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Combination Therapy with Long-Acting Bronchodilators and the Risk of Major Adverse Cardiovascular Events in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Accumulated high-quality data from randomized controlled trials (RCTs) indicate that long-acting muscarinic antagonist/long-acting β2 agonist (LAMA/LABA) combination therapy significantly improves clinical symptoms, and health status and reduces exacerbation risk of patients with chronic obstructive pulmonary disease (COPD). However, there is a growing concern that LAMA/LABA therapy may increase the risk of cardiovascular disease in patients with COPD. The aim of this paper is to determine whether the use of LAMA/LABA combination therapy modifies the risk of cardiovascular disease in patients with COPD.

Methods: Two reviewers independently searched EMBASE, PubMed, and Cochrane Library to identify relevant RCTs of LAMA/LABA or LABA/LAMA/inhaled corticosteroids (ICS) for the management of patients with COPD that reported on cardiovascular endpoints. The primary outcome was MACE (major adverse cardiovascular events), which was a composite of cardiovascular death, myocardial infarction (MI), or stroke.

Results: Fifty-one RCTs enrolling 91,021 subjects were analyzed. Both dual LAMA/LABA (1.6% vs 1.3%; RR, 1.42, 95% CI, 1.11-1.81) and triple therapy (1.6% vs 1.4%; RR, 1.29, 95% CI, 1.03-1.61) significantly increased the risk of MACE

compared with ICS/LABA. The excess risk was most evident in RCTs in which the average underlying baseline risk for MACE was >1%/year. Compared with LAMA only, LABA only, or placebo, dual LAMA/LABA therapy did not significantly increase the risk of MACE, though these comparisons may have lacked sufficient statistical power.

Conclusion: Compared with ICS/LABA, dual LAMA/LABA or triple therapy increases cardiovascular risk in patients with COPD. This should be considered in the context of the incremental benefits of these therapies on symptoms and exacerbation rates in patients with COPD especially in those with a MACE risk of >1%/year.

Keywords: LAMA; LABA; COPD; triple therapy; MACE

INTRODUCTION

Long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs) are mainstays of therapy in the management of chronic obstructive pulmonary disease (COPD) [1-3]. Increasingly, these medications are used in combination to improve lung function, relieve symptoms, and enhance the health status of patients with COPD [2-4]. A common co-morbidity in COPD is cardiovascular disease (CVD) and there is a growing concern that these medications especially in combination may exacerbate the underlying CVD. However, the accumulated data to date have been conflicting [5-11]. Here, we conducted a systematic review and a meta-analysis to comprehensively ascertain the risks of major adverse cardiovascular events (MACE) related to dual LAMA/LABA therapy or triple therapy (inhaled corticosteroids, ICS, in combination with LABA/LAMA) in patients with COPD.

METHODS

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [15]. Its protocol has been registered with PROSPERO (CRD42021258092).

Search strategy

Two reviewers independently searched PubMed, Embase, and Cochrane library to identify relevant articles from the beginning to August, 2021, and an updated search was made in July, 2022. The search was conducted using the following keywords: long acting antimuscarinics (umeclidinium, glycopyrronium, tiotropium, aclidinium), long acting β2 agonists (indacaterol, salmeterol, vilanterol, olodaterol, formoterol, tulobuterol, bambuterol, clenbuterol), Spiriva, glycopyrrolate, NVA237, Seebri, GSK573719, Incruse, LAS34273, Turdorza, Eklira, Bevespi, Anoro, Duaklir, QVA149, Ultibro, Spiolto, QAB-149, GW642444, BI1744CL, chronic obstructive pulmonary disease, COPD, chronic airflow obstruction, etc. Detailed search terms and the specific search process are shown in Table S1.

Selection criteria

Inclusion criteria were: (1) randomized controlled trials (RCTs); (2) moderate to very severe COPD (FEV1 <80% of predicted value in the presence of FEV1/FVC < 0.70 post-bronchodilator); (3) Dual LAMA/LABA or triple therapy (LABA/LAMA/inhaled corticosteroids, ICS) as the interventional drug; (4) LAMA only, LABA only, ICS/LABA, or placebo as controls; and (5) RCTs providing data on MACE. MACE was defined as cardiovascular death, nonfatal myocardial infarction

(MI), or nonfatal stroke (Table S3). Exclusion criteria were: (I) unpublished studies; (II) reviews, abstracts, or observational cohort or case-control studies; (III) inclusion of patients with asthma; and (IV) non-English manuscripts.

Data extraction

Two reviewers independently extracted the data from the literature. Following information was captured from each RCT: characteristics of the participants (e.g., mean age, sex, and baseline lung function), group assignment (intervention vs controls), duration of follow-up, and the primary outcome of the RCT. The primary outcomes across the RCTs are shown in Table S3. For the present study, MACE was the primary endpoint. Individual components including MI, cardiovascular deaths, and stroke were secondary endpoints. To determine MACE and its components for each RCT, we searched the key secondary outcomes, serious adverse events, and supplementary materials of each paper for MACE. For papers that did not report the full adverse events, we used posted information on ClinicalTrials.gov.

Assessment for risk of bias

We used the Cochrane Toolkit to assess bias for each eligible study. The components of bias assessment included: full blinding of participants and investigators, random sequence generation, allocation concealment, complete reporting of outcomes data, and other potential sources of bias [16]. Any disagreements were resolved by iteration until a consensus was reached.

Subgroup analyses

We performed several subgroup analyses based on components of MACE (MI,

cardiovascular death, or stroke); lengths of follow-up (3 months versus 6 months versus at least 12 months); the mean age of study participants (≥ 65 and <65 years); mean body mass index (BMI, ≥ 25 and < 25 kg/m^2); the severity of COPD (GOLD stage II and GOLD stage III-IV); and whether ICS was used in combination with LAMA/LABA (dual LAMA/LABA versus triple therapy).

Data analyses

We conducted the meta-analysis of RCTs using Review Manager version 5.4 and Stata software (version 12.0). Relative risk (RR) and its associated 95% confidence intervals (CIs) were generated to compare the occurrence of MACE between dual LAMA/LABA (or LAMA/LABA/ICS) and controls. A random effects model was used to pool the data. Because MACE is relatively rare in therapeutic trials of COPD patients, Peto odds ratio (Peto OR) and its associated 95% confidence intervals (CIs) were also used as effect measures for MACE [17]. We also calculated a pooled Mantel-Haenszel risk difference for both primary and secondary endpoints, where possible. Heterogeneity was assessed with the I^2 statistic, with a value ≥ 50% indicating significant heterogeneity. Publication bias was assessed qualitatively by visual inspection of the funnel plot and quantitatively evaluated using the Egger test and the Begg test. We performed sensitivity analyses by excluding trials that had a high risk of bias. A P value of less than 0.05 (two-tailed) was regarded as statistically significant. We also used the GRADE approach to rate the quality of evidence. Because type 1 and 2 errors may result from meta-analyses with small sample sizes, we also performed Trial Sequential Analysis (TSA) using TSA software (version

0.9.5.10). The number needed to harm (NNH) was calculated using the following formula: $NNH = 1/ [Control\ Event\ Proportion\ (CEP) - \{OR/ (1/CEP - 1) + OR\}]$, where CEP denoted the proportion of events in the control group and OR was derived from the Peto's method [6].

RESULTS

Eligible trials

The characteristics of each included RCT are summarized in table 1 and Table S2. A total of 51 eligible RCTs reporting information on MACE (MI, cardiovascular deaths, or stroke) were included in the meta-analysis (Figure 1). These 51 RCTs recruited 91,021 subjects in total. Of these, 42 RCTs (N=71,210) evaluated dual LAMA/LABA therapy vs. controls (LAMA only, LABA only, ICS/LABA, or placebo), and 11 RCTs (N=24,617) assessed LAMA/LABA/ICS vs. controls [11-12, 18-63]. Fifteen RCTs had a follow-up of 12 weeks, 17 had a follow-up of 24 weeks, 2 had a follow-up of 26 weeks, 15 had a follow-up of 52 weeks, 1 had a follow-up of 64 weeks, and 1 had a follow-up of 27 months.

Risk of bias

The results of bias assessment are summarized in Figure S1. Three RCTs were deemed to be at a high risk for performance bias. Three trials were deemed to be at a high risk for detection bias. Three trials were highly susceptible for incomplete outcomes bias. Nine RCTs were deemed to be at a low risk for bias. Information on withdrawal rates was available for all included studies.

Risk of MACE with LAMA/LABA therapy vs. controls (LAMA only, LABA only, ICS/LABA, or placebo)

The pooled results revealed that both dual LAMA/LABA therapy (42 RCTs; 1.2% vs 0.9% for control; RR, 1.24, 95% CI, 1.06-1.44; 2 more MACE for every 1,000 patients per year of treatment) and triple therapy (11 RCTs; 1.5% vs 1.3% for control; RR, 1.27, 95% CI, 1.03-1.58; 3 more MACE for every 1,000 patients per year of treatment) significantly increased the risk of MACE compared with controls. There was no evidence of statistical heterogeneity among the included studies (I^2=0%; Table 2).

Compared with ICS/LABA, both dual LAMA/LABA therapy (9 RCTs; 1.6% vs 1.3% for ICS/LABA; RR, 1.42, 95% CI, 1.11-1.81; 5 more MACE for every 1,000 patients per year of treatment) and triple therapy (9 RCTs; 1.6% vs 1.4% for ICS/LABA; RR, 1.29, 95% CI, 1.03-1.61; 4 more MACE for every 1,000 patients per year of treatment) significantly increased the risk of MACE. There was no evidence of statistical heterogeneity among the included studies (I^2=0%; Figures 2 and 3; Table 2).

Subgroup analysis based on duration of follow-up revealed that both dual LAMA/LABA therapy (3 RCTs; 2.0% vs 1.5% for ICS/LABA; RR, 1.40, 95% CI, 1.08-1.82; 6 more MACE for every 1,000 patients per year of treatment) and triple therapy (3 RCTs; 2.0% vs 1.7% for ICS/LABA; RR, 1.31, 95% CI, 1.04-1.65; 5 more MACE for every 1,000 patients per year of treatment) significantly increased the risk of MACE compared with ICS/LABA in patients who continued the treatment for at

least 12 months, but did not significantly increase the risk of MACE in patients who were on treatment for 3 or 6 months (Table 2; Figures 2 and 3). There was no evidence of statistical heterogeneity among the included RCTs (I^2=0%) (Table 2).

Subgroup analysis based on the severity of COPD revealed that both dual LAMA/LABA therapy (3 RCTs; 2.0% vs 1.5% for ICS/LABA; RR, 1.40, 95% CI, 1.08-1.82; 6 more MACE for every 1,000 patients per year of treatment) and triple therapy (3 RCTs; 1.8% vs 1.5% for ICS/LABA; RR, 1.31, 95% CI, 1.04-1.65; 5 more MACE for every 1,000 patients per year of treatment) significantly increased the risk of MACE compared with ICS/LABA in patients with severe COPD, but the relationship did not reach statistical significance in patients with moderate COPD (Table 2; Figure 2 and 3).

For dual LAMA/LABA therapy vs. ICS/LABA, 6 studies reported a baseline MACE rate of ≥ 1% per year in controls (ICS/LABA) and 3 studies reported a baseline MACE rate of < 1% per year in controls. For triple therapy vs. ICS/LABA, 7 studies reported a baseline MACE rate of ≥ 1% per year in controls and 2 studies reported a baseline MACE rate of < 1% per year in controls. The pooled results revealed that both dual LAMA/LABA therapy (6 RCTs; 1.8% vs 1.4% for ICS/LABA; RR, 1.40, 95% CI, 1.09-1.79; 6 more MACE for every 1,000 patients per year of treatment) and triple therapy (7 RCTs; 1.7% vs 1.5% for ICS/LABA; RR, 1.27, 95% CI, 1.01-1.60; 4 more MACE for every 1,000 patients per year of treatment) significantly increased the risk of MACE compared with ICS/LABA in patient populations with a baseline MACE rate of ≥1% per year, but neither LAMA/LABA

nor triple therapy significantly increased the risk of MACE in patient populations with a baseline MACE rate of <1% per year (Table 2).

An additional subgroup analysis was performed based on whether LAMA/LABA and ICS/LABA was provided as a fixed dose single inhaler. The pooled results revealed that both dual LAMA/LABA therapy (2 RCTs; 2.3% vs 1.6% for ICS/LABA; RR, 1.50, 95% CI, 1.05-2.15; 8 more MACE for every 1,000 patients per year of treatment) and triple therapy (3 RCTs; 2.0% vs 1.7% for ICS/LABA; RR, 1.31, 95% CI, 1.04-1.65; 5 more MACE for every 1,000 patients per year of treatment) significantly increased the risk of MACE compared with ICS/LABA using the same inhalational device (Table S5; Figures S3 and S4).

Sixteen studies provided data comparing dual LAMA/LABA therapy against placebo. Dual LAMA/LABA therapy did not significantly increase the risk of MACE (RR, 1.30, 95% CI, 0.71-2.38) compared with placebo in a meta-analysis of 10,813 patients. There was no evidence of statistical heterogeneity among the included RCTs (I^2=0%; Table 2; Figure S5).

Twenty-two studies provided data comparing dual LAMA/LABA therapy to LABA only. The pooled results revealed that dual LAMA/LABA therapy did not significantly increase the risk of MACE (RR, 1.11, 95% CI, 0.82-1.51) compared with LABA alone in a meta-analysis of 24,074 patients. There was no evidence of statistical heterogeneity among the included RCTs (I^2=0%; Table 2; Figure S6).

Twenty-six studies provided data comparing dual LAMA/LABA therapy to LAMA only. The pooled results revealed that dual LAMA/LABA therapy did not

significantly increase the risk of MACE (RR, 1.11, 95% CI, 0.90-1.38) compared with LAMA only in a meta-analysis of 26 RCTs involving 37,768 patients. There was no evidence of statistical heterogeneity among the included RCTs (I^2=0%; Table 2; Figure S7).

Three RCTs enrolled 13,863 patients directly compared efficacy and safety between dual LAMA/LABA therapy and triple therapy. Pooled results revealed that dual LABA/LAMA therapy did not significantly increase the risk of MACE (1.8 % vs 1.6% for triple therapy; RR, 1.19, 95% CI, 0.82-1.71) compared with triple therapy. Among individual components of the primary outcome, dual LAMA/LABA therapy significantly increased the risk of cardiovascular death (0.8% vs 0.4% for triple therapy; RR, 1.91, 95% CI, 1.23- 2.99) without a statistically significant increase in the risk of non-fatal MI (0.6% vs 0.5% for triple therapy; RR, 1.35, 95% CI, 0.85-2.14) (Table S5).

Risk of MI, cardiovascular death, or stroke associated with LAMA/LABA therapy

Dual LAMA/LABA therapy significantly increased the risk of MI by 77% (9 RCTs; 0.7% vs 0.5% for ICS/LABA; RR, 1.77, 95% CI, 1.20-2.60) compared with ICS/LABA. However, there was no significant difference in the risk for cardiovascular deaths (9 RCTs; 0.6% vs 0.5% for ICS/LABA; RR, 1.37, 95% CI, 0.92-2.03) or stroke (8 RCTs; 0.4% vs 0.4% for ICS/LABA; RR, 0.98, 95% CI, 0.59-1.61; Table S5). There was no evidence of statistical heterogeneity among the included RCTs for cardiovascular death and stroke (I^2=0 %; e-Table 5). Compared

with ICS/LABA, triple therapy significantly increased the risk of stroke by 77% (7 RCTs; 0.6% vs 0.4% for ICS/LABA; RR, 1.77, 95% CI, 1.14-2.74, I^2=0%) without a significant increase in the risk of cardiovascular deaths (7 RCTs; 0.4% vs 0.5% for ICS/LABA; RR, 0.91, 95% CI, 0.59-1.40, I^2=0%) or MI (8 RCTs; 0.7% vs 0.6% for ICS/LABA; RR, 1.05, 95% CI, 0.58-1.89, I^2=23%; e-Table 5).

Sensitivity analyses

Because MACE is relatively rare in therapeutic trials in COPD, Peto odds ratio (OR) was also used to estimate the risk difference in cardiovascular events between dual LAMA/LABA (or LAMA/LABA/ICS) and controls. The pooled results yielded effect sizes similar in magnitude and direction to those estimated by RR (Table S8). Since several studies contained no CVD events, a risk difference was calculated using a fixed effects model, and the pooled results yielded effect sizes similar in magnitude and direction to those estimated by RR (Table S9). When OR was calculated using a Mantel-Haenszel approach in a fixed effects model, the pooled results also yielded effect sizes similar in magnitude and direction to those estimated by RR (Table S10). After excluding 6 studies at a high risk of bias, the pooled results yielded effect sizes similar in magnitude and direction to those obtained from the primary analysis that included 51 trials (Table S11).

Estimated NNH with dual LAMA/LABA therapy or triple therapy for MACE

In COPD patients receiving ICS/LABA therapy, the MACE rate was approximately 15/1,000 person-years. Thus, the NNH for MACE with dual LABA/LABA was approximately 203 patients treated per year (95% CI, 106-2500). The NNH for

MACE with triple therapy was approximately 294 patients treated per year (95% CI, 132-1250).

DISCUSSION

In this systematic review and meta-analysis of 51 high-quality RCTs that included 91,021 participants with COPD, we found that both LAMA/LABA and triple therapy significantly elevated the risk of MACE compared with ICS/LABA. This excess risk for cardiovascular events was most evident in patient populations with an average baseline MACE risk of >1% per year and in those with GOLD 3 severity. In contrast, we did not find a significant difference in the relative risk of MACE between dual LAMA/LABA or triple therapy and other control groups including placebo, LAMA alone or LABA alone. However, these latter analyses should be interpreted cautiously as the overall sample size for these comparisons was small.

Our findings are in general agreement with several previously published observational studies, which showed that LABAs and/or LAMAs increase the underlying cardiovascular risk in patients with COPD. In 2017, Suissa et al reported that adding a second long-acting bronchodilator to patients with COPD increased the risk of heart failure [64]. Interestingly, they found that the elevation in risk was limited to COPD patients who used ICS at baseline. In 2021, a real-world cohort study demonstrated that the use of dual LAMA/LABA therapy was associated with a higher risk of acute coronary syndromes (1.28-fold) in patients with COPD [65]. Similar to Suissa's report, when stratified by ICS therapy, dual LAMA/LABA significantly increased the risk of cardiovascular complications only when compared

with ICS-based therapies, but not when compared with LABA only or LAMA only. Our findings are also consistent with a recent nested case-control study, which showed that the initiation of LABAs or LAMAs in patients with COPD increased the risk of severe CVD events (by ~1.50-fold), irrespective of prior CVD status or their history of exacerbations [7]. However, this study did not explore the potential modifying effects of ICS on this relationship. A major limitation of these previous studies is the potential for confounding (by both measured and unmeasured factors) and various biases including misclassification bias that may be fraught in observational studies. We extend these results by showing in high-quality RCTs that dual LAMA/LABA or triple therapy significantly increases the risk of MACE compared to ICS/LABA in patients with a mean 1-year MACE risk of >1%. Among individual components of MACE, the major drivers of outcome were non-fatal MI, whose risk increased by 77% (with dual LAMA/LABA therapy vs ICS/LABA) and non-fatal stroke, whose risk increased by 77% (with triple therapy vs ICS/LABA).

The underlying mechanisms by which LAMA/LABA therapy increases the risk of MACE compared with ICS/LABA are unclear but several possibilities exist. One possibility is that ICS therapy may reduce the risk of MACE (rather than LAMA/LABA increasing the risk). Atherosclerosis, the primary precursor lesion of MIs and stroke, is a pro-inflammatory condition [66]. ICS has significant anti-inflammatory effects locally and systemically that may modulate the risk of MACE [67-68]. ICS also regulates local and systemic expression of surfactants. Increased levels of surfactant protein-D have been associated with increased risk of

atherosclerosis and cardiovascular events in both mice and humans [69-70]. Further, the risk of cardiovascular events is highest during exacerbations [71] and ICS therapy reduces the risk of exacerbations and hospitalizations. Another possibility is that LABA and/or LAMAs may increase the risk of MACE. For example, LAMA/LABA combination may cause sympathetic overactivation by suppressing M3 muscarinic acetylcholine receptor and activating sympathetic β1 and β2-adrenergic receptors [7], which may cause tachyarrythmias, myocardial ischemia, increased myocardial oxygen consumption, decreased coronary blood flow, and sudden death.

We found that the excess risk of MACE related to dual LAMA/LABA or triple therapy compared to ICS/LABA was evident in patients with severe COPD, but not in those with moderate disease. One possibility for this observation was that patients with severe disease in the included primary studies had an average annual risk of MACE that exceeded 1%; whereas those with moderate COPD had underlying MACE risk of less than 1%. Another possibility is that the risk of exacerbations and hospitalizations is highest in those with severe disease. Exacerbations (and in particular those that lead to hospitalizations) are a major risk factor for MACE. Regardless of the mechanism, this finding may explain why the SUMMIT trial, which recruited patients with moderate COPD failed to demonstrate a salutary effect of ICS on cardiovascular endpoints in COPD [72].

Although we found that both dual LAMA/LABA and triple therapy were associated with an excess risk of MACE compared with ICS/LABA, the overall impact of these combinatorial therapies on MACE appeared to be different. To

explore this further, we meta-analyzed three RCTs that directly compared dual LAMA/LABA therapy against triple therapy (Figure S8). The pooled results revealed a higher proportion of MACE in patients receiving dual LAMA/LABA therapy than in patients receiving triple therapy, but did not reach a statistical significance. Interestingly, among individual components of the primary outcome, dual LAMA/LABA therapy significantly increased the risk of cardiovascular death compared with triple therapy, which is consistent with data from the INSPIRE trial (N=1,323 patients with moderate to severe COPD), which showed a 60% lower risk of CV mortality in patients receiving ICS/LABA versus those receiving LAMA alone. We speculate that the main reason for the failure to achieve statistical significance on the primary outcome in the above pooled analysis may be due to the small sample size. Overall, these data are consistent with the notion that ICS may be protective against CVD when used in combination with long-acting bronchodilators.

