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Could patients with chronic obstructive pulmonary disease benefit from renin angiotensin system inhibitors? A meta-analysis

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ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) is considered related to chronic systemic inflammation. Renin angiotensin system (RAS) inhibitor, exerting an anti-inflammatory action in many systems, has been demonstrated relevant to the pathogenesis of COPD. However, the association between RAS inhibitor use and prognosis of patients with COPD remains controversial. Therefore, we conducted a meta-analysis and systematic review to summarise current evidence.

Material and methods Databases, including Medline, Embase, Web of Science and Cochran Library, were searched for eligible studies by the end of 30 September 2022. Observational studies or randomised controlled trials (RCTs) that investigated the association of RAS inhibitor use with prognosis of COPD (mortality or risk of acute exacerbation) were selected. The Newcastle-Ottawa Scale was used for quality assessment of observational studies, while the Cochrane risk-of-bias tool was used to assess the quality of RCTs. Statistical analyses were performed using Stata V.15. We selected relative risk (RR) with 95% CI as the effect measure. Heterogeneity was assessed by I-squared (I^2) statistics. The funnel plot was used for visual assessment of publication bias.

Results A total of 20 studies with 5 51 649 subjects were included in the meta-analysis. The overall analysis indicated that RAS inhibitor use decreased the risk of death in patients with COPD (RR: 0.69, 95% CI: 0.61 to 0.78). Subgroup analyses were conducted according to comorbidities, race and type of RAS inhibitors, and the results kept consistent. However, in the pooled analysis of prospective studies, RAS inhibitor use did not significantly decrease the mortality (RR: 0.89, 95% CI: 0.78 to 1.02). Additionally, the risk of exacerbations of COPD did not decrease in patients who were prescribed RAS inhibitors (RR: 0.99, 95% CI: 0.80 to 1.23). The funnel plot indicated significant publication bias.

Conclusion RAS inhibitor use seemed to be associated with a reduction of mortality in patients with COPD. However, the available evidence is weak due to potential biases from retrospective studies and the heterogeneity across included studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic obstructive pulmonary disease (COPD) is considered related to chronic systemic inflammation. Renin angiotensin system (RAS) inhibitor, exerting an anti-inflammatory action in many systems, has been demonstrated relevant to the pathogenesis of COPD. However, the association between RAS inhibitor use and prognosis of patients with COPD remains controversial.

WHAT THIS STUDY ADDS

⇒ RAS inhibitors seem to be associated with a reduction of mortality in patients with COPD, although the evidence that supported this positive association was not strong.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Considering the proven benefits of RAS inhibitors in cardiovascular diseases, routine administration of RAS inhibitors in patients with COPD and these comorbidities seems to be acceptable.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, which is characterised clinically by persistent and irreversible airflow limitation.[1] Currently, pharmacotherapies for COPD include long-acting bronchodilators, inhaled corticosteroid, etc.[2] Although these drugs have shown great benefits to symptom relief and prognosis improvement, the mortality of COPD still ranked third worldwide.[3] High prevalence and mortality of COPD has brought huge health hazards and economic burden.

COPD is considered as a multisystemic disorder, in which not only pulmonary inflammation, but also chronic systemic inflammation occurs.[4] It has been demonstrated that renin angiotensin system (RAS) is relevant to the pathogenesis of pulmonary

and extrapulmonary manifestations of COPD, which have led to increased therapeutic interest in RAS inhibitors (ie, ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB)).[5] Several clinical studies suggested that RAS inhibitors were related to slower lung function decline and emphysema progression.[6 7] A reduction of mortality was also observed in patients with COPD who were prescribed with ACEI/ARB.[8–10] However, Ozyilmaz *et al* found that the use of ACEI was an independent predictor of acute exacerbation of COPD (AECOPD).[11] Moreover, a randomised controlled trial (RCT) also indicated that ACEI reduced the improvement in maximal exercise capacity seen with pulmonary rehabilitation in patients with COPD.[12] These conflicting results made the association between RAS inhibitor use and prognosis of COPD remains unknown. We therefore conducted a meta-analysis and systematic review to summarise current evidence about the association between use of RAS inhibitor and prognosis of COPD.

MATERIAL AND METHODS
We conducted the study and wrote this manuscript in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[13] The Meta-analysis Of Observational Studies in Epidemiology proposal was also taken as a reference.[14]

Patient and public involvement
No patients were involved.

