

Review

A Long-acting Muscarinic Antagonist (LAMA) Added to an Inhaled Corticosteroid and Long-acting Beta-2 Agonist Versus LAMA Alone in Moderate-to-severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis of Randomized Trials

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Abstract : We assessed the overall efficacy and safety of a long-acting muscarinic antagonist (LAMA) added to an inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) as a combination therapy (LAMA + ICS/LABA) versus LAMA monotherapy in patients with chronic obstructive pulmonary disease (COPD). The overall efficacy and safety of LAMA + ICS/LABA versus LAMA in patients with COPD were assessed by a meta-analysis of randomized controlled trials (RCTs). We identified LAMA + ICS/LABA RCTs by searching PubMed, Scopus, and the Cochrane Library database. Primary efficacy outcomes were changes in forced expiratory volume in 1 second (FEV_{1.0}) from baseline. Incidences of all adverse events (AAEs) were the primary safety outcomes. Pooled estimates are presented as mean differences (MDs) or risk ratios (RRs) with 95% confidence intervals (CIs). Analyses included intention-to-treat cases. Three LAMA + ICS/LABA RCTs met the criteria for inclusion in this study. The MD, RRs, and their 95% CIs regarding changes in FEV_{1.0} for LAMA + ICS/LABA compared with those of LAMA were 0.08 (0.04 to 0.13); RRs and 95% CIs for AAEs of LAMA + ICS/LABA compared with those of LAMA were 1.03 (0.82 to 1.29). Conclusions : Pulmonary function was significantly improved in the LAMA + ICS/LABA group with no significant increase in AAE risk. These results provide important analysis regarding the overall efficacy and safety of LAMA + ICS/LABA in patients with COPD.

Key words : long-acting muscarinic antagonist, inhaled corticosteroid and long-acting beta-2 agonist, chronic obstructive pulmonary disease, systematic review, meta-analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is now a major cause of death worldwide and its prevalence continues to grow, in part due to the accelerated aging of the population¹⁾.

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Additional treatment strategies for patients with COPD are therefore needed^{1,2}.

Several drug therapies for the management of COPD combine a long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) (LABA/LAMA) as a more effective means of increasing pulmonary function and quality of life while preventing exacerbation. This combination therapy also shows increased safety regarding adverse outcomes including major cardiovascular events compared with monotherapy using an LABA or LAMA alone³. Inhaled corticosteroids (ICSs) and LABA combination therapies (ICS/LABA) are also recommended in Japanese guidelines for patients with COPD who experience frequent exacerbations².

Previously, several randomized controlled trials (RCTs) compared the efficacy and safety of LAMA + ICS/LABA combination therapies with that of the respective monotherapies (LABA or LAMA only)^{4,5}. These studies revealed that LAMA + ICS/LABA combinations improved lung function and patient-reported outcomes in COPD. Moreover, several studies found that the incidence rates of drug-related adverse outcomes, including cardiovascular events, with LAMA + ICS/LABA combination therapies were comparable to those observed with LABA or LAMA monotherapies^{4,5}. Based on these results, LAMA + ICS/LABA triple therapy is now expected to be the cornerstone of maintenance therapy for patients with COPD².

Despite this trend towards LAMA + ICS/LABA combinational therapies for COPD, some questions remain regarding their overall efficacy compared with LAMA alone. Moreover, the adverse effect profiles conflict among the studies of drug combinations for COPD. The present study thus aimed to assess the overall efficacy and safety of LAMA + ICS/LABA versus LAMA in COPD.

Materials and methods

Publication search

We searched MEDLINE (PubMed), Scopus, and the Cochrane Library database (up to December, 2016) using the terms “long acting muscarinic antagonists”, “long acting adrenergic beta-2 receptor agonists”, “inhaled corticosteroids”, and “COPD”. No restrictions were imposed on the search language. Additional relevant articles were also sourced from the reference lists of the retrieved articles. Two investigators (KA and TO) independently searched the electronic databases, and when discrepancies occurred between the investigators, a third investigator (HS) conducted an additional evaluation or our research team resolved the discrepancy through discussion.

Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: 1) RCTs that assessed the clinical efficacy and safety of LAMA + ICS/LABA in adults 40 years or older with a diagnosis of COPD; and 2) studies that included the following outcomes: pulmonary function and all adverse events (AEs). Observational, case-control, cohort, and non-blinded clinical trials were excluded.

Data extraction

Related data from eligible studies were extracted based on predefined criteria for the present

meta-analysis. Pulmonary function was assessed by changes from baseline during 1 second of forced expiratory volume (FEV_{1.0}). The primary safety outcome was defined as the risk of AAEs.

Risk of bias assessments

The Cochrane-recommended methodology was used to examine each included study for the following factors: random sequence generation; allocation concealment; blinding of the participants, personnel, or outcome assessment; incomplete outcome data; selective reporting; and other forms of potential bias⁶.

Statistical analysis

Statistical heterogeneity among the trials was assessed using I^2 statistics, which measure the degree of heterogeneity in outcome measures by calculating the percentage of total variation among the included studies⁶. An I^2 value of 50% or higher indicates significant heterogeneity, which was tested with χ^2 statistics. Random-effects models were planned for cases regardless of the presence of statistically significant heterogeneity⁶⁻⁸.

The predefined safety and efficacy outcomes were assessed between the LAMA + ICS/LABA therapies and LAMA monotherapies; pooled estimates are presented as the mean differences (MDs) (change in FEV_{1.0} from baseline) or relative risks (RRs, AAEs) with 95% confidence intervals (CIs). For studies comparing several dosages and administrations of LAMA + ICS/LABA combination therapies in the same trial, we drew comparisons with the currently recommended dosages and administration routes for LAMA + ICS/LABA and LAMA. The analyses were based on the intention-to-treat population. Publication bias was evaluated with a funnel plot and statistically assessed using Egger's test. All P values were two-sided and $P < 0.05$ was considered statistically significant. All analyses were performed using RevMan software (version 5.3, Cochrane Corporation, Oxford, UK) and STATA (version 14.0, Stata Corp., College Station, TX, USA).

Results

Study characteristics

The study selection process is shown in Figure 1. We identified 995 manuscripts from databases and other sources, with 457 records remaining after duplicates were removed. Based on title/abstract and full-text screening, three reports with a total of 2,834 randomized patients (intention-to-treat population) were ultimately included in the present meta-analysis^{4,5,9}.

Table 1 details the study characteristics. The sample size ranged from 51 to 1,078 subjects, and the treatment duration ranged from 12 to 52 weeks. One study compared the combination of tiotropium and budesonide/formoterol versus tiotropium alone; the second study compared a combination of tiotropium added to salmeterol/fluticasone propionate versus tiotropium alone; and the final study compared a combination of beclometasone/formoterol/glycopyrronium versus tiotropium alone. The mean age ranged from 63.3 to 67.3 years. The proportion of men ranged from 77% to 98%. The percent predicted FEV_{1.0} ranged from 35.8% to 59.3%.

