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Renin—angiotensin-system inhibitors and all-cause mortality in patients with COVID-19: a systematic review and meta-analysis of observational studies

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Abstract

Aims: We sought to evaluate the association of angiotensin-converting-enzyme inhibitors (ACEI) or AT1 blockers (ARB) therapy with clinical outcomes in patients with coronavirus disease 2019 (COVID-19).

Methods and results: Electronic databases were searched to identify published studies that reported clinical outcomes in patients with COVID-19 who were or were not taking an ACEI/ARB. We studied all-cause mortality and/or severe disease outcomes. Fully adjusted effect estimates from individual studies were pooled using a random-effects model. In total, 34 (31 cohort-based and three case–control) studies met our eligibility criteria. Due to the inherent differences between cohort and case–control studies, we did not combine results of these studies but used them to identify the consistency of their results. The 31 cohort studies provided outcome data for 87 951 patients with COVID-19, of whom 22 383/83 963 (26.7%) were on ACEI/ARB therapy. In pooled analysis, we found no association between the use of ACEI/ARB and all-cause mortality/severe disease [relative risk: 0.94, 95% confidence interval (CI): 0.86–1.03, I^2 = 57%, P = 0.20] or occurrence of severe disease (relative risk: 0.93, 95% CI: 20.74–1.17, I^2 = 56%, P = 0.55). Analysis of three population-based case–control studies identified no significant association between ACEI/ARB (pooled odds ratio: 1.00, 95% CI: 0.81–1.23, I^2 = 0, P = 0.98) and all-cause mortality/severe disease. In 13 of the 31 cohort studies as well as in three case–control studies that reported outcomes separately for ACEI and ARB, there was no differential effect for mortality/severe disease outcomes.

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Conclusion: In patients with COVID-19, we found no association between ACEI/ARB treatment and mortality/severe disease. ACEI/ARB should not be discontinued, unless clinically indicated.

Keywords

coronavirus disease 2019; mortality; renin-angiotensin-system inhibitors; severe disease

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19), uses the angiotensin-converting enzyme-2 (ACE2) receptors for entry into target cells. The same receptor plays an important mechanistic role in regulating the human renin–angiotensin–aldosterone system. Because angiotensin-converting-enzyme inhibitors (ACEI) and AT1 blockers (ARB) may upregulate ACE2 expression, there has been intense debate regarding whether use of ACEI or ARB (ACEI/ARB) is associated with clinical outcomes in patients with COVID-19 [1,2]. It is important to address this controversy because comorbidities such as hypertension, diabetes and cardiovascular disease are highly prevalent in patients with COVID-19 [3] and ACEI/ARB are one of the most common medications for management of these conditions. Many professional societies have recommended continuation of ACEI/ARB therapy unless cessation is clinically indicated but have called for additional research. Recently, several reports of the association between ACEI/ARB use and COVID-19 outcomes have been published, with conflicting results. To provide the most reliable clinical guidance, we conducted a comprehensive systemic review and meta-analysis of studies that have published relevant information on this topic and obtained additional data from a recently published population-based case–control study [4].

METHODS

The study protocol was registered (CRD42020185115) with the PROSPERO, the international database of prospectively registered systematic reviews (managed by the Center for Reviews and Dissemination). Our meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [5]. We conducted a systematic search of PubMed, Scopus and Google scholar literature from 2019 to 27 August 2020 using the following key words and Medical Subject Headings: ‘COVID-19,’ ‘coronavirus’ ‘SARS-CoV-2,’ ‘ACE inhibitors,’ ‘ARB,’ ‘angiotensin-convert-ing enzyme inhibitors,’ ‘angiotensin receptor blockers,’ ‘RAS inhibitors’ ‘renin–angiotensin system inhibitors’. No language restriction was employed (Supplement Table 1, http://links.lww.com/HJH/B554). In addition, we searched references from included studies to identify other reports that might meet our selection criteria.

Two of the authors (C.B. and F.H.M.) independently assessed search generated article titles and abstracts for potential eligibility and ultimately selected studies that reported data with regards to ACEI/ARBs use and all-cause mortality and/or severe disease outcomes in patients with COVID-19. To minimize the effect of confounding, we selected only

those studies that reported adjusted effect estimates for ACEI/ARBs and outcomes. Our primary outcome was all-cause mortality/severe disease, but we also evaluated occurrence of severe disease as a secondary outcome. The outcome of all-cause mortality/severe disease includes either all-cause mortality or combined outcome of all-cause mortality or severe disease, if the study didn't report mortality as a separate outcome. The outcome of severe disease includes admission to the ICU, need for mechanical ventilation or as defined in the individual study. Data were extracted using a standardized protocol and reporting form. The following information was obtained: study characteristics (study authors, publication year, country of origin, sample size, study design and follow-up duration), number of patients on ACEI/ARBs, main study outcomes (all-cause mortality, severe disease), reported adjusted effect estimates. We also extracted information about the variables used for adjustment in multivariable analysis from selected studies (Supplement Table 2, http://links.lww.com/HJH/B554). Study quality was assessed by use of the Newcastle-Ottawa scale with quality grades assigned based on the following three domains: selection of the study groups, comparability and assessment of outcomes.

