CCI, and anti-HTN medication.	0.774 (0.53, 1.13)*
				ARB	731	810		0.877 (0.611, 1.258)*
Liabeuf, S.[74]	France	COVID-19	Death or requiring ICU admission	ACEI/ARB	96	172	Age, sex, chronic heart disease, HTN, COPD, and use of β-blockers, diuretics, and anti-inflammatory	1.73 (1.02, 2.93)

Author [ref]	Country	Population	Outcome	Exposure	Ex #	Un #	Adjusted for	aOR* (95% CI)
							drugs.	
Lopez-Otero, D.[59]	Spain	COVID-19	Requiring ICU admission	ACEI/ARB	N.A.	N.A.	Arterial oxygen saturation <95%, diabetes, hypoxemia, and laboratory test results.	1.13 (0.37, 3.42)
				ACEI	N.A.	N.A.		1.23 (0.27, 5.60)
				ARB	N.A.	N.A.		1.02 (0.28, 3.64)
Mehta, N.[41]	US	COVID-19	Requiring mechanical ventilation	ACEI/ARB	212	1523	Age, sex, HTN, CHD, HF, and COPD.	1.32 (0.80, 2.18)
				ACEI	116	1619		1.35 (0.74, 2.47)
				ARB	98	1637		1.12 (0.59, 2.12)
Million, M.[75]	France	COVID-19	Death or requiring ICU admission	ARB	36	983	Age, medications, NEWS score, viral load at admission.	18.4 (6.28, 53.9)
Pinto-Sietsma, S.[76]	Netherland	COVID-19 (including clinical diagnosis)	Death or requiring ICU admission	ACEI	134	635	Age, sex, HTN, and DM.	1.18 (0.75, 1.86)
	Germany			ARB	91	678		0.94 (0.56, 1.58)
Rentsch, C.[44]	US	COVID-19	Requiring ICU admission	ACEI/ARB	255	330	Age, race, NSAID, CKD, COPD, DM, HTN, CVD, baseline vital signs and laboratory findings.	1.66 (0.94, 2.93)
Reynolds, H.[45]	US	COVID-19	Death, requiring ICU admission, or requiring mechanical ventilation	ACEI	627	653	Age, sex, ethnicity, BMI, medical history (HTN, MI, HF, DM, CKD, asthma, COPD), medication, and smoking.	0.90 (0.71, 1.13)
				ARB	664	639		0.96 (0.77, 1.21)

Author [ref]	Country	Population	Outcome	Exposure	Ex #	Un #	Adjusted for	aOR* (95% CI)
Rhee, S.[77]	Korea	COVID-19 with diabetes	Death or requiring ICU admission	ACEI/ARB	327	505	Age, sex, comorbidity, medication.	0.599 (0.251, 1.431)
Senkal, N.[78]	Turkey	COVID-19	hospitalization ≥14d, ICU, death (including clinical diagnosis)	ACEI	58	78	Age, sex, sick days before hospital admission, medical history, smoking, use of anti-HTN and serum creatinine.	0.37 (0.15, 0.87)
				ARB	105	78		0.61 (0.27, 1.40)
Son, M.[46]	Korea	COVID-19 with HTN and taking anti-HTN medication	Requiring high-flow oxygenation	ACEI/ARB	109	27	End-stage renal disease with dialysis and CCI.	0.663 (0.272, 1.619)
				ACEI	12	124		0.358 (0.074, 1.734)
				ARB	101	35		0.972 (0.424, 2.226)
Xu, J.[63]	China	COVID-19 with HTN and taking anti-HTN medication	Requiring mechanical ventilation	ACEI/ARB	40	61	Age and sex.	0.92 (0.32, 2.63)
Yan, H.[47]	China	COVID-19	Severe and critical COVID-19 according to Chinese Guideline	ACEI			Age, sex, and BMI.	1.23 (0.19, 7.93)
				ARB				0.77 (0.36, 1.63)
Ye, C.[79]	China	COVID-19 with HTN	Death, shock, requiring ICU admission, or requiring mechanical ventilation.	ACEI/ARB	62	80	Age and sex.	1.17 (0.46, 2.97)
Zhou, X.[80]	China	COVID-19 with HTN and taking anti-HTN	Death or requiring transfer to higher level hospital	ACEI/ARB	15	21	Age, sex, hospital stay, and time from onset to hospital	0.14 (0.009, 2.208)

Author [ref]	Country	Population	Outcome	Exposure	Ex #	Un #	Adjusted for	aOR* (95% CI)
		medication					admission.	

Ex # (exposure number), Un # (un-exposure number).

