Original Article

Comparison of clinical efficacy between ultra-LABAs and ultra-LAMAs in COPD: a systemic review with meta-analysis of randomized controlled trials

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Background: A single long-acting bronchodilator, ultra-long acting muscarinic antagonist (ultra-LAMA) or ultra-long acting β_2-agonist (ultra-LABA) is preferred for the initial treatment of patients with chronic obstructive pulmonary disease (COPD); however, there are few head-to-head comparative studies between the two. Here, a meta-analysis of randomized controlled trials was performed to compare the clinical efficacy between ultra-LABA and ultra-LAMA in patients with moderate-to-severe COPD.

Methods: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched (to March 1, 2017) to identify all published randomized controlled trials.

Results: Of the 12,906 articles found by searching the databases, we obtained data from 10,591 patients with COPD (LABA, n=5,058; LAMA, n=5,533) in seven published studies. Our results showed that COPD exacerbation were significantly lower in patients taking ultra-LAMA than those taking ultra-LABA (odds ratio =0.857, P=0.0008). However, no significant differences were observed between ultra-LAMA and ultra-LABA patients regarding improvement in trough forced expiratory volume in 1 s, the transitional dyspnea index, or St. George's Respiratory Questionnaire score.

Conclusions: This study suggests that COPD exacerbation occurred less often in patients taking an ultra-LAMA than in those taking an ultra-LABA with similar efficacy of lung function and quality of life.

Keywords: Chronic obstructive pulmonary disease (COPD); ultra-long acting β_2-agonist (LABA); ultra-long-acting muscarinic antagonist (LAMA); meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by largely irreversible airflow limitation (1). It is a major global health burden, and its prevalence is expected to increase, with an estimated annual death rate of over 4.5 million worldwide by 2030 (2). COPD patients often have chronic respiratory symptoms, exercise intolerance, and poor health-related quality of life, contributing to significant use of healthcare resources (1). In addition, a considerable proportion of COPD patients experience acute exacerbation and the frequent exacerbations are associated with rapid decline in lung function (3,4), aggravated quality of life (5,6), and increased mortality (7-10).

Long-acting bronchodilators are the cornerstone of the maintenance treatment in moderate to very severe COPD patients (1). Recently, numerous combinations of a long acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) have been introduced in a single inhaler device, which showed consistently greater improvement in lung function than long acting bronchodilator monotherapy (11). However, single bronchodilators (LAMA or LABA) are still preferred as an initial treatment in a majority of COPD patients, and the combination of LABA/LAMA is recommended when patients have persistent symptoms despite the use of a single long-acting bronchodilator or experience frequent exacerbations (1). In addition, when patients do not obtain relief of symptoms with the addition of a second bronchodilator, step-down to a single bronchodilator is suggested. Among single long-acting bronchodilators, once-daily long-acting bronchodilators are preferred to twice-daily long-acting bronchodilators due to the advantage of covering a 24 h therapeutic window, which leads to improvements in drug adherence and treatment response (12-14).

Among long-acting bronchodilators, tiotropium is preferred for exacerbation prevention based on comparison to LABAs in two head-to-head comparisons (15,16). However, one of these two studies compared efficacy between tiotropium and salmeterol, a twice-daily LABA (15), and there is an absence of head-to-head comparative trials with newly introduced once-daily LAMA and LABA. Since there are no sufficient data supporting the use of once-daily LAMA (ultra-LAMA) over once-daily LABA (ultra-LABA) for exacerbation in COPD patients, we conducted a systemic review and meta-analysis for the comparisons of the clinical efficacy and safety of ultra-LABA (indacaterol, olodaterol, or vilanterol) and ultra-LAMA (tiotropium, glycopyrronium or umeclidinium) in stable patients with moderate to severe COPD.

Methods

Search strategy

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (*Figure 1*) (17). We identified published studies from MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (up to March 1, 2017) databases using keywords related to COPD, LABAs, LAMAs, and randomized control trials (RCTs). The title and abstract were independently analyzed by two authors (E.Y.C and S.Y.K) for screening. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed. They independently assessed all studies for inclusion based on the criteria for study design, outcome, and intervention for participants. After they obtained full texts that could be potential candidates, they assessed and confirmed eligibility for the analysis. Disagreements were discussed and resolved by consensus.

