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REVIEW

Relationship of inhaled long-acting bronchodilators with cardiovascular outcomes among patients with stable COPD: a meta-analysis and systematic review of 43 randomized trials

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Chenxi Li[1]
Wenke Cheng[2]
Jin Guo[1]
Wei Guan[1]

[1]Department of Respiratory, Affiliated Hospital of Qinghai University, Xining, People's Republic of China; [2]Department of Cardiology, Affiliated Hospital of Qinghai University, Xining, People's Republic of China

Background: Long-acting muscarinic antagonists (LAMAs) and long-acting β2–agonists (LABAs) are the mainstay of maintenance therapy for chronic obstructive pulmonary disease (COPD). Although previous studies have supported inhaled long-acting bronchodilators (ILABs) for overall cardiovascular safety, the risk of specific cardiovascular outcomes such as arrhythmia, heart failure and stroke is still unknown.

Materials and methods: We systematically searched from PubMed, the Embase database and the Cochrane Library for published studies on ILABs and COPD, from its inception to November 10, 2018, with no language restrictions. The RRs and corresponding 95% CIs were pooled to evaluate ILAB/placebo.

Results: Finally, 43 randomized controlled trials were included. Compared with placebo, ILABs do not increase the risk of overall and specific cardiovascular adverse events (AEs); on the contrary, they can reduce the incidence of hypertension (RR 0.73, 95% CI 0.55–0.98; $I^2$19.9%; P= 0.221). However, when stratified according to the specific agents of ILABs, olodaterol might reduce the risk of overall cardiovascular adverse events (OCAEs) (RR 0.65, 95% CI 0.49–0.88;$I^2$27.5%; P= 0.000), and the protective effect of lowing blood pressure disappeared. Similarly, the use of inhaled LABA might increase the risk of cardiac failure (RR 1.71, 95% CI 1.04–2.84;$I^2$0%; P= 0.538), but this risk disappeared when stratified according to the specific agents of LABA. Besides, formoterol might decrease the risk of cardiac ischemia (RR 0.53, 95% CI 0.32–0.91; $I^2$0%; P= 0.676).

Conclusions: Overall, the use of ILABs was not associated with overall cardiovascular AEs in patients with stable COPD. When stratified according to the specific agents of LABA, olodaterol might reduce the risk of OCAE; and formoterol might decrease the risk of cardiac ischemia. LABA might reduce the incidence of hypertension, but might increase the risk of heart failure. Therefore, COPD patients with a history of heart failure should use it with caution.

Keywords: bronchodilators, long-acting muscarinic antagonists, long-acting β2–agonists, adverse events, meta-analysis

Correspondence: Wei Guan
Department of Respiratory, Affiliated Hospital of Qinghai University, No. 29 Tongren Road, Xining 810000, People's Republic of China
Tel +860 971 623 0883
Email qhdxfsyyhxnk@163.com

Introduction

Chronic obstructive pulmonary disease (COPD) is a disabling chronic lung disease characterized by poor reversibility and progressive airflow limitation.[1] COPD is prevalent in both industrialized and developing countries, with a prevalence of 5%

in western countries. However, in people >65 years, the prevalence can be as high as 10%.[2] Among COPD patients, cardiovascular disease is the most common comorbidity, which is one of the main causes of hospitalization and death.[3] COPD will be the third leading cause of death worldwide by 2020.[4]

Long-acting muscarinic antagonists (LAMAs) and long-acting β2–agonists (LABAs) are the mainstay of maintenance therapy for COPD.[1,5] Currently, inhaled long-acting bronchodilators (ILABs), LABA and/or LAMA are recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the management of moderate-to-severe COPD.[4] When LABAs and LAMAs are inhaled, they can be transported systemically through the large surface area of the lung, which is characterized by minimal barriers to blood flow.[6]Therefore, this feature may enable LABAs and LAMAs to successfully reach the heart and induce potential adverse events (AEs). Although previous studies[7–9] have supported ILABs for overall cardiovascular safety, the risk of specific cardiovascular outcomes such as arrhythmia, heart failure and stroke is still unknown. Therefore, the purpose of this meta-analysis was to evaluate the relationship between ILABs and cardiovascular outcomes including overall and specific cardiovascular AEs in COPD patients.

