ORIGINAL ARTICLE

Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis

Yuji Oba,[1] Siva T Sarva,[1] Sofia Dias[2]

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[1]Division of Pulmonary, Critical Care and Environmental Medicine, University of Missouri, School of Medicine, Columbia, USA
[2]School of Social and Community Medicine, University of Bristol, Bristol, UK

Correspondence to
Dr Yuji Oba, Division of Pulmonary, Critical Care and Environmental Medicine, University of Missouri, School of Medicine, One Hospital Drive, CE 412 Columbia, MO 65212, USA; obay@health.missouri.edu

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ABSTRACT

Background The place of long-acting β agonist/long-acting muscarinic antagonist (LABA/LAMA) combinations in stable patients with COPD is not well defined. The purpose of this study was to systematically review the efficacy and safety of LABA/LAMA combinations.

Methods Several databases and manufacturers' websites were searched for relevant clinical trials. Randomised control trials, at least 12 weeks duration, comparing a LABA/LAMA combination with placebo and/or monotherapy were included. The data were pooled using a network as well as a traditional direct comparison meta-analysis.

Results Twenty-three trials with a total of 27 172 patients were included in the analysis. LABA/LAMA combinations were associated with a greater improvement in lung function, St. George's Respiratory Questionnaire (SGRQ) score, and Transitional Dyspnoea Index (TDI) than monotherapies. LABA/LAMA combinations were associated with a significantly greater proportion of SGRQ and TDI responders than monotherapies (OR 1.23 (95% credible interval (CrI) 1.06–1.39), OR 1.34 (95% CrI 1.19–1.50) versus LABAs and OR 1.24 (95% CrI 1.11–1.36), OR 1.31 (95% CrI 1.18–1.46) versus LAMAs, respectively) and fewer moderate-to-severe exacerbations compared with LABAs (HR 0.82 (95% CrI 0.73–0.93)), but not when compared with LAMAs (HR 0.92 (95% CrI 0.84–1.00)). There were no statistically significant differences associated with LABA/LAMA combinations compared with monotherapies in safety outcomes as well as in severe exacerbations.

Conclusions The combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores and moderate-to-severe exacerbation rates, and had similar effects on safety outcomes and severe exacerbations as compared with monotherapies.

Key messages

What is the key question?

- Do greater improvements of lung function with long-acting β agonist/long-acting muscarinic antagonist (LABA/LAMA) combinations translate into better clinical benefits compared with monotherapies in stable patients with COPD?

What is the bottom line?

- The combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores and moderate-to-severe exacerbation rates, and had similar effects on safety outcomes and severe exacerbations as compared with monotherapies.

Why read on?

- Our systematic review summarises the efficacy and safety of LABA/LAMA combination therapy in patients with moderate-to-severe COPD and describes the limitations of the current data.

INTRODUCTION

COPD will likely become the third leading cause of death by 2030 according to WHO and continues to be a major cause of disability and rising healthcare costs worldwide.[1] The total cost of COPD in 2010 was $49.9 billion, including healthcare expenditures of $29.5 billion in direct healthcare costs, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs in the USA.[2] These costs were the highest among common lung diseases.

Current guidelines developed by Global Initiative for COPD (GOLD) recommend a maintenance therapy either with a long-acting muscarinic antagonist (LAMA) or a long-acting β agonist (LABA) in symptomatic patients with moderate or more severe COPD.[3] When patients are not adequately controlled with a single long-acting bronchodilator, combining a LAMA with a LABA may be beneficial.[4]

European and Japanese regulatory agencies recently approved a once-daily fixed-dose combination of indacaterol and glycopyrronium as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. A fixed-dose combination of umeclidinium/vilanterol was approved in the USA and Canada for maintenance treatment of COPD.[5] Although LABA/LAMA combination therapies were superior to monotherapies with regards to lung function improvement, it is less clear that the surplus of bronchodilation by combination therapy would translate into better clinical outcomes such as better quality of life and fewer exacerbations.[6 7]

The purpose of this study was to systematically review the efficacy and safety of LABA/LAMA

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combinations in COPD from randomised controlled trials with a network meta-analysis (NMA) as well as with a traditional direct comparison meta-analysis. When no clinical trials exist that directly compare all relevant treatment options, indirect comparisons can be made by comparing the relative effects of treatments against a common comparator or combining a variety of comparisons that taken together from one or more chains linking the treatments of interest (variously referred to as a multiple treatment comparison or NMA).[8]

METHODS

Identification of trials and data extraction

We identified all relevant clinical trials which evaluated clinical efficacies and safety of a LABA/LAMA combination in stable patients with COPD without an acute or recent exacerbation. Two authors (YO, STS) independently searched the Ovid Medline database for studies published from 1946 to 21 May 2015 using the MeSH headings and keywords: randomised controlled trial AND Pulmonary Disease, Chronic Obstructive AND aclidinium, glycopyrronium, or tiotropium AND formoterol, indacaterol, olodaterol, salmeterol, or vilanterol OR QVA149. In addition, we searched Scopus, CINAHL and the internet including the online trial registries of manufacturers of the above mentioned fixed-dose LABA/LAMA products. Bibliographies of all selected articles and review articles which included information on a LABA/LAMA combination in COPD were also reviewed for other relevant articles. We included any randomised clinical trial, published or unpublished, evaluating patients with COPD with a LABA/LAMA combination. Randomised control trials had to be of at least 12 weeks duration. A control intervention had to include a placebo, a LABA or a LAMA. We chose change from baseline (CFB) in trough FEV_1 in litres, Transitional Dyspnoea Index (TDI), CFB in St. George's Respiratory Questionnaire (SGRQ), a proportion of SGRQ and TDI responders (defined as a subject with an improvement of at least 4 units in SGRQ total score or 1 unit in TDI score),[9] COPD exacerbations, mortality, total serious adverse events (SAEs), cardiac SAEs and dropouts due to adverse event, as the outcome assessment criteria for the purpose of our meta-analysis.

Two authors (YO, STS) independently screened studies by title and abstract to evaluate whether a trial met the inclusion criteria. We extracted data on COPD exacerbations as moderate and severe. Moderate was generally defined as 'worsening respiratory status which required treatment with systemic corticosteroids and/or antibiotics' and severe as 'rapid deterioration which required hospitalisation'. Data were abstracted on study design, study size, population severity of illness, and the impact of a LABA/LAMA combination on the end points of interest. The risk of bias was assessed with the following items: (1) adequacy of sequence generation, (2) allocation concealment, (3) blinding of participants and investigators, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting and other bias.[10] Disagreements regarding values or analyses were resolved by discussion.