Pooled analysis was performed using a random-effects model, which takes into account variance between and within studies. As reported by individual cohort studies, relative risk (RR), odds ratio (OR) or hazards ratio from multivariable or propensity-matched analysis were combined to estimate pooled RR. We transformed each study's effect estimates and their confidence intervals (CIs) to natural logarithms to stabilize the variances [6]. Maximally adjusted risk estimates were used for the pooled analysis. Heterogeneity among the studies was assessed using the Higgins and Thompson I^2 statistic. The I^2 describes the proportion of total variation observed among the studies that is attributable to differences between studies rather than sampling error (chance), with I^2 values corresponding to the following levels of heterogeneity: low (<25%), moderate (25–75%) and high (>75%). We performed sensitivity analyses using a more conservative Hartung–Knapp–Sidik–Jonkman model for random-effects meta-analysis [7]. Publication bias was tested using the Begg and Mazumdar's rank correlation test and visual inspection of a funnel plot. The Duval and Tweedie nonparametric trim-and-fill method [8] was used to further assess the possible effect of publication bias in our meta-analysis.

The three case–control studies by Mancia *et al.* [4], Son *et al.* [9] and de Abajo et al. [10] was used to provide corresponding population-based information by comparing ACEI/ARB treatment in patients with COVID-19 who had mortality/severe disease outcome and population-based matched controls. Adjusted ORs for the association between ACEI/ARB, ACEI, and ARB and all-cause mortality/severe disease were used in this meta-analysis. Due to the inherent differences between cohort and case–control studies, we did not combine the results of these studies but used them to identify the consistency of their results. A two-tailed P less than 0.05 was considered statistically significant for all analyses. All analyses were performed using Stata statistical software, version 16 (StataCorp, College Station, Texas, USA).

RESULTS

Based on the selection criteria, 34 observational (31 cohort-based and three case–control) studies [4,9–41] were included in this systematic review (Table 1). The 31 cohort studies [11–41] included a total of 87 951 patients with COVID-19, 22 383/83 963 (26.7%) of whom were being treated with an ACEI/ARB. Twelve studies were conducted in Asia, 13 in Europe and six studies were from the North America continent. 25 studies reported all-cause mortality [11,12,14–18,20–22,24–30,32–37,39,40] while six studies [13,19,23,31,38,41] reported a combined outcome of all-cause mortality and severe disease. All the studies were of good to fair quality signifying a low-to-moderate risk for bias (Supplement Table 2, http://links.lww.com/HJH/B554).

In a pooled analysis of the 31 cohort studies [11–41], there was no association between the use of ACEI/ARB and all-cause mortality/severe disease (RR: 0.94, 95% CI: 0.86–1.03, $P = 0.20$) (Fig. 1). Moderate heterogeneity was observed in the analysis ($I^2 = 57\%$). Sensitivity analysis using a conservative Hartung–Knapp–Sidik–Jonkman random-effects model yielded similar results. Meta-analysis of studies reporting RR or ORs and those reporting hazards ratios as effect estimates, also showed consistent results (Table 2). Subgroup analysis by sample size at least 1000 patients and by location of study (Asia, Europe, North America) also showed no association between ACEI/ARBs and all-cause mortality/severe disease. No publication bias was observed on visual inspection of funnel plot or using Egger's regression test ($P = 0.09$) or Begg's rank correlation test ($P = 0.55$). On recalculating pooled risk estimate using nonparametric Trim-and-Fill method and imputing seven studies, the overall RR (0.99, 95% CI: 0.90–1.09) remained nonsignificant (Supplement Fig. 1, http://links.lww.com/HJH/B554). Fifteen of the 31 cohort studies [11,18–21,24–28,30,32–34,39] reported on the association between ACEI/ARB use and occurrence of severe disease. We found no association between use of ACEI/ARBs and severe disease (pooled RR: 0.93, 95% CI: 0.74–1.17, $P = 0.55$, $I^2 = 56\%$) (Fig. 2).

We performed a separate analysis to evaluate whether there was any evidence of a differential effect of ACEI or ARB on the study outcomes. 13 of the 31 cohort studies [13,16,17,20,21,23,26,27,29,31,34,39,40] reported outcomes separately for ACEI and ARB. Eleven of these studies reported all-cause mortality, one while the other two studies [13,31] reported a combined outcome of all-cause mortality and severe disease. In pooled analysis, there was no association between ACEI (RR: 0.99, 95% CI: 0.87–1.12, $I^2 = 30\%$, $P = 0.85$) or ARB (RR: 0.88, 95% CI: 0.73–1.05, $I^2 = 64\%$, $P = 0.16$) for all-cause mortality/severe disease compared with controls (Figs. 3 and 4).

Case–control studies

The three population-based case–control studies [4,9,10] compared 882 patients and 6144 matched controls for outcome of all-cause mortality/severe disease. Two studies [4,9] provided data on all-cause mortality while one study [10] reported combined endpoint of all-cause mortality/severe disease. The pooled adjusted ORs provided no evidence of a significant independent association between all-cause mortality/severe disease and treatment with ACEI/ARB (OR: 1.00, 95% CI: 0.81–1.23), or monotherapy with either ACEI (OR: 0.85, 95% CI: 0.68–1.06) or ARB (OR: 1.12, 95% CI: 0.70–1.78).

DISCUSSION

In this comprehensive systemic review and meta-analysis, we studied the relationship between ACEI and/or ARB and all-cause mortality as well as occurrence of severe disease in patients with COVID-19. We found no association for use of ACEI/ARBs and all-cause mortality/severe disease, overall or in the studies that also reported outcomes separately. The corresponding results in the three population-based case–control studies were consistent with those identified in the cohort meta-analysis.