Literature search
We searched databases including Medline, Embase, Cochrane Library and Web of Science for articles by the end of 30 September 2022. Publications in any language were considered. We used the following items as keywords: ('angiotensin converting enzyme inhibitor' OR 'angiotensin receptor blocker' OR 'renin angiotensin system') AND ('chronic obstructive pulmonary disease' OR 'COPD' OR 'chronic obstructive lung disease', 'emphysema'). Please see the details in online supplemental material 1.

Inclusion criteria and exclusion criteria
Observational studies (including cohort and case–control studies) and RCTs were selected. The subjects were patients with COPD. The primary outcome of our meta-analysis was mortality. Studies that reported results including a measure of association between use of RAS inhibitor and rate of AECOPD were also included. Effect measures could be OR, relative risk (RR) or HR. We excluded the literature that did not provide complete data for the quantitative synthesis.

Data extraction and risk-of-bias evaluation
Two researchers (HL and JH) managed literature screening, data extraction and quality assessment independently. The third researcher (CH) was consulted when disagreements arose.

We used The Newcastle-Ottawa Scale (NOS)[15] for quality assessment of included cohort or case–control studies, which was developed specifically for non-randomised studies.[16] It focuses on three important sources of bias, that is, selection bias, information bias and confounding bias. The details of NOS assessment and grading scale of good, fair and poor are presented in online supplemental table 1.

Data synthesis and analysis
We performed statistical analyses using Stata V.15.0 (StataCorp, College Station, Texas, USA). In individual studies, OR, RR and HR were reported as the measure for the association between RAS inhibitors and prognosis of COPD. We selected RR with 95% CI as the effect measure in the present meta-analysis. HRs were directly considered as RRs. ORs were converted into RRs according to the following formula: $RR=OR/[(1–P_0)+(P_0 \times OR)]$, where P_0 is the incidence of the outcome of interest in the non-exposed group.[17] We used forest plots to display results of individual and pooled estimates. Heterogeneity was evaluated by I-squared (I^2) statistics. We chose the fixed-effects model if it is not notable ($I^2 < 50\%$), otherwise, the random effects model would be selected.

The effect of comorbidities on patients with COPD was considered as one of potential sources of bias. COPD often coexists with multiple diseases including cardiovascular diseases and pulmonary hypertension (PH). Meanwhile, RAS inhibitors have shown proven beneficial effects in these diseases.[18] In included studies, the endpoint was all-cause mortality rather than COPD-related mortality. Thus, benefits of RAS inhibitor in these comorbidities may distort its real effects on COPD. Besides, we also focused on the following factors, which might modify the association between RAS inhibitor use and outcome of interest: (1) methodological quality of included studies, (2) the study design, (3) type of RAS inhibitors and (4) race. Subgroup analyses were performed according to the possible biases. In addition, sensitivity analysis was conducted to evaluate the robustness of our results, and the funnel plot was used for visual assessment of publication bias.

RESULTS
Study selection and characteristics
We obtained 837 publications in total after the initial research, and then removed 573 duplicates. After screening abstracts and texts of the remaining articles, 20 studies[8–11 19–34] were finally included in the present meta-analysis. The flowchart shows the whole process of study selection (figure 1).
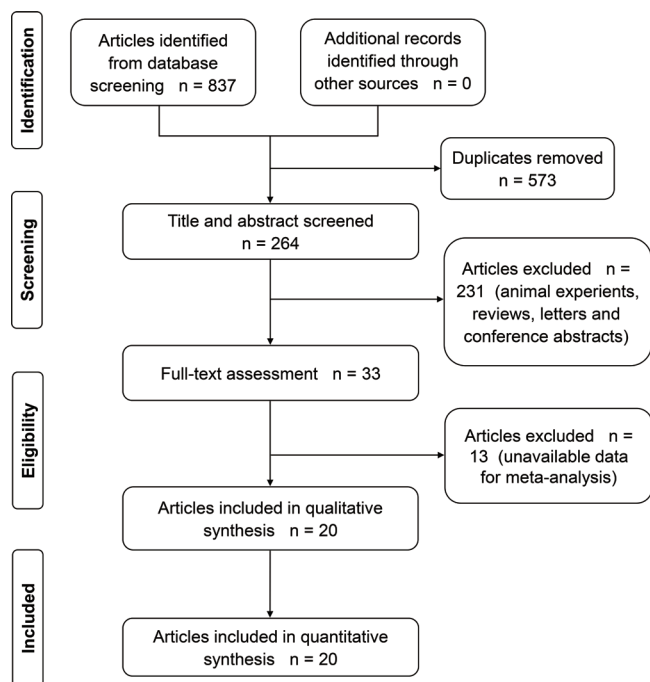
Figure 1 Selection of eligible studies for the meta-analysis.

