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Efficacy and cardiovascular safety of LAMA in patients with COPD: a systematic review and meta-analysis

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is at present the third leading cause of death in the world. Long-acting muscarinic antagonist (LAMA) is widely used as a bronchodilator in patients with COPD. However, there is controversy concerning their cardiovascular safety. This meta-analysis aims to assess the efficacy and cardiovascular safety of LAMAs versus placebo in patients with COPD. We searched Pub Med, Embase, Cochrane Library, and Web of Science to identify studies that compared LAMA with placebo in patients with COPD. Twenty-one studies involving 24,987 participants were finally included in the analysis. There was no significant difference in the incidence of all adverse events (risk ratio (RR)=1.01, 95% CI 1.00 to 1.02, I^2=15.2%) and cardiovascular events (RR=0.98, 95% CI 0.88 to 1.09, I^2=4.9%) in patients treated with LAMAs versus placebo. LAMAs significantly improved trough forced expiratory volume in 1 s (weighted mean difference (WMD)=0.12, 95% CI 0.10 to 0.14, I^2=86.6%), Transitional Dyspnea Index (WMD=0.75, 95% CI 0.56 to 0.94, I^2=0%), and St. George's Respiratory Questionnaire (WMD=–2.50, 95% CI –3.32 to –1.69, I^2=39.8%). Moreover, LAMAs significantly reduced the incidence of exacerbation in patients with COPD (RR=0.85, 95% CI 0.79 to 0.91, I^2=69.9%). LAMAs are safe therapy and play a pivotal role in improving lung function, dyspnea, and health status, and reducing the exacerbation in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation. According to the top 10 causes of death released by the WHO on May 24, 2018, it is the third leading cause of death in the world.[1–3] The bronchodilator is the cornerstone in the treatment of patients with COPD.[1] Long-acting muscarinic antagonist (LAMA) is one of the bronchodilators, containing glycopyrronium, umeclidinium, aclidinium, tiotropium, and revefenacin.[4] Besides, LAMAs are recommended for patients with COPD in Global Initiative for Chronic Obstructive Lung Disease groups A–D.[1 5]

Although LAMAs are widely used for maintenance bronchodilation in patients with COPD,[1] there is controversy regarding their cardiovascular safety.[6–11] Dong *et al* reported that tiotropium had a higher risk of mortality compared with other inhaled medications.[8] Similarly, Singh *et al* demonstrated that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular mortality.[12] However, several large clinical randomized controlled trials (RCTs) regarding LAMA in patients with COPD reported that there was no increasing risk in major adverse cardiovascular events (MACEs), which indicated a composite of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke.[9 13 14] Furthermore, Wise *et al* recently carried out a 3-year large RCT to assess the cardiovascular safety and efficacy of aclidinium in patients with COPD and found no increased risk in MACE compared with placebo.[15]

Also, it is a pivotal issue to assess the effect of LAMA versus placebo on relevant outcomes of patients with COPD. However, high-quality meta-analyses available did not include the recently published large RCTs.[15 16] Moreover, they included a single LAMA whereas did not conduct a general analysis of different LAMAs.[17–19]

Accordingly, this meta-analysis aimed to determine the efficacy and cardiovascular safety of LAMA. We assessed the cardiovascular safety of LAMA based on all adverse events (treatment emergent and other adverse events) and expand MACE that defined as MACE and other serious cardiovascular events (such as acute heart failure, life-threatening arrhythmias and so on). Lung function, dyspnea symptoms, and health-related quality of life (HRQoL) were used to evaluate the efficacy of LAMA. Furthermore, we expected this meta-analysis to provide more precise evidence for the clinical use of LAMAs.

METHODS

This systematic review methodology complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidance.[20] It is based on a protocol that was

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registered in the PROSPERO register of systematic reviews (CRD42020163598).

