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SYSTEMATIC REVIEW AND META-ANALYSIS

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Comparison of infection risks and clinical outcomes in patients with and without SARS-CoV-2 lung infection under renin–angiotensin–aldosterone system blockade: Systematic review and meta-analysis

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Aims: Angiotensin-converting enzyme-2 (ACE2) is the receptor for SARS-CoV-2. Animal studies suggest that renin–angiotensin–aldosterone system (RAAS) blockers might increase the expression of ACE2 and potentially increase the risk of SARS-CoV-2 infection.

Methods and Results: The effect of ACE inhibitor (ACEI) treatment on the pneumonia incidence in non-COVID-19 patients (25 studies, 330 780 patients) was associated with a 26% reduction of pneumonia risk (odds ratio [OR]: 0.74, $P < .001$). Pneumonia-related death cases in ACEI-treated non-COVID-19 patients were reduced by 27% (OR: 0.73, $P = .004$). However, angiotensin II receptor blockers (ARB) treatment (10 studies, 275 621 non-COVID-19 patients) did not alter pneumonia risk in patients. Pneumonia-related death cases in ARB-treated non-COVID-19 patients was analysed only in 1 study and was significantly reduced (OR, 0.47; 95% confidence interval, 0.30 to 0.72). Results from 11 studies (8.4 million patients) showed that the risk of getting infected with the SARS-CoV-2 virus was reduced by 13% (OR: 0.87, $P = .014$) in patients treated with ACEI, whereas analysis from 10 studies (8.4 million patients) treated with ARBs showed no effect (OR, 0.92, $P = .354$). Results from 34 studies in 67 644 COVID-19 patients showed that RAAS blockade reduces all-cause mortality by 24% (OR = 0.76, $P = .04$).

Conclusion: ACEIs reduce the risk of getting infected with the SARS-CoV-2 virus. Blocking the RAAS may decrease all-cause mortality in COVID-19 patients. ACEIs also reduce the risk of non-COVID pneumonia. All-cause mortality due to non-COVID pneumonia is reduced by ACEI and potentially by ARBs.

KEYWORDS

ACE inhibitors, ACE2, angiotensin II receptor blockers, SARS-CoV-2

1 | INTRODUCTION

Patients with cardiovascular and renal diseases are frequently treated with drugs interfering with the renin–angiotensin–aldosterone system (RAAS). The clinical benefit of angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are well established and hence became part of treatment guidelines for these patients worldwide. ACE2 is an isoenzyme of ACE1 (ACE). Both are essential parts of the RAAS (Figure 1). ACE2 is involved in cardiac function, the development of hypertension and diabetes mellitus. Also, ACE2 has been identified as a functional receptor for coronaviruses, including SARS-CoV and SARS-CoV-2. SARS-CoV-2 infection is triggered by the binding of the spike protein of the virus to ACE2.

It was suggested that patients with cardiac and renal diseases, hypertension, and diabetes, who are treated with drugs potentially increasing ACE2 expression in the lungs such as ACEIs or angiotensin II receptor blockers are at higher risk for getting infected as well as having severe COVID-19 infection.[1,2] In the current review, we summarize the molecular evidence for this hypothesis (see Figure 1 and supplementary material: Molecular Background); next, we present results of a meta-analysis of studies analysing the effects of RAAS blocking drugs (ACEIs, ARBs) on the risk of getting and dying from pneumonia in non-COVID-19 patients and compare these findings to the so far published evidence coming from COVID-19 studies. In the COVID-19 studies, we meta-analysed the risk of getting infected with the SARS-CoV-2 virus, the risk of having severe adverse clinical outcomes and risk of all-cause mortality in COVID-19 patients treated with either ACEIs or ARBs.