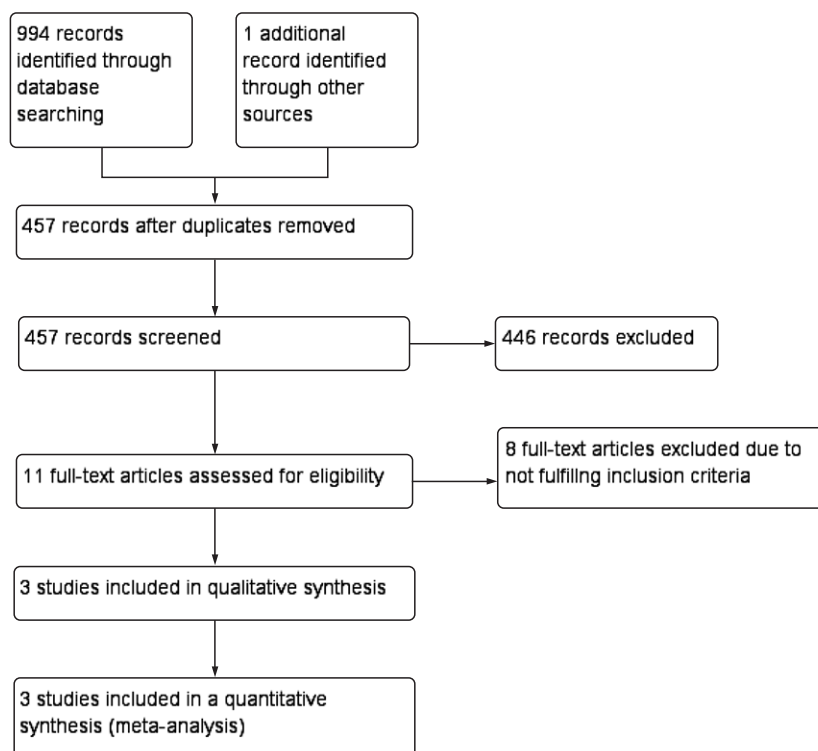


Fig. 1. The study selection process

Table 1. Characteristics of the included studies

Study, year	N [†]	Duration (weeks)	Treatment comparisons (µg)	n [‡]	Mean age (years)	Men (%)	Baseline FEV _{1.0} (%) ^{¶¶}
Saito <i>et al.</i> 2015 ⁴⁾	103	20	SFC 250 + TIO*	52	67.3	98	59.3
			TIO*	51			
			SFC250	51			
LEE <i>et al.</i> 2016 ⁵⁾	578	12	BUD/FF + TIO*	287	66.6	97.2	35.8
			TIO*	290			
Vestbo <i>et al.</i> 2017 ⁹⁾	2,153	52	BDP/FF/GB*	1,077	63.4	77	36.6
			TIO*	1,076			

[†] The number of patients included from each trial in the present meta-analysis (intention-to-treat population); *treatment groups included in the present meta-analysis; [‡] number of patients in each treatment group (intention-to-treat population); ^{¶¶} baseline percent predicted FEV_{1.0}. FEV_{1.0}, forced expiratory volume in 1 second; SFC, salmeterol/fluticasone propionate; TIO, tiotropium; BUD, beclometasone dipropionate; FF, formoterol fumarate; GB, glycopyrronium bromide.

Bias assessment

The risk of study bias was evaluated based on the following factors: random sequence generation; allocation concealment; blinding of the participants, personnel, and outcome assessment; incomplete outcome data; selective reporting; and other forms of potential bias. Each study

was considered to have a low risk of bias for all factors, except for blinding of the outcome assessment in two studies and blinding of the participants and personnel in one study. The authors' determinations of these assessments are shown in Figure 2. No study was excluded from the meta-analysis because of poor quality or differences in baseline characteristics.

Primary efficacy outcomes

Pulmonary functions

Three studies compared changes in FEV_{1.0} from baseline between patients receiving LAMA + ICS/LABA therapies and those receiving LAMA alone. There was significant inter-study heterogeneity among studies comparing LAMA + ICS/LABA versus LAMA ($I^2 = 59%$); a meta-analysis of the comparisons was performed using a random-effects model. Results of the present meta-analysis reveal that improvements in FEV_{1.0} were significantly greater in patients receiving LAMA + ICS/LABA therapies than in those receiving LAMA alone, with an MD and 95% CI of 0.08 (0.04 to 0.13) (Fig. 3).

