Title

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Journal

Journal of Cardiology, 77(5)

ISSN

0914-5087

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Publication Date

2021-05-01

DOI

10.1016/j.jjcc.2020.10.015

Peer reviewed

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.

Journal of Cardiology xxx (2019) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis

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ARTICLE INFO

Article history:
Received 18 July 2020
Received in revised form 8 September 2020
Accepted 23 October 2020
Available online xxx

Keywords:
Antihypertensive drugs
COVID-19
Meta-analysis
Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2

ABSTRACT

Background: The association of antihypertensive drugs with the risk and severity of COVID-19 remains unknown.

Methods and Results: We systematically searched PubMed, MEDLINE, The Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and medRxiv for publications before July 13, 2020. Cohort studies and case-control studies that contain information on the association of antihypertensive agents including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium-channel blockers (CCBs), β-blockers, and diuretics with the risk and severity of COVID-19 were selected. The random or fixed-effects models were used to pool the odds ratio (OR) with 95% confidence interval (CI) for the outcomes.

The literature search yielded 53 studies that satisfied our inclusion criteria, which comprised 39 cohort studies and 14 case-control studies. These studies included a total of 2,100,587 participants. We observed no association between prior usage of antihypertensive medications including ACEIs/ARBs, CCBs, β-blockers, or diuretics and the risk and severity of COVID-19. Additionally, when only hypertensive patients were included, the severity and mortality were lower with prior usage of ACEIs/ARBs (overall OR of 0.81, 95% CI 0.66–0.99, $p < 0.05$ and overall OR of 0.77, 95% CI 0.66–0.91, $p < 0.01$).

Conclusions: Taken together, usage of antihypertensive drugs is not associated with the risk and severity of COVID-19. Based on the current available literature, it is not recommended to abstain from the usage of these drugs in COVID-19 patients.

Registration: The meta-analysis was registered on OSF (https://osf.io/ynd5g).

Introduction

The 2019 coronavirus disease (COVID-19) pandemic is caused by the novel and highly infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of August 30, 2020, there were 25,099,237 confirmed cases globally and 844,176 deaths from the disease [1]. Emerging evidence has demonstrated a relatively elevated mortality in patients with preexisting cardiovascular comorbidities [2,3].

Viral infection occurs when the S protein of SARS-CoV-2 binds to the host angiotensin-converting enzyme 2 (ACE2) receptor to gain entry into the cells [4]. ACE2 serves a crucial role in the counter regulation of the blood pressure regulating system—the renin-angiotensin-aldosterone system (RAAS) pathway—by primarily degrading angiotensin II to angiotensin-(1-7), thereby attenuating the effects of angiotensin II [5]. In patients with cardiovascular disease, ACE2 expression may be differentially regulated not only by diseased states [6,7], but also by commonly prescribed antihypertensive medications [8–12].

Previous evidence has suggested that antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) can elevate ACE2 expression [8–10], which may increase susceptibility to and worsen the prognosis of COVID-19. Due to the high prevalence of COVID-19 in

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https://doi.org/10.1016/j.jjcc.2020.10.015
0914-5087/

patients with preexisting cardiovascular conditions such as hypertension [13–16], coronary artery disease, and congestive heart failure [17], the usage of these antihypertensive drugs warrants great concerns. Indeed, controversy remains regarding the usage of these antihypertensive medications on the vulnerable population. We postulated that there may be an association between the usage of antihypertensive medications and the incidence and severity of COVID-19 due to the high mortality of patients with cardiovascular comorbidities.

To this end, we designed a meta-analysis to address whether there is an association of antihypertensive medications and the incidence and severity of COVID-19. In addition to ACEIs and ARBs, we also investigated other antihypertensive drugs [calcium channel blockers (CCBs), β-blockers, and diuretics] to evaluate whether these drugs may potentially be better substitutes for ACEIs/ARBs in the event that ACEIs/ARBs had a significant, negative association with COVID-19. We comprehensively searched through large databases to acquire relevant studies. We performed meta-analyses on 53 studies, 39 of which were cohort studies and the remaining 14 were case-control studies.

Methods

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.

Literature search and inclusion criteria

A comprehensive search strategy was designed to retrieve relevant data from published literature. Our objective was to identify all randomized controlled trials (RCTs), cohort studies, and case-control studies that contain information on the association of antihypertensive agents including ACEIs, ARBs, CCBs, β-blockers, and diuretics, with the risk and severity of COVID-19. We systematically searched PubMed, MEDLINE, The Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and medRxiv for publications before July 13, 2020. We also searched conference proceedings and performed manual reference list searching to acquire relevant papers.

Medical subject headings (MeSH) terms and keywords including randomized controlled trial, case-control study, cohort study, angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, calcium-channel blockers, beta-blockers, diuretics, antihypertensive agents, ACEIs, ARBs, coronavirus, 2019-nCoV, COVID-2019, and SARS-COV-2 were used. This review was not restricted to studies conducted in the English language; it includes reports from any countries that satisfy the inclusion criteria.

To be included in the analysis, the study had to fulfill the following criteria: 1) RCTs (open-label, single-blind, double-blind, or parallel group studies); 2) Cohort studies; 3) Case-control studies; 4) Studies that report anti-hypertensive medication data.

Studies were excluded from meta-analysis if they were: 1) Animal studies or *in vitro* studies; 2) Studies that did not report the usage of anti-hypertensive medications; 3) Full texts that could not be sourced; 4) Review papers; 5) Case reports; 6) Studies with unrelated outcomes or unreported outcomes; 7) Cross-sectional studies; 8) Clinical Trial Registries.

Data collection and outcome measures

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded to Endnotes X9. All studies were screened and evaluated by two independent reviewers (LR, PNT), which were then checked by a third reviewer (SY). Discrepancies were resolved by discussion in group conferences. Completed data were then thoroughly checked by two additional reviewers (WX, JLO). Data including first author, year of publication, country where studies took place, study type, number of participants, number of hypertensive patients, age, sex, follow-up duration, type of antihypertensive drugs, and outcomes were extracted using a standardized form and presented in table format. We used the adjusted OR if the information was available from the studies. If the reports did not provide adjusted OR, we used the crude OR. We calculated all the crude ORs when not provided. We were unable to adjust for age, sex, and/or underlying conditions, due to lack of information from the studies. Additionally, some of the studies used hazard ratio (HR) or adjusted HR. Table 1 provides further information on which information was used for each study.

