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Original

Efficacy and Safety of Long-acting Beta-2 Agonist and Long-acting Muscarinic Antagonist Combinations in Patients with Chronic Obstructive Pulmonary Disease : Meta-analysis of Phase 3 Randomized Trials†

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Abstract : The aim of the present study was to assess the overall efficacy and safety of long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) combination therapies (LABA/LAMA) versus monotherapies or placebo in patients with chronic obstructive pulmonary disease (COPD). The overall efficacy and safety of LABA/LAMA versus LABA, LAMA, or placebo in patients with COPD were assessed by meta-analysis of Phase 3 trials. Primary efficacy outcomes included changes in forced expiratory volume in 1 second ($FEV_{1.0}$) from baseline and responder rates using St. George's Respiratory Questionnaire (SGRQ). The incidence of serious adverse events (SAEs) was the primary safety outcome. Pooled estimates are presented as standard mean differences (SMD), odds ratios (ORs), or risk differences (RDs) with 95% confidence intervals (CIs). Eleven articles reporting on 13 randomized controlled trials of LABA/LAMA met the criteria for inclusion in the present study. Comparing LABA/LAMA with LAMA, LABA, and placebo, the SMD (95% CI) for a change in $FEV_{1.0}$ from baseline was 0.08 (0.06–0.09), 0.09 (0.07–0.11), and 0.24 (0.19–0.30), respectively; the corresponding ORs (95% CI) for changes in SGRQ score were 1.39 (1.24–1.57), 1.39 (1.06–1.83), and 1.80 (1.47–2.19), respectively. The RDs (95% CIs) for SAEs with LABA/LAMA compared with LAMA, LABA, and placebo were −0.01 (−0.02, 0.00), −0.01 (−0.03, 0.00), and 0.01 (−0.01, 0.02), respectively. Pulmonary function and health-related quality of life were significantly higher for LABA/LAMA, and the risk of SAEs did not increase significantly with combination therapy. These results indicate the overall efficacy and safety of LABA/LAMA in patients with COPD.

Key words : chronic obstructive pulmonary disease (COPD), long-acting beta-2 agonist (LABA), long-acting muscarinic antagonist (LAMA), LABA/LAMA, meta-analysis

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Introduction

Several drug combinations using long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA), such as umeclidinium/vilanterol, tiotropium/olodaterol, and glycopyrronium/indacaterol, are available for the management of chronic obstructive pulmonary disease (COPD)[1]. However, the overall efficacy and safety of LABA/LAMA combinations remain to be conclusively established. In particular, the overall safety of these drug combinations remains to be confirmed statistically[2].

Several Phase 3 studies have compared the efficacy and safety of LABA/LAMA combination therapies with their respective monotherapies (LABA or LAMA only). These studies revealed that LABA/LAMA combinations improve lung function and patient-reported outcomes in COPD[3–5]. Moreover, the incidence rate of drug-related adverse events, including cardiovascular events, with LAMA/LABA combination therapies was almost the same as that observed for LABA or LAMA monotherapies. Based on these results, LABA/LAMA combinations are now considered the cornerstone of maintenance therapy for patients with COPD[1,6].

However, the overall efficacy of LABA/LAMA combinations compared with LABA, LAMA, or placebo remains to be fully explored. Several previous randomized controlled trials or meta-analyses demonstrated that monotherapy with LABA or LAMA is associated with a higher risk of cardiovascular events compared with placebo in patients with COPD[7,8]. However, the incidence rates of drug-induced adverse events, including cardiovascular events, were not evaluated statistically in previous Phase 3 studies, and relevant statistical data are needed to confirm the overall efficacy and safety of LABA/LAMA combination therapies. Therefore, the aim of the present study was to compare pulmonary function efficacy, health-related quality of life (HRQoL), and safety profiles (including cardiovascular safety) among LABA and LAMA combination and monotherapies or placebo by performing a meta-analysis of Phase 3 randomized trials.

Materials and methods

Publication search

MEDLINE (PubMed), Scopus, and the Cochrane library database were searched up to December 2016 using the terms "muscarinic antagonists", "adrenergic beta-2 receptor agonists", "vilanterol", "umeclidinium", "glycopyrronium", "indacaterol", "olodaterol", "tiotropium", and "QVA149"[9]. No restrictions were imposed on the search language. Furthermore, the reference lists of retrieved articles were searched to identify additional relevant articles. The electronic databases were independently searched by two investigators (KA and TO). When discrepancies occurred between the two investigators, a third investigator (HS) conducted an additional evaluation or the discrepancy was resolved by discussion among the research team.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion in the present study if they met the follow-

ing criteria : 1) Phase 3 studies that assessed the clinical efficacy and safety of LABA/LAMA combinations in adults aged ≥ 40 years with a diagnosis of COPD ; and 2) studies that reported on the following outcomes : pulmonary function, St. George's Respiratory Questionnaire (SGRQ) scores, serious adverse events (SAEs), all cardiovascular events (ACEs), major cardiovascular events (MACEs), non-major cardiovascular events (non-MACEs), COPD worsening, nasopharyngitis, and all adverse events (AAEs). Observational, case-control, cohort, and non-blinded clinical trials were excluded from the present meta-analysis. All references were independently screened by KA and TO in accordance with the inclusion and exclusion criteria. When discrepancies occurred between the two investigators, a third investigator (HS) conducted an additional evaluation or the discrepancy was resolved by discussion among the research team.

