JAMA Network Open

Original Investigation | Cardiology

Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19

A Systematic Review and Meta-analysis

Ranu Baral, MRes, MBBS; Vasiliki Tsampasian, MSc, MD; Maciej Debski, MD, PhD; Brendan Moran, MBBS; Pankaj Garg, MD, PhD; Allan Clark, PhD; Vassilios S. Vassiliou, MBBS, PhD

Abstract

IMPORTANCE The chronic receipt of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has been assumed to exacerbate complications associated with COVID-19 and produce worse clinical outcomes.

OBJECTIVE To conduct an updated and comprehensive systematic review and meta-analysis comparing mortality and severe adverse events (AEs) associated with receipt vs nonreceipt of ACEIs or ARBs among patients with COVID-19.

DATA SOURCES PubMed and Embase databases were systematically searched from December 31, 2019, until September 1, 2020.

STUDY SELECTION The meta-analysis included any study design, with the exception of narrative reviews or opinion-based articles, in which COVID-19 was diagnosed through laboratory or radiological test results and in which clinical outcomes (unadjusted or adjusted) associated with COVID-19 were assessed among adult patients (≥18 years) receiving ACEIs or ARBs.

DATA EXTRACTION AND SYNTHESIS Three authors independently extracted data on mortality and severe AEs associated with COVID-19. Severe AEs were defined as intensive care unit admission or the need for assisted ventilation. For each outcome, a random-effects model was used to compare the odds ratio (OR) between patients receiving ACEIs or ARBs vs those not receiving ACEIs or ARBs.

MAIN OUTCOMES AND MEASURES Unadjusted and adjusted ORs for mortality and severe AEs associated with COVID-19.

RESULTS A total of 1788 records from the PubMed and Embase databases were identified; after removal of duplicates, 1664 records were screened, and 71 articles underwent full-text evaluation. Clinical data were pooled from 52 eligible studies (40 cohort studies, 6 case series, 4 case-control studies, 1 randomized clinical trial, and 1 cross-sectional study) enrolling 101 949 total patients, of whom 26 545 (26.0%) were receiving ACEIs or ARBs. When adjusted for covariates, significant reductions in the risk of death (adjusted OR [aOR], 0.57; 95% CI, 0.43-0.76; $P < .001$) and severe AEs (aOR, 0.68; 95% CI, 0.53-0.88; $P < .001$) were found. Unadjusted and adjusted analyses of a subgroup of patients with hypertension indicated decreases in the risk of death (unadjusted OR, 0.66 [95% CI, 0.49-0.91]; $P = .01$; aOR, 0.51 [95% CI, 0.32-0.84]; $P = .008$) and severe AEs (unadjusted OR, 0.70 [95% CI, 0.54-0.91]; $P = .007$; aOR, 0.55 [95% CI, 0.36-0.85]; $P = .007$).

(continued)

Key Points

Question Is the receipt of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) associated with worse clinical outcomes among patients with COVID-19?

Findings In this systematic review and meta-analysis of 52 studies that evaluated clinical outcomes among 101 949 total patients with COVID-19 who did and did not receive ACEIs or ARBs, a significantly lower risk of multivariable-adjusted mortality and severe adverse events was found among patients who received ACEIs or ARBs compared with patients who did not. A subgroup analysis of patients with hypertension indicated significant decreases in mortality and severe adverse events among patients receiving ACEIs or ARBs in both unadjusted and adjusted analyses.

Meaning The study's findings suggest that ACEIs and ARBs may be associated with protective benefits for patients with COVID-19 and that patients may continue receiving ACEIs and ARBs for the treatment of any condition without an increased risk of worse outcomes unless specifically advised to avoid them by treating clinicians.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY License.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, receipt of ACEIs or ARBs was not associated with a higher risk of multivariable-adjusted mortality and severe AEs among patients with COVID-19 who had either hypertension or multiple comorbidities, supporting the recommendations of medical societies. On the contrary, ACEIs and ARBs may be associated with protective benefits, particularly among patients with hypertension. Future randomized clinical trials are warranted to establish causality.

JAMA Network Open. 2021;4(3):e213594. doi:10.1001/jamanetworkopen.2021.3594

Introduction

Coronavirus disease 2019 (COVID-19), a rapidly evolving pandemic infecting more than 93 million people worldwide to date,[1] is associated with worse clinical outcomes in patients with existing cardiovascular diseases, including hypertension and diabetes.[2,3] Renin-angiotensin-aldosterone system (RAAS) inhibitors, specifically angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which are frequently used for the treatment of cardiovascular conditions, are subjects of debate because angiotensin-converting enzyme 2 acts as a binding site for the virus to gain cellular entry.[4] This debate has elicited several theories suggesting that the chronic receipt of RAAS inhibitors may exacerbate COVID-19 and produce worse outcomes.[4]

Several observational studies have since evaluated the association of ACEIs and ARBs (ACEIs/ARBs) with clinical outcomes in patients with COVID-19. Although a few studies have reported an increased risk of severe disease,[5,6] most have found no association[7,8] or even beneficial associations with the receipt of these drugs.[9,10] A previous meta-analysis[11] that examined 16 studies with 28 000 total patients reported no significant association between the receipt of ACEIs/ARBs and mortality or severe adverse events (AEs) among individuals with multiple comorbidities (OR, 0.67; 95% CI, 0.44-1.03; $P = .07$) and a significant association between ACEIs/ARBs and protective benefits among individuals with hypertension (OR, 0.67; 95% CI, 0.50-0.91; $P = .01$). Since the publication of that meta-analysis, more original studies have been published, allowing increased statistical power to further investigate specific subgroups.

Given the increasing number of COVID-19 cases and an evolving second wave of infections, it is important to summarize the data thus far to provide an updated perspective and an understanding of the association between ACEIs/ARBs and clinical COVID-19 outcomes. The inclusion of more studies and patients will allow the identification of more accurate associations with smaller CIs, producing findings that are more likely to represent true associations. In addition, the inclusion of only peer-reviewed studies will reinforce the conclusions. Findings from the present meta-analysis will be relevant for the clinical management of millions of patients receiving these drugs worldwide.[12]

Methods

Study Selection

The PubMed and Embase databases were systematically searched from December 31, 2019, until September 1, 2020, for studies published in English. Terms such as *angiotensin-converting enzyme inhibitors*, *angiotensin receptor blockers*, *coronavirus disease 2019*, and *SARS-COV-2* were used for a comprehensive search. Additional details about the search strategy are available in eMethods in the Supplement. The references of retrieved articles were manually screened for relevant studies to expand the search. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

All studies identified in our search were screened by 3 authors (R.B., M.D., and V.T.) using article titles and abstracts. Duplicate studies and multiple reports using the same data were removed. Any

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

article identified as having the potential to fulfill our inclusion criteria underwent full-text evaluation. We included studies meeting the following criteria: (1) any study design, with the exception of narrative reviews and opinion-based articles; (2) adult (≥18 years) study population; (3) participants with COVID-19 diagnosed through laboratory or radiological test results; and (4) assessment of clinical or mortality outcomes (unadjusted or adjusted) among patients receiving ACEIs/ARBs. The mortality and clinical severity data of patients receiving ACEIs/ARBs were compared with those of patients not receiving ACEIs/ARBs.

Data Extraction and Quality Assessment

Three authors (R.B., V.T., and M.D.) independently extracted relevant data from included studies using a standardized extraction form. Any disagreements were resolved by discussion. The data extracted included the type of study, the number and characteristics of patients receiving ACEIs/ARBs, and mortality and severe AEs associated with COVID-19.

Severe AEs were defined as intensive care unit admission or the need for invasive or noninvasive ventilation. Studies reporting severe AEs based on information from the Chinese Center for Disease Control and Prevention[13] were included. To avoid double-counting of patients in studies reporting multiple severe AE outcomes, we included the outcome with the largest number of patients in our analyses. For instances in which distinct data for ACEIs/ARBs were available, an aggregate was used given the small likelihood of combined receipt of both drugs.

The Newcastle-Ottawa Scale,[14] a 9-point measure assessing the quality of cohort studies and case-control studies or case series, was used to evaluate the observational studies included. The Cochrane Risk of Bias 2 tool was used to assess the risk of bias in randomized clinical trials.[15]

Statistical Analysis

For each outcome, a random-effects model was used to compare the odds ratios (ORs) and 95% CIs between patients who did and did not receive ACEIs/ARBs using Review Manager software, version 5.3 (Nordic Cochrane Center), and OpenMeta[Analyst] software, version 10.12 (Center for Evidence Synthesis, Brown University).[16] For studies reporting hazard ratios (HRs), those HRs were converted to ORs using methodology defined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[17] Results from studies were grouped according to a prespecified variable (patients with hypertension [hypertension subgroup] vs patients with multiple mixed comorbidities [mixed subgroup]), and a series of subgroup analyses were performed. We also conducted a sensitivity analysis, in which studies reporting HRs (which were converted to ORs) were excluded to assess the robustness of results.

Statistical heterogeneity was assessed using the I^2 statistic. Potential publication bias was assessed using funnel plots. The statistical significance threshold was $P < .05$.

Results

Our search identified 1788 records from the PubMed and Embase databases; after removal of duplicates, 1664 records were screened, and 71 articles underwent full-text evaluation (eFigure 1 in the Supplement). Of those, 52 studies (40 cohort studies, 6 case series, 4 case-control studies, 1 randomized clinical trial, and 1 cross-sectional study) with 101 949 total participants met inclusion criteria and were included in the meta-analysis. The cohorts and methodological characteristics of the studies are described in the **Table**. Ten studies were ranked as having moderate quality and 41 studies were ranked as having high quality based on the Newcastle-Ottawa Scale (eTable in the Supplement). Funnel plots indicated no substantial publication biases (eFigure 2 and eFigure 3 in the Supplement).