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: (I) patients with moderate-to-severe COPD by Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria; (II) randomized control trials (RCTs) with comparisons of ultra-LABAs (indacaterol, olodaterol, or vilanterol) and ultra-LAMAs (glycopyrronium, tiotropium, or umeclidinium); (III) at least 12 weeks of follow-up; and (IV) written in English. In this study, ultra-LABAs and ultra-LAMAs were defined as once-daily bronchodilators (18).

Data extraction

Data from the included studies were extracted and assessed for study characteristics and duration, doses of medications, inhaler devices, disease characteristics, age, sex, smoking history, trough forced expiratory volume in 1 second (FEV_1), St. George's Respiratory Questionnaire (SGRQ) total score, transition dyspnea index (TDI), and COPD worsening and exacerbation.

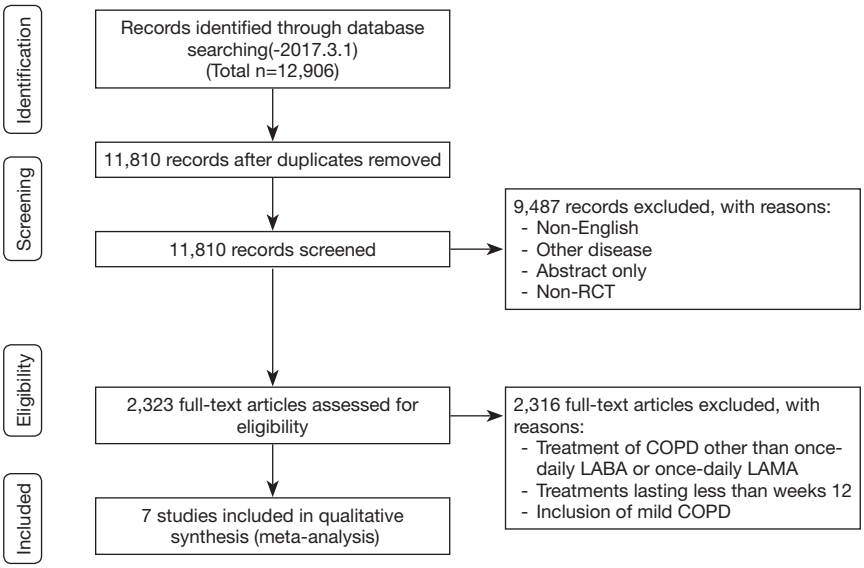

Figure 1 Flowchart for the identification of studies included in the meta-analysis.

End points

The primary end point of this meta-analysis was the COPD exacerbation of ultra-LABAs versus ultra-LAMAs. COPD exacerbation was extracted from the reports of COPD worsening as the adverse events from six studies and in Decramer *et al.*, the reports of COPD exacerbation with treatments was applied to COPD exacerbation (19). It is because Decramer *et al.* (19) reported only serious adverse events of exacerbation as adverse events. The secondary end points were change of trough FEV_1 from baseline to the first follow-up after week 12 (≥ week 12), and St. SGRQ total score and TDI at the first follow-up after week 12 (≥ week 12). Since trough FEV_1, SGRQ score, and TDI were measured at different time points according to the study protocol of each study, we used the data obtained at the first follow-up (week 12, week 24, or week 26) after week 12 from each study for the comparisons. The mean value of outcomes was used in the one study including two ultra-LAMAs (glycopyrronium and tiotropium) (20).

Risk of bias assessment

Two reviewers independently assessed the risk of bias of the included studies for sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data addressed, and free of selective reporting as recommended in the Cochrane Handbook of Systematic Reviews 5.1. (21).

Statistical analysis

Statistical analysis was performed using the R 3.3.2 (Vienna, Austria; http://www.R-project.org/) package 'metafor' for meta-analysis of the included studies. Mean differences (MDs) or odds ratios (ORs) for end points were estimated and tested under the fixed effect model or the random effect model. The pooled data were applied to a random effect model if heterogeneity was present in the data of more than 4 studies and to a fixed effect model otherwise. The precision of the estimates was quantified by the 95% confidence interval (CI). Heterogeneity was measured using the Higgins and Green I^2 test, which is calculated as 100%×(Q–df)/Q, where Q is the observed chi-square statistic, and the degrees of freedom (df) is the number of studies less one. The value of I^2 ranges between 0% (no heterogeneity) and 100% (maximal heterogeneity), and heterogeneity was considered to be mild (<30%), moderate (30–60%), and high (>60%) (21). We also evaluated potential publication bias using Egger's regression test and the funnel-plot (22). P values <0.05 (two-tailed test) were considered significant.

