Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Meta-analysis

# The effect of renin–angiotensin–aldosterone system inhibitors in patients with hypertension and COVID-19: A meta-analysis of randomized controlled trials and propensity score-matched studies

Kai Zhang [1], Lanxin Cao [1], Nanxia Xuan [1], Tiancha Huang [1], Baoping Tian [1], Wei Cui [1], Gensheng Zhang [1,2,*], Shufang Zhang [3,*]

[1] Department of Critical Care Medicine, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China
[2] Zhejiang Province Clinical Research Center for Emergency and Critical Care Medicine, Hangzhou, Zhejiang 310009, China;
[3] Department of Cardiology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China.

A R T I C L E   I N F O

A B S T R A C T

*Background:* High-quality evidence for whether the use of renin–angiotensin–aldosterone system (RAAS) inhibitors worsens clinical outcomes for patients with coronavirus disease 2019 (COVID-19) is lacking. The present study aimed to evaluate the effect of RAAS inhibitors on disease severity and mortality in patients with hypertension and COVID-19 using randomized controlled trials (RCTs) and propensity score-matched (PSM) studies.

*Methods:* A literature search was conducted with PubMed, Embase, and Scopus databases from 31 December 2019 to 10 January 2022. We included RCTs and PSM studies comparing the risk of severe illness or mortality in patients with hypertension and COVID-19 treated or not treated with RAAS inhibitors. Individual trial data were combined to estimate the pooled odds ratio (OR) with a random-effects model.

*Results:* A total of 17 studies (4 RCTs and 13 PSM studies) were included in the meta-analysis. The use of RAAS inhibitors was not associated with an increased risk of severe illness (OR=1.00, 95% confidence interval [CI]: 0.88–1.14, $I^2$=28%) or mortality (OR=0.96, 95% CI: 0.83–1.11, $I^2$=16%) for patients with hypertension and COVID-19. Furthermore, there was no significant difference in the severity of COVID-19 when patients continued or discontinued treatment with RAAS inhibitors (OR=1.01, 95% CI: 0.78–1.29, $I^2$=0%).

*Conclusions:* This study suggests that there was no association between treatment with RAAS inhibitors and worsened COVID-19 disease outcomes. Our findings support the current guidelines that RAAS inhibitors should be continued in the setting of the COVID-19 pandemic. However, the benefit of RAAS inhibitor medications for COVID-19 patients should be further validated with more RCTs.

## Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly developed into a pandemic and threatened global health.[1] As of 21 January 2022, SARS-CoV-2 has resulted in >340.5 million confirmed cases of COVID-19, with >5.5 million deaths.[2] There is currently a lack of specific or effective intervention approved for treating COVID-19. Thus, the presence of risk factors associated with negative clinical outcomes arouses concern for those with COVID-19. Therefore, identifying these risk factors is needed. Previous research suggests that pre-existing chronic diseases, including hypertension, diabetes, cardiovascular disease, and chronic kidney disease, are associated with a greater risk of the development of COVID-19 into a critical or mortal condition.[3,4] In fact, 21.8% of 1,320,488 COVID-19 patients in the United States and 26.0% of 20,982 COVID-19 patients in China had at least one comorbidity, and hypertension seems to be one of the most common comorbidities.[5,6]

* Corresponding authors: Gensheng Zhang, Department of Critical Care Medicine, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang Province Clinical Research Center for Emergency and Critical Care Medicine, Hangzhou, Zhejiang 310009, China; Shufang Zhang, Department of Cardiology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China.
   *E-mail addresses:* genshengzhang@zju.edu.cn (G. Zhang), zhangsf08@zju.edu.cn (S. Zhang).

Inhibitors of the renin–angiotensin–aldosterone system (RAAS), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are widely used for different clinical indications, and the above-mentioned chronic conditions frequently require treatment with these two classes of medications.[7] Animal and human studies have shown that ACEIs/ARBs may increase the expression of angiotensin-converting enzyme 2, which is a coreceptor for SARS-CoV2.[8–11] Therefore, it is concerning that treatment with ACEIs and/or ARBs may increase both susceptibility to SARS-CoV2 infection and the risk of its developing into a severe form of COVID-19.[12,13] On the contrary, a recent study suggested that the ACEI treatment was associated with dampened hyperinflammation related to COVID-19 and increased cell intrinsic antiviral responses, whereas ARBs treatment was associated with enhanced epithelial-immune cell interactions.[14] Therefore, the effect of ACEIs/ARBs on patients with COVID-19 has been at the forefront of clinical debates.

Several observational studies with large sample sizes consistently demonstrated that the use of ACEIs/ARBs was not associated with severe disease or mortality among patients with COVID-19.[15–17] One study performed multivariable analyses and the adjusted estimates suggested that in-hospital use of ACEIs/ARBs might reduce the risk of severe disease or all-cause mortality for COVID-19 patients with hypertension.[18] However, one study suggested that taking ACEIs/ARBs might be associated with worsened clinical outcomes, such as requiring intensive care or mechanical ventilation.[19] The conflicting results obtained from observational studies combined with the recent completion of randomized controlled trials (RCTs)[20–23] prompted us to summarize the data thus far to provide an updated perspective and an understanding of the association between the use of ACEIs/ARBs and clinical COVID-19 outcomes. In addition, a large body of statistical literature and meta-epidemiological studies have shown that propensity score-matched (PSM) studies are empirically equivalent to RCTs in their ability to derive unbiased estimates.[24–26] Therefore, the aim of the updated meta-analysis was to summarize the latest evidence of RCTs and PSM studies to evaluate the association between the use of ACEIs/ARBs and the prognosis of patients with hypertension and COVID-19.

## Methods

### Study selection

This meta-analysis was conducted in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[27] (see Supplementary Material 1). The study protocol was registered in PROSPERO (CRD42020187284). Two authors (Kai Zhang and Lanxin Cao) independently searched PubMed, Embase, and Scopus databases for relevant articles published in English from 31 December 2019 to 10 January 2022 (search strategies are listed in Supplementary Material 2). The inclusive criteria were as follows: (1) population: patients with hypertension and COVID-19 infection that was diagnosed on the basis of the standard procedure proposed by the World Health Organization; (2) intervention: patients treated with ACEIs or ARBs; (3) comparator: patients not treated with ACEIs or ARBs; (4) outcomes: severe COVID-

19 (characterized by admission to the intensive care unit [ICU], use of mechanical ventilation, in-hospital mortality or defined according to the diagnosis and treatment guidelines for COVID-19); and (5) study design: RCTs and PSM studies. In addition, case reports, non-human studies, studies without adequate information or concerning outcomes, and studies focusing on special populations (e.g., pediatric, pregnant, and cancer patients) were excluded.

### Data extraction and quality assessment

Two reviewers (Kai Zhang and Lanxin Cao) independently extracted detailed information (first author, study period, study location, sample size, population characteristics, and outcomes) using a predesigned table. If relevant information was not reported in the article, we contacted the corresponding authors for further information.