Interestingly, in our meta-analysis, we found that neither dual LAMA/LABA therapy nor triple therapy significantly increased the risk of MACE compared with LAMA only or LABA only. Although the exact reasons are obscure, there are several possibilities. First, LAMA or LABA by itself may increase cardiovascular toxicity and amplify the risk of cardiovascular events in certain susceptible individuals. In 2008, Singh et al reported that inhaled LAMA significantly increased the risk of MACE by 58% in COPD patients. The excess risk of MACE was particularly notable among long-term users of LAMA [73]. Salpeter et al reported that LABA therapy increased the risk of congestive heart failure, arrhythmias, and sudden death in COPD patients

[74]. Second, COPD exacerbations are a major risk factor for cardiovascular events. In certain cases, single therapy (especially with LAMA) may be similarly effective in reducing exacerbations compared with dual therapy [31]. Third, we cannot discount the possibility of a chance finding. Interestingly, when further stratified according to baseline MACE rates, we found that dual LAMA/LABA therapy significantly increased the risk of MACE compared with LABA or LAMA only in patient populations with a baseline MACE rate of < 1% per year. However, these data should be interpreted cautiously owing to very small number of MACE episodes in both groups.

Although we also found that dual LAMA/LABA therapy did not significantly increase cardiovascular risk compared to placebo (RR 1.30, 95% CI 0.71-2.38), the direction of the drug effect was consistent with that of dual LAMA/LABA therapy vs ICS/LABA. The underlying reasons may include relatively small sample size and the increased risk of drop-outs in the placebo group owing to poor control of symptoms or repeated exacerbations.

The current findings are slightly discordant with several published studies. For example, in 2016, Calzetta and colleagues performed a meta-analysis and found that LAMA/LABA combinations did not significantly increase the risk of cardiovascular events compared with controls [13]. However, this paper may have been underpowered as it included only 15 studies (N=23,168 subjects) and did not incorporate the recently published high-quality RCTs [12, 21-22, 25, 34-37, 39-40]. In 2019, a Bayesian network meta-analysis was published and reported that LAMAs

combined with LABAs may increase the risk of cardiac failure in patients with stable COPD [14]. Similar to the previous meta-analysis, this paper only included 16 studies (N=35,529 subjects) and did not incorporate the recently published high-quality RCTs [12, 22, 36-37, 39].

Limitations and Strengths

Our paper had some limitations. First, none of the primary RCTs included in this review was powered on MACE or individual components of MACE such as MI, cardiovascular deaths, or stroke. Further, criteria for determining MACE may have differed across the included trials, leading to potential misclassification of events (or non-events). However, any misclassification bias arising from this issue would have been non-differential, leading to a dilution of risk estimates. Thus, our findings may be a conservative estimate of the CVD risk imposed by LAMA/LABA-based therapies (relative to ICS/LABA). Second, due to insufficient data, some relevant studies were not included, which may have led to a selection bias. Third, there could have been significant differences in the baseline cardiovascular risk among participants between the RCTs. However, individual CVD risk could not be ascertained during the review. In the future, investigators should carefully document CV risk profile in therapeutic trials in COPD, as CVD is a very common comorbidity in patients with COPD in the real-world.

Notwithstanding these and other limitations, there are important clinical implications to the current work. First, to our knowledge, this paper is the largest meta-analysis to date that has comprehensively assessed the risk of MACE associated

with LAMA/LABA combination therapy in patients with COPD. Our work included 51 trials, which enrolled 91,021 participants. Second, CVD is a common comorbidity in patients with COPD, affecting 28% to 70% of patients [75]. MACE is also common, with an annual rate of ~3% in patients with moderate to severe COPD. In the SUMMIT trial, the leading MACE was CV mortality, followed by non-fatal MI, stroke, unstable angina and transient ischemic attacks [71]. Our findings in this context suggest that dual LAMA/LABA or triple therapy has a worse cardiovascular safety profile than ICS/LABA in patients with underlying CVD with moderate to high risk of CV events, as determined by validated risk calculators such as the Framingham Risk Score [76]. Third, most RCTs excluded patients with severe cardiovascular disease or high cardiovascular risk. Thus, in the “real-world” setting, the impact of cardiovascular events in COPD may be significantly higher than in RCTs.

Conclusions

Compared with ICS/LABA, both dual LAMA/LABA and triple therapy increase the risk of MACE and in particular non-fatal MIs and stroke in patients with COPD. However, the excess MACE risks should be balanced against their salutary effects. The benefits of dual LAMA/LABA or triple therapy include reduction in the frequency of exacerbations and hospitalizations, improvements in dyspnea, and health-related quality of life. For example compared with ICS/LABA, the number needed to treat (NNT) for dual LAMA/LABA therapy to prevent 1 COPD exacerbation per year is 16 (95% CI,11-28) [77], and that for triple therapy is 26 (95% CI,20-36) [78]. In comparison, the NNH is 203 (95% CI,106-2500) for MACE with

dual LAMA/LABA therapy and 294 (95% CI,132-1250) with triple therapy. Notably, ICS-based therapies have been associated with increased risk of pneumonia especially in those with severe or very severe disease [79-80]. Thus, one reasonable approach is for clinicians to determine the risk of MACE before initiating dual LAMA/LABA or triple therapy using widely used tools such as the Framingham global risk calculator [81], which has been validated for use in COPD patients and to avoid these medications (or use them very cautiously) in those whose average risk of MACE is >1% per year.

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Contributors

All authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Declaration of Interest

DDS has received honoraria for speaking engagements from GSK, AstraZeneca and Boehringer Ingelheim. The other authors declare no conflicts of interest.

Ethical approval

Not required.

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Clinical Perspective

COMPETENCY IN MEDICAL KNOWLEDGE:

Meta-analysis of data from previous studies revealed for the first time that both dual LAMA/LABA and triple therapy are associated with a significantly increased risk of MACE compared with ICS/LABA. This increase in the risk of MACE was most evident in patient populations with an average baseline MACE risk of >1% per year and in those with GOLD 3 severity.

TRANSLATIONAL OUTLOOK:

Our results raise concerns about cardiovascular safety of dual LAMA/LABA and triple therapy.

Future RCTs should be designed to further evaluate the cardiovascular safety of LAMA/LABA therapy in different populations according to baseline cardiovascular risk.

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Table 1. Summary characteristics of included RCTs.

Characteristic	Number of RCTs	Percentage of Total (%)
Published year		
<2000	0	0
2000–2004	0	0
2005–2009	1	2.0
2010–2014	14	27.5
2015–2020	36	70.6
Follow-up duration		
12 weeks	15	29.4
24 weeks	17	33.3
26 weeks	2	4.0
52 weeks	15	29.4
64 weeks	1	2.0
108 weeks	1	2.0
Type of intervenes, number		
LAMA/LABA	42	82.4
LAMA/LABA/ICS	11	21.6
Evaluated outcome		
MACE	51	100.0
Cardiovascular deaths	39	76.5
Myocardial infarction	40	78.4
Stroke	33	64.7
Male, %		
≤50	1	2.0
50-75	39	76.5
>75	11	21.6
Mean age, y		
≤65	40	78.4
>65	9	17.6
Current smoker, %		
≤25	0	0
25-50	30	58.9
>50	13	25.5
Unclear	8	15.7
Grade FEV1(% predicted)		
GOLD 1 (≥80%)	0	0
GOLD 2 (50-79%)	29	56.9
GOLD 3 (30-49%)	20	39.2
GOLD 4 (<30%)	0	0
Unclear	2	3.9
Cardiovascular risk factors, %		
<10	1	2.0

10-20	0	0
21-30	0	0
31-40	1	2.0
41-50	2	3.9
≥50	2	3.9
Unclear	45	88.2

RCTs, randomized controlled trials; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-2 agonists; FEV1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MACE, major adverse cardiovascular events; cardiovascular risk factors defined as current medical history of angina, myocardial infarction, stroke, diabetes, hypertension, or hyperlipidemia.

Table 2. Results of meta-analysis of dual LAMA/LABA therapy or triple therapy vs. LAMA only, LABA only, ICS/LABA, or placebo for MACE according to different levels of baseline MACE event rates, the duration of treatment, and COPD severity.

Groups and subgroups	No. of Studies	Participants	Risk Ratio (M-H, Random,95% CI)	P value	I^2 (%)	GRADE evidence
Risk of MACE for LAMA/LABA-based therapy vs. controls						
Dual LAMA/LABA therapy vs. controls	42	71,210	1.24 [1.06, 1.44]	**0.006**	0	Low
Triple therapy vs. controls	11	24,617	1.27 [1.03, 1.58]	**0.03**	0	Moderate
Risk of MACE for dual LAMA/LABA therapy vs. different controls						
Dual LAMA/LABA therapy vs. LABA/ICS	9	18,170	1.42 [1.11, 1.81]	**0.005**	0	Moderate
Dual LAMA/LABA therapy vs. placebo	16	10,813	1.30 [0.71, 2.38]	0.39	0	Moderate
Dual LAMA/LABA therapy vs. LABA only	22	24,074	1.11 [0.82, 1.51]	0.51	0	Moderate
Dual LAMA/LABA therapy vs. LAMA only	26	37,768	1.11 [0.91, 1.37]	0.32	0	Moderate
Risk of MACE for dual LAMA/LABA therapy vs. LABA/ICS according to different duration of treatment						
3 months	3	2,157	1.48 [0.41, 5.35]	0.55	0	Moderate
6 months	3	2,196	1.70 [0.55, 5.24]	0.35	0	Moderate
12 months	3	13,817	1.40 [1.08, 1.82]	**0.01**	2	High
Risk of MACE for dual LAMA/LABA therapy vs. LABA/ICS according to COPD severity						
Moderate COPD	6	4,353	1.60 [0.69, 3.73]	0.27	0	Moderate
Severe COPD	3	13,817	1.40 [1.08, 1.82]	**0.01**	2	High
Risk of MACE for dual LAMA/LABA therapy vs. ICS/LABA according to different levels of baseline MACE event rates in controls						
Baseline MER ≥ 1% per year in controls	6	16191	1.40 [1.09, 1.79]	**0.009**	0	Moderate
Baseline MER < 1% per year in controls	3	1979	2.49 [0.55, 11.28]	0.24	0	Moderate
Risk of MACE for triple therapy vs. different controls						
Triple therapy vs. LABA/ICS	9	21,036	1.29 [1.03, 1.61]	**0.03**	0	Moderate
Triple therapy vs. placebo	-	-	-	-	-	-
Triple therapy vs. LABA only	-	-	-	-	-	-
Triple therapy vs. LAMA only	2	3,267	1.11 [0.55, 2.24]	0.77	0	Low
Risk of MACE for triple therapy vs. LABA/ICS according to different duration of follow-up						
3 months	5	3185	0.80 [0.26, 2.41]	0.69	0	Moderate
6 months	-	-	-	-	-	-
12 months	3	16041	1.31 [1.04, 1.65]	**0.02**	0	High
Risk of MACE for triple therapy vs. LABA/ICS according to COPD severity						
Moderate COPD	2	1729	0.66 [0.14, 2.99]	0.27	0	Moderate
Severe COPD	7	19307	1.31 [1.04, 1.64]	**0.02**	0	Moderate
Risk of MACE for triple therapy vs. ICS/LABA according to different levels of baseline MACE event rates in controls						
Baseline MER in controls ≥ 1% per year	7	18990	1.27 [1.01, 1.60]	**0.04**	0	Moderate
Baseline MER in controls < 1% per year	2	2046	1.77 [0.55, 5.67]	0.34	0	Moderate

No., number of including studies; Peto OR, Peto odds ratio; CI, confidence interval;

LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; LAMA/LABA therapy, all studies involving LAMA/LABA and LAMA/LABA/ICS; BMI, body mass index; Triple therapy, LAMA/LABA/ICS; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; GRADE, grading of recommendations assessment, development, and evaluation;

Figure 1. Flow of study selection.

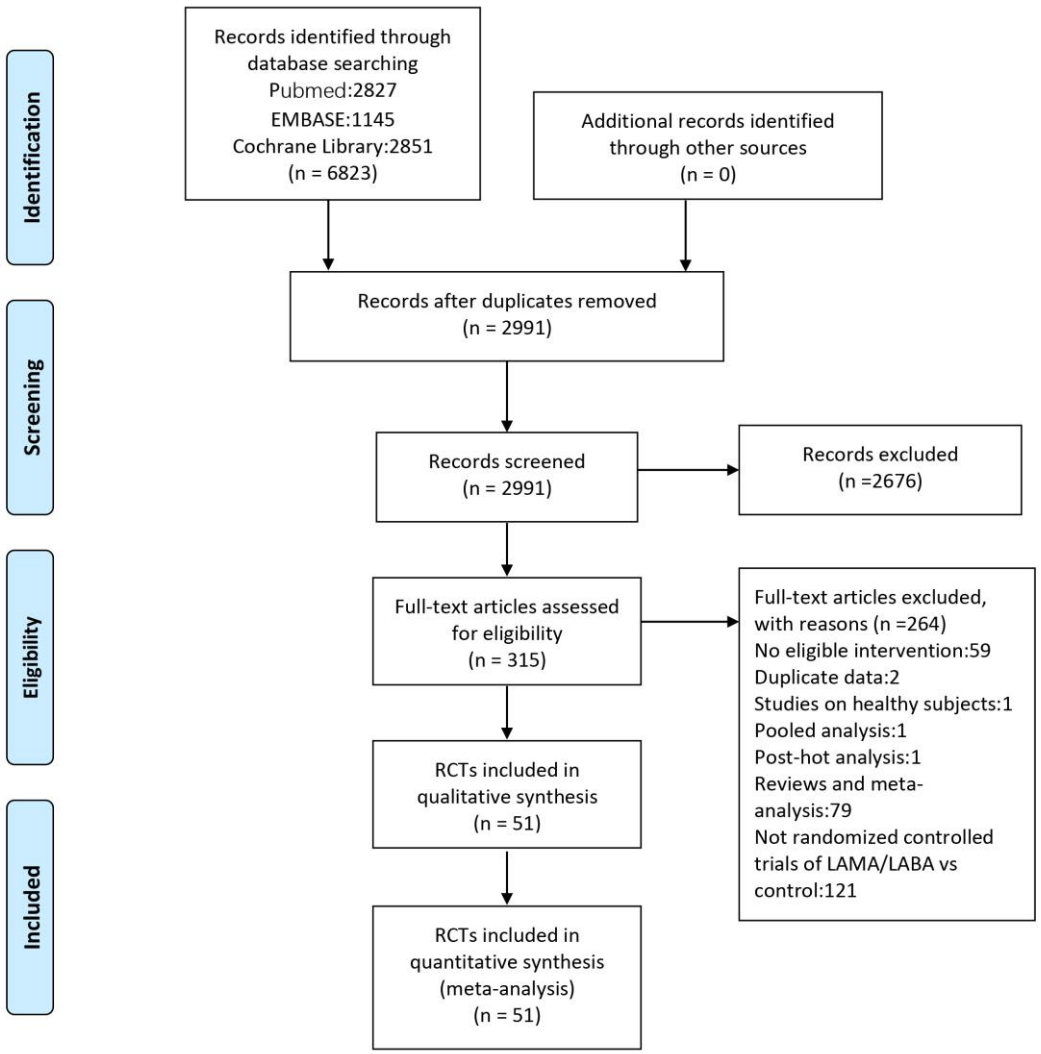
Figure 2. Meta-analysis of included RCTs of dual LAMA/LABA therapy vs. ICS/LABA for MACE. **a**. Risk of MACE for dual LAMA/LABA therapy vs. LABA/ICS according to different duration. **b**. Risk of MACE for dual LAMA/LABA therapy vs. LABA/ICS in patients with different severities. Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β2-agonists; MACE, major adverse cardiovascular events;

Figure 3. Meta-analysis of included RCTs of triple therapy vs. ICS/LABA for MACE. **a**. Risk of MACE for triple therapy vs. LABA/ICS according to different duration. **b**. Risk of MACE for triple therapy vs. LABA/ICS in patients with different severities. Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β2-agonists; MACE, major adverse cardiovascular events

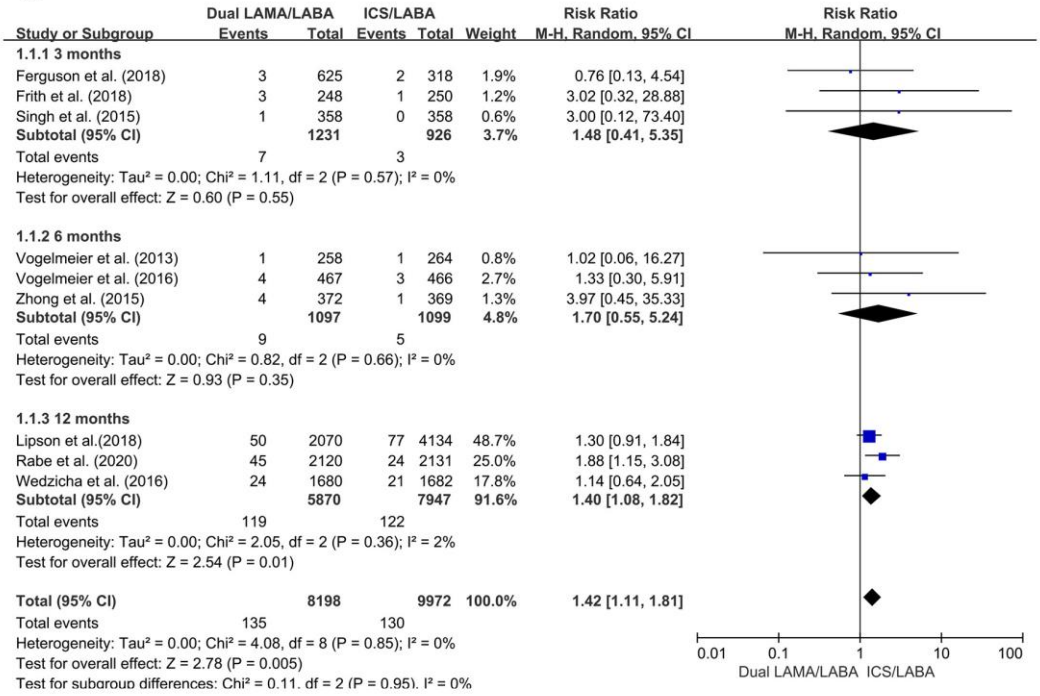
PRISMA 2009 Flow Diagram



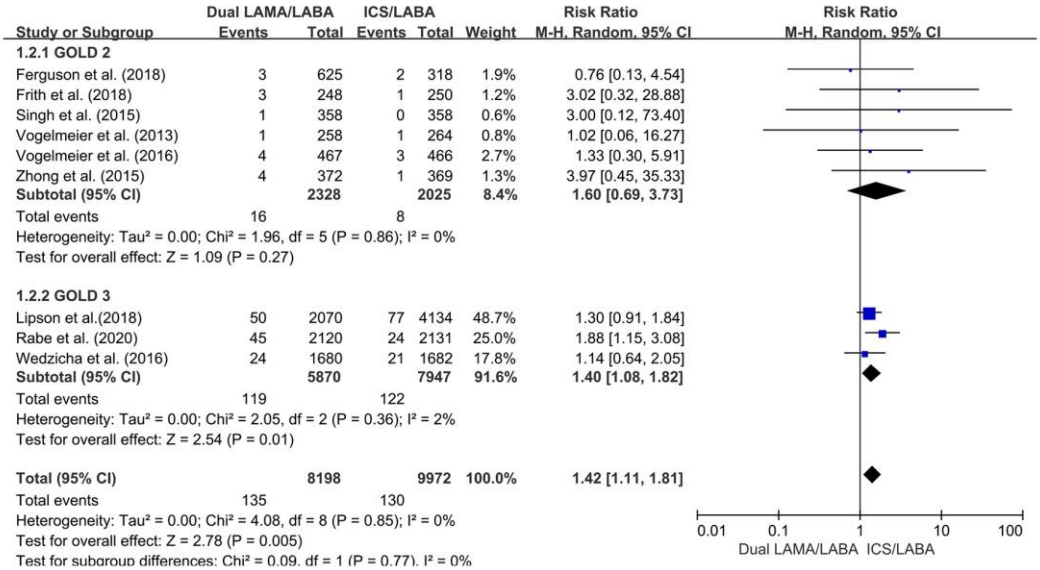
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