Literature search

We searched Pub Med, Embase, Cochrane Library, and Web of Science from inception to December 2019 (update on March 2021), to identify RCTs that compared LAMA versus placebo in patients with COPD. There was no restriction about language or population. We checked reference lists of all studies that were identified by the above-mentioned searches. Also, the ClinicalTrials.gov database was searched for the completed eligible study. The following keywords were used in our search: long-acting muscarinic antagonists (glycopyrronium, umeclidinium, aclidinium, tiotropium, revefenacin), chronic obstructive pulmonary disease, and RCT. The detailed search strategy was shown in the online supplemental file 1.

Inclusion and exclusion criteria

Inclusion criteria

- Studies which were placebo-controlled, parallel-group RCT with at least 8 weeks' duration, in patients with COPD confirmed by spirometry, comparing the efficacy and safety of LAMA with placebo.
- Studies were required to report at least one of the following outcomes: all adverse events, expand MACE (including coronary artery disease: MI, angina, angioplasty/stent/coronary artery bypass graft; peripheral vascular disease: history of claudication; or cerebrovascular disease: stroke or transient ischemic attack, carotid stenosis), trough forced expiratory volume in 1 s (trough FEV_1), HRQoL assessed with the St. George's Respiratory Questionnaire (SGRQ), symptoms (dyspnea) assessed with the Mahler Transitional Dyspnea Index focal score (TDI), and COPD exacerbation.

Exclusion criteria

- Studies that described LAMA treatment on other lung disease, such as asthma, obstructive sleep apnea hypopnea syndrome, acute respiratory distress syndrome, and asthma–COPD overlap.
- Studies that researched animals or cells.
- Studies that are conference abstracts, letters, editorials, reviews, and meta-analyses.

Study selection and data extraction

Two authors (CCZ and MZ) reviewed the search results for relevant article titles meeting the inclusion criteria. All titles screening and full-text eligibility assessment were performed by one of the authors (CCZ), the references that did not meet the eligibility criteria were excluded. Another reviewer reassessed and validated study selection (MZ). Minor disagreements were settled by discussion. Data from each study were extracted by one author (CCZ) and validated by a second author (MZ) in exhaustive tabulated data extraction forms, with a cross-check against the original papers. For every study included, the following data were extracted: participant (sample size, mean age, gender, and current smoker), intervention (drug, inhaler, dosage, and frequency), outcomes (all adverse events, cardiovascular events, trough FEV_1, SGRQ score, TDI score, and exacerbation), and design (authors, location, publication year, study design, and duration of follow-up).

Assessment of risk of bias in included studies

We assessed the quality following 6 points outlined in the Cochrane Handbook for Systematic Reviews of Interventions, which included random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (attrition bias) and other potential sources of bias. The criteria to grade included studies were as follows: (1) trials were graded as low quality if either randomization or allocation concealment was assessed as a high risk of bias, regardless of other items; (2) trials were graded as high quality when both randomization and allocation concealment were assessed as a low risk of bias, and all other items were assessed as low or unclear risk of bias in a trial; (3) trials were graded as moderate quality if they did not meet criteria for high or low risk. The risk of bias was assessed by two reviewers independently (HX and YW) and the discrepancy was solved by consulting an evidence-based medicine professor.

Data analysis

Stata/SE V.15.0 was used to perform all data analyses. We explained the metric of analysis for outcomes as the following: risk ratios (RRs) and their associated 95% CIs were used as the effective measures for the outcomes of dichotomous data. Weighted mean difference (WMD) and the corresponding 95% CI were used for continuous outcomes. We used p value and I^2 statistic to measure heterogeneity among the trials in each analysis. The fixed or random effect models were used without important heterogeneity (I^2 <50%) or with moderate heterogeneity (I^2 ≥50%), respectively. We performed a subgroup analysis to analyze any possible source of heterogeneity when the heterogeneity was high. A sensitivity analysis was performed to detect if the results were stable and reliable. If there were 10 or more publications, a funnel plot, Egger's test, and Begg's test were used to assess publication bias.[21 22]

RESULT

Eligible studies and risk of bias

We obtained 3565 records from four databases and other sources, and 2463 remained after deduplication. Full texts of 108 records were read, of which 32 RCTs from 29 records met the eligibility criteria and were included in the final meta-analysis.[14–16 23–48] There were 3 articles that each reported 2 RCT studies.[23 29 40] The 32 RCTs included 29,857 participants, of whom 16,548 received LAMA and 13,309 received placebo.[14–16 23–39] The selection process was shown in figure 1. In eligible studies, 18 RCTs were high-quality studies. The risk of bias in the 6 items of the Cochrane instrument was shown in the online supplemental figures S1 and S2.