Results

Study characteristics

Figure 1 shows how the relevant studies were identified. A total of 12,906 articles were found by searching databases.

Table 1 Characteristics of included studies

Study	Patient characteristics	Treatment period (weeks)	Number of subjects	Age (mean)	Male (%)	Drug (μg)	Device	Current smokers (%)	Smoking history, pack-y	Baseline FEV_1 L (%)	Primary outcome
Donohue *et al.* 2010 (23)	Moderate-to-severe	26	416	63.4	259 (62.3)	I [150]	DPI	NA	48.3	1.52 (56.1)	Trough FEV_1 at week 12
			415	64	269 (64.8)	T [18]	DPI	NA	50.8	1.45 (53.9)	
Buhl *et al.* 2011 (24)	Moderate-to-severe	12	794	63.6	555 (69.8)	I [150]	DPI	357 (45.0)	43.2	1.53 (NA)	Trough FEV_1 at week 12
			799	63.4	535 (67.0)	T [18]	DPI	351 (43.9)	41.8	1.52 (NA)	
Bateman *et al.* 2013 (20)	Moderate-to-severe	26	476	63.9	354 (74.4)	I [150]	DPI	184 (38.7)	NA	1.5 (54.9)	Trough FEV_1 at week 26
			473	64.3	365 (77.2)	G [50]	DPI	189 (40.0)	NA	1.5 (55.1)	
			480	63.5	360 (75.0)	T [18]	DPI	189 (37.4)	NA	1.5 (55.1)	
Decramer *et al.* 2013 (16)	Severe	52	1,721	64	1,344 (78.1)	I [150]	DPI	596 (34.6)	42.8	1.133 (40.2)	Trough FEV_1 at week 12
			1,718	64	1,313 (76.4)	T [18]	DPI	585 (34.0)	43.2	1.138 (40.7)	
Celli *et al.* 2014 (25)	Moderate-to-severe	24	404	62.8	265 (65.6)	V [25]	DPI	210 (52.0)	42.8	NA (47.7)	Trough FEV_1 at week 24
			407	63.1	270 (66.3)	U [125]	DPI	216 (53.0)	39.6	NA (47.6)	
Decramer *et al.* 2014 (19)	Moderate-to-severe	24	209	63.2	143 (68.4)	V [25]	DPI	106 (51.0)	41.6	NA (47.7)	Trough FEV_1 at week 24
			208	62.6	140 (67.3)	T [18]	DPI	99 (48.0)	41.9	NA (47.8)	
Buhl *et al.* 2015 (26)	Moderate-to-severe	52	1,038	64.2	764 (73.6)	O [5]	SMI	378 (36.4)	NA	1.377 (50.3)	Trough FEV_1 and SGRQ total score at week 24
			1,033	63.9	755 (73.1)	T [5]	SMI	370 (35.8)	NA	1.37 (49.7)	

DPI, dry powder inhaler; SMI, soft mist inhaler; G, glycopyrronium; I, indacaterol; O, olodaterol; T, tiotropium; V, vilanterol; U, umeclidinium; SGRQ, St George's Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 s.

Results obtained from 10,591 patients with COPD [LABA (n=5,058); LAMA (n=5,533)] were selected from 7 published papers. Three studies reported on indacaterol *vs.* tiotropium (16,23,24) and one study on indacaterol *vs.* tiotropium and indacaterol *vs.* glycopyrronium (20). There were one study with vilanterol *vs.* umeclidinium (25), one study with vilanterol *vs.* tiotropium (19), and one study with olodaterol *vs.* tiotropium (26).

All studies published by March 2017 were included, and relevant patient baseline characteristics are summarized in *Table 1*. All RCTs were randomized and double-blind, and we included comparisons with open-label tiotropium in the RCTs. The duration of follow-up ranged from 12 to 56 weeks.

Primary outcome

As shown in *Figure 2A*, the analysis of 7 studies comparing ultra-LABA with ultra-LAMA showed that ultra-LAMA resulted in less frequent COPD exacerbations than ultra-LABA (OR =0.857; 95% CI, 0.783–0.938; P=0.0008). When the one paper with only severe COPD was excluded in the meta-analysis (16), COPD exacerbation also occurred less frequently with ultra-LAMA than ultra-LABA (OR =0.885; 95% CI, 0.784–0.998; P=0.0471) (*Figure 2B*).