Two reviewers (Tiancha Huang and Baoping Tian) independently assessed the quality of the included RCTs using the Cochrane risk of bias tool[28] and the quality of the included PSM studies using the Newcastle-Ottawa Scale for cohort studies.[29] Publication bias was assessed using Egger's regression test. Any discrepancies in all phases were ultimately resolved by arriving at a team consensus.

### Statistical synthesis and analysis

We performed pooled analysis to estimate the association between the use of ACEIs/ARBs and the risk of severe illness or mortality. A random-effects model was used to calculate the odds ratio (OR) with a 95% confidence interval (95% CI). For studies reporting hazard ratios (HRs), we converted the HR into an OR using the methodology defined in the Cochrane Handbook for Systematic Reviews of Interventions. We calculated the $I^2$ statistic to quantify the heterogeneity between studies, where $I^2$ values of <25%, 25–75%, and >75% indicate low, moderate, and high heterogeneity, respectively.[30] We stratified studies by study design (RCTs *vs.* PSM studies) and severity of COVID-19 disease according to the Guidelines of Diagnosis and Treatment of COVID-19 (ninth edition) from the National Health Commission to perform subgroup analyses. Furthermore, a sensitivity analysis was employed to examine the effect of an individual study by omitting each at a time. All analyses were performed with Review Manager 5.3 (Nordic Cochrane Center), and a *P*-value <0.05 was assumed to have statistical significance.

## Results

### Study selection and study characteristics

The flow chart [Figure 1] summarizes the search and study selection processes. A total of 1209 articles were initially identified. After removing duplicate articles and screening abstracts, we identified 72 relevant studies. Fifty-five studies were excluded according to our criteria upon reading the full text of the articles. Ultimately, we included 17 studies[16–41] comprising 30,416 patients with hypertension and COVID-19 in our meta-analysis. The basic characteristics of the included studies are summarized in Table 1. Four of the included studies in the meta-analysis were RCTs[20–23] and the other 13 were observational studies.[16–18,31–41] We used the propensity-matched scores to adjust potential confounders. Patients in five studies[20–23,33]
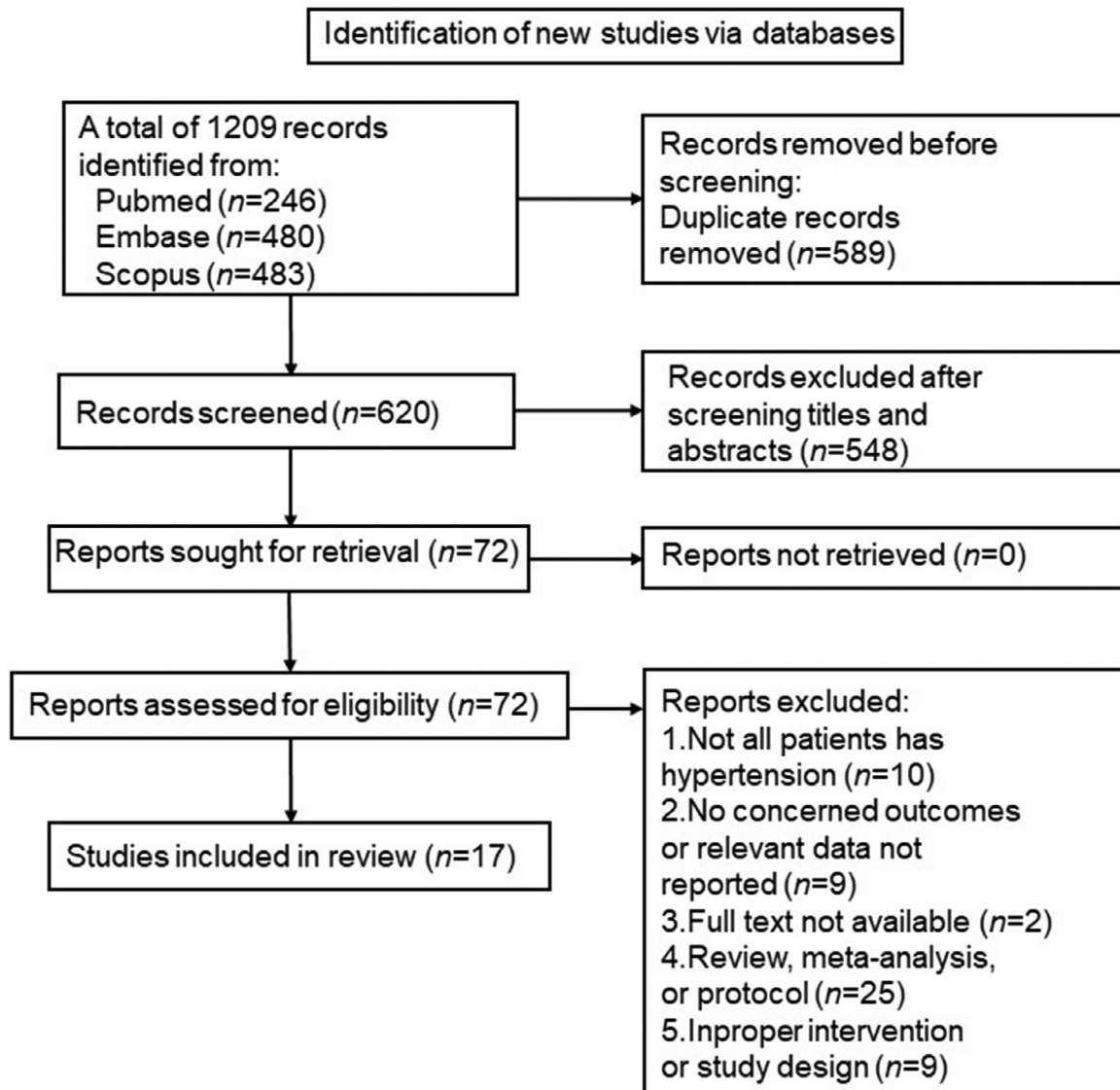
**Identification of new studies via databases**

A total of 1209 records identified from:
Pubmed (*n*=246)
Embase (*n*=480)
Scopus (*n*=483)

→ Records removed before screening:
Duplicate records removed (*n*=589)

Records screened (*n*=620)

→ Records excluded after screening titles and abstracts (*n*=548)

Reports sought for retrieval (*n*=72)

→ Reports not retrieved (*n*=0)

Reports assessed for eligibility (*n*=72)

→ Reports excluded:
1. Not all patients has hypertension (*n*=10)
2. No concerned outcomes or relevant data not reported (*n*=9)
3. Full text not available (*n*=2)
4. Review, meta-analysis, or protocol (*n*=25)
5. Inproper intervention or study design (*n*=9)

Studies included in review (*n*=17)

**Figure 1.** PRISMA 2020 flow diagram for the meta-analysis. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

receiving ACEIs/ARBs before hospital admission were divided into continuing or discontinuing ACEIs/ARBs therapy groups for the subgroup analysis to evaluate the effect of continuing *vs.* discontinuing ACEIs/ARBs on severe illness or mortality. The primary outcomes for the included studies were death, severe illness (defined as the need for intensive care or mechanical ventilation), or a composite of ICU admission, mechanical ventilation, and death.