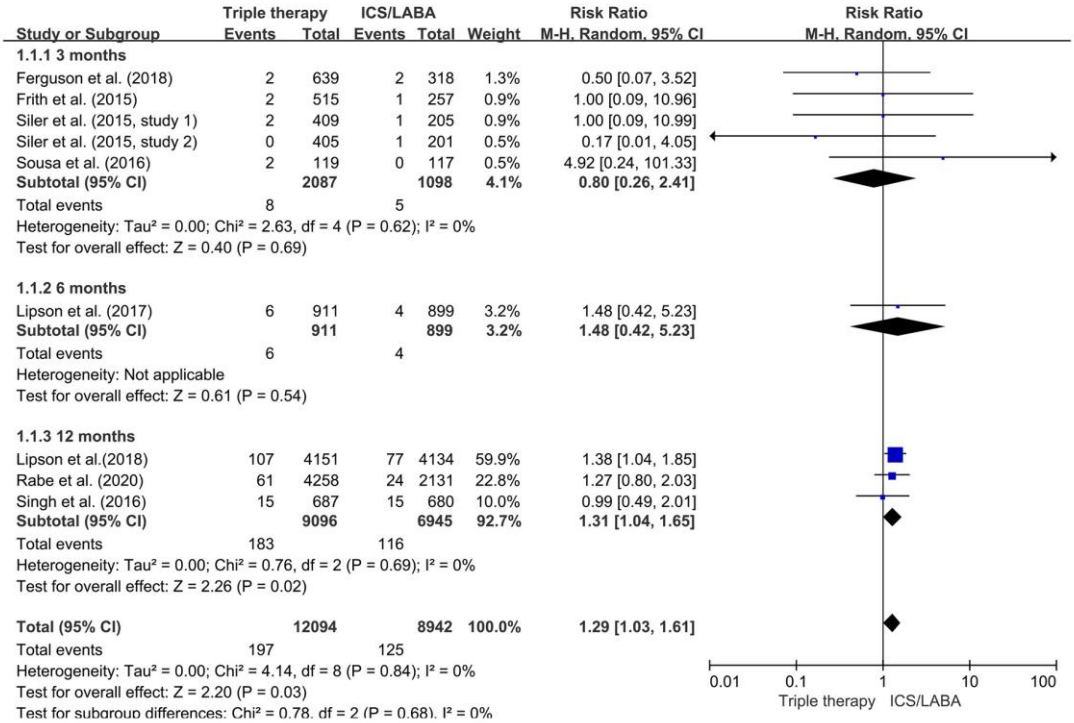
a


Dual LAMA/LABA
ICS/LABA
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 3 months
Ferguson et al. (2018) 3 625 2 318 1.9% 0.76 [0.13, 4.54]
Frith et al. (2018) 3 248 1 250 1.2% 3.02 [0.32, 28.88]
Singh et al. (2015) 1 358 0 358 0.6% 3.00 [0.12, 73.40]
Subtotal (95% CI) 1231 926 3.7% 1.48 [0.41, 5.35]
Total events 7 3
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
1.1.2 6 months
Vogelmeier et al. (2013) 1 258 1 264 0.8% 1.02 [0.06, 16.27]
Vogelmeier et al. (2016) 4 467 3 466 2.7% 1.33 [0.30, 5.91]
Zhong et al. (2015) 4 372 1 369 1.3% 3.97 [0.45, 35.33]
Subtotal (95% CI) 1097 1099 4.8% 1.70 [0.55, 5.24]
Total events 9 5
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
1.1.3 12 months
Lipson et al.(2018) 50 2070 77 4134 48.7% 1.30 [0.91, 1.84]
Rabe et al. (2020) 45 2120 24 2131 25.0% 1.88 [1.15, 3.08]
Wedzicha et al. (2016) 24 1680 21 1682 17.8% 1.14 [0.64, 2.05]
Subtotal (95% CI) 5870 7947 91.6% 1.40 [1.08, 1.82]
Total events 119 122
Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 2 (P = 0.36); I² = 2%
Test for overall effect: Z = 2.54 (P = 0.01)
Total (95% CI) 8198 9972 100.0% 1.42 [1.11, 1.81]
Total events 135 130
Heterogeneity: Tau² = 0.00; Chi² = 4.08, df = 8 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Chi² = 0.11, df = 2 (P = 0.95), I² = 0%
0.01
0.1
1
10
100
Dual LAMA/LABA
ICS/LABA

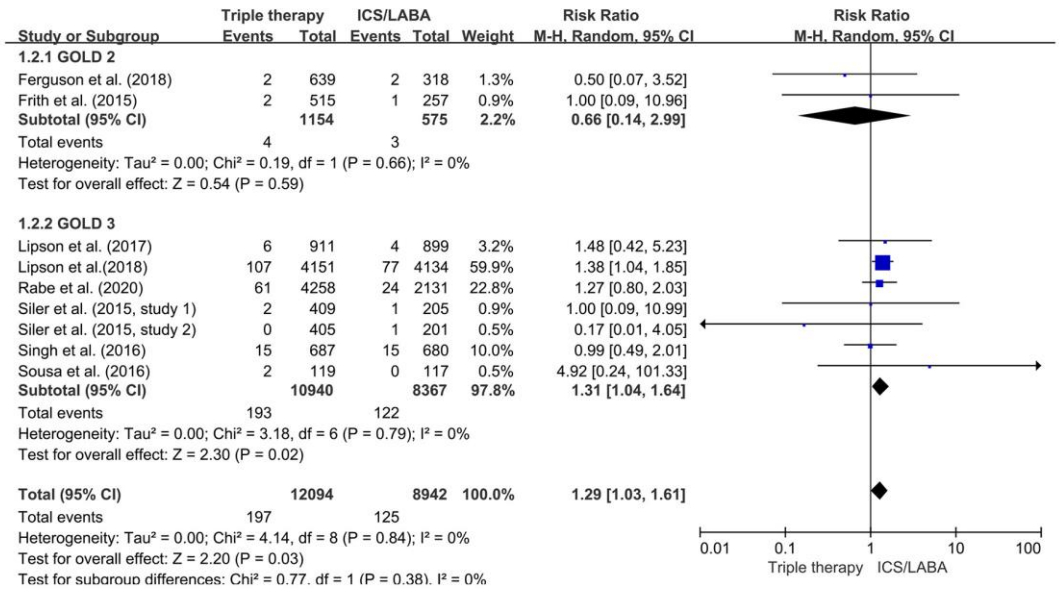
b


Dual LAMA/LABA
ICS/LABA
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 GOLD 2
Ferguson et al. (2018) 3 625 2 318 1.9% 0.76 [0.13, 4.54]
Frith et al. (2018) 3 248 1 250 1.2% 3.02 [0.32, 28.88]
Singh et al. (2015) 1 358 0 358 0.6% 3.00 [0.12, 73.40]
Vogelmeier et al. (2013) 1 258 1 264 0.8% 1.02 [0.06, 16.27]
Vogelmeier et al. (2016) 4 467 3 466 2.7% 1.33 [0.30, 5.91]
Zhong et al. (2015) 4 372 1 369 1.3% 3.97 [0.45, 35.33]
Subtotal (95% CI) 2328 2025 8.4% 1.60 [0.69, 3.73]
Total events 16 8
Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 5 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.27)
1.2.2 GOLD 3
Lipson et al.(2018) 50 2070 77 4134 48.7% 1.30 [0.91, 1.84]
Rabe et al. (2020) 45 2120 24 2131 25.0% 1.88 [1.15, 3.08]
Wedzicha et al. (2016) 24 1680 21 1682 17.8% 1.14 [0.64, 2.05]
Subtotal (95% CI) 5870 7947 91.6% 1.40 [1.08, 1.82]
Total events 119 122
Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 2 (P = 0.36); I² = 2%
Test for overall effect: Z = 2.54 (P = 0.01)
Total (95% CI) 8198 9972 100.0% 1.42 [1.11, 1.81]
Total events 135 130
Heterogeneity: Tau² = 0.00; Chi² = 4.08, df = 8 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%
0.01
0.1
1
10
100
Dual LAMA/LABA
ICS/LABA

a


Triple therapy ICS/LABA Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
1.1.1 3 months
Ferguson et al. (2018) 2 639 2 318 1.3% 0.50 [0.07, 3.52]
Frith et al. (2015) 2 515 1 257 0.9% 1.00 [0.09, 10.96]
Siler et al. (2015, study 1) 2 409 1 205 0.9% 1.00 [0.09, 10.99]
Siler et al. (2015, study 2) 0 405 1 201 0.5% 0.17 [0.01, 4.05]
Sousa et al. (2016) 2 119 0 117 0.5% 4.92 [0.24, 101.33]
Subtotal (95% CI) 2087 1098 4.1% 0.80 [0.26, 2.41]
Total events 8 5
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
1.1.2 6 months
Lipson et al. (2017) 6 911 4 899 3.2% 1.48 [0.42, 5.23]
Subtotal (95% CI) 911 899 3.2% 1.48 [0.42, 5.23]
Total events 6 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
1.1.3 12 months
Lipson et al.(2018) 107 4151 77 4134 59.9% 1.38 [1.04, 1.85]
Rabe et al. (2020) 61 4258 24 2131 22.8% 1.27 [0.80, 2.03]
Singh et al. (2016) 15 687 15 680 10.0% 0.99 [0.49, 2.01]
Subtotal (95% CI) 9096 6945 92.7% 1.31 [1.04, 1.65]
Total events 183 116
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)
Total (95% CI) 12094 8942 100.0% 1.29 [1.03, 1.61]
Total events 197 125
Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 8 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Chi² = 0.78, df = 2 (P = 0.68), I² = 0%
0.01 0.1 1 10 100
Triple therapy ICS/LABA

b


Triple therapy ICS/LABA Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
1.2.1 GOLD 2
Ferguson et al. (2018) 2 639 2 318 1.3% 0.50 [0.07, 3.52]
Frith et al. (2015) 2 515 1 257 0.9% 1.00 [0.09, 10.96]
Subtotal (95% CI) 1154 575 2.2% 0.66 [0.14, 2.99]
Total events 4 3
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)
1.2.2 GOLD 3
Lipson et al. (2017) 6 911 4 899 3.2% 1.48 [0.42, 5.23]
Lipson et al.(2018) 107 4151 77 4134 59.9% 1.38 [1.04, 1.85]
Rabe et al. (2020) 61 4258 24 2131 22.8% 1.27 [0.80, 2.03]
Siler et al. (2015, study 1) 2 409 1 205 0.9% 1.00 [0.09, 10.99]
Siler et al. (2015, study 2) 0 405 1 201 0.5% 0.17 [0.01, 4.05]
Singh et al. (2016) 15 687 15 680 10.0% 0.99 [0.49, 2.01]
Sousa et al. (2016) 2 119 0 117 0.5% 4.92 [0.24, 101.33]
Subtotal (95% CI) 10940 8367 97.8% 1.31 [1.04, 1.64]
Total events 193 122
Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 6 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)
Total (95% CI) 12094 8942 100.0% 1.29 [1.03, 1.61]
Total events 197 125
Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 8 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Chi² = 0.77, df = 1 (P = 0.38), I² = 0%
0.01 0.1 1 10 100
Triple therapy ICS/LABA

Combination Therapy with Long-Acting Bronchodilators and the Risk of Major Adverse Cardiovascular Events in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis

Mingjin Yang; Yishi Li; Youfan Jiang; Shuliang Guo; Jian-Qing He; Don D Sin

Supplementary Appendix

Contents

Table S8. Results of meta-analysis of LAMA/LABA therapy vs. LAMA only, LABA only, ICS/LABA, or placebo for MACE according to the duration, the type of inhalation device, and the severities of COPD (Peto OR).

Table S9. Sensitivity analysis performed by calculating the RD by Mantel-Haenszel approach.

Table S10. Sensitivity analysis performed by calculating the OR by Mantel-Haenszel approach.

Table S11. Sensitivity Analyses Removing Studies with High Risks in Assessment of Risk of Bias.

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Figure S12. Trial sequential analysis of dual LAMA/LABA therapy vs. ICS/LABA for MACE in RCTs.

Figure S13. Trial sequential analysis of triple therapy vs. ICS/LABA for MACE in RCTs.

Figure S14. Trial sequential analysis of dual LAMA/LABA therapy vs. placebo for MACE in RCTs.

Figure S15. Trial sequential analysis of dual LAMA/LABA therapy vs. LAMA for MACE in RCTs.

Figure S16. Trial sequential analysis of dual LAMA/LABA therapy vs. LABA for MACE in RCTs.

Figure S17. Trial sequential analysis of dual LAMA/LABA therapy vs. triple therapy for cardiovascular death.

Figure S18. Trial sequential analysis of dual LAMA/LABA therapy vs. triple therapy for stroke.

Table S1. **Literature Search Strategy**

Concept	Term(s) Searched/Databases	Number
General search strategy	(chronic obstructive pulmonary disease OR COPD OR chronic airflow obstruction OR AECOPD) and (tiotropium OR bronchodilator OR anticholinergic drugs OR LAMA OR glycopyrronium OR aclidinium OR umeclidinium OR Spiriva OR glycopyrrolate OR NVA237 OR Seebri OR GSK573719 OR Incruse OR LAS34273 OR Turdorza OR Eklira OR Bevespi) and (LABA OR salmeterol OR olodaterol OR formoterol OR indacaterol OR long-acting β-agonists OR Anoro OR Duaklir OR QVA149 OR Ultibro OR Spiolto OR QAB-149 OR GW642444 OR BI1744CL OR tulobuterol OR bambuterol OR clenbuterol) with the clinical trial filters (Clinical Trial, Humans, English)	
PubMed Search	#1 COPD: "pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]	95858
	#2 Chronic airflow obstruction: "pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "airflow"[All Fields] AND "obstruction"[All Fields]) OR "chronic airflow obstruction"[All Fields]	89363
	#3 Acute exacerbation of chronic obstructive pulmonary disease: ("acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]) AND ("exacerbate"[All Fields] OR "exacerbated"[All Fields] OR "exacerbates"[All Fields] OR "exacerbating"[All Fields] OR "exacerbation"[All Fields] OR "exacerbations"[All Fields] OR "exacerbator"[All Fields] OR "exacerbators"[All Fields]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields]))	5749

	# 4 tiotropium OR bronchodilator OR anticholinergic drugs OR LAMA OR glycopyrronium OR aclidinium OR umeclidinium OR Spiriva OR glycopyrrolate OR NVA237 OR Seebri OR GSK573719 OR Incruse OR LAS34273 OR Turdorza OR Eklira OR Bevespi: "tiotropium bromide"[MeSH Terms] OR ("tiotropium"[All Fields] AND "bromide"[All Fields]) OR "tiotropium bromide"[All Fields] OR "tiotropium"[All Fields] OR ("bronchodilate"[All Fields] OR "bronchodilated"[All Fields] OR "bronchodilating"[All Fields] OR "bronchodilation"[All Fields] OR "bronchodilative"[All Fields] OR "bronchodilator agents"[Pharmacological Action] OR "bronchodilator agents"[MeSH Terms] OR ("bronchodilator"[All Fields] AND "agents"[All Fields]) OR "bronchodilator agents"[All Fields] OR "bronchodilator"[All Fields] OR "bronchodilators"[All Fields]) OR ("cholinergic antagonists"[Pharmacological Action] OR "cholinergic antagonists"[MeSH Terms] OR ("cholinergic"[All Fields] AND "antagonists"[All Fields]) OR "cholinergic antagonists"[All Fields] OR ("anticholinergic"[All Fields] AND "drugs"[All Fields]) OR "anticholinergic drugs"[All Fields]) OR "LAMA"[All Fields] OR ("glycopyrrolate"[MeSH Terms] OR "glycopyrrolate"[All Fields] OR "glycopyrronium"[All Fields]) OR "aclidinium"[All Fields] OR ("gsk573719"[Supplementary Concept] OR "gsk573719"[All Fields] OR "umeclidinium"[All Fields]) OR ("tiotropium bromide"[MeSH Terms] OR ("tiotropium"[All Fields] AND "bromide"[All Fields]) OR "tiotropium bromide"[All Fields] OR "spiriva"[All Fields] OR "tiotropium"[All Fields]) OR ("glycopyrrolate"[MeSH Terms] OR "glycopyrrolate"[All Fields]) OR ("glycopyrrolate"[MeSH Terms] OR "glycopyrrolate"[All Fields] OR "nva237"[All Fields]) OR ("glycopyrrolate"[MeSH Terms] OR "glycopyrrolate"[All Fields] OR "glycopyrronium"[All Fields] OR "seebri"[All Fields]) OR ("gsk573719"[Supplementary Concept] OR "gsk573719"[All Fields] OR "gsk573719"[All Fields]) OR ("gsk573719"[Supplementary Concept] OR "gsk573719"[All Fields] OR "umeclidinium"[All Fields] OR "incruse"[All Fields]) OR "LAS34273"[All Fields] OR "Eklira"[All Fields] OR ("bevespi"[All Fields] OR "formoterol fumarate"[MeSH Terms] OR ("formoterol"[All Fields] AND "fumarate"[All Fields]) OR "formoterol fumarate"[All Fields] OR "eformoterol"[All Fields] OR "formoterol"[All Fields] OR "glycopyrrolate"[MeSH Terms] OR "glycopyrrolate"[All Fields] OR "glycopyrronium"[All Fields])	345,196
	#5 LABA OR salmeterol OR olodaterol OR formoterol OR indacaterol OR long-acting β-agonists OR Anoro OR Duaklir OR QVA149 OR Ultibro OR Spiolto OR QAB-149 OR GW642444 OR BI1744CL OR tulobuterol OR bambuterol OR clenbuterol: "LABA"[All Fields] OR ("salmeterol xinafoate"[MeSH Terms] OR ("salmeterol"[All Fields] AND "xinafoate"[All Fields]) OR "salmeterol xinafoate"[All Fields] OR "salmeterol"[All Fields] OR "salmeterol s"[All Fields]) OR ("olodaterol"[Supplementary Concept] OR	10,166

	"olodaterol"[All Fields]) OR ("formoterol fumarate"[MeSH Terms] OR ("formoterol"[All Fields] AND "fumarate"[All Fields]) OR "formoterol fumarate"[All Fields] OR "eformoterol"[All Fields] OR "formoterol"[All Fields]) OR ("indacaterol"[Supplementary Concept] OR "indacaterol"[All Fields]) OR ("long-acting"[All Fields] AND "beta-agonists"[All Fields]) OR ("gsk573719"[Supplementary Concept] OR "gsk573719"[All Fields] OR "umeclidinium"[All Fields] OR "anoro"[All Fields] OR "vilanterol"[Supplementary Concept] OR "vilanterol"[All Fields]) OR ("aclidinium"[All Fields] OR "duaklir"[All Fields] OR "formoterol fumarate"[MeSH Terms] OR ("formoterol"[All Fields] AND "fumarate"[All Fields]) OR "formoterol fumarate"[All Fields] OR "eformoterol"[All Fields] OR "formoterol"[All Fields]) OR ("indacaterol glycopyrronium combination"[Supplementary Concept] OR "indacaterol glycopyrronium combination"[All Fields] OR "qva149"[All Fields]) OR "Ultibro"[All Fields] OR "Spiolto"[All Fields] OR ("indacaterol"[Supplementary Concept] OR "indacaterol"[All Fields] OR "qab 149"[All Fields]) OR "GW642444"[All Fields] OR "BI1744CL"[All Fields] OR ("tulobuterol"[Supplementary Concept] OR "tulobuterol"[All Fields]) OR ("bambuterol"[Supplementary Concept] OR "bambuterol"[All Fields]) OR ("clenbuterol"[MeSH Terms] OR "clenbuterol"[All Fields])	
	(#1 or #2 or #3) and #4 and #5	2827
Cochrane Library	#1 'chronic obstructive pulmonary disease' OR 'COPD' OR 'chronic airflow obstruction' OR 'AECOPD'	21173
	#2 'tiotropium' OR 'bronchodilator' OR 'anticholinergic drugs' OR 'LAMA' OR 'glycopyrronium' OR 'aclidinium' OR 'umeclidinium' OR 'Spiriva' OR 'glycopyrrolate' OR 'NVA237' OR 'Seebri' OR 'GSK573719' OR 'Incruse' OR 'LAS34273' OR 'Turdorza' OR 'Eklira' OR 'Bevespi'	15312
	#3 'LABA' OR 'salmeterol' OR 'olodaterol' OR 'formoterol' OR 'indacaterol' OR 'long-acting β-agonists' OR 'Anoro' OR 'Duaklir' OR 'QVA149' OR 'Ultibro' OR 'Spiolto' OR 'QAB-149' OR 'GW642444' OR 'BI1744CL' OR 'tulobuterol' OR 'bambuterol' OR 'clenbuterol'	15825
	#4 "trial"	
	#1 and #2 and #3 and #4	2851
EMBASE	#1 ('chronic obstructive pulmonary disease' OR 'copd' OR 'chronic airflow obstruction' OR 'aecopd') AND [humans]/lim AND [english]/lim AND [embase]/lim	97567

	#2 'tiotropium'/exp OR tiotropium OR 'bronchodilator'/exp OR bronchodilator OR 'anticholinergic drugs' OR (('anticholinergic'/exp OR anticholinergic) AND ('drugs'/exp OR drugs)) OR 'lama'/exp OR lama OR 'glycopyrronium'/exp OR glycopyrronium OR 'aclidinium'/exp OR aclidinium OR 'umeclidinium'/exp OR umeclidinium OR 'spiriva'/exp OR spiriva OR 'glycopyrrolate'/exp OR glycopyrrolate OR 'nva237'/exp OR nva237 OR 'seebri'/exp OR seebri OR 'gsk573719'/exp OR gsk573719 OR 'incruse'/exp OR incruse OR 'las34273'/exp OR las34273 OR turdorza OR 'eklira'/exp OR eklira OR 'bevespi'/exp OR bevespi	387501
	#3 laba OR 'salmeterol'/exp OR salmeterol OR 'olodaterol'/exp OR olodaterol OR 'formoterol'/exp OR formoterol OR 'indacaterol'/exp OR indacaterol OR 'long-acting β-agonists' OR ('long acting' AND 'β agonists') OR 'anoro'/exp OR anoro OR 'duaklir'/exp OR duaklir OR 'qva149'/exp OR qva149 OR 'ultibro'/exp OR ultibro OR 'spiolto'/exp OR spiolto OR 'qab 149'/exp OR 'qab 149' OR 'gw642444'/exp OR gw642444 OR bi1744cl OR 'tulobuterol'/exp OR tulobuterol OR 'bambuterol'/exp OR bambuterol OR 'clenbuterol'/exp OR clenbuterol	26363
	#4 Randomized Controlled Trial	
	#1 and #2 and #3 and #4	1145

Table S2. Baseline Characteristics of 51 Randomized Controlled Trials of LABA/LAMA Combination Therapy Included in the Meta-analysis.