The characteristics of eligible studies are displayed in table 1 and online supplemental table 2. Twelve studies[9–11 19 20 22–24 26 28 29 32] were conducted in Europe and North America, and eight studies[8 21 25 27 30 31 33 34] were conducted in Asia. These studies were published between 2006 and 2022. The sample size of included studies ranged from 107 to 275 436. Nine studies[8 19 21 24 25 28 30 31 34] included subjects with COPD and other diseases (eg, heart failure (HF), asthma and PH).

Three studies[27 28 32] reported crude HRs (or ORs) and were distinguished as poor quality by NOS assessment. Other studies were considered as high quality (online supplemental table 3).

Meta-analyses and bias analyses
RAS inhibitor use and mortality of COPD

A total of 17 studies[8–10 19–22 24–33] contributed to the primary analysis, which indicated that use of RAS inhibitor decreased the mortality in patients with COPD (RR: 0.69, 95% CI: 0.61 to 0.78, I^2=99.7%; figure 2). Sensitivity analysis suggested that the results were reliable (online supplemental figure 1). Subsequently, we conducted subgroup analyses, and the results were displayed in table 2. (1) In six studies,[10 19 21 24 25 30] the included subjects were COPD patients with HF, PH or high cardiovascular risk. No matter in the studies including COPD patients with these comorbidities or in those including subjects without these comorbidities, RAS inhibitor use decreased the mortality of COPD (RR: 0.67, 95% CI: 0.59 to 0.77 and RR: 0.73, 95% CI: 0.60 to 0.89, respectively; online supplemental figure 2); (2) Three studies[27 28 32] were regarded as poor quality and fourteen

studies[8–10 19–22 24–26 29–31 33] were regarded as high quality, judged by the NOS assessment. In the pooled analysis of high-quality studies, we found a decreased risk of death in patients with COPD who were prescribed RAS inhibitors (RR: 0.69, 95% CI: 0.61 to 0.78; Online supplemental figure 3). (3) Two prospective cohort studies,[22 28] fourteen retrospective cohort studies[8 9 19–21 24–27 29–33] and one nested case–control study[10] were included in our study. In the pooled analysis of retrospective cohort studies, RAS inhibitors decreased the mortality of COPD (RR: 0.73, 95% CI: 0.64 to 0.84; Online supplemental figure 4). However, in the pooled analysis of prospective cohort studies, the mortality of COPD did not significantly decrease (RR: 0.89, 95% CI: 0.78 to 1.02; figure 3). (4) Six studies reported[9 10 21 26 27 33] estimates of association between ARB use and the mortality of COPD, and six studies[10 20 21 26 27 29] measured the association between ACEI use and the mortality. In subgroup analyses, the results remained consistent no matter ARBs or ACEIs that were prescribed (RR: 0.68, 95% CI: 0.60 to 0.77 and RR: 0.76, 95% CI: 0.60 to 0.96, respectively; online supplemental figure 5). (5) A previous meta-analysis reported that the insertion or deletion polymorphism of the ACE gene may be associated with susceptibility to COPD only in the Asian population.[35] Therefore, we also conducted subgroup analyses according to race. No matter in Asian population[8 21 25 27 30 31 33] or in European and North American,[9 10 19 20 22 24 26 28 29 32] RAS inhibitor use decreased the mortality of COPD (RR: 0.71, 95% CI: 0.58 to 0.87 and RR: 0.68, 95% CI: 0.58 to 0.79, respectively; online supplemental figure 6). The funnel plot indicated significant publication bias.

RAS inhibitor use and exacerbations of COPD

Four studies[10 11 23 34] were included in the meta-analysis, and the result indicated that RAS inhibitor use could not decrease the risk of exacerbations of COPD (RR: 0.99, 95% CI: 0.80 to 1.23; figure 4), no matter ARBs or ACEIs were prescribed (RR: 0.90, 95% CI: 0.72 to 1.14 and RR: 0.99, 95% CI: 0.88 to 1.12, respectively; figure 5).