Statistical analysis

The primary analyses were NMAs using a Bayesian Markov chain Monte Carlo (MCMC) method and fitted in WinBUGS V.1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, UK) using code adapted from Dias *et al*,[11] which correctly accounts for correlations in trials with more than two arms. In a Bayesian analysis, a prior distribution of a parameter is the probability distribution that represents uncertainty about the parameter before the current data are examined. Current data and assumptions concerning how they were generated are summarised in the likelihood. Combining the prior distribution and the likelihood functions leads to the posterior distribution of the parameter which is used for inference. This distribution will be summarised by its median and 95% credible interval (CrI). CrIs are the Bayesian equivalent of classical CIs, but they are interpreted as defining the probability (usually 95%) that the relative treatment effects lie between its bounds. NMA estimates the comparative efficacy between all treatments, including those that have not been directly compared by including all relevant evidence (direct and indirect), and provide the most flexible approach to indirect comparison modelling. For the analyses in WinBUGS, inference was based on 100 000 iterations of MCMC with an initial burn-in period of 50 000 iterations.[12]

A data structure table was constructed to choose an optimal model for each outcome (see online supplementary table S1). Model selection and its rationale are summarised in the online supplementary table S2. Each pair of treatments was compared by estimating an OR or HR for a dichotomous outcome and a difference in mean or median for a continuous outcome. Treatment baselines and effects were given vague normal priors with mean 0 and variance 10 000 and between-trials SDs were given uniform distribution with lower bound 0 and upper bound 5. The upper bound of 5 was thought to be sufficiently large for outcomes on a log scale. The posterior distribution was examined to ensure it was sufficiently different from the prior and that the prior was therefore not having undue influence on the resulting posterior.

The probability that each intervention arm was associated with being the most efficacious was calculated by counting the proportion of iterations of the Markov chain in which each intervention arm had the highest HR, OR or mean difference (MD). The surface under the cumulative ranking (SUCRA), which is a simple numerical summary of these probabilities, was also calculated. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst.[13]

Assessment of model fit was based on comparison of residual deviance to the number of unconstrained data points, and between-study SD. We compared fixed and random effects models using the deviance information criterion (DIC), a measure of model fit that penalises model complexity. The model with lower values on the DIC was preferred, with differences of three or more units considered meaningful.[14] If two models had a similar DIC, a fixed-effects model was preferred unless there was heterogeneity in the pairwise comparison, in which case a random-effects model was used. Inconsistency was assessed by comparing the model fit and between-study heterogeneity from the NMA models with those from an unrelated effects (inconsistency) model.[15]

The presence of heterogeneity was assessed by comparing a between-trials SD to the size of the relative treatment effects, on log-scale for OR and HR. If the between-trials SD approximates the size of treatment effect, heterogeneity is likely very high so that results from a future trial could include zero or even harmful effects. Heterogeneity was further explored by fitting covariates (ie, FEV_1 at baseline, treatment duration (a minimum of 6 months), publication status (published vs unpublished) and smoking status) in a meta-regression analysis.[16] A subgroup interaction model was used for the treatment duration and a continuous covariate model was used for the rest of the covariates.

We conducted traditional pairwise meta-analyses, considering only direct evidence comparing the combination therapy with monotherapies or placebo using the same outcome variables. For the pairwise meta-analysis, we tested heterogeneity between trials with I^2 statistic with I^2>50% indicating significant heterogeneity. A random effects model (DerSimonian-Laird) was used if significant heterogeneity was detected. A fixed-effects model was used otherwise. Haldane correction was applied by adding 0.5 to each count when a data set contained zero in any cell to make a calculation possible for the main effect or variance.[17] Results from our NMA were qualitatively compared with direct pairwise estimates. The data analysis was performed using meta-analysis software (StatsDirect V.2.7.8, StatsDirect, Cheshire UK).

Sample size calculations and power analyses were conducted for clinically relevant outcomes such as SGRQ and TDI responders and COPD exacerbations with a method described by Thorlund and Mills.[18] A required sample size was calculated by applying a mean event rate of the comparator arm from the included trials, a type I error of 5% and a power of 90%, expecting to detect an additional 20% relative efficacy with the combination arm. Heterogeneity was estimated from I^2 index of a head-to-head comparison and used for correcting the sample sizes.

RESULTS

Study selection

The electronic database searches identified 112 citations. Ninety-seven studies were excluded on abstract review. The remaining 15 studies were reviewed for further details. Additional five studies were excluded for various reasons as shown in figure 1. Further search on manufactures' website and internet identified 10 additional studies including 3 unpublished studies. We included 23 trials from 20 reports with a total of 27 172 randomised patients.[19–38] The study and patient characteristics are presented in table 1.

Formoterol, indacaterol, olodaterol, salmeterol and vilanterol were grouped as LABA and aclidinium, glycopyrronium, umeclidinium and tiotropium were grouped as LAMA. The mean age ranged from 61.3 years to 69.3 years. The proportion of male patients and current smokers ranged from 52% to 96% and 26% to 63%, respectively. The mean baseline FEV_1 ranged from 0.90 L to 1.5 L. FEV_1 per cent predicted ranged from 37.2% to 57.4%. The network of treatments is displayed in figure 2. The treatments formed a closed network, which was amenable to a NMA.

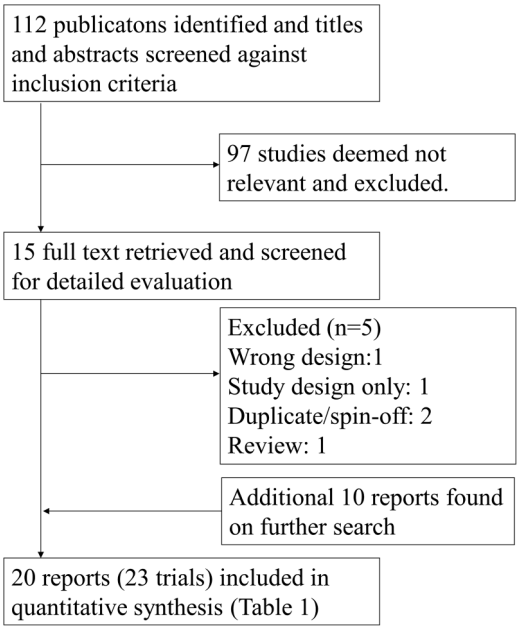

Figure 1 Flow of study selection.

Methodological quality of included studies

Generally, the risk of bias in the included studies was deemed moderate to low. Allocation concealment was appropriate in 16 studies, and unclear in 3 studies. All trials presented intention-to-treat analyses except for two trials which excluded 2 patients out of 1134 and 1137 patients who did not receive the study treatment.[26] Nineteen studies were double blinded (see online supplementary table S3). In the opinion of the authors, there were no studies that clearly should have been excluded from the analysis because of differences in baseline characteristics or poor quality.

