



Safety and Efficacy of Renin–Angiotensin–Aldosterone System Inhibitors in COVID-19 Population

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Abstract

Introduction The safety of renin–angiotensin–aldosterone system inhibitors (RAASi) among COVID-19 patients has been controversial since the onset of the pandemic.

Methods Digital databases were queried to study the safety of RAASi in COVID-19. The primary outcome of interest was mortality. The secondary outcome was seropositivity improvement/viral clearance, clinical manifestation progression, and progression to intensive care units. A random-effect model was used to compute an unadjusted odds ratio (OR).

Results A total of 49 observational studies were included in the analysis consisting of 83,269 COVID-19 patients (RAASi n = 34,691; non-RAASi n = 48,578). The mean age of the sample was 64, and 56% were males. We found that RAASi was associated with similar mortality outcomes as compared to non-RAASi groups (OR 1.07; 95% CI 0.99–1.15; $p > 0.05$). RAASi was associated with seropositivity improvement including negative RT-PCR or antibodies, (OR 0.96; 95% CI 0.93–0.99; $p < 0.05$). There was no association between RAASi versus control with progression to ICU admission (OR 0.99; 95% CI 0.79–1.23; $p > 0.05$) or higher odds of worsening of clinical manifestations (OR 1.04; 95% CI 0.97–1.11; $p > 0.05$). Metaregression analysis did not change our outcomes for effect modifiers including age, sex, comorbidities, RAASi type, or study type on outcomes.

Conclusions COVID-19 is not a contraindication to hold or discontinue RAASi as they are not associated with higher mortality or worsening symptoms. Continuation of RAASi might be associated with favorable outcomes in COVID-19, including seropositivity/viral clearance.

Keywords Renin–angiotensin–aldosterone system inhibitors · RAASi · COVID-19 · Angiotensin-converting enzyme inhibitor · ACEi · Angiotensin receptor blocker · ARB

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Key Points

RAASi of any type compared to placebo/non-RAASi does not affect mortality, severity, or ICU admissions in COVID 19 patients.

RAASi enhance viral clearance.

Age, sex, comorbidities, and RAASi type have no effect on the clinical outcomes in COVID 19 patients that are on RAASi.

1 Introduction

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV2) has affected more than 80 million individuals worldwide, with 1.7 million deaths as of December 2020 [1]. The association of renin–angiotensin–aldosterone system inhibitors (RAASi) in the pathogenesis of COVID-19 has been well documented in the literature [2]. It has been widely accepted that COVID-19 uses angiotensin-converting enzyme two receptors (ACE2) to enter the cell [3–5]. COVID-19 can have fatal outcomes among patients with baseline comorbidities, including hypertension, heart failure, end-stage renal disease, chronic kidney disease, stroke, and chronic pulmonary diseases [2]. Patients with the comorbidities mentioned above are frequently on RAASi [2]. As a result, there have been concerns regarding the unintentional effect of RAASi's on adverse outcomes in COVID-19 [2, 3]. However, several professional societies, including the International Society of Hypertension, the European Society of Hypertension, Joint American Heart Association, American College of Cardiology, and Heart Failure Society of United States, released a consensus statement supporting the continuing use of RAASi in patients [6–8].

To date, multiple meta-analyses have been conducted evaluating the association of ACEi and/or ARBs with COVID-19 outcomes [9–11]. While the results are consistent, many more extensive studies have since been conducted evaluating the effect of RAASi on many different outcomes in COVID-19 patients. Furthermore, findings from the recent BRACE CORONA trial also suggest that discontinuing RAASi does not affect the management of COVID-19 in hospitalized patients [12]. Because of this, we have designed this meta-analysis to provide an updated pooled quantitative estimate of the association between the use of RAASi and odds of COVID-19 mortality, seropositivity (SP)/viral clearance, the severity of clinical manifestations (SCM), and progression to intensive care unit (ICU).

2 Methods

The MEDLINE, PubMed, EMBASE, Cochrane Central Registry, Clinicaltrials.gov, and MedRxiv Preprint databases were queried using various combinations of medical subject headings (MeSH) to capture all studies on the safety and efficacy of RAASi in COVID-19 (Supplementary section 1). Databases were last assessed on November 14th, 2020. Two subsets of MeSH terms for COVID-19 and RAASi were combined using Boolean operators. All citations were downloaded to EndNote, and duplicates were removed. The titles and abstracts were searched for studies showing results of safety and efficacy of RAASi in COVID-19. There was no language or publication type filter applied for the search. Potentially relevant articles were read in full-text form, and desired outcomes of interest were extracted in an excel sheet. The primary outcome of interest was mortality. The secondary outcome was SP/viral clearance, SCM, and progression to ICU. The standard definitions of variables of interest are given in supplementary section 2. The inclusion criteria included any randomized trials or observational studies including patients with confirmed COVID-19 positive on oral/nasopharyngeal swab and compared the outcomes of those receiving any RAASi including ACE inhibitors or angiotensin II receptor blockers (ARBs) versus a control group with no RAASi use. Our study was conducted using MOOSE (Meta-analyses Of Observational Studies in Epidemiology) protocol and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13, 14]. The detailed search strategy is showing in the PRISMA flow diagram (Fig. 1) (Supplementary section 1).