Methods

Literature retrieval and study selection

This meta-analysis was performed on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Since this meta-analysis only used data from published studies, no ethical approval was provided.

Two researchers systematically searched from PubMed, the Embase database and the Cochrane Library for published studies on ILABs and COPD, from its inception to November 10, 2018, with no language restrictions. Meanwhile, manual retrieval was also carried out. Generally, literature search was conducted, including three keywords such as "bronchodilators", "chronic obstructive pulmonary disease" and "cardiovascular". Besides, the Boolean operator "AND" is used in these three sets of keywords, and "OR" is used within each group. The detailed search process is shown in Appendix S1. The inclusion criteria for the study are as follows: 1) patients with stable COPD aged at least 40 years have been in clinical stable phase for nearly 3 months without cardiac complications; 2) the experimental group was an ILAB and the intervention group was a placebo; 3) the duration of the treatment was >12 weeks and the endpoint was cardiovascular AE; 4) the type of study was limited to a randomized, double-blind trial. In addition, the exclusion criteria are as follows: 1) the patient had a history of asthma, nearly 3 months in acute exacerbation, or had a cardiac complication; 2) the experimental group was a noninhaled long-acting bronchodilator and the intervention group was not a placebo control; 3) the duration of the treatment was <12 weeks and the endpoint was a noncardiovascular AE; 4) the study type was a nonrandomized, double-blind trial; 5) if duplicate data were used, the study with the longest or most populated follow-up data would be used; 6) Polled studies, conference abstracts, letters and case reports were excluded.

Data extraction and quality assessment

The following data were extracted by using a unified data list which includes first author, year of publication, clinical trials identifier, treatment duration, number of patients, predicted FEV_1(%), mean age, intervention and outcome. The primary outcome of the present meta-analysis was overall cardiovascular AEs and specific cardiovascular AEs during treatment. Overall cardiovascular adverse events (OCAEs) were defined as the total of any cardiovascular-related side-effect events recorded in one study. Fatal cardiovascular adverse events (FCAEs) were defined to include fatal cardiovascular negative events, sudden death and cardiac death, as described in the previous meta-analysis.[10] Meanwhile, if the included studies reported serious cardiovascular events, we classified serious cardiovascular negative events as FACEs. All cardiovascular AEs were encoded by the Medical Dictionary for Regulatory Activities (MedDRA). The included study population should be stable COPD patients with a duration of continuous treatment of at least 12 weeks, and the total number of people in the experimental and control group was extracted. Since most studies only reported the mean value of predicted FEV1 in COPD patients and the corresponding SD, we could not accurately analyze the severity of COPD in all patients. However, the predicted FEV1 of the majority of patients was in the range of 30–80%, so we considered that the severity of COPD in patients was moderate to severe. The RRs and corresponding 95% CIs were pooled to evaluate ILABs/placebo. When the required data were not clear or

missing, the original author would be contacted. Any disagreement in the research process was resolved through consensus. The modified JADAD scale was used to evaluate the quality of the study, which included 8 items such as randomization, blinding, withdrawals/dropouts, inclusion/exclusion criteria, adverse effects and statistical analysis, with a total score of 8 points. Specifically, studies with 4–8 points were considered high quality, studies with 0–3 points were considered low quality.[11]

Statistical analyses

All statistical analyses were performed using Stata 12.0. The heterogeneity was evaluated using the I^2 statistic. The 25%, 50% and 75% I^2 values represent low, medium and high heterogeneity, respectively.[12] To estimate the combined RRs more conservatively, we used a random-effect model rather than a fixed-effect model because the former was more able to explain the heterogeneity between the studies. Besides the pooled results were more stable. In addition, subgroup analysis and sensitivity analysis were used to explain the potential sources of heterogeneity. And also, the potential publication bias was assessed using the Begg's test.[13]

In addition, we divide the ILABs into LAMA and LABA and divide OCAE into hypertension, arrhythmia, heart failure, etc. for subgroup analysis. Besides, a sensitivity analysis was conducted to assess the impact of each study on the results of the pooled study by eliminating each study one by one. And also, analysis trimming and filling would be carried out if necessary.