Consistency assessment (similarity of participants, interventions and trial methodology)

All trials were consistent in their key inclusion and exclusion criteria (see online supplementary table S4). All studies recruited patients aged >35–40 years with a diagnosis of COPD in accordance with the American Thoracic Society-European Respiratory Society or GOLD guidelines, at least 10 pack-years of smoking history, and moderate or severe disease with FEV_1 ranging 30–70% of predicted. Patients with asthma and other respiratory or cardiovascular disease were excluded in all trials. The concomitant use of a fixed dose of inhaled corticosteroids (ICS) was allowed in most studies, prohibited in two studies[26 38] and unclear in one study[35] which was addressed in a sensitivity analysis. A recent COPD exacerbation within a month of study entry was usually excluded from the study. Baseline characteristics of studied patients were similar in all included studies (table 1) as well as in class pairwise comparisons (eg, LABA vs combination, LAMA vs Placebo, see online supplementary table S5). Baseline FEV_1 was somehow lower in the combination versus LAMA comparison, but summary baseline characteristics were comparable across pairwise comparisons between classes. Trial duration varied across studies, which was addressed by including only data relevant to the time points specified or by modelling the data as hazards with the binomial-complementary log-log (cloglog) model which allows for the different follow-up time. In general, characteristics of participants, interventions and trial methodology were fairly comparable in all studies and across pairwise comparisons, and therefore we found nothing to suggest that the consistency assumption may not hold.

Network meta-analysis

The clinical trials were synthesised with a NMA. The individual study results are presented in online supplementary table S6–S8. The autocorrelation plots showed that throughout the iterative process the autocorrelation was satisfactorily reduced to a nominal amount and the Brooks-Gelman-Rubin plots showed that the model had converged satisfactorily.[39] When examining outcome measures, a fixed-effects model showed largely similar DIC values and results as a random-effects model. A random-effects model was chosen in all outcomes according to our prespecified selection criteria except for CFB in SGRQ at 3 months, TDI, proportion of TDI responders, severe exacerbations, mortality and total SAEs. The between-study heterogeneity and DICs were similar between the NMA and inconsistency models suggesting no evidence of inconsistency in the network, although this should be interpreted with caution as there may

Table 1 Study characteristics of included trials

Study, year	No. of patients*	Duration of treatment (weeks)	Treatment comparisons (µg)	Mean age	Male %	Current smoker %	Baseline FEV_1%†	Baseline FEV_1 (L)‡
Buhl *et al* 2015[19]	5162	52	TIO/OLO 5/5 TIO/OLO 2.5/5 TIO 5 TIO 2.5 OLO 5	64.0	73	37	50.0	1.17
Celli *et al* 2014[20]	1489	24	UMEC/VI 125/25 UMEC 125 VI 25 Placebo	62.9	65	52	48.2	1.28
Decramer *et al* 2014[21]	843	24	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 TIO 18	62.9	69	51	47.7	1.31
Decramer *et al* 2014[21]	869	24	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 TIO 18	64.6	68	45	47.1	1.16
D'Urzo *et al* 2014[22]	1669	24	ACL/FM 400/12 ACL/FM 400/6 ACL 400 FM 12 Placebo	63.9	53	52	53.5	1.36
Donohue *et al* 2014[31]	562	52	UMEC/VI 125/25 UMEC 125 Placebo	61.3	67	63	54.7	1.49
Maleki-Yazdi *et al* 2014[23]	905	24	UMEC/VI 62.5/25 TIO 18	62.3	68	57	46.3	1.41§
Singh *et al* 2014[24]	1729	24	ACL/FM 400/12 ACL/FM 400/6 ACL 400 FM 12 Placebo	63.2	68	47	54.3	1.41
Vincken *et al* 2014[25]	447	12	IND/Glyco 110/50 IND 150	63.6	81	42	54.9	1.46
ZuWallack *et al* 2014[26]§ (ANHELTO 1 and 2)	2267	12	TIO/OLO 18/5 TIO 18	64.3	52	49	53.7	1.25
Bateman *et al* 2013[27]	2135	26	IND/Glyco 110/50 IND 150 Glyco 50 TIO 18 Placebo	63.9	75	40	55.2	1.30
Dahl *et al* 2013[28]	338	52	IND/Glyco 110/50 Placebo	62.6	77	45	57.4	1.45
Donohue *et al* 2013[29]	1532	24	UMEC/VI 62.5/25 UMEC 62.5 VI 25 Placebo	63.1	71	50	47.4	1.23
Wedzicha *et al* 2013[30]	2205	64	IND/Glyco 110/50 Glyco 50 TIO 18	63.3	75	38	37.2	0.90
DB2114417 2012[32]	641	12	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 UMEC 125 UMEC 62.5 Placebo	61.6	56	63	NR	1.44
DB2114418 2012[33]	554	12	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 UMEC 125 UMEC 62.5 Placebo	62.6	55	61	NR	1.32
Mahler *et al* 2012[34]	1131	12	TIO 18 /IND 150 TIO 18	63.7	69	38	48.6	1.15
Mahler *et al* 2012[34]	1142	12	TIO 18 /IND 150 TIO 18	63	66	40	48.6	1.14

Continued

Table 1 Continued

Study, year	No. of patients*	Duration of treatment (weeks)	Treatment comparisons (µg)	Mean age	Male %	Current smoker %	Baseline FEV_1%†	Baseline FEV_1 (L)‡
Novartis A1301 2012[35]	158	52	IND/Glyco 110/50 TIO 18	69.3	96	NR	NR	1.33¶
Tashkin *et al* 2009[36]	243	12	TIO 18 /FM 12 TIO 18	63.9	66	47	NR	NR
Vogelmeier *et al* 2008[37]	847	24	TIO 18 /FM 10 FM 10 TIO 18 Placebo	62.6	78	NR	51	1.5
Aaron *et al* 2007[38]	304	52	TIO 18/SAL 50 TIO 18	67.9	56	26	41.7	1.01

*Number of patients included in this analysis.
†Postbronchodilator.
‡Prebronchodilator.
§Includes 2 trials making a total of 23 trials.
¶At week 3.
ACL, aclidinium; FM, formoterol; Glyco, glycopyrronium; IND, indacaterol; NR, not reported; OLO, olodaterol; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

not be sufficient power to detect inconsistency. Ranking results of each outcome are presented in table 2.

FEV_1

Trough FEV_1 data were available in 13 trials, 12 trials and 4 trials at 3 months, 6 months and 12 months (n=12 224, 16 065 and 4836, respectively). Improvement in trough FEV_1 to the end of the trials was greater with LABA/LAMA combinations than with placebo, LABAs or LAMAs at all time points. LABA/LAMA combinations were ranked first (95% CrI 1, 1) at all time points, with a mean improvement over placebo of 201 mL (95% CrI 172, 230) to 243 ml (95% CrI 139, 351). LAMAs and LABAs were ranked second and third with the MDs of 64 mL (95%CrI 51, 78) to 73 mL (95% CrI 43, 149) and 95 mL (95% CrI 71, 117) to 104 mL (95% CrI 84, 126) compared with LABA/LAMA combinations. Class differences did not appear significantly different at 3 months, 6 months and 12 months, except for LABAs at 12 months at which time point data were not available (figure 3). Wider 95% CrIs were observed at 12 months as the number of included studies decreased.