Study quality assessment

Newcastle–Ottawa Quality Assessment Scale was used to assess the quality of cohort studies and case-control studies. The assessment was performed by two independent reviewers (WX, JLO) and further verified by two additional reviewers (LR, PNT). Discussion was performed if obvious discrepancies existed in assigning the study quality assessment. An additional reviewer was consulted when necessary (SY). The completed information is provided in Online Tables 1 and 2.

Population selection

This meta-analysis focuses on determining the association between taking antihypertensive drugs and the risk and severity of COVID-19 in both non-hypertensive and hypertensive patients. We first screened for studies to include (Fig. 1). Fig. 2 focuses on ACEIs/ARBs in the whole population taking these antihypertensive medications. Fig. 3 evaluates these drugs specifically on hypertensive patients. Fig. 4 extends the meta-analysis to the whole population taking other antihypertensive medications. If “hypertensive patients” was not mentioned for the patient population, then it can be assumed that the patient population includes both hypertensive and non-hypertensive patients.

Statistical analysis

Outcomes were summarized as odds ratio (OR). Fixed-effects or random-effects model were used to pool the OR with 95% confidence interval (CI) for the outcomes. If $I^2 \leq 40\%$, studies were considered homogeneous and fixed-effects model of meta-analysis were used. If $I^2 \geq 40\%$, the heterogeneity was high, so a random-effects model was used. I^2 statistics was included in all the meta-analyses performed, which is a percentage of variance attributed to study heterogeneity. Sensitivity analyses were also included. Publication bias was assessed by funnel plots. Meta-analyses were performed with STATA 16 (Stata, College Station, TX, USA). Leave-one-out meta-analyses were performed with OpenMeta[Analyst] (CEBM, Brown University, Providence, RI, USA).

Results

Process of identifying eligible studies and assessing study quality

The PRISMA flowchart (Fig. 1) includes the summary of the study selection process and search results. We initially screened 309 records using the studies' titles and abstracts. A total of 140 studies were identified after removal of duplicate records. Of these remaining records, 71 studies were removed, since they were animal studies, review papers, commentaries, part of a registry, or the full texts were not available, which left us with 69 records.

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Table 1
Study Characteristics.

Study	Country	Study Type	Number of Participants	Number of Hypertension Patients	Age (years)	Male	Study Duration (days)	Drugs	Outcomes	Odds Ratio (OR)
Andrea et al. (2020) [32]	Italy	Single-Center Cohort Study	191	96	63.4	68.6%	28	ACEI, ARB	All-cause mortality	Crude OR
Ayed et al. (2020) [33]	Kuwait	Cohort Study	103	36	53	85.5	80	ACEI, β-blockers	Mortality	Crude OR
Bean et al. (2020) [34]	UK	Cohort Study	1200	645	67.96	57.2%	21	ACEI, ARB	Death or transfer to ICU	Adjusted OR
Bravi et al. (2020) [35]	Italy	Case-Control Study	1603	543	58.0	47.3%	24	ACEI, ARB	Mortality and severity	Adjusted OR
Chang et al. (2020) [36]	USA	Case-Control Study	26602	–	–	44%	98	ACEI, ARB	COVID-19 Infection, hospitalization and severity	Crude OR
Choi et al. (2020) [37]	Korea	Retrospective Case-control Study	1585	1585	65	42.7%	116	ACEI, ARB	Severe infection or all-cause mortality	Adjusted OR
De Abajo et al. (2020) [38]	Spain	Case-Control Study	1139	617	69.1	61%	24	RAAS inhibitors	Admission to hospital	Adjusted OR
De Spiegeleer et al. (2020) [39]	Belgium	Retrospective Multi-Center Cohort Study	154	39	85.9	33.1%	47	ACEI, ARB	Serious COVID-19 or death	Adjusted OR
Dublin et al. 2020 [40]	USA	Cohort study	322044	66443	51	46%	106	ACEI, ARB, CCB, β-blockers, diuretics	COVID-19 Infection and hospitalization	Adjusted OR
Ebinger et al. (2020) [41]	USA	Case-control Study	442	161	52.7	58%	25	ACEI, ARB	COVID-19 illness severity	Adjusted OR
Felice et al. (2020) [19]	Italy	Cohort study	133	133	73	28%	22	ACEI, ARB	Mortality, ICU admission, hospital admission	Adjusted OR
Feng Yun et al. (2020) [42]	China	Case-Control Study	476	113	53	56.9%	45	ACEI, ARB	Severity of COVID-19	Crude OR
Feng Zhichao et al. (2020) [43]	China	Retrospective, Observational, Multi-Center Cohort Study	564	82	47	50.4%	15-57	ACEI, ARB	COVID-19 illness severity	Adjusted OR
Fosbøl et al. (2020) [44]	Denmark	Retrospective Cohort Study	4480	843	54.7	55.1%	30	ACEI, ARB	Mortality and severity	Adjusted HR
Fosbøl et al. (2020) [44]	Denmark	Case-control Study	6281	6281	73.9	54.3%	94	ACEI, ARB, CCB	Incidence rate of COVID-19	Adjusted HR
Gao et al. (2020) [45]	China	Retrospective Cohort Study	2877	850	58	51%	30-50	RAAS inhibitors	All-cause mortality	Adjusted HR
Golpe et al. (2020) [46]	Spain	Cohort Study	539	157	70.4	45.8%	23	ACEI, ARB	Hospitalization	Adjusted OR
Huh et al. (2020) [47]	South Korea	Retrospective case-control cohort study	65149	21370	44.6	49.44%	NA	ACEI, ARB	Drug association with risk of COVID-19	Adjusted OR
Imam et al. (2020) [48]	USA	Cohort Study	1305	734	61	53.8%	32	ACEI, ARB	Mortality	Adjusted OR
Ip et al. (2020) [49]	USA	Case-Control Study	3017	1584	NA	NA	NA	ACEI, ARB, non-ACEI/ ARB drugs	Severity and mortality	Crude OR
Jung et al. (2020) [50]	South Korea	Cohort Study	5179	1157	44.6	44%	Before April 8	RAAS inhibitors	Mortality rate	Adjusted OR
Jurado et al. (2020) [51]	Spain	Case-Control Study	574	290	63.2	59.4%	21	ACEI, ARB	COVID-19 illness severity	Crude OR
Khawaja et al. (2020) [52]	UK	Prospective Cohort Study	406793	135604	68	45%	30	ACEI, ARB, CCB, β-blockers, diuretics	Hospitalization with COVID-19	Adjusted OR
Khera et al. (2020) [53]	USA	Cohort Study	10196	10196	69 and 77	47.5% and 45.4%	59 and 127	ACEI, ARB	COVID-19 infection and mortality	Hazard ratio
Li Juyi et al. (2020) [54]	China	Case-Control Study	1178	362	55.5	46.3%	51	ACEI, ARB, CCB, β-blockers	COVID-19 mortality and severity in patients with hypertension	Crude OR
Li Xiaochen et al. (2020) [55]	China	Cohort Study	548	166	60	50.9%	26-36	ACEI, ARB	Severity	Crude OR
Liabeuf et al. 2020 [56]	France	Cohort Study	268	152	73	58%	44	ACEI, ARB, diuretics	ICU admission, death	Adjusted OR
Liu et al. (2020) [57]	China	Retrospective Cohort Study	78	78	65.2	55.1%	26-64	ACEI, ARB, CCB, β-blockers, thiazide	COVID-19 illness severity	Adjusted OR
Lo pez-Otero et al. (2020) [58]	Spain	Cohort Study	965	298	59.5	43.9%	28	ACEI, ARB	Mortality, hospitalization and ICU admission	Adjusted OR
Mancia et al. (2020) [20]	Italy	Case–Control Study	37031	NA	86	63%	20	ACEI, ARB, CCB, β-blockers, diuretics	COVID-19 illness severity	Adjusted OR
Mehta et al. (2020) [59]	USA	Retrospective Cohort Study	18472	NA	49	40%	36	ACEI, ARB	COVID-19 infection; hospitalizations, ICU admissions, mechanical ventilation	Adjusted OR