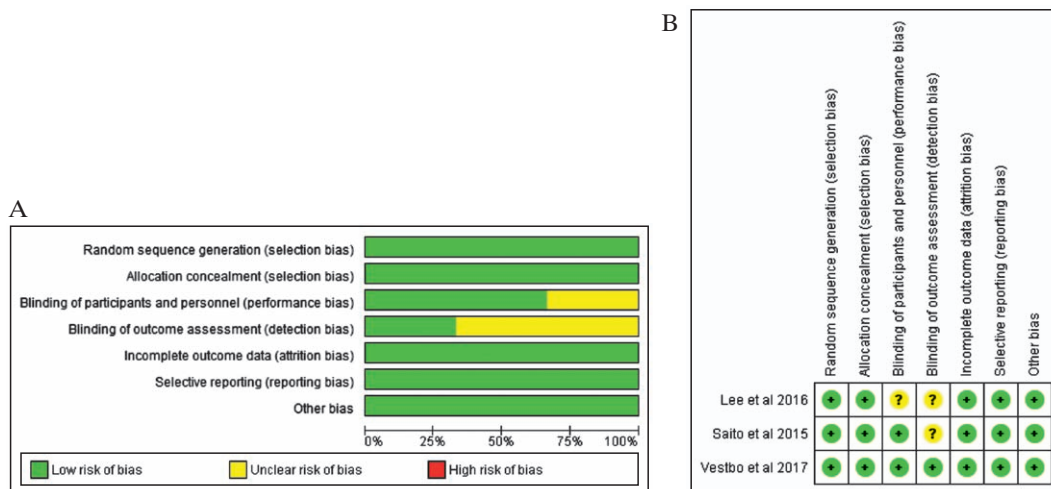


Fig. 2. Bias assessment summary. (A) The risk-of-bias graph shows the authors' determination of items with a risk of bias presented as percentages in both included studies. (B) The risk-of-bias summary showing the authors' determination of items with a risk of bias for each included study.

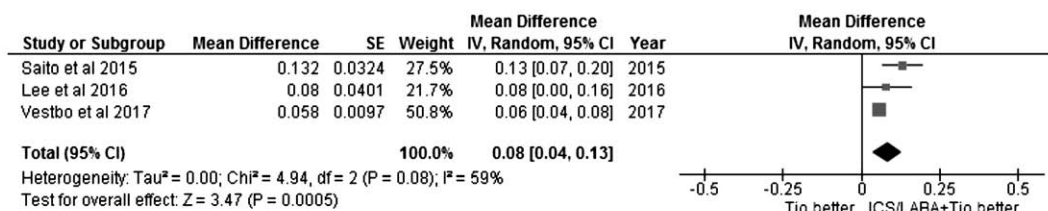


Fig. 3. Forest plots of FEV_{1.0} changes from baseline. Comparisons between LAMA + ICS/LABA versus LAMA are shown. FEV_{1.0}, forced expiratory volume in 1 second; CI, confidence interval; MD, mean difference; SE, standard error; ICS, inhaled corticosteroid; Tio, tiotropium; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

Primary safety outcome

AAEs

Three studies compared the incidences of AAEs between patients receiving LAMA + ICS/LABA and those receiving LAMA alone. There was significant inter-study heterogeneity among these studies determined by I^2 statistics ($I^2 = 53%$); a meta-analysis of this outcome was performed using a random-effects model. Results of the present meta-analysis revealed no significant differences in the risk of AAEs between LAMA + ICS/LABA therapies and LAMA alone, with an RR and 95% CI of 1.03 (0.82 to 1.29) (Fig. 4).

Secondary outcome

COPD worsening

Two studies compared the incidences of COPD worsening between patients receiving LAMA + ICS/LABA and those receiving LAMA alone. There was no significant inter-study heterogeneity among these studies as determined by I^2 statistics ($I^2 = 0%$); a meta-analysis of this comparison was performed using a random-effects model. The results of the present meta-analysis reveal that the risk of COPD worsening was improved in patients receiving LAMA + ICS/LABA compared with those receiving LAMA alone with an RR and 95% CI of 0.74 (0.56 to 0.97) (Fig. 5).