Health-related quality of life and symptom scales (SGRQ and TDI scores and responders)

The data for CFB in SGRQ and TDI were available in nine and six trials at 3 months and nine and eight trials at 6 months

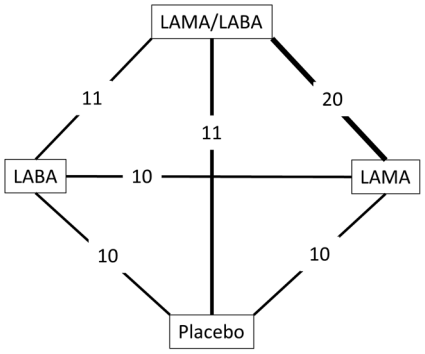

Figure 2 Diagram displaying the network of four arms involved in the Bayesian analysis. The links between nodes are used to indicate a direct comparison between pairs of treatments. The numbers shown along the link lines indicate the number of trials comparing pairs of treatments head-to-head. LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

(n=12 042, 7315, 12 716 and 14 568, respectively). The data for SGRQ and TDI responders at 6 months were available in 12 and 7 trials (n=18 536 and 9045, respectively). The combination therapy was ranked highest, followed by LABAs and LAMAs in all SGRQ outcomes. The efficacy of combination therapy in CFB in SGRQ was less prominent at 6 months as compared with 3 months, especially with LABAs (MD −4.6 (95% CrI −5.9, −3.3), −2.3 (95% CrI −3.3, −1.3) and −2.3 (95% CrI −2.9, −1.7) for placebo, LABAs and LAMAs, respectively at 3 months and −4.1 (95% CrI −5.9, −2.3), −1.1 (95% CrI −2.5, 0.4) and −1.6 (95% CrI −2.8, −0.5) at 6 months, figure 4A). Although the MD and its 95% CrI between combination therapy and monotherapies did not reach the minimum clinically important difference of 4 points in SGRQ score, LAMA/LABA combinations were associated with a significantly greater proportion of SGRQ responders compared with LAMAs and LABAs (OR 1.23 (95% CrI 1.06, 1.39) and1.24 (95% CrI 1.11, 1.36), respectively, figure 5).

As for TDI, the combination therapy was ranked highest, followed by LABAs or LAMAs. The combination therapy yielded a significant improvement in TDI score compared with placebo, LABAs and LAMAs at 3 months (MD 1.21 (95% CrI 0.95, 1.48), 0.37 (95% CrI 0.16, 0.57) and 0.41 (95% CrI 0.23, 0.59), respectively). The class differences remained constant and statistically significant at 6 months (figure 4B). Although the MD and its 95% CrI between combination therapy and monotherapies did not reach the minimum clinically important difference of 1 point in TDI, LAMA/LABA combinations were associated with a significantly greater proportion of TDI responders compared with LAMAs and LABAs (OR 1.34 (95% CrI 1.16, 1.56) and 1.30 (95% CrI 1.13, 1.48), respectively, figure 5). The 95% CrIs of ranking suggested that only combination therapy could be ranked first in all SGRQ and TDI outcomes (table 2).

COPD exacerbations

COPD exacerbation data were available in 16 trials (n=18 224) for moderate-to-severe exacerbations and in 19 trials (n=25 401) for severe exacerbations. LABA/LAMA combinations were ranked first and second for the prevention of moderate-to-severe and severe exacerbations with a probability of being the best therapy of 97.0% and 30.2%, respectively. The combination therapy was associated with significantly fewer moderate-to-severe exacerbations compared with placebo and LABAs (HR 0.66(95% CrI 0.57, 0.77), 0.82 (95% CrI 0.73,

Table 2 Probability of best therapy, SUCRA values and ranking of therapy

	Probability of being the best therapy (%)	SUCRA value (%)	Median ranking (95% CrI)
Treatment	CFB in FEV_1 (L)—3 months		
Placebo	0	0	4 (4–4)
LABA	0	33.4	3 (3–3)
LAMA	0	66.6	2 (2–2)
LABA/LAMA	100	100	1 (1–1)
Treatment	CFB in FEV_1 (L)—6 months		
Placebo	0	0	4 (4–4)
LABA	0	33.6	3 (3–3)
LAMA	0	66.4	2 (2–2)
LABA/LAMA	100	100	1 (1–1)
	CFB in FEV_1 (L)—12 months		
Placebo	0.1	0.5	3 (3–3)
LABA	N/A	N/A	N/A
LAMA	2.1	50.7	2 (2–2)
LABA/LAMA	97.7	98.8	1 (1–1)
	CFB in SGRQ—3 months		
Placebo	0	0	4 (4–4)
LABA	0	49.0	2 (2–3)
LAMA	0	51.0	3 (2–3)
LAMA/LABA	100	100	1 (1–1)
	CFB in SGRQ—6 months		
Placebo	0	0.1	4 (4–4)
LABA	0.6	52.2	2 (2–3)
LAMA	0.1	47.9	3 (2–3)
LAMA/LABA	99.2	99.7	1 (1–2)
	SGRQ responder*—6 months		
Placebo	0	0.4	4 (4–4)
LABA	0.4	67.2	2 (2–3)
LAMA	0	36.8	3 (2–3)
LAMA/LABA	99.5	95.6	1 (1–2)
	TDI—3 months		
Placebo	0	0	4 (4–4)
LABA	0	55.7	2 (2–3)
LAMA	0	44.3	3 (2–3)
LABA/LAMA	99.9	100	1 (1–1)
	TDI—6 months		
Placebo	0	0	4 (4–4)
LABA	0	43.0	3 (2–3)
LAMA	0	57.0	2 (2–3)
LABA/LAMA	99.4	100	1 (1–1)
	TDI responder†—6 months		
Placebo	0	0	4 (4–4)
LABA	0	44.2	3 (2–3)
LAMA	0.1	55.8	2 (2–3)
LABA/LAMA	99.9	100	1 (1–1)
	Moderate-to-severe exacerbations		
Placebo	0	2.6	4 (4–4)
LABA	0.2	34.3	3 (2–3)
LAMA	2.9	66.5	2 (1–3)
LAMA/LABA	97.0	99.0	1 (1–2)
	Severe exacerbations		
Placebo	4.6	10.2	4 (1–4)
LABA	37.4	66.0	2 (1–4)
LAMA	7.5	44.8	3 (1–4)
LAMA/LABA	50.5	79.0	1 (1–3)
	Mortality		
Placebo	84.8	91.4	1 (1–4)
LABA	7.6	41.3	3 (1–4)
LAMA	0.6	14.5	4 (2–4)
LAMA/LABA	7.1	52.7	3 (1–4)
	Total serious adverse events		
Placebo	62.7	76.4	1 (1–4)
LABA	6.6	23.6	4 (1–4)
LAMA	26.0	64.7	2 (1–4)
LAMA/LABA	4.7	35.2	3 (1–4)
	Cardiac serious adverse events		
Placebo	89.6	94.7	1 (1–3)
LABA	2.1	22.3	4 (2–4)
LAMA	1.6	28.3	3 (2–4)
LAMA/LABA	6.7	54.6	2 (1–4)
	Dropout due to adverse event		
Placebo	22.7	42.8	3 (1–4)
LABA	11.7	29.6	3 (1–4)
LAMA	42.0	70.0	2 (1–4)
LAMA/LABA	23.5	57.6	2 (1–4)

*Defined as a subject with a SGRQ score of 4 units below baseline or lower.
†Defined as a subject with a TDI score of 1 unit or more.
CFB, change from baseline; CrI, credible interval; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable; SGRQ, St. George's Respiratory Questionnaire; SUCRA, surface under the cumulative ranking curve; TDI, Transitional Dyspnoea Index.