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Table1 (*Continued*)

Study	Country	Study Type	Number of Participants	Number of Hypertension Patients	Age (years)	Male	Study Duration (days)	Drugs	Outcomes	Odds Ratio (OR)
Meng et al. (2020) [60]	China	Cohort Study	417	51	64.5	57.10%	43	ACEI, ARB, non-ACEI/ ARB drugs	COVID-19 Infection	Crude OR
Morales et al. (2020) [61]	Multinational	Cohort Study	1.1 M	1.1M	–	–	92	ACEI, ARB, CCB, diuretics	COVID-19 Infection	Adjusted HR
Nguyen et al. (2020) [62]	USA	Cohort Study	689	372	55	43%	71	ACEI, ARB, CCB, β-blockers, diuretics	Mortality and hospitalization	Adjusted OR
Oussalah et al. (2020) [63]	France	Cohort Study	149	75	65	61%	31	ACEI, ARB	Mortality rate	Adjusted OR
Palaiodimos et al. (2020) [64]	USA	Retrospective Cohort Study	200	152	64	49%	21	ACEI, ARB	In-hospital death	Adjusted OR
Raisi-Estabragh et al. (2020) [65]	UK	Cohort Study	1474	728	69.3	53.40%	29	ACEI, ARB	COVID-19 infection	Crude OR
Regina et al. (2020) [21]	Switzerland	Retrospective Observational Study	200	87	70	60%	≥14	ACEI, ARB	Need for mechanical ventilation at day 14	Crude OR
Rentsch et al. (2020) [18]	USA	Retrospective Cohort Study	3789	2463	65.7	90.2%	50	ACEI, ARB	Infection, hospitalization, ICU admission	Adjusted OR
Reynolds et al. (2020) [66]	USA	Retrospective Cohort Study	12594	4357	49	41.50%	45	ACEI, ARB, CCB, β-blockers, thiazide diuretics	Severity and mortality	Adjusted OR
Rossi et al. (2020) [67]	Italy	Prospective Cohort Study	2653	430	63.2	50.1%	14-28	ACEI, ARB	Hospitalization and mortality	Hazard ratio
Sardu et al. (2020) [68]	Italy	Cohort Study	62	62	58	41%	NA	ACEI, ARB, CCB	Mortality and ICU admission	Crude OR
Şenkal et al. (2020) [69]	Turkey	Cohort Study	611	249	57	59.4%	64	ACEI, ARB	Severity	Adjusted OR
Solaimanzadeh et al. (2020) [22]	USA	Retrospective Study	65	22	75.3	49.2%	45	CCB	Survival to discharge, severity, mechanical ventilation, and mortality	Crude OR
Tan et al. (2020) [70]	China	Retrospective Cohort Study	204	100	NA	NA	72	ACEI, ARB	Mortality rate	Crude OR
Tedeschi et al. (2020) [71]	Italy	Cohort Study	609	311	68	68%	41	ACEI, ARB	Mortality rate	Adjusted HR
Trecarichi et al. (2020) [72]	Italy	Single-Center Cohort Study	50	–	80	57.1%	41	ACEI, ARB	Mortality rate	Adjusted OR
Yan et al. (2020) [73]	China	Case-Control Study	49277	9992	49.9	48.3%	49	ACEI, ARB, CCB, β-blockers, diuretics	Risk and severity of COVID-19	Adjusted OR
Yang et al. (2020) [74]	China	Retrospective Cohort Study	251	126	66.1	49.1%	57	ACEI, ARB, non-ACEI/ ARB drugs	Discharge, mortality, length of stay	Crude OR
Zeng et al. (2020) [75]	China	Retrospective, Single-Center, Observational Study	274	75	60	55%	14-62	ACEI, ARB, non-ACEI/ ARB drugs	Severity and mortality	Crude OR
Zhang et al. (2020) [76]	China	Retrospective, Multi-Center Study	1128	1128	64	53.4%	15-66	ACEI, ARB	Mortality rate	Hazard ratio
Zhou Feng et al. (2020) [77]	China	Cohort Study	3572	–	66	51.1%	28	ACEI, ARB	Mortality rate	Adjusted HR
Zhou Jiandong et al. (2020) [78]	China	Cohort Study	1043	108	35	54%	145	ACEI, ARB	ICU admission	Adjusted OR
Zhou Xian et al. (2020) [79]	China	Cohort Study	110	36	57.7	54.5%	27	ACEI, ARB	Mortality rate	Crude OR

Characteristics of patient population, study type, treatment intervention, and outcomes are displayed. We also indicated the type of ORs used for each study. ACEI, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin II Receptor Blocker; CCB, Calcium-Channel Blocker; OR: Odds Ratio; ICU, Intensive Care Unit.