In addition, the funnel plot indicated significant publication bias (figure 6).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis designed to investigate the potential effects of RAS inhibitors in patients with COPD. We comprehensively reviewed available literature and found that RAS inhibitors use were connected with a reduction of mortality. However, evidence from prospective studies did not support a positive association. We did not find a decreased risk of exacerbations of COPD in patients who were prescribed RAS inhibitors. These findings dampened our confidence on the conclusion. Additionally, the interpretation of our results was also limited by the high heterogeneity across the included studies, which could not be satisfactorily explained.

Table 1 Characteristics of studies included in the meta-analysis

Author	Study design	Publish year	Region	Study population	Sample size	Exposure	Outcome	Follow-up
Andersson et al[19]	Retrospective cohort	2019	Denmark	Patients with COPD and RHF	5991	ACEI or ARB	Mortality	2.2 years (mean)
Su et al[34]	Retrospective cohort	2022	Taiwan, China	Patients with asthma–COPD overlap	582	ACEI or ARB	AECOPD	2.98 years (mean)
Ozyilmaz et al[11]	Retrospective cohort	2013	Turkey	Patients hospitalised for AECOPD	107	ACEI or ARB	AECOPD	NA
Mortensen et al[20]	Retrospective cohort	2009	USA	Patients hospitalised for AECOPD	11 212	ACEI	90-day mortality	NA
Mancini et al[10]	Nested case–control	2006	Canada	COPD patients with high cardiovascular risk	19 720	ACEI or ARB	Mortality and COPD hospitalisation	NA
				COPD patients with low cardiovascular risk	103 040			
Ekström et al[22]	Prospective cohort	2013	Sweden	Patients with COPD	2249	ACEI or ARB	Mortality	1.1 years (median)
Paulin et al[9]	Retrospective cohort	2017	Italy	Patients with COPD	4331	ARB	8-year mortality	2557 days (median)
Ho et al[33]	Retrospective cohort	2014	Taiwan, China	Patients hospitalised for AECOPD	4204	ARB	In-hospital and 1-year mortality	NA
Ellingsen et al[26]	Retrospective cohort	2020	Sweden	Patients with COPD	17 745	ACEI or ARB	Mortality	64 306 person-years (total)
Søyseth et al[32]	Retrospective cohort	2007	Norway	Patients hospitalised for AECOPD	854	ACEI or ARB	Mortality	1.9 years (mean)
Su et al[21]	Retrospective cohort	2019	Taiwan, China	Patients with COPD–HF overlap	275 436	ACEI or ARB	Mortality	9.32 years (mean)
Axson et al[23]	Retrospective cohort	2021	UK	Patients with COPD and RHF	8901	ACEI or ARB	AECOPD	NA
Andreoli et al[24]	Retrospective cohort	2013	Multicentre	Hospitalised patients with HF and COPD	1075	ACEI or ARB	In-hospital mortality	NA
Chen et al[25]	Retrospective cohort	2021	Taiwan, China	Patients with PH and COPD	8577	ACEI or ARB	Mortality	5 years (mean)
Zeng et al[27]	Retrospective cohort	2013	China	Patients with COPD	220	ACEI or ARB	Mortality	NA
Kubota et al[30]	Retrospective cohort	2015	Japan	Patients with acute HF and COPD	132	ACEI or ARB	Mortality	33.9 months (mean)
Short et al[29]	Retrospective cohort	2011	UK	Patients with COPD	5977	ACEI	Mortality	4.35 years (mean)
Su et al[31]	Retrospective cohort	2017	Taiwan, China	Hospitalised patients with AMI and COPD	1921	ACEI or ARB	In-hospital mortality	NA
Rodriguez-Mañero et al[28]	Prospective cohort	2019	Spain	Patients with AF and COPD	937	ACEI or ARB	Mortality	707 days (mean)
Ruan et al[8]	Retrospective cohort	2022	USA	Patients with AECOPD and ARF	544	ACEI or ARB	30-day mortality	NA