Infection with SARS-CoV-2 is responsible for the ongoing COVID-19 pandemic. The virus enters human cells by attaching itself to the ACE2 receptor. Both animal and human studies have shown that treatment with an ACEI or ARB increases the expression of ACE2. Based on this, some researchers [42,43] have speculated that use of ACEI/ARB may not only predispose to an increased risk of COVID-19 but can be associated with worse outcomes in patients with COVID-19. In contrast, others [44,45] have postulated that the increased ACE2 expression enhances the degradation of angiotensin II and mitigates some of the risks associated with COVID-19. This concept is supported by findings from several observational studies [46–48] that have identified a reduction in the risk of influenza, pneumonia and pneumonia-related mortality in patients treated with an ACEI/ARB.

In the population-based case–control study by Mancia *et al.* [4], an overall multivariate adjusted analysis that compared treatment in 6272 cases and 30 759 matched controls, identified no significant association between use of either ACEI (OR: 0.96, 0.87–1.07) or ARB (OR: 0.95, 0.86–1.05) and COVID-19. This and other reports [13,49] suggest that there is no evidence of an independent relationship between renin–angiotensin–system inhibitors and susceptibility to COVID-19. Furthermore, our meta-analysis found no association between treatment with an ACEI or ARB and an increased likelihood of mortality or severe disease in patients with COVID-19.

The most common comorbidities in patients with COVID-19 are hypertension and diabetes. Patients with hypertension also appear to have increased risk for COVID-19 and risk for complications including mortality [50]. However, it is unclear if the increased risk is due to hypertension and its pathophysiologic effects or because patients with hypertension tend to be older and have increased burden of other comorbidities such as diabetes, cardiovascular disease, kidney diseases. Furthermore, ACEI/ARBs, commonly used in treatment of hypertension, also interact with ACE2 receptors, leading to a complex interplay between renin–angiotensin system, and COVID-19. Considering the controversy related to ACEI/ARB treatment in patients with COVID-19, with some researchers [42,43] even recommending stopping their use due to risk for harm, the results of our meta-analysis are reassuring. Our findings are consistent with the advice from several professional societies to continue ACEI/ARB therapy in patients with COVID-19 unless cessation is clinically indicated [1]. The current state of knowledge was summarized by Jarcho et al. [51] in an editorial that accompanied the publication of simultaneous studies [4,13] ‘Taken together, these three studies do not provide evidence to support the hypothesis that ACE inhibitor or ARB use is associated with the risk of SARS-CoV-2 infection, the risk of severe COVID-19 among those infected, or the risk of in-hospital death among those with a positive test’.

However, the potential pleiotropic and salutary effects of ACEI/ARB treatment in patients with COVID-19 remains intriguing [2]. Several randomized controlled trials designed to study the effect of inhibitors of renin–angiotensin–aldosterone system in COVID-19 are in progress, although none of them are powered to assess an ACEI/ARB effect on mortality outcomes.

It is uncertain whether there is any differential effect of ACEI and ARBs on outcomes in COVID-19. In a laboratory study on Lewis rats, Ferrario et al. [52] experimentally documented the ARB losartan to almost triple cardiac ACE2 activity, whereas the ACEI lisinopril had no effect. Other animal models have shown mixed findings with respect to the effects of ACEIs or ARBs on ACE2 levels or activity in tissue. We found no difference in outcome between ACEI and ARBs in the 13 of the 31 cohort studies that reported outcomes separately. If there is a difference between ACEIs and ARBs in ACE2 upregulation, it seems to be of limited importance, if any with regard to COVID-19 infectivity or its clinical course.

Limitations

Our meta-analysis has several limitations. First, like any meta-analysis of observational reports, the limitations inherent to individual studies also apply to the overall analysis. Second, although we used only adjusted effect estimates in our meta-analysis, residual confounding cannot be excluded. Although, included studies adjusted for several covariates, the adjusted variables were not consistent across the studies and not all the studies adjusted for important covariates, and hence, combined results should be interpreted with caution. Third, lack of patient-level data precluded us in evaluating some important clinical variables such as duration of ACEI/ARBs use, dosage, medication adherence and changes after infection. Fourth, we combined different risk estimates across the studies which is not ideal and may introduce bias since OR can substantially overestimate the RR if the outcome is not rare. Fifth, observational studies evaluating the efficacy and safety of medications are susceptible to selection bias and immortal-time bias. The latter may have limited relevance for our results because we did not identify a significant treatment effect.

In conclusion, in our systematic review and meta-analysis including more than 87 000 patients, we found no association between treatment with an ACEI or ARB and risk for all-cause mortality and/or severe disease in patients with COVID-19. Similar findings were identified in population-based case–control studies. ACEI or ARB should not be discontinued, unless clinically indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

G.M. reports personal fees from Bayer, Boehringer Ingelheim, CVRx, Daiichi Sankyo, Ferrer, Medtronic, Menarini Int., Merck, Novartis, Recordati, Servier, outside the submitted work. G.C. reports grants from European Community, grants from Italian Medicines Agency (AIFA), Italian Ministry of Education, University and Research (MIUR), Novartis, GSK, other from Roche, AMGEN, BMS, outside the submitted work. F.H.M. reports consulting fees from Medtronic, Daiichi Sankyo and Menarini Int. C.B., and P.K.W. report no conflicts of interest.