Interventions/Control (ug); Inhaler device	Cardiovascular events, N				No. of Participants (% Male)	Age, Mean (SD), y	% Predicted FEV_1, Mean (SD)	Current Smokers, (N%; PY)	Primary outcome
	MI	Stroke	CV-death	MACE					
≤ 3 months									
Vincken et al. 2014 (12 weeks); Separate Breezhaler® devices									Trough FEV1
IND/GLY 150/50 qd	0	0	0	0	226 (79.6)	63.4 (8.4)	54.2 (12.9)	42.5; 44.5	
IND 150 qd + PBO qd	0	0	0	0	221 (84.2)	64.1 (7.7)	55.5 (12.6)	41.6; 44.4	
Mahler et al. 2015 (12 weeks); The Neohaler® device									FEV1 AUC0-12h
IND/GLY 27.5/15.6 bid	NA	NA	0	3	508 (63.4)	63.4 (8.6)	54.9 (13.3)	50.4; NA	
IND 27.5 bid	NA	NA	0	2	511 (65.8)	63.7 (8.3)	54.4 (13.5)	52.1; NA	
GLY 15.6 bid	NA	NA	0	1	511 (63.8)	63.4 (8.4)	54.6 (13.2)	52.3; NA	
PBO bid	NA	NA	0	1	508 (60.2)	63.2 (8.1)	54.4 (13.1)	51.6; NA	
Singh et al. 2015 (12 weeks); The ELLIPTA®1 dry powder inhaler; The DISKUS inhaler									0–24 h wm FEV1
UMEC/VI 62.5/25 qd	0	0	1	1	358 (73)	61.8 (7.9)	50.2 (10.9)	57; 40.7	
SFC 50/500 bid	0	0	0	0	358 (71)	61.4 (8.1)	51.1 (10.5)	61; 39.4	
Siler et al. 2016 (12 weeks); The ELLIPTA®dry powder inhaler									SGRQ
UMEC/VI 62.5/25 qd	2	0	1	2	248 (58)	64.1 (8.7)	46.5 (12.8)	55; 38.8	
PBO qd	2	0	0	2	248 (60)	62.6 (8.2)	48.4 (14.1)	52; 38.4	
Frith et al. 2018 (12 weeks); A single dose dry powder inhaler (SDDPI); The Accuhaler®/Diskus® device									FEV1

IND/GLY 110/50 qd	0	2	1	3	248 (88.7)	65 (9.1)	51.3 (12.8)	36.7; 44.3	
SFC 50/500 bid	1	0	0	1	250 (89.6)	65.1 (8.4)	51.7 (12.7)	38; 45.3	
Frith et al. 2015 (12 weeks); The Breezhaler inhaler; The Accuhaler inhaler; The HandiHaler inhaler									trough FEV1
GLY 50 qd + SFC 50/500 bid	NA	0	1	1	257 (63.4)	68.2 (8.4)	57.4 (14)	35.4; 47.2	
TIO 18 qd + SFC 50/500 bid	NA	1	NA	1	258 (62)	68 (7.7)	56.9 (13.8)	35.7; 49.4	
PBO qd + SFC 50/500 bid	NA	0	1	1	257 (67.7)	67.8 (8.5)	57.4 (13.6)	36.2; 49.7	
Lee et al. 2016 (12 weeks); Symbicort Turbuhaler									Pre-dose FEV1 from baseline
TIO 18 qd + BUD/FM 320/9 bid	NA	NA	1	1	287 (97.2)	66.6 (8)	35.8 (11.3)	NA	
TIO 18 qd	NA	NA	0	0	290 (94.1)	66.9 (8.5)	37 (10.6)	NA	
Siler et al. 2015 Study 1 (12 weeks) NCT01772134; The ELLIPTA™ dry powder inhaler; The DISKUS™ inhaler									trough FEV1
UMEC 125 qd + SFC 50/250 bid	1	1	1	2	205 (69)	63.2 (9)	46.7 (13.1)	56; 50.4	
UMEC 62.5 qd + SFC 50/250 bid	0	0	0	0	204 (65)	62.7 (7.8)	46.8 (12.4)	50; 49.8	
PBO qd + SFC 50/250 bid	1	0	0	1	205 (64)	63.4 (8.3)	47.4 (13.3)	57; 48.4	
Siler et al. 2015 Study 2 (12 weeks) NCT01772147; The ELLIPTA™ dry powder inhaler; The DISKUS™ inhaler									trough FEV1
UMEC 125 qd + SFC 50/250 bid	0	0	0	0	202 (59)	65.5 (7.9)	47.6 (12.8)	39; 42.8	
UMEC 62.5 qd + SFC 50/250 bid	0	0	0	0	203 (69)	64.5 (8.3)	43.9 (11.5)	36; 44.3	
PBO qd + SFC 50/250 bid	1	0	0	1	201 (61)	65.7 (7.9)	44.8 (13.3)	38; 45.1	
Kerwin et al. 2017 (12 weeks); The ELLIPTA® dry powder inhaler;									trough FEV1

The HandiHaler®									
UMEC/VI 62.5/25 qd	1	1	0	2	247(66)	64.5 (8.7)	59.8 (5.5)	52;20.5	
TIO 18 qd	0	0	0	0	247(65)	64.3 (8.7)	59.4 (5.3)	48;20.2	
Sousa et al. 2016 (12 weeks); The ELLIPTA inhaler;									trough FEV1
UMEC+ICS/LABA 62.5 mcg qd, 500/50 mcg bid	1	1	NA	2	119(70)	65.2 (7.5)	47.6 (12.0)	49;25.8	
PBO+ICS/LABA 500/50 mcg bid	0	0	NA	0	117(64)	63.1 (7.9)	47.8 (11.6)	61;19.8	
Singh et al. 2015 (12 weeks) study1 NCT01964352; The Respimat® inhaler									SGRQ FEV1 AUC0-3 Trough FEV1
Tiotropium/olodaterol 5/5,2.5/5	1	0	0	1	405(56.8)	64.7 (8.4)	NA	NA; NA	
Tiotropium 5	1	1	0	2	203(61.1)	64.9 (8.2)	54.7 (12.8)	48.3;	
Placebo	0	0	0	0	204(62.3)	65.1 (8.3)	56.3 (12.8)	43.1;	
Singh et al. 2015 (12 weeks) study2 NCT02006732; The Respimat® inhaler									SGRQ FEV1 AUC0-3 Trough FEV1
Tiotropium/olodaterol 5/5,2.5/5 qd	2	0	0	2	404	65.0 (8.5)	NA	NA; NA	
Tiotropium 5 qd	2	0	0	2	203 (64.0)	64.7 (8.4)	55.9 (12.2)	44.8; NA	
Placebo qd	0	0	0	0	202(57.9)	64.0 (8.3)	54.3 (13.4)	47.0; NA	
ZuWallack et al. 2014 (12 weeks) study1 NCT01694771; The Respimat® inhaler; The HandiHaler® dry powder inhaler									FEV 1 AUC 0-3 Trough FEV 1
Olodaterol(5μg) +Tiotropium(18μg) qd	2	1	NA	3	567(49.2)	64.3 (9.1)	54.2 (13.0)	49.7;54.0	
Tiotropium 18μg qd	1	0	NA	1	565(50.4)	64.8 (9.1)	53.9 (13.0)	52.2;52.7	
ZuWallack et al. 2014 (12 weeks) study2 NCT01696058; The Respimat® inhaler; The HandiHaler® dry powder inhaler									FEV 1 AUC 0-3 Trough FEV 1
Olodaterol(5μg) +Tiotropium(18μg) qd	0	NA	1	1	566(53.9)	64.6 (9.0)	53.6 (13.6)	45.8;53.9	
Tiotropium 18μg qd	2	NA	0	2	569(53.3)	63.6 (8.9)	53.0 (13.9)	48.2;51.4	

About 6 months									
Bateman et al. 2013 (24 weeks) **The Breezhaler® device;** **The HandiHaler® device**									Trough FEV1
IND/GLY 110/50 qd	0	0	0	0	474 (76.4)	64 (8.9)	55.7 (13.2)	40.5; NA	
IND 150 qd	0	1	1	2	476 (74.4)	63.6 (8.8)	54.9 (12.9)	38.7; NA	
GLY 50 qd	1	0	1	2	473 (77.2)	64.3 (9)	55.1 (13.4)	40; NA	
TIO 18qd	0	2	0	2	480 (75)	63.5 (8.7)	55.1 (13.5)	39.4; NA	
PBO qd	0	0	0	0	232 (72.8)	64.4 (8.6)	55.2 (12.7)	40.1; NA	
Donohue et al. 2013 (24 weeks); **The dry powder inhaler (DPI)**									Trough FEV1
UMEC/VI 62.5/25 qd	2	0	1	3	413 (74)	63.1 (8.7)	47.8 (13.2)	49; 46.5	
UMEC 62.5 qd	0	0	1	1	418 (71)	64 (9.2)	46.8 (13.4)	50; 46.8	
VI 25 qd	0	2	1	2	421 (68)	62.7 (8.5)	48.2 (13.3)	47; 44.7	
PBO qd	0	1	0	1	280 (70)	62.2 (9)	46.7 (12.7)	54; 47.2	
Vogelmeier et al. 2013 (26 weeks); **The Breezhaler device;** **The Accuhaler device**									FEV1 AUC(0-12h)
IND/GLY 110/50 qd	1	0	0	1	258 (70.2)	63.2 (8.2)	60.5 (10.5)	47.7; NA	
SFC 50/500 bid	0	1	1	1	264 (71.6)	63.4 (7.7)	60 (10.7)	48.1; NA	
Celli et al. 2014 (24 weeks); **A drypowder inhaler**									Trough FEV1
UMEC/VI 125/25 qd	1	NA	0	1	403 (66)	63.4 (8.1)	47.7 (12.5)	50; 45.4	
UMEC 125 qd	2	NA	0	2	407 (66)	63.1 (8.5)	48.8 (12.3)	53; 44	
VI 25 qd	2	NA	1	2	404 (66)	62.8 (8.8)	48.5 (12.7)	52; 42.8	
PBO qd	0	NA	0	0	275 (64)	62.2 (8.5)	47.6 (12.5)	52; 43.6	
Decramer et al. 2014 study 1 (24 weeks) NCT01316900; **The ELLIPTA dry powder inhaler;** **The HandiHaler inhaler**									Trough FEV1
UMEC/VI 125/25 qd	0	NA	0	0	214 (63.8)	62.9 (8.9)	47.2 (12.8)	NA; 43.5	
UMEC/VI 62.5/25 qd	0	NA	1	1	212 (65)	63 (8.7)	48 (12.9)	NA; 44.8	
VI 25 qd	1	NA	1	2	209 (54.5)	63.2 (9.1)	47.7 (12.7)	NA; 41.6	
TIO 18qd	0	NA	0	0	208 (65.2)	62.6 (9.4)	47.8 (13.4)	NA; 41.9	
Decramer et al. 2014 study 2 (24 weeks)									Trough FEV1

NCT01316913; The ELLIPTA dry powder inhaler; The HandiHaler inhaler									
UMEC/VI 125/25 qd	0	1	0	1	215 (71)	63.8 (85)	47.1 (12.9)	NA; 46.9	
UMEC/VI 62.5/25 qd	1	1	1	2	217 (70)	65 (8.6)	47.7 (13.5)	NA; 47.8	
UMEC 125 qd	0	1	0	1	222 (68)	64.5 (8.3)	46.2 (13)	NA; 47.6	
TIO 18qd	0	0	0	0	215 (67)	65.2 (8.3)	47.4 (13.1)	NA; 54	
Singh et al. 2014 (24 weeks); A breath-actuated, multiple-dose dry powder inhaler (Genuair®/Pressair®)									Trough FEV1
AB/FM 400/12 bid	3	0	0	3	385 (67.8)	62.7 (8.1)	54.6 (13.1)	47; NA	
AB/FM 400/6 bid	0	1	1	2	381 (68)	62.9 (7.7)	54.1 (13)	47.8; NA	
AB bid	1	0	0	1	385 (66.5)	63.1 (8.2)	53.6 (13)	47.3; NA	
FM bid	0	1	1	3	384 (66.4)	63.4 (7.8)	54.5 (13.2)	46.6; NA	
PBO bid	0	1	0	1	194 (71.1)	64.2 (8)	55 (13.4)	48.5; NA	
Urzo et al. 2014 (24 weeks); A breath-actuated, multiple-dose dry powder inhaler (Genuair®/Pressair®)									Change from baseline at 1-hour morning postdose FEV1
AB/FM 400/12 bid	1	0	1	2	335 (50.1)	64.2 (8.9)	53.2 (13.4)	51.6; 53.3	
AB/FM 400/6 bid	3	1	0	4	333 (56.2)	63.9 (9.2)	54.7 (12.9)	52.9; 52.1	
AB 400 bid	1	0	1	1	337 (55.8)	64.4 (8.7)	53 (13.3)	50.7; 52	
FM 12 bid	2	0	1	3	332 (50.9)	63.7 (8.7)	53.9 (13.1)	51.5; 52.5	
PBO bid	1	2	0	2	332 (52.7)	63.5 (8.9)	52.6 (13.3)	50.9; 53.3	
Zheng et al. 2015 (24 weeks)									Trough FEV1
UMEC/VI 125/25 qd	0	NA	0	0	193 (94)	63.7 (8.3)	NA	25; 38.9	
UMEC/VI 62.5/25 qd	1	NA	0	1	194 (94)	64 (8.7)	NA	29; 37.6	
PBO qd	0	NA	0	0	193 (92)	64.3 (8.8)	NA	34; 37.1	
Zhong et al. 2015 (26 weeks); The Breezhaler® device; The Accuhaler® device									Trough FEV1
IND/GLY 110/50 qd	1	2	1	4	372 (91.7)	64.8 (7.8)	51.6 (12.8)	25.8; NA	
SFC 50/500 bid	0	1	0	1	369 (89.7)	65.3 (7.9)	52 (12.9)	26; NA	
Martinez et al. 2016									Trough FEV1

Study 1 (24 weeks) NCT01854645									
GLY/FM 18/9.6 bid	2	1	1	4	526 (55.1)	62.6 (8.4)	51.4 (13.6)	53.4; 50.9	
GLY 18 bid	2	2	0	4	451 (56.5)	62.9 (8.4)	50.7 (13.7)	54.3; 50.4	
FM 9.6 bid	0	2	0	2	449 (54.8)	63 (8.3)	51.2 (14.1)	54.3; 52.9	
PBO bid	1	0	0	1	219 (55.7)	62.5 (8.3)	50.6 (13.9)	57.5; 50.8	
TIO 18 qd	0	1	1	2	451 (59.6)	63 (8.6)	51.4 (13.8)	52.8; 53	
Martinez et al. 2016 Study 2 (24 weeks) NCT01854658									Trough FEV1
GLY/FM 18/9.6 bid	1	0	1	2	510 (53.3)	62.8 (8.2)	52.1 (14.1)	52.5; 50.5	
GLY 18 bid	1	2	0	3	439 (55.1)	62.8 (8.4)	51.5 (14)	51.5; 50.4	
FM 9.6 bid	1	3	1	5	437 (56.5)	62.6 (7.8)	51.9 (13.8)	57.7; 50.6	
PBO bid	2	0	1	3	223 (56.1)	64.2 (8.7)	52.5 (13.9)	49.3; 53.2	
Vogelmeier et al. 2016 (24 weeks) NCT01908140; The Genuair/Pressair device; The Accuhaler device									peak FEV1
AB/FM 400/12 bid	1	2	2	4	467 (65.7)	63.5 (8.1)	53.3 (14.4)	NA; 41.6	
SFC 50/500 bid	0	0	1	3	466 (64.4)	63.3 (7.5)	53.2 (14.8)	NA; 42.6	
Lipworth et al. 2018 (24 weeks)									The annual rate of moderate or severe COPD exacerbations
GFF 18/9.6 bid	1	3	0	4	551 (74)	64.7 (7.4)	54 (13.7)	45.7; 45.9	
GLY 18 bid	2	1	1	3	474 (73)	64 (8.1)	54.8 (14.1)	44.1; 44.8	
FM 9.6 bid	2	0	0	2	480 (76)	64.1 (7.6)	53.9 (13.2)	43.3; 46.9	
PBO bid	0	0	0	0	235 (72.8)	63.9 (7.5)	54.4 (13.9)	48.1; 45.7	
Sethi et al. 2019 (24 weeks); The Genuair™/Pressair® inhaler; The HandiHaler inhalers®									Post-dose FEV1; Morning pre-dose (trough) FEV1
AB/FM 400/12 bid	0	1	NA	2	314 (61.5)	64.4 (8.5)	50.9 (15.1)	52.2; 46.2	
AB 400 bid	0	1	NA	2	475 (64)	64.4 (8.1)	49.6 (14.8)	52.2; 45.4	
FM 12 bid	0	2	NA	4	319 (59.6)	64 (8.6)	49.6 (14.7)	51.1; 45.2	
TIO 18 qd	3	0	NA	3	475 (58.1)	64.3 (8.4)	51.2 (13.9)	52.6; 46.4	

Ferguson et al. 2018 (24 weeks); **A single MDI device;** **A dry-powder inhaler (DPI)**									FEV1 area under the curve from 0 to 4 h; Change from baseline in morning pre-dose trough FEV1
BGF	1	NA	2	2	639 (72)	64.9 (7.8)	50.2 (14.3)	40.1; 45	
GFF	2	NA	1	3	625 (68.8)	65.1 (7.7)	50.2 (13.8)	41.1; 45	
BFF	1	NA	0	2	314 (71.3)	65.2 (7.2)	50 (14)	36.6; 45	
BUD/FORM	1	NA	0	2	318 (74.2)	65.9 (7.7)	50.7 (13.8)	38.4; 45	
Lipson et al. 2017(24 weeks); **The ELLIPTA® inhaler;** **The Turbuhaler®**									Trough FEV1; SGRQ
Fluticasone furoate/umeclidinium/vilanterol 100 µg/62.5 µg/25 µg bid	1	3	2	6	911(74)	64.2(8.6)	45.5 (12.97)	44;39.5	
BUD/FOR 400/12 µg bid	3	1	0	4	899(74)	63.7(8.7)	45.1 (13.64)	44;39.2	
Maltais et al. 2019(24 weeks); **The ELLIPTA inhaler;** **The DISKUS inhaler**									Change from baseline in trough FEV1
UMEC/VI 62.5/25 µg qd	1	1	3	5	812(61)	64.6(8.4)	54.9(12.8)	49;49.4	
Umeclidinium 62.5 µg qd	1	1	1	3	804(59)	64.9(8.5)	55.9(12.6)	49;47.6	
Salmeterol 50 µg bid	0	1	0	1	809(58)	64.4(8.5)	55.6(12.8)	51;48.1	
Buhl et al. 2015(24 weeks) NCT01431274; NCT01431287; **The Respimat inhaler**									FEV1 AUC0–3
Tiotropium+olodaterol 5/5 µg qd	7	3	1	11	1029(71.2)	63.8(8.3)	49.3(15.3)	38.9	
Tiotropium+olodaterol 2.5/5 µg qd	5	4	0	9	1030(73.5)	64.1(7.8)	50.2(14.9)	36.1;	
Tiotropium 5 µg qd	2	6	1	9	1033(73.1)	63.9(8.6)	50.3(15.0)	35.8;	
Tiotropium 2.5 µg qd	2	4	0	6	1032(73.0)	64.0(8.7)	50.3(15.0)	37.6;	
Olodaterol 5 µg	4	6	0	10	1038(73.6)	64.2(8.2)	50.3(15.6)	36.4;	
≥ 12 months									

Dahl et al. 2013 (52 weeks); **The Breezhaler device**									Safety and tolerability of 52-week treatment; Frequency of treatment-emergent AEs
IND/GLY 110/50 qd	NA	1	1	2	225 (77.3)	62.5 (8.8)	NA	45.3; 36.3	
PBO qd	NA	0	0	0	113 (76.1)	62.9 (8.1)	NA	51; 38.1	
Donohue et al. 2014 (52 weeks); **The ELLIPTA™ dry powder inhaler**									Trough FEV1
UMEC/VI 125/25 qd	1	0	0	1	226 (69)	61.4 (9)	55 (12.1)	NA; 45.7	
UMEC 125 qd	1	1	1	3	227 (64)	61.7 (9.1)	54.2 (11.8)	NA; 39.2	
PBO qd	1	0	1	1	109 (67)	60.1 (8.3)	55.1 (11.7)	NA; 42.8	
Buhl et al. 2016 (52 weeks); **The Respimat® inhaler**									FEV1 AUC(0-3h)
TIO/Olo 5/5 qd	11	7	6	24	1029 (71.2)	63.8 (8.3)	49.3 (15.3)	38.9; NA	
TIO 5 qd	8	7	5	19	1033 (73.1)	63.9 (8.6)	49.7 (15.7)	35.8; NA	
Olo 5 qd	10	10	5	25	1038 (73.6)	64.2 (8.2)	50.3 (15.6)	36.4; NA	
Ferguson et al. 2016 (52 weeks); **The Neohaler® device**									Number of Patients With Adverse Events, Serious Adverse Events, and Death
IND/GLY 27.5/15.6 bid	2	1	NA	3	204 (64.2)	64 (7.9)	55 (13.2)	49.5; NA	
IND/GLY 27.5/31.2 bid	1	1	NA	4	204 (60.3)	63.9 (8.5)	54.2 (12.6)	51.5; NA	
IND 75 qd	0	0	NA	0	207 (72)	63.8 (8.3)	53.9 (11.8)	51.7; NA	
Ichinose et al. 2016 (52 weeks); **The Respimats inhaler**									FEV1 AUC0–3
TIO/Olo 5/5 qd	0	NA	0	0	41 (92.7)	68.1 (7.1)	59.1 (16.2)	31.7; NA	
TIO/Olo 2.5/5 qd	1	NA	0	1	40 (97.5)	70 (7.5)	53.8 (14.6)	27.5; NA	
Olo 5 qd	0	NA	0	0	41 (97.6)	71.5 (7.2)	59.6 (14.2)	24.4; NA	
Wedzicha et al. 2016 (52 weeks);									The annual rate of all