0.93), respectively), but not when compared with LAMAs (HR 0.92 (95% CrI 0.84, 1.00)). LAMAs had a median rank of 2 in preventing moderate-to-severe exacerbations and the 95% CrI suggested that they could also be ranked first, second or third (median ranking 2 (95% CrI 1, 3)). There were no significant differences in severe exacerbations associated with LABA/LAMA combinations compared with placebo, LABAs or LAMAs and there was a large degree of overlap in ranking (figure 6 and table 2).

Adverse events

The results of safety outcomes are presented in table 3. There were no significant differences in mortality, total SAEs or dropouts due to adverse event among all comparators (table 3).

There was considerable overlap in CrIs and rankings. Any arm including placebo could be ranked as the best therapy in all safety outcomes except for LAMAs in mortality and cardiac SAEs and LABAs in cardiac SAEs. Placebo was ranked highest in mortality, total SAEs and cardiac SAEs. LABA/LAMA combinations were ranked second in mortality, cardiac SAEs and dropouts due to adverse event, but again, there was a large degree of overlap (table 3).

Assessment of consistency and exploration of heterogeneity

The between-trials SDs were relatively large compared with the relative treatment effects in severe exacerbations, mortality, total SAEs, cardiac SAEs and dropouts due to adverse event (see online supplementary table S9). The meta-regression adjustment for the proportion of active smokers, FEV_1 at baseline, study duration (a minimum of 6 months), and publication status (published vs unpublished) did not alter the main findings. Between-trials heterogeneity was either unchanged, increased or only slightly reduced with the introduction of those covariates. Comparisons between network and direct pairwise meta-analyses were similar in magnitude and direction of effect

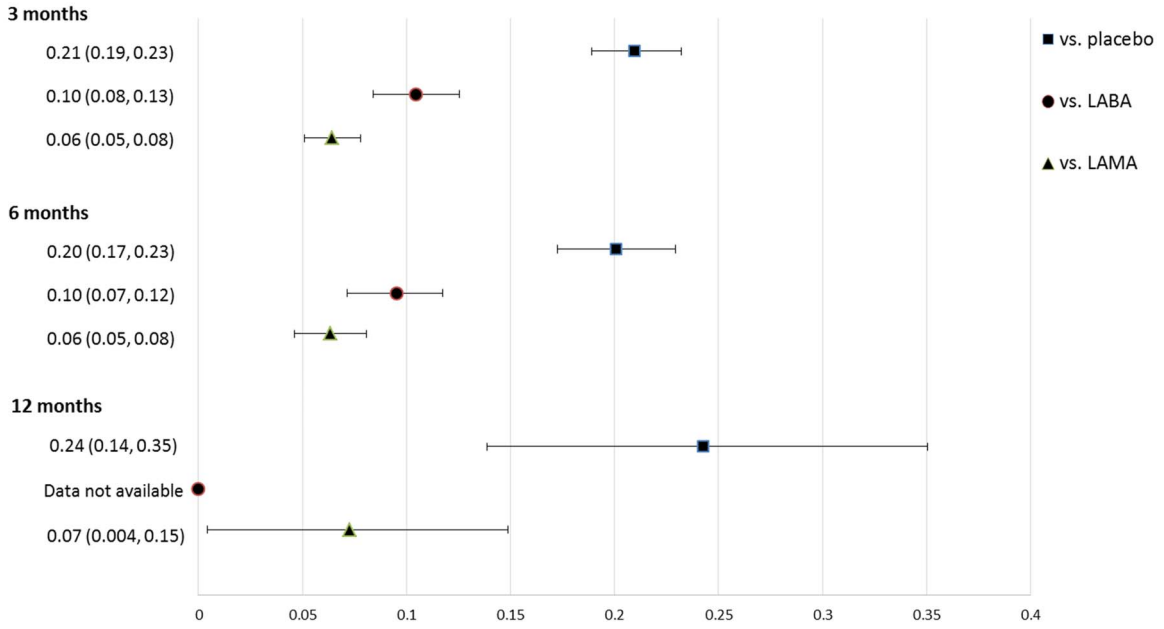

Figure 3 Summary effects of LABA/LAMA combination versus comparators on changes in trough FEV_1 at 3 months, 6 months and 12 months. *Note*: Mean difference in litres (95% credible interval). LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

estimates, with the exception of the combination versus LAMA comparison in moderate-to-severe exacerbations and the combination versus LAMA comparison in dropouts due to adverse event. However, these inconsistencies did not alter the main findings (see online supplementary table S10). Two studies included a randomly assigned group that received tiotropium as an open-label treatment.[30 37] The concomitant use of ICS was prohibited in two studies[26 38] and unclear in one study.[30] We performed a sensitivity analysis excluding these studies and the results were essentially unchanged.

Power analyses and sample size calculations

The heterogeneity-corrected effective total sample size for the SGRQ and TDI responders and moderate-to-severe exacerbations was greater than the required sample size to detect additional 20% relative efficacy with a power of 90% (see online supplementary table S11). Statistical power for combination therapy versus comparators was 95% or greater in those outcomes. On the other hand, the effective total sample size for severe exacerbations was substantially smaller than the required sample size except for the combination therapy versus LAMA comparison. Statistical power estimates for the combination therapy versus placebo, LABA and LAMA comparisons were 29.8%, 55.5% and 93.5%, respectively, in severe exacerbations.

DISCUSSION

Our systematic review of the currently available randomised trials of LABA/LAMA combinations for stable COPD demonstrated that LABA/LAMA combinations yielded a greater improvement in trough FEV_1, and SGRQ and TDI scores than monotherapies. The ranking statistics demonstrated that combination therapy was the most effective strategy in improving lung function, quality of life and symptom scores as well as in reducing moderate-to-severe exacerbations. The combination therapy was associated with a significantly greater proportion of SGRQ and TDI responders than monotherapies. The combination therapy was ranked highest in reducing moderate-to-severe exacerbations and was associated with significantly fewer exacerbations than LABAs, but not when compared with LAMAs. LAMAs could also be ranked first in reducing moderate-to-severe exacerbations. There were no statistically significant differences among all comparators in severe exacerbations or safety outcomes, including mortality, total SAEs, cardiac SAEs and dropouts due to adverse event. The sample size analysis suggested that the analyses for severe exacerbations were underpowered except for the combination versus LAMA comparison. The sample size for SGRQ and TDI responders and moderate-to-severe exacerbations appeared adequate.