Abbreviations:

ACE2	angiotensin converting enzyme-2
ACEI	angiotensin-converting-enzyme inhibitors
ARB	AT1 blockers
COVID-19	coronavirus disease 2019
OR	odds ratio
RR	relative risk

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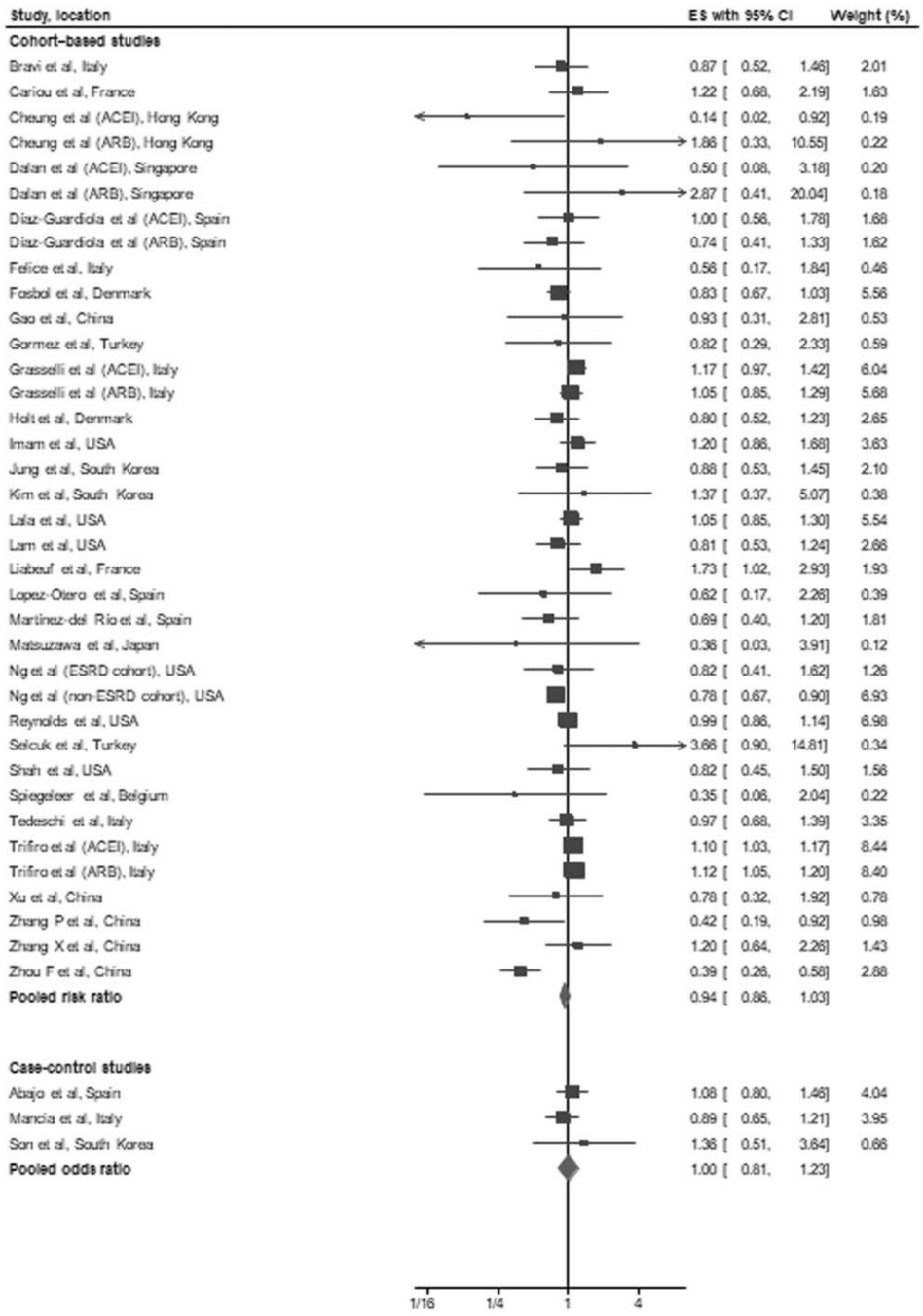

FIGURE 1.

Forest plot of the association between treatment with an angiotensin-converting-enzyme inhibitors and/or AT1 blockers and all-cause mortality/severe disease in patients with coronavirus disease 2019. The figure shows effect estimates of outcomes (boxes) with 95% confidence limits (bars) for each study selected; pooled relative risk for cohort studies and pooled odds ratio for case–control studies is represented by a diamond in this forest plot. The confidence intervals for some studies may differ slightly due to log transformation of all

effect estimates. ACEI, angiotensin-converting enzyme inhibitors; ARB; AT1 blockers; CI; confidence interval; ES; effect estimates.