The dry powder inhaler (SDDPI) devices; **The Accuhaler® device;**									COPD exacerbations (mild, moderate, or severe)
IND/GLY 110/50 qd	13	6	9	24	1680 (77.3)	64.6 (7.9)	44 (9.5)	39.5; NA	
SFC 50/500 bid	7	9	11	21	1682 (74.8)	64.5 (7.7)	44.1 (9.4)	39.8; NA	
Hanania et al. 2017 (52 weeks); **The Spiriva® device;** **The HandiHaler® device**									Change From Baseline in Morning -Pre-dose Trough FEV1
GLY/FM 18/9.6 bid	4	1	1	6	1036 (54.3)	62.7 (8.3)	43.4 (13.6)	53; 50.7	
GLY 18 bid	1	2	0	3	890 (55.9)	62.8 (8.4)	42.6 (13.3)	53; 50.4	
FM 9.6 bid	1	0	0	1	890 (55.7)	62.8 (8.1)	43.4 (13.6)	55.9; 51.8	
TIO 18 qd	1	0	0	1	451 (59.6)	62.9 (8.6)	42.7 (13.2)	52.9; 52.8	
Urzo et al. 2017 (52 weeks)									Percentage of Patients to Experience Any Treatment-emergent Adverse Event
AB/FM 400/12 bid	0	0	1	1	182 (48.4)	63.7 (9.1)	52.1 (13.2)	53.8; 53.3	
AB/FM 400/6 bid	1	0	1	2	204 (58.8)	63.6 (9.2)	55.1 (12.9)	54.4; 53.7	
AB 400 bid	2	1	0	3	194 (53.6)	62.9 (8.3)	52.7 (13.2)	59.3; 52.3	
FM 12 bid	0	0	0	1	192 (46.9)	62.8 (8.7)	55.1 (13.2)	53.6; 53.1	
PBO bid	1	0	1	1	146 (55.5)	63.2 (8.6)	53.2 (12.6)	52.7; 54.5	
Singh et al. 2016 (52 weeks); **A pressurised metered-dose inhaler**									Change from baseline in pre-dose morning FEV1; Change from baseline to the 2-hour post-dose value of FEV1; TDI

									focal score
BDP/FF/GLY 100/6/125 bid	1	NA	NA	10	687 (74)	63.3 (7.9)	< 50%	47; NA	
BDP/FF 100/6 bid	6	NA	NA	10	680 (77)	63.8 (8.2)	< 50%	47; NA	
Lipson et al. 2018 (52 weeks); The Ellipta inhaler									Annual Rate of On-treatment Moderate/Severe Exacerbations
FF/UMEC/VI 100/62.5/25 qd	49	38	20	107	4151 (67)	65.3 (8.2)	45.7 (15)	35; NA	
UMEC/VI 62.5/25 qd	24	10	16	50	2070 (66)	65.2 (8.3)	45.4 (14.7)	35; NA	
FF/VI 100/25 qd	29	21	27	77	4134 (66)	65.3 (8.3)	45.5 (14.8)	34; NA	
Rabe et al. 2020 (52 weeks); The metered-dose inhalers (Aerosphere, AstraZeneca)									Adjusted Rate of Moderate or Severe Exacerbations
Budesonide/gly/formoterol 320/18/9·6 bid	9	12	10	31	2137 (59)	64.6 (7.6)	43.6 (10.3)	42.6; 47	
Budesonide/gly/formoterol 160/18/9·6 bid	13	6	11	30	2121 (61.2)	64.6 (7.6)	43.1 (10.4)	40.8; 47.9	
Glycopyrrolate/formoterol 18/9.6 bid	17	6	22	45	2120 (58.7)	64.8 (7.6)	43.5 (10.2)	40.4; 48.4	
Budesonide/formoterol 320/9.6 bid	8	6	10	24	2131 (60)	64.6 (7.6)	43.4 (10.4)	40.5; 47.1	
Donohue et al. 2016 (52 weeks); A multidose dry powder inhaler (Genuair™/Pressair®)									Treatment-emergent adverse events and serious AEs
AB/FF 400/12 bid	0	0	2	2	392(55.1)	63.9 (9.3)	51.8 (13.0)	46.9;27.2	
FF 12 bid	0	1	0	1	198(55.1)	64.7 (9.4)	50.5 (13.5)	43.9;26.8	
Bateman and Tashkin et al. (2010) (1year) (Study 1); The Respimat inhaler									Trough FEV1; The time to first exacerbation
Tiotropium/LABA bid	NA	NA	10	10	1058(77.8)	64.9 (9.0)	43.85	33.6; 46.4	

							(12.82)		
LABA bid	NA	NA	4	4	1033(74.2)	64.6 (8.8)	44.63 (12.78)	32.5; 46.0	
Vestbo et al. 2017 (52 weeks); The HandiHaler inhaler									COPD exacerbation rate
Tiotropium qd, BDP/6 µg FF/12.5 µg bid	4	NA	NA	19	1614(76.0)	NA	36.6 (8.2)	NA; NA	
Tiotropium 18 qd	3	NA	NA	12	1076(77.0)	63.3(8.4)	36.6 (8.2)	47.0; NA	
Peter et al. 2018 (52 weeks); The Respimat device									Annualised Rate of Moderate to Severe COPD Exacerbations During the Actual Treatment Period.
Tiotropium/olodaterol 5 µg/5 µg qd	NA	NA	NA	75	3939(71)	66.5(8.4)	44.6 (37.5)	36;44.8	
Tiotropium 5 µg qd	NA	NA	NA	71	3941(72)	66.3 (8.5)	44.5 (11.5)	38;44.7	
Wedzicha et al. 2013 (64 weeks); The Breezhaler device; The Handihaler device									Rate of Moderate to Severe COPD Exacerbations
Indacaterol 110µg+glycopyrronium50 µg qd	3	4	1	8	729 (76)	63.1 (8.1)	37.0 (8·1)	38;45	
Glycopyrronium qd	7	3	1	11	740 (73)	63.1 (8.0)	37.3(8·1)	38;44	
Tiotropium qd	6	4	0	10	737 (75)	63.6 (7.8)	37.4(8·1)	37;47	
Aaron et al. 2007 (27months); The Handihaler device; A spacer device (Aerochamber Plus)									The proportion of patients in each treatment group who experienced a COPD exacerbation
TIO 18qd +SAL 50 bid	2	NA	NA	2	148 (57.4)	67.6 (8.2)	41.2 (13)	24.3; 48.7	

TIO 18qd +PBO bid	2	NA	NA	2	156 (57.8)	68.1 (8.9)	42.1 (13.5)	26.9; 51.8	

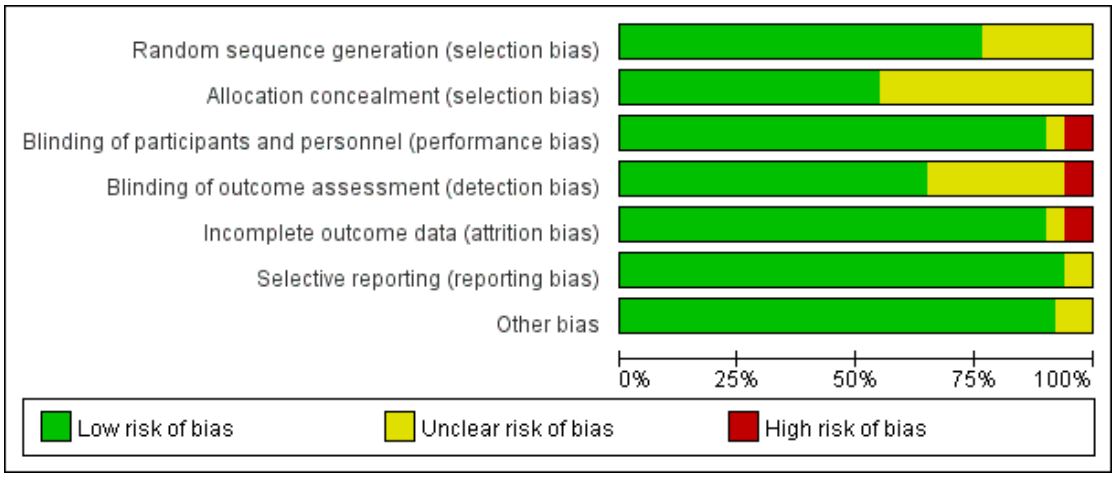
Abbreviations: MI, myocardial infarction; CV-death, cardiovascular- death; MACE, major adverse cardiovascular events, defined as cardiovascular death, nonfatal MI, or nonfatal stroke; FEV_1, forced expiratory volume in the first second of expiration; PY, pack years; NA, not available; *qd*, once a day, *bid*, twice a day; IND, indacaterol; GLY, glycopyrronium; PBO, placebo; SFC, salmeterol/fluticasone propionate; TIO, tiotropium; UMEC, umeclidinium; FF, fluticasone furoate; VI, vilanterol; AB, ABidinium bromide; FM, formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol; GFF, glycopyrrolate/formoterol; BFF, budesonide/formoterol fumarate; BUD, budesonide; Olo, olodaterol; SGRQ, Saint George's Respiratory Questionnaire

Table S3. Definitions

Outcomes	**Definitions**
Major adverse cardiovascular events	MACE was prespecified as a composite of nonfatal MI, nonfatal stroke, or cardiovascular deaths (including sudden deaths)
Cardiovascular death	Deaths due to cardiovascular disease
Myocardial infarction	The presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia.
All LAMA/LABA therapy	All studies involving dual LAMA/LABA therapy and LAMA/LABA/ICS
Dual LAMA/LABA therapy	Only LAMA and LABA were used in combination
Triple therapy	Combination of LAMA/LABA/ICS

Figure S1 (a and b). Risk of bias of the included RCTs.

a. Risk of bias graph



b. Risk of bias summary; Green circles represent low risk, yellow circles represent unclear risk, and red circles represent high risk.

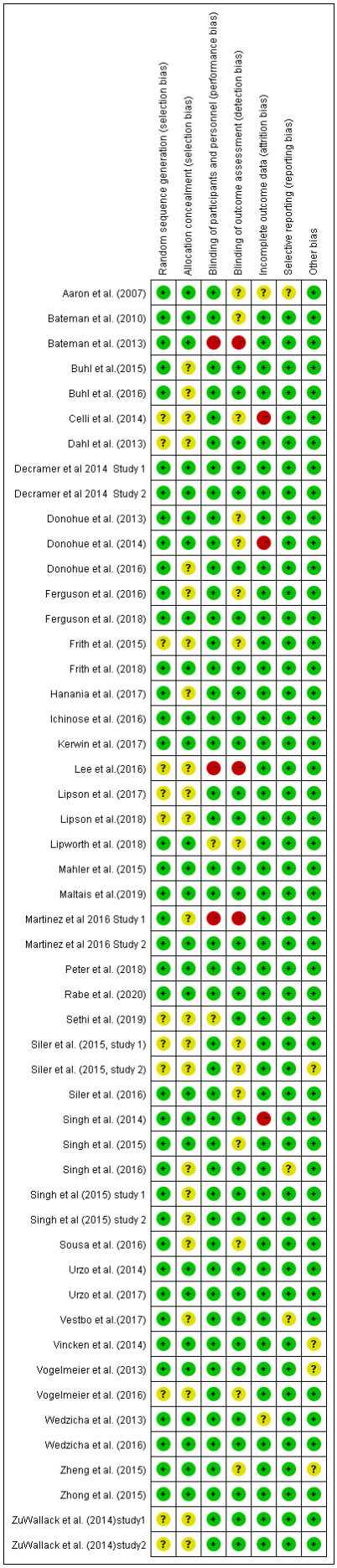

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Aaron et al. (2007)
Bateman et al. (2010)
Bateman et al. (2013)
Buhl et al.(2015)
Buhl et al. (2016)
Celli et al. (2014)
Dahl et al. (2013)
Decramer et al 2014 Study 1
Decramer et al 2014 Study 2
Donohue et al. (2013)
Donohue et al. (2014)
Donohue et al. (2016)
Ferguson et al. (2016)
Ferguson et al. (2018)
Frith et al. (2015)
Frith et al. (2018)
Hanania et al. (2017)
Ichinose et al. (2016)
Kerwin et al. (2017)
Lee et al.(2016)
Lipson et al. (2017)
Lipson et al.(2018)
Lipworth et al. (2018)
Mahler et al. (2015)
Maltais et al.(2019)
Martinez et al 2016 Study 1
Martinez et al 2016 Study 2
Peter et al. (2018)
Rabe et al. (2020)
Sethi et al. (2019)
Siler et al. (2015, study 1)
Siler et al. (2015, study 2)
Siler et al. (2016)
Singh et al. (2014)
Singh et al. (2015)
Singh et al. (2016)
Singh et al (2015) study 1
Singh et al (2015) study 2
Sousa et al. (2016)
Urzo et al. (2014)
Urzo et al. (2017)
Vestbo et al.(2017)
Vincken et al. (2014)
Vogelmeier et al. (2013)
Vogelmeier et al. (2016)
Wedzicha et al. (2013)
Wedzicha et al. (2016)
Zheng et al. (2015)
Zhong et al. (2015)
ZuWallack et al. (2014)study1
ZuWallack et al. (2014)study2

Table S4. GRADE summary of findings.

LAMA/LABA therapy compared to controls for risk of MACE.

Quality assessment							Summary of Findings				
Participants (studies) follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rate (%)**		**Relative effect** (95% CI)	**Absolute Risk Difference According to Baseline Risk (per 1,000 person-years)**	
							With Control	**With dual bronchodilator**		**Baseline Risk in controls**	**Additional Events** (95% CI)
Dual LAMA/LABA vs. control for MACE											
71,210 (42 studies) 12-108 weeks	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to inconsistency, imprecision	389/42501 (0.9%)	337/28709 (1.2%)	**RR 1.24** (1.06 to 1.44)	**9 per 1000**	**2 more per 1000** (from 1 more to 4 more)
LAMA/LABA/ICS vs. control for MACE											
24,617 (11 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	134/10622 (1.3%)	212/13995 (1.5%)	**RR 1.27** (1.03 to 1.58)	**13 per 1000**	**3 more per 1000** (from 0 more to 7 more)
All LAMA/LABA vs. ICS/LABA for MACE											
32,623 (15 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	147/12331 (1.2%)	327/20292 (1.6%)	**RR 1.33** (1.09 to 1.62)	**12 per 1000**	**4 more per 1000** (from 1 more to 7 more)
All LAMA/LABA vs. LAMA for MACE											
41,035 (28 studies) 12-108 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	186/20590 (0.9%)	206/20445 (1%)	**RR 1.11** (0.91 to 1.37)	**9 per 1000**	**1 more per 1000** (from 1 fewer to 3 more)
All LAMA/LABA vs. LABA for MACE											
24,713 (22 studies) 12-52 weeks	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to inconsistency, imprecision	75/10403 (0.7%)	114/14310 (0.8%)	**RR 1.07** (0.79 to 1.45)	**7 per 1000**	**1 more per 1000** (from 2 fewer to 3 more)
All LAMA/LABA vs. placebo for MACE											

10,813 (17 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	13/3713 (0.4%)	40/7100 (0.6%)	**RR 1.3** (0.71 to 2.38)	**4 per 1000**	**1 more per 1000** (from 1 fewer to 5 more)
Dual LAMA/LABA vs. LAMA for MACE											
37,768 (26 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	174/19224 (0.9%)	186/18544 (1%)	**RR 1.11** (0.9 to 1.38)	**9 per 1000**	**1 more per 1000** (from 1 fewer to 3 more)
Dual LAMA/LABA vs. LABA for MACE											
24,074 (22 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	73/10403 (0.7%)	112/13671 (0.8%)	**OR 1.18** (0.88 to 1.58)	**7 per 1000**	**1 more per 1000** (from 1 fewer to 4 more)
Dual LAMA/LABA vs. placebo for MACE											
12,904 (17 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	17/4746 (0.4%)	50/8158 (0.6%)	**RR 1.49** (0.87 to 2.54)	**4 per 1000**	**2 more per 1000** (from 0 fewer to 6 more)
Dual LAMA/LABA vs. ICS/LABA for MACE											
18,170 (9 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	130/9972 (1.3%)	135/8198 (1.6%)	**RR 1.42** (1.11 to 1.81)	**13 per 1000**	**5 more per 1000** (from 1 more to 11 more)
Dual LAMA/LABA vs. ICS/LABA for MACE - 3 months											
2,157 (3 studies) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	3/926 (0.3%)	7/1231 (0.6%)	**RR 1.48** (0.41 to 5.35)	**3 per 1000**	**2 more per 1000** (from 2 fewer to 14 more)
Dual LAMA/LABA vs. ICS/LABA for MACE - 6 months											
2,196 (3 studies) 24 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	5/1099 (0.5%)	9/1097 (0.8%)	**RR 1.7** (0.55 to 5.24)	**5 per 1000**	**3 more per 1000** (from 2 fewer to 19 more)
Dual LAMA/LABA vs. ICS/LABA for MACE - 12 months											

13,817 (3 studies) 13 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊕ **HIGH**	122/7947 (1.5%)	119/5870 (2%)	**RR 1.4** (1.08 to 1.82)	**15 per 1000**	**6 more per 1000** (from 1 more to 13 more)
Dual LAMA/LABA vs. ICS/LABA for MACE - GOLD 2											
4,353 (6 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	8/2025 (0.4%)	16/2328 (0.7%)	**RR 1.6** (0.69 to 3.73)	**4 per 1000**	**2 more per 1000** (from 1 fewer to 11 more)
Dual LAMA/LABA vs. ICS/LABA for MACE - GOLD 3											
13,817 (3 studies) 13 months	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	122/7947 (1.5%)	119/5870 (2%)	**RR 1.4** (1.08 to 1.82)	**15 per 1000**	**6 more per 1000** (from 1 more to 13 more)
Inhalational devices were different in the two groups (LABA/LAMA vs. ICS/LABA)											
7,715 (7 studies) 12-52 weeks	serious	serious[1]	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, inconsistency, imprecision	29/3707 (0.8%)	40/4008 (1%)	**RR 1.28** (0.79 to 2.06)	**8 per 1000**	**2 more per 1000** (from 2 fewer to 8 more)
Inhalation devices were identical in the two groups (LABA/LAMA vs. ICS/LABA)											
10,455 (2 studies) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	101/6265 (1.6%)	95/4190 (2.3%)	**RR 1.5** (1.05 to 2.15)	**16 per 1000**	**8 more per 1000** (from 1 more to 19 more)
ICS/LAMA/LABA vs. ICS/LABA for MACE											
21,036 (9 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	125/8942 (1.4%)	197/12094 (1.6%)	**RR 1.29** (1.03 to 1.61)	**14 per 1000**	**4 more per 1000** (from 0 more to 9 more)
ICS/LAMA/LABA therapy vs. ICS/LABA for MACE - 3 months											
3,185 (5 studies) 3 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	5/1098 (0.5%)	8/2087 (0.4%)	**RR 0.8** (0.26 to 2.41)	**5 per 1000**	**1 fewer per 1000** (from 3 fewer to 6 more)
ICS/LAMA/LABA vs. ICS/LABA for MACE - 12 months											

16,041 (3 studies) 13 months	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	116/6945 (1.7%)	183/9096 (2%)	**RR 1.31** (1.04 to 1.65)	**17 per 1000**	**5 more per 1000** (from 1 more to 11 more)
ICS/LAMA/LABA vs. ICS/LABA for MACE - GOLD 2											
1,729 (2 studies) 12 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	3/575 (0.5%)	4/1154 (0.3%)	**RR 0.66** (0.14 to 2.99)	**5 per 1000**	**2 fewer per 1000** (from 4 fewer to 10 more)
ICS/LAMA/LABA vs. ICS/LABA for MACE - GOLD 3											
19,307 (7 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	122/8367 (1.5%)	193/10940 (1.8%)	**RR 1.31** (1.04 to 1.64)	**15 per 1000**	**5 more per 1000** (from 1 more to 9 more)
Inhalation devices were different in the two groups (ICS/LABA/LAMA vs. ICS/LABA)											
4,995 (6 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	9/1997 (0.5%)	14/2998 (0.5%)	**RR 1.04** (0.45 to 2.4)	**5 per 1000**	**0 more per 1000** (from 2 fewer to 6 more)
Inhalation devices were identical in the two groups (ICS/LABA/LAMA vs. ICS/LABA)											
16,041 (3 studies) 13 months	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	116/6945 (1.7%)	183/9096 (2%)	**RR 1.31** (1.04 to 1.65)	**17 per 1000**	**5 more per 1000** (from 1 more to 11 more)
Dual LAMA/LABA vs. LAMA/LABA/ICS											
13863 (3 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	143/9048 (1.6%)	85/4815 (1.8%)	**RR 1.19** (0.82 to 1.71)	**16 per 1000**	**3 more per** 1000(from 3 fewer to 11 more)
Dual LAMA/LABA vs. ICS/LABA Base on Baseline MACE Event Rate Per Year ≥1%											
16191 (6 studies) 12-52 week	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊕⊕⊖ **MODERATE** due to imprecision	128/8981 (1.4%)	129/7210 (1.8%)	**RR 1.4** (1.09 to 1.79)	**14 per 1000**	**6 more per 1000**(from 1 more to 11 more)
Dual LAMA/LABA vs. ICS/LABA Base on Baseline MACE Event Rate Per Year＜1%											
1979 (3 studies)	no serious	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊕⊕⊖ **MODERATE**	2/991 (0.2%)	6/988 (0.61%)	**RR 2.49** (0.55 to	**2 per 1000**	**3 more per 1000**(from 1

12-52 weeks	risk of bias					due to imprecision			11.28)		fewer to 21 more)
LAMA/LABA/ICS vs. ICS/LABA Base on Baseline MACE Event Rate Per Year ≥1%											
18990 (7 studies) 12-52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊕⊕⊖ **MODERATE** due to imprecision	121/7926 (1.5%)	189/11064 (1.7%)	**RR 1.27**(1.01 to 1.6)	**15 per 1000**	**4 more per 1000** (from 0 more to 9 more)
LAMA/LABA/ICS vs. ICS/LABA Base on Baseline MACE Event Rate Per Year＜1%											
2046 (2 studies) 12-24 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	undetected	⊕⊕⊕⊖ **MODERATE** due to imprecision	4/1016 (0.39%)	8/1030 (0.78%)	**RR 1.77** (0.55 to 5.67)	**4 per 1000**	**3 more per 1000** (from 2 fewer to 18 more)

Abbreviations: MACE, major adverse cardiovascular events, defined as cardiovascular death, nonfatal MI, or nonfatal stroke; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; LAMA/LABA therapy, all studies involving LAMA/LABA and LAMA/LABA/ICS; BMI, body mass index; Triple therapy, LAMA/LABA/ICS.