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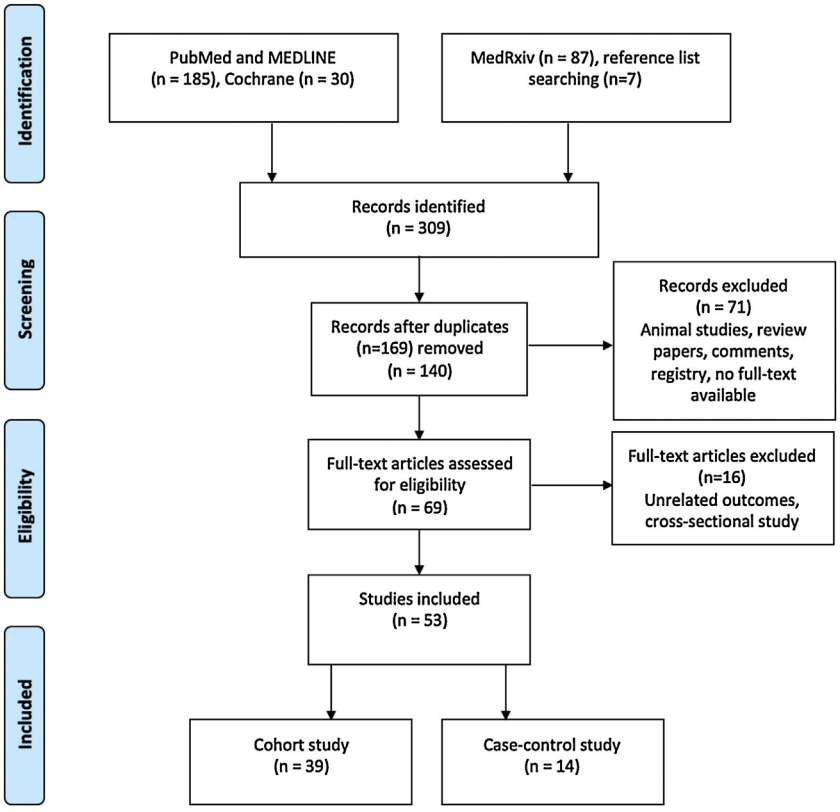

Fig. 1. Process of identifying eligible studies. We searched for relevant studies using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses approach.

After the exclusion of 16 studies that were assessing unrelated outcomes and/or were cross-sectional studies and a thorough review according to the inclusion and exclusion criteria, 53 records satisfied our requirements. We included 39 cohort studies and 14 case-control studies. No RCTs were identified. The studies that were included were subjected to the Newcastle-Ottawa Quality Assessment, which is reported in Online Tables 1 and 2. Studies deemed low quality (less than or equal to 4 stars) by independent reviewers were excluded.

Characteristics of studies, patients, and interventions

Table 1 describes the overall characteristics of the studies. We included the first author, year of publication, country, study type, number of participants, number of hypertensive patients, age, sex, follow-up duration, type of antihypertensive drugs, and outcomes. We included a total of 35 studies that investigated ACEIs and ARBs, while the other 18 focused on ACEIs, ARBs, or other antihypertensive drugs (CCBs, β-blockers, and diuretics). There was a total of 2,100,587 participants across all 53 studies. Studies were conducted in a variety of countries, predominantly in the USA and China, but also included Spain, Italy, and the United Kingdom. There was an equal number of males and females for most studies, however, one study had 90.2% male participants [18] and another had 28% male participants [19]. On average, most studies included middle-aged participants, but three trended more toward elderly participants [20–22]. Study durations varied, with the shortest being 14 days and the longest being 145 days. The outcomes of these studies included incidence, hospitalization, severity, and mortality. Incidence was defined as patients who took antihypertensive medications and tested positive for COVID-19, while severity was defined as a combination of hospitalization, intensive care unit (ICU) admission, and mortality. Severity was then further broken down into their individual components for analysis.

Incidence and severity of COVID-19 with ACEIs/ARBs

We performed meta-analyses on the incidence (26 studies), severity (40 studies), hospitalization (23 studies), ICU admission (12 studies), and mortality (38 studies) of COVID-19 in patients with prior usage of either ACEI, ARB, or a combination of both (Fig. 2). As shown in the forest plots, there was no association with the incidence (overall OR of 0.96, 95% CI 0.86–1.08), severity (overall OR of 0.92, 95% CI 0.77–1.11), hospitalization (overall OR of 1.09, 95% CI 0.91–1.31), ICU admission (overall OR of 1.19, 95% CI 0.85–1.66), or mortality (overall OR of 0.92, 95% CI 0.74–1.13). Overall heterogeneity between trials was observed with incidence (I^2 = 88.40%), severity (I^2 = 83.08%), hospitalization (I^2 = 70.27%), ICU admission (I^2 = 56.64%), and mortality (I^2 = 84.72%). Together, these data suggest that there was no association between prior drug usage and risk or severity of COVID-19 in patients taking ACEIs/ARBs.

Incidence and severity of COVID-19 with ACEIs/ARBs in hypertensive patients

We further conducted meta-analyses of severity and mortality of COVID-19 with prior usage of ACEIs, ARBs, or ACEI/ARBs in hypertensive patients (Fig. 3). We observed a significant decrease in severity (overall OR of 0.81, 95% CI 0.66–0.99, $p < 0.05$) and mortality (overall OR of 0.77, 95% CI 0.66–0.91, $p < 0.01$) in favor of ACEIs/ARBs. The heterogeneity between trials was observed with severity (I^2 = 50.52%) and mortality (I^2 = 46.96%). Together, these data suggest that prior usage of ACEIs/ARBs in hypertensive

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patients is associated with significantly lower severity and mortality than the control group.

Incidence and Severity of COVID-19 with CCBs, β-blockers, and diuretics

We next examined whether prior usage of other antihypertensive medications exhibited an association with the risk and severity of COVID-19 (Fig. 4). There was no association between usage of CCBs with incidence (overall OR of 1.15, 95% CI 0.87–1.53) or severity (overall OR of 0.94, 95% CI 0.80–1.10) of COVID-19. Heterogeneity between trials was evident for both incidence (I^2 = 93.61%) and severity (I^2 = 17.11%). Similarly, there was no association between the use of β-blockers with incidence (overall OR of 1.03, 95% CI 0.78–1.35) or severity (overall OR of 1.23, 95% CI 0.74–2.04). There was heterogeneity in incidence (I^2 = 92.59%) and severity (I^2 = 85.42%) with β-blockers. Like CCBs and β-blockers, there was no evidence that prior usage of diuretics was associated with the incidence (overall OR of 0.86, 95% CI 0.54–1.38) or severity (overall OR of 0.96, 95% CI 0.81–1.15). Heterogeneity was also