Description of included studies

We listed specific characteristics of included studies in online supplemental table S1. All included studies were randomized, double-blind, placebo-controlled trials. In eligible studies, 6 RCTs studied aclidinium versus placebo

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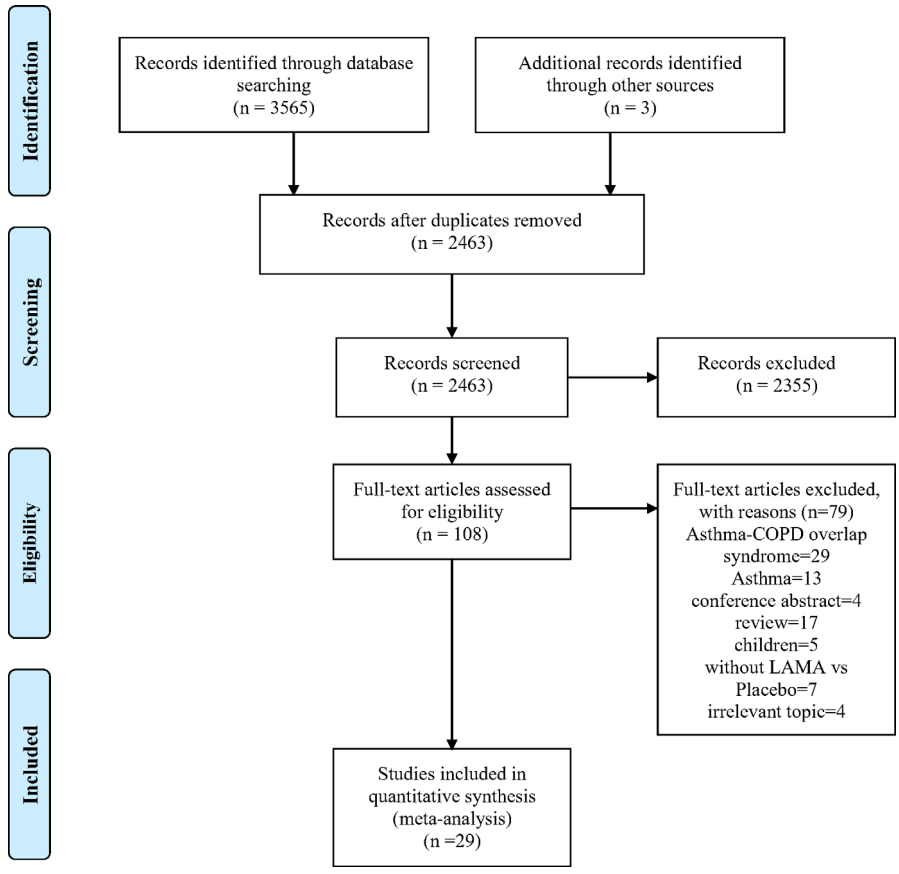

Figure 1 Study selection process: PRISMA flow diagram identifying studies included in the meta-analysis. COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

in patients with COPD.[15 25 26 28 29] The dosage of aclidinium was 200 µg once daily or 400 µg two times per day. There were 7 RCTs that described glycopyrronium which was administrated as 50 µg once daily, 18 µg two times per day or 15.6 µg two times per day.[23 24 27 30 41 45] Eleven RCTs assessed tiotropium 5 µg, 10 µg, or 18 µg two times per day on administrating patients with COPD.[14 16 31–39] Six RCTs reported umeclidinium 62.5 µg or 125 µg once daily in patients with COPD.[42–44 46–48] Also, revefenacin 175 µg once daily on patients with COPD was reported by 2 RCTs which was contained in 1 article.[40]