Data extraction

Related data from eligible studies were extracted based on the predefined criteria for the present meta-analysis. Pulmonary function was assessed by changes in forced expiratory volume in 1 second ($FEV_{1.0}$) from baseline. HRQoL was assessed using the SGRQ score. Primary efficacy outcomes were defined as changes in $FEV_{1.0}$ from baseline and odds of SGRQ responders. The primary safety outcome was defined as the risk of SAEs. Secondary safety outcomes included the risk of ACEs, MACEs, non-MACEs, nasopharyngitis, COPD worsening, and AAEs.

Risk of bias assessments

Cochrane-recommended methodology was used to examine each study included in the present analysis for random sequence generation, allocation concealment, blinding of participants, personnel, or outcome assessment, incomplete outcome data, selective reporting, and other forms of potential bias[9].

Statistical analysis

Statistical heterogeneity among 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 studies[10]. I^2 values of 50% or higher indicate significant heterogenity, and the significance of heterogeneity was tested using χ^2 statistics. Random[11] and fixed-effects[12] models were planned for cases with and without statistically significant heterogeneity, respectively.

The predefined safety and efficacy outcomes were assessed between the LABA/LAMA combination therapies, LABA and LAMA monotherapies, or placebo groups ; pooled estimates are presented as standard mean differences (SMD ; change in $FEV_{1.0}$ from baseline), odds ratios (ORs ; rate of SGRQ responders), and risk differences (RDs ; the risk of ACEs, MACEs, non-MACEs, nasopharyngitis, COPD worsening, or AAEs) with 95% confidence intervals (CIs). For studies that compared outcomes between LABA/LAMA combination therapies and several types of LABA or LAMA monotherapies, we compared the LABA/LAMA combination with its component agents. For studies comparing several dosage and administration routes of LABA/LAMA combination therapies in the same trial, comparisons were made with the currently recommended

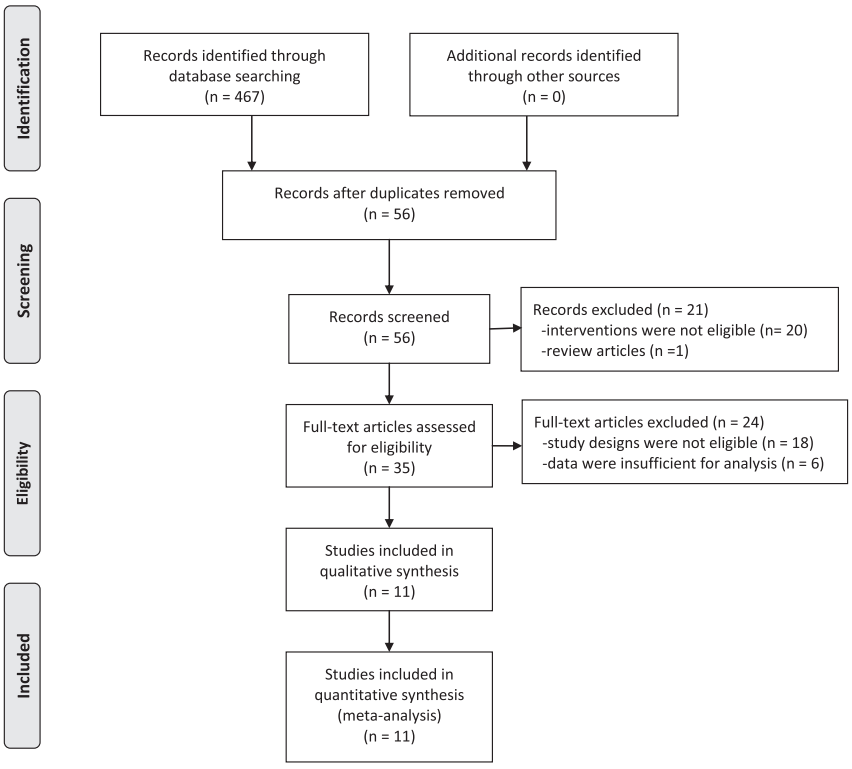

Fig. 1. Study selection process

dosage and administration routes for LABA/LAMA, LABA, and LAMA therapies or placebo. The analyses were based on the intention-to-treat population. Publication bias was evaluated with a funnel plot and assessed statistically using Begg's and Egger's tests. All *p*-values are two-sided, and $p<0.05$ was considered statistically significant. All analyses were performed using RevMan 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 Fig. 1. In all, 467 articles were identified, 216 from PubMed, 192 from Scopus, and 59 from the Cochrane Library database. After removal of duplicates, 56 records remained. Based on title/abstract and full-text screening, 13 individual trials from 11 reports with a total of 13,348 randomized patients (intention-to-treat population) were ultimately included in the present meta-analysis [3–5, 13–20].

The study characteristics are listed in Tables 1 and 2. Sample size ranged from 384 to 3,100 subjects and treatment duration ranged from 12 to 56 weeks. Nine studies used the umeclidinium/vilanterol LABA/LAMA combination, and three studies used the glycopyrronium/indacaterol LABA/LAMA combination. Only one study used the tiotropium/olodaterol LABA/LAMA combination. Mean patient age ranged from 61.3 to 64.6 years. The proportion of male