The results of our analysis are in line with a previous meta-analysis which demonstrated tiotropium/LABA combinations were associated with a small increase in lung function and a statistically significant improvement in quality of life compared with tiotropium alone. Improvement in other secondary outcomes, such as COPD exacerbations and SAEs was similar between both groups.[40] It is not surprising that dual therapies were not associated with significantly fewer exacerbations compared with LAMAs in the current analysis given that the concomitant use of LABA did not enhance the efficacy of LAMAs in reducing COPD exacerbations in a recent meta-regression analysis.[41] A similar phenomenon was observed among short-acting bronchodilators. Only ipratropium containing arms had reduced COPD exacerbations and adding albuterol to ipratropium did not reduce COPD exacerbations compared with ipratropium alone.[42] It was speculated that alterations in mucus production, rheology by glands, or mucus clearance in small airways were primarily responsible for COPD exacerbations which were favourably affected by anticholinergics rather than by β2 agonists. The above notion is further supported by the current analysis with the strength of the NMA, which is the correct inclusion of multiarm trials, of which this network had many, including several studies comparing all four interventions.

It is important to note the limitations of our study. First, heterogeneity was observed in pairwise and network meta-analyses. None of the trial-level covariates we assessed explained the heterogeneity. Patient and study characteristics of the included

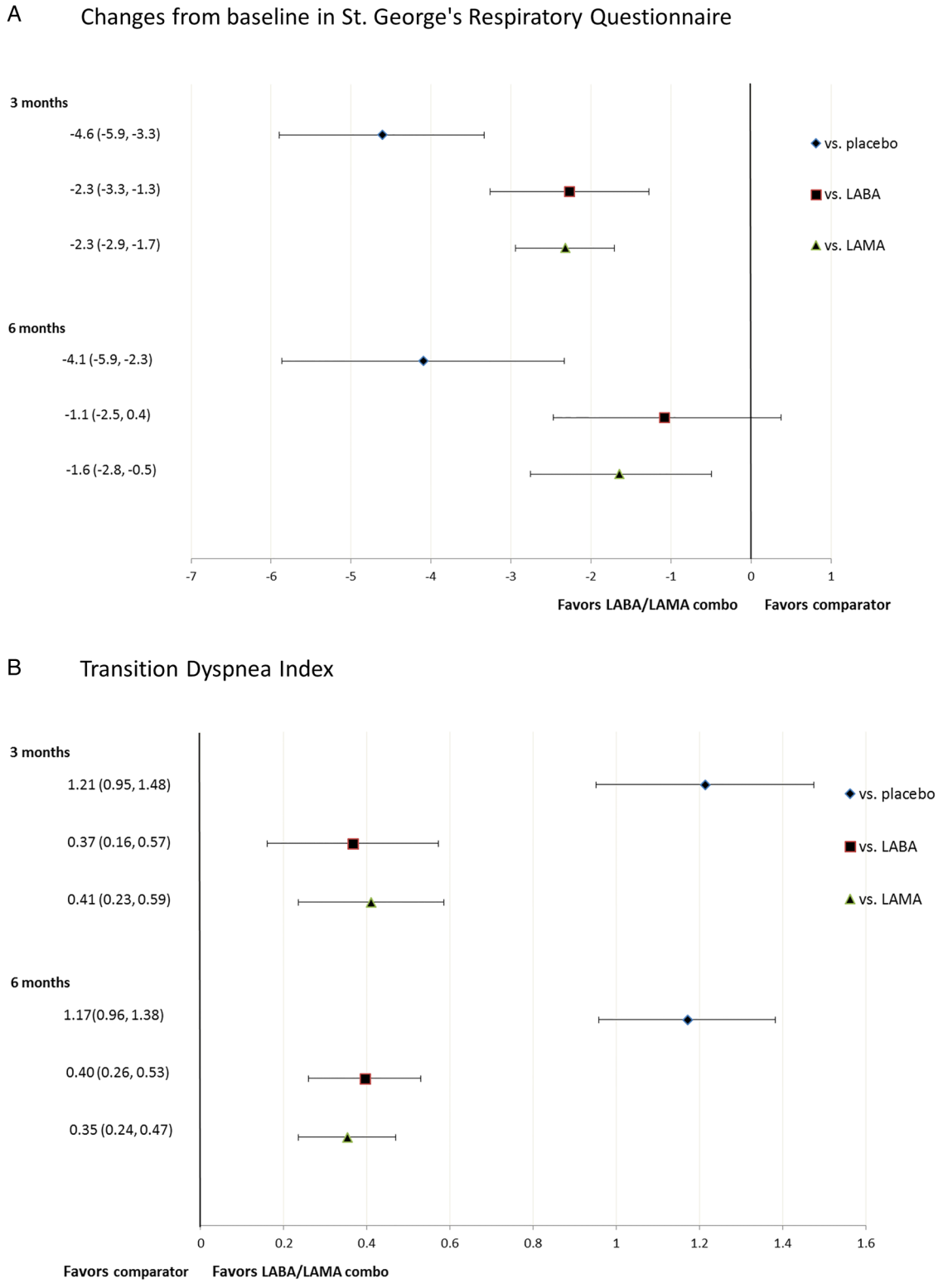

Figure 4 Summary effects of LABA/LAMA combination versus comparators on changes in (A) St. George's Respiratory Questionnaire and (B) Transition Dyspnoea Index at 3 months and 6 months. *Note*: Mean difference (95% credible interval). LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

studies were relatively homogenous, but between-trial comparisons are known to be vulnerable to ecological bias.[13] The subgroup analysis to assess biases by systematic differences between studies was also compromised due to limited information. For example, the proportion of current smokers and baseline pre-bronchodilator FEV_1 values were not available in a few studies included in this analysis (table 1). Individual patient data would be necessary to avoid ecological bias and gain a much greater statistical power to detect a true covariate effect. Other effect modifiers including body mass index, Medical Research Council dyspnoea score, exercise capacity (6-min walk distance), presence of emphysema on chest CT and cardiac comorbidities may

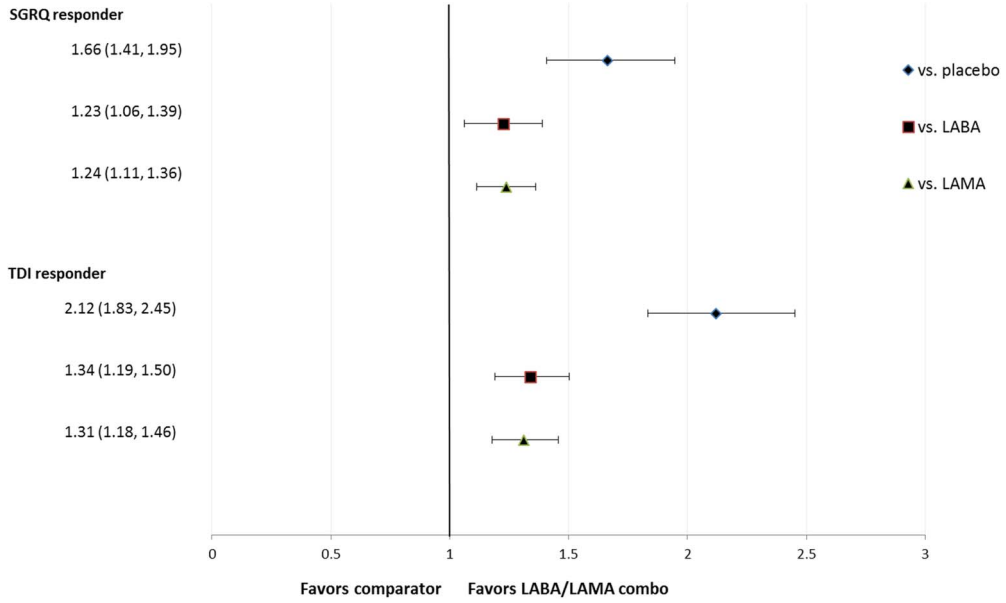

Figure 5 Summary effects of LABA/LAMA combination versus comparators on proportion of SGRQ and TDI responders at 6 months. *Note*: OR (95% credible interval). A responder was defined as a subject with an improvement of at least 4 units in SGRQ total score or 1 unit in TDI score. LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index.