The statistical analysis was performed using a random effect model using *meta size* in STATA to calculate Odds ratios (OR) for binary outcomes (Supplementary section 3). The summary statistics analysis was performed by using a random effect model *mean* module in STATA (Supplementary section 4). The OR of binary outcomes was combined with the studies that had data available in precomputed effect size (OR, lower confidence interval [lci], and upper confidence interval [uci]). The OR, lci, uci were pooled using *metan* in STATA. The results were considered statistically significant if the probability value (*p* value) was less than 0.05 with a 95% confidence interval (CI) not crossing 1. The test of overall effect was reported as *z*-value with the association of 95% CI. Subgroup analysis was performed based on the type of RAASi or combination regimens. Higgin I-squared (I^2) statistical model was used to assess the variations in outcomes of interest. I^2 values were divided into 0 to 25%, 25 to < 75%, and > 75% as mild, moderate, and severe heterogeneity, respectively. For outcomes with severe heterogeneity

($I^2 = > 75\%$), we performed a jackknife sensitivity analysis, where the effect on I^2 was noticed by removing one study at a time with a goal to bring to the lowest value [15] (Supplementary section 5). The publication bias was depicted graphically and numerically as forest plot and Egger’s Regression Equation (ERE) (Supplementary section 6). Meta-regression was performed to see any potential effect modifiers using random effect models for study variance and Knapp-Hartung modification. [16–18] Univariate meta regression was performed on demographics (age, sex), comorbidities (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease), the type of RAASi used, the type of study, and the following outcomes: severity, seropositivity, icu admission, and mortality (supplementary section 7). The quality of the included randomized trials was assessed using the Cochrane Quality Assessment tool, where individual studies were assessed for five different types of bias (selection, performance, detection, attrition, and reporting bias). The quality of observational studies was assessed by using Newcastle–Ottawa Scale (NOS) [19] (supplementary section 8). All statistical analysis was performed using STATA Version 16.1, College Station, TX: StataCorp LLC [20].

3 Results

3.1 Search Results

The initial search revealed 2078 numbers of articles. After excluding duplicates (n = 1589), the remaining articles were searched for the outcome of interest-based on title and abstract. After removing irrelevant items based on the title and abstract, 141 studies were deemed for full-text reading. A total of 49 numbers of articles were used in quantitative analysis [12, 21–69]. The reason for article inclusion and exclusion is shown in the PRISMA flow (Fig. 1).

3.2 Study Characteristics

A total of 49 studies with 83,269 of COVID-19 patients (RAASi n = 34,691; non-RAASi n = 48,578) were included in the study [12, 21–69]. The included study population had confirmed COVID-19 diagnosis by nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR). The mean age of the study population was 64 years, 56% were males, and the most common comorbidity or indication for RAASi was hypertension. The doses of RAASi were not presented in the majority of studies, but over 40 articles