The risk of bias assessment is presented in Supplementary Material 3. Three of the four RCTs were rated as having a high risk of bias because they were open-label trials.[20–22] Furthermore, all the PSM studies were rated as high quality, each with a total score of >6. In addition, there was no significant publication bias detected with Egger's regression test ($P$=0.779, Supplementary Material 3).

### Meta-analysis results

All included studies compared clinical severity-related outcomes between COVID-19 patients treated with ACEIs/ARBs

and those who were not. In the pooled analysis of all included studies, the use of ACEIs/ARBs was not associated with severe COVID-19 (OR=1.00, 95% CI:0.88–1.14, $I^2$=28%, Figure 2). Sixteen studies reported mortality rates and the results indicated no difference between groups (OR=0.96, 95% CI: 0.83–1.11, $I^2$=16%, Figure 3A). Furthermore, continuation and discontinuation of ACEIs/ARBs had similar effects on disease severity (OR=1.01, 95% CI: 0.78–1.29, $I^2$=0%, Figure 3B).

We grouped studies according to study design (RCTs *vs.* PSM studies) and severity of COVID-19 disease (mild *vs.* severe cases). The subgroup analysis of the RCTs and PSM studies indicated no difference in the risk of severe COVID-19 or death among patients treated with ACEIs/ARBs or not (RCTs: OR=0.99, 95% CI: 0.69–1.42, $I^2$=0%; PSM studies: OR=1.01, 95% CI: 0.87–1.16, $I^2$=38%, Figure 4). Moreover, the use of ACEIs/ARBs was not associated with worsened COVID-19 disease outcomes in patients with mild or severe COVID-19 (mild: OR=1.00, 95% CI: 0.76–1.32, $I^2$=49%; severe: OR=1.03, 95% CI: 0.91–1.17, $I^2$=0%, Figure 5).

In addition, the sensitivity analysis showed a robust estimation of the pooled effect (Supplementary Material 3). The ORs

**Table 1**
Characteristics of included studies.

| Reference | Publication date | Study period and location | Study design | Population | Number of participants | Outcomes |
|---|---|---|---|---|---|---|
| Bauer et al.[21] | 2021 | April 2020 to January 2021, in Austria and Germany | Randomized, controlled, open-label trial | Adult patients with COVID-19 and chronically treated with ACEIs or ARBs | 204 (100 for continuation of ACEIs/ARBs, 104 for discontinuation of ACEIs/ARBs) | Composite of ICU admission, mechanical ventilation, and mortality |
| Lopes et al.[22] | 2021 | April to June 2020, in Brazil | Randomized, controlled, open-label trial | Adult patients with mild to moderate COVID-19 who were taking ACEIs or ARBs prior to hospitalization | 659 (334 for continuation of ACEIs/ARBs, 325 for discontinuation of ACEIs/ARBs) | Mechanical ventilation; 30-day mortality |
| Cohen et al.[20] | 2021 | March to August 2020, in the USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina | Randomized, controlled, open-label trial | Adult patients admitted to the hospital with COVID-19 and receiving ACEIs or ARBs before admission | 152 (75 for continuation of ACEIs/ARBs, 77 for discontinuation of ACEIs/ARBs) | Composite of ICU admission and mechanical ventilation; in-hospital mortality |
| Najmeddin et al.[23] | 2021 | April to September 2020, in Iran | Randomized, controlled, triple-blind trial | Adult patients with COVID-19 and hypertension consuming ACEIs or ARBs | 64 (31 for continuation of ACEIs/ARBs, 33 for discontinuation of ACEIs/ARBs) | ICU admission; in-hospital mortality |
| Reynolds et al.[16] | 2020 | March to April 2020, in the USA | PSM (variables: age, sex, race, ethnic, BMI, smoking history, comorbidities, and other classes of medication) | Adult patients with COVID-19 and a history of hypertension | 2005 (1019 in ACEIs/ARBs group, 986 in non-ACEIs/ARBs group) | Composite of ICU admission, mechanical ventilation, and mortality |
| Bae et al.[32] | 2020 | January to March 2020, in Korea | PSM (variables: age, sex, types of insurance coverage, comorbidities, depression, and duration of CVD) | Adult patients with COVID-19 and hypertension | 610 (305 in ACEIs/ARBs group and 305 in non-ACEIS/ARBS group) | In-hospital mortality |
| Zhang et al.[18] | 2020 | 31 December 2019 to 20 February 2020, in China | PSM (variables: age, gender, fever, cough, dyspnea, comorbidities, and the incidence of increased CRP and creatinine) | Adult patients with hypertension hospitalized with COVID-19 | 522 (174 in ACEIs/ARBs group and 348 in non-ACEIS/ARBS group) | In-hospital mortality |
| de Abajo et al.[33] | 2021 | 1 March to 31 March 2020, in Spain | PSM (variables: baseline comorbidities, outpatient treatments, hospital of admission, date of admission, severity score at admission, presence of pneumonia, and treatments prescribed in the first 3 days of hospitalization) | Adult patients with hypertension and diagnosis of COVID-19 | 625 (285 for continuation of ACEIs/ARBs, 340 for discontinuation of ACEIS/ARBS) | Composite of ICU admission and mortality |
| Lee et al.[36] | 2021 | Data up to 15 May 2020, in Korea | PSM (variables: age, sex, comorbidities, and use of other classes of antihypertensive medications) | Adult patients with hypertension and COVID-19 | 1070 (535 in ACEIs/ARBs group and 535 in non-ACEIS/ARBS group) | Composite of ICU admission and mortality |
| Park et al.[39] | 2021 | Data up to 15 May 2020, in Korea | PSM (variables: age, sex, medical history including cardiovascular disease, neoplasms, and other diseases) | Adult patients with hypertension and COVID-19 | 1332 (666 in RAAS group and 666 in non-RAAS group) | In-hospital mortality |
| Wang et al.[40] | 2020 | February to March 2020, in China | PSM (variables: age, sex, BMI, previous comorbidities, vital signs, disease severity, ion concentration, hepatic and renal function, blood cell count, CRP, and IL-6) | Adult COVID-19 patients with hypertension | 124 (62 in ACEIs/ARBs group and 62 in non-ACEIS/ARBS group) | ICU admission; in-hospital mortality |
| Zhong et al.[41] | 2020 | January to March 2020, in China | PSM (variables: age, sex, coronary heart disease, and statin use) | Severe COVID-19 patients with hypertension | 60 (30 in ACEIs/ARBs group and 30 in non-ACEIS/ARBS group) | In-hospital mortality |
| Aparisi et al.[31] | 2021 | March to April 2020, in Spain | PSM (variables: age, comorbidities, creatinine, and hospital) | Adult hypertensive COVID-19 patients | 92 (45 in RAAS group and 47 in non-RAAS group) | ICU admission; in-hospital mortality |
| Derington et al.[34] | 2021 | January to August 2020, in the USA | PSM (variables: age, sex, race, income, insurance type, priority group status, current tobacco use, BMI, blood pressure, heart rate, total cholesterol, HDL, LDL, triglycerides, hemoglobin, potassium, creatinine, and glomerular filtration rate) | Adult hypertensive COVID-19 patients | 485 (210 in ACEIs/ARBs group and 275 in non-ACEIS/ARBS group) | ICU admission; in-hospital mortality |