Figure S2. Meta-analysis of included RCTs of LABA/LAMA therapy vs. controls for MACE.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events

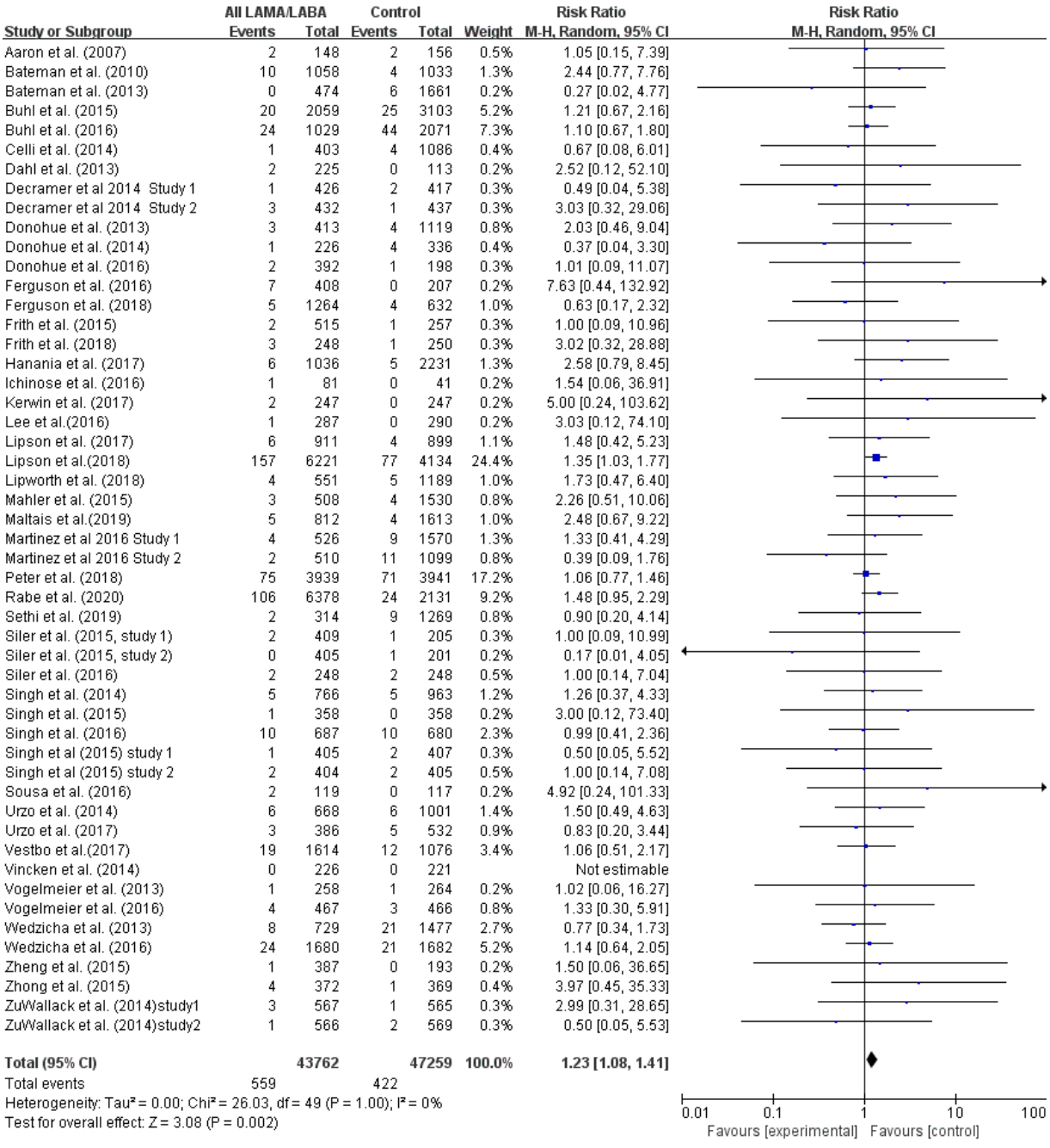


Figure S3. Meta-analysis of included RCTs of dual LABA/LAMA therapy vs. ICS/LA BA for MACE according to whether the inhalation device was identical.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 v alue indicates the percentage of variability across the pooled estimates attributable to statist ical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; Experimental, dual LAMA/LABA therapy

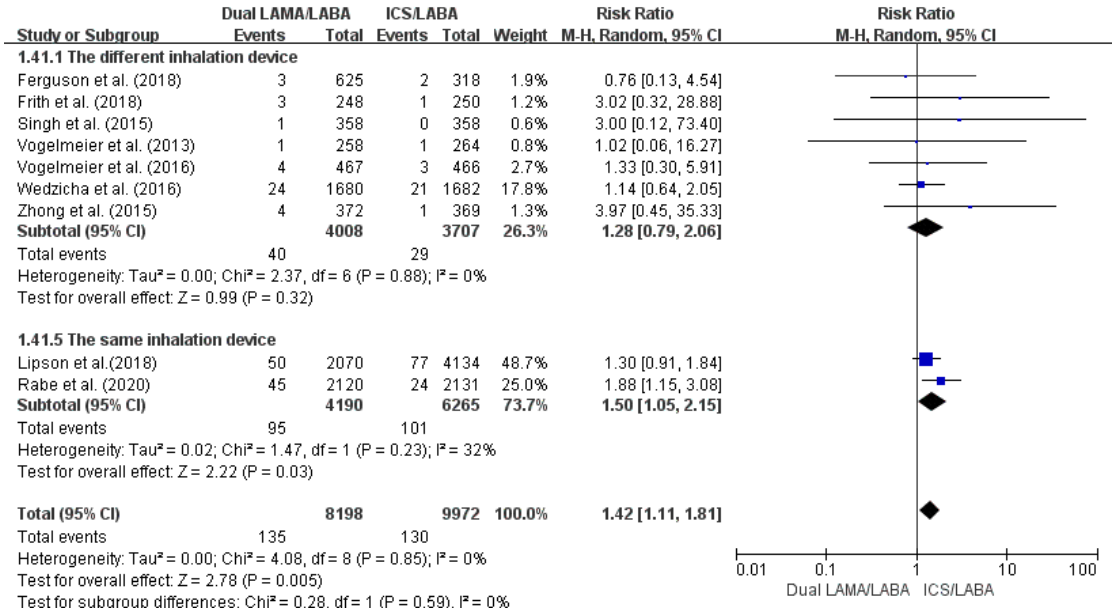


Figure S4. Meta-analysis of included RCTs of triple therapy vs. ICS/LABA for MAC E according to whether the inhalation device was identical.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 v alue indicates the percentage of variability across the pooled estimates attributable to statist ical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; Experimental, dual LAMA/LABA therapy

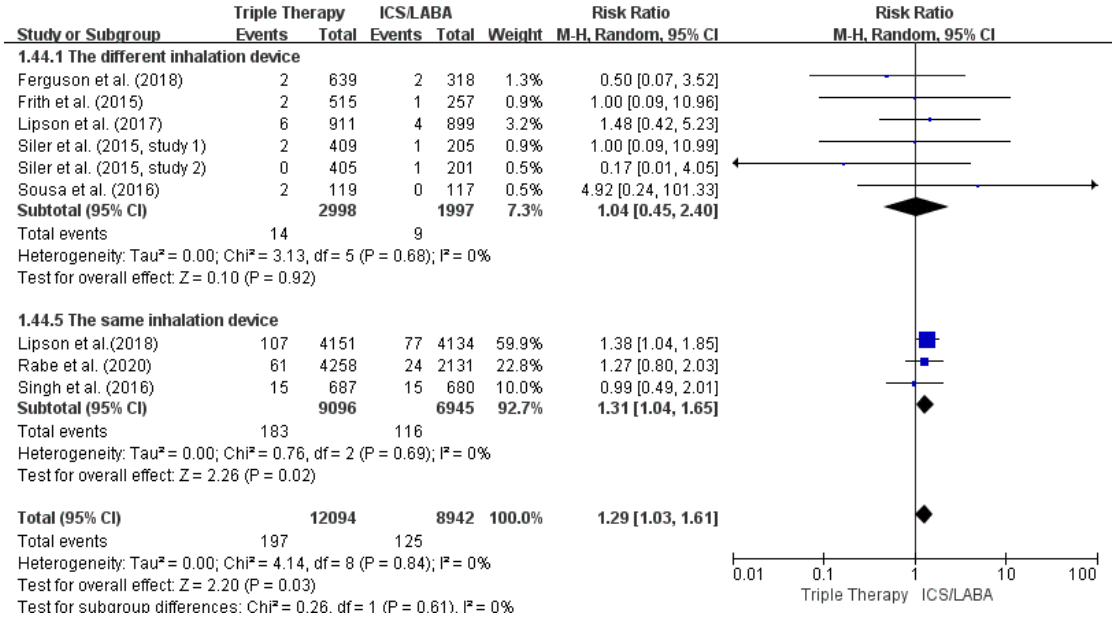


Figure S5. Meta-analysis of included RCTs of dual LABA/LAMA therapy vs. placebo for MACE.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 v alue indicates the percentage of variability across the pooled estimates attributable to statist ical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; Experimental, LAMA/LABA therapy; Control, LAMA only;

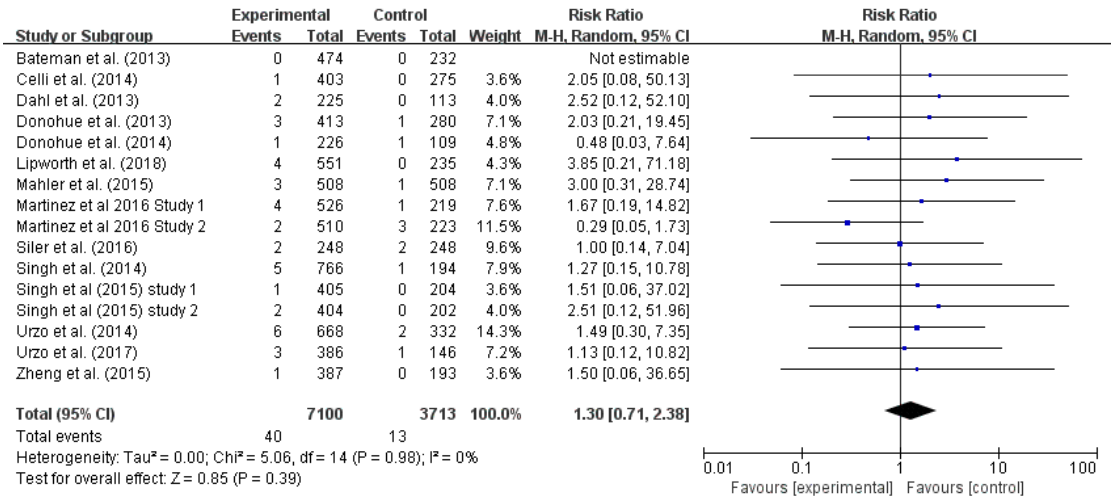


Figure S6. Meta-analysis of included RCTs of dual LABA/LAMA therapy vs. LABA o nly for MACE.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 v alue indicates the percentage of variability across the pooled estimates attributable to statist ical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; Experimental, LAMA/LABA therapy; Control, LABA only;

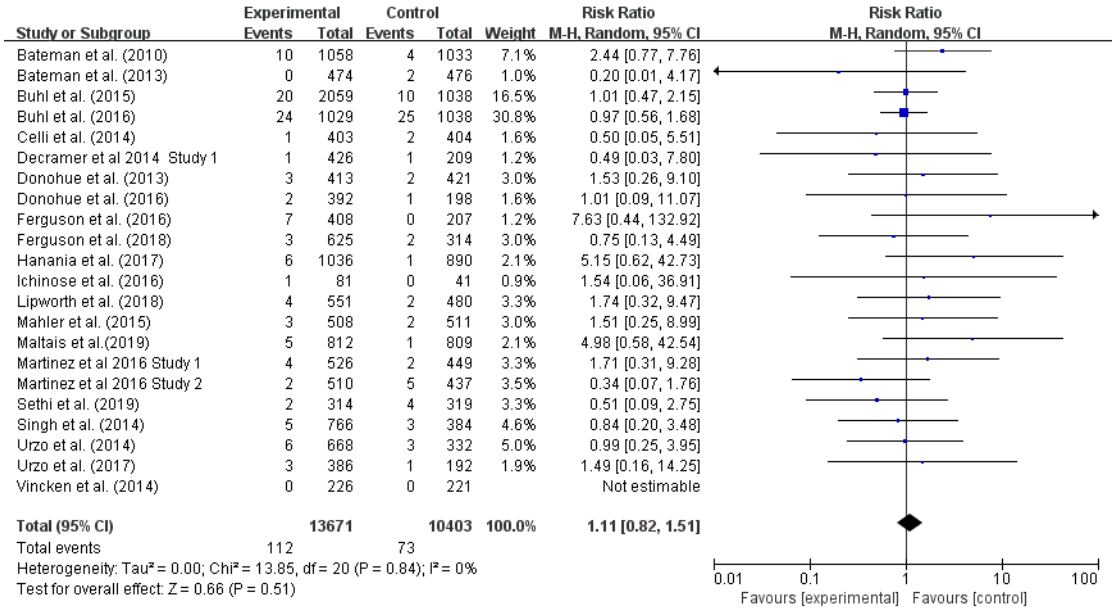


Figure S7. Meta-analysis of included RCTs of dual LABA/LAMA therapy vs. LAMA only for MACE.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 v alue indicates the percentage of variability across the pooled estimates attributable to statist ical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; Experimental, LAMA/LABA therapy; Control, LABA only;

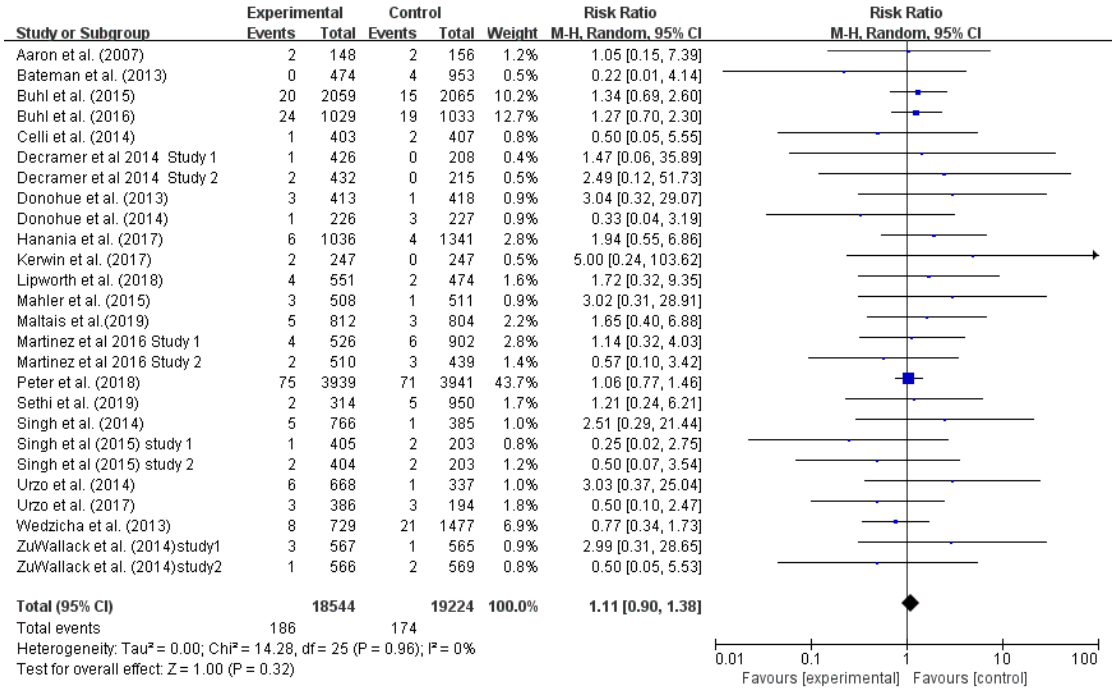


Figure S8. Meta-analysis of included RCTs of dual LABA/LAMA therapy vs. triple th erapy for MACE.

Horizontal lines indicate 95% CIs. Sizes of box are proportional to study weight. The I^2 v alue indicates the percentage of variability across the pooled estimates attributable to statist ical heterogeneity, and the p-value is a test of heterogeneity across all studies.

Abbreviations: CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events; Experimental, LAMA/LABA therapy; Control, triple th erapy;

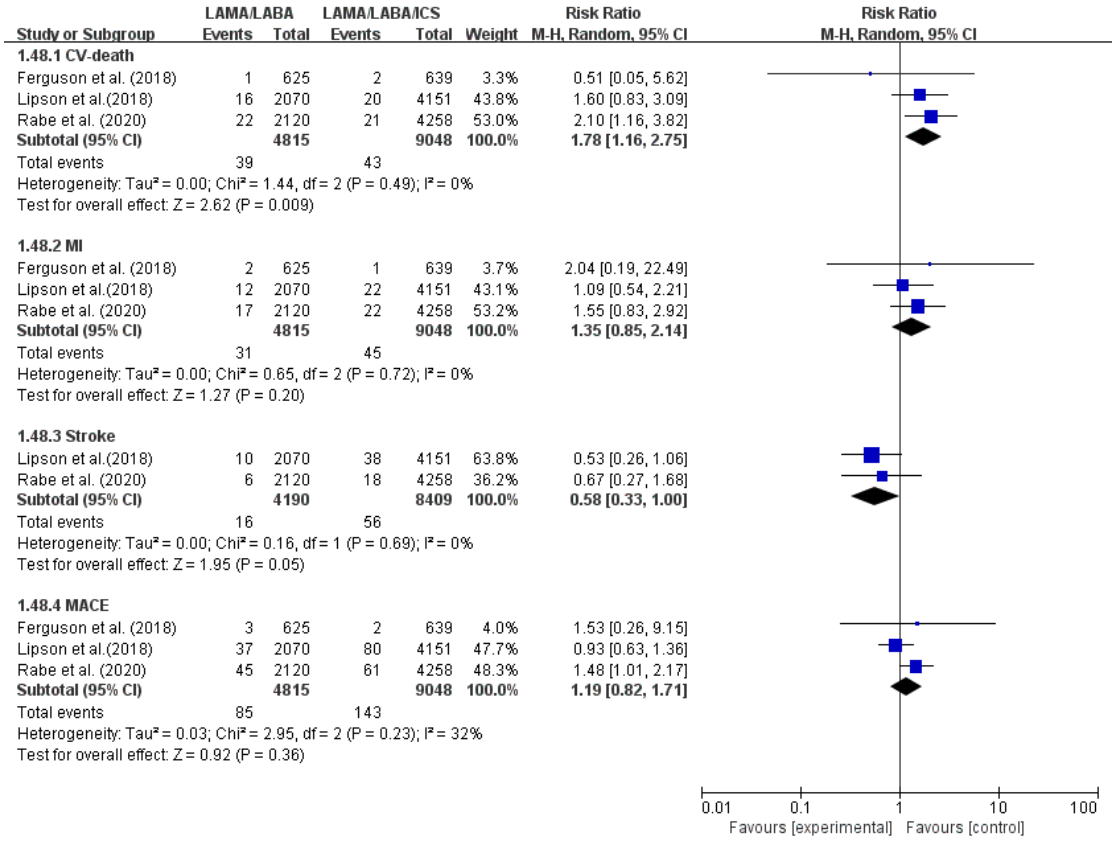


Table S5. Results of meta-analysis of LAMA/LABA therapy vs ICS/LABA for MI, CV-death, and stroke; results of meta-analysis of LAMA/LABA therapy vs ICS/LABA for MACE according to the duration, age, current smoking, inhalation devices, and BMI; results of meta-analysis of LAMA/LABA therapy vs ICS/LAMA/LABA for MACE, MI, CV-death, and stroke.

Groups and subgroups	No. of Studies	Participants	Peto OR (Fixed, 95% CI)	P value	I^2 (%)
Risk of CV-death for LAMA/LABA therapy vs. ICS/LABA					
Dual LAMA/LABA therapy	9	18170	1.42 [0.95, 2.11]	0.08	0
Triple therapy	7	19175	0.94 [0.61, 1.46]	0.79	0
Risk of MI for LAMA/LABA therapy vs. ICS/LABA					
Dual LAMA/LABA therapy	9	18170	1.83 [1.23, 2.72]	**0.003**	0
Triple therapy	8	20264	1.29 [0.90, 1.84]	0.17	42
Risk of stroke for LAMA/LABA therapy vs. ICS/LABA					
Dual LAMA/LABA therapy	8	17227	1.01 [0.62, 1.66]	0.96	0
Triple therapy	7	18712	1.79 [1.17, 2.73]	**0.007**	0
Risk of CV-death for LAMA/LABA therapy vs. LABA only					
Dual LAMA/LABA therapy	20	22826	1.65 [0.93, 2.93]	0.09	0
Triple therapy	-	-	-	-	-
Risk of MI for LAMA/LABA therapy vs. LABA only					
Dual LAMA/LABA therapy	20	20964	1.46 [0.91, 2.34]	0.12	0
Triple therapy	-	-	-	-	-
Risk of stroke for LAMA/LABA therapy vs. LABA only					
Dual LAMA/LABA therapy	16	18461	0.66 [0.38, 1.13]	0.13	5
Triple therapy	-	-	-	-	-
Risk of CV-death for LAMA/LABA therapy vs. LAMA only					
Dual LAMA/LABA therapy	22	27188	1.52 [0.78, 2.95]	0.22	0
Triple therapy	-	-	-	-	-
Risk of MI for LAMA/LABA therapy vs. LAMA only					
Dual LAMA/LABA therapy	24	28869	1.16 [0.79, 1.70]	0.46	0
Triple therapy	-	-	-	-	-
Risk of stroke for LAMA/LABA therapy vs. LAMA only					
Dual LAMA/LABA therapy	20	25986	0.87 [0.54, 1.39]	0.55	0
Triple therapy	-	-	-	-	-
Risk of CV-death for LAMA/LABA therapy vs. placebo					
Dual LAMA/LABA therapy	16	10813	1.38 [0.40, 4.73]	0.61	0
Triple therapy	-	-	-	-	-
Risk of MI for LAMA/LABA therapy vs. placebo					
Dual LAMA/LABA therapy	15	9797	1.38 [0.64, 2.99]	0.41	0
Triple therapy	-	-	-	-	-
Risk of stroke for LAMA/LABA therapy vs. placebo					
Dual LAMA/LABA therapy	12	8201	0.55 [0.14, 2.22]	0.40	0

Triple therapy	-	-	-	-	-
Risk of MACE for LAMA/LABA therapy vs. ICS/LABA in patients with different ages					
≥ 65 years	5	13813	1.32 [1.02, 1.71]	**0.03**	0
< 65 years	10	18810	1.36 [1.02, 1.80]	**0.04**	0
Risk of MACE for LAMA/LABA therapy vs. ICS/LABA in patients with different BMI					
BMI < 25 kg/m2	2	1239	3.05 [0.82, 11.32]	0.09	0
BMI ≥ 25 kg/m2	3	13304	1.30 [1.01, 1.67]	**0.04**	0
Risk of MACE for LAMA/LABA therapy vs. ICS/LABA (Current smoker, %)					
Current smokers ≤ 50%	11	30124	1.32 [1.09, 1.61]	**0.005**	0
Current smokers > 50%	2	850	2.35 [0.38, 14.46]	0.36	11
Risk of MACE for LAMA/LABA therapy vs. ICS/LABA according to whether the inhalation device was identical					
Inhalation devices were identical in the two groups	3	20231	1.35 [1.09, 1.67]	**0.004**	0
Inhalation devices were different in the two groups	12	12392	1.30 [0.85, 1.99]	0.22	0
Dual LAMA/LABA therapy vs. ICS/LAMA/LABA					
MACE	3	13863	1.19 [0.82, 1.71]	0.36	32
CV-death	3	13863	1.78 [1.16, 2.75]	**0.009**	0
MI	3	13863	1.35 [0.85, 2.14]	0.20	0
Stroke	2	12599	0.58 [0.33, 1.00]	0.05	0
Risk of MACE for dual LAMA/LABA therapy vs. ICS/LABA according to whether the inhalation device was identical					
Inhalation devices were identical in the two groups	2	10455	1.50 [1.12, 2.02]	**0.006**	22
Inhalation devices were different in the two groups	7	7715	1.32 [0.82, 2.13]	0.25	0
Risk of MACE for triple therapy vs. ICS/LABA according to whether the inhalation device was identical					
Inhalation devices were identical in the two groups	3	16041	1.31 [1.04, 1.65]	**0.02**	0
Inhalation devices were different in the two groups	6	4995	1.12 [0.48, 2.60]	0.92	0

No., number of including studies; Peto OR, Peto odds ratio; CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; LAMA/LABA therapy, all studies involving LAMA/LABA and LAMA/LABA/ICS; BMI, body mass index; Triple therapy, LAMA/LABA/ICS; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events

Table S6. Results of meta-analysis of all LAMA/LABA therapy vs. control (LAMA only, LABA only, ICS/LABA, or placebo) for MACE according to the duration of treatment, the type of inhalation device, and COPD severity.