Effect of treatments on safety outcomes

In eligible studies, 32 RCTs reported all adverse events.[14–16 23–48] There were no significant differences in the incidence of all adverse events of patients with LAMA versus those with placebo (RR=1.01, 95% CI 1.00 to 1.02, I^2=15.2%, figure 2). Similarly, 23 RCTs described cardiovascular events (expand MACE)[14–16 23 24 26–32 38 40 42–47] and we found no higher increase risk of cardiovascular events in patients with COPD with LAMA versus placebo (RR=0.98, 95% CI 0.88 to 1.09, I^2=4.9%, figure 3). Furthermore, considering that the duration of included studies varied from 8 to 192 weeks, we conducted subgroup analysis based on the duration. The results indicated that there was no increased risk in all adverse events and cardiovascular events in patients with COPD receiving LAMA compared with those receiving placebo (online supplemental figures S3 and S4).

Effect of treatments on trough FEV_1

We evaluated the improvement of lung function by the change of trough FEV_1 from baseline. Twenty-four RCTs reported trough FEV_1.[23–27 30–35 39 41–44 46–48] Overall, LAMA was proved to be superior to placebo in all studies (WMD=0.12, 95% CI 0.10 to 0.14, I^2=86.6%, figure 4). As for the heterogeneity, we performed subgroup analysis based on the type of LAMA, the treatment duration, and the inhaler of LAMA, which indicated that they are not the main sources of the heterogeneity (online supplemental figures S5–S7).

Effect of treatments on dyspnea and HRQoL (TDI, SGRQ)

The effect of treatment on dyspnea and HRQoL was assessed by TDI and SGRQ, respectively. Nine RCTs measured the TDI score from baseline and indicated that LAMA led to significant improvement in TDI compared with placebo (WMD=0.75, 95% CI 0.56 to 0.94, I^2=0%, online supplemental figure S8).[23 25–28 30 41 46 47] Thirteen RCTs reported TDI responders, indicating that more participants receiving LAMA had a clinically meaningful difference in TDI score compared with placebo (RR=1.29, 95% CI 1.23 to 1.35, I^2=0%, online supplemental figure