**Table 1** (*continued*)

| Reference | Publication date | Study period and location | Study design | Population | Number of participants | Outcomes |
|---|---|---|---|---|---|---|
| Pan et al.[38] | 2020 | January to February 2020, in China | PSM (variables: age, sex, COPDs, asthma, and arrhythmia) | COVID-19 Patients with hypertension | 282 (41 in RAAS group and 241 in non-RAAS group) | ICU admission; in-hospital mortality |
| Li et al.[17] | 2020 | 28 February 2020 and 18 August 2020, in the USA | PSM (variables: race, sex, ethnicity, comorbidities, alcohol or drug dependency, Charlson Comorbidity Index, and BMI) | COVID-19 Patients with hypertension | 21,420 COVID-19 positive patients | ICU admission; in-hospital mortality |
| Gao et al.[35] | 2020 | 5 February to 15 March 2020, in China | PSM (variables: age, sex, medical history of diabetes, insulin-treated diabetes, myocardial infarction, underwent PCI/CABG, renal failure, stroke, heart failure, and COPD) | COVID-19 Patients with hypertension | 710 (183 in RAAS group and 527 in non-RAAS group) | In-hospital mortality |

ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; BMI: Body mass index; CABG: Coronary-artery-bypass-grafting; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; CVD: Cerebrovascular disease; HDL: High density lipoprotein; ICU: Intensive care unit; IL-6: Interleukin 6; LDL: Low density lipoprotein; PCI: Percutaneous transluminal coronary intervention; PSM: Propensity score-matched; RAAS: Renin–angiotensin–aldosterone system.
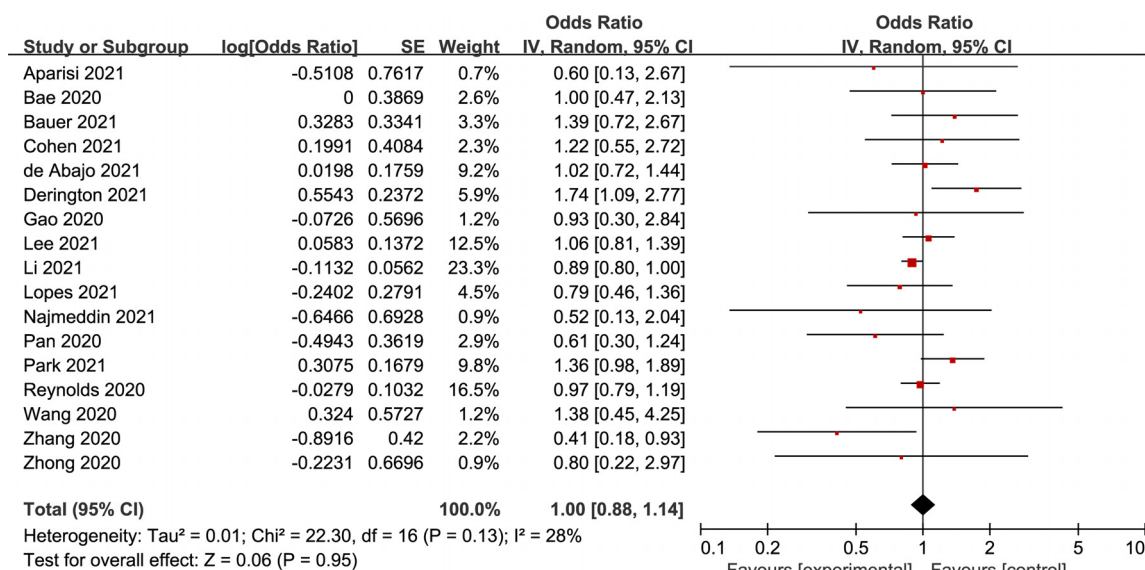


**Figure 2.** Forest plot showing the association between the use of ACEIs/ARBs and the risk of severe COVID-19. ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; COVID-19: Coronavirus disease 2019; CI: Confidence interval; IV: Independent variable; SE: Standard error.

ranged from 0.96 (95% CI: 0.87–1.05) to 1.04 (95% CI: 0.90–1.20).

## Discussion

The interplay between SARS-CoV-2 and inhibitors of the RAAS has led to competing speculation about the effect of these medications on patients with COVID-19.[10] Considering the common use of ACEIs and ARBs worldwide, guidance on the use of these drugs in patients with hypertension and COVID-19 is urgently needed. Thus, we performed this meta-analysis to summarize the existing evidence from RCTs and PSM studies on the effect of treatment with ACEIs/ARBs on disease severity and mortality in COVID-19 patients. Two main findings emerge from the analyses of 17 included studies: first, there were no significant differences in mortality or the risk of developing severe COVID-19 between patients treated with ACEIs/ARBs and those who were not. Second, there were no significant

differences in the severe or mortality events in patients prescribed continued use of ACEIs/ARBs *vs.* discontinuation of their use.

Our results are generally consistent with previous meta-analyses[42–46] of observational studies that the use of ACEIs/ARBs appears to have no significant effect on mortality or disease severity in patients with COVID-19. However, because a substantial proportion of the trials included in previous meta-analyses did not match for confounders, the crude OR may not accurately reflect the association between the use of RAAS inhibitors and COVID-19 clinical outcomes.