Groups and subgroups	No. of Studies	Participants	Risk Ratio (M-H, Random,95% CI)	P value	I^2 (%)
Risk of MACE for LAMA/LABA therapy vs. controls					
All LAMA/LABA therapy vs. controls	51	91,021	1.23 [1.08, 1.41]	**0.002**	0
Risk of MACE for all LAMA/LABA therapy vs. different controls					
All LAMA/LABA therapy vs. LABA/ICS	15	32,623	1.34 [1.11, 1.62]	**0.003**	0
All LAMA/LABA therapy vs. placebo	16	10,813	1.30 [0.71, 2.38]	0.39	0
All LAMA/LABA therapy vs. LABA only	22	24,074	1.07 [0.79, 1.45]	0.66	0
All LAMA/LABA therapy vs. LAMA only	28	41,035	1.11 [0.91, 1.37]	0.30	0
Risk of MACE for all LAMA/LABA therapy vs. LABA/ICS according to different duration					
3 months	15	11,382	1.45 [0.77, 2.70]	0.25	0
6 months	19	31,363	1.24 [0.91, 1.69]	0.18	0
12 months	16	47,972	1.22 [1.05, 1.42]	**0.01**	0
Risk of MACE for all LAMA/LABA therapy vs. LABA/ICS according to COPD severity					
Moderate COPD	29	35,501	1.26 [0.94, 1.69]	0.12	0
Severe COPD	20	53,899	1.23 [1.06, 1.43]	**0.007**	0
Risk of MACE for all LAMA/LABA therapy vs. ICS/LABA according to whether the inhalational device was identical					
Inhalation devices were identical in the two groups	3	20,231	1.36 [1.09, 1.69]	**0.007**	0
Inhalation devices were different in the two groups	12	12,392	1.24 [0.81, 1.90]	0.31	0

No., number of including studies; CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; LAMA/LABA therapy, all studies involving LAMA/LABA and LAMA/LABA/ICS; Triple therapy, LAMA/LABA/ICS; MACE, major adverse cardiovascular events;

Table S7. MACE event rate per year for each study included.

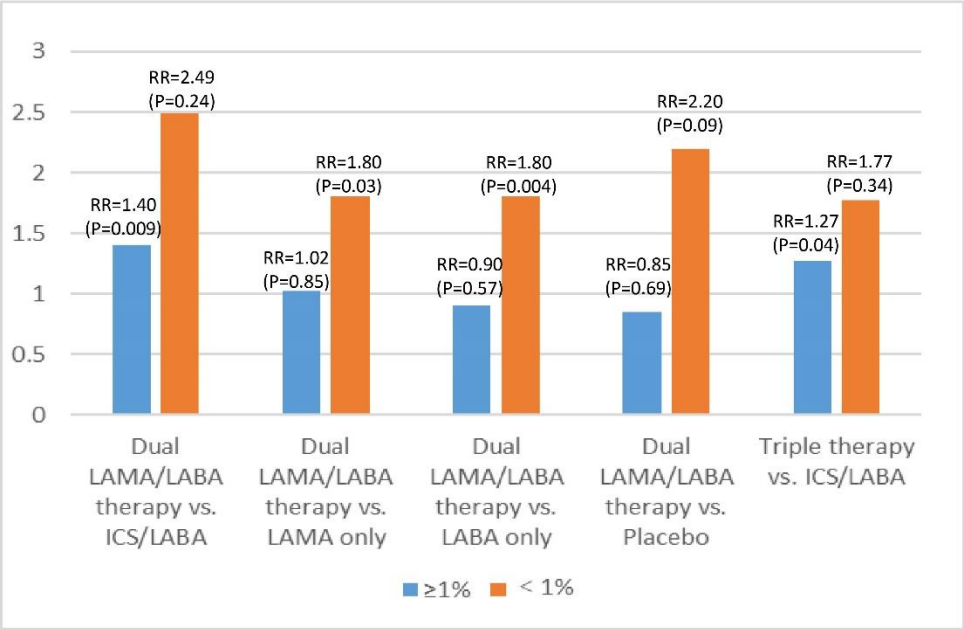
Studies	Duration of Follow up, M	Events, N (MACE)	Total Patients, N	Event Rate per Year (%)	Events, N (MACE)	Total Patients, N	Event Rate per Year (%)
		Dual LAMA/LABA			ICS/LABA		
Ferguson et al. (2018)	6.0	3	625	0.96	2	318	1.26
Frith et al. (2018)	3.0	3	248	4.84	1	250	1.60
Lipson et al. (2018)	12.0	50	2070	2.42	77	4134	1.86
Rabe et al. (2020)	12.0	45	2120	2.12	24	2131	1.13
Singh et al. (2015)	3.0	1	358	1.12	0	358	0.00
Vogelmeier et al. (2013)	6.5	1	258	0.72	1	264	0.70
Vogelmeier et al. (2016)	6.0	4	467	1.72	3	466	1.28
Wedzicha et al. (2016)	12.0	24	1680	1.43	21	1682	1.25
Zhong et al. (2015)	6.5	4	372	1.99	1	369	0.50
Total	67	135	8198	1.93	130	9972	**1.40**
		Dual LAMA/LABA			Placebo		
Bateman et al. (2013)	6	0	474	0	0	232	0
Celli et al. (2014)	6	1	403	0.50	0	275	0
Dahl et al. (2013)	12	2	225	0.89	0	113	0
Donohue et al. (2013)	6	3	413	1.45	1	280	0.71
Donohue et al. (2014)	12	1	226	0.44	1	109	1.83
Lipworth et al. (2018)	6	4	551	1.45	0	235	0
Mahler et al. (2015)	3	3	508	2.36	1	508	0.39
Martinez et al 2016 Study 1	6	4	526	1.52	1	219	0.91
Martinez et al 2016 Study 2	6	2	510	0.78	3	223	2.69
Siler et al. (2016)	3	2	248	3.23	2	248	1.61
Singh et al. (2014)	6	5	766	1.31	1	194	1.03
Singh et al (2015) study 1	3	1	405	0.99	0	204	0
Singh et al (2015) study 2	3	2	404	1.98	0	202	0
Urzo et al. (2014)	6	6	668	1.80	2	332	1.20
Urzo et al. (2017)	12	3	386	0.78	1	146	1.37
Zheng et al. (2015)	6	1	387	0.52	0	193	0
Total	102	40	7100	1.27	13	3713	**0.70**
		Dual LAMA/LABA			LABA only		
Bateman et al. (2010)	12	10	1058	0.95	4	1033	0.39
Bateman et al. (2013)	6	0	474	0	2	476	0.84
Buhl et al. (2015)	6	20	2059	1.94	10	1038	1.93
Buhl et al. (2016)	12	24	1029	2.33	25	1038	2.41
Celli et al. (2014)	6	1	403	0.50	2	404	0.99
Decramer et al 2014 Study 1	6	1	426	0.47	1	209	0.96
Donohue et al. (2013)	6	3	413	1.45	2	421	0.95
Donohue et al. (2016)	12	2	392	0.51	1	198	0.51
Ferguson et al. (2016)	12	7	408	1.72	0	207	0
Ferguson et al. (2018)	6	3	625	0.96	2	314	1.27

Hanania et al. (2017)	12	6	1036	0.58	1	890	0.11
Ichinose et al. (2016)	12	1	81	1.23	0	41	0
Lipworth et al. (2018)	6	4	551	1.45	2	480	0.83
Mahler et al. (2015)	3	3	508	2.36	2	511	1.57
Maltais et al.(2019)	6	5	812	1.23	1	809	0.25
Martinez et al 2016 Study 1	6	4	526	1.52	2	449	0.89
Martinez et al 2016 Study 2	6	2	510	0.78	5	437	2.29
Sethi et al. (2019)	6	2	314	1.27	4	319	2.51
Singh et al. (2014)	6	5	766	1.31	3	384	1.56
Urzo et al. (2014)	6	6	668	1.80	3	332	1.81
Urzo et al. (2017)	12	3	386	0.78	1	192	0.52
Vincken et al. (2014)	3	0	226	0	0	221	0
Total	168	112	13671	1.29	73	10403	**1.14**
		Dual LAMA/LABA			**LAMA only**		
Aaron et al. (2007)	27	2	148	0.60	2	156	0.57
Bateman et al. (2013)	6	0	474	0	4	953	0.84
Buhl et al. (2015)	6	20	2059	1.94	15	2065	1.45
Buhl et al. (2016)	12	24	1029	2.33	19	1033	1.84
Celli et al. (2014)	6	1	403	0.50	2	407	0.98
Decramer et al 2014 Study 1	6	1	426	0.47	0	208	0
Decramer et al 2014 Study 2	6	2	432	0.93	0	215	0
Donohue et al. (2013)	6	3	413	1.45	1	418	0.48
Donohue et al. (2014)	12	1	226	0.44	3	227	1.32
Hanania et al. (2017)	12	6	1036	0.58	4	1341	0.30
Kerwin et al. (2017)	3	2	247	3.24	0	247	0
Lipworth et al. (2018)	6	4	551	1.45	2	474	0.84
Mahler et al. (2015)	3	3	508	2.36	1	511	0.78
Maltais et al. (2019)	6	5	812	1.23	3	804	0.75
Martinez et al 2016 Study 1	6	4	526	1.52	6	902	1.33
Martinez et al 2016 Study 2	6	2	510	0.78	3	439	1.37
Peter et al. (2018)	12	75	3939	1.90	71	3941	1.80
Sethi et al. (2019)	6	2	314	1.27	5	950	1.05
Singh et al. (2014)	6	5	766	1.31	1	385	0.52
Singh et al (2015) study 1	3	1	405	0.99	2	203	3.94
Singh et al (2015) study 2	3	2	404	1.98	2	203	3.94
Urzo et al. (2014)	6	6	668	1.80	1	337	0.59
Urzo et al. (2017)	12	3	386	0.78	3	194	1.55
Wedzicha et al. (2013)	16	8	729	0.82	21	1477	1.07
ZuWallack et al.(2014)study1	3	3	567	2.12	1	565	0.71
ZuWallack et al.(2014)study2	3	1	566	0.71	2	569	1.41
Total	199	186	18544	1.50	174	19224	**1.23**
		Triple therapy			**ICS/LABA**		
Ferguson et al. (2018)	6.0	2	639	0.62	2	318	1.26

Frith et al. (2015)	3.0	2	515	1.56	1	257	1.56
Lipson et al. (2017)	6.0	6	911	1.32	4	899	0.88
Lipson et al. (2018)	12.0	107	4151	2.58	77	4134	1.86
Rabe et al. (2020)	12.0	61	4258	1.43	24	2131	1.13
Siler et al. (2015, study 1)	3.0	2	409	1.96	1	205	1.96
Siler et al. (2015, study 2)	3.0	0	405	0.00	1	201	2.00
Singh et al. (2016)	12.0	15	687	2.18	15	680	2.21
Sousa et al. (2016)	3.0	2	119	6.72	0	117	0.00
Total	60	197	12094	1.84	125	8942	1.57
		Triple therapy			**LAMA only**		
Lee et al. (2016)	3	1	287	1.39	0	290	0
Vestbo et al. (2017)	12	19	1614	1.18	12	1076	1.11
Total	15	20	1901	1.21	12	1366	**0.88**

No., number of including studies; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; LAMA/LABA therapy, all studies involving LAMA/LABA and LAMA/LABA/ICS; Triple therapy, LAMA/LABA/ICS; MACE, major adverse cardiovascular events;

Figure S9. Results of meta-analysis of dual LAMA/LABA therapy vs. LAMA only, LABA only, ICS/LABA, or placebo for MACE according to levels of MACE event rate per year (≥1% or ＜1%) in control.



LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; RR, risk ratio;

Table S8. Results of meta-analysis of LAMA/LABA therapy vs. LAMA only, LABA only, ICS/LABA, or placebo for MACE according to the duration, the type of inhalation device, and the severities of COPD (Peto OR).

Groups and subgroups	No. of Studies	Participants	Peto OR (Fixed, 95% CI)	P value	I^2 (%)
Risk of MACE for LAMA/LABA therapy vs. controls					
All LAMA/LABA therapy vs. controls	51	91021	1.24 [1.09, 1.42]	**0.001**	0
Dual LAMA/LABA therapy vs. controls	42	71210	1.25 [1.07, 1.45]	**0.004**	0
Triple therapy vs. controls	11	24617	1.28 [1.03, 1.59]	**0.03**	0
Risk of MACE for all LAMA/LABA therapy vs. controls according to different duration					
About 3 months	15	11382	1.60 [0.85, 2.98]	0.14	0
About 6 months	19	31363	1.21 [0.89, 1.65]	0.23	0
About 12 months	16	47972	1.24 [1.06, 1.43]	**0.006**	0
Risk of MACE for all LAMA/LABA therapy vs. controls in patients with different severities					
Moderate COPD	29	35501	1.29 [0.97, 1.72]	0.08	0
Severe COPD	20	53899	1.24 [1.07, 1.44]	**0.004**	0
Risk of MACE for LAMA/LABA therapy vs. LABA/ICS					
All LAMA/LABA therapy vs. LABA/ICS	15	32623	1.34 [1.11, 1.62]	**0.003**	0
Dual LAMA/LABA therapy vs. LABA/ICS	9	18170	1.45 [1.13, 1.86]	**0.003**	0
Triple therapy vs. LABA/ICS	9	21036	1.29 [1.03, 1.62]	**0.02**	0
Risk of MACE for all LAMA/LABA therapy vs. LABA/ICS according to different duration					
About 3 months	7	5338	1.17 [0.50, 2.75]	0.72	6
About 6 months	4	4006	1.64 [0.74, 3.67]	0.22	0
About 12 months	4	23593	1.32 [1.08, 1.62]	**0.007**	0
Risk of MACE for all LAMA/LABA therapy vs. LABA/ICS in patients with different severities					
Moderate COPD	7	6078	1.40 [0.68, 2.89]	0.36	0
Severe COPD	8	26859	1.32 [1.09, 1.61]	**0.005**	0
Risk of MACE for LAMA/LABA therapy vs. placebo					
All LAMA/LABA therapy vs. placebo	16	10813	1.53 [0.85, 2.73]	**0.15**	0
Dual LAMA/LABA therapy vs. placebo	16	10813	1.53 [0.85, 2.73]	**0.15**	0
Triple therapy vs. placebo	-	-	-	**-**	-
Risk of MACE for LAMA/LABA therapy vs. LABA only					
All LAMA/LABA therapy vs. LABA only	22	24713	1.14 [0.85, 1.53]	0.39	0
Dual LAMA/LABA therapy vs. LABA only	22	24074	1.18 [0.88, 1.58]	0.28	0
Triple therapy vs. LABA only	-	-	-	-	-
Risk of MACE for LAMA/LABA therapy vs. LAMA only					
All LAMA/LABA therapy vs. LAMA only	28	41035	1.13 [0.92, 1.38]	0.25	0
Dual LAMA/LABA therapy vs. LAMA only	26	37768	1.13 [0.91, 1.39]	0.27	0
Triple therapy vs. LAMA only	-	-	-	-	-
Risk of MACE for LAMA/LABA therapy vs. ICS/LABA according to whether the inhalation device was identical					
Inhalation devices were identical in the two groups	3	20231	1.35 [1.09, 1.67]	**0.004**	0
Inhalation devices were different in the two groups	12	12392	1.30 [0.85, 1.99]	0.22	0

No., number of including studies; CI, confidence interval; LAMAs, long-acting muscarinic

antagonists; LABAs, long-acting β-agonists; All LAMA/LABA, all studies involving LAMA/LABA and LAMA/LABA/ICS; Triple therapy, LAMA/LABA/ICS; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events

Table S9. Sensitivity analysis performed by calculating the RD by Mantel-Haenszel approach.

Groups and subgroups	No. of Studies	Participants	Risk Difference (M-H, Random, 95% CI)	P value	I^2 (%)
Risk of MACE for LAMA/LABA therapy vs. controls					
All LAMA/LABA combination therapy	51	91021	0.00 [0.00, 0.00]	0.001	0
Dual LAMA/LABA therapy	42	71210	0.00 [0.00, 0.00]	0.005	0
Triple therapy	11	24617	0.00 [0.00, 0.01]	0.02	0
Risk of MACE for LAMA/LABA therapy vs. ICS/LABA					
All LAMA/LABA combination therapy	15	32623	0.00 [0.00, 0.01]	0.002	0
Dual LAMA/LABA therapy	9	18170	0.01 [0.00, 0.01]	0.004	0
Triple therapy	9	21036	0.00 [0.00, 0.01]	0.02	0
Risk of MACE for LAMA/LABA therapy vs. placebo					
All LAMA/LABA therapy vs. placebo	16	10813	0.00 [-0.00, 0.01]	0.06	0
Dual LAMA/LABA therapy vs. placebo	16	10813	0.00 [-0.00, 0.01]	0.06	0
Triple therapy vs. placebo	-	-	-	-	-

No., number of including studies; CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; All LAMA/LABA, all studies involving LAMA/LABA and LAMA/LABA/ICS; Triple therapy, LAMA/LABA/ICS; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events

Table S10. Sensitivity analysis performed by calculating the OR by Mantel-Haenszel approach.

Groups and subgroups	No. of Studies	Participants	Odds Ratio (M-H, Fixed, 95% CI)	P value	I^2 (%)
Risk of MACE for LAMA/LABA combination therapy vs. controls					
All LAMA/LABA combination therapy	51	91021	1.24 [1.09, 1.42]	0.001	0
Dual LAMA/LABA therapy	42	71210	1.24 [1.07, 1.44]	0.005	0
Triple therapy	11	24617	1.28 [1.03, 1.59]	0.03	0
Risk of MACE for LAMA/LABA combination therapy vs. ICS/LABA					
All LAMA/LABA combination therapy	15	32623	1.35 [1.11, 1.64]	0.003	0
Dual LAMA/LABA therapy	9	18170	1.44 [1.13, 1.85]	0.004	0
Triple therapy	9	21036	1.29 [1.03, 1.62]	0.03	0
Risk of MACE for LAMA/LABA therapy vs. placebo					
All LAMA/LABA therapy vs. placebo	16	10813	1.38 [0.77, 2.46]	0.28	0
Dual LAMA/LABA therapy vs. placebo	16	10813	1.38 [0.77, 2.46]	0.28	0
Triple therapy vs. placebo	-	-	-	-	-

No., number of including studies; CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; All LAMA/LABA, all studies involving LAMA/LABA and LAMA/LABA/ICS; Triple therapy, LAMA/LABA/ICS; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events

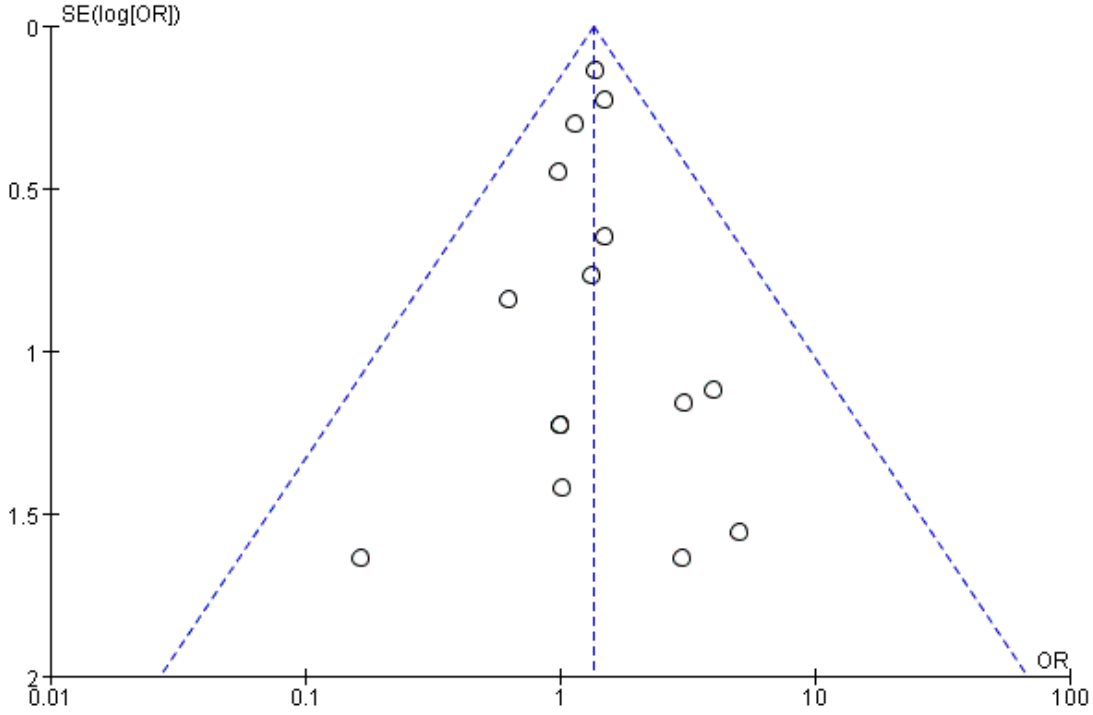
Table S11. Sensitivity Analyses Removing Studies with High Risks in Assessment of Risk of Bias.