Publication bias

Publication bias was assessed using Egger's tests. Differences in FEV_{1.0} changes from baseline

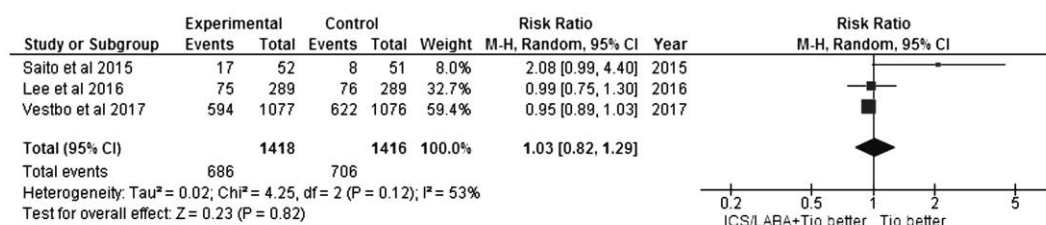


Fig. 4. Forest plots of the incidence of AAEs. Comparisons between LAMA + ICS/LABA versus LAMA are shown. CI, confidence interval; AAEs, all adverse events; ICS, inhaled corticosteroid; Tio, tiotropium; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; M-H, Mantel-Haenzel.

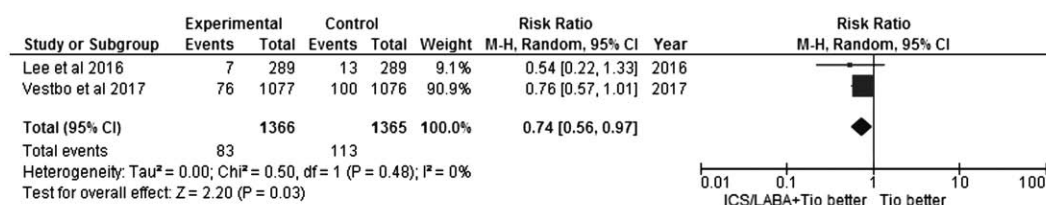


Fig. 5. Forest plots of the incidence of COPD worsening. Comparisons between LAMA + ICS/LABA versus LAMA are shown. CI, confidence interval; COPD, chronic obstructive pulmonary disease; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; M-H, Mantel-Haenzel test.

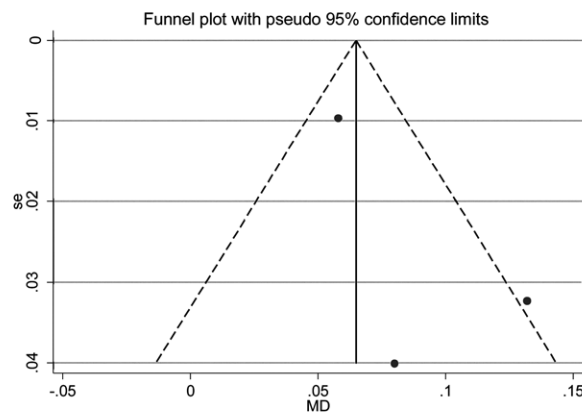


Fig. 6. Egger's funnel plot of the three studies evaluated. The effect of LAMA + ICS/LABA versus LAMA on the FEV_{1.0} CFB is shown. MD, mean differences ; SE, standard error.

between patients receiving LAMA + ICS/LABA and those receiving LAMA alone were evaluated with an Egger's funnel plot for three studies, suggesting no publication bias ($P=0.40$) (Fig. 6). Similarly, no publication bias was observed for all other outcomes as determined by Egger's tests (all $P > 0.05$) (data not shown). These results suggest that publication bias did not substantially affect the conclusions. Therefore, the results of the meta-analysis are considered valid.

Discussion

In this meta-analysis, we compared the efficacy and safety of LAMA + ICS/LABA therapies with those of LAMA alone. Results of the meta-analysis for efficacy profiles revealed that improvements in the FEV_{1.0} and incidence of COPD worsening were significantly greater in patients receiving LAMA + ICS/LABA than in those receiving LAMA alone. Analysis results for safety profiles showed no significant differences between the risk of AAEs in patients receiving LAMA + ICS/LABA and those receiving LAMA alone.