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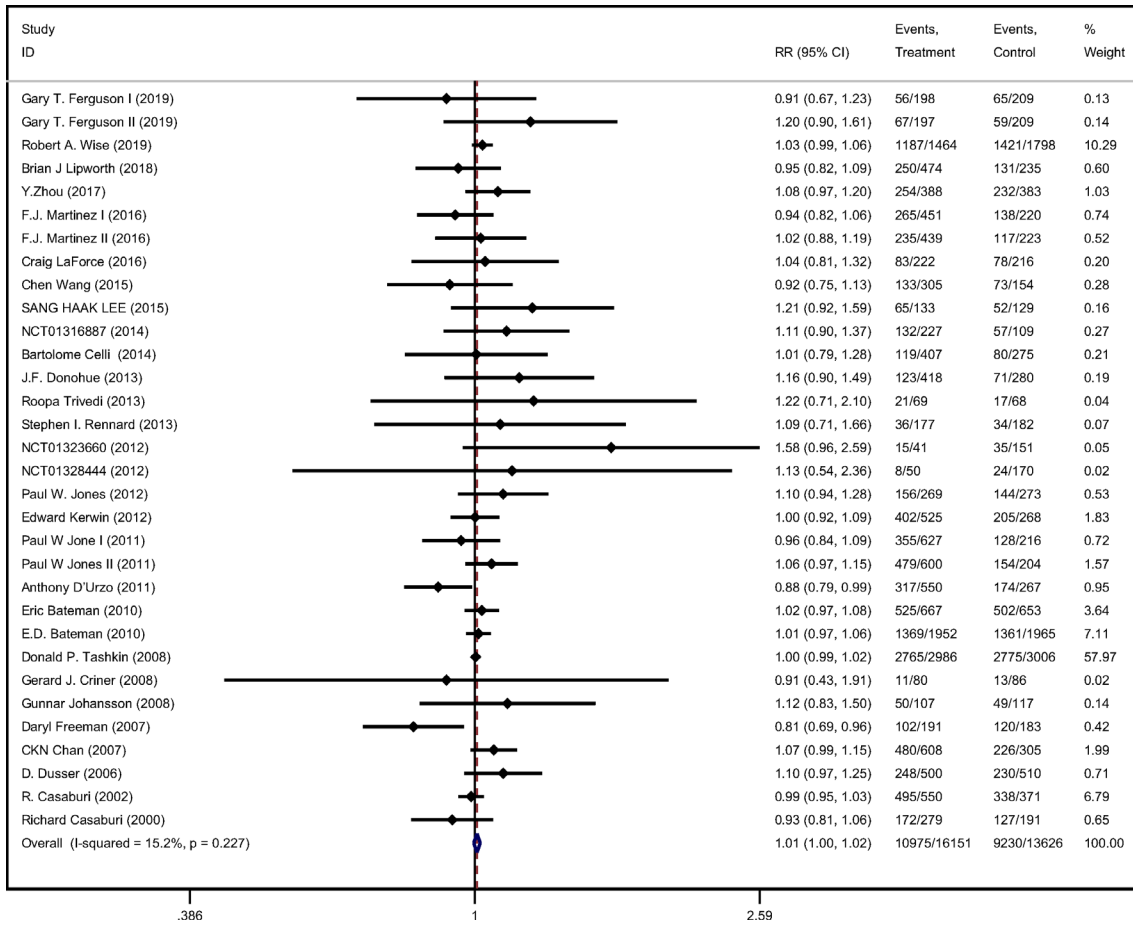

Figure 2 Forest plot of all adverse events in patients with COPD with LAMAs versus placebo. COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; RR, risk ratio.

S9).[23–30 32 41 46 47] Likewise, 9 RCTs reported SGRQ and demonstrated that LAMA was associated with an improved quality of life compared with placebo (WMD=–2.50, 95% CI –3.32 to –1.69, I^2=39.8%, online supplemental figure S10).[23 25–27 30 41 45 47] More participants with LAMA had a clinically meaningful difference in SGRQ compared with placebo (RR=1.23, 95% CI 1.19 to 1.27, I^2=0%, online supplemental figure S11).[14 23–32 36 38 40 41 45–47]

Effect of treatments on COPD exacerbation

Nineteen RCTs reported the number of patients with at least one moderate or severe exacerbation. The meta-analysis results indicated that LAMA reduced the incidence of COPD exacerbation over placebo (RR=0.85, 95% CI 0.79 to 0.91, I^2=69.9%, online supplemental figure S12).[14–16 23 24 26–34 36–38 41] The subgroup analysis showed that glycopyrronium had a more significant effect on reducing the number of patients with at least one moderate or severe exacerbation (online supplemental figure S12). Besides, due to the inconsistency of the duration, we performed subgroup analysis based on the duration which indicated that LAMAs did decrease the exacerbation of patients with COPD (online supplemental figure S13).

Sensitivity analysis and publication bias

As for the safety outcome (including all adverse events and cardiovascular events), the results of the sensitivity analysis did not change after removing the included studies one by one (online supplemental figures S14 and S15). With regard to the efficacy outcome of trough FEV_1 and the reduction of COPD exacerbation, the results of the sensitivity analysis remained consistent after excluding the studies one by one (online supplemental figures S16 and S17, online supplemental table S2). The Egger's test and the Begg's test both indicated that there was no significant publication bias (Egger's test, p=0.337; Begg's test, z=0.92, p=0.355). The result of the funnel plot was shown in online supplemental figure S18.

DISCUSSION

Based on the findings of this systematic review and meta-analysis, LAMA is an effective and safe treatment for patients with COPD. There was no significant difference observed in all adverse events (treatment emergent and other adverse events) and cardiovascular events between LAMA and placebo group. Also, LAMA led to conspicuous improvements in lung function, HRQoL (SGRQ), dyspnea (TDI), and a reduction in the number of patients with COPD exacerbation.