Groups and subgroups	No. of Studies	Participants	Risk Ratio (M-H, Fixed, 95% CI)	P value	I^2 (%)
Risk of MACE for LAMA/LABA combination therapy vs. controls					
All LAMA/LABA combination therapy	45	82433	1.24 [1.08, 1.42]	0.002	0
Dual LAMA/LABA therapy	37	63199	1.25 [1.07, 1.46]	0.004	0
Triple therapy	10	24040	1.27 [1.03, 1.58]	0.03	0
Risk of MACE for LAMA/LABA combination therapy vs. ICS/LABA					
All LAMA/LABA combination therapy	15	32623	1.33 [1.09, 1.62]	0.004	0
Dual LAMA/LABA therapy	9	18170	1.42 [1.11, 1.81]	0.005	0
Triple therapy	9	21036	1.29 [1.03, 1.61]	0.03	0
Risk of MACE for LAMA/LABA therapy vs. placebo					
All LAMA/LABA therapy vs. placebo	16	10813	1.37 [0.77, 2.44]	0.28	0
Dual LAMA/LABA therapy vs. placebo	16	10813	1.37 [0.77, 2.44]	0.28	0
Triple therapy vs. placebo	-	-	-	-	-

No., number of including studies; CI, confidence interval; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β-agonists; All LAMA/LABA, all studies involving LAMA/LABA and LAMA/LABA/ICS; Triple therapy, LAMA/LABA/ICS; MI, myocardial infarction; CV-death, cardiovascular death; MACE, major adverse cardiovascular events

Figure S10. Publication bias of LAMA/LABA therapy vs. ICS/LABA for MACE.

a. Funnel plot



b. Tests for publication bias by Begg's test and Eegg's test

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Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =       1
         Std. Dev. of Score =   20.21
          Number of Studies =      15
                          z  =    0.05
                    Pr > |z| =   0.961
                          z  =    0.00 (continuity corrected)
                    Pr > |z| =   1.000 (continuity corrected)
```

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.2894941	.1066857	2.71	0.018	.0590136	.5199746
bias	.0055674	.2826786	0.02	0.985	-.6051225	.6162573

LAMA, long-acting muscarinic antagonists; LABA, long-acting β-agonists; MI, myocardial infarction; MACE, major adverse cardiovascular events; controls, LAMA only, LABA only, ICS/LABA, and placebo;

Figure S11. Meta-regression of all LAMA/LABA therapy vs. ICS/LABA for MACE base on age, duration, and the severity of COPD.

Meta-regression	Number of obs	=	15
REML estimate of between-study variance	tau2	=	0
% residual variation due to heterogeneity	I-squared_res	=	0.00%
Proportion of between-study variance explained	Adj R-squared	=	.%
Joint test for all covariates	Model F(2,12)	=	0.39
With Knapp-Hartung modification	Prob > F	=	0.6857

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Age	-.3454119	.4424628	-0.78	0.450	-1.309456	.6186317
Goldgrade	.0186198	.469081	0.04	0.969	-1.00342	1.04066
_cons	.5947039	.4350779	1.37	0.197	-.3532493	1.542657

Figure S12. Trial sequential analysis of dual LAMA/LABA therapy vs. ICS/LABA for MACE in RCTs.

Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 19472 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). Relative risk of MACE reduction was -42.0%. The cumulative Z curve crosses the conventional boundary and TSA boundary for benefit or harm.

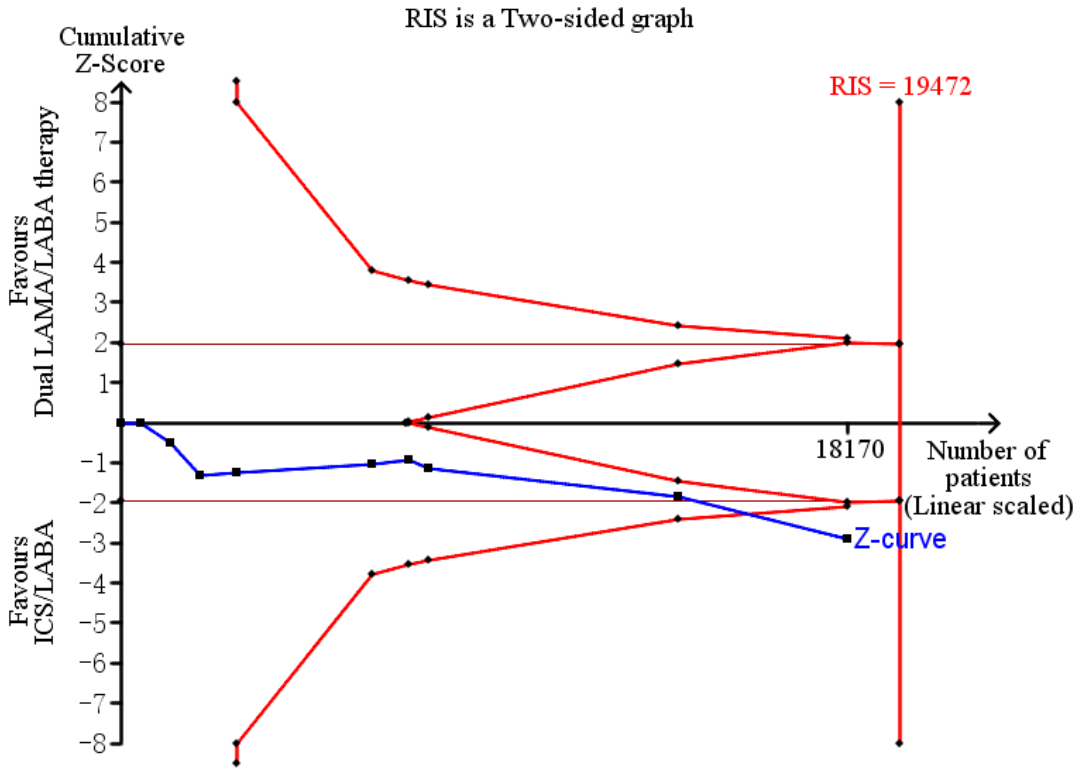

Figure S13. Trial sequential analysis of triple therapy vs. ICS/LABA for MACE in RCTs. Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 32261 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). Relative risk of MACE reduction was -32.2%. The cumulative Z curve crosses the conventional boundary for benefit or harm.

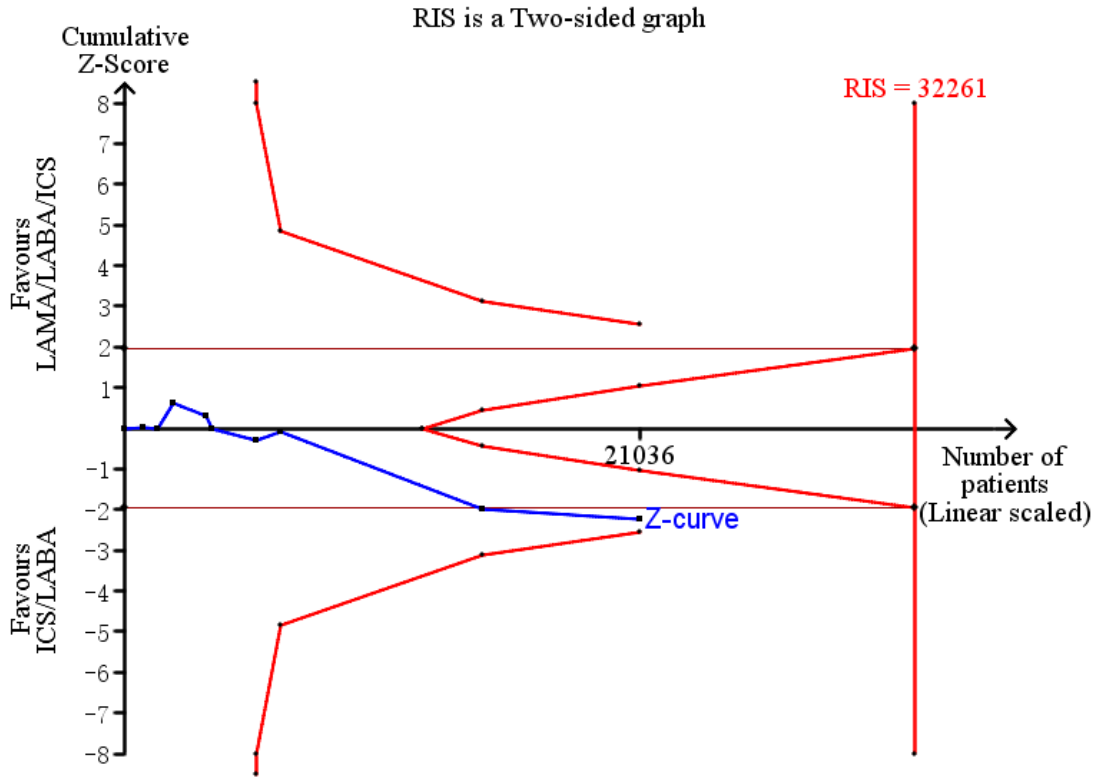

Figure S14. Trial sequential analysis of dual LAMA/LABA therapy vs. placebo for MACE in RCTs.

Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 14969 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). Relative risk of MACE reduction was -30.0%. The cumulative Z curve does not cross the conventional boundary and TSA boundary for benefit or harm.

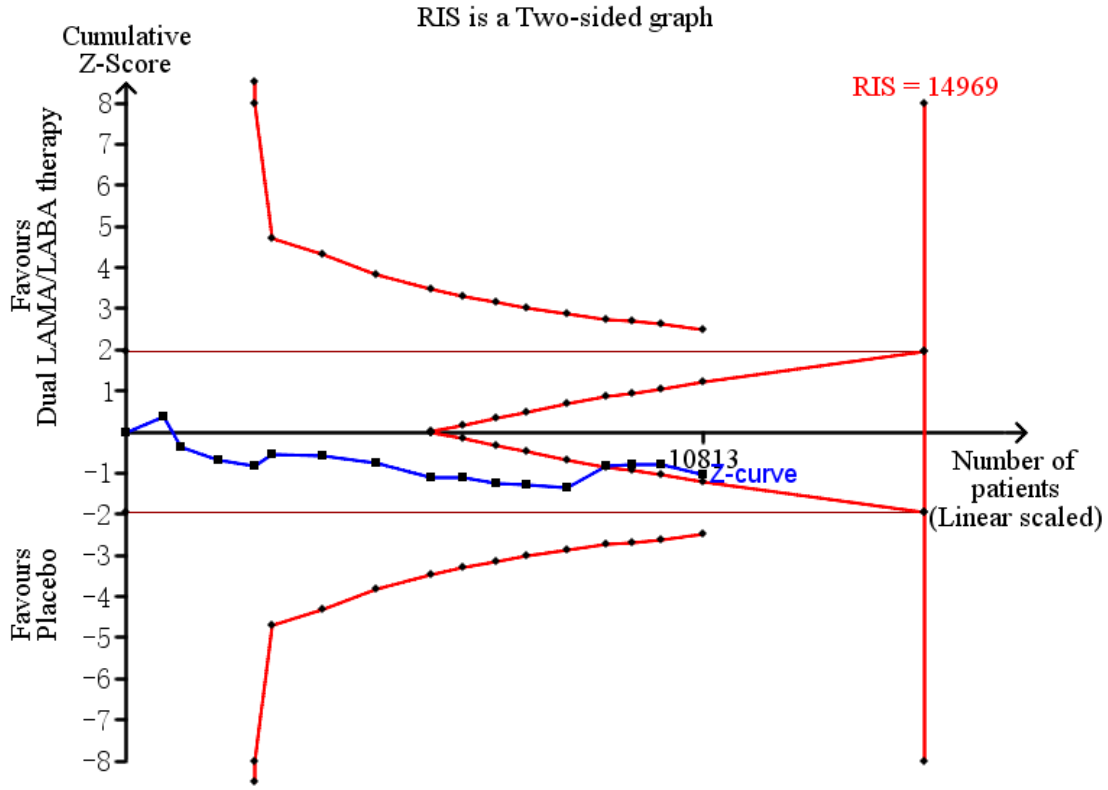

Figure S15. Trial sequential analysis of dual LAMA/LABA therapy vs. LAMA for MACE in RCTs.

Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 49618 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). Relative risk of MACE reduction was -19.17%. The cumulative Z curve does not cross the conventional boundary and TSA boundary for benefit or harm.

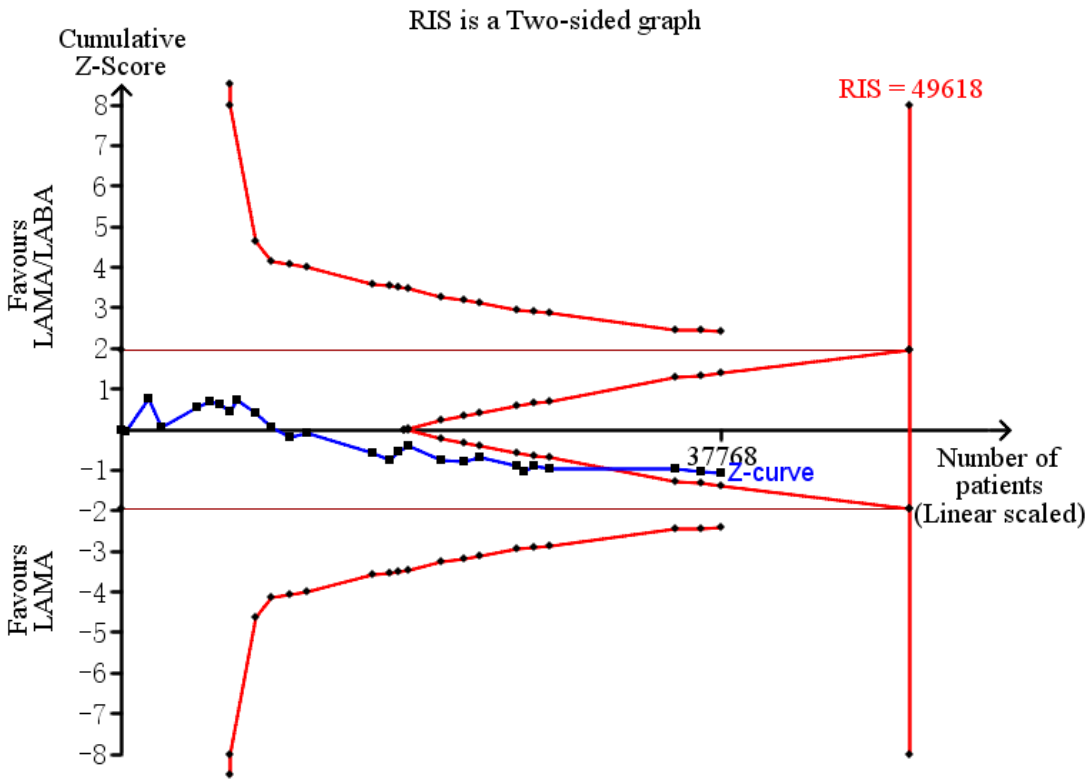

Figure S16. Trial sequential analysis of dual LAMA/LABA therapy vs. LABA for MACE in RCTs.

Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 29400 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). Relative risk of MACE reduction was -42.56%. The cumulative Z curve does not cross the conventional boundary and TSA boundary for benefit or harm.

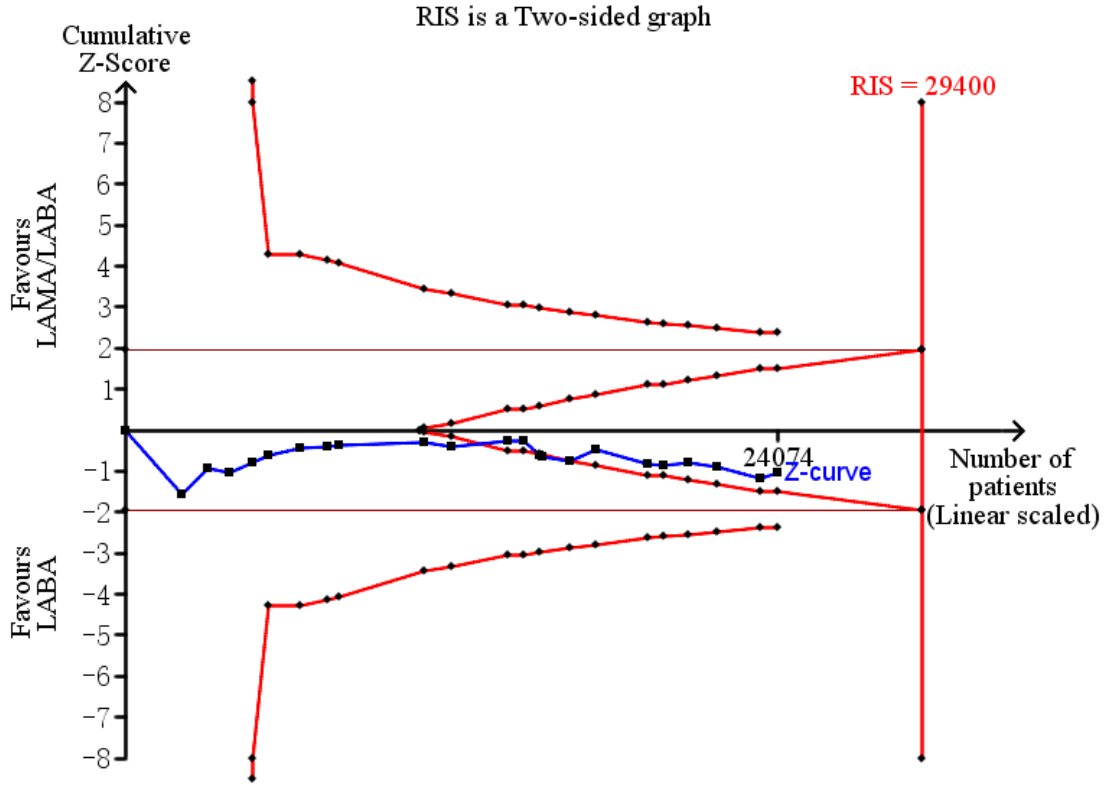

Figure S17. Trial sequential analysis of dual LAMA/LABA therapy vs. triple therapy for cardiovascular death.

Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 17886 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). The cumulative Z curve crosses the conventional boundary and TSA boundary for benefit or harm.

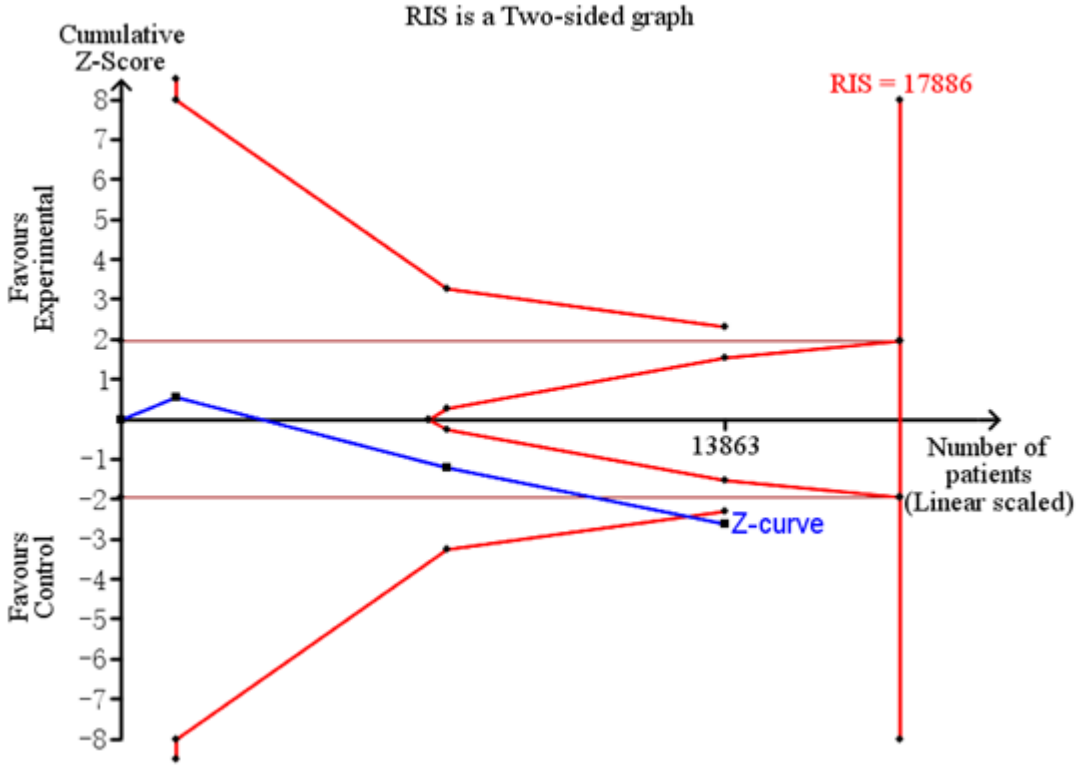

Figure S18. Trial sequential analysis of dual LAMA/LABA therapy vs. triple therapy for stroke.

Horizontal lines represent the traditional boundaries of statistical significance. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for harm. The cumulative Z curve represents the included RCTs data. A diversity-adjusted required information size (RIS) is 38957 ($\alpha = 0.05$, two sided, $\beta = 0.20$, power 80%). The cumulative Z curve does not cross the conventional boundary for benefit or harm.