ACEI, ACE inhibitor; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; HF, heart failure; NA, not available; PH, pulmonary hypertension; RHF, right-sided heart failure.
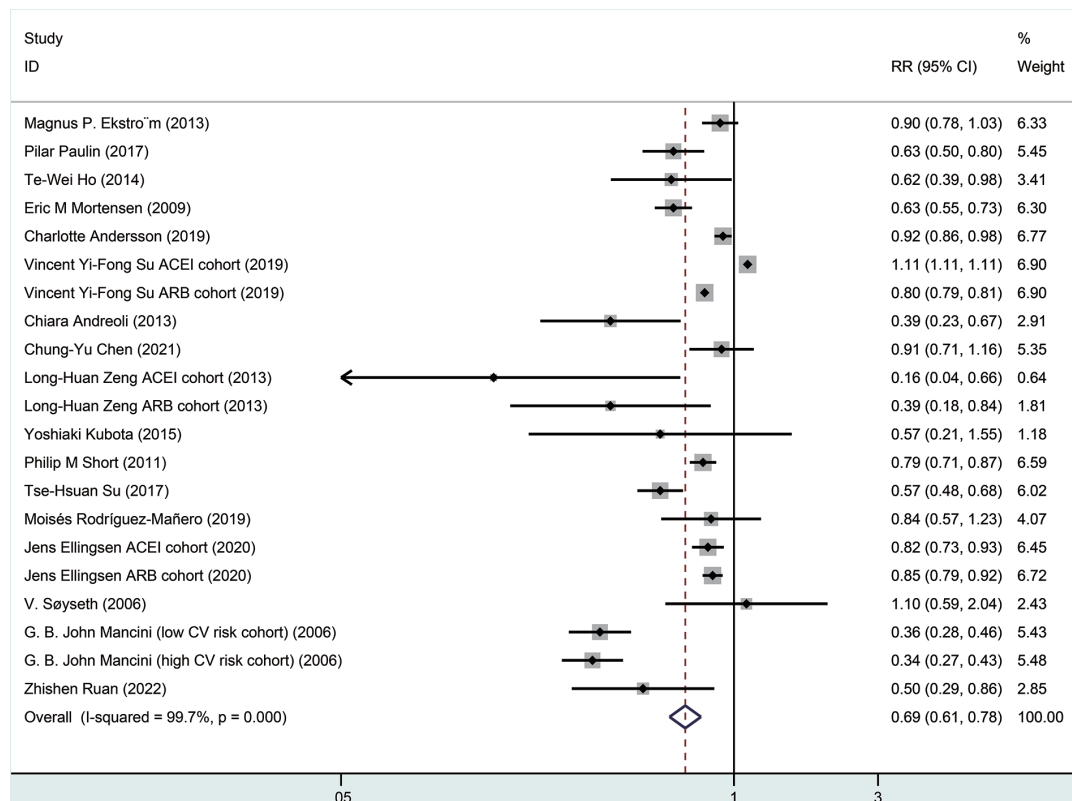
Figure 2 Individual and overall effects of renin angiotensin system inhibitor on the mortality in patients with chronic obstructive pulmonary disease. Note: weights are from random effects analysis. ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular.

It remains unknown whether RAS inhibitors have a beneficial role in respiratory system. Results of previous individual studies are conflicting, which can be attributed to several factors. On the one hand, the effects of RAS inhibitors could be dose dependent. Some retrospective studies were based on databases, in which details about duration and dose of drug use were not available. Some studies included only patients who were exposed to RAS inhibitors in the short term (eg, patients with AECOPD who were prescribed with RAS inhibitors during hospitalisation). Thus, treatment duration may differ a lot across studies. On the other hand, patients with more serious COPD often have a worse prognosis, and the effects of RAS inhibitors could also be different according to the severity of COPD. In most included studies, the data of lung function were not provided, and the severity of COPD was unknown. The pooled analysis suggested that RAS inhibitor use was associated with decreased

Table 2 Subgroup analyses for association of RAS inhibitor use with mortality of patients with COPD