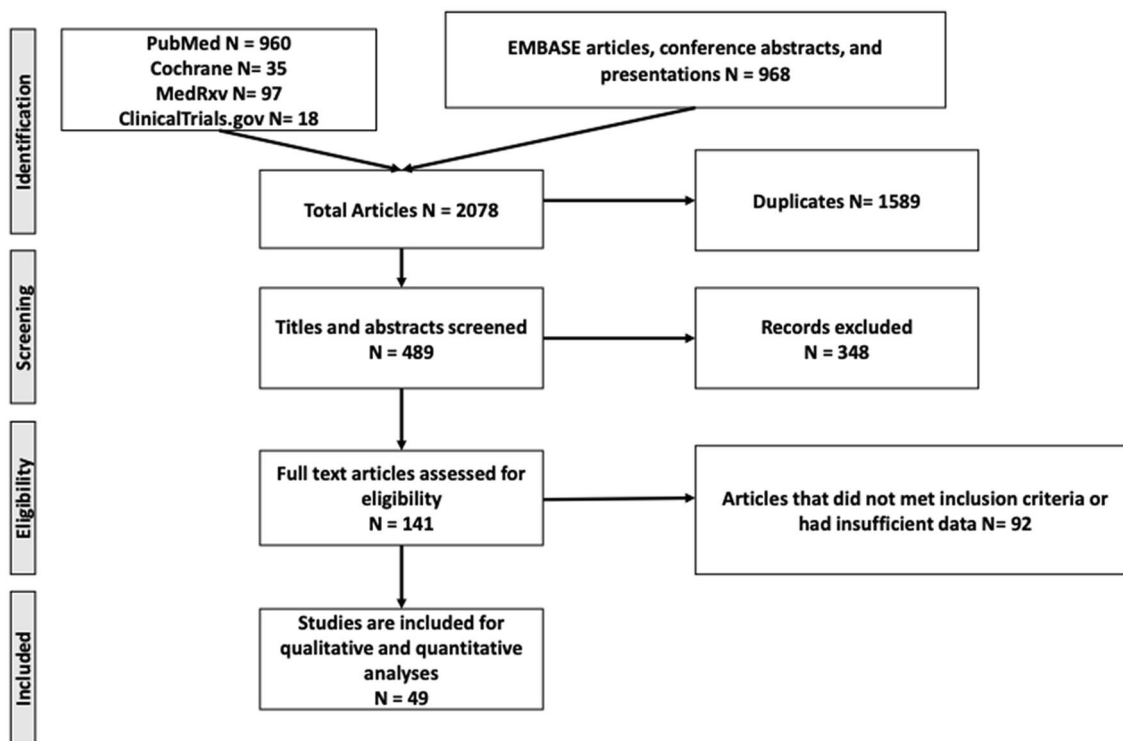


Fig. 1 PRISMA strategy for systematic review and meta-analysis

studied combined data of ACEi and ARBs while the remaining 9 studies reported data for ACEi and ARBs separately. A completed baseline demographics and comorbidities of the included studies are shown in Table 1.

All included studies were observational, including 41 retrospective and 8 prospective in total. As randomization may not be achievable in observational designs, many studies' quality may be moderate at best. However, few studies used propensity matching for subjects to attempt minimizing selection bias. Reporting bias across most of the studies was reduced due to an adequate description of the study results. The risks of bias graph and summary are shown in Supplementary section 8. Furthermore, The Newcastle–Ottawa Scale (NOS) was also utilized to evaluate the included publications' methodological quality. The NOS features eight criteria and yields scores ranging from 0 (high risk of bias) to 9 (low risk of bias). Studies with NOS scores of > 7 were regarded as high quality (Supplementary section 8). Using NOS, 13 of the studies were considered moderate or low quality.

3.3 Pooled Results

On random effect analyses, RAASi use was not associated with an increased odds of mortality as compared to non RAASi groups in COVID-19 patients (OR 1.07; 95% CI 0.99–1.15; $p > 0.05$) (32 studies, RAASi $n = 10,850$, nonRAASi $n = 14,914$; $I^2 = 67.4\%$) (Fig. 2). RAASi use was associated with seropositivity improvement, including negative RT-PCR or antibodies, (OR 0.96; 95% CI 0.93–0.99; $p < 0.05$) (14 studies, RAASi $n = 7859$, nonRAASi $n = 25,911$; $I^2 = 88.0\%$) (Fig. 2). RAASi use was not associated with worsening clinical manifestations (OR 1.04; 95% CI 0.97–1.11; $p > 0.05$) (22 studies, RAASi $n = 12,622$, nonRAASi $n = 26,450$; $I^2 = 77.2\%$) or increased odds of ICU admission (OR 0.99; 95% CI 0.79–1.23; $p > 0.05$) (6 studies, RAASi $n = 2378$, nonRAASi $n = 5188$; $I^2 = 81.0\%$) (Fig. 3).

3.4 Subgroup Analysis

A subgroup analysis (SG) was performed to delineate the results with combination of ACEi and ARBs (RAASi $n = 17,801$, nonRAASi $n = 37,817$) or lone use of ACEi or ARBs (RAASi $n = 16,890$, nonRAASi $n = 10,761$) in COVID-19 patients. The SG results were synonymous to pooled outcomes except ICU admission (ARBs OR 1.56; 95% CI 1.02–2.39; $p < 0.05$) (6 studies, ACEi or ARB $n = 144$, ACEi + ARB $n = 2234$), and seropositivity conversion (ACEi OR 0.96; 95% CI 0.73–1.26; $p > 0.05$ and ARBs OR 1.21; 95% CI 0.96–1.53; $p > 0.05$) (14 studies, ACEi or ARB $n = 278$, ACEi + ARB $n = 7581$) as compared to combination of ARBs and ACEi (Supplementary Sect. 3).