Table 1. Characteristics of the studies included in the meta-analysis

Study	Year	N^A	Duration (weeks)	Treatment comparisons and dose (μg)	n^C	Mean age (years)	Male (%)	Baseline $FEV_{1.0}{}^D$ (%)
Buhl *et al* [15]	2015	3,100	52	TIO/OLO 5/5[B]	1,029	64	73	50
				TIO/OLO 2.5/5	1,030			
				TIO 5[B]	1,033			
				TIO 2.5	1,032			
				OLO 5[B]	1,038			
Zheng *et al* [16]	2015	386	24	UMEC/VI 125/25[B]	193	64	93	NR
				UMEC/VI 62.5/25	194			
				Placebo[B]	193			
Celli *et al* [18]	2014	1,489	24	UMEC/VI 125/25[B]	403	62.9	65	48.2
				UMEC 125[B]	407			
				VI 25[B]	404			
				Placebo[B]	275			
Decramer *et al* [17]								
Study 1	2014	631	24	UMEC/VI 125/25[B]	214	62.9	69	47.7
				UMEC/VI 62.5/25	212			
				VI 25[B]	209			
				TIO 18[B]	208			
Study 2	2014	437	24	UMEC/VI 125/25[B]	215	64.6	68	47.1
				UMEC/VI 62.5/25	217			
				UMEC 125[B]	222			
				TIO 18	215			
Donohue *et al* [13]	2014	562	52	UMEC/VI 125/25[B]	226	61.3	67	54.7
				UMEC 125[B]	227			
				Placebo[B]	109			
Maleki-Yazdi *et al* [14]	2014	905	24	UMEC/VI 62.5/25[B]	454	62.3	68	46.3
				TIO 18[B]	451			
Maltais *et al* [20]								
Study 418	2014	384	12	UMEC/VI 125/25[B]	128	62.6	54	51.3
				UMEC/VI 62.5/25	130			
				UMEC 125[B]	41			
				UMEC 62.5	40			
				VI 25[B]	64			
				Placebo[B]	151			

[A]Number of patients included from each trial in the present meta-analysis (intention-to-treat population)

[B]Treatment groups included in the present meta-analysis.

[C]Number of patients in each treatment group (intention-to-treat population).

[D]Baseline percentage predicted forced expiratory volume in one second ($FEV_{1.0}$).

TIO, tiotropium; OLO, olodaterol; UMEC, umeclidinium; VI, vilanterol; IND, indacaterol; Glyco, glycopyrronium; NR, not reported.

patients and current smokers ranged from 54% to 93%. Predicted $FEV_{1.0}$ ranged from 37.2% to 57.4%.

Table 2. Characteristics of included studies

Study	Year	N^A	Duration (weeks)	Treatment comparisons and dose (μg)	n^C	Mean age (years)	Male (%)	Baseline $FEV_{1.0}{}^D$ (%)
Maltais *et al* [20]	2014							
Study 417		440	12	UMEC/VI 125/25[B]	144	61.6	56	51.3
				UMEC/VI 62.5/25	152			
				UMEC 125[B]	50			
				UMEC 62.5	49			
				VI 25[B]	76			
				Placebo[B]	170			
Bateman *et al* [3]	2013	1,661	26	IND/Glyco 110/50[B]	475	63.9	75	55.2
				IND 150[B]	477			
				Glyco 50[B]	475			
				TIO 18	483			
				Placebo[B]	234			
Dahl *et al* [4]	2013	339	52	IND/Glyco 110/50[B]	226	62.6	77	57.4
				Placebo[B]	113			
Donohue *et al* [19]	2013	1,532	24	UMEC/VI 62.5/25[B]	413	63.1	71	47.4
				UMEC/VI 62.5[B]	418			
				VI 25[B]	421			
				Placebo[B]	280			
Wedzicha *et al* [5]	2013	1,482	64	IND/Glyco 110/50[B]	741	63.3	75	37.2
				Glyco 50[B]	741			
				TIO 18	742			

[A]Number of patients included from each trial in the present meta-analysis (intention-to-treat population)

[B]Treatment groups included in the present meta-analysis.

[C]Number of patients in each treatment group (intention-to-treat population).

[D]Baseline percentage predicted forced expiratory volume in one second ($FEV_{1.0}$).

TIO, tiotropium ; OLO, olodaterol ; UMEC, umeclidinium ; VI, vilanterol ; IND, indacaterol ; Glyco, glycopyrronium.

Primary efficacy outcomes

・*Pulmonary function*

Changes in $FEV_{1.0}$ from baseline were compared between patients receiving LABA/LAMA combination therapies and those receiving LAMA alone, LABA alone, or placebo in five, three, and four studies, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA or LABA ($I^2 = 35\%$ [$P = 0.19$] and $I^2 = 14\%$ [$P = 0.31$], respectively) ; meta-analysis of these two comparisons was performed using the fixed-effects model. In contrast, there was interstudy heterogeneity among studies comparing LABA/LAMA with placebo ($I^2 = 83\%$; $P < 0.001$) ; the meta-analysis of this comparison was performed using the random effects model. The results of these meta-analyses revealed that improvements in $FEV_{1.0}$ were significantly greater in patients receiving LABA/LAMA combination therapies than in those receiving LABA and LAMA alone or placebo, with SMD (95% CIs) of 0.08 (0.06–0.09), 0.09 (0.07–0.11), and 0.24 (0.19–0.30), respectively (Fig. 2).

・*HRQoL assessed by SGRQ score*

The rate of SGRQ responders was compared between patients receiving LABA/LAMA combination therapies and those receiving LAMA alone, LABA alone, or placebo in four, three, and three studies, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA or placebo as determined by I^2 statistics ($I^2=0\%$ [$P=0.65$] and $I^2=0\%$ [$P=0.83$], respectively); the meta-analysis of these two comparisons was performed using the fixed-effects model. In contrast, there was significant interstudy heterogeneity among studies comparing LABA/LAMA with LABA ($I^2=74\%$; $P=0.02$); the meta-analysis of this comparison was performed using a random effects model. The results of these meta-analyses revealed that ORs (95% CIs) of SGRQ responders were significantly greater in patients receiving LABA/LAMA combination therapies than in those receiving LABA or LAMA alone or placebo: 1.39 (1.24–1.57), 1.39 (1.06–1.83), and 1.61 (1.47–2.19), respectively (Fig. 3).