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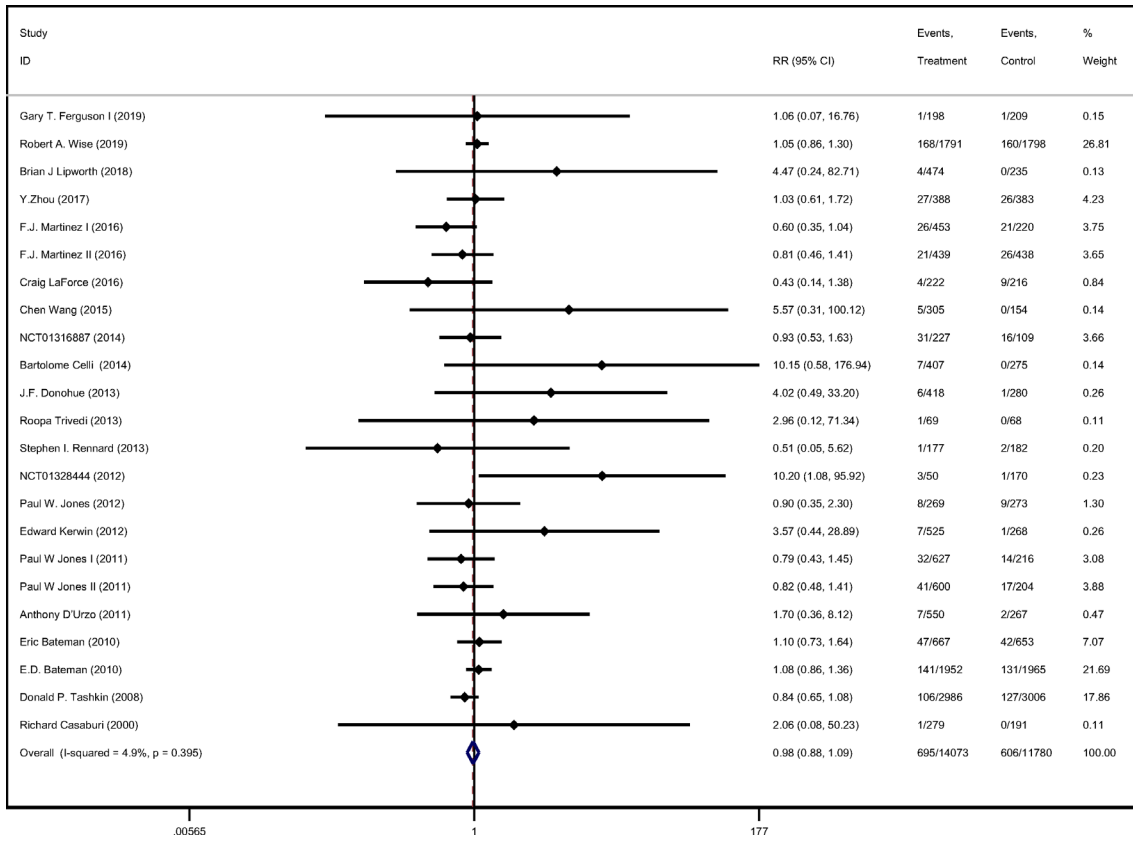

Figure 3 Forest plot of cardiovascular events in patients with COPD with LAMAs versus placebo. COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; RR, risk ratio.