* Adjust Hazard Ratio (aHR) is marked with star (*). Otherwise, it is adjusted odds ratio (aOR).

[$] Abbreviations: ARDS (acute respiratory distress syndrome), AF (atrial fibrillation), BMI (body weight index), CCI (Charlson Comorbidity Index), CHD (coronary heart disease), COPD (chronic obstructive pulmonary disease), CKD (chronic kidney disease), cTnI (cardiact troponin I), CVD (cardiovascular disease), DM (diabetes mellitus), ECOG (Eastern Cooperative Oncology Group), HTN (hypertension), HF (heart failure), IHD (ischemic heart disease), MI (myocardial infarction), MODS (multi-organ dysfunction syndrome), NEWS (national early warning score), NSAID (non-steroid anti-inflammation drug), SARS (severe acute respiratory syndrome), SOFA (sequential organ failure assessment).

Figure Legends

Figure 1. Study Selection

Figure 2. Forest plot showing association between prior ACEI/ARB use and risk of SARS-CoV-2 infection after adjustment. Data is pooled from adjusted OR (A) or HR (B). OR = odds ratio, SE = standard error, IV = inverse variance, aOR = adjusted odds ratio, 95%-CI = 95% confidence interval. See Table 1 for details.

Figure 3. Forest plot showing association between prior ACEI/ARB use and risk of COVID-19 mortality after adjustment. Data is pooled from adjusted OR (A) or HR (B). OR = odds ratio, SE = standard error, IV = inverse variance, aOR = adjusted odds ratio, 95%-CI = 95% confidence interval. See Table 2 for details.

Figure 4. Forest plot showing association between prior ACEI/ARB use and risk of severe COVID-19 after adjustment. Data is pooled from adjusted OR (A) or HR (B). OR = odds ratio, SE = standard error, IV = inverse variance, aOR = adjusted odds ratio, 95%-CI = 95% confidence interval. See Table 3 for details.