Most studies included in the meta-analysis were retrospective[20,21,33,44] or observational[4,6,26,37,61-63] and were conducted in China,[4,8,10,23-25,28,31,32,35,39,41,45,48,55,58-60,62,64-66] Europe,[5,7,9,18,19,22,30,34,40,43,46,47,51-53,56,57] or North America.[6,20,49,50,54] Two studies[22,38] included a

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Table. Baseline Characteristics of Included Studies

Source	Study type and location	Participants receiving ACEIs or ARBs, No.	Total participants, No.	Participant age, y	Male sex, %	Participants with hypertension, %	Participant clinical characteristics, %	Outcomes measured	Adjustment methods
Amat-Santos et al,[18] 2020	Ongoing open-label RCT (RASTAVI), Spain	5	11	Median (IQR), 86 (84-88)	54.5	54.5	CKD: 36.4 Diabetes: 18.2 CAD: 18.2	Mortality	NA
Conversano et al,[19] 2020	Retrospective case series, Italy	68	96	NR	NR	100	Hypertension: 100 CHD: 28.1 Diabetes: 22.9 Heart failure: 8.3	Mortality; median follow-up of 28 d	NA
Bae et al,[20] 2020	Retrospective cohort study, US	78	590	NR	48.8	25.4	Diabetes: 26.3 CAD: 5.3 Heart failure: 3.6	Mortality and critical severity (ICU admission)	Multivariate logistic regression with propensity matching for age and comorbidities (hypertension, dyslipidemia, diabetes or prediabetes, CAD, heart failure, CVA, chronic lung disease, and CKD or ESRD)
Bean et al,[21] 2020	Prospective multicenter cohort study, United Kingdom	399	1200	Mean (SD), 68 (17)	57.2	53.8	Diabetes: 34.8 IHD: 13.3 Heart failure: 8.9	Mortality and critical severity (ICU admission); follow-up of 21 d	Multivariate logistic regression adjusted for age, sex, and comorbidities (hypertension, diabetes, IHD, heart failure, and CKD)
Bravi et al,[7] 2020	Retrospective case-control study, Italy	450	543	Mean (SD), 58 (21)	47.3	33.9	Diabetes: 12.1 COPD: 6.0	Very severe or lethal (ICU admission or death)	Multivariate logistic regression adjusted for age, sex, and comorbidities (diabetes, major cardiovascular diseases, COPD, cancer, and renal diseases)
Cannata et al,[22] 2020	Prospective cohort study, Italy	173	397	NR	NR	NR	NR	Mortality; follow-up until death or discharge	Multivariate logistic regression adjusted for age, BMI, comorbidities (diabetes, COPD, LVEF<50%, and cancer), vital parameters, and laboratory values within 24 h after admission
Chen et al,[23] 2020	Retrospective, cohort study, China	355	1182	Median (IQR), 68 (60-75)	49.1	100	Diabetes: 22.1 CHD: 17.4 CKD: 5.3	Mortality and critical severity (need for IMV); follow-up of 45 d	Multivariable Cox proportional hazards regression analyses adjusted for age, sex, comorbidities (CHD and diabetes), laboratory findings (creatinine levels), and receipt of various medications
Chen et al,[24] 2020	Retrospective cohort study, China	81	312	Median (IQR), 69 (61-77)	55.1	93.9	CAD: 25.6	Mortality	Multivariable logistic regression models adjusted for clinically relevant parameters (age, sex, comorbidities, and laboratory findings) that differed between the 2 groups
Chen et al,[25] 2020	Retrospective cohort study, China	32	71	NR	NR	NR	Diabetes: 100 Hypertension: 100	Mortality and clinical outcome of discharge or death in hospital	NA
Hippisley-Cox et al,[26] 2020	Prospective cohort study, United Kingdom	4281	19 486	Mean (SD), 62 (21)	48.12	38.9	CVD: 18.2 COPD: 7.3 Diabetes: 7.0	Critical severity (ICU admission)	Cox proportional hazards models using imputed analysis including all exposure and explanatory variables

(continued)

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Table. Baseline Characteristics of Included Studies (continued)

Source	Study type and location	Participants receiving ACEIs or ARBs, No.	Total participants, No.	Participant age, y	Male sex, %	Participants with hypertension, %	Participant clinical characteristics, %	Outcomes measured	Adjustment methods
Felice et al,[9] 2020	Prospective cohort study, Italy	82	133	NA	64.7	100	Diabetes: 25.6 Heart failure: 18.0 COPD: 10.5	Mortality and critical severity (ICU admission); mean follow-up of 15.8 d	Multivariable logistic regression adjusted for age, sex, BMI, days with duration of symptoms before admission, and comorbidities (previous cardiovascular events, diabetes, and cancer)
Feng et al,[4] 2020	Retrospective cohort study, China	33	113	NR	NR	100	NR	Mortality and critical severity based on CCDC report	NA
Fosbol et al,[27] 2020	Retrospective cohort study, Denmark	895	4480	NR	47.9	18.8	COPD:14.2 Diabetes: 9.2 CVD: 9.0 Heart failure: 5.4	Mortality and critical severity (ICU admission); median follow-up of 34 d	Cox regression adjusted for sex, highest obtained education, income, comorbidities (myocardial infarction, heart failure, CKD, stroke, peripheral artery disease, AF, diabetes, COPD, and cancer) and various medications
Gao et al,[28] 2020	Retrospective cohort study, China	183	850	Mean (SD), 64 (11)	52.1	100	Diabetes: 26.8 COPD: 1.3 Heart failure: 1.2	Mortality and critical severity based on CCDC report	Cox proportional hazards model adjusted for age, sex, medical history (diabetes and IHD), sex, RAAS inhibitor (ACEI or ARB), insulin-treated diabetes, myocardial infarction, treatment by PCI or CABG, renal failure, chronic heart failure, asthma, COPD, and stroke
Gormez et al,[29] 2020	Retrospective cohort study, Turkey	49	247	NR	62.3%	31.6%	Diabetes: 39.7% COPD: 5.7% CKD: 4.0% Heart failure: 0.8%	Critical severity (ICU admission); median follow-up of 13 d (ICU) and 7 d (other)	Bayesian logistic regression adjusted for age, sex, D-dimer level, neutrophil to lymphocyte ratio, CRP, and history of hypertension
Grasselli et al,[30] 2020	Retrospective cohort study, Italy	NR	1608	NR	NR	100%	NR	Mortality	Multivariable Cox proportional hazards regression models including baseline characteristics, comorbidities, medications, and physiological variables at admission
Guo et al,[31] 2020	Retrospective case series, China	19	187	Mean (SD), 59 (15)	48.7	32.6	Diabetes: 15.0 CHD: 11.2	Mortality	NA
Hu et al,[64] 2020	Retrospective cohort study, China	65	149	Median (IQR), 57 (50-66)	59.1	100	Diabetes: 20.1 CKD: 4.0 COPD: 1.3	Mortality and critical severity (ICU admission)	NA
Huang et al,[32] 2020	Prospective cohort study, China	20	50	NR	54.0	100	Diabetes: 8.0 COPD: 2.0	Mortality and critical severity based on CCDC report	NA
Hwang et al,[33] 2020	Retrospective cohort study, South Korea	13	103	Mean (SD), 68 (15)	50.5	55.3	Diabetes: 34.0 CKD: 16.5 CVD: 11.7	Mortality	NA
Iaccarino et al,[34] 2020	Cross-sectional study, Italy	655	1591	Mean (SD), 67 (0.4)	64.0	54.9	Diabetes: 16.9 CAD: 13.6 Heart failure: 11.8 CKD: 5.5	Mortality	NA

(continued)

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Table. Baseline Characteristics of Included Studies (continued)

Source	Study type and location	Participants receiving ACEIs or ARBs, No.	Total participants, No.	Participant age, y	Male sex, %	Participants with hypertension, %	Participant clinical characteristics, %	Outcomes measured	Adjustment methods
Jung et al,[35] 2021	Prospective study (part of COVIP), Germany	157	324	Median (IQR), 75 (70-93)	69.1	65.1	Diabetes: 29.4 Heart failure: 14.1	Mortality	Multivariate logistic regression with propensity matching for age, BMI, sex, sequential organ failure assessment score, comorbidities (heart failure, IHD, renal insufficiency, chronic pulmonary disease, hypertension, and diabetes)
Jung et al,[36] 2020	Retrospective cohort study, Korea	377	1954	NR	NR	NR	NR	Mortality and critical severity (need for IMV)	Multivariate logistic regression analysis adjusted for age, sex, Charlson Comorbidity Index score, immunosuppression, and hospital type
Khan et al,[37] 2020	Prospective cohort study, United Kingdom	27	88	Mean (SD), 72 (14)	56.8	100	NR	Mortality and critical severity (ICU admission); follow-up for 60 d or until discharge or death	NA
Lam et al,[38] 2020	Retrospective cohort study, US	335	614	NR	55.0	100	Diabetes: 40.7 CKD: 15.4 COPD: 13.4 Heart failure: 13.4	Mortality and critical severity (ICU admission)	NA
Li et al,[39] 2020	Retrospective case series, China	115	362	Median (IQR), 66 (59-73)	53.2	100	Diabetes: 35.2% CVD: 18.8% CHD: 17.1% Heart failure: 2.8%	Mortality and critical severity based on CCDC report	NA
Liabeuf et al,[40] 2020	Retrospective cohort study, France	96	268	Median (IQR), 73 (61-84)	58.2	56.7	Diabetes: 20.5 COPD: 9.7 CKD: 7.1	Mortality and critical severity (ICU admission)	Multivariate logistic regression model adjusted for age, sex, BMI, and CHD
Liu et al,[41] 2021	Retrospective single-center case series, China	74	157	NR	46.5	100	Diabetes: 27.3 CAD: 10.2	Critical severity based on CCDC criteria	NA
Lopez-Otero et al,[42] 2020	Retrospective single-center cohort study, Spain	210	965	Mean (SD), 60 (20)	43.9	30.9	Diabetes: 12.8 CAD: 4.4	Mortality and critical severity (ICU admission)	Multivariate logistic regression models adjusted for variables with $P < .05$ in the univariate analysis (fever, oxygen saturation <95%, age, sex, obesity, health personnel, and dependency status)
Mancia et al,[43] 2020	Case-control study, Italy	2896	6272	Mean (SD), 68 (13)	63.3	NR	CHD: 7.5 Heart failure: 5.1	Critical severity (assisted ventilation) and fatal infection	NA
Matsuzawa et al,[44] 2020	Retrospective cohort study, Japan	21	39	Mean (SD), 71 (12)	69.2	100	Diabetes: 35.9 CKD: 7.7 COPD: 2.6 Heart failure: 2.6	Mortality and critical severity (ICU admission)	Multivariate logistic regression model adjusted for age, sex, and presence of diabetes
Mehta et al,[6] 2020	Retrospective cohort study, US	212	1735	NR	NR	NR	NR	Mortality and critical severity (ICU admission)	Propensity score estimated using multivariable logistic regression model adjusted for age, sex, and comorbidities (hypertension, diabetes, heart failure, COPD, and CAD)
Meng et al,[45] 2020	Retrospective cohort study, China	17	42	Median (IQR), 65 (56-69)	57.1	100	CHD: 19.0 Diabetes: 14.2	Mortality	NA