To our knowledge, this study is the first meta-analysis to summarize the evidence from RCTs or PSM studies on this topic. A total of 4 RCTs and 13 PSM studies comprising 30,416 COVID-19 cases were ultimately analyzed. Randomized trials and PSM studies constitute the highest level of evidence in addressing the effects of RAAS inhibitors in patients with hypertension and COVID-19. The accumulating evidence, large sample size, and
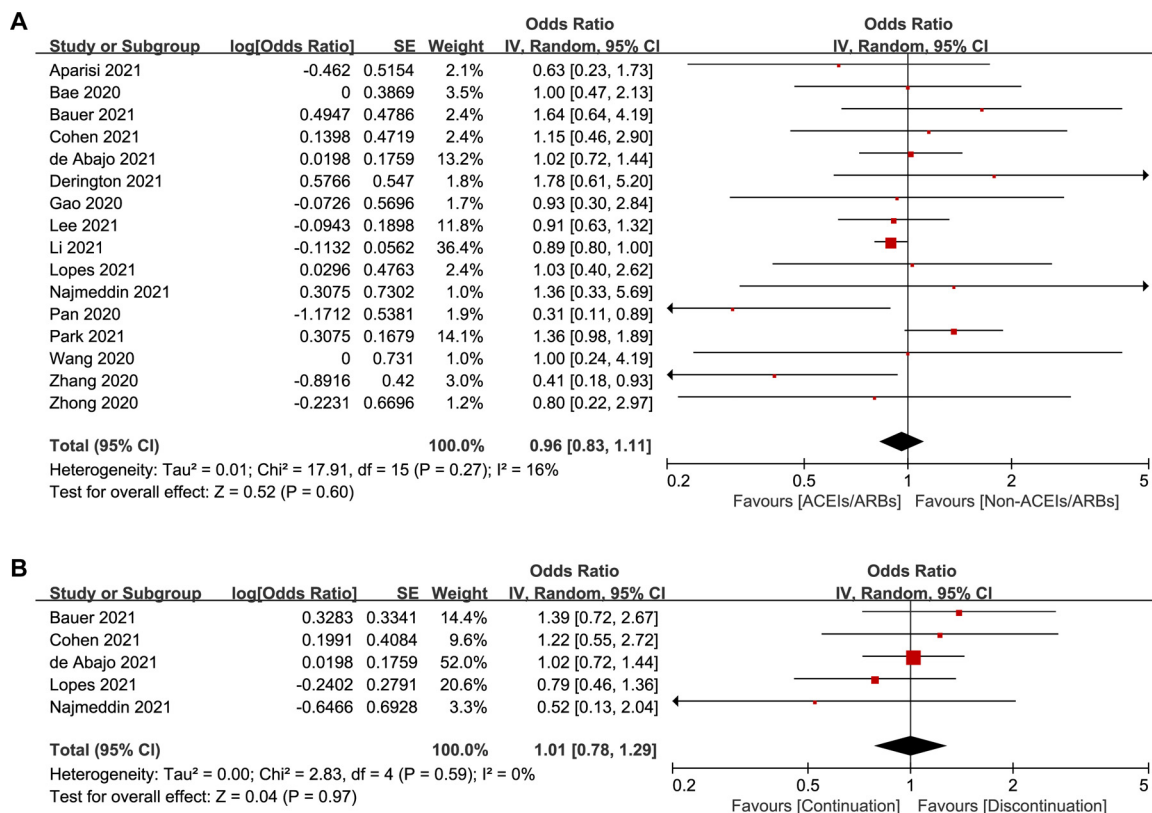
**A**

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Aparisi 2021 | -0.462 | 0.5154 | 2.1% | 0.63 [0.23, 1.73] |
| Bae 2020 | 0 | 0.3869 | 3.5% | 1.00 [0.47, 2.13] |
| Bauer 2021 | 0.4947 | 0.4786 | 2.4% | 1.64 [0.64, 4.19] |
| Cohen 2021 | 0.1398 | 0.4719 | 2.4% | 1.15 [0.46, 2.90] |
| de Abajo 2021 | 0.0198 | 0.1759 | 13.2% | 1.02 [0.72, 1.44] |
| Derington 2021 | 0.5766 | 0.547 | 1.8% | 1.78 [0.61, 5.20] |
| Gao 2020 | -0.0726 | 0.5696 | 1.7% | 0.93 [0.30, 2.84] |
| Lee 2021 | -0.0943 | 0.1898 | 11.8% | 0.91 [0.63, 1.32] |
| Li 2021 | -0.1132 | 0.0562 | 36.4% | 0.89 [0.80, 1.00] |
| Lopes 2021 | 0.0296 | 0.4763 | 2.4% | 1.03 [0.40, 2.62] |
| Najmeddin 2021 | 0.3075 | 0.7302 | 1.0% | 1.36 [0.33, 5.69] |
| Pan 2020 | -1.1712 | 0.5381 | 1.9% | 0.31 [0.11, 0.89] |
| Park 2021 | 0.3075 | 0.1679 | 14.1% | 1.36 [0.98, 1.89] |
| Wang 2020 | 0 | 0.731 | 1.0% | 1.00 [0.24, 4.19] |
| Zhang 2020 | -0.8916 | 0.42 | 3.0% | 0.41 [0.18, 0.93] |
| Zhong 2020 | -0.2231 | 0.6696 | 1.2% | 0.80 [0.22, 2.97] |
| **Total (95% CI)** | | | **100.0%** | **0.96 [0.83, 1.11]** |

Heterogeneity: Tau² = 0.01; Chi² = 17.91, df = 15 (P = 0.27); I² = 16%
Test for overall effect: Z = 0.52 (P = 0.60)

Favours [ACEIs/ARBs]  Favours [Non-ACEIs/ARBs]

**B**

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Bauer 2021 | 0.3283 | 0.3341 | 14.4% | 1.39 [0.72, 2.67] |
| Cohen 2021 | 0.1991 | 0.4084 | 9.6% | 1.22 [0.55, 2.72] |
| de Abajo 2021 | 0.0198 | 0.1759 | 52.0% | 1.02 [0.72, 1.44] |
| Lopes 2021 | -0.2402 | 0.2791 | 20.6% | 0.79 [0.46, 1.36] |
| Najmeddin 2021 | -0.6466 | 0.6928 | 3.3% | 0.52 [0.13, 2.04] |
| **Total (95% CI)** | | | **100.0%** | **1.01 [0.78, 1.29]** |

Heterogeneity: Tau² = 0.00; Chi² = 2.83, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)

Favours [Continuation]  Favours [Discontinuation]