Results

From the electronic database (PubMed, Embase database and Cochrane), a total of 1,545 studies were identified, as shown in Figure S1. No additional studies that met the inclusion criteria were found by manual search. In the 1,545 studies, 1,225 studies remained after the duplicated studies were excluded. By reading the title or abstract screening, 1,038 unrelated studies were excluded. After reviewing the full text of 187 studies, 144 studies were excluded. The reasons for exclusion are: a) short-acting anticholinergic agents (n=2); b) hormone compound inhalation agents (n=6); c) the duration of trails was <12 weeks (n=5); d) nonplacebo control (n=18); e) outcomes were not cardiovascular events or not related to treatment (n=16); f) cohort studies and case–control studies (n=26); g) conference abstracts (n=29); h) pooled studies (n=5); i) reviews and meta-analysis (n=37). Finally, 43 randomized controlled trials were included. The detailed characteristics of the 43 studies[14–55] included are shown in Table S1. All studies had a JADAD score of 4–8 points, of which both were high-quality studies.

Meta-analysis

Overall cardiovascular AEs

As shown in Figure 1, the use of inhaled LABA/LAMA, LABA or LAMA was not associated with overall cardiovascular negative events ([RR 1.03, 95% CI 0.73–1.46; I^2 19.1% ;P= 0.256], [RR 0.92, 95% CI 0.81–1.04; I^2 48%; P= 0.000], [RR 1.02, 95% CI 0.85–1.24; I^2 50.7%; P= 0.002]), respectively. Meanwhile, the use of ILABs was not associated with overall cardiovascular AEs in the overall population, regardless of the type of inhaled bronchodilator

(RR 0.96, 95% CI 0.87–1.06; I^2 44.7%; P= 0.000). However, when stratified according to the specific agents of LABA, it is shown that olodaterol might reduce the risk of OCAE (RR 0.65, 95% CI 0.49–0.88; I^2 27.5%; P= 0.000), as shown in Table 1. The funnel plot of ILABs and OCAE is shown in Figure S2. Subjectively, the funnel plot was not significantly symmetrical. However, the Begg's test did not find significant evidence of publication bias (P=0.534). In the sensitivity analysis, after each individual study was excluded, the results were only slightly changed. Although 8 additional studies needed to be added by the trimming and filling analysis, there was no significant change in the pooled results (HR 0.958, 95% CI 0.912–1.006 ;P= 0.082).

Fatal cardiovascular AEs

As shown in Figure 2, the use of inhaled LABA/LAMA, LABA or LAMA was not associated with fatal cardiovascular negative events ([RR 1.03, 95% CI 0.38–2.8; I^2 0%; P= 0.699], [RR 0.93, 95% CI 0.75–1.15 I^2 0%; P= 0.908), [RR 0.92, 95% CI 0.81–1.04; I^2 0%; P= 0.797]), repsectively. Meanwhile, the use of ILABs was not associated with fatal cardiovascular AEs in the overall population, regardless of the type of inhaled bronchodilator (RR 0.92, 95% CI 0.83–1.02; I^2 0%; P= 0.973). Not only that, the subgroup analysis showed that any kind of inhaled agents did not increase the risk of FCAE, as shown in Table 1. The funnel plot of ILABs and FCAE is shown in Figure S3. Subjectively, the funnel plot was not significantly symmetrical. However, the Begg's test did not find significant evidence of publication bias (P=0.276). In the sensitivity analysis, after each individual study was excluded, the results were only slightly changed. In addition,