Figure 1

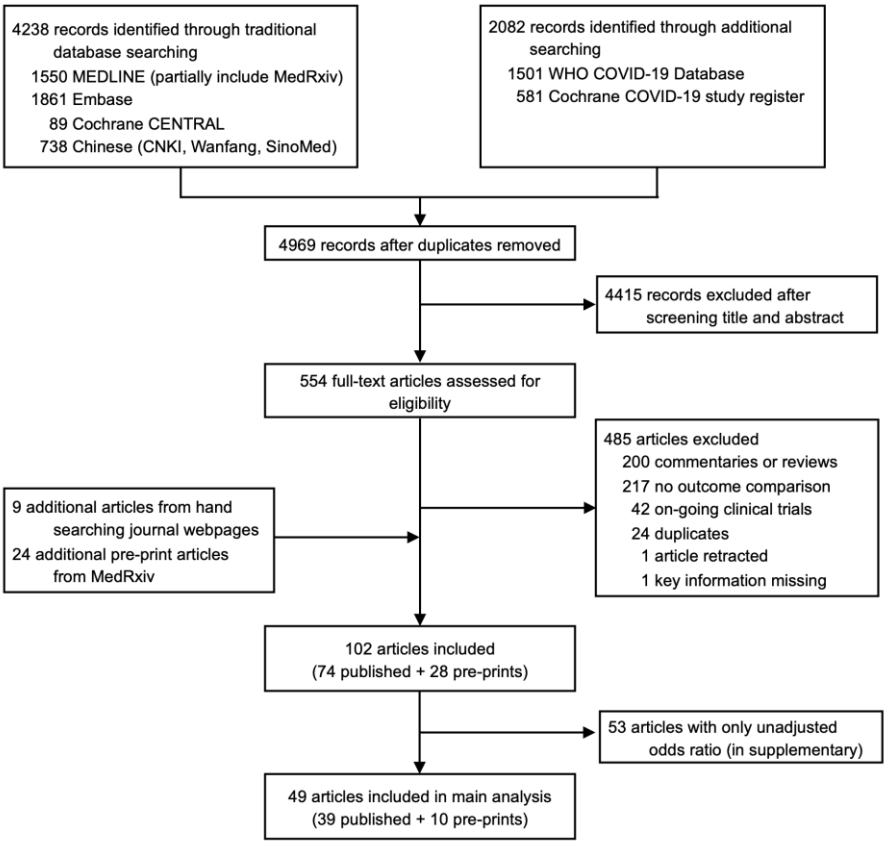

Figure 2

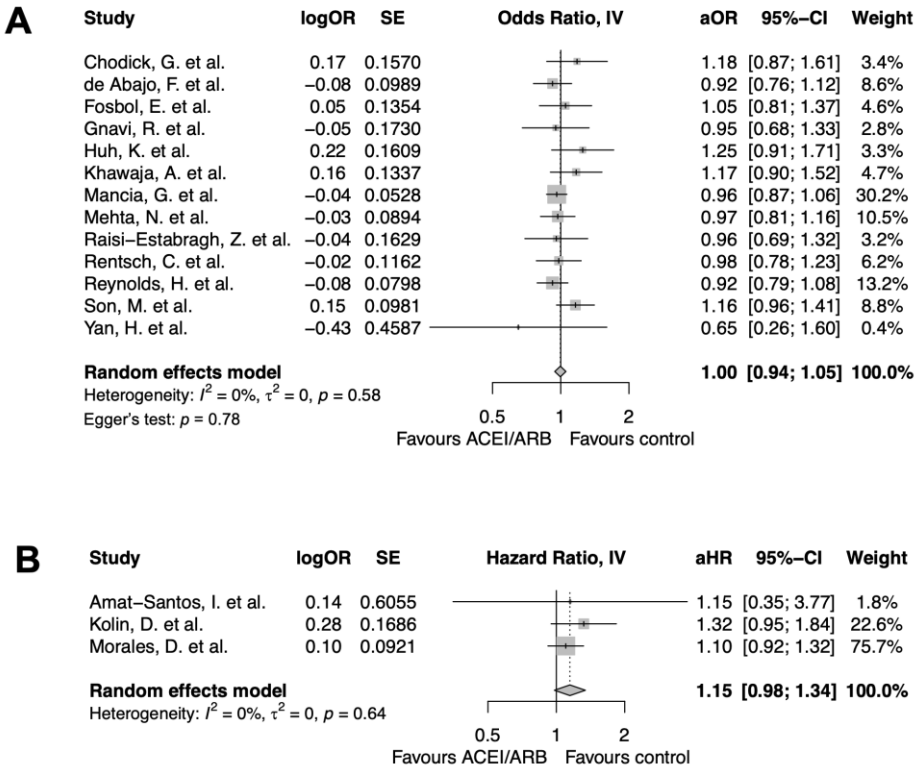

Figure 3

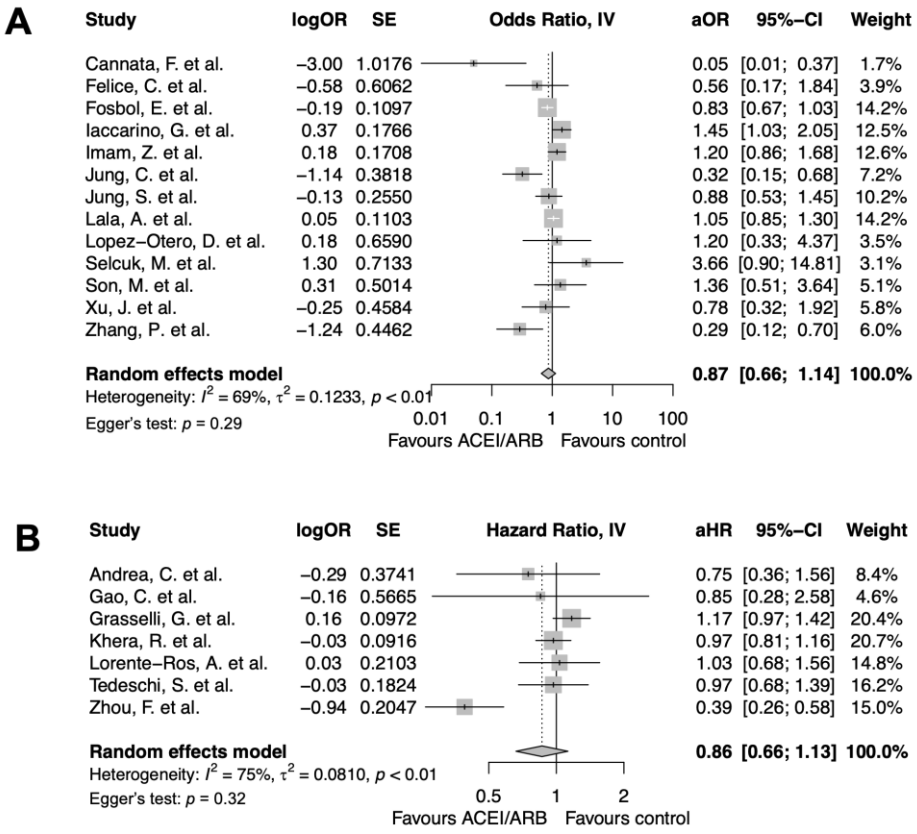

Figure 4