**Figure 3.** Forest plot showing the association between (A) the use of ACEIs/ARBs and the risk of mortality; (B) continuation of ACEIs/ARBs and the risk of severe COVID-19. ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin II receptor blockers; COVID-19: Coronavirus disease 2019; CI: Confidence interval; IV: Independent variable; SE: Standard error.
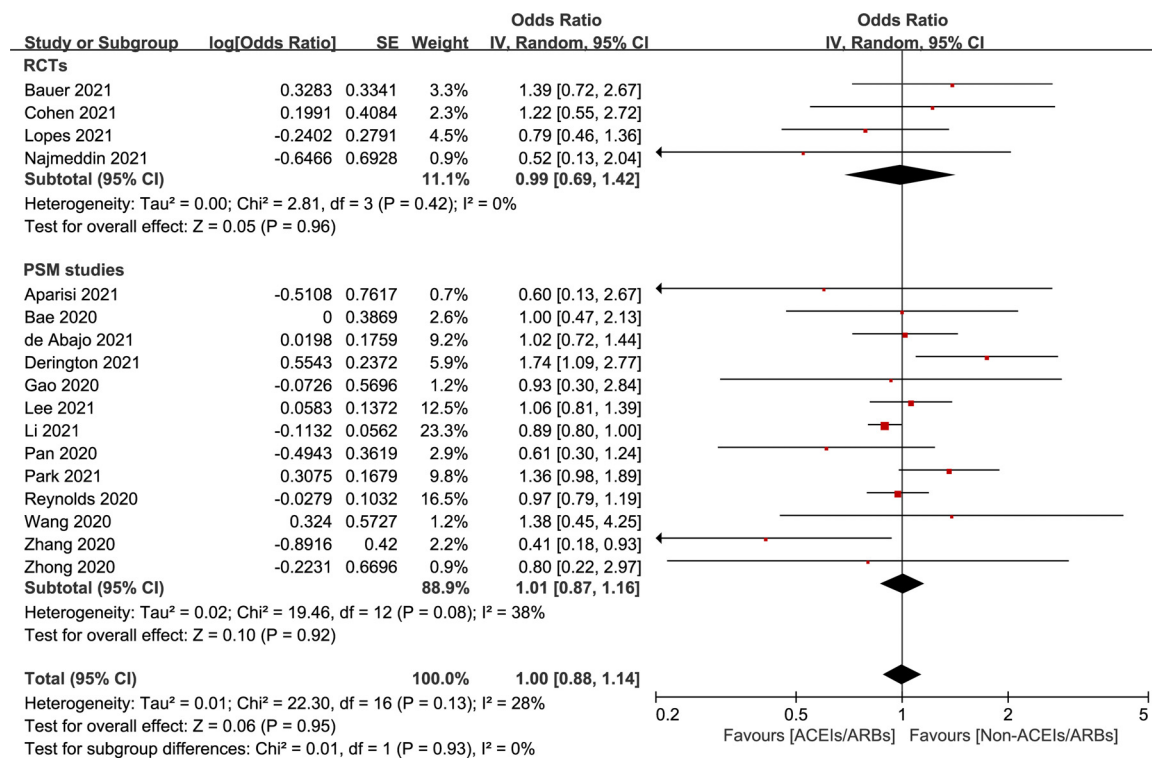
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **RCTs** | | | | |
| Bauer 2021 | 0.3283 | 0.3341 | 3.3% | 1.39 [0.72, 2.67] |
| Cohen 2021 | 0.1991 | 0.4084 | 2.3% | 1.22 [0.55, 2.72] |
| Lopes 2021 | -0.2402 | 0.2791 | 4.5% | 0.79 [0.46, 1.36] |
| Najmeddin 2021 | -0.6466 | 0.6928 | 0.9% | 0.52 [0.13, 2.04] |
| **Subtotal (95% CI)** | | | **11.1%** | **0.99 [0.69, 1.42]** |
| Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0% | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | |
| | | | | |
| **PSM studies** | | | | |
| Aparisi 2021 | -0.5108 | 0.7617 | 0.7% | 0.60 [0.13, 2.67] |
| Bae 2020 | 0 | 0.3869 | 2.6% | 1.00 [0.47, 2.13] |
| de Abajo 2021 | 0.0198 | 0.1759 | 9.2% | 1.02 [0.72, 1.44] |
| Derington 2021 | 0.5543 | 0.2372 | 5.9% | 1.74 [1.09, 2.77] |
| Gao 2020 | -0.0726 | 0.5696 | 1.2% | 0.93 [0.30, 2.84] |
| Lee 2021 | 0.0583 | 0.1372 | 12.5% | 1.06 [0.81, 1.39] |
| Li 2021 | -0.1132 | 0.0562 | 23.3% | 0.89 [0.80, 1.00] |
| Pan 2020 | -0.4943 | 0.3619 | 2.9% | 0.61 [0.30, 1.24] |
| Park 2021 | 0.3075 | 0.1679 | 9.8% | 1.36 [0.98, 1.89] |
| Reynolds 2020 | -0.0279 | 0.1032 | 16.5% | 0.97 [0.79, 1.19] |
| Wang 2020 | 0.324 | 0.5727 | 1.2% | 1.38 [0.45, 4.25] |
| Zhang 2020 | -0.8916 | 0.42 | 2.2% | 0.41 [0.18, 0.93] |
| Zhong 2020 | -0.2231 | 0.6696 | 0.9% | 0.80 [0.22, 2.97] |
| **Subtotal (95% CI)** | | | **88.9%** | **1.01 [0.87, 1.16]** |
| Heterogeneity: Tau² = 0.02; Chi² = 19.46, df = 12 (P = 0.08); I² = 38% | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | |
| | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.00 [0.88, 1.14]** |

Heterogeneity: Tau² = 0.01; Chi² = 22.30, df = 16 (P = 0.13); I² = 28%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Favours [ACEIs/ARBs]  Favours [Non-ACEIs/ARBs]

**Figure 4.** Forest plot showing the subgroup analysis of RCTs *vs.* PSM studies. CI: Confidence interval; IV: Independent variable; PSM: Propensity score-matched; RCTs: Randomized controlled trials; SE: Standard error.
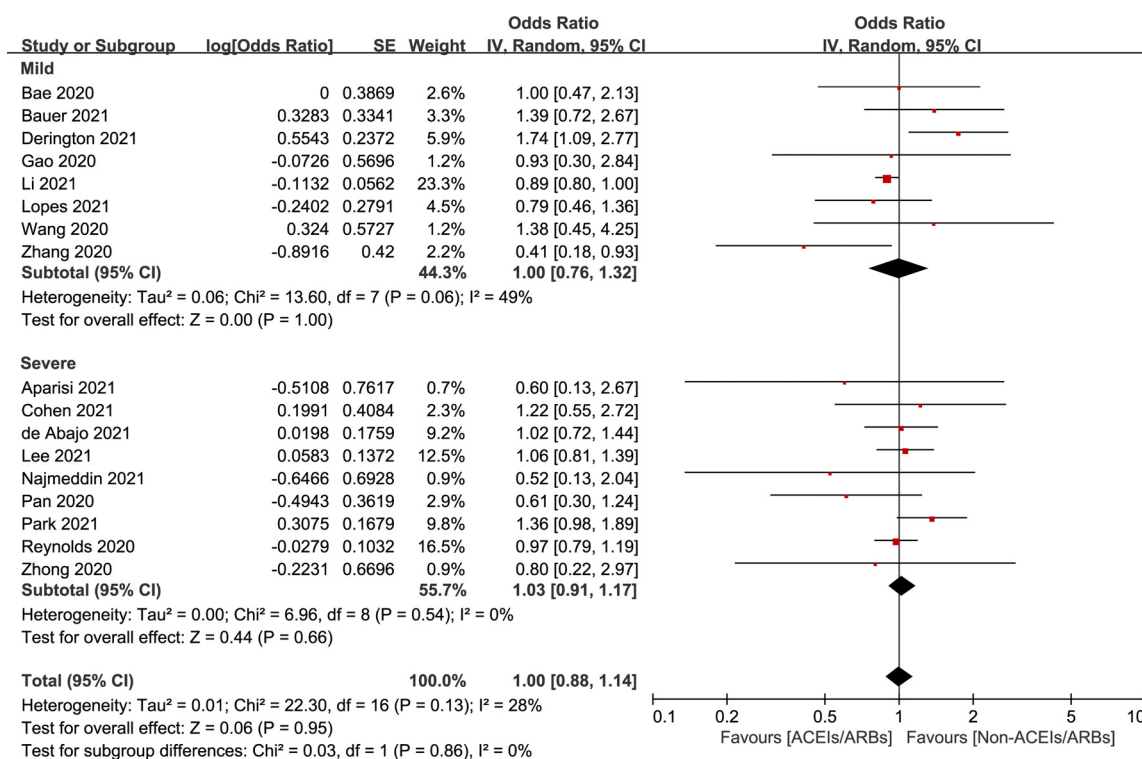
**Figure 5.** Forest plot showing the subgroup analysis of patients with mild *vs.* severe COVID-19. COVID-19: Coronavirus disease 2019; CI: Confidence interval; IV: Independent variable; SE: Standard error.

