

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

Jiuyang Xu<sup>1\*</sup>, Yaqun Teng<sup>1,2\*</sup>, Lianhan Shang<sup>3,4\*</sup>, Xiaoying Gu<sup>4,5</sup>, Guohui Fan<sup>4,5</sup>, Yijun Chen<sup>1</sup>, Ran  
Tian<sup>2</sup>, Shuyang Zhang<sup>1,2,6,7</sup>, and Bin Cao<sup>4,7#</sup>

<sup>1</sup> Tsinghua University School of Medicine, Beijing 100084, China

<sup>2</sup> Department of Cardiology, Peking Union Medical College Hospital, Beijing 100730, China

<sup>3</sup> Beijing University of Chinese Medicine, Beijing 100029, China

<sup>4</sup> Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, National Center for Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China

<sup>5</sup> Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing 100029, China

<sup>6</sup> Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China.

<sup>7</sup> Tsinghua University-Peking University Joint Center for Life Sciences, Beijing 100084, China

\* These authors contributed equally.

# Corresponding author:

Prof. Bin Cao, MD

Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital

Email: [caobin\\_ben@163.com](mailto:caobin_ben@163.com)

No 2 East Yinghua Road, Chaoyang District, Beijing 100029, China

**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<sub>1-7</sub>-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  $\leq 6$ , (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<sub>1-7</sub> 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.

Accepted Manuscript

## 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.

### Funding

This work was supported by National Key R&D Program of China [2020YFC0861000 to S.Z.], Major Projects of National Science and Technology on New Drug Creation and Development [2020ZX09201001 and 2020ZX09201012 to B.C.], Chinese Academy of Medical Sciences (CAMS) Emergency Project of COVID-19 [2020HY320001 to B.C.], and CAMS Innovation Fund for Medical Sciences [2020-I2M-CoV19-001 to S.Z.].

## References

1. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and Cardiovascular Disease. *Circulation* **2020**; 141(20): 1648-55.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **2020**; 395(10229): 1054-62.
3. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* **2020**; 382(17): 1653-9.
4. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? *JAMA* **2020**; 323(18): 1769-70.
5. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. *Nat Rev Nephrol* **2020**; 16(6): 305-7.
6. Williams B, Zhang Y. Hypertension, renin-angiotensin-aldosterone system inhibition, and COVID-19. *Lancet* **2020**; 395(10238): 1671-3.
7. Wang K, Gheblawi M, Oudit GY. Angiotensin Converting Enzyme 2: A Double-Edged Sword. *Circulation* **2020**, (online first) doi: 10.1161/CIRCULATIONAHA.120.047049.
8. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet* **2007**; 369(9568): 1208-19.
9. Kreutz R, Algharably EAE, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res* **2020**; 116(10): 1688-99.
10. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res* **2020**; 126(10): 1456-74.
11. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* **2020**; 181(2): 281-92 e6.
12. Mackey K, King VJ, Gurley S, et al. Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults: A Living Systematic Review. *Ann Intern Med* **2020**; 173(3): 195-203.
13. Kow CS, Hasan SS. Do the meta-analyses provide a clean bill of health to the use of renin-angiotensin system inhibitors in COVID-19? *Clin Infect Dis* **2020**, (online first) doi: 10.1093/cid/ciaa1167.
14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* **2016**; 5(1): 210.
15. World Health Organization. Clinical management of COVID-19: Interim guidance. Available at: <https://www.who.int/publications/i/item/clinical-management-of-covid-19>. Accessed May 30, 2020.
16. China National Health Commission. Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (Trial Version 5). Available at: <http://www.nhc.gov.cn/jkj/s3577/202002/a5d6f7b8c48c451c87dba14889b30147/files/3514cb996ae24e2faf65953b4ecd0df4.pdf>. Accessed May 26, 2020.
17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**; 395(10223): 497-506.
18. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* **2019**; 366: 14898.
19. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. Available at: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Accessed May 26, 2020.
20. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* **2014**; 14: 135.
21. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* **2019**; 22(4): 153-60.
22. Amat-Santos IJ, Santos-Martinez S, Lopez-Otero D, et al. Ramipril in High-Risk Patients With COVID-19. *J Am Coll Cardiol* **2020**; 76(3): 268-76.
23. Guo X, Zhu Y, Hong Y. Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension: A Meta-Analysis. *Hypertension* **2020**; 76(2): e13-e4.
24. Pirola CJ, Sookoian S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor effect on COVID-19 outcome: A Meta-analysis. *J Infect* **2020**; 81(2): 276-81.