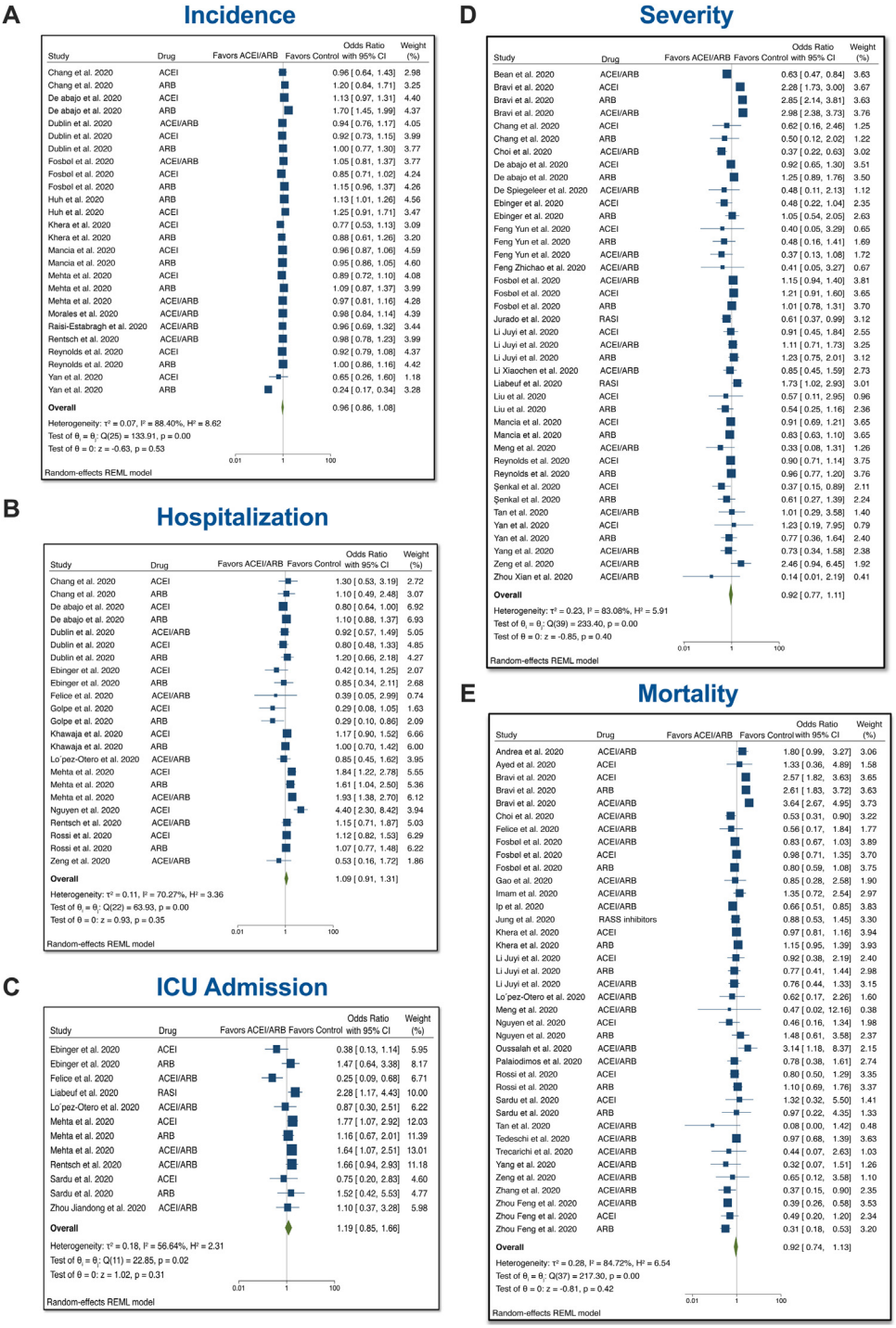

Fig. 2. Incidence and Severity of COVID-19 with ACEIs/ARBs. We pooled data from ACEIs, ARBs, and a combination of ACEIs/ARBs to perform meta-analyses on the **A**) incidence, **B**) hospitalization, **C**) ICU admission, **D**) severity, and **E**) mortality. Statistics are provided in the forest plots.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICU, intensive care unit.

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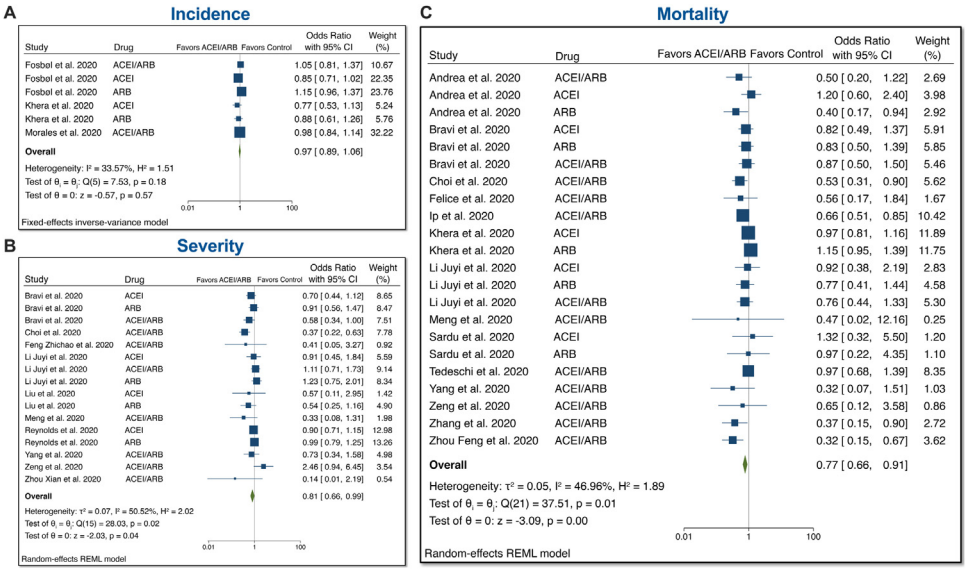

Fig. 3. Incidence and Severity of COVID-19 with ACEIs/ARBs in Hypertensive Patients. We pooled data from ACEIs, ARBs, and a combination of ACEIs/ARBs to perform meta-analyses on the **A**) incidence, **B**) severity and **C**) mortality of COVID-19 in hypertensive patients. Statistics are provided in the forest plots.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

observed with diuretics and the incidence of COVID-19 (I^2 = 97.26%). Together, there was no evidence for an association between prior usage of these antihypertensive medications and risk or severity of COVID-19 in patients taking any of these antihypertensive medications.