(continued)

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Table. Baseline Characteristics of Included Studies (continued)

Source	Study type and location	Participants receiving ACEIs or ARBs, No.	Total participants, No.	Participant age, y	Male sex, %	Participants with hypertension, %	Participant clinical characteristics, %	Outcomes measured	Adjustment methods
Mostaza et al,[46] 2020	Retrospective cohort study, Spain	192	404	Mean (SD), 85 (5)	54.7	73.8	Diabetes: 28.0 Heart failure: 18.8 CKD: 15.6	Mortality; follow-up until death or discharge	NA
Oussalah et al,[47] 2020	Retrospective longitudinal cohort study, France	44	149	Median (IQR), 65 (54-77)	61.0	49.6	Diabetes: 28.6 COPD: 11.3 CKD: 6.0	Mortality and critical severity (ICU admission and IMV)	NA
Pan et al,[48] 2020	Retrospective cohort study, China	41	282	Median (IQR), 69 (62-76)	50.7	100	Diabetes: 27.2 CVD: 7.8 COPD: 2.8	Mortality and critical severity (ICU admission)	NA
Reynolds et al,[49] 2020	Retrospective cohort study, US	1293	2141	NR	NR	100	NR	Severity (ICU admission, need for assisted ventilation, or death)	Multivariable logistic regression adjusted for demographic characteristics and comorbidities
Richardson et al,[50] 2020	Case series, US	456	1366	NR	NR	100	NR	Mortality and critical severity (ICU admission); median follow-up of 4 d	NA
Rossi et al,[51] 2020	Prospective cohort study, Italy	818	2653	NR	50.1	18.1	Diabetes: 12.0 Heart failure: 5.8 COPD: 5.4 CKD: 2.5	Mortality	Multivariate proportional hazards models adjusted for age, sex, and Charlson Comorbidity Index score
Sardu et al,[52] 2020	Prospective cohort study, Italy	45	62	Mean (SD), 58 (18)	66.1	100	Diabetes: 25.8 COPD: 16.1 CVD: 11.3	Mortality and critical severity (ICU admission)	NA
Selcuk et al,[5] 2020	Retrospective cohort study, Turkey	74	113	NR	52.2	100	Diabetes: 42.5 CAD: 24.8 Heart failure: 8.0	Mortality and critical severity (ICU admission)	Multivariate logistic regression analysis adjusted for age, CAD, receipt of ACEIs or ARBs, and laboratory findings (WBC count and D-dimer, creatinine, plasma glucose, and lactate dehydrogenase levels)
Senkal et al,[53] 2020	Retrospective cohort study, Turkey	165	248	NR	NR	100	NR	Mortality and critical severity (ICU admission)	Cases matched to controls according to age, sex, number of days ill before hospital admission, comorbidities (diabetes, COPD or asthma, CAD, chronic heart failure, and CKD), current smoking status, and various medications
Shah et al,[54] 2020	Retrospective cohort study, US	207	531	NR	41.1	80.0	Diabetes: 42.9 Chronic heart failure: 14.9 COPD: 7.5 CAD: 7.0	Mortality and critical severity (ICU admission)	Multivariable logistic regression analysis adjusted for age, sex, BMI, baseline comorbidities, and presenting illness severity
Tan et al,[55] 2020	Retrospective cohort study, China	31	100	NR	51.0	100	Diabetes: 28.0 CHD: 18.0	Mortality and critical severity (ICU admission)	NA
Tedeschi et al,[56] 2020	Prospective cohort study, Italy	175	311	Median (IQR), 76 (67-83)	72.3	100	CVD: 42.1 Diabetes: 23.8 COPD: 15.8	Mortality	Multivariate Cox regression analysis adjusted for age, sex, presence of comorbidities, and COPD

(continued)

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Table. Baseline Characteristics of Included Studies (continued)

Source	Study type and location	Participants receiving ACEIs or ARBs, No.	Total participants, No.	Participant age, y	Male sex, %	Participants with hypertension, %	Participant clinical characteristics, %	Outcomes measured	Adjustment methods
Trifiro et al,[57] 2020	Retrospective cohort study, Italy	9522	42 926	Median (IQR), 69 (57-79)	62.6	13.1	Diabetes: 18.0 COPD: 3.5 Heart failure: 6.5	Mortality and critical severity (ICU admission)	Mixed-effects Cox proportional hazards model adjusted for center, age, sex, Charlson Comorbidity Index score, drug receipt, and comorbidities (pneumonia and influenza, IHD, AF, heart failure, hypertension, CVD, diabetes, liver disease, dementia, renal failure, COPD, cancer, and rheumatic diseases)
Xu et al,[58] 2020	Retrospective cohort study, China	40	101	Median (IQR), 65 (58-73)	52.5	100	Diabetes: 18.8 COPD: 2.0 Heart failure: 1.0	Mortality and critical severity (ICU admission)	Multivariable analysis with logistic model adjusted for age and sex
Yang et al,[59] 2020	Retrospective case-control study, China	43	126	Median (IQR), 66 (61-73)	49.2	100	Diabetes: 30.2	Death and severity based on CCDC report	NA
Yuan et al,[60] 2020	Retrospective cohort study, China	196	733	NR	NR	100	NR	Mortality	Propensity score estimated using multivariable logistic regression adjusted for age, sex, history of hypertension, chronic heart disease, diabetes, tumor, COPD, chronic liver disease, CKD, and baseline vital signs
Zhang et al,[61] 2020	Retrospective cohort study, China	188	1128	Median (IQR), 64 (56-69)	53.5	100	Diabetes: 21.3 CHD: 11.6 CVD: 3.6 COPD: 0.5	Mortality and critical severity (ICU admission); follow-up of 28 d	Cox proportional hazards model adjusted for age, sex, comorbidities (CHD, CKD, CVD, and diabetes), and in-hospital medications
Zhou et al,[10] 2020	Retrospective cohort study, China	989	3572	NR	NR	NR	NR	Mortality; follow-up of 28 d	Propensity score matching for age, sex, disease severity, comorbidities, and receipt of calcium channel blocker medication
Zhou et al,[8] 2020	Retrospective case series, China	15	36	Mean (SD), 65 (10)	52.8	100	Diabetes: 25.0 CVD: 19.4	Mortality and transfer to high-level hospital	Multivariate logistic regression adjusted for age, sex, hospitalization time, and time from onset to hospital admission

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; CAD, coronary artery disease; CCDC, Chinese Center for Disease Control and Prevention; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVIP, Corona Virus Disease in Very Elderly Intensive Care Patients study; CRP, C-reactive protein; CVA, cardiovascular accident; CVD, cerebrovascular disease; ESRD, end-stage renal disease; ICU, intensive care unit; IHD, ischemic heart disease; IMV, invasive mechanical ventilation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not applicable; NR, not reported; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; RASTAVI, Remodeling After Transcatheter Aortic Valve Implantation clinical trial; RCT, randomized clinical trial; WBC, white blood cell.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

subgroup of patients receiving ACEIs/ARBs that were explicitly discontinued during hospital admission. The results from this subgroup of patients were included in the group of patients receiving ACEIs/ARBs and compared with those not receiving ACEIs/ARBs. In studies in which both multivariate and propensity-matched scores were reported,[28,42,61] data from the multivariate analyses were used. A total of 26 545 of 101 949 patients (26.0%) overall and 4813 of 11 696 patients (41.2%) in the hypertension subgroup were receiving ACEIs/ARBs (Table).

Mortality

A total of 41 studies (69 577 total participants) that compared mortality rates of patients receiving vs not receiving ACEIs/ARBs were included in the meta-analysis. Overall, the results of the pooled unadjusted meta-analysis indicated no increases in the risk of death among those who received ACEIs/ARBs (unadjusted OR, 1.05; 95% CI, 0.86-1.29; $P = .61$; $I^2 = 85.0\%$) compared with those who did not (**Figure 1**). The subgroup analysis revealed significant reductions in mortality among patients in the hypertension subgroup who were receiving ACEIs/ARBs (unadjusted OR, 0.66; 95% CI, 0.49-0.91; $P = .01$). In contrast, the mixed subgroup comprising patients with multiple comorbidities indicated significant increases in mortality among those receiving ACEIs/ARBs (unadjusted OR, 1.46; 95% CI, 1.15-1.85; $P = .002$)

However, a pooled analysis of 17 studies (17 392 total participants) using an adjusted analysis of mortality found reductions in the risk of death among patients receiving vs not receiving ACEIs/ARBs (adjusted OR [aOR], 0.57; 95% CI, 0.43-0.76; $P < .001$; $I^2 = 54.0\%$) (**Figure 2**). A significant decrease in the risk of death was observed in both subgroups (for the hypertension subgroup, aOR, 0.51 [95% CI, 0.32-0.84]; $P = .008$; for the mixed subgroup, aOR, 0.64 [95% CI, 0.46-0.88]; $P = .006$).