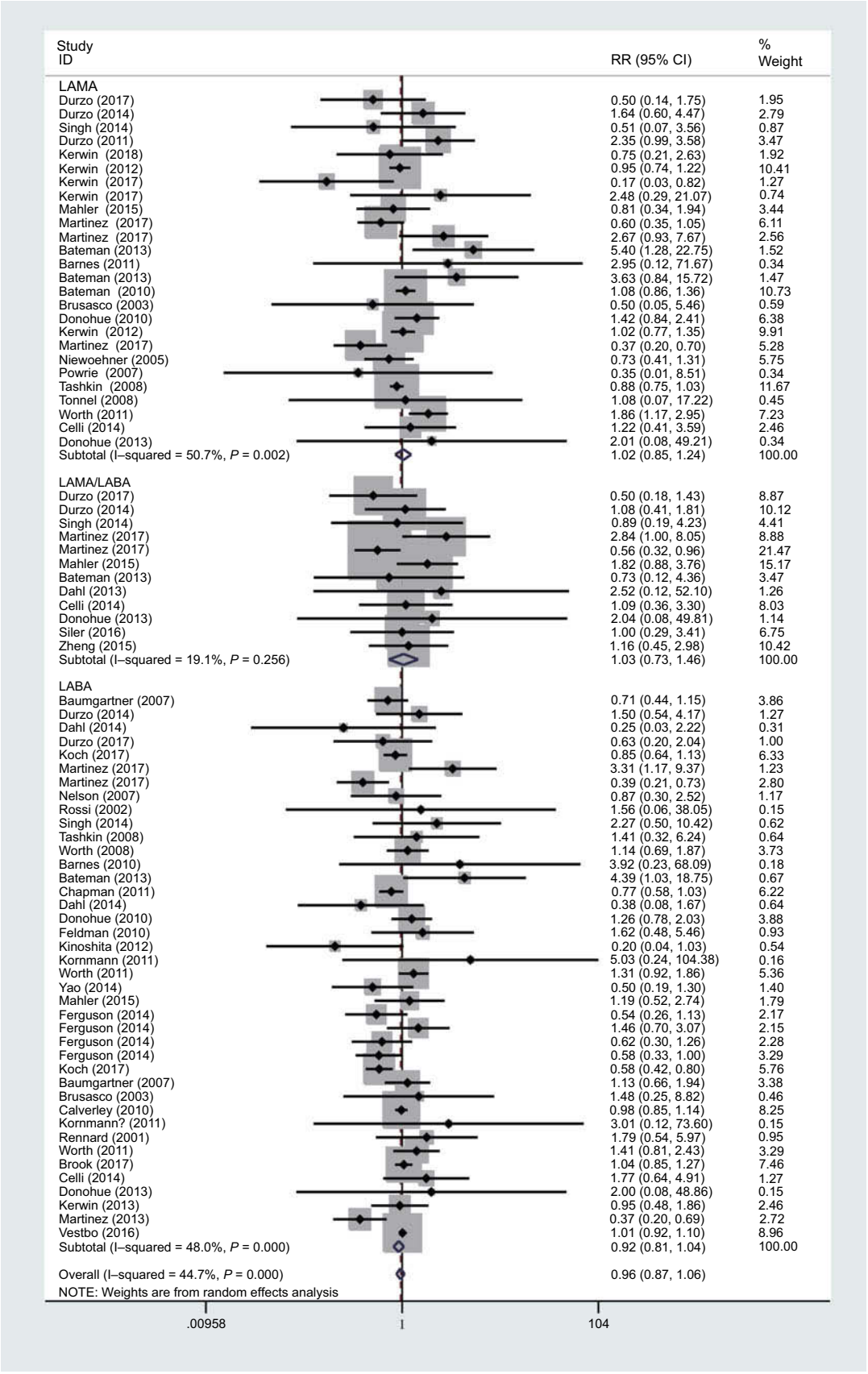

Figure 1 The RRs of ILABs for the risk of OCAE in stable COPD.
Abbreviations: RR, relative risk; ILAB, inhaled long-acting bronchodilator; OCAE, overall cardiovascular adverse event; COPD, chronic obstructive pulmonary disease.