Study characteristic	Studies, n	RR	95% CI	Heterogeneity
Studies including COPD patients with HF, PH or high cardiovascular risk[10 19 21 24 25 30]	6	0.73	0.60 to 0.89	I^2=99.9%
Studies including COPD patients without comorbidities[8–10 20 22 26–29 31–33]	12	0.67	0.59 to 0.77	I^2=84.9%
High-quality studies[8–10 19–22 24–26 29–31 33]	14	0.69	0.61 to 0.78	I^2=99.8%
Prospective cohort studies[22 28]	2	0.89	0.78 to 1.02	I^2=0%
Retrospective cohort studies[8 9 19–21 24–27 29–33]	14	0.73	0.64 to 0.84	I^2=99.8%
Studies including patients exposed to ARB[9 10 21 26 27 33]	6	0.68	0.60 to 0.77	I^2=84.3%
Studies including patients exposed to ACEI[10 20 21 26 27 29]	6	0.76	0.60 to 0.96	I^2=97.4%
Studies conducted in Asia[8 21 25 27 30 31 33]	7	0.71	0.58 to 0.87	I^2=99.9%
Studies conducted in Europe and North America[9 10 19 20 22 24 26 28 29 32]	10	0.68	0.58 to 0.79	I^2=92.2%

ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; HF, heart failure; PH, pulmonary hypertension; RAS, renin angiotensin system.
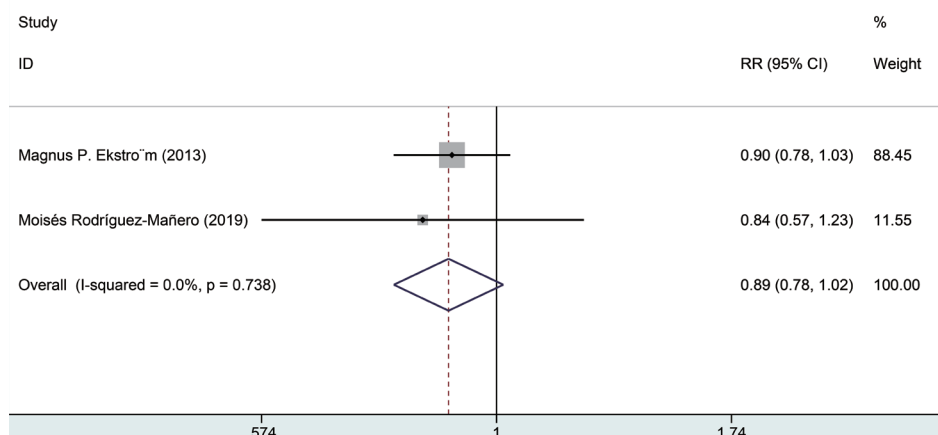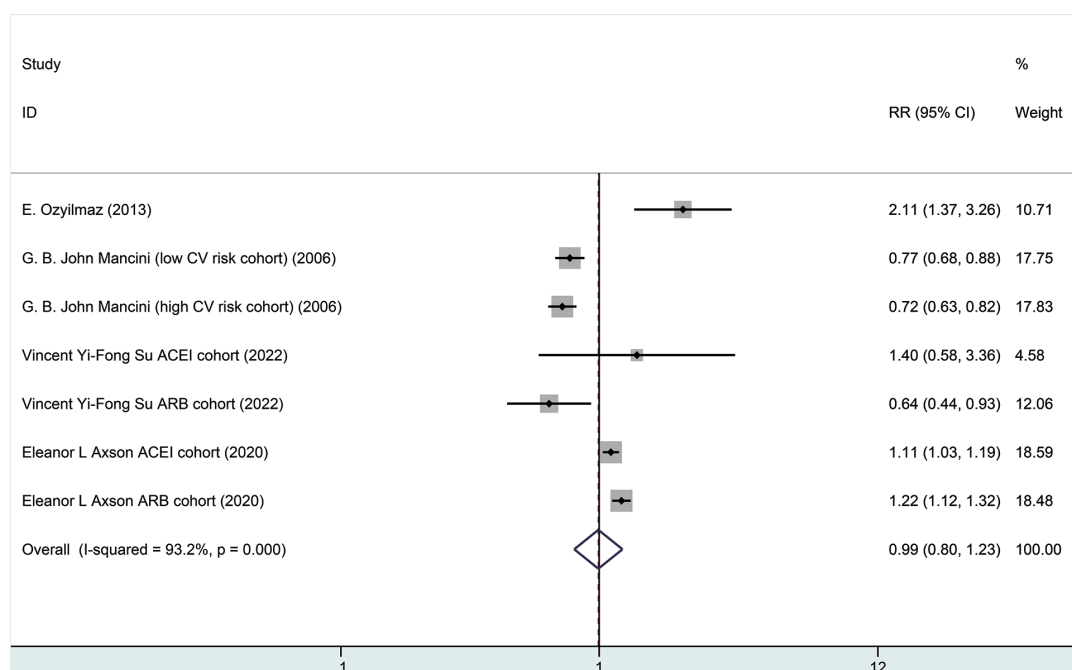
Figure 3 Individual and overall effects of renin angiotensin system inhibitor on the mortality in patients with chronic obstructive pulmonary disease in prospective studies.