Secondary outcomes

Change of trough FEV_1 from baseline

Regarding change of trough FEV_1 from baseline to the first follow-up after week 12 (≥ week 12), the data from 3 out of 7 studies were available for the means and standard errors of changes. The one study reported results at week 12 (23), and the remaining two studies reported results at week 24 (19,25). The analysis of three studies of ultra-LABA and ultra-LAMA showed no significant differences in the change of trough FEV_1 at either week 12 or 24 from baseline (MD =−11.510 mL; 95% CI, −33.330–10.309; P=0.3012) (*Figure 3*).

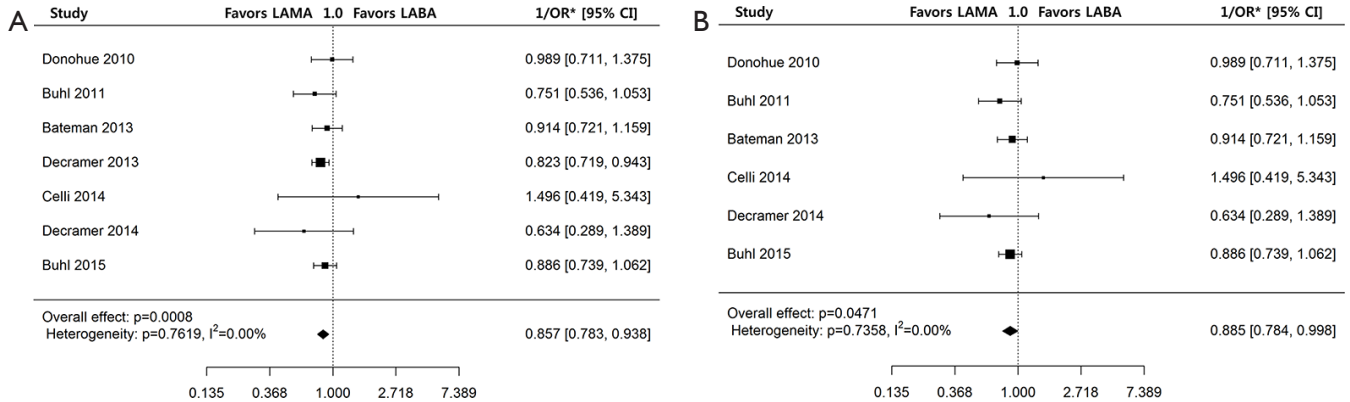

Figure 2 Forest plot of meta-analysis for the impact of ultra-LAMA *vs.* ultra-LABA on COPD exacerbations in patients with moderate to (A) severe COPD/fixed effect model (B) severe COPD except for one study including severe COPD patients (16)/fixed effect model. *reference=ultra-LAMA. COPD, chronic obstructive pulmonary disease; ultra-LAMA, ultra-long acting muscarinic antagonist; ultra-LABA, ultra-long acting β_2-agonist.

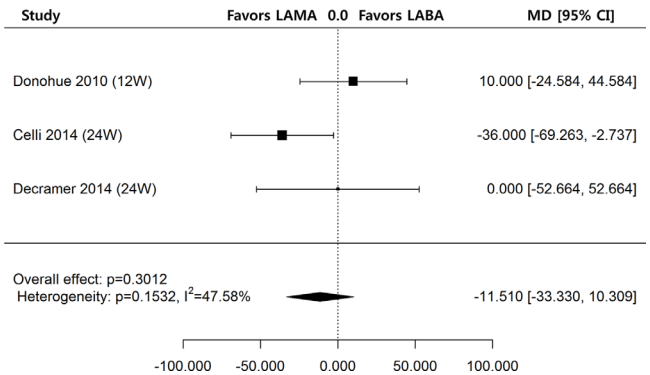

Figure 3 Forest plot of meta-analysis for the impact of ultra-LAMA versus ultra-LABA on changes in trough FEV_1 (mL) at weeks 12 and 24 from baseline/fixed effects model. FEV_1, forced expiratory volume in one second; Ultra-LAMA, ultra-long acting muscarinic antagonist; ultra-LABA, ultra-long acting β_2-agonist.