Assessments of publication Bias and quality of studies and sensitivity analysis

To assess publication bias, we constructed funnel plots of all the parameters that were tested (Online Fig. 1). Additionally, two independent reviewers performed the quality assessment, while two others confirmed results using the Newcastle-Ottawa Quality Assessment (Online Tables 1 and 2). Finally, to determine if removing a study would skew the results, we performed sensitivity analyses on all the parameters that we examined in the main text. Results can be found in Online Figs. 2–4.

Discussion

The pandemic has disproportionately affected the lives of patients with cardiovascular comorbidities [17]. Although many variables may contribute to this outcome, we sought to address whether prior usage of antihypertensive medications is associated with the risk and severity of COVID-19 in this study. Our motivation stems from two factors. First, a previous study suggests that antihypertensive drugs may increase the expression of ACE2—a protein that is paramount for SARS-CoV-2 viral infection [4]. Second, there is high mortality in patients with cardiovascular complications [13–16].

We identified 53 studies that satisfied our inclusion criteria, which comprised 39 cohort and 14 case-control studies (Fig. 1). The characteristics for these studies are detailed in Table 1. The studies included a total of 2,100,587 patients. Meta-analyses were performed to determine the risk and severity of COVID-19 in patients with prior usage of ACEIs/ARBs. We observed no evidence of an association with regards to incidence, hospitalization, severity, and mortality.

Since the findings in Fig. 2 included both non-hypertensive and hypertensive patients, we determined whether there was an association of prior usage of these medications and the risk and severity of COVID-19 in hypertensive patients (Fig. 3). We noted that severity ($p < 0.05$) was significantly lower in hypertensive patients taking ACEIs/ARBs than controls. Additionally, mortality was significantly lower in patients taking ACEIs/ARBs versus control patients ($p < 0.01$). These findings support the benefits of using ACEIs/ARBs in hypertensive patients. Therefore, our analyses suggest that abstaining from ACEIs/ARBs, especially in the context of hypertensive patients, will not provide benefits.

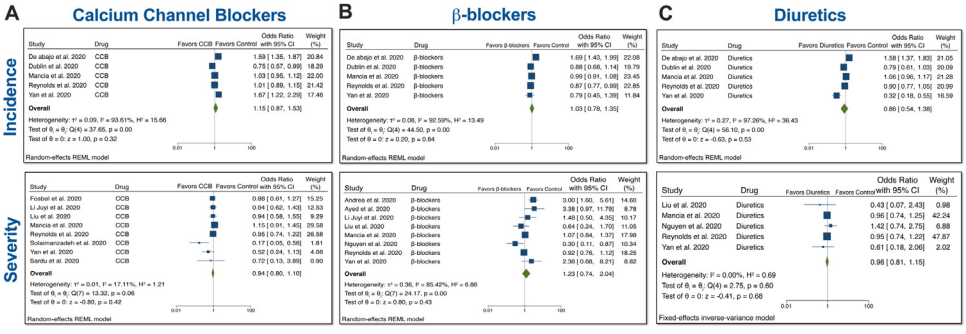

Fig. 4. Incidence and Severity of COVID-19 with CCBs, β-blockers, and diuretics. Severity and mortality of COVID-19 with the usage of **A**) CCBs, **B**) β-blockers, and **C**) diuretics. Statistics are provided in the forest plots.
CCB, calcium channel blocker.

Please cite this article in press as: Ren L, et al. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. J Cardiol (2020), https://doi.org/10.1016/j.jjcc.2020.10.015

Additionally, we examined whether other commonly prescribed antihypertensive medications are associated with the risk and severity of COVID-19. There was no evidence of an association between taking these antihypertensive medications (CCBs, β-blockers, and diuretics) and the incidence and severity of COVID-19. With the leave-one-out-meta-analysis (Online Figs. 2–4), there were no significant differences in most of the parameters except for a significant increase in ICU admission, with more ACEIs/ARBs patients being admitted, when the study of Felice et al. was excluded (Online Fig. 2) [19]. However, severity, a parameter that takes into account ICU admission, mechanical ventilation, duration of hospital stay, hospital admittance, noninvasive ventilation, and organ dysfunction, was not significantly different between ACEIs/ARBs and control patients. Therefore, caution is required for the interpretation of the ICU admission findings.

Multiple studies have reported high mortality in patients with cardiovascular complications [12–15]. Our results suggest that taking antihypertensive medications did not increase the incidence or severity of COVID-19 in patients taking antihypertensive medications. In fact, ACEIs/ARBs may be beneficial in hypertensive patients. Our findings do not support abstaining from antihypertensive medications when patients are already taking them.

Additionally, it is critical to note that data regarding ACE2 expression with the usage of antihypertensive medications remains controversial, with some studies reporting an increase [8–12], while others show no changes [23,24]. Therefore, additional studies are required to test the effects of antihypertensive medications on ACE2 expression, as well as applicability of the findings across species. Current data support potential benefits compared to harms in the use of RAAS blockers in patients [25]. Our meta-analysis of currently available data further support the lack of an association between antihypertensive medications and the risk or severity of COVID-19.

Our current study provides several advantages relative to previous meta-analysis studies [26–31]. In contrast to previous meta-analysis studies, which analyzed approximately 9–16 records, our study included 53 records to generate a large dataset. Additionally, while other studies primarily focused on assessing ACEIs/ARBs, our study included analyses of other antihypertensive drugs such as CCBs, β-blockers, and diuretics. New insights from the comprehensive meta-analysis in the current study have important implications in clinical decisions.

Limitations

There are some limitations in the current study. Only observational studies are currently available in the literature due to the urgency of the pandemic resulting in the need to rapidly gather information. There were no available RCTs. Additionally, some studies did not provide ORs, necessitating the calculation of the values without adjustment for age, sex, and underlying comorbidities. Nonetheless, by taking advantage of meta-analysis on the large available and up-to-date dataset of more than two million patients, these observational studies can be impactful to drive clinical decisions.

Conclusions

Based on all currently available literature, the usage of antihypertensive drugs is not associated with the risk and severity of COVID-19. It is not recommended to abstain from the use of these drugs in COVID-19 patients, especially those with hypertension. More clinical trials are needed to further validate these findings.

Authors' contributions

LR and PNT designed the study. LR and PNT screened and evaluated studies. LR and SY performed statistical analyses. PNT checked statistical analyses. LR, WX, JO, and PNT performed comprehensive characterization of studies. SY and NC provided expertise. LR, PNT, and NC wrote the manuscript.