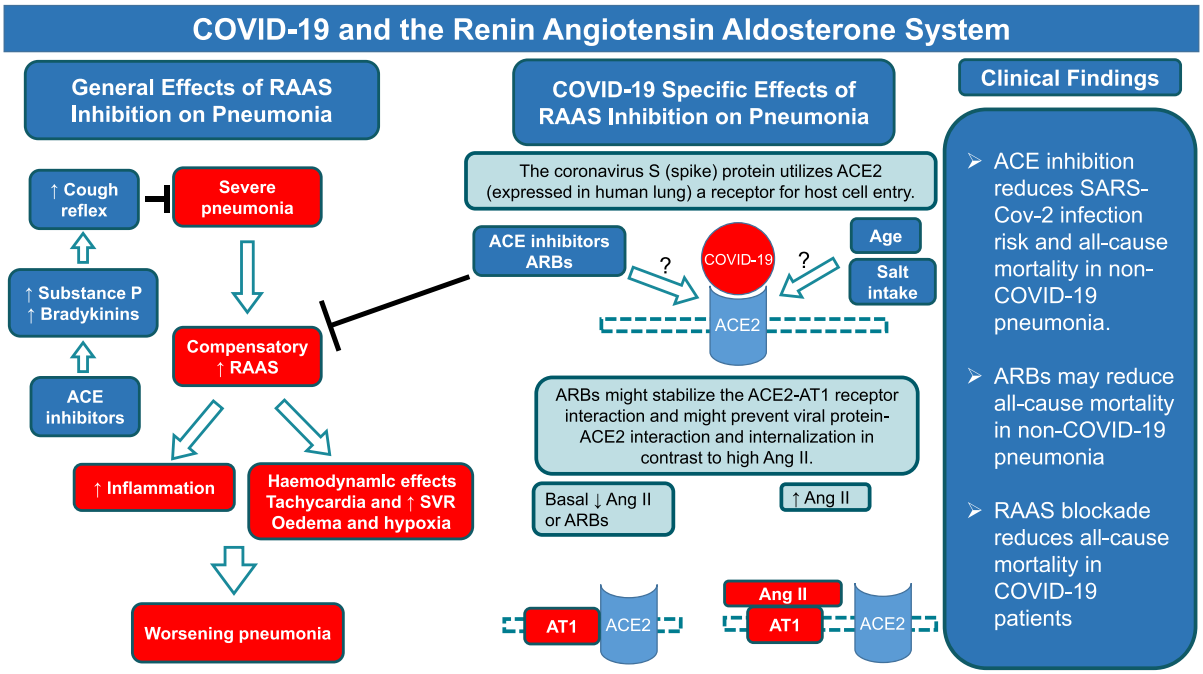

FIGURE 1 In patients with severe pneumonia, there is likewise a compensatory activation of the RAAS, resulting in tachycardia and an elevation of SVR that may be deleterious in this setting. Tachycardia, which shortens the duration of diastole, impairs the filling of the left ventricle. An elevated SVR increases left ventricular afterload (wall stress), increasing myocardial oxygen demand. These changes can lead to a further increase in left ventricular end-diastolic pressure and more edema formation. To the degree that pulmonary edema results in hypoxia, there maybe a further worsening of myocardial function. Besides these haemodynamic effects of an activated RAAS in critically ill patients with pneumonia, an activated RAAS promotes also inflammation in the lung and heart likewise contributing to impaired heart and lung function in these patients. This might explain our finding that all-cause mortality in non-COVID-19 pneumonia patients was significantly reduced when blocking the RAAS in general either with ACEI or ARBs. ACEIs do have an additional effect that might be of clinical impact. They increase levels of substance P and bradykinins which can sensitise the sensory nerves of the airways and enhance the cough reflex which may have a protective role on the tracheobronchial tree. ACE2 is expressed in human lungs and COVID-19 spike (S) protein seems to use it as a cellular entry receptor. It is still a research question whether age and the use of ACE inhibitors and/or ARBs could impact on ACE2 expression and consequently affect the infection pattern of COVID-19. Another aspect is that ARBs might stabilize the ACE2-AT1 receptor interaction and might prevent viral S protein-ACE2 interaction and internalization. Clinical data indicated that SARS-CoV-2 infection related myocarditis and heart failure may negatively influence outcome of SARS-CoV-2 pneumonia. ACE inhibitor treatment reduces the risk of pneumonia and pneumonia related mortality, whereas ARBs do not reduce the risk of pneumonia in non-COVID-19 patients. RAAS blockade reduces severe adverse clinical outcomes and all-cause mortality in COVID-19 patients. RAAS = renin–angiotensin–aldosterone system, SVR = systemic vascular resistance; Ang = angiotensin, ACE = angiotensin converting enzyme, AT1 receptors = angiotensin 1 receptors, ARBs = angiotensin receptor blockers, MCRA = mineralocorticoid receptor antagonists, COVID-19 = coronavirus disease 19

2 | METHODS

2.1 | Data sources and search strategy

A systematic literature search was conducted to identify studies investigating the association between ACEIs or ARBs and pneumonia or COVID-19 in PubMed, Embase (searches using OVID), The Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical trial.gov. The last search was updated on 7 September 2020. The following MeSH terms were used: "angiotensin-converting enzyme inhibitors" or "angiotensin receptor antagonists" or "mineralocorticoid receptor antagonists" and "pneumonia". The key words used for the search strategy are listed in the supplementary materials. The references cited in the retrieved studies were hand-searched for the collection of missing relevant studies.

2.2 | Study selection and quality assessment

Two reviewers independently screened titles and abstracts, and further assessed the full text of each potentially relevant study to determine eligibility for inclusion. Reviews, congress reports, case reports, animal experiments and publications in languages other than English were excluded.

We considered the incidence of pneumonia in all adult patients, irrespective of risk factors at baseline, as the primary outcome. Every case of pneumonia considered in our investigation was either a new case, a recurrent case or a hospital-acquired pneumonia. Diagnosis of pneumonia was based on clinical, radiological or microbiological criteria, or International Classification of Disease codes. We did not consider undefined data or data on upper respiratory tract infections or radiation pneumonitis. The secondary outcome was pneumonia-related mortality, including fatal pneumonia or in-hospital death or 30-day mortality. All of these secondary outcomes had to be caused primarily by pneumonia rather than other co-existing comorbid conditions.[3] All relevant clinical studies (randomized–controlled trials [RCTs], cohort studies, case–control studies and nested case–control studies, as well as case-crossover studies) with ACEIs or ARBs as interventions and with an incidence of pneumonia were considered.

The diagnosis of COVID-19 must be proven by detection of SARS-CoV-2 RNA in the patient's upper or lower respiratory tract system. Treatment with RAAS blocking agents was defined as treatment with either an ACEI or an ARB or both (just 3 patients in 1 study). COVID-19 related adverse severe clinical outcomes are defined as admission to the intensive care unit, the use of assisted ventilation or death. However, we only include peer-reviewed articles; considering the current situation, some observation studies are online available without careful peer review, and thus the quality might raise concerns.

To avoid considering duplicated published data, we excluded the earlier publications conducted in the same study cohort and only considered the latest publications. In our investigation, the treatment group was defined as being treated with any kind of ARBs or any kind of ACEIs. The control group was defined as being treated with a placebo or any other cardiovascular drug such as calcium-channel blockers or β-blockers. Cohort studies had to follow patients to determine pneumonia outcomes. In case–control studies, cases had to be patients with a diagnosis of pneumonia. Controls should be randomly selected to match the cases. A nested case–control study is a variation of a case–control study in which cases and controls are drawn from the population in a fully predefined cohort. In a case–crossover study, as described,[4] the study population consists of subjects who have experienced an episode of pneumonia. Similar to a crossover trial, each study subject serves as their own control.

The methodological quality of RCTs was evaluated using the Cochrane Collaboration's tool for RCTS with the following parameters: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting. The quality of included cohort and case control studies was assessed using the Newcastle–Ottawa scale, which has 3 aspects including 8 criteria and yield scores ranging from 0 (high risk of bias) to 9 (low risk of bias). Studies with Newcastle–Ottawa scale scores <6/9 (considered moderate-to-high risk of bias) were excluded (Table S1).

Overall quality of evidence was evaluated using the Grading of Recommendations, Assessment, and Evaluation (GRADE) framework.[5]

2.3 | Data extraction and analysis

Two independent authors extracted the following data from full-text articles: study design and size, location, population characteristics, primary outcomes, data of relevant outcomes. Data were obtained irrespective of whether they had been reported as predefined outcomes or as adverse effects. We chose the odds ratio (OR) as the measurement estimate for effect because relative estimates are better comparable than absolute effects across studies with different designs, populations, and lengths of follow-up as described previously.[6] We aimed to extract the maximally adjusted OR that included the greatest number of covariates from the original publication for predescribed outcomes. Otherwise, we used the raw data to convert to crude OR through classic methods, or Peto's method if 1 arm had a zero-count cell.[7] We used the hazard ratio (HR) when OR was not available nor possible to calculate. To explore differences in estimates for outcomes, we presented the results stratified according to study design. Considering the potential risk of bias, subgroup analysis in which compare results from the adjusted and unadjusted studies was also conducted. Studies that met the inclusion criteria but could not be pooled due to insufficient data were summarized qualitatively. Either fixed-effects model or, in the presence of heterogeneity, the random-effects method was used in the pooled results. Data were expressed as OR and 95% confidence intervals (95% CIs). Heterogeneity across studies was assessed by testing with the I^2-statistic, considering 25%, 50% and 75% as an indication of low, moderate, and high variability, respectively.[8]

Funnel-plot analysis and Begg test were performed to evaluate potential publication bias. All analyses were performed using Stata/SE

version 14.0 (StataCorp LP, College Station, Texas, USA) and RevMan version5.3.5 (Nordic Cochrane Centre, Cochrane Collaboration, 2014). Tests were 2-sided, and a *P*-value <.05 was considered statistically significant.