SGRQ score and TDI changes

At the first follow-up, SGRQ total score was reported in six studies; the exception was one study in which only the change in SGRQ score was available (*Figure 4A*) (19). The SGRQ total scores at week 12 were reported in 3 studies (16,23,24), at week 24 in 2 studies (25,26), and at week 26 in the remaining studies (20). In these six studies, the MD was –0.621, which was not significant (95% CI, –1.603 to 0.362; P=0.2159).

At the first follow-up, TDI was reported in all 7 studies. The TDI at week 12 was reported in 3 studies (16,23,24), at week 24 in 3 studies (19,25,26), and at week 26 (20) in the remaining one study (*Figure 4B*). As shown in *Figure 4B*, there was no significant difference in TDI at the first follow-up between the ultra-LABA and ultra-LAMA groups (MD =0.054; 95% CI, –0.197 to 0.305; P=0.6746).

Heterogeneity and Bias in the included studies

High levels of heterogeneity were detected on SGRQ total score change (I^2=99.82%, P<0.0001) and TDI change (I^2=99.82%, P<0.0001). There was moderate level of heterogeneity on change of trough FEV_1 from baseline (I^2=47.58%, P=0.1532) and mild level of heterogeneity on COPD exacerbation (I^2=0.00%, P=0.7619). The assessments performed by the authors of each risk of bias item for each included RCT are summarized in *Table 2*. All papers were funded by pharmaceutical companies. Two studies were at high risk for blinding of participants and personnel because they used open-labeled tiotropium (20,23). For publication bias, significant asymmetry in the funnel-plot was not detected for the primary and secondary outcomes (P=0.6630 for COPD exacerbation, P=0.7898 for change of trough FEV_1 from baseline, P=0.7078 for SGRQ total score change, and P=0.7495 for TDI change) (*Figure 5*). Therefore, we assumed there was no evidence of publication bias.

Discussion

In this study, we performed a meta-analysis on the clinical efficacy and safety of ultra-LABA (indacaterol, olodaterol, or vilanterol) versus ultra-LAMA (glycopyrronium,

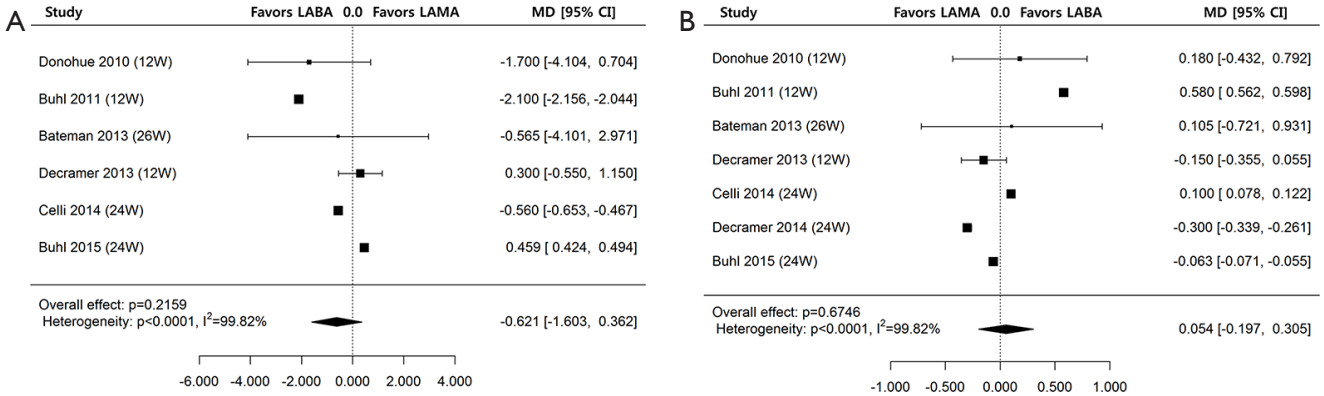

Figure 4 Forest plot of meta-analysis for the impact of ultra-LAMA versus ultra-LABA on (A) St. George's Respiratory Questionnaire score and (B) transition dyspnea index of the first time after follow-up/random effects model. Ultra-LAMA, ultra-long acting muscarinic antagonist; ultra-LABA, ultra-long acting β_2-agonist.