methods to eliminate confounding factors enhanced the statistical power of this study to provide more precise and reliable risk estimates. Furthermore, long-term outcomes are worsened when long-term medications that had been discontinued during hospitalization are not restarted as a result of clinical inertia.[47] Thus, our meta-analysis evaluated this important question, contributing information that is novel, to the best of our knowledge, of the effects of continuing *vs.* discontinuing therapy with ACEIs or ARBs in patients admitted to the hospital with hypertension and COVID-19. Our findings, derived from four RCTs and one PSM study, support the continued use of ACEIs or ARBs in patients hospitalized with COVID-19. These findings provide solid evidence from properly adjusted estimates across different countries on the absence of risk from treatment with RAAS inhibitors during the pandemic, strongly supporting the recommendation from scientific societies that patients should not discontinue ACEIs or ARBs therapy during the COVID-19 pandemic.

Nonetheless, our study has some limitations and the findings need to be interpreted cautiously. First, although a great number of existing observational studies took important steps, such as multivariate analysis, to minimize the effects of bias and confounding, these studies were not included in our analyses. This may introduce selective bias. Moreover, even if the PSM method was applied to eliminate selection bias resulting from measured patient characteristics that affect both treatment and outcomes in observational studies, potential bias and confounding factors could not be fully controlled. Thus, more RCTs that are well designed are needed to further confirm the effects of ACEIs/ARBs in COVID-19 patients.

Second, although we focused on patients with a history of hypertension, we did not have access to data related to the control

of blood pressure and did not consider the dose of ACEIs, ARBs, or other drugs that patients may have received. Moreover, we did not define the criteria for chronic treatment of ACEIs/ARBs. The descriptions were insufficient to distinguish between study participants, a factor this is likely to contribute to the increased heterogeneity in this study. Moreover, the control groups were heterogenous by nature because we compared the use of RAAS inhibitors with the absence of RAAS inhibitors, rather than with the use of specific antihypertensive drug alternatives. This may have introduced further confounding by indication.

Another important limitation is the heterogeneity that was observed in the analyses. The existence of clinical heterogeneity is expected to lead to a degree of statistical heterogeneity in the results. The definitions of the outcomes were inconsistent among the included studies and we investigated the two well-defined outcomes of severe COVID-19 and death. However, the threshold for ICU admission and mechanical ventilation is likely to vary from institution to institution. In addition, retrospective design and data extraction from electronic health record systems may introduce selection bias and treatment misclassification. For instance, the status of ACEIs/ARBs use was determined through medical record review in some of the included studies, which is less reliable than other methods.

### Conclusions

In conclusion, our results suggest that the use of ACEIs/ARBs in patients with COVID-19 is not associated with an increased risk of severe disease or death. These findings support the recommendation of major international cardiovascular societies that treatment with ACEIs/ARBs should be continued during the COVID-19 outbreak. Furthermore, the benefit of ACEIs/ARBs in

COVID-19 treatment should be validated in more RCTs in the future. Long-term follow-up of patients is needed to evaluate whether the use of RASS inhibitors during the acute phase of infection may influence the long-term sequelae in patients with hypertension and COVID-19.

## Ethics Statement

This article is a meta-analysis and does not require ethics committee approval or a consent statement.

## Funding

## Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2022.05.004.

## References

[1] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3. doi:10.1038/s41586-020-2012-7.

[2] WHOWHO Coronavirus (COVID-19) Dashboard. Available from 2022. https://covid19.who.int/ [Last accessed on 2022 January 21].

[3] Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: A systemic review and meta-analysis. Research (Wash D C) 2020;2020:2402961. doi:10.34133/2020/2402961.

[4] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20. doi:10.1056/NEJMoa2002032.

[5] Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Burai El, Felix S, et al. Coronavirus disease 2019 case surveillance – United States. MMWR Morb Mortal Wkly Rep 2020;69(24):759–65 2020. doi:10.15585/mmwr.mm6924e2.

[6] Team TNCPERE. The epidemiological characteristics of an outbreak of 2019 novel Coronavirus diseases (COVID-19) – China. China CDC Wkly 2020;2(8):113–22 2020. doi:10.46234/ccdcw2020.032.

[7] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland J, Coats A, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129–200. doi:10.1093/eurheartj/ehw128.

[8] Diaz JH. Hypothesis: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med 2020;27(3) taaa041. doi:10.1093/jtm/taaa041.

[9] Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26(7):1017–32. doi:10.1038/s41591-020-0968-3.

[10] Vaduganathan M, Vardeny O, Michel T, McMurray J, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. N Engl J Med 2020;382(17):1653–9. doi:10.1056/NEJMsr2005760.

[11] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46(4):586–90. doi:10.1007/s00134-020-05985-9.

[12] Watkins J. Preventing a COVID-19 pandemic. BMJ 2020;368:m810. doi:10.1136/bmj.m810.

[13] Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: Should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020;41(19):1801–3. doi:10.1093/eurheartj/ehaa235.

[14] Trump S, Lukassen S, Anker MS, Chua RL, Liebig J, Thürmann L, et al. Hypertension delays viral clearance and exacerbates airway hyperinflammation in patients with COVID-19. Nat Biotechnol 2021;39(6):705–16. doi:10.1038/s41587-020-00796-1.

[15] 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. doi:10.1056/NEJMoa2006923.

[16] Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin–angiotensin–aldosterone system inhibitors and risk of COVID-19. N Engl J Med 2020;382(25):2441–8. doi:10.1056/NEJMoa2008975.

[17] Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin–angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol 2020;5(7):825–30. doi:10.1001/jamacardio.2020.1624.