3 | RESULT

3.1 | Literature search & description of studies

We identified 2894 potentially relevant studies using the search terms described in the method section. After removing duplicates and screening titles and abstracts, a total of 2611 publications were excluded. Of the remaining 283 publications, 200 were excluded after full-text examination based on our in- and exclusion criteria. Overall, 83 studies included in qualitative synthesis, and 82 studies included in quantitative synthesis, including 51 cohort studies, 12 RCTs, 14 case–control studies, 3 nested case–control studies and 2 case-crossover studies (Figure S1).

As for the primary and secondary pneumonia-related outcomes, totally 36 studies were included.[9–44] All the RCTs were multicentre, except 1 done by Hou *et al*.[34] Seven of them compared ACEIs with controls,[9–13,34,35] 4 compared ARBs with controls.[41–44] Regarding demographic distribution, 2 were done worldwide,[13,44] 4 in Europe[9,10,12,43] (Germany, Czech Republic and Slovakia, Austria, Denmark and Italy), 4 in Asia[11,34,35,42] (China, Japan), and 1 study was located in both Europe and the USA.[41] Among observational studies, 10 were carried out in Asia,[14–18,20,21,24,32,33] 10 in the USA and Canada,[19,22,23,28–31,36,37,40] 5 in Europe,[25–27,38,39] 18 studies were retrospective and 7 were prospective. Twenty studies evaluated ACEIs, 6 ARBs. Tables S2–4 summarize the main characteristics of the included studies.

With regard to the COVID-19-infected patients, 48 studies[45–92] published clinical data whether ACEIs and ARBs are associated with COVID-19 infection or clinical outcomes in patients with COVID-19 in above mentioned databases. One of them was a global study,[92] however, this study was retracted on 4 June 2020 with concern about the quality of the information in the database, thus we only qualitatively summarized this study.

The included studies consist of 37 cohort studies,[45–54,56–75,85–89,91] 9 case–control studies[76–83,90] and 1 RCTs.[84] 23 of them were conducted in Asia,[46–48,50–56,58,60,61,64,66,68,71,72,77,79,80,82,83] 18 in Europe,[63,67,69,70,73–76,78,81,84–91] and 6 in USA[45,49,57,59,62,65] (main characteristics of the included studies were summarized in Table S5).

3.2 | Primary outcomes: Incidence of pneumonia

The effect of ACEI treatment on the incidence of pneumonia was analysed in 25 studies (a total of 330 780 patients coming from 5 RCTs,[9–13] 7 cohort studies,[14–20] 8 case–control studies,[21–28] 3 nested case–control studies[29–31] and 2 case-crossover studies[32,33]). Overall, the use of ACEIs was associated with a significant 26% reduction in risk of pneumonia compared with controls (pooled OR, 0.74, 95% CI, 0.65 to 0.85, $P < .001$; $I^2 = 76.9\%$; for further details see Table 1).

The effect of ARB treatment on the incidence of pneumonia was analysed in 10 studies (a total of 275 621 patients from 4 RCTs,[41–44] 1 cohort study,[19] 1 case–control study,[28] 2 nested case–control studies[30,31] and 2 case-crossover studies.[32,33] Pooled results showed that the risk of pneumonia was not significantly different between patients who did or did not use ARBs (pooled OR, 0.90, 95% CI, 0.79 to 1.02, $P = .11$; $I^2 = 53.3\%$). However, 2 individual study types revealed a potential effect of ARBs on the risk of pneumonia. The odds ratios were 0.84 (95% CI, 0.72 to 0.98, $P = .03$; $I^2 = 0\%$) in RCTs and 0.52 (95% CI, 0.36 to 0.76, $P = .001$) in the cohort study, respectively (Table 1).

3.3 | Secondary outcome: Pneumonia-related mortality

Data of pneumonia-related deaths were available in 10 studies: 1 comparing ARBs with control summarized qualitatively;[40] 9 studies comparing ACEIs with controls (4 RCTs;[11,13,34,35] and 5 cohort studies[37–40,93]) were included in the meta-analysis.

Pooled results showed that ACEIs were associated with a significant 27% reduction in risk of pneumonia-related mortality (OR, 0.73, 95% CI, 0.59 to 0.90, $P = .004$; $I^2 = 60.1\%$) compared with controls (Table 2).

For ARBs, a meta-analysis for the secondary end-point mortality was not possible due to the lack of enough eligible studies. Mortensen *et al*.,[40] conducted the only eligible study providing data on ARB and pneumonia-related mortality. They showed, in a cohort of 22 996 patients where 839 subjects were treated with ARBs, that treatment with ARBs reduced the pneumonia-related mortality (OR, 0.47, 95% CI, 0.30 to 0.72).

3.4 | Mineralocorticoid receptor antagonists

We did not find any eligible studies addressing the effects of mineralocorticoid receptor antagonists on pneumonia or pneumonia-related death.

3.5 | RAAS inhibitors and risk of COVID-19 infection

Pooled result from 11 studies,[45,49,60,73,76,78–80,84,90,91] 12 cohorts (143 696 patients) showed that the risk of getting infected (whatever degree of disease—from no symptoms to severe adverse clinical outcomes) was not associated with the treatment of overall RAAS blockade (ACEIs or ARBs; OR, 1.04, 95% CI, 0.94 to 1.14, $P = .47$; $I^2 = 71.0\%$; Figure 2).

However, use of ACEIs alone was associated with a significant 13% reduction in risk of COVID-19 positive compared with controls

TABLE 1 Renin–angiotensin–aldosterone system inhibitors and risk of non-SARS-CoV-2 pneumonia infection

Non-SARS-CoV-2 pneumonia infection	OR (95% CI)	*P* value
*ACE inhibitors (25, n = 330 780)**	0.74 (0.65, 0.85)	<.0001
Cohort studies (7)	0.46 (0.35, 0.62)	<.0001
Case–control studies (8)	0.72 (0.60, 0.88)	.001
Randomized controlled trial (5)	0.78 (0.54, 1.14)	.200
Nested case–control studies (3)	1.03 (0.97, 1.10)	.360
Case-crossover studies (2)	0.86 (0.67, 1.10)	.234
Adjusted risk factors ORs studies (15)	0.80 (0.70, 0.92)	.001
Crude ORs studies (5)	0.39 (0.27, 0.56)	<.0001
ARBs (10, n = 275 621)	0.90 (0.79, 1.02)	.108
Cohort studies (1)	0.52 (0.36, 0.76)	.001
Case–control studies (1)	0.48 (0.17, 1.36)	.168
Randomized controlled trial (4)	0.84 (0.72, 0.98)	.031
Nested case–control studies (2)	1.01 (0.93, 1.09)	.794
Case-crossover studies (2)	1.01 (0.88, 1.15)	.933
Adjusted risk factors ORs studies (6)	0.91 (0.77, 1.07)	.265

*number of studies and population. OR = odds ratio; 95% CI = 95% confidence interval; ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blockers.