The results of this meta-analysis revealed that LAMA is a cardiovascular safe therapy for patients with COPD compared with placebo based on current evidence. In contrast, a meta-analysis by Singh *et al*[12] reported that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD. The meta-analysis included clinical trials regarding ipratropium, which is one of the short-acting muscarinic antagonists. However, the subgroup analysis indicated that tiotropium was not associated with higher cardiovascular risk compared with placebo (RR=1.43, 95% CI 0.95 to 2.16, I^2=0%). This meta-analysis was later considered with several methodology limitations, such as potential study selection bias, which was limited to trials reporting cardiovascular events; lack of assessment of patient follow-up time and so on.[13] As for several clinical trials reported that ipratropium was associated with increased risk of cardiovascular events or death, these studies are retrospective analyses and there are inherent limitations and problems that preclude definitive conclusion.[49] Thus, the result actually is consistent with our findings. Also, a post hoc study of tiotropium found no increased risk in patients with recent cardiovascular events.[50] Similarly, a pooled analysis of aclidinium found no evidence of increased cardiovascular risk with aclidinium versus placebo.[51] On the other hand, observational studies also reported conflicting results.[10] This discrepancy can be explained with the exclusion of patients who have cardiovascular comorbidities and renal impairment in clinical trials.[52 53] Consequently, more high-quality RCTs assessing the safety of LAMAs which specifically enrolled patients with increased cardiovascular risk are needed in the future.

This meta-analysis demonstrated that LAMAs were associated with significant improvement in lung function compared with placebo. LAMAs led to a greater improvement in trough FEV_1 of between 100 mL and 140 mL over placebo. This has the physiological rationality: antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle; LAMAs have prolonged binding to M3 muscarinic receptors, thus prolonging the duration of bronchodilator effect.[4] The result was consistent with several meta-analyses that studied the safety and efficacy of aclidinium or tiotropium.[17 19]

The results found in lung function were paralleled with significant improvements in the SGRQ score and TDI focal score. Mean differences in SGRQ reduction between LAMA and placebo observed in our analysis were between 1.69 and 3.32 units. The minimal clinically important difference for SGRQ score is 4 units.[54] The mean differences were not reached to 4 units, but the probability of having a response superior to 4 units was significantly increased by 23% versus placebo. The mean difference in TDI score improvement was observed as 0.56–0.94 units. The minimal clinically important difference for TDI score is 1 unit.[55] Patients with LAMAs had a 29% higher probability to experience an improvement >1 unit in the TDI dyspnea score versus patients treated with placebo. The results are consistent

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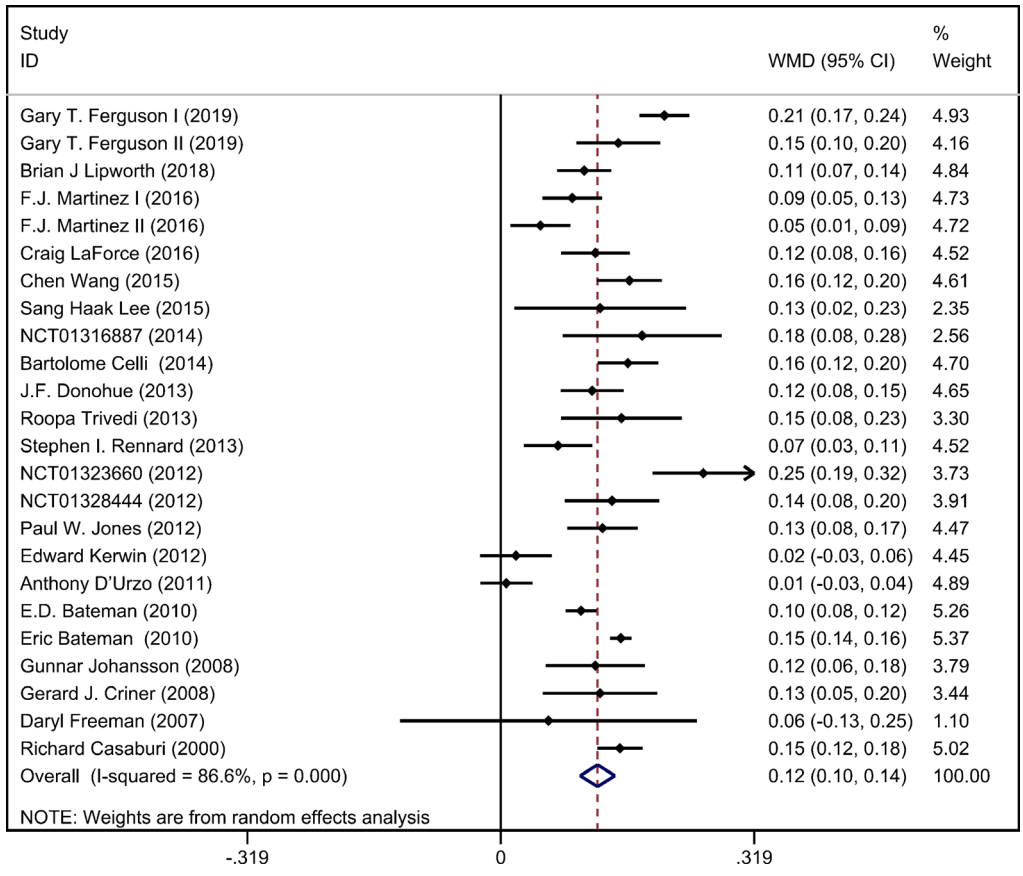