have influenced the study results. Second, as with all meta-analyses, we are limited by the amount of evidence that is published, consequently some of the analyses may fail to detect a true treatment effect. Our sample size calculation suggested that the assessment of severe exacerbations was significantly underpowered except for the combination versus LAMA comparison (see online supplementary table S11). Future studies enrolling patients at much higher risk for COPD exacerbations would be helpful to increase the statistical power and shed further light on the efficacy of LABA/LAMA combinations on severe exacerbations. An imbalance in study and patient characteristics across trials cannot be completely excluded as with all meta-analyses because patients are not randomised to different trials and randomisation would not hold across the set of trials used for the analysis. The results were unchanged when adjusted for study level covariates, but the risk of residual confounding bias from unknown or unmeasured effect modifiers cannot be excluded.[43] However, it is unlikely that the results are substantially biased given the consistency of results between network and direct comparison meta-analyses and the purpose of our evidence synthesis is to provide an estimate, and its uncertainty, based on the current available evidence. Third, the data included in the NMA was extracted from randomised trials and the results may not be generalisable to all patients with COPD. Forth, a cost analysis was not conducted. Future studies, especially ones that compare LABA/LAMA, LABA/ICS and LABA/LAMA/ICS combinations are necessary to determine the most cost-effective treatment option.

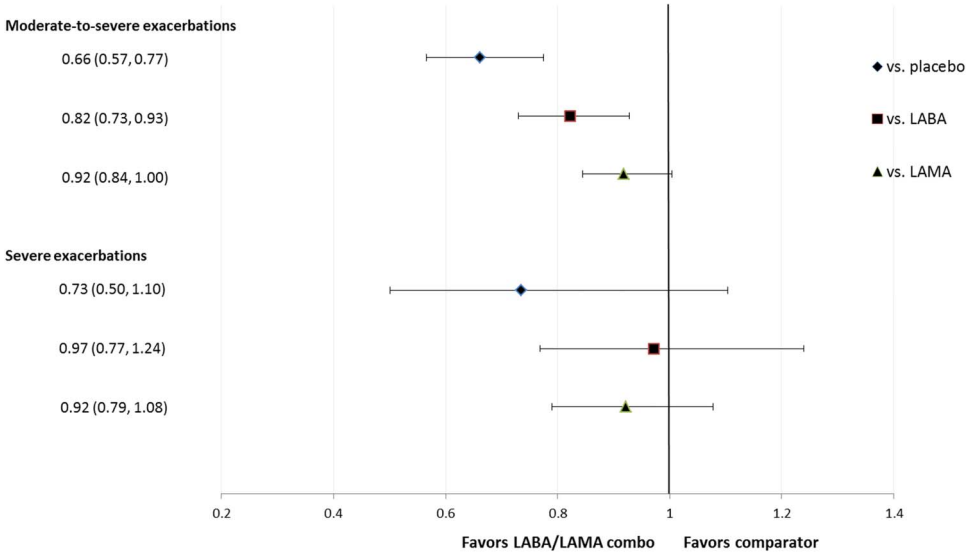

Figure 6 Summary effects of LABA/LAMA combination versus comparators on COPD exacerbations. *Note*: HR (95% credible interval). LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

Table 3 Summary effects of LABA/LAMA combinations versus comparators on adverse events

	Mortality FE HR (95% CrI)	Total SAEs FE HR (95% CrI)	Cardiac SAEs RE HR (95% CrI)	Dropouts due to AE RE HR (95% CrI)
No. of studies	15	20	16	16
No. of patients	24 041	27 172	25 913	23 529
vs placebo	1.95 (0.73, 7.71)	1.10 (0.89, 1.38)	1.65 (0.81, 3.35)	0.95 (0.71, 1.28)
vs LABA	0.99 (0.61, 1.66)	0.96 (0.84, 1.10)	0.82 (0.46, 1.35)	0.92 (0.72, 1.19)
vs LAMA	0.87 (0.64, 1.16)	1.04 (0.95, 1.14)	0.87 (0.59, 1.27)	1.03 (0.84, 1.26)

AE, adverse event; CrI, credible interval; FE, fixed-effects; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; RE, random-effects; SAE, serious adverse event.

CONCLUSIONS

Our network analysis demonstrated that the combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores and moderate-to-severe exacerbation rates. The combination therapy was associated with fewer moderate-to-severe exacerbations compared with LABAs, but not when compared with LAMAs. The combination therapy had similar effects on safety outcomes and severe exacerbations as compared with monotherapies. Future studies including patients with a more severe form of COPD and comparing LABA/LAMA, LABA/ICS and LABA/LAMA/ICS combinations would help healthcare practitioners and societies to better position the place of LABA/LAMA combinations in the armamentarium of COPD therapies.

Contributors YO and STS conceived the study and were responsible for the data search and extraction. SD advised on the choice of Bayesian models, created the binomial-cloglog model and conducted the analyses on exacerbation outcomes. YO produced the figures and all authors contributed to the writing of the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Table S1. Data structure of included outcomes.

			FEV1 (reported as mean with SE)			SGRQ (reported as mean with SE)			SGRQ Responder (reported as no. events/ no. patients)		
Study, year	**No. of patients†**	**Duration of treatment (weeks)**	3 months	6 months	12 months	3 months	6 months	12 months	3 months	6 months	12 months
Buhl 2015[19]	**5162**	**52**	No	Yes	No	No	No*	No	No	Yes	No
Celli 2014 [20]	**1489**	**24**	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Decramer 2014a [21]	**843**	**24**	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Decramer 2014b [21]	**869**	**24**	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
D'Urzo 2014[22]	**1669**	**24**	No	Yes	No	No	Yes	No	No	Yes	No
Maleki-Yazdi 2014[22]	**905**	**24**	No	Yes	No	Yes	Yes	No	No	Yes	No
Singh 2014[24]	**1729**	**24**	No	Yes	No	No	Yes	No	No	Yes	No
ZuWallack 2014[26]	**2267**	**12**	Yes	No	No	Yes	No	No	Yes	No	No
Donohue 2013 [29]	**1532**	**24**	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Donohue 2014 [31]	**562**	**52**	Yes	Yes	Yes	No	No	No	No	No	No
DB2114417 2012 [32]	**641**	**12**	Yes	No	No	No	No	No	No	No	No
DB2114418 2012 [33]	**554**	**12**	Yes	No	No	No	No	No	No	No	No
Vincken 2014 [25]	**447**	**12**	No	No	No	No	No	No	No	No	No
Bateman 2013 [27]	**2135**	**26**	No	Yes	No	Yes	Yes	No	No	Yes	No
Dahl 2013 [28]	**338**	**52**	No	No	Yes	No	No	No	No	No	No
Wedzicha 2013 [30]	**2205**	**64**	Yes	Yes	Yes	Yes	Yes	Yes	Yes¶	Yes¶	Yes¶
Novartis A1301 2012 [35]	**158**	**52**	Yes	Yes	Yes	No	No	No	No	No	No
Mahler 2012a [34]	**1131**	**12**	Yes	No	No	No	No	No	No	No	No
Mahler 2012b [34]	**1142**	**12**	Yes	No	No	No	No	No	No	No	No
Tashkin 2009 [36]	**243**	**12**	Yes	No	No	No*	No	No	No	No	No
Vogelmeier 2008 [37]	**847**	**24**	No	No	No	No	No	No	No	No	No
Aaron 2007 [38]	**304**	**52**	No	No	No*	No	No	No*	No	No	No