TABLE 2 Renin–angiotensin–aldosterone system inhibitors and risk of non-SARS-CoV-2 related all-cause mortality

Non-SARS-CoV-2 related all-cause mortality	OR (95% CI)	*P* value
*ACE inhibitors (9, n = 35 727)**	0.73 (0.59, 0.90)	.004
Cohort studies (5)	0.71 (0.57, 0.88)	.002
Randomized controlled trial (4)	0.83 (0.31, 2.17)	.697
Adjusted risk factors ORs studies (5)	0.73 (0.59, 0.90)	.002
ARB (1, n = 22 996)	0.47 (0.30, 0.72)	-
Cohort studies (1)	0.47 (0.30, 0.72)	Not given

*number of studies and population. OR = odds ratio; 95% CI = 95% confidence interval; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

(OR, 0.87, 95% CI, 0.78 to 0.97, P = .014; I^2 = 73.5%). Similar results were obtained from subgroup of cohort study (OR, 0.82, 95% CI, 0.70 to 0.94, P = .006; I^2 = 67.8%) and studies with adjusted odd ratio (OR, 0.87, 95% CI, 0.77 to 0.98, P = .026; I^2 = 80.8%; Table 3).

It is of interest to mention that even if we excluded a huge population based cohort study[87] (n = 8.3 million), which showed a significant beneficial effect of ACEIs or ARB treatment on COVID-19 positive, the pooled odd ratio for the treatment of ACEIs showed the consistent result even when we excluded this study (OR, 0.92, 95% CI, 0.87 to 0.98, P = .012; I^2 = 0.0%).

3.6 | RAAS inhibitors and risk of all-cause mortality in COVID-19 patients

Furthermore, 34 studies[46–49,51,53–75,77,79,80,82–84] including 67 644 patients showed that the risk of all-cause mortality among ACEIs/ARBs users was significantly reduced when compared to COVID-19 patients without ACEIs/ARBs treatment (OR 0.76, 95% CI, 0.59 to 0.99, P = .04; I^2 = 88%; Figure 3). When we only considered studies with adjusted odd ratios, treatment with RAAS inhibitors was associated with a significant 31% reduction in risk of COVID-19 related mortality compared with controls (OR, 0.81, 95% CI, 0.65 to 0.99, P = .04; I^2 = 73.1%; Table 4).

3.7 | RAAS inhibitors and risk of COVID-19 related severe adverse clinical outcomes

Pooled result from 40 studies,[45–84] a total of 78 960 patients, showed a nonsignificant 11% reduction in risk of COVID-19 related severe adverse clinical outcomes (admission to the intensive care unit, the use of assisted ventilation or death) associated with use of RAAS inhibitors (OR, 0.89, 95% CI, 0.78 to 1.01, P = .076; I^2 = 71.0%; Figure 4).

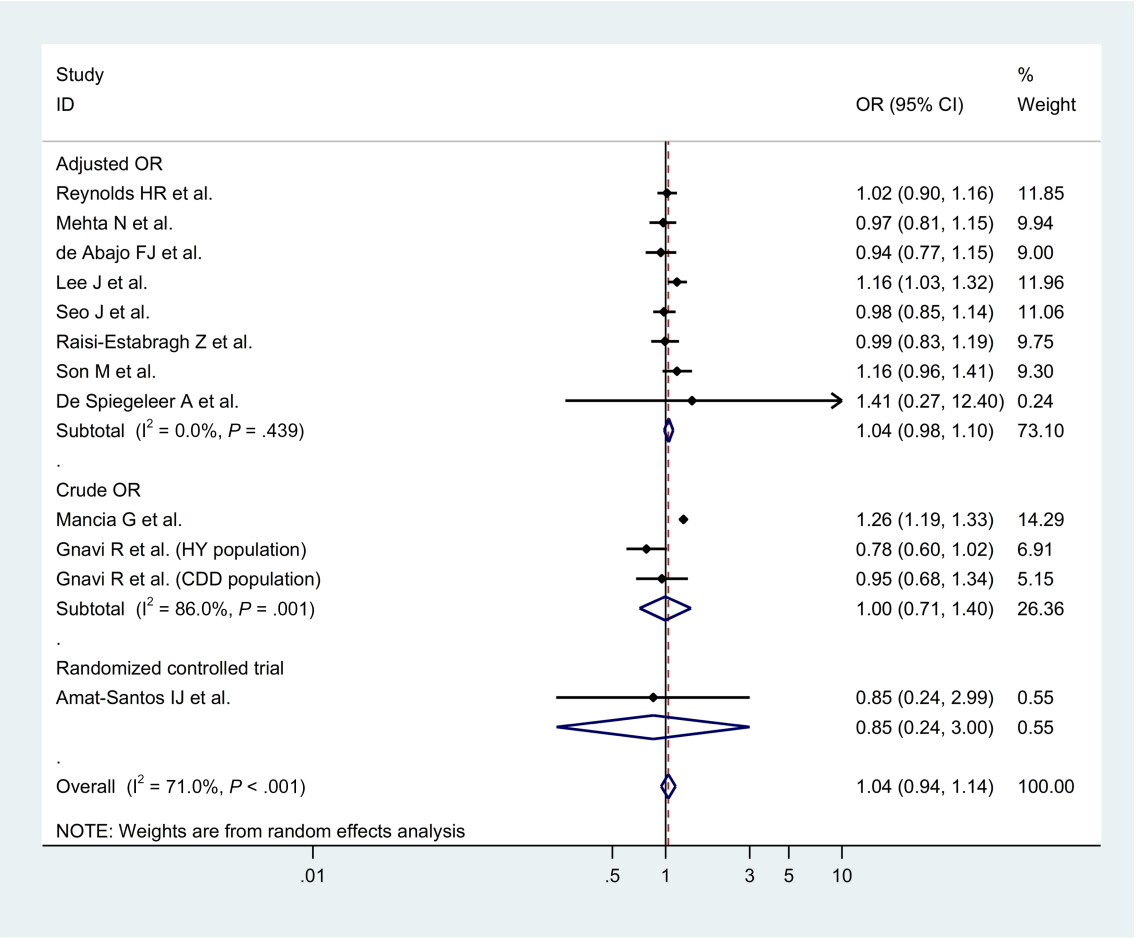

FIGURE 2 Forest plots for association between renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 infection

In the subgroup analysis, subgroup of cohort studies (69 091 patients) revealed that RAAS inhibitors significantly reduced the risk of COVID-19 related adverse clinical outcome (OR, 0.82, 95% CI, 0.71 to 0.95, P = .008; I^2 = 69.7%). Moreover, the subgroup which only considered adjusted odd ratios (25 096 patients) also showed a significant reduction (OR, 0.81, 95% CI, 0.65 to 0.99, P = .04; I^2 = 73.1%; Table S6).

The differentiation analysis of ACEIs and ARBs treatment showed the same trend as RAAS inhibitors, ACEIs (OR, 0.95, 95% CI, 0.85 to 1.06, P = .34; I^2 = 53.0%) and ARB (OR, 0.93, 95% CI, 0.82 to 1.05, P = .24; I^2 = 59.4%). However, these associations were not significant.