Primary safety outcome: SAEs

Ten, seven, and six studies were identified comparing the incidence of SAEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone, LABA alone, and placebo, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA, LABA, or placebo as determined by I^2 statistics ($I^2=0\%$ [$P=0.84$], $I^2=20\%$ [$P=0.28$], and $I^2=0\%$ [$P=0.51$], respectively); the meta-analysis of this outcome was performed using the fixed-effects model. The results of this meta-analysis revealed no significant differences in the risk of SAEs between LABA/LAMA combination therapies and LAMA and LABA monotherapies or placebo, with RDs (95% CIs) of −0.01 (−0.02, 0.00), −0.01 (−0.03, 0.00), and 0.01 (−0.01, 0.02), respectively (Fig. 4).

Secondary safety outcomes

・*ACEs*

Three studies compared the incidence of ACEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone, and two studies compared differences between patients receiving LABA/LAMA combinations and those receiving placebo; there were no studies identified comparing ACEs between patients receiving LABA/LAMA combinations and those receiving LABA alone. There was significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA or placebo as determined by I^2 statistics ($I^2=68\%$ [$P=0.04$] and $I^2=84\%$ [$P=0.01$], respectively); the meta-analysis of these two comparisons was performed using a random-effects model. Although no trials were found comparing the risk of ACEs between patients receiving LABA/LAMA combinations and those receiving LABA alone, the results of the present meta-analysis revealed no significant differences in the risk of ACEs between patients receiving LABA/LAMA and those receiving LAMA alone or placebo, with RDs (95% CIs) of −0.01 (−0.03, 0.02) and −0.02 (−0.15, 0.10), respectively.

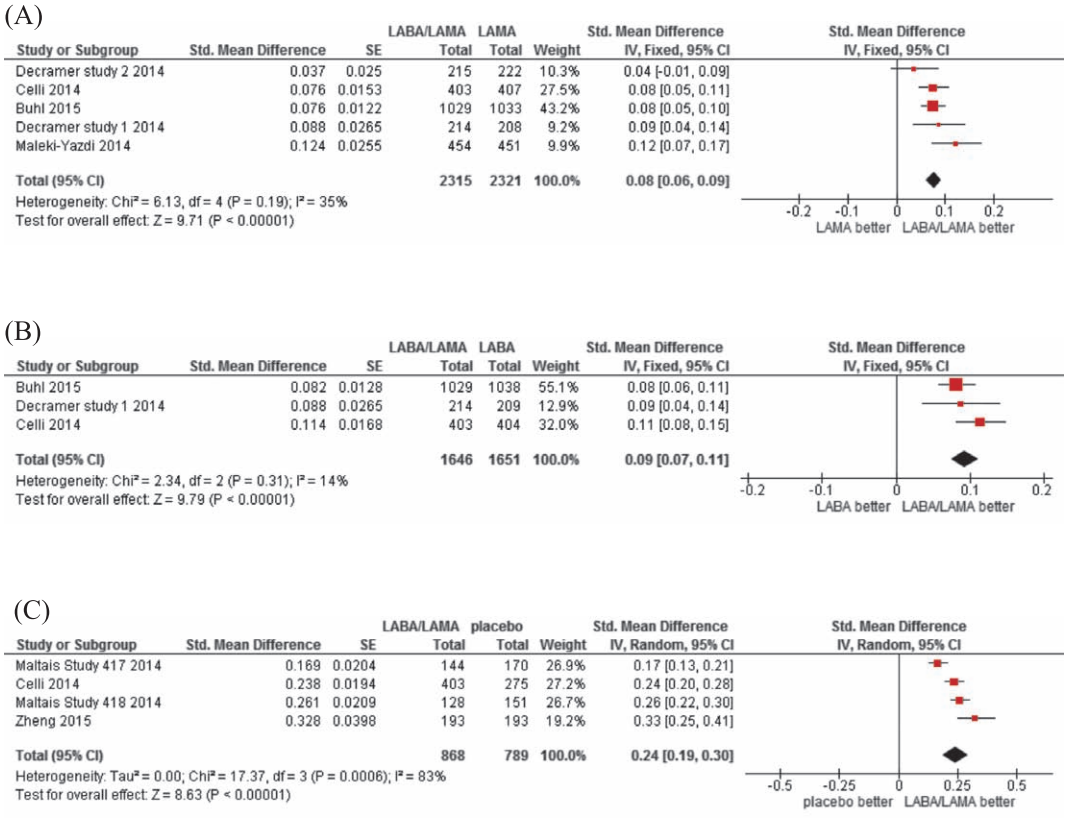

Fig. 2. Forest plots of changes from baseline for forced expiratory volume in one second ($FEV_{1.0}$) for comparisons of combined long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapies with (A) LAMA alone, (B) LABA alone, and (C) placebo. CI, confidence interval; Std, standard; SE, standard error.