Table 1 Subgroup of specific cardiovascular outcome

Type of ILAB	OCAE HR (95% CI), *P*	SCAE HR (95% CI), *P*	Arrhythmia HR (95% CI), *P*	Hypertension HR (95% CI), *P*	MI HR (95% CI), *P*	Cardiac Failure HR (95%CI), *P*	Stroke HR (95%CI), *P*	Cardiac ischemia HR (95%CI), *P*
Aclidinium	0.89 (0.38–2.08), 0.278	-	-	0.87 (0.44–1.71), 0.408	-	-	-	-
Acldinium/ formoterol	0.7 8(0.41–1.48), 0.000	-	-	0.78 (0.41–1.48), 0.566	-	-	-	-
Formoterol	0.91 (0.67–1.25), 0.056	0.62 (0.30–1.29), 0.475	0.85 (0.60–1.19), 0.319	0.76 (0.50–1.14), 0.408	0.67 (0.22–1.99), 0.221	1.63 (0.50–5.33), 0.103	0.74 (0.12–4.72), 0.236	0.53 (0.32–0.91), 0.676
Glycopyrrolate	0.98 (0.63–1.53), 0.024	0.80 (0.31–2.06), 0.775	1.34 (0.46–3.98), 0.012.	0.68 (0.43–1.07), 0.391	0.49 (0.09–2.68), 0.432	0.96 (0.37–2.45), 0.555	1.99 (0.50–7.92), 0.997	0.56 (0.28–1.10), 0.685
Glycopyrrolate/ formoterol	1.19 (0.23–6.06), 0.005	0.82 (0.14–4.75), 0.845	-	-	-	1.37 (0.54–3.48), 0.314	-	-
Indacaterol	1.03 (0.72–1.47), 0.022	1.07 (0.71–1.60), 0.487	0.94 (0.62–1.43), 0.331	0.61 (0.29–1.28), 0.178	1.02 (0.60–1.72), 0.532	2.06 (0.87–4.88), 0.828	0.68(0.32–1.49), 0.630	-
Indacaterol/ glycopyrrolate	1.63 (0.85–3.15), 0.626	-	-	-	-	-	-	-
Olodaterol	0.65 (0.49–0.88), 0.238	-	1.22 (0.38–3.85), 0.096	0.66 (0.43–1.03), 0.309	-	-	-	-
Salmeterol	1.03 (0.89–1.18), 0.671	0.91 (0.76–1.08), 0.906	1.41 (0.71–2.79), 0.551		-	-	-	1.68 (0.65–4.37), 0.576
Tiotropium	1.01 (0.80–1.28), 0.006	0.92 (0.74–1.15), 0.825	0.73 (0.44–1.22), 0.194	0.83 (0.39–1.75), 0.194	0.81 (0.62–1.05), 0.378	0.90 (0.60–1.35), 0.897	1.04 (0.78–1.39), 0.905	1.13 (0.16–7.93), 0.011
Umeclidinium	1.28 (0.46–3.57), 0.000	0.67 (0.07–6.46), 43	-		-	-	-	-
Vilanterol	0.94 (0.74–1.19), 0.047	0.95 (0.78–1.16), 0.961	-	0.77 (0.06–9.88), 0.095	-	-	-	-
Umeclidinium/ vilanterol	1.12 (0.61–2.06)	0.68 (0.07–6.53)	-	-	-	-	-	-

Abbreviations: ILAB, inhaled long-acting bronchodilator; OCAE, overall cardiovascular adverse event; SCAE, severe fatal cardiovascular adverse event; MI,myocardial infarction.