3.8 | Publication bias

For the primary outcome of pneumonia referring to RAAS inhibitors, funnel plots did not show apparent visual asymmetry. The Begg tests showed no evidence of publication bias (ACEI, P = .66; ARB, P = .21). For the secondary outcome, funnel plot also did not show any visual asymmetry; testing for publication bias showed no statistic significant result (Begg's P-value for asymmetry >.999).

As for the COVID-19 studies referring to RAAS inhibitors, funnel-plot showed a qualitatively asymmetrical shape for mortality, but not for severity and infection. The Begg test showed a borderline significance of publication bias for COVID-19-related severity outcome (P = .05), and a significant publication bias for mortality (P = .02), but no indication of publication bias for infection (P = .84). Referring to ACEIs, funnel-plot showed the same direction as RAAS inhibitors. The Begg test showed no indication of publication bias for severity outcome, mortality and infection (P = .29; 0.10; 0.84, respectively). For the COVID-19 studies referring to ARBs, the funnel-plot showed a qualitatively asymmetrical shape for infection. The Begg test showed no indication of publication bias for severity outcome, mortality and infection (P = .26; 0.66; 0.28, respectively). There are more studies contributing to the favourable effect, indicating possibility of publication bias.

3.9 | Quality/certainty of the evidence

The quality/certainty of the evidence regarding the impact of RAAS blockers in patients with SARs-CoV-2 and non-SARS-CoV-2 lung

TABLE 3 Renin–angiotensin–aldosterone system (RAAS) inhibitors and risk of COVID-19 infection

COVID-19 infection	OR (95% CI)	*P* value
*RAAS inhibitors (11, n = 143 696)**	1.04 (0.94, 1.14)	.467
Cohort studies (5)	1.05 (0.98, 1.13)	.170
Case–control studies (5)	1.02 (0.87, 1.20)	.787
Randomized controlled trial (1)	0.85 (0.24, 3.00)	.801
Adjusted risk factors ORs studies (8)	1.04 (0.98, 1.10)	.196
Crude ORs studies (2)	1.00 (0.71, 1.40)	.988
ACE inhibitors (10, n = 8 405 242)	0.87 (0.78, 0.97)	.014
Cohort studies (4)	0.82 (0.70, 0.94)	.006
Case–control studies (5)	0.94 (0.87, 1.01)	.081
Randomized controlled trial (1)	0.85 (0.24, 3.00)	.801
Adjusted risk factors ORs studies (8)	0.87 (0.77, 0.98)	.026
Crude ORs studies (1)	0.90 (0.73, 1.10)	.310
ARBs (9, n = 8 405 326)	0.92 (0.77, 1.10)	.354
Cohort studies (4)	0.85 (0.59, 1.22)	.371
Case–control studies (5)	0.98 (0.89, 1.06)	.569
Adjusted risk factors ORs studies (8)	0.94 (0.76, 1.15)	.549
Crude ORs studies (1)	0.84 (0.70, 1.01)	.064

*number of studies and population. COVID-19 = coronavirus disease 19; OR = odds ratio; 95% CI = 95% confidence interval; ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blockers.

infection is summarized in Table 5, according to certainty of the evidence (GRADE).[5]

4 | DISCUSSION

Patients treated with RAAS blocking drugs due to cardiac and renal diseases certainly belong to the patients with the highest risk for SARS-CoV-2 related nonfatal and fatal pneumonia. RAAS blocking drugs belong to drug classes with the clearest proven clinical benefit to patients with cardiac and renal diseases. Given that ACE2 is the receptor for the SARS-CoV-2 virus mediating entry to human cells, drugs that might affect the expression of ACE2 in humans and hence potentially disease severity are of major concern. The definitive answer whether RAAS blocking drugs are beneficial, neutral or even harmful can only come from adequately powered clinical trials that are currently initiated (NCT04311177 [Losartan for Patients With COVID-19 Not Requiring Hospitalization] and NCT04312009 [Losartan for Patients With COVID-19 Requiring Hospitalization]). This will take some time. Only 1 placebo-controlled trial with RAAS blocking agents has been reported so far.[84] However, this study is too small and had too few fatal events to allow firm conclusions.

Our data (Tables 1–4) would rather suggest to study in particular ACEIs instead of ARBs in patients with SARS-CoV-2 infection. In any case, general practitioners and physicians in hospitals, especially on intensive care units, treating patients with SARS-CoV-2 infection ask for guidance now. As is often the case in everyday clinical medicine, one has to critically summarize and weigh the existing facts and then make clinical decisions. This is, therefore, the ultimate goal of our investigation and below the key points for decision making are summarized:

i. There is currently no doubt among scientists that ACE2 is the functional receptor of SARS-CoV-mediated upper and lower respiratory tract infections.[94] Wrapp *et al.*[95] showed that the COVID-19 S protein binds ACE2 with a much higher affinity than SARS-CoV-2. This could partly explain the high infection rate of this virus.
ii. Some animal studies do suggest that treatment with either ACEIs or ARBs might increase ACE2 expression in the cardiovascular system. Few animal data exist on the pulmonary expression of ACE2 under RAAS blockade. It should also be emphasized that some animal studies found no effect or even an opposite effect on ACE2 expression.[96–101] It is worth mentioning that 1 of these studies showed beneficial effects of ACE inhibition even though pulmonary ACE2 expression increased[101] (for more details see supplementary file Molecular Background).
iii. The human heart and kidney express ACE2, the receptor for SARS-CoV-2. Several independent studies have reported that the heart and potentially the kidney seem to be—in addition to the respiratory tract—a primary target of SARS-CoV-2 infections leading to clinical signs of myocarditis and heart failure[102–105] and potentially renal failure.[106,107] The RAAS is activated in heart failure patients and RAAS blockade is a clinical mainstay in the treatment of heart failure.[108–110]