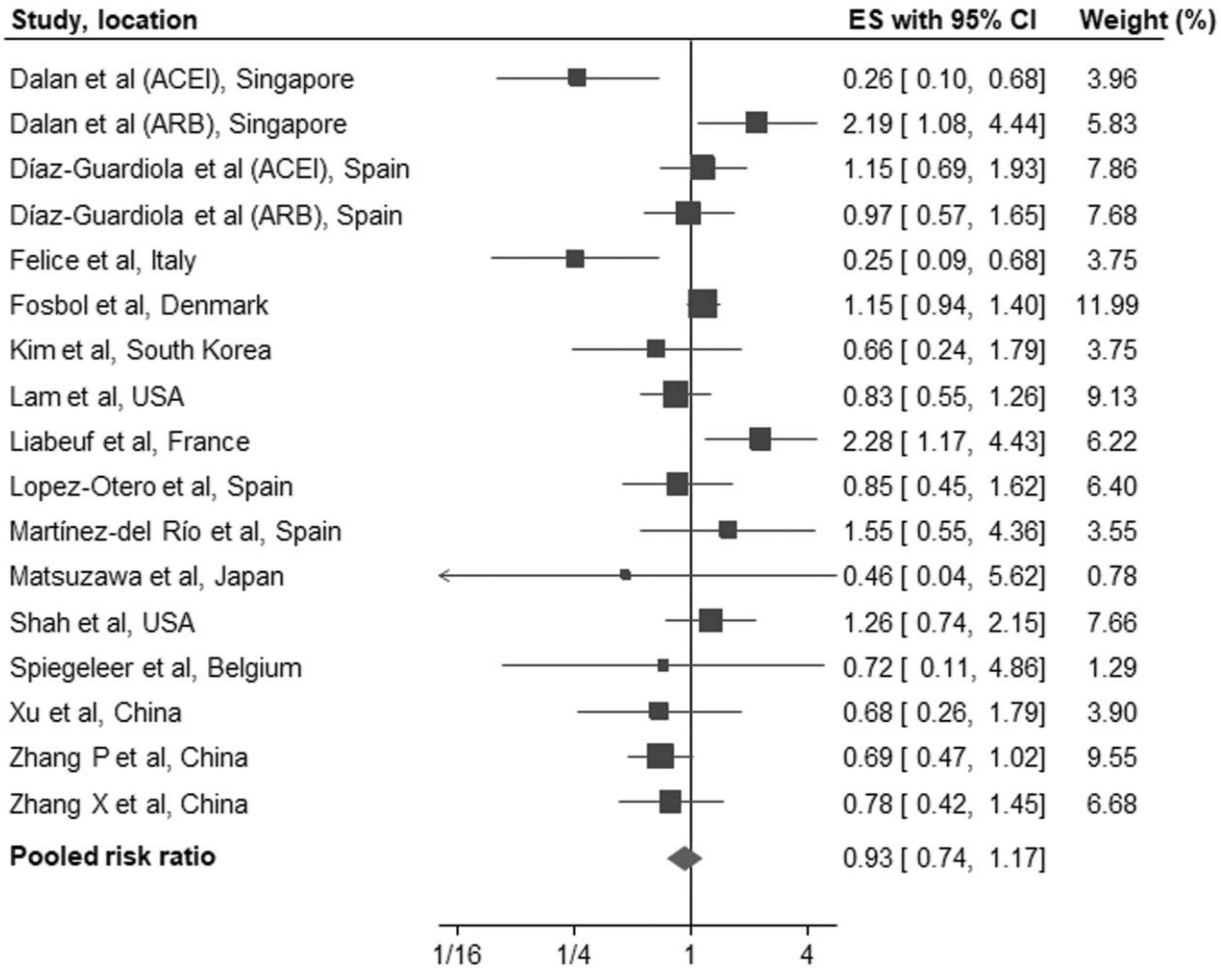

FIGURE 2.

Forest plot of the association between treatment with an angiotensin-converting-enzyme inhibitors and/or AT1 blockers and severe disease in patients with coronavirus disease 2019. The figure shows effect estimates of outcomes (boxes) with 95% confidence limits (bars) for each study selected; pooled relative risk is represented by a diamond in this forest plot. ES, effect estimates.