Severe Adverse Events

Unadjusted values for severe AEs were reported in 48 studies that included a total of 98 985 participants. A pooled analysis found comparable results among patients who did and did not receive ACEIs/ARBs (unadjusted OR, 1.11; 95% CI, 0.95-1.31; $P = .20$; $I^2 = 86.0\%$) (**Figure 3**). Notably, the 26 studies including a hypertension subgroup (unadjusted OR, 0.70; 95% CI, 0.54-0.91; $P = .007$) and the 33 studies including a mixed subgroup (unadjusted OR, 1.50; 95% CI, 1.25-1.81; $P < .001$) reported statistically significant results.

A total of 23 studies (23 129 total participants) reported an adjusted risk of severe AEs associated with the receipt of ACEIs/ARBs in a COVID-19 cohort. The adjusted covariates for each study are listed in the Table. A significant decrease in severe AEs was found in patients who received ACEIs/ARBs compared with those who did not (aOR, 0.68; 95% CI, 0.53-0.88; $P = .003$; $I^2 = 67.0\%$) (**Figure 4**). This reduced risk remained significant among the hypertension subgroup in 12 studies (aOR, 0.55; 95% CI, 0.36-0.85; $P = .007$). However, in the mixed subgroup, the decreased risk was not statistically significant (OR, 0.79; 95% CI, 0.59-1.07; $P = .12$). A sensitivity analysis that excluded studies reporting HRs indicated statistically significant results for mortality but nonsignificant results for severe AEs (eFigure 4 and eFigure 5 in the Supplement). Subgroup analyses of studies of moderate quality (OR, 0.36; 95% CI, 0.25-0.51; $P < .001$) and high quality (OR, 0.78; 95% CI, 0.60-1.00; $P = .05$) indicated reduced risk of adjusted severe AEs among both hypertension and mixed subgroups (eFigure 6 in the Supplement).

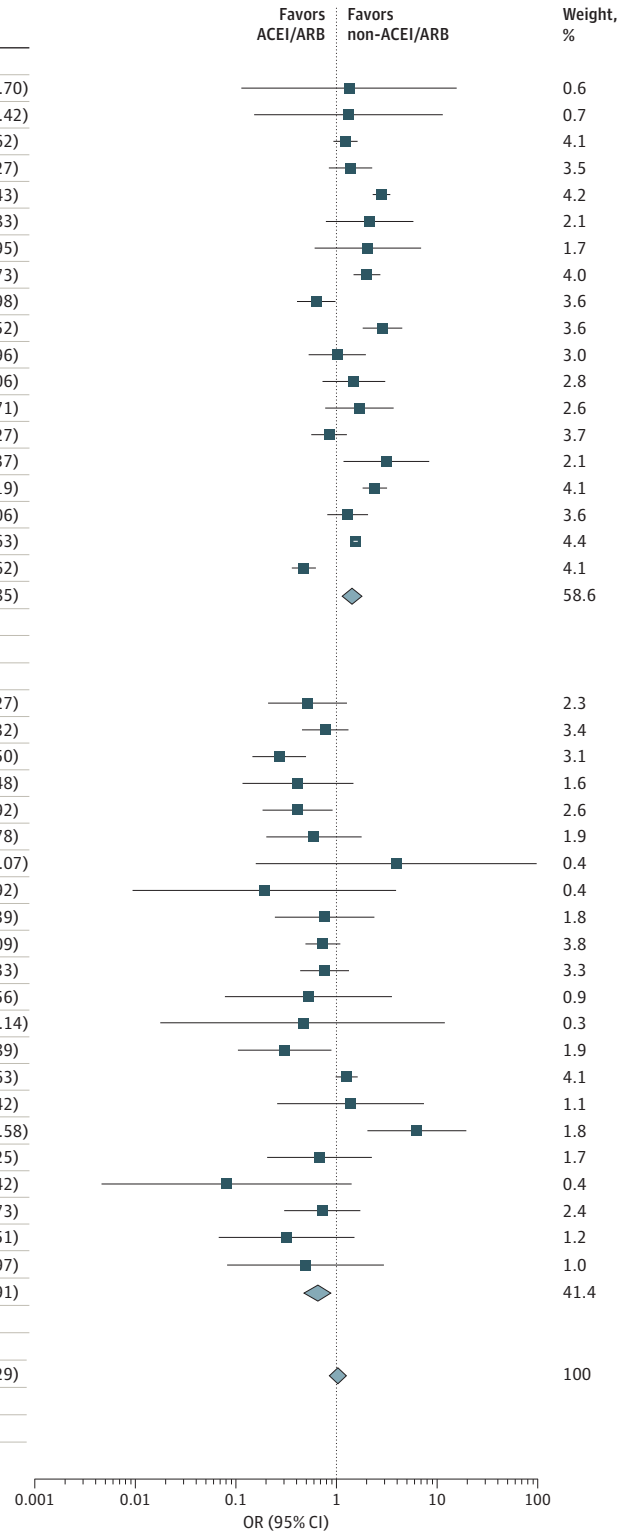
Discussion

The results of this systematic review and meta-analysis of 52 studies with 101 949 total patients indicated a significant association between the receipt of ACEIs/ARBs and reductions in mortality and severe AEs among patients in the hypertension subgroup. In the mixed subgroup of patients with multiple comorbidities, this association was observed only when the analysis was adjusted for significant covariates.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Figure 1. Subgroup Analysis of Unadjusted Mortality Among Patients Who Did and Did Not Receive ACEIs or ARBs

Source	ACEI/ARB Events	ACEI/ARB Total	Non-ACEI/ARB Events	Non-ACEI/ARB Total	OR (95% CI)	Weight, %
Mixed subgroup						
Amat-Santos et al,[18] 2020	2	5	2	6	1.33 (0.11-15.70)	0.6
Bae et al,[20] 2020	1	78	5	512	1.32 (0.15-11.42)	0.7
Bean et al,[21] 2020	106	399	182	801	1.23 (0.93-1.62)	4.1
Cannata et al,[22] 2020	39	173	39	224	1.38 (0.84-2.27)	3.5
Fosbol et al,[27] 2020	181	895	297	3585	2.81 (2.29-3.43)	4.2
Guo et al,[31] 2020	7	19	36	168	2.14 (0.79-5.83)	2.1
Hwang et al,[33] 2020	5	13	21	90	2.05 (0.61-6.95)	1.7
Iaccarino et al,[34] 2020	106	655	82	936	2.01 (1.48-2.73)	4.0
Jung et al,[35] 2021	62	157	85	167	0.63 (0.41-0.98)	3.6
Jung et al,[36] 2020	33	377	51	1577	2.87 (1.82-4.52)	3.6
Liabeuf et al,[40] 2020	17	96	30	172	1.02 (0.53-1.96)	3.0
Lopez-Otero et al,[42] 2020	11	210	27	755	1.49 (0.73-3.06)	2.8
Mehta et al,[6] 2020	8	211	34	1494	1.69 (0.77-3.71)	2.6
Mostaza et al,[46] 2020	65	192	80	212	0.84 (0.56-1.27)	3.7
Oussalah et al,[47] 2020	10	44	9	105	3.14 (1.18-8.37)	2.1
Rossi et al,[51] 2020	108	818	109	1835	2.41 (1.82-3.19)	4.1
Shah et al,[54] 2020	38	207	48	324	1.29 (0.81-2.06)	3.6
Trifiro et al,[57] 2020	3146	9522	8059	33404	1.55 (1.48-1.63)	4.4
Zhou et al,[10] 2020	70	906	272	1812	0.47 (0.36-0.62)	4.1
Subtotal	4015	14977	9468	48179	1.46 (1.15-1.85)	58.6
Heterogeneity: $T^2 = 0.19$; $\chi^2 = 156.09$; df = 18; $P < .001$; $I^2 = 88.0\%$						
Test for overall effect: $z = 3.07$; $P = .002$						
Hypertension subgroup						
Conversano et al,[19] 2020	21	68	13	28	0.52 (0.21-1.27)	2.3
Bravi et al,[7] 2020	87	450	22	93	0.77 (0.45-1.32)	3.4
Chen et al,[23] 2020	12	355	95	827	0.27 (0.15-0.50)	3.1
Chen et al,[25] 2020	4	32	10	39	0.41 (0.12-1.48)	1.6
Felice et al,[9] 2020	15	82	18	51	0.41 (0.18-0.92)	2.6
Gao et al,[28] 2020	4	183	19	527	0.60 (0.20-1.78)	1.9
Hu et al,[64] 2020	1	65	0	84	3.93 (0.16-98.07)	0.4
Huang et al,[32] 2020	0	20	3	30	0.19 (0.01-3.92)	0.4
Khan et al,[37] 2020	5	27	14	61	0.76 (0.24-2.39)	1.8
Lam et al,[38] 2020	58	335	62	279	0.73 (0.49-1.09)	3.8
Li et al,[39] 2020	21	115	56	247	0.76 (0.44-1.33)	3.3
Matsuzawa et al,[44] 2020	2	21	3	18	0.53 (0.08-3.56)	0.9
Meng et al,[45] 2020	0	17	1	25	0.47 (0.02-12.14)	0.3
Pan et al,[48] 2020	4	41	63	241	0.31 (0.10-0.89)	1.9
Richardson et al,[50] 2020	130	413	254	953	1.26 (0.98-1.63)	4.1
Sardu et al,[52] 2020	7	45	2	17	1.38 (0.26-7.42)	1.1
Selcuk et al,[5] 2020	31	74	4	39	6.31 (2.03-19.58)	1.8
Senkal et al,[53] 2020	7	104	5	52	0.68 (0.20-2.25)	1.7
Tan et al,[55] 2020	0	31	11	69	0.08 (0.00-1.42)	0.4
Xu et al,[58] 2020	11	40	21	61	0.72 (0.30-1.73)	2.4
Yang et al,[59] 2020	2	43	11	83	0.32 (0.07-1.51)	1.2
Zhou et al,[8] 2020	2	15	5	21	0.49 (0.08-2.97)	1.0
Subtotal	424	2576	692	3845	0.66 (0.49-0.91)	41.4
Heterogeneity: $T^2 = 0.24$; $\chi^2 = 52.51$; df = 21; $P < .001$; $I^2 = 60.0\%$						
Test for overall effect: $z = 0.24$; $P = .01$						
Total	4439	17553	10160	52024	1.05 (0.86-1.29)	100
Heterogeneity: $T^2 = 0.23$; $\chi^2 = 269.12$; df = 40; $P < .001$; $I^2 = 85.0\%$						
Test for overall effect: $z = 0.52$; $P = .61$						
Test for subgroup differences: $\chi^2 = 15.27$; df = 1; $P < .001$; $I^2 = 93.5\%$						



Subgroup analysis of mortality in 41 studies of patients who did and did not receive ACEIs or ARBs. A total of 19 studies included a mixed subgroup (a sample population with multiple mixed comorbidities), and 22 studies included a hypertension subgroup (a sample population with hypertension). Diamonds represent 95% CIs for subtotal and total ORs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and OR, odds ratio.