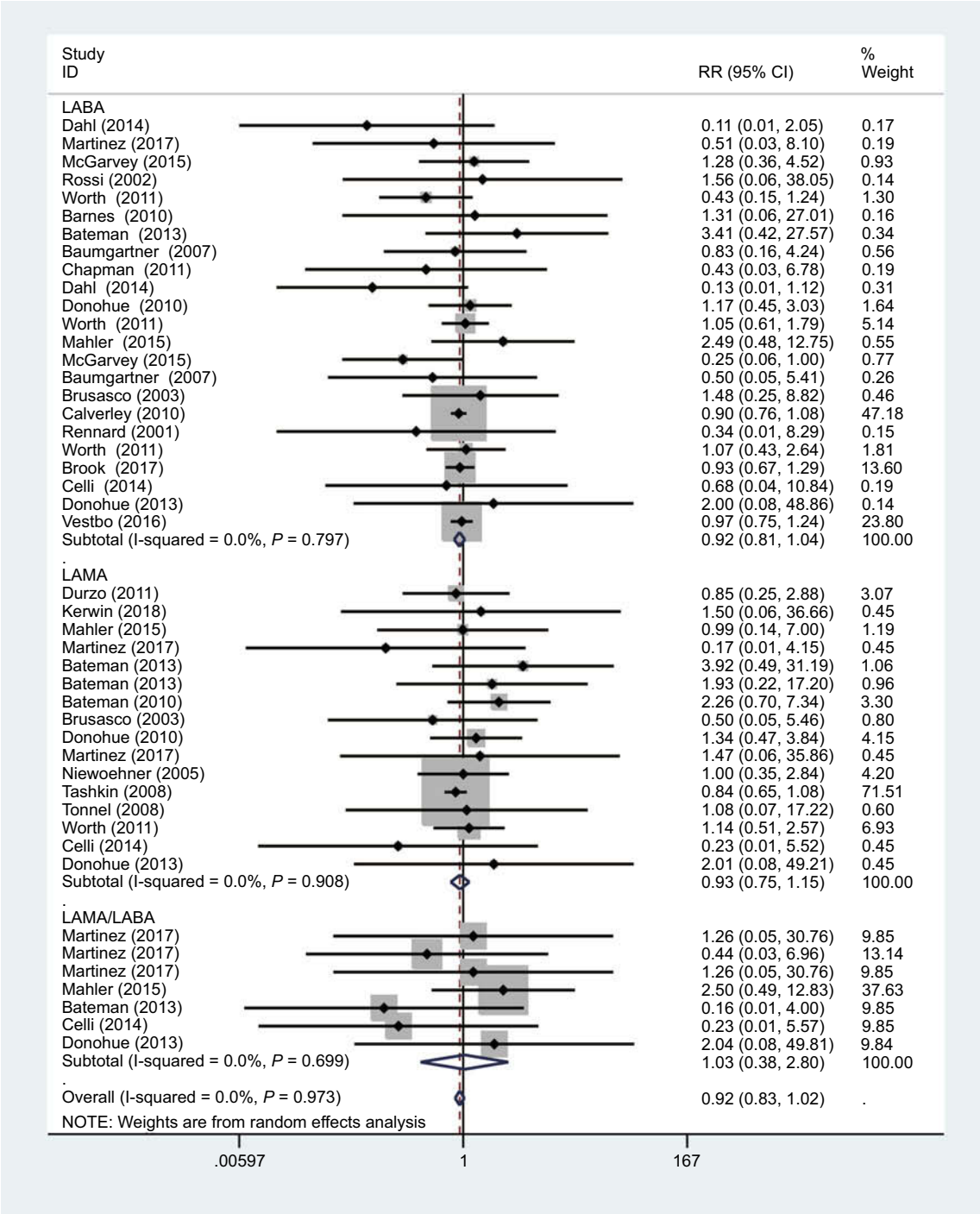

Figure 2 The RRs of ILABs for the risk of FCAE in stable COPD.
Abbreviations: RR, relative risk; ILAB, inhaled long-acting bronchodilator; FCAE, fatal cardiovascular adverse event; COPD, chronic obstructive pulmonary disease.

no additional studies needed to be added by the trimming and filling analysis.