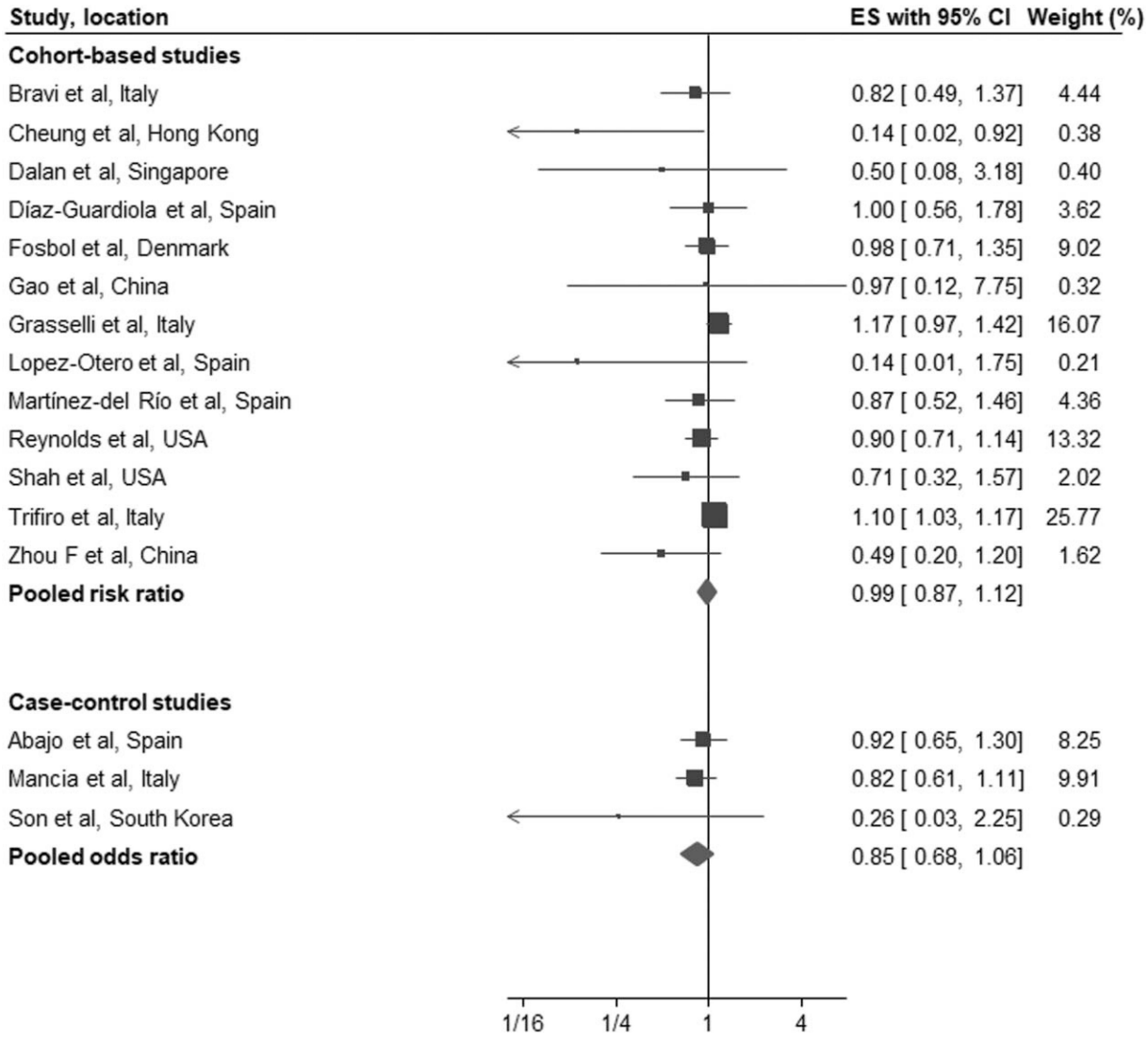

FIGURE 3.

Forest plot of the association between treatment with an angiotensin-converting-enzyme inhibitors (a) or AT1 blockers (b) and all-cause mortality/severe disease in patients with coronavirus disease 2019. ACEI, angiotensin-converting enzyme inhibitors; ARB; AT1 blockers; CI; confidence interval; ES; effect estimates.

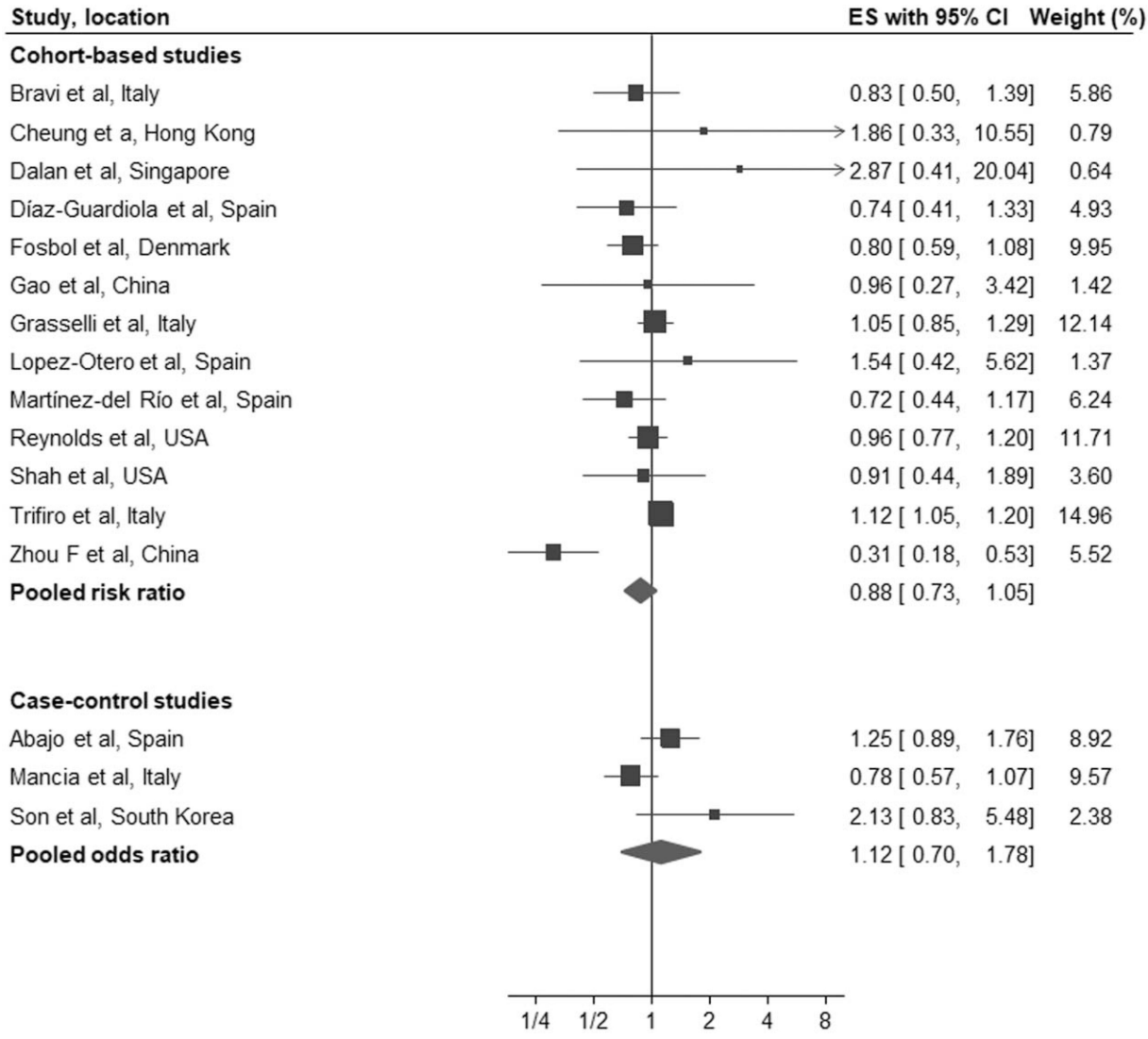

FIGURE 4.

Forest plot of the association between treatment with an AT1 blockers and all-cause mortality/severe disease in patients with coronavirus disease 2019. ACEI, angiotensin-converting enzyme inhibitors; ARB; AT1 blockers; CI; confidence interval; ES; effect estimates.