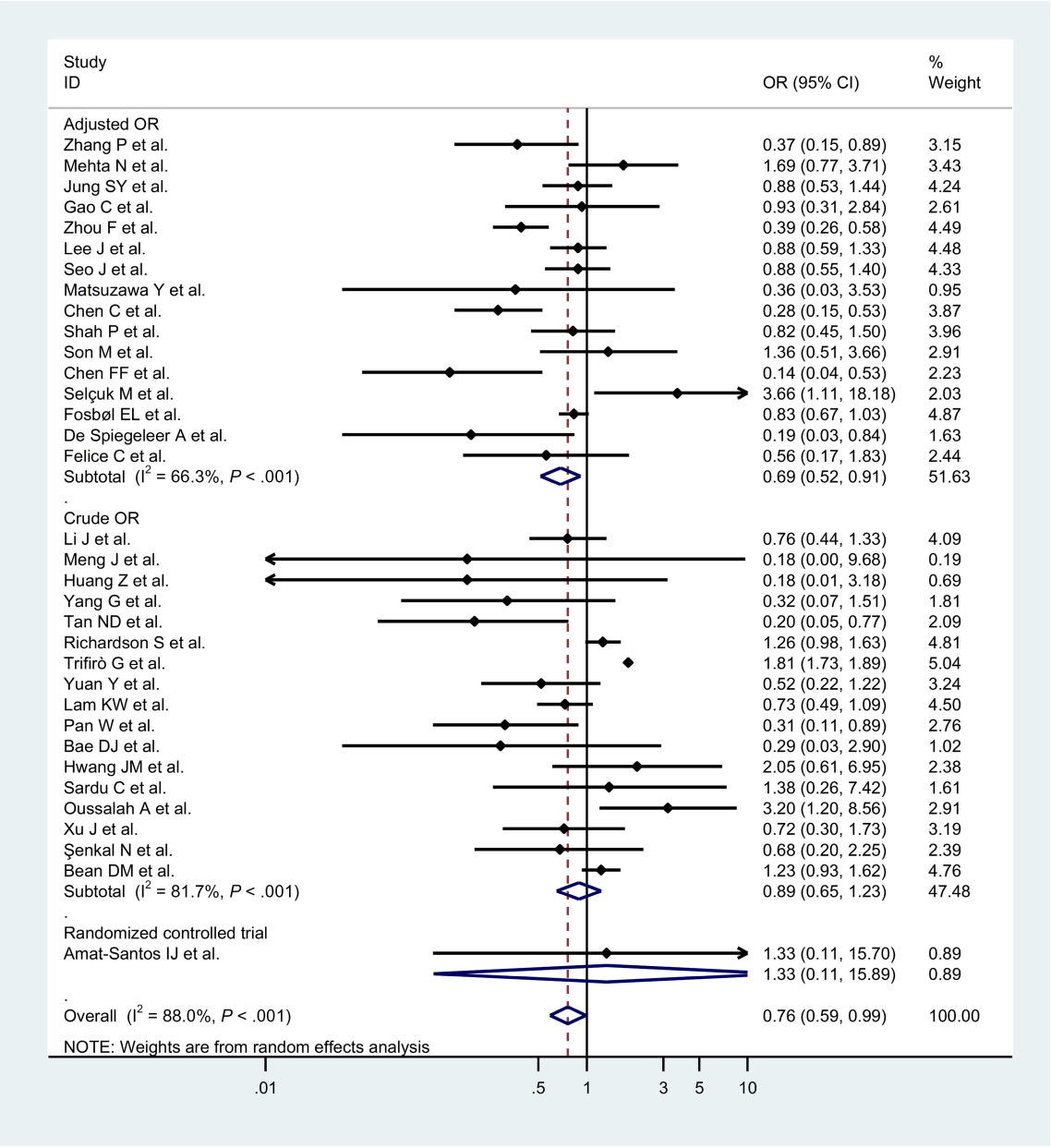

FIGURE 3 Forest plots for association between renin–angiotensin–aldosterone system inhibitors and risk of all-cause mortality in COVID-19 patients

iv. In patients with severe pneumonia requiring intensive care treatment, there is a compensatory activation of the RAAS and sympathetic nervous systems, resulting in tachycardia and an elevation of systemic vascular resistance that may be deleterious in this setting.[7] Tachycardia, which shortens the duration of diastole, impairs the filling of the left ventricle. An elevated systemic vascular resistance increases left ventricular afterload (wall stress), increasing myocardial oxygen demand. These changes can lead to a further increase in left ventricular end-diastolic pressure and more oedema formation. To the degree that pulmonary oedema results in hypoxia, there may be a further worsening of myocardial function. Besides these haemodynamic effects of an activated RAAS in critically ill patients with pneumonia, an activated RAAS also promotes inflammation in the lung and heart likewise contributing to impaired heart and lung function in these patients. This might explain our finding that all-cause mortality in non-COVID-19 pneumonia patients (Table 2) was significantly reduced when blocking the RAAS in general either with ACEIs or ARBs. Similar findings were also seen in COVID-19 patients (Table 4) when analysing both drug classes together. However, when analysing the effects of ACEIs and ARBs separately, a reduction of all-cause mortality was not seen. This might be explained by the substantially lower number of analysed patients in the ACEI or ARB group, as compared to studies were RAAS

TABLE 4 Renin–angiotensin–aldosterone system (RAAS) inhibitors and COVID-19 all-cause mortality

COVID-19 all-cause mortality	OR (95% CI)	*P* value
RAAS inhibitors (34, n = 67 644)	0.76 (0.59, 0.99)	.040
Cohort studies (28)	0.75 (0.57, 1.00)	.047
Case–control studies (5)	0.80 (0.40, 1.60)	.531
Randomized controlled trial (1)	1.33 (0.11, 15.89)	.822
Adjusted risk factors ORs studies (16)	0.69 (0.52, 0.91)	.010
Crude ORs studies (18)	0.89 (0.65, 1.23)	.488
ACE inhibitors (16, n = 21 163)	1.03 (0.90, 1.16)	.683
Cohort studies (13)	1.04 (0.91, 1.18)	.598
Case–control studies (2)	0.63 (0.30, 1.33)	.225
Randomized controlled trial (1)	1.33 (0.11, 15.89)	.822
Adjusted risk factors ORs studies (7)	1.02 (0.85, 1.22)	.817
Crude ORs studies (9)	0.97 (0.76, 1.23)	.791
ARBs (14, n = 20 283)	0.90 (0.70, 1.16)	.416
Cohort studies (12)	0.85 (0.65, 1.12)	.250
Case–control studies (2)	1.31 (0.66, 2.58)	.442
Adjusted risk factors ORs studies (7)	0.92 (0.72, 1.19)	.526
Crude ORs studies (7)	0.91 (0.51, 1.60)	.734

*number of studies and population. COVID-19 = coronavirus disease 19; OR = odds ratio; 95% CI = 95% confidence interval; ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blockers.

blockade was analysed together (Table 4). ACEIs have an additional effect that might be of clinical impact. They increase levels of substance P and bradykinins. Basic science studies showed that bradykinin and substance P sensitize the sensory nerves of the airways and enhance the cough reflex,[111–115] which may have a protective role on the tracheobronchial tree. These mechanisms also improve swallowing by avoiding the exposure of the respiratory tree to oropharynx secretions.[115,116] Taken together, the pleiotropic effects of ACEIs were suggested to reduce the incidence of pneumonia. This hypothesis is further supported by a meta-analysis indicating markedly higher pneumonia incidence in subjects with a specific polymorphism in ACE that reduces substance P and bradykinin, both of which drive the cough reflex,[117] also consistent with the notion that airway reflex sensitivity contributes to pulmonary definitions. ARBs do not increase the levels of Substance P or bradykinin and hence do not have this protective effect. This might at least be 1 reason why ACEIs do reduce the risk of getting non-COVID-19 pneumonia (Table 1) or being infected with SARS CoV-2 (Table 3)

Our findings in COVID-19-infected patients with regard to RAAS blocking agents are thus in good agreement with findings in non-COVID-19-infected patients with pneumonias. The smaller numbers of analysed COVID-19 positive patients and the study design of these studies do not allow a differentiation of ACEIs and ARBs effects with regard to severe adverse clinical outcomes and all-cause mortality. The findings in COVID-19 patients are for sure less robust compared to the non-COVID-19 studies.