Previous RCTs assessing the efficacy and safety of LAMA + ICS/LABA compared with LAMA in patients with COPD revealed that the combination therapies improved pulmonary function, patient-reported symptoms, and health-related quality of life ; however, statistical analyses were not performed. Moreover, because of differences in the distribution of COPD severity and definitions of complications, past studies provided mixed safety profile results for LAMA + ICS/LABA compared with LAMA in patients with COPD^{4,5,9}.

The present meta-analysis assessed the overall efficacy and safety of LAMA + ICS/LABA therapies in patients with COPD, and showed similar efficacy profiles to those in previous RCTs. Furthermore, the safety of LAMA + ICS/LABA therapies was determined statistically. Pulmonary function was significantly improved in patients receiving LAMA + ICS/LABA compared to those receiving LAMA with no significant increase in the incidence of adverse events. We consider that the difference of 0.08 in change in FEV_{1.0} is important from a clinical standpoint in

light of a previous study showing that LABA/LAMA combination therapy significantly improved the patient-reported symptoms in patients with moderate to severe COPD compared to LAMA alone with only a marginal deference in FEV_{1.0}^{10,11}). Our results strongly support the theory that LAMA + ICS/LABA therapies are more effective and generally better tolerated than LAMA therapies in patients with COPD. There is therefore an unmet medical need for clinical studies to identify the patient characteristics conferring benefit from LAMA + ICS/LABA.

Further, previous randomized trials assessing the efficacy and safety of LAMA + ICS/LABA versus ICS/LABA in patients with uncontrolled asthma revealed that LAMA + LALBA/ICS improves pulmonary functions and patient-reported symptoms¹²). These results indicate the clinical efficacy of LAMA + ICS/LABA extends beyond COPD to other obstructive lung diseases including bronchial asthma.

Several limitations of the present meta-analysis should be acknowledged. First, we only considered published studies thus publication bias may be present; however, neither the funnel plot analysis nor statistical analysis by Egger's tests revealed any such bias. Second, meta-analyses are a form of retrospective research, making them subject to the same methodological limitations. For example, all studies included in the present meta-analysis were supported by pharmaceutical companies, and the authors reported receiving personal fees and grant support. Therefore, the sources of funding may have contributed to any publication bias. Moreover, an outcome selection bias may have occurred. Third, we intended to assess the overall efficacy and safety of LAMA + ICS/LABA therapies on COPD; however, the severity of COPD and baseline COPD might have varied among the studies included in the present meta-analysis and this effect is difficult to define or analyze. For example, the dosage and administration of LABA/LAMA varied among studies included in the present meta-analysis. Thus, heterogeneity among the studies makes it difficult to draw any conclusions about the general COPD population, and there definitely remains an unmet need for subgroup analyses to identify subpopulations who would benefit from LAMA + ICS/LABA therapy. Fourth, as per the Cochrane Handbook, several interventions were included in the monotherapy groups regardless of the dosage, route of administration, type of LAMA + ICS/LABA therapy, or LAMA therapy alone. Moreover, the total dosages of these agents varied among the studies included in the present meta-analysis, partially due to differences in study durations. These variations may further contribute to heterogeneity among the studies. Finally, although we used a random-effects model to account for the significant heterogeneity, it could only be partially corrected.

In conclusion, we assessed the efficacy and safety profiles of LAMA + ICS/LABA therapies compared with those of LAMA alone. The results revealed overall efficacy in pulmonary function and the prevention of COPD worsening in patients receiving LAMA + ICS/LABA compared with those receiving LAMA. Furthermore, the risk of AAEs was not significantly higher in patients receiving LAMA + ICS/LABA than in those receiving LAMA alone. The identification of some limitations in this meta-analysis indicates that further research is required to confirm the efficacy and safety profiles of LAMA + ICS/LABA therapies in patients with COPD.

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Conflict of interest disclosure

The authors received no specific funding for this work.

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