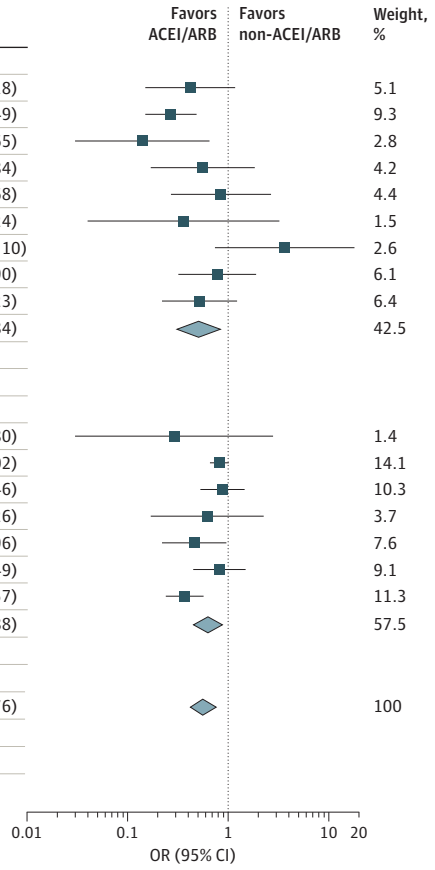
Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Our results are consistent with those of another meta-analysis[67] comprising 18 studies and 17 311 patients with hypertension. This previous meta-analysis reported a lower risk (risk ratio, 0.84; 95% CI, 0.73-0.95; *P* = .007) of the composite outcome (death, intensive care unit admission, mechanical ventilation, and progression to severe or critical pneumonia) among patients receiving ACEIs/ARBs. The present meta-analysis extends this finding to patients with multiple mixed comorbidities, suggesting that ACEIs/ARBs may have a substantial protective role in COVID-19 outcomes across all patient groups.

Notably, the protective implications of ACEIs/ARBs in the mixed subgroup were observed only after adjustments to potential and important confounders, such as age and comorbidities. This finding suggests that comorbidities may have an important role in COVID-19 clinical outcomes and that ACEIs/ARBs might be associated with further improvements in potential outcomes. In a large retrospective cohort study by Fosbol et al[27] that included 4480 patients with COVID-19, an unadjusted analysis indicated worse outcomes among those who received ACEIs/ARBs. However, after multivariate adjustments, this finding was no longer statistically significant. Similar results were observed in multiple small retrospective cohort studies.[29,36,42,54] It is worth noting that most studies included in the meta-analyses were retrospective and observational; with these study designs, unmeasured confounding factors and potential biases are inevitable. In addition, patients receiving ACEIs/ARBs are more likely to have heart failure, cardiovascular disease, hypertension, and comorbidities, which are associated with an increased risk of death among patients with COVID-19.[3] Therefore, it is necessary to adjust for these confounders when evaluating the protective benefits of ACEIs/ARBs for mortality and severe AEs.

Figure 2. Subgroup Analysis of Adjusted Mortality Among Patients Who Did and Did Not Receive ACEIs or ARBs

Source	log OR	SE	OR (95% CI)
Hypertension subgroup			
Conversano et al,[19] 2020	−0.8675	0.5253	0.42 (0.15-1.18)
Chen et al,[23] 2020	−1.3093	0.2999	0.27 (0.15-0.49)
Chen et al,[24] 2020	−1.9661	0.7860	0.14 (0.03-0.65)
Felice et al,[9] 2020	−0.5798	0.6082	0.56 (0.17-1.84)
Gao et al,[28] 2020	−0.1625	0.5851	0.85 (0.27-2.68)
Matsuzawa et al,[44] 2020	−1.0217	1.1211	0.36 (0.04-3.24)
Selcuk et al,[5] 2020	1.2975	0.8156	3.66 (0.74-18.10)
Xu et al,[58] 2020	−0.2485	0.4546	0.78 (0.32-1.90)
Yuan et al,[60] 2020	−0.6539	0.4389	0.52 (0.22-1.23)
Subtotal	NA	NA	0.51 (0.32-0.84)
Heterogeneity: $T^2 = 0.23$; $\chi^2 = 14.62$; df = 8; $P = .07$; $I^2 = 45.0\%$			
Test for overall effect: z = 2.66; $P = .008$			
Mixed subgroup			
Bae et al,[20] 2020	−1.2379	1.1575	0.29 (0.03-2.80)
Fosbol et al,[27] 2020	−0.2000	0.1100	0.82 (0.66-1.02)
Jung et al,[36] 2020	−0.1278	0.2587	0.88 (0.53-1.46)
Lopez-Otero et al,[42] 2020	−0.4780	0.6602	0.62 (0.17-2.26)
Mostaza et al,[46] 2020	−0.7765	0.3763	0.46 (0.22-0.96)
Shah et al,[54] 2020	−0.1985	0.3062	0.82 (0.45-1.49)
Zhou et al,[10] 2020	−0.9943	0.2209	0.37 (0.24-0.57)
Subtotal	NA	NA	0.64 (0.46-0.88)
Heterogeneity: $T^2 = 0.09$; $\chi^2 = 13.26$; df = 6; $P = .04$; $I^2 = 55.0\%$			
Test for overall effect: z = 2.73; $P = .006$			
Total	NA	NA	0.57 (0.43-0.76)
Heterogeneity: $T^2 = 0.14$; $\chi^2 = 32.74$; df = 15; $P = .005$; $I^2 = 54.0\%$			
Test for overall effect: z = 3.82; $P = .001$			
Test for subgroup differences: $\chi^2 = 0.51$; df = 1; $P = .48$; $I^2 = 0\%$			

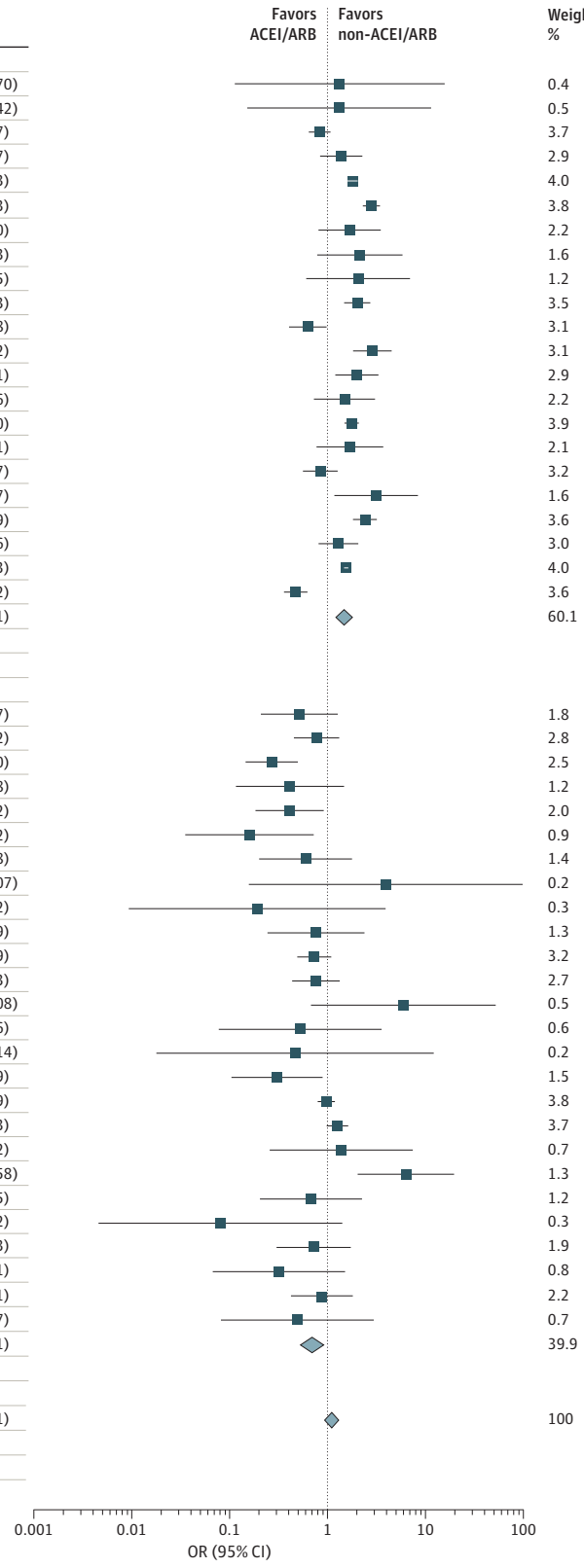


Subgroup analysis of adjusted mortality in 16 studies of patients who did and did not receive ACEIs or ARBs. A total of 7 studies included a mixed subgroup (a sample population with multiple mixed comorbidities), and 9 studies included a hypertension subgroup (a sample population with hypertension). Diamonds represent 95% CIs for subtotal and total ORs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and OR, odds ratio.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Figure 3. Subgroup Analysis of Unadjusted Mortality and Severe Adverse Events Among Patients Who Did and Did Not Receive ACEIs or ARBs