・*MACEs*

The incidence of MACEs was compared between patients receiving LABA/LAMA combinations and those receiving LAMA alone, LABA alone, or placebo in two, one, and two studies, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA or placebo as determined by I^2 statistics ($I^2 = 0\%$ [$P = 0.95$] and $I^2 = 13\%$ [$P = 0.28$], respectively); meta-analysis of these two comparisons was performed using the fixed-effects model. The results of this meta-analysis revealed no significant differences in the risk of MACEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone or placebo, with RDs (95% CIs) of −0.01 (−0.02, 0.00) and 0.00 (−0.00, 0.01), respectively.

Only one trial compared the incidence of MACEs between patients receiving LABA/LAMA and those receiving LABA alone. There were no significant differences in the risk of MACEs between patients receiving LABA/LAMA combinations and those receiving LABA alone, with an RD (95% CI) of −0.00 (−0.01, 0.00).

・*Non-MACEs*

Two studies compared the incidence of non-MACEs between patients receiving LABA/LAMA

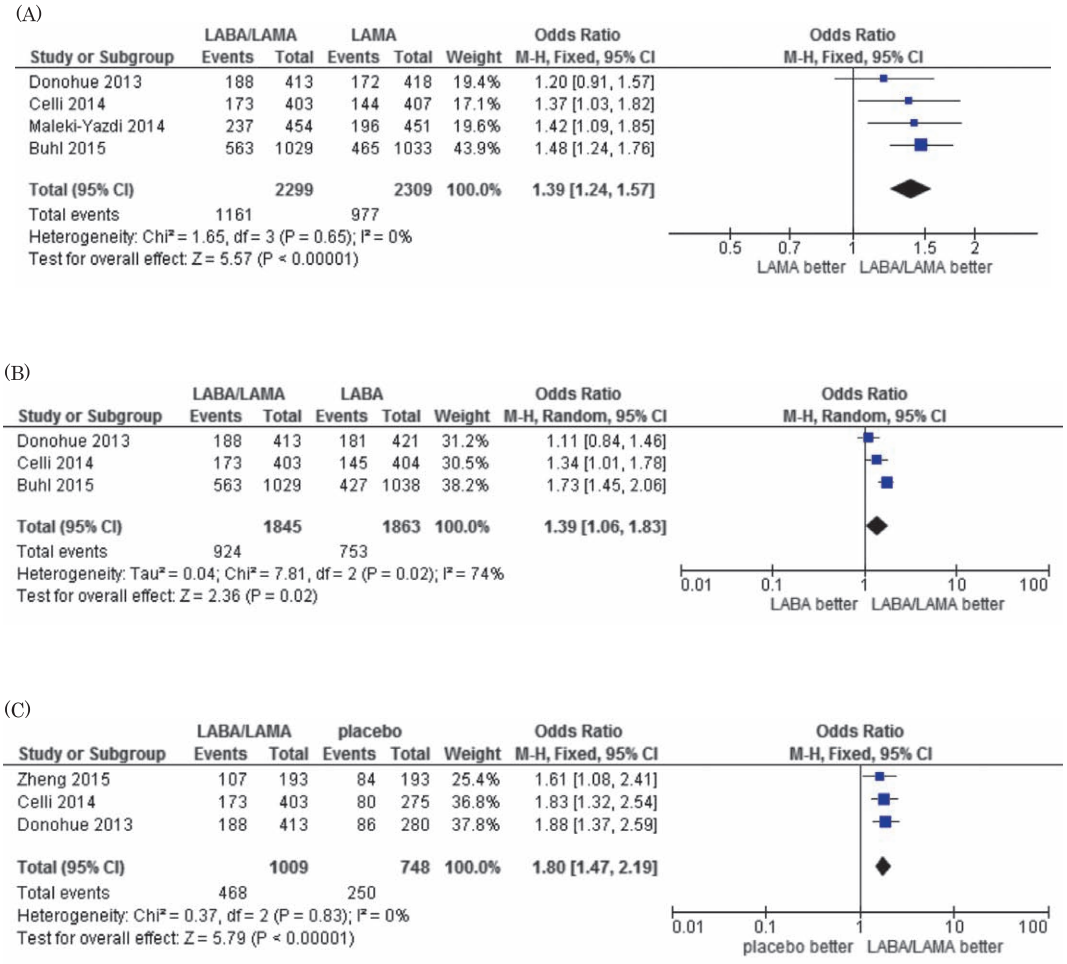

Fig. 3. Forest plots of odds of St. George's Respiratory Questionnaire (SGRQ) responders for comparisons of combined long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapies with (A) LAMA alone, (B) LABA alone, and (C) placebo. CI, confidence interval; OR, odds ratio.

combinations and those receiving LAMA alone, whereas one study each compared the differences between patients receiving LABA/LAMA combinations and those receiving LABA alone or placebo. There was interstudy heterogeneity among studies comparing LABA/LAMA combinations with those receiving LAMA alone as determined by I^2 statistics ($I^2 = 82\%$; $P = 0.02$); meta-analysis of this comparison was performed using a random effects model. The results of the meta-analysis revealed no significant differences in the risk of non-MACEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone, with an RD (95% CI) of −0.00 (−0.03, 0.02).