Univariate regression for COVID patients taking RAASi showed no evidence of age, sex, hypertension, diabetes, chronic kidney disease, coronary artery disease, COPD, RAASi type, or study type having an effect on outcomes (i.e., mortality, seropositivity, ICU admission, and severity) (all $P > 0.05$) (Table 2, supplemental file section 7).

A sensitivity analysis was performed for outcomes with high heterogeneity ($I^2 > 75\%$). In terms of ICU admissions, high heterogeneity ($I^2 = 81\%$) was likely secondary to Bean et al. After removal; the heterogeneity was $< 75\%$ ($I^2 = 34.9\%$). The high heterogeneity ($I^2 = 88\%$) with seropositivity was likely due to Khawaja et al. de Abajo et al. and Yan et al. After removal of both studies; heterogeneity was $< 75\%$ ($I^2 = 46.7\%$). In terms of severity, the heterogeneity was high ($I^2 = 77.2\%$), likely due to studies by Bean et al. and Feng et al. After removal of both studies, heterogeneity was $< 75\%$ ($I^2 = 66.3\%$) (Supplementary section 5).

The funnel plot's visual assessment was symmetrical, ruling out any visible publication bias (Supplementary section 6) The numerical assessment of publication bias was done using Egger's regression model that also failed to show any publication bias or small study effects (ERE $\approx > 0.05$). The limited scatter seen on the funnel plot can be secondary to variation in the cohort selection for individual study.

4 Discussion

In this updated meta-analysis of 49 articles with > 83 K COVID-19 patients, we found that the use of RAASi was not associated with increased short-term mortality. RAASi use was associated with improved seropositivity, a form of indirect evidence of viral clearance. RAASi use was also not associated with increased risk of admission to ICU or worsening of clinical manifestations. Collectively, these findings support the recommendations by professional societies for continuing RAASi irrespective of COVID-19 infection [70].

The use of RAASi in COVID-19 has been controversial since the start of the pandemic, with some studies hypothesizing that the use of RAASi may increase the expression of the ACE2 receptor, the principal receptor for viral entry into the host cell [71]. Although pre-existing cardiovascular disease increased the severity and mortality associated with COVID-19 infection, we have found that the use of ACEi/ARBs is likely not a contributing factor. Our analysis summarized the available studies with the effect of ACEi or ARBs or ACEi + ARBs on COVID-19 outcomes to analyze protective or detrimental effects against severe COVID-19 infection.

In our study, RAASi use was not associated with an increased risk of mortality. BRACE CORONA is the only

Table 1 Baseline demographics and characteristics of the articles included in our study

Author	Study design	RAASi/controls (n)	RAASi	Male %	Age (mean years)	HTN %	DM %	CKD %	CAD/CVD %	COPD %	Primary outcome
BRACE CORONA [12]	Clinical trial	334/325	ACEi + ARBs	59.6	55.7	100	32	1.4	4.6		Mortality
Mehta [21]	Retrospective	211/1494	ACEi + ARBs	55	63	93	46		22	14	Mortality, Severity, Seropositivity, Hospitalization, ICU admission
Bravi [22]	Prospective	450/1153	ACEi + ARBs	47.3	58						Mortality, Severity
Tan [23]	Retrospective	31/69	ACEi + ARBs	45	67	100	26	13	16	7	Mortality
Rossi [24]	Prospective	819/1833	ACEi	50.1	63.2	18	12		7		Mortality, Severity, Hospitalization
Bean [25]	Prospective	37/168	ACEi + ARBs	57	68						Mortality, Severity, ICU admission
Dauchet [26]	Retrospective	62/125	ACEi + ARBs	59	58						Seropositivity
Caraballo [27]	Retrospective	312/588	ACEi + ARBs	49.2	73	74			30		Seropositivity
Yan [28]	Case-control	55/552	ACEi + ARBs	51.1	48.8	22.5	10		3		Severity, Seropositivity
Ip [29]	Retrospective	460/669	ACEi + ARBs			100					Mortality, Severity
Liabeuf [30]	Retrospective	52/64	ACEi + ARBs	63	73	62	18	9	19	13	Severity
Amat-Santos [31]	Retrospective	50/52	ACEi	56.9	82.3						Mortality
Benelli [32]	Prospective	144/267	ACEi or ARBs	66.6	66.8	47	16		23		Mortality, ICU admission
Chen [33]	Retrospective	32/309	ACEi + ARBs	53.6	67	100	100		15		Mortality
Conversano [34]	Retrospective	68/28	ACEi or ARBs	76.3	70.6	100					Mortality
de Abajo [35]	Case-control	484/655	ACEi + ARBs	61		54	27		28		Severity, Seropositivity
de Spiegeleer [36]	Retrospective	31/123	ACEi + ARBs	33	86	25	18				Severity
Ebinger [37]	Retrospective	70/372	ACEi + ARBs	58	52.7	36	19		11		Severity, Hospitalization
Felice [38]	Retrospective	82/51	ACEi or ARBs	72	70.9	100	24		36	9	Mortality
Feng [39]	Retrospective	16/49	ACEi + ARBs	62.5	57	100	13	6	0	0	Severity
Gao [40]	Retrospective	183/527	ACEi + ARBs	67.8	62.64	100	30	1	18	1	Mortality, Severity
Guo [41]	Retrospective	19/168	ACEi + ARBs	48.7	58.5	32	15		11		Mortality
Hu [42]	Prospective	65/84	ACEi + ARBs	59.1	57						Mortality
Huang [43]	Retrospective	20/30	ACEi + ARBs	27	52.65		8		2	2	Mortality
Huh [44]	Case-control	714/4458	ACEi + ARBs	49.4	48.3	33	28		16		Seropositivity
Inciardi [45]	Prospective	30/69	ACEi + ARBs	81	67	64	31	15	16	9	Mortality
Jung [46]	Retrospective	719/438	ACEi + ARBs	52	62.5	100					Mortality
Khawaja [47]	Prospective	109/496	ACEi + ARBs	45	68	33	10		17		Seropositivity
Khera [48]	Retrospective	4586/3347	ACEi + ARBs	45.4	77	100	90		5		Mortality, Severity, Hospitalization
Li [49]	Retrospective	115/247	ACEi or ARBs	59.1	65	100	37	11	24	7	Mortality, Severity