Source	ACEI/ARB Events	ACEI/ARB Total	Non-ACEI/ARB Events	Non-ACEI/ARB Total	OR (95% CI)
Mixed subgroup					
Amat-Santos et al,[18] 2020	2	5	2	6	1.33 (0.11-15.70)
Bae et al,[20] 2020	1	78	5	512	1.32 (0.15-11.42)
Bean et al,[21] 2020	127	399	288	801	0.83 (0.64-1.07)
Cannata et al,[22] 2020	39	173	39	224	1.38 (0.84-2.27)
Hippisley-Cox et al,[26] 2020	420	4281	866	15 205	1.80 (1.59-2.03)
Fosbol et al,[27] 2020	181	895	297	3585	2.81 (2.29-3.43)
Gormez et al,[29] 2020	13	49	35	198	1.68 (0.81-3.50)
Guo et al,[31] 2020	7	19	36	168	2.14 (0.79-5.83)
Hwang et al,[33] 2020	5	13	21	90	2.05 (0.61-6.95)
Iaccarino et al,[34] 2020	106	655	82	936	2.01 (1.48-2.73)
Jung et al,[35] 2021	62	157	85	167	0.63 (0.41-0.98)
Jung et al,[36] 2020	33	377	51	1577	2.87 (1.82-4.52)
Liabeuf et al,[40] 2020	52	96	64	172	1.99 (1.20-3.31)
Lopez-Otero et al,[42] 2020	11	210	27	755	1.49 (0.73-3.06)
Mancia et al,[43] 2020	364	2896	253	3376	1.77 (1.50-2.10)
Mehta et al,[6] 2020	8	211	34	1494	1.69 (0.77-3.71)
Mostaza et al,[46] 2020	65	192	80	212	0.84 (0.56-1.27)
Oussalah et al,[47] 2020	10	44	9	105	3.14 (1.18-8.37)
Rossi et al,[51] 2020	108	818	109	1835	2.41 (1.82-3.19)
Shah et al,[54] 2020	38	207	48	324	1.29 (0.81-2.06)
Trifiro et al,[57] 2020	3146	9522	8059	33404	1.55 (1.48-1.63)
Zhou et al,[10] 2020	70	906	272	1812	0.47 (0.36-0.62)
Subtotal	4868	22203	10762	66958	1.50 (1.25-1.81)
Heterogeneity: $T^2 = 0.12$; $\chi^2 = 183.53$; df = 21; $P < .001$; $I^2 = 89.0\%$					
Test for overall effect: z = 4.34; $P < .001$					
Hypertension subgroup					
Conversano et al,[19] 2020	21	68	13	28	0.52 (0.21-1.27)
Bravi et al,[7] 2020	87	450	22	93	0.77 (0.45-1.32)
Chen et al,[23] 2020	12	355	95	827	0.27 (0.15-0.50)
Chen et al,[25] 2020	4	32	10	39	0.41 (0.12-1.48)
Felice et al,[9] 2020	15	82	18	51	0.41 (0.18-0.92)
Feng et al,[4] 2020	2	33	23	80	0.16 (0.04-0.72)
Gao et al,[28] 2020	4	183	19	527	0.60 (0.20-1.78)
Hu et al,[64] 2020	1	65	0	84	3.93 (0.16-98.07)
Huang et al,[32] 2020	0	20	3	30	0.19 (0.01-3.92)
Khan et al,[37] 2020	5	27	14	61	0.76 (0.24-2.39)
Lam et al,[38] 2020	58	335	62	279	0.73 (0.49-1.09)
Li et al,[39] 2020	21	115	56	247	0.76 (0.44-1.33)
Liu et al,[41] 2021	5	74	1	83	5.94 (0.68-52.08)
Matsuzawa et al,[44] 2020	2	21	3	18	0.53 (0.08-3.56)
Meng et al,[45] 2020	0	17	1	25	0.47 (0.02-12.14)
Pan et al,[48] 2020	4	41	63	241	0.31 (0.10-0.89)
Reynolds et al,[49] 2020	252	1019	249	986	0.97 (0.79-1.19)
Richardson et al,[50] 2020	130	413	254	953	1.26 (0.98-1.63)
Sardu et al,[52] 2020	7	45	2	17	1.38 (0.26-7.42)
Selcuk et al,[5] 2020	31	74	4	39	6.31 (2.03-19.58)
Senkal et al,[53] 2020	7	104	5	52	0.68 (0.20-2.25)
Tan et al,[55] 2020	0	31	11	69	0.08 (0.00-1.42)
Xu et al,[58] 2020	11	40	21	61	0.72 (0.30-1.73)
Yang et al,[59] 2020	2	43	11	83	0.32 (0.07-1.51)
Zhang et al,[61] 2020	9	188	51	940	0.88 (0.42-1.81)
Zhou et al,[8] 2020	2	15	5	21	0.49 (0.08-2.97)
Subtotal	692	3890	1016	5934	0.70 (0.54-0.91)
Heterogeneity: $T^2 = 0.17$; $\chi^2 = 62.14$; df = 25; $P < .001$; $I^2 = 60.0\%$					
Test for overall effect: z = 2.70; $P = .007$					
Total	5560	26093	11778	72892	1.11 (0.95-1.31)
Heterogeneity: $T^2 = 0.17$; $\chi^2 = 330.29$; df = 47; $P < .001$; $I^2 = 86.0\%$					
Test for overall effect: z = 1.29; $P = .20$					
Test for subgroup differences: $\chi^2 = 22.28$; df = 1; $P < .001$; $I^2 = 95.5\%$					



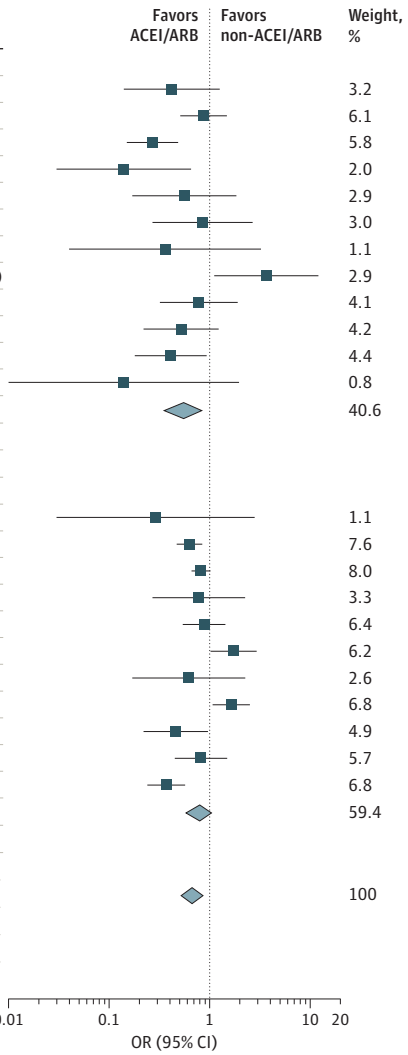
Subgroup analysis of mortality and severe adverse events in 48 studies of patients who did and did not receive ACEIs or ARBs. A total of 22 studies included a mixed subgroup (a sample population with multiple mixed comorbidities), and 26 studies included a hypertension subgroup (a sample population with hypertension). Diamonds represent 95% CIs for subtotal and total ORs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and OR, odds ratio.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

The potential mechanisms underlying the beneficial consequences of ACEIs/ARBs remain unknown. Our results suggest that these benefits are not solely associated with better blood pressure control, as patients receiving antihypertensive medications that were not ACEIs/ARBs had comparably inferior clinical outcomes in the adjusted subgroup analysis. Concerns about upregulation of angiotensin-converting enzyme 2 receptors with the receipt of RAAS inhibitors, which are derived from inconsistent results in studies with small samples,[68,69] have been challenged by reports of deactivation of RAAS[61] with chronic receipt of ACEIs/ARBs. Such downregulation may limit the inflammatory process, reducing acute lung injury among patients with COVID-19.[49]

Nevertheless, the findings of the present meta-analysis are consistent with those of national and international scientific experts,[70-72] who recommend continuation of ACEIs/ARBs unless they are clinically contraindicated. This meta-analysis also indicated that, after adjustment for case mix, patients with hypertension and COVID-19 who received ACEIs/ARBs were 0.55 times as likely to experience a severe AE than those who did not receive ACEIs/ARBs, with a similar extent of benefit observed in the combined hypertension and mixed comorbidities subgroups. Although our study clarifies the association between RAAS inhibitors and mortality among patients with COVID-19, future randomized clinical trials are warranted to establish causality.

Figure 4. Subgroup Analysis of Adjusted Mortality and Severe Adverse Events Among Patients Who Did and Did Not Receive ACEIs or ARBs



Source	log OR	SE	OR (95% CI)	Weight, %
Hypertension subgroup				
Conversano et al,[19] 2020	-0.8675	0.5605	0.42 (0.14-1.26)	3.2
Bravi et al,[7] 2020	-0.1393	0.2725	0.87 (0.51-1.48)	6.1
Chen et al,[23] 2020	-1.3093	0.2999	0.27 (0.15-0.49)	5.8
Chen et al,[24] 2020	-1.9661	0.7860	0.14 (0.03-0.65)	2.0
Felice et al,[9] 2020	-0.5798	0.6082	0.56 (0.17-1.84)	2.9
Gao et al,[28] 2020	-0.1625	0.5851	0.85 (0.27-2.68)	3.0
Matsuzawa et al,[44] 2020	-1.0217	1.1211	0.36 (0.04-3.24)	1.1
Selcuk et al,[5] 2020	1.2975	0.6087	3.66 (1.11-12.07)	2.9
Xu et al,[58] 2020	-0.2485	0.4546	0.78 (0.32-1.90)	4.1
Yuan et al,[60] 2020	-0.6539	0.4389	0.52 (0.22-1.23)	4.2
Zhang et al,[61] 2020	-0.8916	0.4200	0.41 (0.18-0.93)	4.4
Zhou et al[8] 2020	-1.9661	1.3465	0.14 (0.01-1.96)	0.8
Subtotal	NA	NA	0.55 (0.36-0.85)	40.6
Heterogeneity: $T^2 = 0.28$; $\chi^2 = 24.24$; df = 11; $P = .01$; $I^2 = 55.0\%$				
Test for overall effect: z = 2.69; $P = .007$				
Mixed subgroup				
Bae et al,[20] 2020	-1.2379	1.1575	0.29 (0.03-2.80)	1.1
Bean et al,[21] 2020	-0.4620	0.1495	0.63 (0.47-0.84)	7.6
Fosbol et al,[27] 2020	-0.1985	0.1107	0.82 (0.66-1.02)	8.0
Gormez et al,[29] 2020	-0.2485	0.5413	0.78 (0.27-2.25)	3.3
Jung et al,[36] 2020	-0.1278	0.2492	0.88 (0.54-1.43)	6.4
Liabeuf et al,[40] 2020	0.5481	0.2696	1.73 (1.02-2.93)	6.2
Lopez-Otero et al,[42] 2020	-0.4780	0.6602	0.62 (0.17-2.26)	2.6
Mehta et al,[6] 2020	0.4947	0.2179	1.64 (1.07-2.51)	6.8
Mostaza et al,[46] 2020	-0.7765	0.3763	0.46 (0.22-0.96)	4.9
Shah et al,[54] 2020	-0.1985	0.3062	0.82 (0.45-1.49)	5.7
Zhou et al,[10] 2020	-0.9943	0.2209	0.37 (0.24-0.57)	6.8
Subtotal	NA	NA	0.79 (0.59-1.07)	59.4
Heterogeneity: $T^2 = 0.15$; $\chi^2 = 37.04$; df = 10; $P < .001$; $I^2 = 73.0\%$				
Test for overall effect: z = 1.54; $P = .12$				
Total	NA	NA	0.68 (0.53-0.88)	100
Heterogeneity: $T^2 = 0.19$; $\chi^2 = 66.95$; df = 22; $P < .001$; $I^2 = 67.0\%$				
Test for overall effect: z = 3.01; $P = .003$				
Test for subgroup differences: $\chi^2 = 1.78$; df = 1; $P = .18$; $I^2 = 43.9\%$				