Disclosures

None

Sources of funding

This work was supported by UC Davis Dissertation-Year Fellowship and American Heart Association Predoctoral Award 18PRE34030199 (LR); Postdoctoral Fellowships from NIH/NHLBI Institutional Training Grant in Basic and Translational Cardiovascular Science (T32 NIH HL086350) and NIH F32 HL149288 (PNT); NIH R01 HL085727, HL085844, HL137228 and VA Merit Review Grant I01 BX000576 and I01 CX001490 (NC). The contents of this article do not represent the views of the funding agencies. NC is the holder of the Roger Tatarian Endowed Professorship in Cardiovascular Medicine and a part-time staff physician at VA Northern California Health Care System, Mather, CA, USA.

Independent data access and analysis

The corresponding authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jjcc.2020.10.015.

References

[1] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20:533–4.
[2] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.
[3] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020.
[4] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181271-280.e8.
[5] Patel Vaibhav B, Zhong J-C, Grant Maria B, Oudit Gavin Y. Role of the ACE2/Angiotensin 1–7 Axis of the renin–Angiotensin system in heart failure. Circ Res 2016;118:1313–26.
[6] Goulter AB, Goddard MJ, Allen JC, Clark KL. ACE2 gene expression is up-regulated in the human failing heart. BMC Med 2004;2:19.
[7] Úri K, Fagyas M, Kertész A, Borbély A, Jenei C, Bene O, et al. Circulating ACE2 activity correlates with cardiovascular disease development. J Renin Angiotensin Aldosterone Syst 2016;1714703203166684435.
[8] Ferrario Carlos M, Jessup J, Chappell Mark C, Averill David B, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605–10.
[9] Ishiyama Y, Gallagher Patricia E, Averill David B, Tallant EA, Brosnihan KB, Ferrario Carlos M. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension 2004;43:970–6.
[10] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8. e21-e21.
[11] Ocaranza MP, Godoy I, Jalil JE, Varas M, Collantes P, Pinto M, et al. Enalapril attenuates downregulation of Angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. Hypertension 2006;48:572–8.

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[12] Burrell LM, Risvanis J, Kubota E, Dean RG, MacDonald PS, Lu S, et al. Myocardial infarction increases ACE2 expression in rat and humans. Eur Heart J 2005;26:369–75. discussion 322-324.
[13] Roncon L, Zuin M, Zuliani G, Rigatelli G. Patients with arterial hypertension and COVID-19 are at higher risk of ICU admission. Br J Anaesth 2020.
[14] Li J, He X, Yuan Y, Zhang W, Li X, Zhang Y, et al. Meta-analysis investigating the relationship between clinical features, outcomes, and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. Am J Infect Control 2020.
[15] Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst 2020;211470320320926899.
[16] Gold MS, Sehayek D, Gabrielli S, Zhang X, McCusker C, Ben-Shoshan M. COVID-19 and comorbidities: a systematic review and meta-analysis. Postgrad Med 2020;1–7.
[17] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323:2052–9.
[18] Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT, Skanderson M, et al. Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years. medRxiv 2020. 2020.04.09.20059964.
[19] Felice C, Nardin C, Di Tanna GL, Grossi U, Bernardi E, Scaldaferri L, 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.
[20] 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.
[21] Regina J, Papadimitriou-Olivgeris M, Burger R, Filippidis P, Tschopp J, Desgranges F, et al. Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: an observational retrospective study. medRxiv 2020. 2020.05.11.20097741.
[22] Solaimanzadeh I. Nifedipine and amlodipine are associated with improved mortality and decreased risk for intubation and mechanical ventilation in elderly patients hospitalized for COVID-19. Cureus 2020;12:e8069.
[23] Campbell DJ, Zeitz CJ, Esler MD, Horowitz JD. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. J Hypertens 2004;22:1971–6.
[24] Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK, Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in experimental myocardial infarction: implications for future therapeutic directions. Clin Sci 2012;123:649–58.
[25] 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;382:1653–9.
[26] Pranata R, Permana H, Huang I, Lim MA, Soetedjo NNM, Supriyadi R, et al. The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Diabetes Metab Syndr 2020;14:983–90.
[27] Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, Cappadona R, Mascitelli A, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart 2020.
[28] 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.
[29] 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;158104927.
[30] Pirola CJ, Sookoian S. Estimation of renin-angiotensin-Aldosterone-System (RAAS)-inhibitor effect on COVID-19 outcome: a meta-analysis. J Infect 2020.
[31] 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:e13–4.
[32] Andrea C, Francesco M, Antonio N, Evgeny F, Marzia S, Fabio C, et al. Renin-angiotensin-Aldosterone system inhibitors and outcome in patients with SARS-CoV-2 pneumonia: a case series study. Hypertension 2020;76:e10–2.
[33] Ayed M, Borahmah A, Yazdani A, Sultan A, Mossad A, Rawdhan H. Assessment of clinical characteristics and mortality-associated factors in COVID-19 Critical cases in Kuwait. medRxiv 2020. 2020.06.17.20134007.
[34] Bean D, Kraljevic Z, Searle T, Bendayan R, Pickles A, Folarin A, et al. ACE-inhibitors and Angiotensin-2 Receptor Blockers are not associated with severe SARS- COVID19 infection in a multi-site UK acute Hospital Trust. medRxiv 2020. 2020.04.07.20056788.
[35] Bravi F, Flacco ME, Carradori T, Volta CA, Cosenza G, De Togni A, 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. medRxiv 2020. 2020.05.21.20109082.
[36] Chang TS, Ding Y, Freund MK, Johnson R, Schwarz T, Yabu JM, et al. Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System. medRxiv 2020. 2020.07.03.20145581.
[37] Choi HK, Koo H-J, Seok H, Jeon JH, Choi WS, Kim DJ, et al. ARB/ACEI use and severe COVID-19: a nationwide case-control study. medRxiv 2020. 2020.06.12.20129916.
[38] de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet 2020.
[39] De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tre G, Belmans L, et al. The effects of ARBs, ACEIs and statins on clinical outcomes of COVID-19 infection among nursing home residents. medRxiv 2020. 2020.05.11.20096347.
[40] Dublin S, Walker RL, Floyd JS, Shortreed SM, Fuller S, Albertson-Junkans LH, et al. Renin-angiotensin-aldosterone system inhibitors and COVID-19 infection or hospitalization: a cohort study. medRxiv 2020. 2020.07.06.20120386.
[41] Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. medRxiv 2020. 2020.04.29.20084533.
[42] Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med 2020;201:1380–8.
[43] Feng Z, Li J, Yao S, Yu Q, Zhou W, Mao X, et al. The use of adjuvant therapy in preventing progression to severe pneumonia in patients with coronavirus disease 2019: a multicenter data analysis. medRxiv 2020. 2020.04.08.20057539.
[44] Fosbol EL, Butt JH, Ostergaard L, Andersson C, Selmer C, Kragholm K, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 2020.
[45] 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;41:2058–66.
[46] Golpe R, Perez-de-Llano LA, Dacal D, Guerrero-Sande H, Pombo-Vide B, Ventura-Valcarcel P, et al. Risk of severe COVID-19 in hypertensive patients treated with renin-angiotensin-aldosterone system inhibitors. Med Clin (Barc) 2020.
[47] Huh K, Ji W, Kang M, Hong J, Bae GH, Lee R, et al. Association of previous medications with the risk of COVID-19: a nationwide claims-based study from South Korea. medRxiv 2020. 2020.05.04.20089904.
[48] Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, 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.
[49] Ip A, Parikh K, Parrillo JE, Mathura S, Hansen E, Sawczuk IS, et al. Hypertension and renin-angiotensin-Aldosterone system inhibitors in patients with Covid-19. medRxiv 2020. 2020.04.24.20077388.
[50] Jung S-Y, Choi JC, You S-H, Kim W-Y. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. Clin Infect Dis 2020.
[51] Jurado A, Martin MC, Abad-Molina C, Orduna A, Martinez A, Ocana E, et al. COVID-19 in Spain: age, Interleukin-6, C Reactive Protein and lymphocytes as key clues from a multicentre retrospective study. medRxiv 2020. 2020.05.13.20101345.
[52] Khawaja AP, Warwick AN, Hysi PG, Kastner A, Dick A, Khaw PT, et al. Associations with covid-19 hospitalisation amongst 406,793 adults: the UK Biobank prospective cohort study. medRxiv 2020. 2020.05.06.20092957.
[53] Khera R, Clark C, Lu Y, Guo Y, Ren S, Truax B, 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. 2020.05.17.20104943.
[54] 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.
[55] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020.
[56] Liabeuf S, Moragny J, Bennis Y, Batteux B, Brochot E, Schmit JL, et al. Association between renin-angiotensin system inhibitors and COVID-19 complications. Eur Heart J Cardiovasc Pharmacother 2020.
[57] Liu Y, Huang F, Xu J, Yang P, Qin Y, Cao M, et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxiv 2020. 2020.03.20.20039586.
[58] Lopez-Otero D, Lopez-Pais J, Cacho-Antonio CE, Antunez-Muinos PJ, Gonzalez-Ferreiro T, Perez-Poza M, 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.
[59] 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.
[60] Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020;9:757–60.
[61] Morales DR, Conover MM, You SC, Pratt N, Kostka K, Duarte Salles T, et al. Renin-angiotensin system blockers and susceptibility to COVID-19: a multinational open science cohort study. medRxiv 2020. 2020.06.11.20125849.
[62] Nguyen AB, Upadhyay GA, Chung B, Smith B, Besser SA, Johnson JA, et al. Outcomes and cardiovascular comorbidities in a predominantly african-american population with COVID-19. medRxiv 2020. 2020.06.28.20141929.
[63] Oussalah A, Gleye S, Clerc Urmes I, Laugel E, Callet J, Barbe F, et al. Long-term ACE Inhibitor/ARB use is associated with severe renal dysfunction and acute kidney injury in patients with severe COVID-19: results from a referral center cohort in the North East of France. Clin Infect Dis 2020.