25. Grover A, Oberoi M. A systematic review and meta-analysis to evaluate the clinical outcomes in COVID-19 patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. *Eur Heart J Cardiovasc Pharmacother* **2020**, (online first) doi: 10.1093/ehjcvp/pvaa064.
26. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. *Pharmacol Res* **2020**; 158: 104927.
27. Joint Committee for Guideline Revision. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol* **2019**; 16(3): 182-241.
28. Mourad JJ, Levy BI. Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. *Nat Rev Cardiol* **2020**; 17(5): 313.
29. Frolidi G. What could be the better choice between ACE inhibitors and AT1R antagonists in coronavirus disease 2019 (COVID-19) patients? *J Med Virol* **2020**, (online first) doi: 10.1002/jmv.25974.
30. Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J* **2020**; 41(19): 1810-7.
31. Wu C, Ye D, Mullick AE, et al. Effects of Renin-Angiotensin Inhibition on ACE2 (Angiotensin-Converting Enzyme 2) and TMPRSS2 (Transmembrane Protease Serine 2) Expression: Insights Into COVID-19. *Hypertension* **2020**; 76(4): e29-e30.
32. Wysocki J, Lores E, Ye M, Soler MJ, Battle D. Kidney and Lung ACE2 Expression after an ACE Inhibitor or an Ang II Receptor Blocker: Implications for COVID-19. *J Am Soc Nephrol* **2020**; 31(9): 1941-3.
33. Chodick G, Nutman A, Yiekutiel N, Shalev V. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are not associated with increased risk of SARS-CoV-2 infection. *J Travel Med* **2020**; 27(5).
34. de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *The Lancet* **2020**; 395(10238): 1705-14.
35. Fosbol EL, Butt JH, Ostergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA* **2020**; 324(2): 168-77.
36. Gnani R, Demaria M, Picariello R, Dalmasso M, Ricceri F, Costa G. Therapy with agents acting on the renin-angiotensin system and risk of SARS-CoV-2 infection. *Clin Infect Dis* **2020**, (online first) doi: 10.1093/cid/ciaa634.
37. Huh K, Ji W, Kang M, et al. Association of previous medications with the risk of COVID-19: a nationwide claims- based study from South Korea. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.05.04.20089904.
38. Khawaja AP, Warwick AN, Hysi PG, et al. Associations with covid-19 hospitalisation amongst 406,793 adults: the UK Biobank prospective cohort study. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.05.06.20092957.
39. Kolin DA, Kulm S, Elemento O. Clinical and Genetic Characteristics of Covid-19 Patients from UK Biobank. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.05.05.20075507.
40. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med* **2020**; 382(25): 2431-40.
41. Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* **2020**; 5(9): 1020-6.
42. Morales DR, Conover MM, You SC, et al. Renin-angiotensin system blockers and susceptibility to COVID-19: a multinational open science cohort study. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.06.11.20125849.
43. Raisi-Estabragh Z, McCracken C, Ardissino M, et al. Non-white ethnicity, male sex, and higher body mass index, but not medications acting on the renin-angiotensin system are associated with coronavirus disease 2019 (COVID-19) hospitalisation: review of the first 669 cases from the UK Biobank. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.05.10.20096925.
44. Rentsch CT, Kidwai-Khan F, Tate JP, et al. Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.04.09.20059964.
45. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med* **2020**; 382(25): 2441-8.