Subgroup analysis of adjusted mortality and severe adverse events in 23 studies of patients who did and did not receive ACEIs or ARBs. A total of 11 studies included a mixed subgroup (sample population with multiple mixed comorbidities), and 12 studies included a hypertension subgroup (defined as a sample population with hypertension). Diamonds represent 95% CIs for subtotal and total ORs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and OR, odds ratio.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

Limitations

This study has limitations. First, the study was limited by the insufficient data and varying study designs available, which did not allow for comparison of these analyses with a control group. The meta-analysis was primarily composed of observational studies because studies with higher levels of evidence, such as randomized clinical trials, were lacking. Second, the meta-analysis indicated substantial unadjusted and moderate adjusted levels of heterogeneity, which is typical in observational studies that include patients with diverse characteristics across large geographic regions. Nevertheless, measures were taken to maintain a homogeneous study population. A standard definition for severe AEs was used, and patients with unconfirmed COVID-19 were excluded. Third, we did not define the criteria for chronic receipt of ACEIs/ARBs. Insufficient description was available to distinguish between study participants, which is likely a factor associated with the increased heterogeneity observed in the study. With these limitations in mind, there were no data indicating that the receipt of ACEIs/ARBs was associated with harm if patients subsequently contracted COVID-19; on the contrary, ACEIs/ARBs may be associated with substantial protective benefits.

Conclusions

This comprehensive systematic review and meta-analysis of 52 studies indicated no higher risks of multivariable-adjusted mortality or severe AEs associated with the receipt of ACEIs/ARBs, which is consistent with recommendations for the continuation of these medications among patients for whom they are prescribed for the treatment of any condition. On the contrary, ACEIs and ARBs may be associated with protective benefits, particularly among patients with hypertension. Future randomized clinical trials are warranted to confirm the beneficial implications of these medications.

ARTICLE INFORMATION

Accepted for Publication: February 7, 2021.

Published: March 31, 2021. doi:10.1001/jamanetworkopen.2021.3594

Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2021 Baral R et al. *JAMA Network Open*.

Corresponding Author: Vassilios S. Vassiliou, MBBS, PhD, Associate Professor, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich NR4 7UQ, United Kingdom (v.vassiliou@uea.ac.uk).

Author Affiliations: Department of Cardiology, Norfolk and Norwich University Hospital, Norwich, United Kingdom (Baral, Tsampasian, Debski, Garg, Vassiliou); Department of Cardiology, Norwich Medical School, University of East Anglia, Norwich, United Kingdom (Baral, Garg, Vassiliou); National Health Service 111 COVID-19 Clinical Assessment Service, Bicester, United Kingdom (Moran); Neasden Medical Centre, London, United Kingdom (Moran); Healix International, Esher, United Kingdom (Moran); Department of Medical Statistics, Norwich Medical School, University of East Anglia, Norwich, United Kingdom (Clark).

Author Contributions: Drs Baral and Tsampasian had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Baral and Tsampasian contributed equally.

Concept and design: Baral, Moran, Garg, Vassiliou.

Acquisition, analysis, or interpretation of data: Baral, Tsampasian, Debski, Clark, Vassiliou.

Drafting of the manuscript: Baral, Tsampasian, Clark, Vassiliou.

Critical revision of the manuscript for important intellectual content: Baral, Tsampasian, Debski, Moran, Garg, Vassiliou.

Statistical analysis: Baral, Tsampasian, Clark.

Obtained funding: Vassiliou.

Administrative, technical, or material support: Baral, Tsampasian.

Supervision: Garg, Vassiliou.

Conflict of Interest Disclosures: Dr Vassiliou reported receiving grants from the Norfolk Heart Trust and personal fees from Daiichi Sankyo and Novartis outside the submitted work. No other disclosures were reported.

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

REFERENCES

1. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. Updated February 13, 2021. Accessed January 18, 2021. https://covid19.who.int/

2. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811-818. doi:10.1001/jamacardio.2020.1017

3. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-538. doi:10.1007/s00392-020-01626-9

4. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med*. 2020;201(11):1380-1388 doi:10.1164/rccm.202002-0445OC .

5. Selcuk M, Cınar T, Keskin M, et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? *Clin Exp Hypertens*. 2020;42(8):738-742. doi:10.1080/10641963.2020.1783549

6. Mehta N, Kalra A, Nowacki AS, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1020-1026. doi:10.1001/jamacardio.2020.1855

7. Bravi F, Flacco ME, Carradori T, et al. Predictors of severe or lethal COVID-19, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, in a sample of infected Italian citizens. *PLoS One*. 2020;15 (6):e0235248. doi:10.1371/journal.pone.0235248

8. Zhou X, Zhu J, Xu T. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin-angiotensin system inhibitors. *Clin Exp Hypertens*. 2020;42(7):656-660. doi:10.1080/10641963.2020.1764018

9. Felice C, Nardin C, Di Tanna GL, et al. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens*. 2020;33(10):944-948. doi:10.1093/ajh/hpaa096

10. Zhou F, Liu YM, Xie J, et al. Comparative impacts of ACE (angiotensin-converting enzyme) inhibitors versus angiotensin II receptor blockers on the risk of COVID-19 mortality. *Hypertension*. 2020;76(2):e15-e17. doi:10.1161/HYPERTENSIONAHA.120.15622

11. Baral R, White M, Vassiliou VS. Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. *Curr Atheroscler Rep*. 2020;22(10):61. doi:10.1007/s11883-020-00880-6

12. World Health Organization. COVID-19 and the use of angiotensin-converting enzyme inhibitors and receptor blockers: scientific brief. May 7, 2020. Accessed October 20, 2020. https://www.who.int/news-room/commentaries/detail/covid-19-and-the-use-of-angiotensin-converting-enzyme-inhibitors-and-receptor-blockers

13. 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(13):1239-1242. doi:10.1001/jama.2020.2648

14. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute; 2019. Accessed October 20, 2020. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

15. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898

16. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49(5):1-15. doi:10.18637/jss.v049.i05

17. Higgins JPT, Li T, Deeks JJ. Chapter 6: choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.1. Cochrane; 2020. Accessed October 20, 2020. https://training.cochrane.org/handbook/current/chapter-06

18. Amat-Santos IJ, Santos-Martinez S, Lopez-Otero D, et al. Ramipril in high-risk patients with COVID-19. *J Am Coll Cardiol*. 2020;76(3):268-276. doi:10.1016/j.jacc.2020.05.040

19. Conversano A, Melillo F, Napolano A, et al. Renin-angiotensin-aldosterone system inhibitors and outcome in patients with SARS-CoV-2 pneumonia: a case series study. *Hypertension*. 2020;76(2):e10-e12. doi:10.1161/HYPERTENSIONAHA

20. Bae DJ, Tehrani DM, Rabadia SV, et al. Angiotensin converting enzyme inhibitor and angiotensin II receptor blocker use among outpatients diagnosed with COVID-19. *Am J Cardiol*. 2020;132:150-157. doi:10.1016/j.amjcard.2020.07.007

21. Bean DM, Kraljevic Z, Searle T, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. *Eur J Heart Fail*. 2020;22(6):967-974. doi:10.1002/ejhf.1924

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

22. Cannata F, Chiarito M, Reimers B, et al. Continuation versus discontinuation of ACE inhibitors or angiotensin II receptor blockers in COVID-19: effects on blood pressure control and mortality. *Eur Heart J Cardiovasc Pharmacother*. 2020:6(6):412-414. doi:10.1093/ehjcvp/pvaa056

23. Chen C, Wang F, Chen P, et al. Mortality and pre-hospitalization use of renin-angiotensin system inhibitors in hypertensive COVID-19 patients. *J Am Heart Assoc*. 2020;9(21):e017736. doi:10.1161/JAHA.120.017736

24. Chen FF, Zhong M, Liu Y, et al. The characteristics and outcomes of 681 severe cases with COVID-19 in China. *J Crit Care*. 2020;60:32-37. doi:10.1016/j.jcrc.2020.07.003

25. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care*. 2020;43(7):1399-1407. doi:10.2337/dc20-0660

26. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart*. 2020;106(19):1503-1511. doi:10.1136/heartjnl-2020-317393

27. Fosbol EL, Butt JH, Ostergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA*. 2020;324(2):168-177. doi:10.1001/jama.2020.11301

28. Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J*. 2020;41(22):2058-2066. doi:10.1093/eurheartj/ehaa433