Table 1 (continued)

Author	Study design	RAASI/controls (n)	RAASI	Male %	Age (mean years)	HTN %	DM %	CKD %	CAD/CVD %	COPD %	Primary outcome
Liu [50]	Retrospective	12/34	ACEi+ARBs	55.1	65.2						Severity
Mancia [51]	Case control	2896/12,479	ACEi+ARBs	63.3	68			6	30	6	Severity, Seropositivity
Meng [52]	Retrospective	17/25	ACEi+ARBs	52.9	64	100	12	0	12	0	Mortality, Severity
Peng [53]	Retrospective	22/90	ACEi+ARBs	53	62	82	21		55		Mortality
Rentsch [54]	Retrospective	1530/2258	ACEi+ARBs	90.2	65.7	65	38		29		Seropositivity, Hospitalization, ICU admission
Reynolds [55]	Retrospective	1019/986	ACEi+ARBs	52	64.9	100	44	25	11	23	Severity, Seropositivity
Richardson [56]	Prospective	413/953	ACEi+ARBs	60.3	63						Mortality, Severity, ICU admission
Tedeschi [57]	Prospective	175/434	ACEi+ARBs	68	68						Mortality
Yang [58]	Retrospective	43/48	ACEi+ARBs	48.8	65	100	30	4	20	4	Mortality, Severity, Seropositivity, ICU admission
Yu [59]	Retrospective	103/173	ACEi+ARBs	53	60						Mortality
Zeng [60]	Retrospective	28/47	ACEi+ARBs	43	64	100	31	5	21	9	Mortality, Severity, Hospitalization
Zhang [61]	Retrospective	174/348	ACEi+ARBs	54	64	100	23	4	14	1	Mortality
Zhou [62]	Retrospective	15/21	ACEi+ARBs	60	58.5	100	25		20		Mortality
Raisi-Estabragh [63]	Retrospective	146/523	ACEi+ARBs	56.5	69	50	18		8		Seropositivity
Choi [64]	Case-control	625/625	ACEi+ARBs	42.7	65	100	47				Mortality, Severity
Chang [65]	Retrospective	65/778	ACEi+ARBs	48							Seropositivity
Schneebeiss [66]	Retrospective	16,055/8653	ACEi or ARBs	48	67	35	20	0	6		Hospitalization
Kim [67]	Retrospective	682/608	ACEi+ARBs	53.4	62.8	100	37	19	28	20	Mortality
Saleknezhad [68]	Cross-sectional	98/214	ACEi or ARBs	54.8		87	47	3.5	48		Mortality
Georges [69]	Retrospective	213/471	ACEi+ARBs	63.6	55.7	41	17		8		Seropositivity