Based on the data in non-COVID-19 and COVID-19 patients, we strongly suggest that ACEIs in particular should not be discontinued in patients who need them due to cardiac and/or renal diseases. The evidence that ACEIs might affect the expression of the molecular target in humans for the SARS CoV-2 virus (ACE2) is controversial and comes from animal experiments. Moreover, the potential implication of an up- or downregulation (except for ACE2 knockout mice) of ACE2 on the risk of infection of the lungs with SARS CoV-2 is not established so far.

The meta-analysis of all available clinical studies in non-COVID-19 patients provides clear-cut results. ACEIs are beneficial for patients with pneumonia. They reduce the odds for pneumonia and also pneumonia-related death. The limited experience so far in COVID-19 patients clearly supports this interpretation.

For ARBs, the situation is less clear. The overall effect in non-COVID-19 pneumonia outcomes were neutral (Figure 3). The data in COVID-19 patients are clear: RAAS blockade—whatever drug class was used—reduces severe adverse clinical outcomes and all-cause mortality. We do not know for the time being whether ACEIs or ARBs or both compound classes were the drivers of these beneficial effects. Final conclusions can only be made when we have enough studies on this topic separating the effects of ACEIs from ARBs in COVID-19 patients.

To ensure the quality of our study, we just accepted studies in international journals after successful peer review, preprints were not considered. We even excluded 1 COVID-19 study published in the *New England Journal of Medicine*,[92] because the quality of the data was questioned after publication by the senior editor of this journal.[118,119]

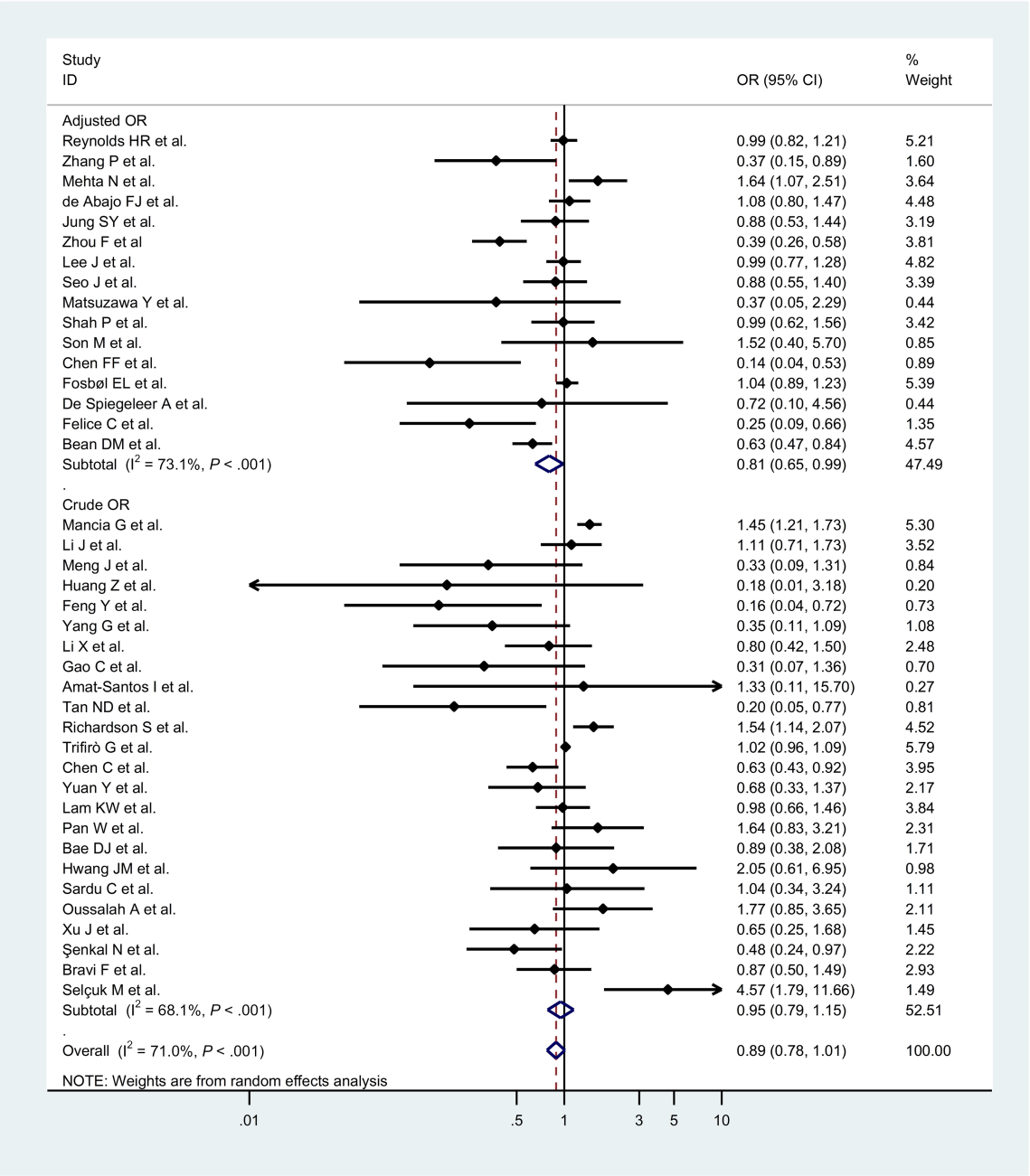

FIGURE 4 Forest plots for association between renin–angiotensin–aldosterone system inhibitors and COVID-19 related severe adverse clinical outcomes defined as admission to the intensive care unit, the use of assisted ventilation, or death

This represents a study limitation that the vast majority of analysed cases of pneumonia in our meta-analysis had not been caused by SARS-CoV-2 infections. Given the current COVID-19 pandemic, some of the COVID-19 studies were done under huge time pressure for designing, conducting and also peer reviewing these studies. This explains at least partially some quality concerns (Table 5). The higher heterogeneity in our analysis—in particular in the COVID-19 studies—is due to differences in the design of the individual studies, different population analysed and the way of statistical analysis of the original studies. Moreover, there was some heterogeneity regarding the controls used in the meta-analysis due to the definition of control group (the control group was defined as being treated with a placebo or any other cardiovascular drug such as calcium-channel blockers or β-blockers) used in our study. In addition, the secondary outcome of the meta-analysis in non-COVID-19 patients was defined as pneumonia-related mortality. We accepted the following definitions in the individual studies as pneumonia related mortality: fatal pneumonia or in-hospital death or 30-day mortality in patients with pneumonia. For COVID-19, outcome severe adverse clinical events, we accepted admission to the intensive care unit, the use of assisted ventilation, or death or combinations as severe adverse

TABLE 5 Summary of renin–angiotensin–aldosterone system (RAAS) inhibitors treatment effects for each outcome measure and GRADE quality of evidence