Table 2 Risk of Bias in the included studies

Study	Sequence generation	allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Donohue *et al.* 2010 (23)	Unclear	Low risk	High risk	Low risk	High risk	Low risk	High risk
Buhl *et al.* 2011 (24)	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Bateman *et al.* 2013 (20)	Unclear	Unclear	High risk	Low risk	Low risk	Low risk	High risk
Decramer *et al.* 2013 (16)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Celli *et al.* 2014 (25)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	High risk
Decramer *et al.* 2014 (19)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Buhl *et al.* 2015 (26)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	High risk

tiotropium, or umeclidinium) in stable patients with moderate-to-severe COPD. The main finding of this meta-analysis was that COPD exacerbation occurred less often with the ultra-LAMAs than ultra-LABAs among patients with moderate-to-severe COPD, while ultra-LAMAs were as effective as ultra-LABAs in terms of trough FEV_1 and quality of life including SGRQ and TDI at the first follow-up.

A previous meta-analysis based on four studies [Donohue *et al.* (23), Buhl *et al.* (24), Bateman *et al.* (20), and Decramer *et al.* (16)] comparing the clinical efficacy and safety of tiotropium, a ultra-LAMA, and indacaterol, a ultra-LABA, showed that COPD worsening was more frequent in the indacaterol group than in the tiotropium group (27). We affirmed these findings with various types of ultra-LABAs and ultra-LAMAs and a larger number of studies. Our findings also support the current recommendations of the GOLD guideline (1), which reports an advantage of ultra-LAMAs over ultra-LABAs in exacerbation-prevention properties. The potential mechanisms might be explained by the anti-inflammatory effects of LAMA (28), which was shown in an animal model of COPD (e.g., reduction of neutrophils and proinflammatory cytokine levels and inhibition of mucus secretion as well as airway remodeling) (29-31). However, the results of our study need careful interpretation. First, we used COPD worsening in the adverse events for the analysis of COPD exacerbation except for Decramer *et al.* (19) as COPD worsening has comprehensive meaning including exacerbation. This is because only one head-to-head comparative study between tiotropium and indacaterol for COPD exacerbation has been published. Secondly, the number of studies including

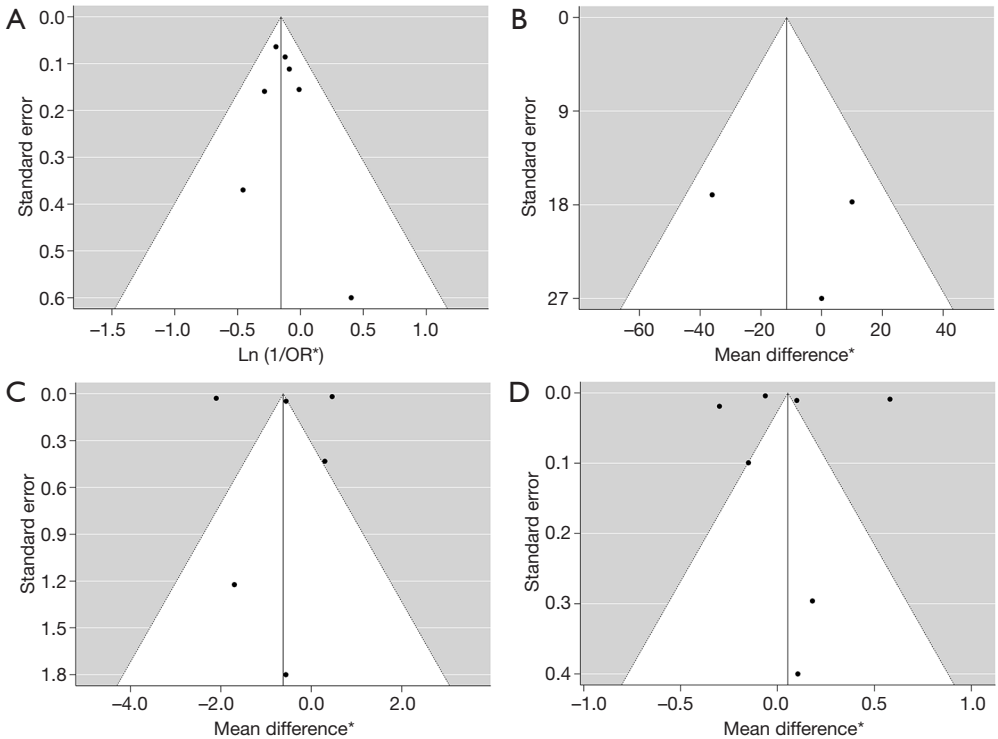

Figure 5 Funnel plots of impact on (A) COPD exacerbation, (B) change of trough FEV_1 (mL) from baseline, (C) St. George's Respiratory Questionnaire score, and (D) transition dyspnea index score. *reference= ultra-LAMA. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second.

ultra-LAMAs or ultra-LABAs other than tiotropium or indacaterol was relatively small. In addition, since a considerable number of studies in our study included tiotropium, it might not be generalized to all ultra-LAMAs. When *in vitro* pharmacological profiles were observed using human bronchus, the potency, onset of action, and offset of action were different among LAMAs (32). In addition, as most studies on the anti-inflammatory effects of LAMAs were performed with tiotropium (33,34), further studies are needed to elucidate whether other ultra-LAMAs exhibit similar features to tiotropium (31).