46. Son M, Seo J, Yang S. Association Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19 Infection in South Korea. *Hypertension* **2020**; 76(3): 742-9.
47. Yan H, Valdes AM, Vijay A, et al. Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zhejiang Province, China. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.04.24.20077875.
48. Andrea C, Francesco M, Antonio N, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Outcome in Patients With SARS-CoV-2 Pneumonia: A Case Series Study. *Hypertension* **2020**; 76(2): e10-e2.
49. Cannata F, Chiarito M, Reimers B, et al. Continuation versus discontinuation of ACE inhibitors or angiotensin II receptor blockers in COVID-19: effects on blood pressure control and mortality. *Eur Heart J Cardiovasc Pharmacother* **2020**, (online first) doi: 10.1093/ehjcvp/pvaa056.
50. Felice C, Nardin C, Di Tanna GL, et al. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens* **2020**, (online first) doi: 10.1093/ajh/hpaa096.
51. Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J* **2020**; 41(22): 2058-66.
52. Grasselli G, Greco M, Zanella A, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med* **2020**, (online first) doi: 10.1001/jamainternmed.2020.3539.
53. Iaccarino G, Grassi G, Borghi C, et al. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. *Hypertension* **2020**; 76(2): 366-72.
54. Imam Z, Odish F, Gill I, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. *J Intern Med* **2020**; 288(4): 469-76.
55. Jung C, Bruno RR, Wernly B, et al. Inhibitors of the Renin-Angiotensin-Aldosterone System and Covid-19 in critically ill elderly patients. *Eur Heart J Cardiovasc Pharmacother* **2020**, (online first) doi: 10.1093/ehjcvp/pvaa083.
56. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis* **2020**, (online first) doi: 10.1093/cid/ciaa624.
57. Khara R, Clark C, Lu Y, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.05.17.20104943.
58. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* **2020**; 76(5): 533-46.
59. Lopez-Otero D, Lopez-Pais J, Cacho-Antonio CE, et al. Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. *CARDIOVID registry. Rev Esp Cardiol (Engl Ed)* **2020**, (online first) doi: 10.1016/j.rec.2020.05.018.
60. Lorente-Ros A, Monteagudo Ruiz JM, Rincon LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. *Cardiol J* **2020**, (online first) doi: 10.5603/CJ.a2020.0089.
61. Selcuk M, Cinar T, Keskin M, et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? *Clin Exp Hypertens* **2020**; 42(8): 738-42.
62. Tedeschi S, Giannella M, Bartoletti M, et al. Clinical Impact of Renin-angiotensin System Inhibitors on In-hospital Mortality of Patients With Hypertension Hospitalized for Coronavirus Disease 2019. *Clin Infect Dis* **2020**; 71(15): 899-901.
63. Xu J, Huang C, Fan G, et al. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in context of COVID-19 outbreak: a retrospective analysis. *Front Med* **2020**, (online first) doi: 10.1007/s11684-020-0800-y.
64. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res* **2020**; 126(12): 1671-81.
65. Zhou F, Liu YM, Xie J, et al. Comparative Impacts of ACE (Angiotensin-Converting Enzyme) Inhibitors Versus Angiotensin II Receptor Blockers on the Risk of COVID-19 Mortality. *Hypertension* **2020**; 76(2): e15-e7.
66. Bean DM, Kraljevic Z, Searle T, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. *Eur J Heart Fail* **2020**; 22(6): 967-74.

67. Bravi F, Flacco ME, Carradori T, et al. Predictors of severe or lethal COVID-19, including Angiotensin Converting Enzyme inhibitors and Angiotensin II Receptor Blockers, in a sample of infected Italian citizens. *PLoS One* **2020**; 15(6): e0235248.
68. Cheung KS, Hung IFN, Leung WK. Association between angiotensin blockade and COVID-19 severity in Hong Kong. *CMAJ* **2020**; 192(23): E635.
69. Choi MH, Ahn H, Ryu HS, et al. Clinical Characteristics and Disease Progression in Early-Stage COVID-19 Patients in South Korea. *J Clin Med* **2020**; 9(6).
70. Chung SM, Lee YY, Ha E, et al. The Risk of Diabetes on Clinical Outcomes in Patients with Coronavirus Disease 2019: A Retrospective Cohort Study. *Diabetes Metab J* **2020**; 44(3): 405-13.
71. De Spiegeleer A, Bronselaer A, Teo JT, et al. The Effects of ARBs, ACEis, and Statins on Clinical Outcomes of COVID-19 Infection Among Nursing Home Residents. *J Am Med Dir Assoc* **2020**; 21(7): 909-14 e2.
72. Ebinger JE, Achamallah N, Ji H, et al. Pre-Existing Traits Associated with Covid-19 Illness Severity. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.04.29.20084533.
73. Golpe R, Perez-de-Llano LA, Dacal D, et al. Risk of severe COVID-19 in hypertensive patients treated with renin-angiotensin-aldosterone system inhibitors. *Med Clin (Barc)* **2020**, (online first) doi: 10.1016/j.medcli.2020.06.013.
74. Liabeuf S, Moragny J, Bennis Y, et al. Association between renin-angiotensin system inhibitors and COVID-19 complications. *Eur Heart J Cardiovasc Pharmacother* **2020**, (online first) doi: 10.1093/ehjcvp/pvaa062.
75. Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* **2020**; 35: 101738.
76. Pinto-Sietsma SJ, Flossdorf M, Buchholz VR, et al. Antihypertensive drugs in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother* **2020**, (online first) doi: 10.1093/ehjcvp/pvaa058.
77. Rhee SY, Lee J, Nam H, Kyoung D-S, Kim DJ. Effects of a DPP-4 inhibitor and RAS blockade on clinical outcomes of patients with diabetes and COVID-19. *MedRxiv* **2020**, (online first) doi: 10.1101/2020.05.20.20108555.
78. Senkal N, Meral R, Medetalibeyoglu A, Konyaoglu H, Kose M, Tukek T. Association between chronic ACE inhibitor exposure and decreased odds of severe disease in patients with COVID-19. *Anatol J Cardiol* **2020**; 24(1): 21-9.
79. Ye C, Zhang S, Zhang X, et al. Impact of comorbidities on patients with COVID-19: A large retrospective study in Zhejiang, China. *J Med Virol* **2020**, (online first) doi: 10.1002/jmv.26183.
80. Zhou X, Zhu J, Xu T. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin-angiotensin system inhibitors. *Clin Exp Hypertens* **2020**; 42(7): 656-60.