RAASI Renin-Angiotensin-Aldosterone System Inhibitors, ACEi Angiotensin Converting Enzyme Inhibitors, ARBs Angiotensin Receptor Blockers, HTN Hypertension, DM Diabetes Mellitus, CKD Chronic Kidney disease, CAD/CVD Coronary Artery Disease/Cardiovascular disease, COPD Chronic Obstructive Pulmonary Disease, ICU Intensive Care Unit

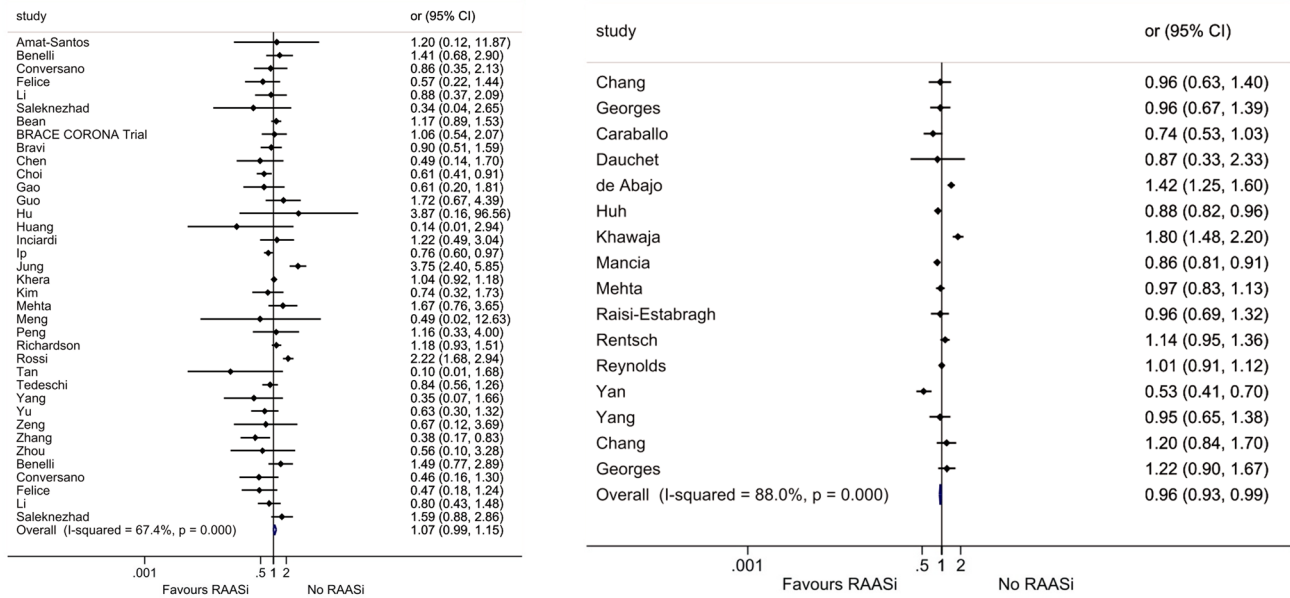


Fig. 2 Forest plots showing pooled mortality outcomes (left) and seropositivity rates (right) among COVID-19 with RAASi