mortality in patients with COPD. However, a prospective cohort study including patients with severe COPD indicated that RAS inhibitors could not decrease the risk of death.[22] Moreover, the effects of cardiovascular-related diseases in patients with COPD should not be neglected. Although the subgroup analysis suggested that benefits of RAS inhibitor in these comorbidities were unlikely to confound its real effect on the mortality of COPD, the underdiagnosis of cardiovascular disease is common in patients with COPD,[36] which is still should be considered.

We also performed subgroup analyses according to type of RAS inhibitor. ACEI decreased the risk of death by 24% (RR: 0.76, 95% CI: 0.60 to 0.96), while ARB decreased the risk by 32% (RR: 0.68, 95% CI: 0.60 to

0.77), which indicated that ARB seemed to show more beneficial effects on COPD. These findings were in line with those of Lai et al's studies, which indicated that ARB use was related to lower risk of pneumonia, sepsis and mortality in patients with COPD.[37 38]

Exacerbations of COPD play a critical role in the disease progression, which would accelerate the decline of lung function and ultimately lead to death.[39–41] Respiratory infection is one of the major reasons for acute exacerbations. Previous consecutive meta-analyses indicated a protective effect of RAS inhibitors against pneumonia only in poststroke patients.[42–44] Kim et al discovered that RAS inhibitors treatment was associated with a lower risk of pulmonary infections in patients with COPD.[45]

Figure 4 Individual and overall effects of renin angiotensin system inhibitor on the risk of acute exacerbation of chronic obstructive pulmonary disease. Note: weights are from random effects analysis. ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular.
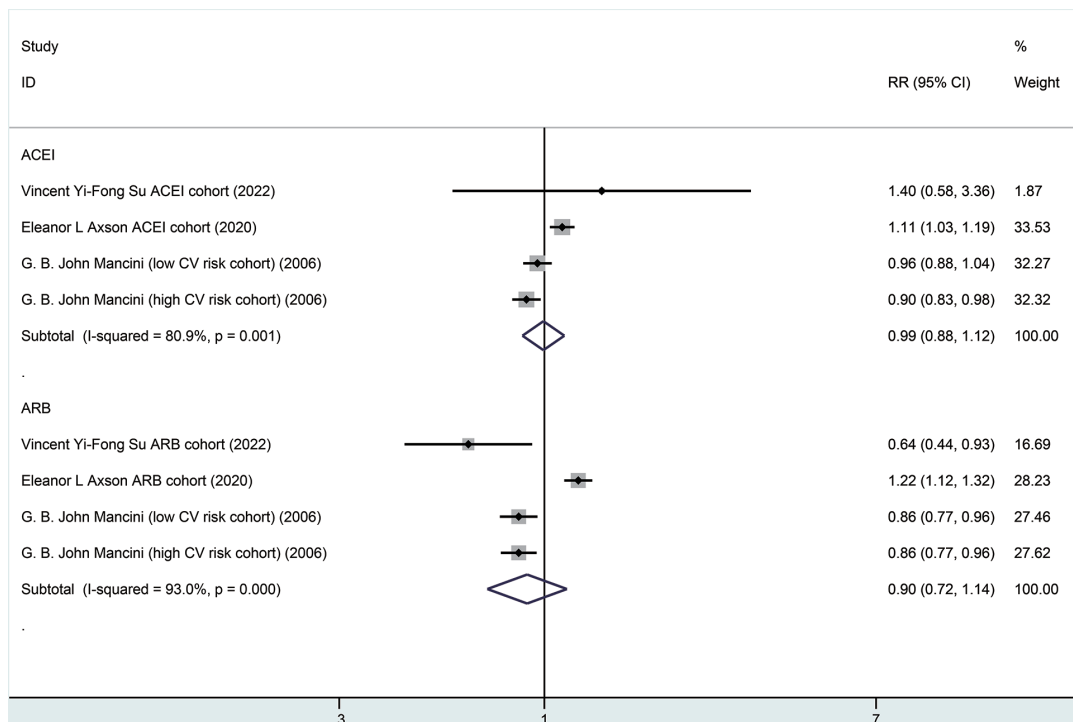
Figure 5 Effects of ACEI and ARB on the risk of AECOPD. Note: weights are from random effects analysis. ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular.