Figure 4 Forest plot of trough FEV_1 in patients with COPD with LAMAs versus placebo. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; LAMA, long-acting muscarinic antagonist; WMD, weighted mean difference.

with an available meta-analysis, which suggested that all LAMAs are efficacious relative to placebo.[56]

Additionally, LAMAs were associated with a reduced number of patients with at least one moderate or severe exacerbation. Based on current evidence, we found that LAMAs led to a 15% lower exacerbation rate compared with placebo. The results were consistent with a meta-analysis of tiotropium which suggested that tiotropium reduced exacerbation of patients with COPD.[18] Reduction in exacerbation is an overarching goal in the management of COPD.[1] Thus, the finding of this meta-analysis indicates that LAMAs are effective therapy for patients with COPD.

However, the heterogeneity of lung function was high. Subgroup analysis does not effectively reduce heterogeneity. After we conducted a sensitivity analysis, the directions of effect sizes were consistent among the included trials. We considered the source of heterogeneity might be as follows: first, medicine factors (the dosage, administration device) were variable in different research. There were 200 µg once daily[29] and 400 µg two times per day[15 25 26 28] of aclidinium usage. Regarding glycopyrronium, the included studies used 15.6 µg two times per day[23] or 50 µg once daily.[24 27 30] There were 5 µg once daily,[32] 10 µg once daily,[31] and 18 µg once daily[14 16 33–39] of tiotropium treatment. The administration device was soft mist inhaler, dry-powder inhaler, metered-dose inhaler, or jet nebulizer from different manufacturers. The differences in dosage and administration device might both influence the treatment effect. Second, the treatment duration was 8–192 weeks, which might influence the heterogeneity of lung function. Third, several factors might impact the measurement of lung function, such as the tester's professional competence and the patients' education status. Finally, the patients' severity of COPD and smoking status might influence the efficacy of LAMA in improving lung function. Thus, these could also be a source of heterogeneity.

Besides, the heterogeneity is high regarding the number of patients with at least one moderate or severe exacerbation. We considered the heterogeneity source might be the diagnosis of COPD exacerbation. Exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.[57 58] However, the diagnosis of COPD exacerbation in clinical setting depends largely on the subjective judgment of the physician, which might be the source of the heterogeneity.

Finally, this meta-analysis had several limitations. First, we did not perform a detailed analysis of every adverse event due to lack of original data. Second, several endpoints such as exercise tolerance and rescue medication use were not included for the reason that there were no consistent definitions and methodology for the two endpoints across trials, precluding accurate comparisons. Finally, several studies included in meta-analysis were sponsored by Pharmaceutical Manufacturing Company. This might cause publication bias for these results and lead to a decrease in the reliability of our results.

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CONCLUSION

Based on the finding of this meta-analysis, LAMAs did not increase cardiovascular risk in patients with COPD compared with placebo. Also, LAMAs play a pivotal role in improving lung function, dyspnea, and health status, and reducing the incidence of exacerbation in patients with COPD.

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