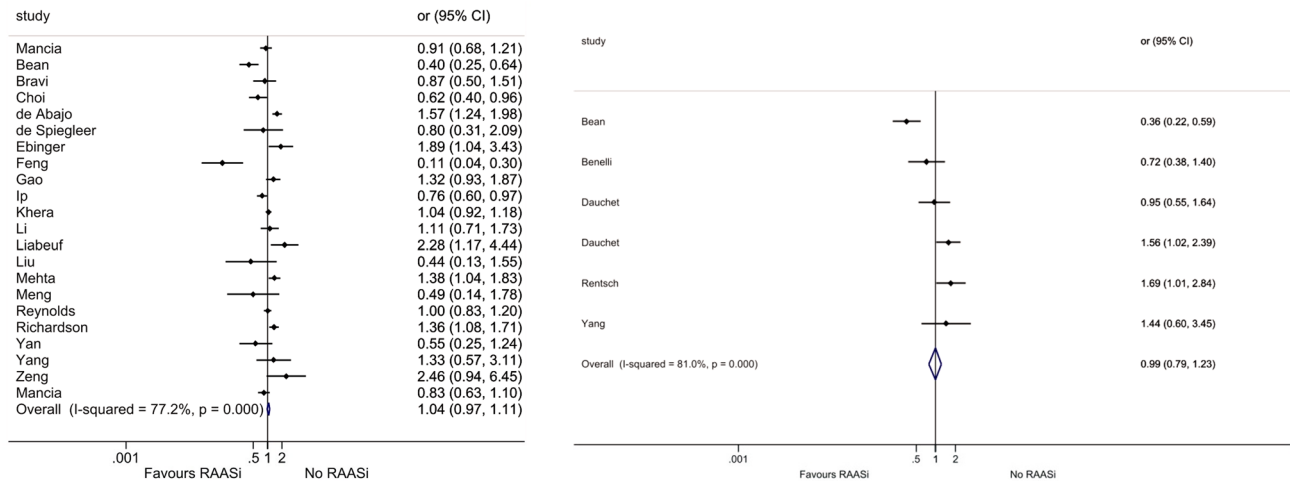


Fig. 3 Forest plot showing pooled severity outcomes (left) and ICU admission rates (right) among COVID-19 patients on RAASi and No RAASi

randomized control trial to date. Inclusion criteria included any 18 year or older patient with COVID 19 that requires hospitalization who are chronically on ACEi/ARBs. Patients were randomized to either continue ACEi/ARBs treatment or suspend the medication. Patients were followed for 30 days. The primary endpoint was the number of days alive and out of the hospital; the secondary endpoint was all causes of death. The study showed suspending ACEi/ARBs showed no benefits, there was no difference in days alive or out of the hospital and all causes of death at 30 days were the same.

With respect to ICU admissions, there was a significant increase in ICU admission odds with ARBs but not in combination with ACEi. Furthermore, ACEi alone did not affect ICU admission. There were relatively few studies that looked at COVID-19 ICU admission in patients taking RAASi. In a study by Bean et al., 14% (5/37) of patients with exposure to an ACEi died or required critical care support compared to 29% (48/168) for patients without such exposure [25]. Bean et al. study findings suggested that ACEi did not increase the severity of COVID-19 as hypothesized but may instead

Table 2 Meta-regression of potential effect modifiers for all study outcomes ($P > 0.05$ shows that our study had no effect modifiers in our studied outcomes)

Meta-regression variables	Mortality		Severity		ICU admission		Seropositivity	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
Age	0.00	0.915	0.00	0.569	-0.06	0.193	0.01	0.259
Male	0.00	0.846	0.00	0.498	0.02	0.355	0.00	0.731
HTN	-	-	0.00	0.538	0.02	0.363	0.00	0.857
DM	0.00	0.727	0.00	0.486	0.04	0.055	0.00	0.830
CKD	0.00	0.830	0.01	0.764	-	-	-	-
CAD	-0.01	0.549	-	-	0.08	0.488	0.01	0.487
COPD	0.03	0.165	0.03	0.184	-	-	-	-
RAASi Type	0.05	0.648	0.03	0.892	-0.11	0.727	-0.02	0.894
Study Type	-0.13	0.143	0.01	0.954	-	-	-0.24	0.050

*= $p < 0.05$

HTN Hypertension, DM Diabetes Mellitus, CKD Chronic Kidney Disease, CAD Coronary artery disease, COPD Chronic obstructive pulmonary disease, RAASi Renin–Angiotensin–Aldosterone system inhibitors

reduce the severity. Our meta-analysis reaffirms Bean et al.'s findings. Notably, Bean et al. could not comment on ARBs users owing to the small number of patients in this subgroup. Furthermore, their study had a short follow-up period, which might have led to missing late outcomes. In Dauchet et al., a statistically significant increase in the Standardised Prevalence Ratio (SPR) of ARBs (1.56 [1.02–2.39]) was observed in intensive care unit patients only while SPRs of ACEi + ARBs did not differ as the severity of the COVID-19 patients increased [26]. The results from these studies further reinforce the need to continue ACEi and ARBs in combination or ACEi's alone in COVID-19 patients. Additionally, it is important to note that when Dauchet et al. controlled for BMI, they found that ARB's were associated with an increase in SPR only in obese patients [26]. As a result, they hypothesize that the increase in SPR is likely due to a higher frequency of deleterious comorbidities on COVID19 outcomes in Obese patients [26]. Combined with the small sample size of ARB only use on ICU admission in our sample, it is likely that these findings are clinically insignificant.