| Author [ref]            | Country   | Population                                                            | Exposure | Exposed number | Unexposed number | Adjusted for <sup>\$</sup>                                                              | 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 <sup>\$</sup>                                                                                  | 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).

<sup>\$</sup> 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<sup>†</sup> for COVID-19 patients

| Author [ref]    | Country | Population                                       | Exposure | Exposed number | Unexposed number | Adjusted for <sup>s</sup>                                                                                                                                                    | 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 <sup>s</sup>                                                                               | 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, $\beta$ -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 <sup>s</sup>                                                                                       | 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,                                                             | 1.20 (0.33, 4.37)     |
|                     |         |                                                  | ACEI     | N.A.           | N.A.             | medical history (HTN, DM, dyslipidemia, arterial disease,                                                       | 0.02 (0.01, 0.63)     |
|                     |         |                                                  | ARB      | N.A.           | N.A.             | heart disease, AF, pneumonia, CKD, CBVD, auto-immune disease), fever, oxygen saturation < 95%, and medications. | 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 <sup>\$</sup>                                                       | 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.

<sup>\$</sup> 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 (cardiac 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 (lactate 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 $\geq 7$ 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 $\beta$ -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 $\geq 14$ d, 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).

<sup>\$</sup> 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 (cardiac 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

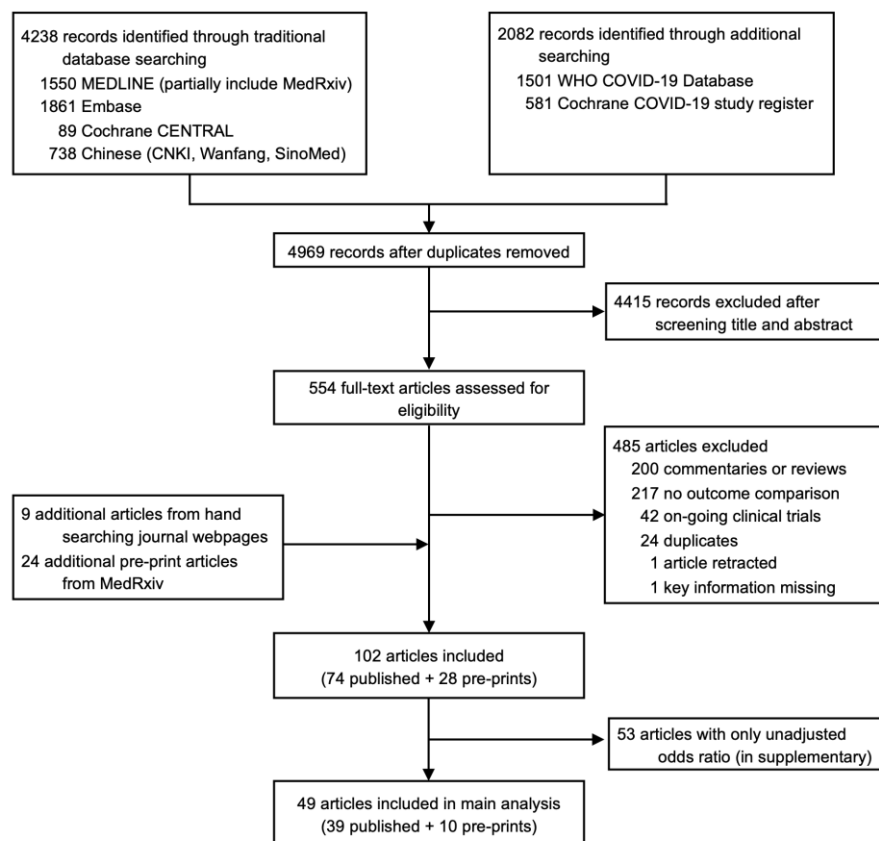
### Figure 1. Study Selection

**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



Accepte

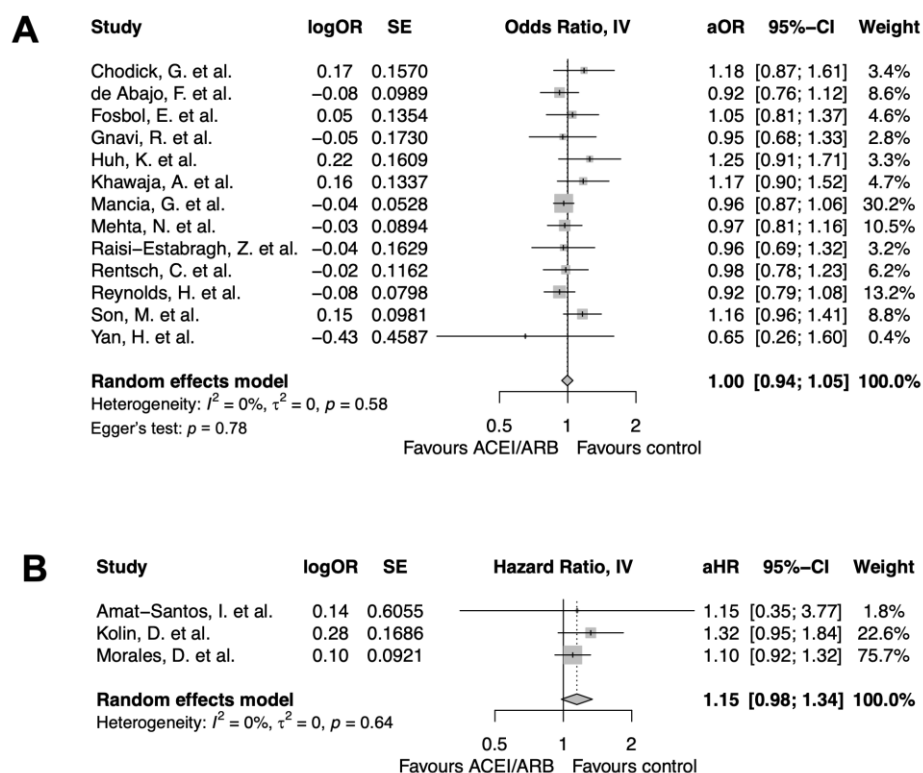


Figure 3

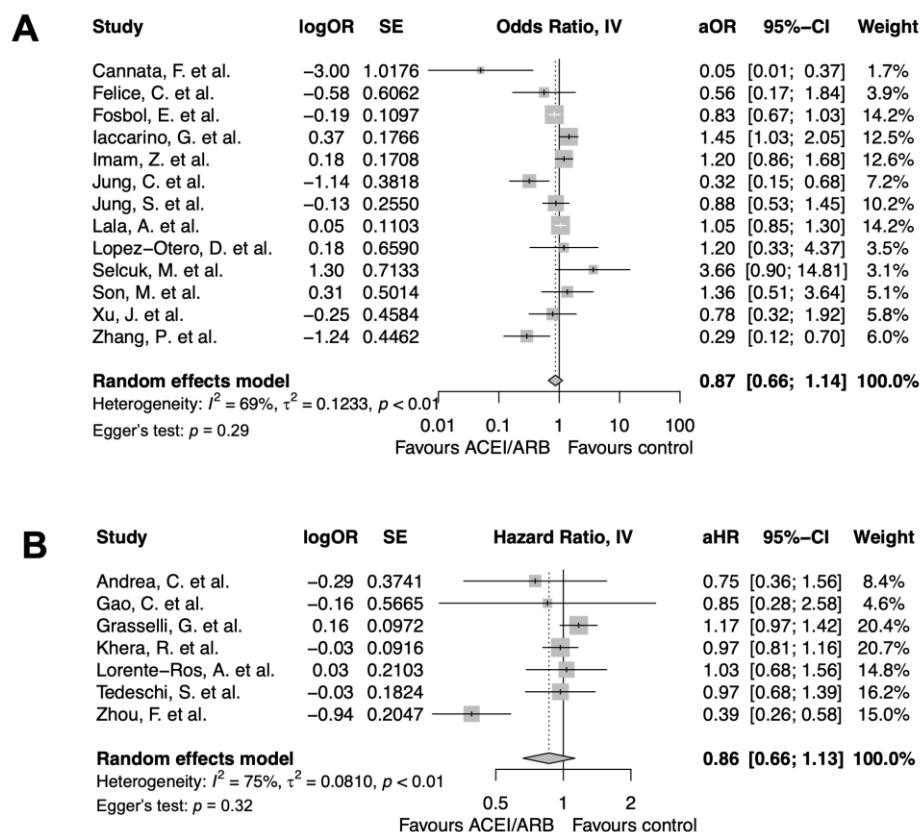


Figure 4