Only one trial each compared the incidence of non-MACEs between patients receiving LABA/LAMA combinations and those receiving LABA alone or placebo; therefore, the meta-analysis of these comparisons was performed using a fixed-effects model. The results showed no significant differences in the risk of non-MACEs between patients receiving LABA/LAMA combinations and those receiving LABA alone or placebo, with RDs (95% CIs) of −0.01 (−0.02, 0.00)

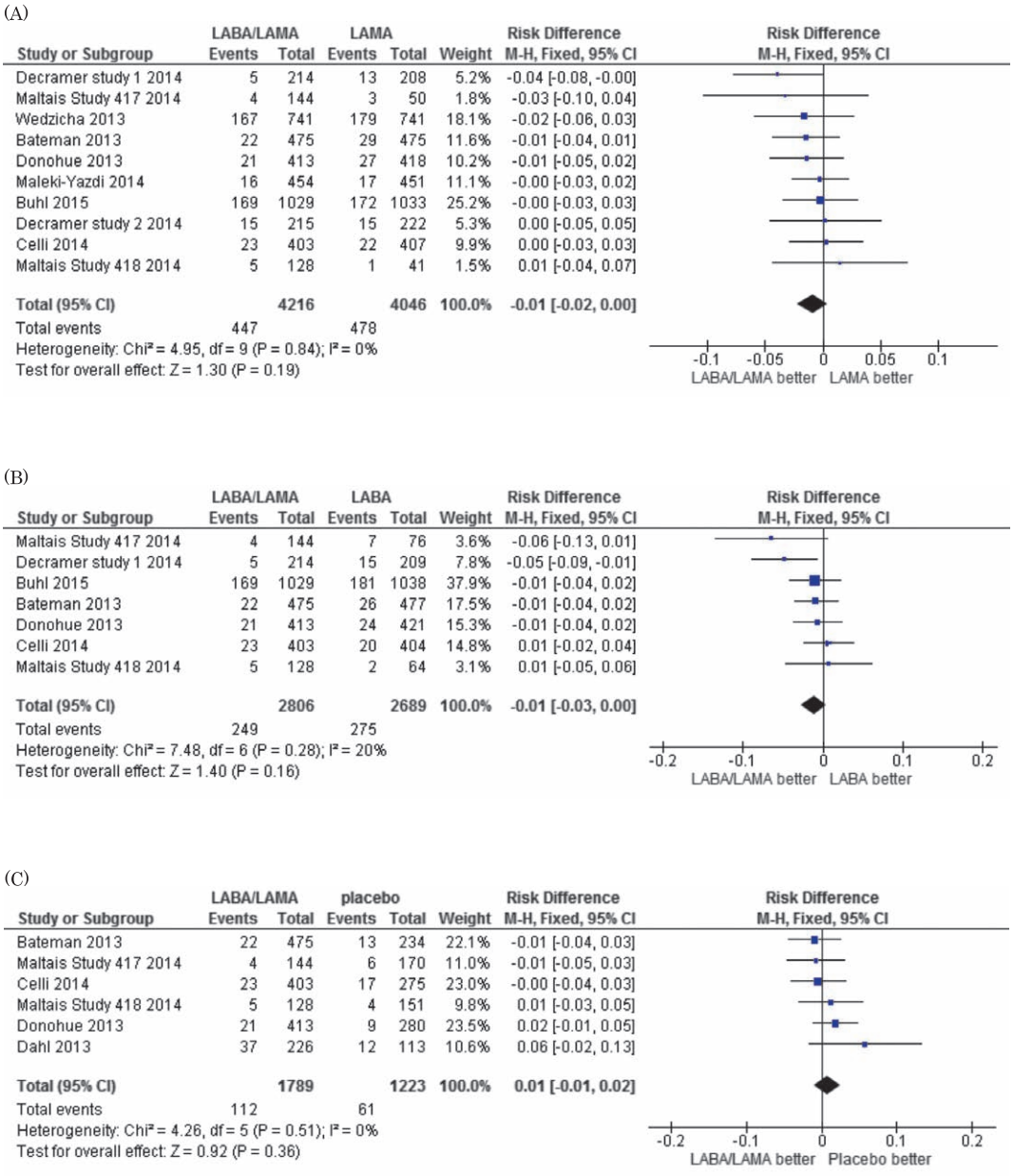

Fig. 4. Forest plots of the incidence of serious adverse events (SAEs) for comparisons between combined long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapies and (A) LAMA alone, (B) LABA alone, and (C) placebo. CI, confidence interval ; RD, risk difference.

and −0.00 (−0.01, 0.01), respectively.

・*COPD worsening*

Five, four, and four studies compared the incidence of COPD worsening between patients receiving LABA/LAMA combinations and those receiving LAMA alone, LABA alone, or placebo, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA as determined by I^2 statistics ($I^2 = 0\%$; $P = 0.79$) ; meta-analysis

of this comparison was performed using the fixed-effects model. In contrast, there was significant interstudy heterogeneity among studies comparing LABA/LAMA with LABA ($I^2=81\%$; $P<0.001$) or placebo ($I^2=81\%$; $P=0.001$); meta-analysis of these comparisons was performed using a random effects model. The results of these meta-analyses revealed no significant differences for the risk of COPD worsening between LABA/LAMA and LABA, LAMA, or placebo, with RDs (95% CIs) of −0.01 (−0.03, 0.01), −0.01 (−0.04, 0.02), and −0.02 (−0.07, 0.03), respectively.

・*Nasopharyngitis*

The incidence of nasopharyngitis was compared between patients receiving LABA/LAMA combinations and those receiving LAMA alone, LABA alone, or placebo in nine, eight, and seven studies, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA or LABA as determined by I^2 statistics ($I^2=49\%$ [$P=0.05$] and $I^2=0\%$ [$P=0.57$], respectively); meta-analysis of these two comparisons was performed using the fixed-effects model. In contrast, there was significant interstudy heterogeneity among studies comparing LABA/LAMA with placebo ($I^2=55\%$; $P=0.04$); meta-analysis of this comparison was performed using a random effects model. The results revealed no significant differences between LABA/LAMA and LAMA, LABA, or placebo, with RDs (95% CIs) of 0.00 (−0.01, 0.02), −0.00 (−0.02, 0.02), and −0.00 (−0.03, 0.02), respectively.