However, our meta-analysis indicated that the risk of COPD exacerbations did not significantly decrease no matter ACEIs or ARBs were prescribed. Perhaps it was a real estimate of the association between RAS inhibitors and COPD, or residual confounding could be another explanation, given that exacerbations of COPD are also related to smoking, air pollution, etc.

The concentration of ACE is high in the lung.[46] Its increased activity is associated with the reduced efficiency of the peripheral use of oxygen and respiratory muscle function.[46 47] Therefore, patients with COPD may benefit from the reduction of ACE activity. In animal models, ARBs have been demonstrated to attenuate cigarette smoke-induced emphysema.[48 49] However, clinical

trials have reported conflicting results. Some indicated that use of RAS inhibitors could slower lung function decline and emphysema progression in subjects with and without smoking habits.[6 7 50] A recently published RCT revealed that losartan failed to show a protective effect on disease progression in patients with COPD with mild-to-moderate emphysema. Additionally, COPD is characterised by systemic inflammation that could affect various extrapulmonary organs.[51] Common systemic consequences include muscle dysfunction and polycythaemia, etc.[5] Interestingly, RAS inhibitors exert an anti-inflammatory action in many systems,[52] which has been considered as another underlying mechanism. Two RCTs have been designed to evaluate the potential benefits of ACEI on exercise function of skeletal muscle. However, one of them suggested that ACEI use reduced exercise training ability in patients with COPD, while the other showed no statistically significant effect of ACEI on improving quadriceps weakness.[12 53] Moreover, mounting evidence indicated that established use of RAS inhibitors led to the shift from polycythaemia to anaemia in patients with COPD.[54]

Due to the mixed results of individual studies, the heterogeneity was very high in the pooled analysis, which was the most obvious limitation of our study. It can be interpreted as some underpowered studies having reported unreliable results. Another possible explanation should be the group differences (eg, age, gender and smoking history), as previous studies have indicated that RAS inhibitors-associated pneumonia risk increased only in poststroke patients. In addition, the heterogeneity
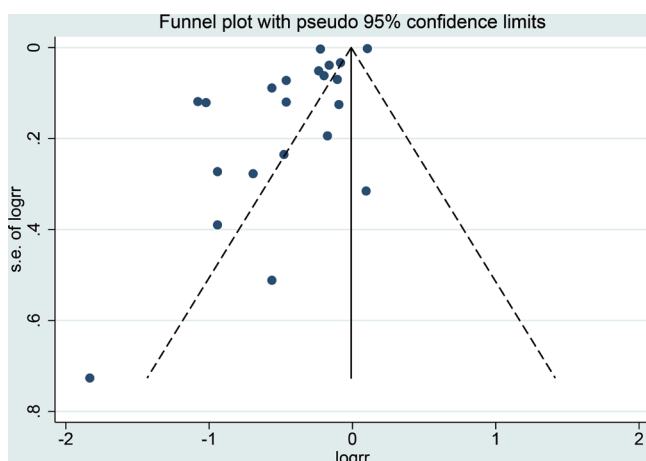
Figure 6 Funnel plot for the evaluation of publication bias.

should be associated with the potential biases in the present meta-analysis. First, most studies were retrospective, so the recall bias is inevitable. Second, the significant publication bias indicated that positive results were more likely to be published. Third, RR was used as the effect measure in our meta-analysis, while some individual studies selected HR. HR involves a time factor, which may lead to potential bias. Last, some individual studies were not mainly designed for the assessment of the relation between RAS inhibitors and prognosis of COPD. Thus, even though numerous covariates had been adjusted, the residual bias may exist.

CONCLUSIONS

In general, the present meta-analysis suggested that RAS inhibitors were associated with a reduction of mortality in patients with COPD. However, current evidence that supported this positive association was not strong. Considering the proven benefits of RAS inhibitors in cardiovascular diseases, routine administration of RAS inhibitors in patients with COPD and these comorbidities seems to be acceptable. In addition, whether RAS inhibitors could decrease COPD-related mortality still need further demonstration in highquality epidemiological studies (eg, well-designed cohort studies) or RCTs.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

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