Outcomes	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative effect, OR (95% CI)	Certainty of evidence (GRADE)
Non-SARS-CoV-2 pneumonia infection									
ACEIs	20	Observational studies	Not serious	Very serious [a]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	0.74 (0.64, 0.85)	⨁◯◯◯ VERY LOW
	5	Randomized controlled trial	Not serious	Serious [b]	Serious	Serious [c]	-	0.78 (0.54, 1.14)	⨁◯◯◯ VERY LOW
ARBs	6	Observational studies	Not serious	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	0.91 (0.77, 1.07)	⨁⨁◯◯ LOW
	4	Randomized controlled trial	Not serious	Not serious	Serious	Not serious	-	0.84 (0.72, 0.98)	⨁⨁⨁◯ MODERATE
All-cause mortality in non-SARS-CoV-2 pneumonia patients									
ACEIs	5	Observational studies	Not serious	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	0.71 (0.57, 0.88)	⨁⨁◯◯ LOW
	4	Randomized controlled trial	Not serious	Serious [b]	Serious	Very serious [c]	-	0.83 (0.31, 2.71)	⨁◯◯◯ VERY LOW
SARS-CoV-2 infection									
RAAS blockers	10	Observational studies	Not serious	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	1.04 (0.94, 1.14)	⨁◯◯◯ VERY LOW
	1	Randomized controlled trial	Not serious	Not serious	Not serious	Very serious [c]	-	0.85 (0.24, 3.00)	⨁⨁◯◯ LOW

(Continues)

TABLE 5 (Continued)

Outcomes	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative effect, OR (95% CI)	Certainty of evidence (GRADE)
ACEIs	9	Observational studies	Not serious	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	0.87 (0.78, 0.97)	⨁⨁◯◯ LOW
	1	Randomized controlled trial	Not serious	Not serious	Not serious	Very serious [c]	-	0.85 (0.24, 3.00)	⨁⨁◯◯ LOW
ARBs	9	Observational studies	Not serious	Very serious [a]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	0.92 (0.77, 1.10)	⨁◯◯◯ VERY LOW
All-cause mortality in SARS-CoV-2 infection patients									
RAAS blockers	33	Observational studies	Serious [d]	Very serious [a]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	0.76 (0.59, 0.98)	⨁◯◯◯ VERY LOW
	1	Randomized controlled trial	Not serious	Not serious	Not serious	Very serious [c]	-	1.33 (0.11, 15.89)	⨁⨁◯◯ LOW
ACEIs	15	Observational studies	Serious [d]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	1.01 (0.89, 1.16)	⨁⨁◯◯ LOW
	1	Randomized controlled trial	Not serious	Not serious	Not serious	Very serious [c]	-	1.33 (0.11, 15.89)	⨁⨁◯◯ LOW

(Continues)

TABLE 5 (Continued)

Outcomes	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative effect, OR (95% CI)	Certainty of evidence (GRADE)
ARBs	14	Observational studies	Serious [d]	Very serious [a]	Not serious	Serious [c]	All plausible residual confounding would reduce the demonstrated effect	0.90 (0.70, 1.16)	⨁◯◯◯ VERY LOW
SARS-CoV-2 infection related severe adverse clinical outcomes									
RAAS blockers	39	Observational studies	Serious [d]	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	0.89 (0.78, 1.01)	⨁◯◯◯ VERY LOW
	1	Randomized controlled trial	Not serious	Not serious	Not serious	Very serious [c]	-	1.33 (0.11, 15.89)	⨁⨁◯◯ LOW
ACEIs	22	Observational studies	Serious [d]	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	0.95 (0.85, 1.06)	⨁◯◯◯ VERY LOW
	1	Randomized controlled trial	Not serious	Not serious	Not serious	Very serious [c]	-	1.33 (0.11, 15.89)	⨁⨁◯◯ LOW
ARBs	21	Observational studies	Serious [d]	Serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	0.93 (0.82, 1.05)	⨁◯◯◯ VERY LOW

[a]High heterogeneity;
[b]moderate heterogeneity;
[c]95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm (serious level was considered for downgrading is a relative risk reduction or relative risk increase >25%, Very serious level was considered >100%);
[d]failure to adequately control confounding. ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers.

clinical event. These differences due to the particular outcome definitions in the individual studies may likewise increase heterogeneity. Moreover, the baseline morbidity and mortality risk of the patients was different in the individual studies furthermore increasing heterogeneity. Finally, we had no information on the dosages of the used RASS blocking agents—so any analysis of dose-dependency of the observed effects was not possible.

An investigation of this topic in a meta-analysis of all so far available studies in non-SARS-CoV-2 pneumonia combined with an analysis of the available studies in COVID-19 patients is the as of today the best available approach to obtain clinical evidence on this extremely important clinical question unless adequately powered, placebo-controlled studies addressing this topic as primary outcome in COVID-19 patients are available. As of today, only 1 RCT was reported. However, this study had by far to less clinical events to be informative.[84]

Furthermore, it is justified to assume that factors that determine the progression, severity and course of pneumonia in general are factors that also determine the course of SARS-CoV-2 pneumonia.[120–122] This hypothesis is supported by findings of pathological lung alterations in early disease stages of SARS-CoV-2 infection. Early histopathological features were non-specific and included oedema, pneumocyte hyperplasia, focal inflammation and multinucleated giant-cell formation; findings also seen in early stages of non-SARS-CoV-2 pneumonias.[123] Figure 1 illustrates the basic science and clinical points discussed above.

5 | CONCLUSION

Our study provides evidence that the use of ACEIs but not ARBs reduces the risk of getting infected with the SARS CoV-2 virus. Blocking the RAAS with either ACEI or ARBs may decrease all-cause mortality in COVID-19 patients. The lack of adequately powered controlled clinical COVID-19 studies, however, limits the power of these conclusions.

ACEIs (but not ARBs) reduce the risk of non-COVID-19 pneumonia. All-cause mortality due to non-COVID-19 pneumonia is reduced by ACEI and may be reduced by ARBs (the statement for all-cause mortality for ARBs is just based on 1 study).

Considering the findings in our meta-analysis as summarized above and the overall very weak evidence in animal studies that the RAAS blockade-related alterations of the pulmonary ACE2 expression is linked to disease severity, RAAS-blocking drugs should not be withdrawn in clinical practice. Our findings provide a stimulus for the initiation of further randomized clinical trials investigating ACEIs in comparison to ARBs in COVID-19 patients to dissect ACEI effects from ARB-related effects in this population.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

CONTRIBUTORS

B.H. and B.K.K. conceived and designed the study. C.C., S.Z. and C.F.H. searched the articles and retrieved the data. C.C., S.Z., A.A.H. and C.F.H. performed the statistical analysis. C.C., A.A.H. and B.H. drafted the article. B.H. and B.K.K. supervised the systematic review and meta-analysis and significantly amended the manuscript. All authors took part in the interpretation of the results and approved the version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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