・*AAEs*

Eight, seven, and seven studies compared the incidence of AAEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone, LABA alone, and placebo, respectively. There was no significant interstudy heterogeneity among studies comparing LABA/LAMA with LAMA, LABA, or placebo as determined by I^2 statistics ($I^2=5\%$ [$P=0.39$], $I^2=0\%$ [$P=0.51$], and $I^2=0\%$ [$P=0.64$], respectively); meta-analysis of this outcome was performed using the fixed effects model. The results revealed no significant differences in the risk of AAEs between LABA/LAMA versus LAMA or placebo, with RDs (95% CIs) of −0.01 (−0.03, 0.02) and −0.02 (−0.04, 0.01), respectively. However, the risk of AAEs was significantly lower in patients receiving LABA/LAMA combinations than in those receiving LABA alone (RD 0.01; 95% CI −0.02, 0.05).

Bias assessment

The risk of study bias was evaluated based on 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 incomplete outcome data in three studies, random sequence generation in one study, and allocation concealment in one study. The authors' determinations of these assessments are shown in Fig. 5. No studies were excluded from the meta-analysis because of poor quality or differences in baseline characteristics. Publication bias was assessed using Begg's and Egger's tests. Differences in responder odds using the SGRQ between patients receiving LABA/LAMA combinations and those receiving LAMA alone were evaluated with an

Egger's funnel plot in four studies, suggesting no publication bias ($P = 0.289$; Fig. 6). Similarly, no publication bias was observed for any other outcome as determined by Begg's and Egger's tests (all $P > 0.05$). However, publication bias could not be assessed using Begg's and Egger's tests for change in $FEV_{1.0}$ due to it being a continuous outcome. In addition, we could not fully exclude publication bias using Begg's and Egger's tests for five comparisons (comparisons of ACEs, MACEs, or non-MACEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone; and comparisons of MACEs or non-MACEs between patients receiving LABA/LAMA combinations and those receiving placebo; 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 the present meta-analysis we compared the efficacy and safety of LABA/LAMA combination therapies with those of LAMA and LABA monotherapies and placebo. The results of the meta-analysis for efficacy profiles revealed that improvements in the $FEV_{1.0}$ and SGRQ scores were significantly greater in patients receiving LABA/LAMA combinations than in those receiving placebo, LABA alone, or LAMA alone. Results of analyses of safety profiles showed no significant differences in the risk of SAEs, ACEs, MACEs, non-MACEs, COPD worsening, nasopharyngitis, and AAEs between patients receiving LABA/LAMA combinations and those receiving LAMA alone or placebo.

Previous Phase 3 studies assessed the efficacy and safety of LAMA/LABA combinations such as umeclidinium/vilanterol[13, 14, 16–20], tiotropium/olodaterol[15], and glycopyrronium/indacaterol[3–5] compared with LABA alone, LAMA alone, or placebo in patients with COPD. The results indicated that LABA/LAMA combination therapies improve pulmonary function, patient-reported symptoms, and HRQoL. Although these Phase 3 studies also reported that LABA/LAMA combination therapies generally exhibit similar safety profiles (including cardiovascular events) as those of LABA or LAMA monotherapies, statistical analyses were not performed.

The present meta-analysis assesses the overall efficacy and safety of LABA/LAMA combination therapies in patients with COPD, showing similar efficacy profiles to those of previous Phase 3 studies. Furthermore, the safety of LABA/LAMA combination therapies was determined statistically, including safety profiles. Pulmonary function and HRQoL were significantly higher in patients receiving LABA/LAMA combinations than in those receiving LAMA alone, LABA alone, or placebo, with no significant increase in the incidence of adverse events. The results of the present study strongly support the theory that LABA/LAMA combination therapies are more effective than LABA and LAMA monotherapies or placebo, and are generally well tolerated.

Because of differences in the distribution of COPD severity and definition of complications[7, 21], past studies have reported mixed results for safety profile evaluations of LABA or LAMA monotherapies compared with placebo in patients with COPD. In the present meta-analysis, no significant differences were observed in the incidence of cardiovascular events between patients receiving LABA/LAMA combination therapies and those receiving LABA and