Arrhythmia

As shown in Figure S4, the use of inhaled LABA/LAMA, LABA or LAMA does not increase the risk of arrhythmia ([RR 0.93, 95% CI 0.34–2.51; I^2 53.5%; P= 0.092], [RR 0.94, 95% CI 0.79–1.12 I^2 14.9%; P= 0.251], [RR 0.84, 95% CI 0.57–1.24; I^2 40.6%; P= 0.063]), respectively. Meanwhile, the use of ILABs was not associated with arrhythmia in the overall population, regardless of the type of inhaled bronchodilator (RR 0.89, 95% CI 0.75–1.06; I^2 27.2%; P= 0.056). And

also, the subgroup analysis showed that any kind of inhaled agents did not increase the risk of arrhythmia, as shown in Table 1.

Hypertension

As shown in Figure S5, the use of inhaled LABA/LAMA or LAMA does not increase the risk of hypertension [RR 0.66, 95% CI 0.40–1.08; I^2 38%; P= 0.127], [RR 0.75,95% CI 0.54–1.04; I^2 14.5%; P= 0.299]), respectively. However, the use of inhaled LABA might reduce the risk of hypertension (RR 0.73, 95% CI 0.55–0.98; I^2 19.9%; P= 0.221). Similarly, the use of ILABs presented a trend of lowering blood pressure in the overall population, regardless of the type of inhaled bronchodilator (RR 0.72, 95% CI 0.59–0.88; I^2 18.7%; P= 0.159). Nevertheless, the subgroup analysis showed that any kind of inhaled agents would not increase the risk of hypertension, as shown in Table 1.

Myocardial infarction

As shown in Figure S6, the use of inhaled LABA or LAMA does not increase the risk of myocardial infarction ([RR 1.01, 95% CI 0.75–1.35; I^2 0%; P= 0.628], [RR 0.80, 95% CI 0.62–1.04; I^2 0%; P= 0.762]), respectively. Due to the limited number of studies, no LABA/LAMA-related studies were included. However, the subgroup analysis showed that any kind of inhaled agents did not increase the risk of myocardial infarction, as shown in Table 1.

Cardiac failure

As shown in Figure S7, the use of inhaled LABA/LAMA or LAMA does not increase the risk of cardiac failure ([RR 1.48, 95% CI 0.62–3.55; I^2 0% ;P= 0.498], [RR 0.91,95% CI 0.63–1.32; I^2 0%; P= 0.967]), respectively. Besides, the use of ILABs was not associated with cardiac failure in the overall population, regardless of the type of inhaled bronchodilator (RR 1.17,95% CI 0.88–1.55; I2 0%; P= 0.767). However, when analyzed according to stratification of bronchodilator type, the use of inhaled LABA might increase the risk of cardiac failure (RR 1.71,95% CI 1.04–2.84; I^2 0%; P= 0.538). Surprisingly, this risk disappeared when stratified according to the specific agents of LABA, as shown in Table 1.

Stroke

As shown in Figure S8, the use of inhaled LABA or LAMA does not increase the risk of stroke ([RR 0.79, 95% CI 0.53–1.18; I^2 0%; P= 0.544], [RR 1.07, 95% CI 0.80–1.42; I^2 0%; P= 0.991]), respectively. Meanwhile, the subgroup analysis showed that any kind of inhaled agents would not increase the risk of stroke, as shown in Table 1. Due to the limited number of studies, no LABA/LAMA-related studies were included.

Cardiac ischemia

As shown in Figure S9, the use of inhaled LABA or LAMA does not increase the risk of cardiac ischemia ([RR 0.9, 95% CI 0.55–1.46; I^2 65.1%; P= 0.001], [RR 0.73, 95% CI 0.33–1.59; $I^2$54.6%; P= 0.040]), respectively. However, when analyzed according to stratification of bronchodilator type, the use of inhaled formoterol might decrease the risk of cardiac ischemia (RR 0.53, 95% CI 0.32–0.91; $I^2$0%; P= 0.676), as shown in Table 1. Due to the limited number of studies, no LABA/LAMA-related studies were included.

Discussion

The results of this meta-analysis suggested that the use of ILABs would not increase the risk of overall cardiovascular AEs in the overall population. Moreover, no significant relationship was found between ILABs and other specific cardiovascular AEs. However, when considering stratified analysis based on bronchodilator type, inhaled LABA might reduce the risk of hypertension, but increase the risk of heart failure.