In our study, ACEi and ARBs use did not increase the chances of testing positive for COVID-19 but instead seem to show a slight beneficial effect. Interestingly, the beneficial effect of RAASi on seropositivity was only present in patients who took ACEi and ARB's in combination. Many studies on seropositivity showed similar results [27, 59, 66]. But, a study by Caraballo et al. revealed that compared to patients on ACEi/ARBs, those not on these therapies were 50% more likely to be COVID-19 positive [27]. However, the study only included patients that tested positive for COVID-19, whereas those who did not wish to be tested or were asymptomatic were missed, which might have led to such a significant finding in ACEi/ARBs group. Yan et al. found that individuals with hypertension taking CCBs had significantly increased risk [odds ratio (OR) = 1.67 (95% CI 1.2–2.9)] of manifesting symptoms of COVID-19 whereas

those taking ARBs had significantly lower disease risk (OR 0.24; 95% CI 0.17–0.34 and OR 0.32; 95% CI 0.19–0.57 respectively) [28]. Although this was a large population-based study, the retrospective nature may have led to under-reporting of symptoms and drug history. Nevertheless, the results are significant and further confirm the neutral effect of ACEi and ARBs in patients with a COVID-19 positive test. Of note, a potential explanation for the beneficial effect of RAASi use on seropositivity in our sample may be due to a decrease in the activation of the RAAS leading to a decreased inflammatory response and lower odds of cytokine storm which has been implicated in the pathogenesis of COVID-19 related lung injury [61].

Several studies were performed to evaluate the association between ACEi/ARBs use and COVID-19. A retrospective study by Ip et al. found that there were lower mortality rates in hypertensive patients prescribed ACEi (27%, $p < 0.01$) or ARBs (33%, $p < 0.05$) compared to other anti-hypertensive agents (39%) [29]. RAASi appeared protective compared to other anti-hypertensive agents ($p = 0.001$). This study carried the usual limitations of a retrospective study but was a multicenter study with a significant result on the outcome's severity. In another study by Liabeuf et al., the risk of severe COVID-19 was higher in patients treated with a RAASi (OR 1.97, 95% CI 1.03–3.78) than in patients not treated with a RAASi [30]. Known confounders were eliminated by adjusting for age and hypertension, but there might be a risk for unknown confounders. However, this study included only hospitalized patients; therefore, their definition of non-severe COVID-19 cannot be applied to the general population. Our meta-analysis results found no evidence of an association between severity of COVID-19 infection and ACEi/ARBs use (OR 1.04; 95% CI 0.97–1.11; $p > 0.05$). This is in congruence with previous studies and the society's recommendations of continuing ACEi and ARBs irrespective of COVID-19 positivity [72].

It is important to note, several of our analyses had to be refined due to high heterogeneity. For example, we removed Bean et al. from the analysis of our ICU admissions outcome to reduce heterogeneity. Bean et al. was likely driving the high heterogeneity due to a large number of patients with severe outcomes, such as organ support [25]. We removed Khawaja et al., Yan et al., and de Abajo et al. to reduce heterogeneity for seropositivity. Khawaja's study likely under-ascertained COVID-19 cases as severe and mild [47]. Yan et al. also included patients taking antihypertensives other than ACEi/ARB [28]. Additionally, de Abajo et al. used different databases for cases and controls, which could have led to information bias and incorrect results [35]. Finally, high heterogeneity in our severity outcome was due to Feng et al. and Bean et al. This is likely because there was an increased number of missing data with Feng et al. and inclusion of patients aged > 80 with Bean et al. (supplementary file section 5) [25, 39].

The key strength of our study lies in the large sample size and comprehensive search. Furthermore, our analysis of comorbidities and effect sizes for both individual treatment and co-administration of ACEi and ARBs could be weighed, which aids in comparing the outcomes in each subgroup. As randomized clinical trials continue to progress, the association between COVID-19 and RAASi will become clearer. [73–78].

4.1 Limitations

The results of our meta-analysis should be interpreted in the context of some limitations. Many studies included in the meta-analysis were observational studies and also included pre-printed versions. Most of the studies are subjective to selection bias secondary to a failure of randomization. There was also a risk of attribution bias and a loss of clinical follow-up. Furthermore, due to a lack of blinding, we could not assess for unknown confounders. Several studies did not match for confounders, which may affect the power of the study. These confounders could change the strength of association between COVID-19 infection and RAASi. Nevertheless, the use of ACEi and ARBs conferred an overall protective benefit for COVID-19 patients. Additionally, high heterogeneity required us to omit several studies from our analysis. Finally, meta regression analysis based on obesity/BMI was not performed due to a limitation in the data leading to linear regression convergence being unable to be achieved. Similarly, the effect of hypertension on mortality, coronary artery disease on severity, both chronic kidney disease and COPD on ICU admission and seropositivity, and study type on ICU admission could not be performed due to a limitation in the data leading to linear regression convergence being unable to be achieved.

5 Conclusion

RAASi use is not associated with increased short-term mortality, severity, or ICU admissions. Thus, our results reinforce the current recommendations by the ESH, HFSA/ACC/AHA against discontinuing ACEi/ARBs in the patients who were previously on these therapies.

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