Please cite this article in press as: Ren L, et al. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. J Cardiol (2020), https://doi.org/10.1016/j.jjcc.2020.10.015

[64] Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity is associated with higher in-hospital mortality in a cohort of patients with COVID-19 in the Bronx, New York. medRxiv 2020. 2020.05.05.20091983.
[65] Raisi-Estabragh Z, McCracken C, Ardissino M, Bethell MS, Cooper J, Cooper C, 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. 2020.05.10.20096925.
[66] 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.
[67] Giorgi Rossi P, Marino M, Formisano D, Venturelli F, Vicentini M, Grilli R. Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the Province of Reggio Emilia, Italy. medRxiv 2020. 2020.04.13.20063545.
[68] Sardu C, Maggi P, Messina V, Iuliano P, Sardu A, Iovinella V, et al. Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from centers of southern Italy. J Am Heart Assoc 2020e016948.
[69] 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;24:21–9.
[70] Tan N-D, Qiu Y, Xing X-B, Ghosh S, Chen M-H, Mao R. Associations between angiotensin converting enzyme inhibitors and angiotensin ii receptor blocker use, gastrointestinal symptoms, and mortality among Patients with COVID-19. Gastroenterology.
[71] Tedeschi S, Giannella M, Bartoletti M, Trapani F, Tadolini M, Borghi C, et al. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19. Clin Infect Dis 2020.
[72] Trecarichi EM, Mazzitelli M, Serapide F, et al. Characteristics, outcome and predictors of in-hospital mortality in an elderly population from a SARS-CoV-2 outbreak in a long-term care facility. medRxiv 2020. 2020.06.30.20143701.
[73] Yan H, Valdes AM, Vijay A, Wang S, Liang L, Yang S, et al. Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zheijang Province, China. medRxiv 2020. 2020.04.24.20077875.
[74] Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J., et al. Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. Hypertension. 0.
[75] Zeng Z, Sha T, Zhang Y, Wu F, Hu H, Li H, et al. Hypertension in patients hospitalized with COVID-19 in Wuhan, China: a single-center retrospective observational study. medRxiv 2020. 2020.04.06.20054825.
[76] Zhang P, Zhu L, Cai J, Lei F, Qin J-J, 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. Circulation Research. 0.
[77] Zhou F, Liu YM, Xie J, Li H, Lei F, Yang H, 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:e15–7.
[78] Zhou J, Tse G, Lee S, Liu T, Wu WK, Cao Z, et al. Identifying main and interaction effects of risk factors to predict intensive care admission in patients hospitalized with COVID-19: a retrospective cohort study in Hong Kong. medRxiv 2020. 2020.06.30.20143651.
[79] 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;1–5.

Please cite this article in press as: Ren L, et al. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. J Cardiol (2020), https://doi.org/10.1016/j.jjcc.2020.10.015