TABLE 1.

Select characteristics of studies included in the meta-analysis

Study	Study period	Region, location	Patients characteristics	Patients	ACEI or ARB, *n*	Age, male	Comorbidities	Outcomes
Cohort studies								
Zhang *et al.* [11]	31 December 2019 to 20 February 2020	Wuhan, China	In-hospital patients with COVID-19 and hypertension	1128	188	64, 53%	HTN 100% DM 21% CVD 12% CKD 3%	28-Day mortality; severe disease
Reynolds *et al.* [13]	1 March 2020 to 15 April 2020	New York, USA	Patients with COVID-19	2211[+]	1110	NR[++]	NR[++]	Combined end-point of in-hospital mortality or severe disease
Tedeschi *et al.* [12]	22 February 2020 to 4 April 2020	10 Hospitals across Italy	In-hospital patients with COVID-19 and hypertension	311	175	76, 72%	HTN 100% DM 24% CVD 42%	In-hospital mortality
Jung *et al.* [14]	Till 8 April 2020	Nationwide database, South Korea	Patients with COVID-19	5179	762	45, 44%	HTN 22% DM 17% CVD 5% CKD 5%	In-hospital mortality
Cariou *et al.* [15]	10 March 2020 to 10 April 2020	53 centers across France	In-hospital patients with COVID-19 and diabetes	1317	752	70, 65%	HTN 77% DM 100% CVD 27% CKD 33%	7-Day mortality
Zhou *et al.* [16]	31 December 2019 to 21 April 2020	Wuhan, China	In-hospital patients with COVID-19	2718[+]	906	NR[++]	NR[++]	28-Day mortality
Gao *et al.* [17]	2 February 2020 to 15 March 2020	Wuhan, China	In-hospital patients with COVID-19	710	527	64, 52%	DM 27% CVD 21% CKD 2%	In-hospital mortality
Felice *et al.* [18]	9–31 March 2020	Treviso, France	Patients with COVID-19 and hypertension referred to emergency department	133	82	73, 65%	HTN 100% DM 26% CVD 60%	In-hospital mortality; severe disease
Liabeuf *et al.* [19]	28 February 2020 to 30 March 2020	Amiens, France	In-hospital patients with COVID-19	268	96	73, 58%	HTN 57% DM 21% CVD 12% CKD 7%	Combined endpoint of in-hospital mortality or severe disease; severe disease
Fosbol *et al.* [20]	1 February 2020 to 4 May 2020	Nationwide database, Denmark	Patients with COVID-19	4480	895	50–73[a], 48%	HTN 19% DM 9% CVD 8% CKD 4%	In-hospital mortality; severe disease
Lopez-Otero *et al.* [21]	10 March 2020 to 6 April 2020	A Coruna, Spain	Patients with COVID-19	965	210	60, 44%	HTN 31% DM 13% CVD 4%	Mortality; severe disease
Selcuk *et al.* [22]	NR	Istanbul, Turkey	In-hospital patients with COVID-19 and hypertension	113	74	64, 59%	HTN 100% DM 36% CVD 28% CKD 10%	In-hospital mortality
Bravi *et al.* [23]	Til 24 April 2020	Province of Ferrara and Pescara, Italy	Patients with COVID-19 and hypertension	543	450	NR[++]	NR[++]	Combined endpoint of mortality or severe disease

Study	Study period	Region, location	Patients characteristics	Patients	ACEI or ARB, *n*	Age, male	Comorbidities	Outcomes
Xu *et al.* [24]	29 December 2019 to 15 February 2020	Wuhan, China	In-hospital patients with COVID-19 and hypertension	101	40	65, 52%	HTN 100% DM 19% CVD 13% CKD 2%	In-hospital mortality
Zhang *et al.* [25]	NR	Wuhan, China	In-hospital patients with COVID-19 and hypertension	922[b]	603	67, 51%	HTN 100% DM 36% CVD 43% CKD 6%	28-Day mortality; severe disease
Dalan *et al.* [26]	Till 15 April 2020	National Centre of Infectious diseases, Singapore	In-hospital patients with COVID-19 and hypertension	139[b]	90	NR	NR	Mortality; severe disease
Shah *et al.* [27]	2 March 2020 to 22 May 2020	Albany, Georgia, USA	In-hospital African-American patients with COVID-19	531	207	60, 41%	HTN 80% DM 43% CVD 22% CKD 15%	In-hospital mortality; severe disease
Lam *et al.* [28]	7 February 2020 to 23 May 2020	New York, USA	In-hospital patients with COVID-19 and hypertension	614	335	68–73[a], 55%	HTN 100% DM 41% CVD 24% CKD 15%	In-hospital mortality; severe disease
Holt *et al.* [41]	1 March 2020 to 1 April 2020	Denmark	In-hospital patients with COVID-19	689	225	70, 58%	NR	Combined endpoint of in-hospital mortality or severe disease
Grasselli *et al.* [29]	20 February 2020 to 22 April 2020	Lombardy, Italy	Critically ill COVID-19 patients admitted to ICU	3988	NR	63, 80%	HTN 41% DM 13% CVD 13% CKD 2%	In-hospital mortality
Kim *et al.* [30]	18 February 2020 to 31 March 2020	Daegu, South Korea	In-hospital patients with COVID-19 and diabetes	235[b]	70	68, 45%	HTN 63% DM 100% CVD 12% CKD 8%	In-hospital mortality
Cheung *et al.* [31]	1 January 2020 to 27 April 2020	Hong Kong Hospital Authority, Hong Kong	In-hospital patients with COVID-19	734	31	NR	NR	Combined endpoint of mortality or severe disease
De Spiegeleer *et al.* [32]	1 March 2020 to 16 April 2020	Belgium	Nursing home residents with COVID-19	154	30	86, 33%	HTN 18% DM 25%	14-Day mortality (in-hospital or nursing home)
Matsuzawa *et al.* [33]	1 February 2020 to 1 May 2020	Kanagawa Prefecture, Japan	In-hospital patients with COVID-19	151	22	60, 60%	HTN 26% DM 21% CVD 2% CKD 3%	In-hospital mortality; severe disease
Martínez-del Río *et al.* [34]	1 March 2020 to 30 April 2020	Ciudad Real, Spain	In-hospital patients with COVID-19	921	400	70, 54%	HTN 59% DM 21% CVD 16%	In-hospital mortality; severe disease
Lala *et al.* [35]	27 February to 12 April 2020	New York, USA	In-hospital patients with COVID-19	2736	601	66, 60%	HTN 39% DM 26% CVD 17% CKD 10%	In-hospital mortality
Imam *et al.* [36]	1 March 2020 to 17 April 2020	Michigan, USA	In-hospital patients with COVID-19	1305	565	61, 54%	HTN 56% DM 30% CVD 22% CKD 18%	In-hospital mortality
Ng *et al.* [37]	1 March 2020 to 27 April 2020	New York, USA	In-hospital patients with COVID-19	10 482	3012	66, 60%	HTN 61% DM 37% CVD 10% CKD 22%	In-hospital mortality