With respect to lung function, our study showed results with the change of trough FEV_1 from baseline, which was consistent with the previous meta-analysis showing no significant differences of trough FEV_1 at week 12 between the indacaterol and tiotropium groups (27). Ultra-LAMAs also showed a similar effect to ultra-LABAs with respect to quality of life measured by SGRQ total score and TDI in the analyses including data at 12 weeks (16,23,24), 24 weeks (19,25,26), or 26 weeks (20). However, in the subgroup analysis, compared to ultra-LAMAs, ultra-LABAs significantly improved SGRQ total score and TDI at 12 weeks (*Figure S1A*,*S1B*). The significant differences in SGRQ total score and TDI at 12 weeks between ultra-LAMAs and ultra-LABAs might suggest a faster improvement of quality of life in ultra-LABAs than ultra-LAMAs despite significant heterogeneities in the analyses.

Our study has an advantage that our analyses were relatively free of publication bias in funnel plots, which enhances the reliability of the results of the meta-analyses. Although high levels of heterogeneity were detected in SGRQ total score change and TDI change, there was only mild heterogeneity in COPD exacerbation. Thus, the exacerbation prevention effect of ultra-LAMA over ultra-LABA, the primary outcome in this study, can be considered to be based on high quality of meta-analyses, which is a major strength of this study.

In summary, this study suggests that COPD exacerbation occurred less often with ultra-LAMAs than ultra-LABAs with no significant differences in improvement of lung function or quality of life in moderate-to-severe COPD patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: CK Rhee has received consulting/lecture fees from MSD, AstraZeneca, Novartis, GSK, Takeda, Mundipharma, Sandoz, Boehringer-Ingelheim, and Teva-Handok. HY Park has received lecture fees from AstraZeneca, Novartis, and Boehringer-Ingelheim. The other authors have no conflicts of interest to declare.

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Supplementary

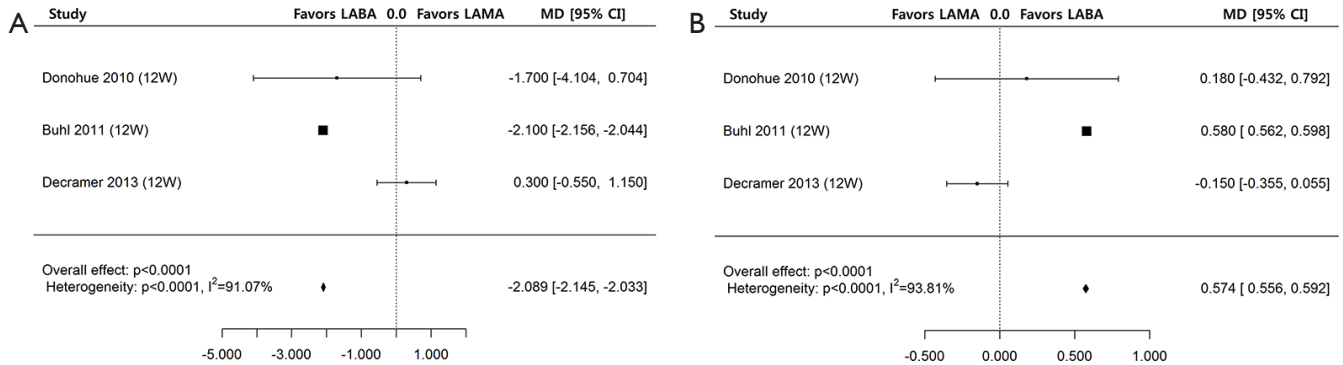

Figure S1 Subgroup analysis for the impact of ultra-LAMA versus ultra-LABA on (A) St. George's Respiratory Questionnaire score and (B) transition dyspnea index at week 12/fixed effects model.