COPD patients are mostly elderly and often have multiple cardiovascular risks. Therefore, a reasonable evaluation of different types of bronchodilators is particularly important for cardiovascular safety. As we all know, LABAs and LAMAs were one of the mainstays of COPD treatment, whether alone or in combination. The use of long-duration bronchodilators improved lung mechanics and cardiovascular function by reducing the required fall in pleural pressure during inspiration and cardiac afterload in COPD patients. However, these drugs not only bound to the lung receptor, but also bound to cardiac receptors. Therefore, these drugs might bring cardiovascular benefits accompanied by potential cardiovascular side effects. Studies conducted by Calzetta et al[56] indicated that there was a synergistic effect between LABA and LAMA in the dual bronchodilation therapy, which would reduce the dose of each single component, thus reducing the risk of negative events. On the other hand, the use of one type of ILABs alone might be more likely to result in cardiovascular AEs.

Studies by Matera et al[57] have shown that the use of LABA might activate stimulating β2-adrenoceptor (β2-AR) in the atria and ventricles, which induces an increase in heart rate, palpitations, and tachyarrhythmias. In addition, activated β2-AR might also induce vasodilation and reflex tachycardia, which might be one of the underlying mechanisms to explain the relationship between inhaled LABA and risk of hypertension and heart failure. Meanwhile, the study of Andreas et al[7] study showed that the use of LABA would reduce blood pressure, which might be related to the diastolic effect of β2-AR on blood vessels. Recently, guidelines for heart failure[58] have shown that the safety of long-term use of cardioactive inhaled pulmonary drugs is uncertain, and patients with heart failure should reconsider the necessity of using these drugs.

Although several previous meta-analyses[59–61] have evaluated the relationship between bronchodilators and cardiovascular AEs, the present meta-analysis still has the following strengths. First, this is the first meta-analysis based on a specific cardiovascular outcome classification. Second, all included studies were high-quality randomized controlled trials, and subgroup analyses were conducted according to the types of long-acting bronchodilators. Third, the results of most studies are highly homogeneous. After sensitivity analysis, publication bias analysis and trimming and filling analysis, only slight changes occurred in the pooled results, which ensured the stability of the study results. Fourth, our findings enrich and validate previous conclusions.

Meanwhile, this meta-analysis inevitably has the following limitations. First, all included study populations were long-term use of long-acting bronchodilators in patients with stable COPD, so the effects of exacerbation of COPD, short-acting bronchodilators, or short-term treatment on cardiovascular outcomes remain unknown. Second, part of the included studies recorded incomplete cardiovascular negative events, which might result in a degree of subjective bias. Third, only the funnel plots of ILABs and OCAE, FCAE were drawn to assess publication bias. In addition, there was a high heterogeneity between some studies, and subgroup analysis cloud not been conducted to find potential sources of heterogeneity due to the limited number of studies. Fourth, the dropout rates in most studies were inevitable, and from the perspective of medical ethics, although the dropout rates in most studies might be significant, it was acceptable. Fifth, in 42 of these included studies, the average age of the study population was over 60 years old,and the severity of COPD was moderate to severe. Generally, cardiovascular disease was the most common complication in elderly patients with COPD and the patients in these 43 included studies did not exclude underlying cardiovascular disease. Therefore,part of the patients included might have a history of cardiovascular disease.

Overall, the use of ILABs was not associated with overall cardiovascular AEs in patients with stable COPD, regardless of the type of inhaled bronchodilator, instead, when stratified according to the specific agents of LABA, olodaterol might reduce the risk of OCAE. and formoterol might decrease the risk of cardiac ischemia. Although the use of inhaled LABA can reduce the incidence of hypertension, but may increase the risk of heart failure. Therefore, COPD patients with a history of heart failure should use it with caution.

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Author contributions

Chenxi Li, Wenke Cheng and Wei Guan conceived and designed the experiments. Chenxi Li, Wenke Cheng and Jin Guo were responsible for acquisition of data. Chenxi Li analyzed the data and wrote the paper. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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