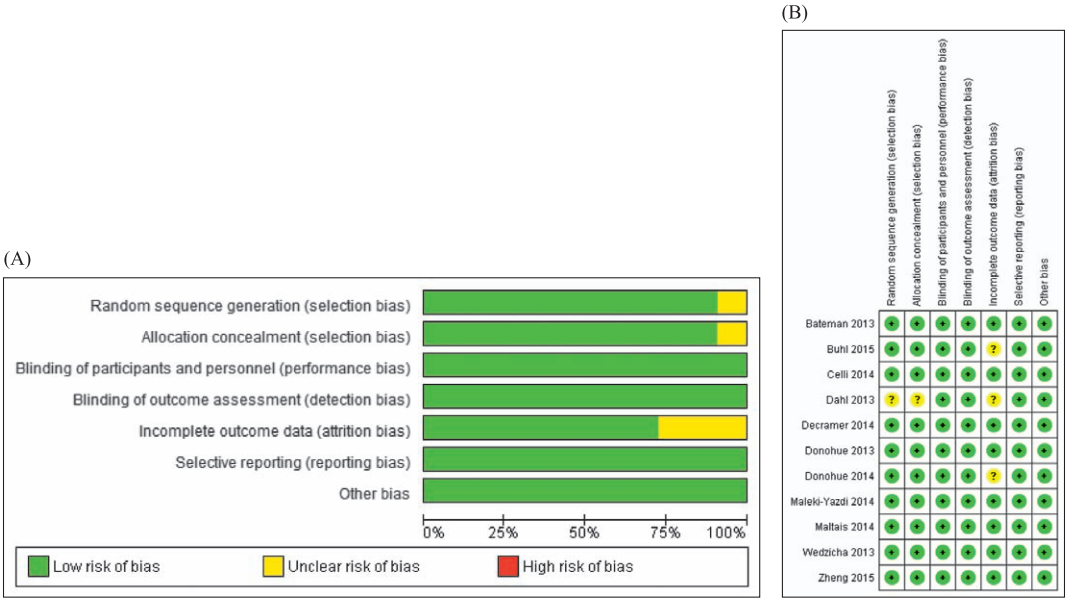

Fig. 5. Bias assessment summary. (A) Risk of bias graph showing the authors' determination of risk of bias items presented as percentages in both studies included. (B) Risk of bias summary showing authors' determination of risk of bias items for each study included.

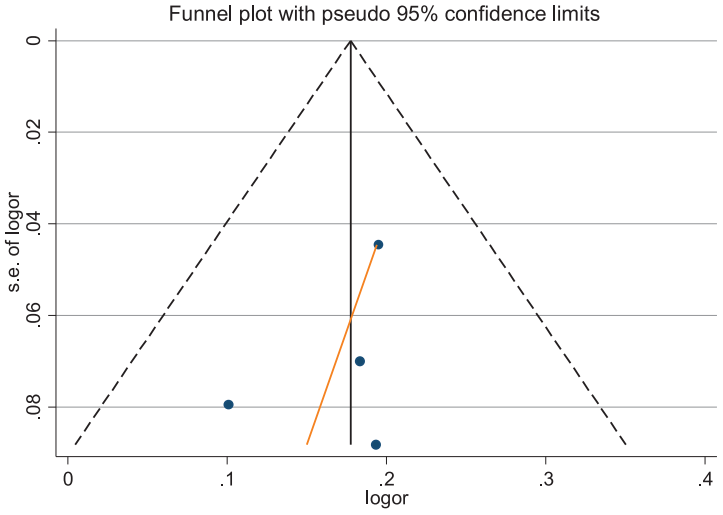

Fig. 6. Egger's funnel plot of the four studies evaluated regarding effects of combined long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapies versus LAMA on responder rates using St. George's Respiratory Questionnaire. OR, odds ratio.

LAMA monotherapies or between patients receiving LABA/LAMA combination therapies and those receiving placebo. These results provide strong evidence for the cardiovascular safety of LABA/LAMA combinations. However, the cardiovascular safety of LABA/LAMA combination therapies remains contentious because several published randomized controlled trials and meta-

analyses have demonstrated that LABA and LAMA therapies are associated with an increased risk of cardiovascular events[7,8].

Previous meta-analyses assessed the efficacy and safety of LABA/LAMA combination therapies compared with LABA and LAMA monotherapies or placebo, and the results indicated the overall efficacy and safety of LABA/LAMA combination therapies[22,23]. However, a detailed risk assessment of adverse events, such as cardiovascular events (including non-severe cardiovascular events), COPD worsening, nasopharyngitis, and AAEs (including non-severe adverse events), has never been conducted. Further, successful maintenance therapies of COPD using LABA/LAMA combination therapies or LABA and LAMA monotherapies are often jeopardized by adverse events. Therefore, a meta-analysis of these outcomes was essential to ensure the efficacy and safety of LABA/LAMA combination therapies for the treatment of COPD. We originally demonstrated no significant differences in the risk of these adverse events between LABA/LAMA combination therapies and LABA and LAMA monotherapies or placebo.

Several limitations of the present meta-analysis should be acknowledged. First, we only considered published studies and it is possible that publication bias may be present; however, this was not apparent in the funnel plot. Second, meta-analyses are a form of retrospective research and, as such, are subject to the same methodological limitations. Third, we intended to assess the overall efficacy and safety of LABA/LAMA combination therapies on COPD; however, the severity of COPD and baseline COPD may have varied among the studies included in the present meta-analysis. Heterogeneity among the studies makes it difficult to draw any conclusions about the generalized COPD population. Fourth, as per the Cochrane handbook, several interventions were included in the monotherapy groups, regardless of dosage and route of administration or type of LABA/LAMA combination therapy or LABA and LAMA monotherapy. Finally, we used a random-effects model to account for the significant heterogeneity, and heterogeneity could only be partially collected.

In conclusion, in the present study we assessed the efficacy and safety profiles of LABA/LAMA combination therapies compared with LABA and LAMA monotherapies and placebo. The results revealed the overall efficacy of LABA/LAMA combinations for pulmonary function and HRQoL compared with placebo and LABA or LAMA monotherapies. Furthermore, the risk of SAEs and cardiovascular events was not significantly higher in patients receiving LABA/LAMA combinations than in those receiving LABA and LAMA alone or placebo. These results demonstrate the overall efficacy and safety of LABA/LAMA combination therapies compared with LABA and LAMA monotherapies or placebo. The identification of some limitations in the present meta-analysis indicates that further research is required to confirm the efficacy and safety profiles of LABA/LAMA combination therapies in patients with COPD.

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Conflict of interest disclosure

The authors have no conflicts of interest to declare.

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