29. Gormez S, Ekicibasi E, Degirmencioglu A, et al. Association between renin-angiotensin-aldosterone system inhibitor treatment, neutrophil-lymphocyte ratio, D-dimer and clinical severity of COVID-19 in hospitalized patients: a multicenter, observational study. *J Hum Hypertens*. 2020:1-10. doi:10.1038/s41371-020-00405-3

30. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345-1355. doi:10.1001/jamainternmed.2020.3539

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(2):e13-e14. doi:10.1161/HYPERTENSIONAHA.120.15572

32. Huang Z, Cao J, Yao Y, et al. The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension. *Ann Transl Med*. 2020;8(7):430. doi:10.21037/atm.2020.03.229

33. Hwang JM, Kim JH, Park JS, Chang MC, Park D. Neurological diseases as mortality predictive factors for patients with COVID-19: a retrospective cohort study. *Neurol Sci*. 2020;41(9):2317-2324. doi:10.1007/s10072-020-04541-z

34. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M; SARS-RAS Investigators. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of Hypertension. *Hypertension*. 2020;76(2):366-372. doi:10.1161/HYPERTENSIONAHA.120.15324

35. Jung C, Bruno RR, Wernly B, et al. Inhibitors of the renin–angiotensin–aldosterone system and COVID-19 in critically ill elderly patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(1):76-77. doi:10.1093/ehjcvp/pvaa083

36. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system inhibitors with coronavirus disease 2019 (COVID-19)–related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis*. 2020;71(16):2121-2128. doi:10.1093/cid/ciaa624

37. Khan KS, Reed-Embleton H, Lewis J, Bain P, Mahmud S. Angiotensin converting enzyme inhibitors do not increase the risk of poor outcomes in COVID-19 disease: a multi-centre observational study. *Scott Med J*. 2020;65(4):149-153. doi:10.1177/0036933020951926

38. Lam KW, Chow KW, Vo J, et al. Continued in-hospital angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use in hypertensive COVID-19 patients is associated with positive clinical outcome. *J Infect Dis*. 2020;222(8):1256-1264. doi:10.1093/infdis/jiaa447

39. 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):825-830. doi:10.1001/jamacardio.2020.1624

40. Liabeuf S, Moragny J, Bennis Y, et al. Association between renin–angiotensin system inhibitors and COVID-19 complications. *Eur Heart J Cardiovasc Pharmacother*. Published online June 12, 2020. doi:10.1093/ehjcvp/pvaa062

41. Liu X, Liu Y, Chen K, et al. Efficacy of ACEIs/ARBs vs CCBs on the progression of COVID-19 patients with hypertension in Wuhan: a hospital-based retrospective cohort study. *J Med Virol*. 2021;93(2):854-862. doi:10.1002/jmv.26315

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

42. Lopez-Otero D, Lopez-Pais J, Cacho-Antonio CE, et al. Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a Western population. *Rev Espanola Cardiol*. 2020;74(2):175-182. doi:10.1016/j.rec.2020.05.018

43. 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):2431-2440. doi:10.1056/NEJMoa2006923

44. Matsuzawa Y, Ogawa H, Kimura K, et al. Renin-angiotensin system inhibitors and the severity of coronavirus disease 2019 in Kanagawa, Japan: a retrospective cohort study. *Hypertens Res*. 2020;43(11):1257-1266. doi:10.1038/s41440-020-00535-8

45. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect*. 2020;9(1):757-760. doi:10.1080/22221751.2020.1746200

46. Mostaza JM, Garcia-Iglesias F, Gonzalez-Alegre T, et al; Carlos III COVID Working Group. Clinical course and prognostic factors of COVID-19 infection in an elderly hospitalized population. *Arch Gerontol Geriatr*. 2020;91:104204. doi:10.1016/j.archger.2020.104204

47. Oussalah A, Gleye S, Urmes IC, 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 northeast of France. *Clin Infect Dis*. 2020;71(9):2447-2456. doi:10.1093/cid/ciaa677

48. Pan W, Zhang J, Wang M, 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):732-741. doi:10.1161/HYPERTENSIONAHA.120.15289

49. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–angiotensin–aldosterone system inhibitors and risk of COVID-19. *N Engl J Med*. 2020;382(25):2441-2448. doi:10.1056/NEJMoa2008975

50. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052-2059. doi:10.1001/jama.2020.6775

51. Rossi PG, Marino M, Formisano D, Venturelli F, Vicentini M, Grilli R; Reggio Emilia COVID-19 Working Group. Characteristics and outcomes of a cohort of COVID-19 patients in the province of Reggio Emilia, Italy. *PLoS One*. 2020;15(8):e0238281. doi:10.1371/journal.pone.0238281

52. Sardu C, Maggi P, Messina 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*. 2020;9(17):e016948. doi:10.1161/JAHA.120.016948

53. Senkal N, Meral R, Medetalibeyoqlu A, Konyaoqlu H, Kose M, Tukek T. Association between chronic ACE inhibitor exposure and decreased odds of severe disease in patients with COVID-19. *Anatol J Cardiol*. 2020;24(1):21-29. doi:10.14744/AnatolJCardiol.2020.57431

54. Shah P, Owens J, Franklin J, Jani Y, Kumar A, Doshi R. Baseline use of angiotensin-converting enzyme inhibitor/AT1 blocker and outcomes in hospitalized coronavirus disease 2019 African-American patients. *J Hypertens*. 2020;38(12):2537-2541. doi:10.1097/HJH.0000000000002584

55. Tan ND, Qiu Y, Xing XB, Ghosh S, Chen MH, Mao R. Associations between angiotensin-converting enzyme inhibitors and angiotensin II receptor blocker use, gastrointestinal symptoms, and mortality among patients with COVID-19. *Gastroenterology*. 2020;159(3):1170-1172. doi:10.1053/j.gastro.2020.05.034

56. Tedeschi S, Giannella M, Bartoletti M, et al. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for coronavirus disease 2019. *Clin Infect Dis*. 2020;71(15):899-901. doi:10.1093/cid/ciaa492

57. Trifiro G, Massari M, Da Cas R, et al; ITA-COVID-19: RAAS Inhibitor Group. Renin-angiotensin-aldosterone system inhibitors and risk of death in patients hospitalised with COVID-19: a retrospective Italian cohort study of 43,000 patients. *Drug Saf*. 2020;43(12):1297-1308. doi:10.1007/s40264-020-00994-5

58. Xu J, Huang C, Fan G, et al. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in context of COVID-19 outbreak: a retrospective analysis. *Front Med*. 2020;14(5):601-612. doi:10.1007/s11684-020-0800-y

59. Yang G, Tan Z, Zhou L, et al. Effects of angiotensin II receptor blockers and ACE (angiotensin-converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study. *Hypertension*. 2020;76(1):51-58. doi:10.1161/HYPERTENSIONAHA.120.15143

60. Yuan Y, Liu D, Zeng S, et al. In-hospital use of ACEI/ARB is associated with lower risk of mortality and critic illness in COVID-19 patients with hypertension. *J Infect*. 2020:81(5):816-846. doi:10.1016/j.jinf.2020.08.014

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021

61. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126(12):1671-1681. doi:10.1161/CIRCRESAHA.120.317134

62. Peng YD, Meng K, Guan HQ, et al. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48(6):450-455. doi:10.3760/cma.j.cn112148-20200220-00105

63. de Abajo FJ, Rodriguez-Martin S, Lerma V, et al; MED-ACE2-COVID19 Study Group. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet*. 2020;395(10238):1705-1714. doi:10.1016/S0140-6736(20)31030-8

64. Hu J, Zhang X, Zhang X, et al. COVID-19 is more severe in patients with hypertension; ACEI/ARB treatment does not influence clinical severity and outcome. *J Infect*. 2020;81(6):979-997. doi:10.1016/j.jinf.2020.05.056

65. Yan H, Valdes AM, Vijay A, et al. Role of drugs affecting the renin-angiotensin-aldosterone system on susceptibility and severity of COVID-19: a large case-control study from Zheijang Province, China. *medRxiv*. Preprint posted online April 29, 2020. doi:10.1101/2020.04.24.20077875

66. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J*. 2020;41(19):1798-1800. doi:10.1093/eurheartj/ehaa231

67. Barochiner J, Martinez 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):1244-1252. doi:10.1111/jcpt.13246

68. Kreutz R, Algharably EAE, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res*. 2020;116(10):1688-1699. doi:10.1093/cvr/cvaa097

69. Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. *Am J Hypertens*. 2015;28(1):15-21. doi:10.1093/ajh/hpu086

70. de Simone G. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. European Society of Cardiology; 2020. Accessed May 25, 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang

71. Bozkurt B, Kovacs R, Harrington B. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. American College of Cardiology; 2020. Accessed May 3, 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19

72. Kreutz R, Januszewicz A. Letter on the COVID-19 pandemic from the president of the European Society of Hypertension. April 7, 2020. Accessed May 25, 2020. https://www.eshonline.org/esh-content/uploads/2020/06/ESH-LETTER-COVID-19-by-ESH-President-and-Secretary-April-7-2020.pdf

SUPPLEMENT.

eMethods. Search Strategy in PubMed
eTable. Quality Assessment of Included Clinical Trials: Newcastle Ottawa Scale for Nonrandomized Clinical Trials and Cochrane Collaboration Tool for Assessing Risk of Bias in Randomized Clinical Trials
eFigure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram of the Clinical Trial Selection Process
eFigure 2. Funnel Plot for Unadjusted Critical or Fatal Outcomes for Patients With COVID-19 Receiving ACEIs or ARBs
eFigure 3. Funnel Plot for Unadjusted Death for Patients With COVID-19 Receiving ACEIs or ARBs
eFigure 4. Sensitivity Analysis Excluding Studies Reporting Hazard Ratios for Critical or Fatal Outcomes
eFigure 5. Sensitivity Analysis Excluding Studies Reporting Hazard Ratios for Mortality Outcomes
eFigure 6. Subgroup Analysis of Studies With Moderate or High Quality for Adjusted Critical or Fatal Outcomes

Downloaded From: https://jamanetwork.com/ by Frida Plavnik on 04/22/2021