Study	Study period	Region, location	Patients characteristics	Patients	ACEI or ARB, *n*	Age, male	Comorbidities	Outcomes
Gormez *et al.* [38]	15 March 2020 to 15 April 2020	Istanbul, Turkey	In-hospital patients with COVID-19	247	49	51, 38%	HTN 32% DM 40% CVD 10% CKD 4%	Combined endpoint of in-hospital mortality or severe disease
Díaz-Guardiola *et al.* [39]	NR	Madrid, Spain	In-hospital patients with COVID-19	1000	176	62, 55%	HTN 46% DM 19% CVD 16% CKD 8%	In-hospital mortality; severe disease
Trifiro *et al.* [40]	21 February 2020 to 21 April 2020	Lombardy, Veneto and the Reggio Emilia Local Health Unit, Italy	In-hospital patients with COVID-19	42 926	9522	69, 63	HTN 13% DM 18% CVD 17% CKD 2%	In-hospital mortality
Case–control studies[c]								
Mancia *et al.* [4]	21 February 2020 to 11 March 2020	Population-based case–control study in Lombardy region, Italy	Case: COVID-19 patients, Control: Residents ≥40 y who are beneficiaries of the Regional Health Service; Matching 1 : 5 by sex, age at index date, and municipality of residence	451 cases, 2150 matched controls	276 in cases, 1166 in controls	68, 63%	Case: CVD 30% CKD 5% Control: CVD 22% CKD 3%	Mortality
de Abajo *et al.* [10]	1–24 March 2020	Seven hospitals in Madrid	Case: COVID-19 patients requiring hospital admission, Control: from a Spanish primary health-care database; Matching 1 : 10 by sex and age	393 Cases, 3930 matched controls	215 In cases, 1592 in controls	69, 61%	Case: HTN 54% DM 27% CVD 11% CKD 8% Control: HTN 50% DM 20% CVD 8% CKD 5%	In-hospital mortality/severe disease
Son *et al.* [9]	Till 8 April 2020	Population-based case–control study in South Korea	Case: COVID-19 hypertensive patients, Control: from Korean National Health Insurance System; Matching 1 : 2 based on age, sex, region and tested hospital	38 Cases, 64 matched controls	30 In cases, 47 in controls	64, 51%	Case: DM 34% CVD 33% CKD 16% Control: DM 36% CVD 35% CKD 8%	Mortality

ACEI, angiotensin-converting enzyme inhibitors; ARB, AT1 blockers; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; NR, not reported.

[+]Sample size for propensity-matched analysis for ACEI/ARBs and mortality/severe disease.

[++]Demographics and comorbidities specific to selected sample of COVID-19 patients used for the analysis was not available.

[a]Median age in ACEI/ARB users and nonusers.

[b]Sample size for ACEI/ARBs and mortality/severe disease as reported by individual study.

[c]Age, sex and comorbidities data are with respect to overall sample of cases and control.

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TABLE 2.

Sensitivity analysis for association of angiotensin-converting enzyme inhibitor/AT1 blockers and primary endpoint of all-cause mortality/severe disease

Analyses, no. of studies	Pooled relative risk (95% CI)
Hartung–Knapp–Sidik–Jonkman model, $n = 31$	0.91 (0.78–1.07)
Studies from Asia, $n = 12$	0.74 (0.54–1.16), $I^2 = 51.1\%$
Studies from Europe, $n = 13$	1.05 (0.97–1.13), $I^2 = 30.9\%$
Studies from North America, $n = 6$	0.93 (0.82–1.06), $I^2 = 41.3\%$
Sample size < 1000, $n = 18$	0.92 (0.77–1.11), $I^2 = 11.5\%$
Sample size ≥ 1000, $n = 13$	0.95 (0.86–1.05), $I^2 = 73.3\%$
Studies reporting outcomes as odds ratio/relative risk, $n = 23$	0.91 (0.82–1.02), $I^2 = 14.3\%$
Studies reporting outcomes as hazards ratio, $n = 8$	0.98 (0.87–1.1), $I^2 = 76.8\%$

CI, confidence interval.