[18] Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie 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. doi:10.1161/CIRCRESAHA.120.317134.

[19] Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, 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. doi:10.1001/jamacardio.2020.1855.

[20] Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: A prospective, randomised, open-label trial. Lancet Respir Med 2021;9(3):275–84. doi:10.1016/S2213-2600(20)30558-0.

[21] Bauer A, Schreinlechner M, Sappler N, Dolejsi T, Tilg H, Aulinger BA, et al. Discontinuation versus continuation of renin–angiotensin–system inhibitors in COVID-19 (ACEI-COVID): A prospective, parallel group, randomised, controlled, open-label trial. Lancet Respir Med 2021;9(8):863–72. doi:10.1016/S2213-2600(21)00214-9.

[22] Lopes RD, Macedo A, de Barros E, Silva P, Moll-Bernardes RJ, Dos Santos TM, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: A randomized clinical trial. JAMA 2021;325(3):254–64. doi:10.1001/jama.2020.25864.

[23] Najmeddin F, Solhjoo M, Ashraf H, Salehi M, Rasooli F, Ghoghaei M, et al. Effects of renin–angiotensin–aldosterone inhibitors on early outcomes of hypertensive COVID-19 patients: A randomized triple-blind clinical trial. Am J Hypertens 2021;34(11):1217–26. doi:10.1093/ajh/hpab111.

[24] Austin PC. The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. Stat Med 2014;33(7):1242–58. doi:10.1002/sim.5984.

[25] Dahabreh IJ, Sheldrick RC, Paulus JK, Chung M, Varvarigou V, Jafri H, et al. Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. Eur Heart J 2012;33(15):1893–901. doi:10.1093/eurheartj/ehs114.

[26] Ioannidis JP, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA 2001;286(7):821–30. doi:10.1001/jama.286.7.821.

[27] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71.

[28] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi:10.1136/bmj.d5928.

[29] Ottawa Hospital Research Institute. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2021. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[30] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in metaanalyses. BMJ 2003;327(7414):557–60. doi:10.1136/bmj.327.7414.557.

[31] Á Aparisi, P Catalá, Amat-Santos IJ, Marcos-Mangas M, López-Otero D, Veras C, et al. Chronic use of renin–angiotensin–aldosterone inhibitors in hypertensive COVID-19 patients: Results from a Spanish registry and meta-analysis. Med Clin (Barc) 2022;158(7):315–23. doi:10.1016/j.medcli.2021.04.005.

[32] Bae S, Kim JH, Kim YJ, Lim JS, Yun SC, Kim YH, et al. Effects of recent use of renin–angiotensin system inhibitors on mortality of patients with coronavirus disease 2019. Open Forum Infect Dis 2020;7(11):ofaa519. doi:10.1093/ofid/ofaa519.

[33] de Abajo FJ, Rodríguez-Miguel A, Rodríguez-Martín S, Lerma V, García-Lledó A. Impact of in-hospital discontinuation with angiotensin receptor blockers or converting enzyme inhibitors on mortality of COVID-19 patients: A retrospective cohort study. BMC Med 2021;19(1):118. doi:10.1186/s12916-021-01992-9.

[34] Derington CG, Cohen JB, Mohanty AF, Greene TH, Cook J, Ying J, et al. Angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor use and COVID-19-related outcomes among US Veterans. PLoS One 2021;16(4):e0248080. doi:10.1371/journal.pone.0248080.

[35] Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: A retrospective observational study. Eur Heart J 2020;41(22):2058–66. doi:10.1093/eurheartj/ehaa433.

[36] Lee J, Jo SJ, Cho Y, Lee JH, Oh IY, Park JJ, et al. Effects of renin-angiotensin system blockers on the risk and outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients with hypertension. Korean J Intern Med 2021;36(1):S123–31 Suppl. doi:10.3904/kjim.2020.390.

[37] Li M, Wang Y, Ndiwane N, Orner MB, Palacios N, Mittler B, et al. The association of COVID-19 occurrence and severity with the use of angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers in patients with hypertension. PLoS One 2021;16(3):e0248652. doi:10.1371/journal.pone.0248652.

[38] Pan W, Zhang J, Wang M, Ye J, Xu Y, Shen B, et al. Clinical features of COVID-19 in patients with essential hypertension and the impacts of renin–angiotensin–aldosterone system inhibitors on the prognosis of COVID-19 patients. Hypertension 2020;76(3):732–41. doi:10.1161/HYPERTENSIONAHA.120.15289.

[39] Park J, Lee SH, You SC, Kim J, Yang K. Effect of renin–angiotensin–aldosterone system inhibitors on Covid-19 patients in Korea. PLoS One 2021;16(3):e0248058. doi:10.1371/journal.pone.0248058.

[40] Wang Z, Zhang D, Wang S, Jin Y, Huan J, Wu Y, et al. A retrospective study from 2 centers in China on the effects of continued use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with hypertension and COVID-19. Med Sci Monit 2020;26:e926651. doi:10.12659/MSM.926651.

[41] Zhong Y, Zhao L, Wu G, Hu C, Wu C, Xu M, et al. Impact of renin–angiotensin system inhibitors use on mortality in severe COVID-19 patients with hypertension: A retrospective observational study. J Int Med Res 2020;48(12):300060520979151. doi:10.1177/0300060520979151.

[42] Barochiner J, Martínez R. Use of inhibitors of the renin–angiotensin system in hypertensive patients and COVID-19 severity: A systematic review and meta-analysis. J Clin Pharm Ther 2020;45(6):1244–52. doi:10.1111/jcpt.13246.

[43] Baral R, Tsampasian V, Debski M, Moran B, Garg P, Clark A, et al. Association between renin–angiotensin–aldosterone system inhibitors and clinical outcomes in patients with COVID-19: A systematic review and meta-analysis. JAMA Netw Open 2021;4(3):e213594. doi:10.1001/jamanetworkopen.2021.3594.

[44] Dai XC, An ZY, Wang ZY, Wang ZZ, Wang YR. Associations between the use of renin–angiotensin system inhibitors and the risks of severe COVID-19 and mortality in COVID-19 patients with hypertension: A meta-analysis of observational studies. Front Cardiovasc Med 2021;8:609857. doi:10.3389/fcvm.2021.609857.

[45] Singh R, Rathore SS, Khan H, Bhurwal A, Sheraton M, Ghosh P, et al. Mortality and severity in COVID-19 patients on ACEIs and ARBs – A systematic review, meta-analysis, and meta-regression analysis. Front Med (Lausanne) 2021;8:703661. doi:10.3389/fmed.2021.703661.

[46] Mackey K, King VJ, Gurley S, Kiefer M, Liederbauer E, Vela K, 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. doi:10.7326/M20-1515.

[47] Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: Findings from the OPTIMIZE-HF program. J Am Coll Cardiol 2008;52(3):190–9. doi:10.1016/j.jacc.2008.03.048.