† Number of patients included in this study. *Insufficient data. ¶ Figure only. FEV1= forced expiratory volume in 1 second; No. =number; SE= standard error; SGRQ= St. George's Respiratory Questionnaire.

			TDI (reported as mean with SE)			TDI Responder (reported as no. events/ no. patients)			Exacerbations (at trial follow-up)		
Study, year	**No. of patients†**	**Duration of treatment (weeks)**	3 months	6 months	12 months	3 months	6 months	12 months	No. events/person years at risk	HR for first event (with SE)	No. patients with ≥ 1 event(s)/total no. of patients
Buhl 2015[19]	**5162**	**52**	No	Yes	No	No	No	No	No	No	Yes
Celli 2014 [20]	**1489**	**24**	Yes	Yes	No	Yes	Yes	No	No	Yes*	Yes
Decramer 2014a [21]	**843**	**24**	Yes	Yes	No	Yes	Yes	No	No	Yes*	Yes
Decramer 2014b [21]	**869**	**24**	Yes	Yes	No	Yes	Yes	No	No	Yes*	Yes
D'Urzo 2014[22]	**1669**	**24**	No	Yes	No	No	Yes	No	Yes	Yes*	No
Maleki-Yazdi 2014[22]	**905**	**24**	No	No	No	No	No	No	No	Yes	Yes
Singh 2014[24]	**1729**	**24**	No	Yes	No	No	Yes	No	Yes	Yes*	Yes
ZuWallack 2014[26]	**2267**	**12**	No	No	No	No	No	No	No	No	Yes
Donohue 2013 [29]	**1532**	**24**	Yes	Yes	No	Yes	Yes	No	No	Yes*	Yes
Donohue 2014 [31]	**562**	**52**	No	No	No	No	No	No	No	No	Yes
DB2114417 2012 [32]	**641**	**12**	No	No	No	No	No	No	No	No	Yes¶
DB2114418 2012 [33]	**554**	**12**	No	No	No	No	No	No	No	No	Yes¶
Vincken 2014 [25]	**447**	**12**	Yes	No	No	No	No	No	No	No	Yes
Bateman 2013 [27]	**2135**	**26**	Yes	Yes	No	No	Yes	No	Yes	Yes*	Yes
Dahl 2013 [28]	**338**	**52**	No	No	No	No	No	No	No	No	Yes
Wedzicha 2013 [30]	**2205**	**64**	No	No	No	No	No	No	Yes	Yes¶	Yes
Novartis A1301 2012 [35]	**158**	**52**	No	No	No	No	No	No	No	No	No
Mahler 2012a [34]	**1131**	**12**	No	No	No	No	No	No	No	No	Yes
Mahler 2012b [34]	**1142**	**12**	No	No	No	No	No	No	No	No	Yes
Tashkin 2009 [36]	**243**	**12**	No*	No	No	No	No	No	No	No	Yes
Vogelmeier 2008 [37]	**847**	**24**	No	No	No	No	No	No	No	No	Yes
Aaron 2007 [38]	**304**	**52**	No	No	Yes	No	No	No	Yes	Yes	Yes

† Number of patients included in this study. *Insufficient data. ¶Data available for severe exacerbation only. HR= hazard ratio; No. =number; SE= standard error; TDI= Transitional Dyspnea Index.

			Cardiac SAE			total SAE		
Study, year	**No. of patients†**	**Duration of treatment (weeks)**	No. events/person years at risk	HR for first event (with SE)	No. events/no. of patients	No. events/person years at risk	HR for first event (with SE)	No. events/no. of patients
Buhl 2015[19]	**5162**	**52**	No	No	Yes	No	No	Yes
Celli 2014 [20]	**1489**	**24**	No	No	Yes	No	No	Yes
Decramer 2014a [21]	**843**	**24**	No	No	Yes	No	No	Yes
Decramer 2014b [21]	**869**	**24**	No	No	Yes	No	No	Yes
D'Urzo 2014[22]	**1669**	**24**	No	No	Yes	No	No	Yes
Maleki-Yazdi 2014[22]	**905**	**24**	No	No	Yes	No	No	Yes
Singh 2014[24]	**1729**	**24**	No	No	Yes	No	No	Yes
ZuWallack 2014[26]	**2267**	**12**	No	No	Yes	No	No	Yes
Donohue 2013 [29]	**1532**	**24**	No	No	Yes	No	No	Yes
Donohue 2014 [31]	**562**	**52**	No	No	Yes	No	No	Yes
DB2114417 2012 [32]	**641**	**12**	No	No	Yes	No	No	Yes
DB2114418 2012 [33]	**554**	**12**	No	No	No	No	No	Yes
Vincken 2014 [25]	**447**	**12**	No	No	Yes	No	No	Yes
Bateman 2013 [27]	**2135**	**26**	No	No	Yes	No	No	Yes
Dahl 2013 [28]	**338**	**52**	No	No	Yes	No	No	Yes
Wedzicha 2013 [30]	**2205**	**64**	No	No	Yes	No	No	Yes
Novartis A1301 2012 [35]	**158**	**52**	No	No	No	No	No	Yes
Mahler 2012a [34]	**1131**	**12**	No	No	Yes	No	No	Yes
Mahler 2012b [34]	**1142**	**12**	No	No	Yes	No	No	Yes
Tashkin 2009 [36]	**243**	**12**	No	No	No	No	No	Yes
Vogelmeier 2008 [37]	**847**	**24**	No	No	Yes	No	No	Yes
Aaron 2007 [38]	**304**	**52**	No	No	No	No	No	Yes

† Number of patients included in this study. HR= hazard ratio; No.= number; SAE= severe adverse event; SE= standard error

			Mortality			Dropouts due to AE		
Study, year	**No. of patients†**	**Duration of treatment (weeks)**	No. events/person years at risk	HR for first event (with SE)	No. events/number of patients	No. events/person years at risk	HR for first event (with SE)	No.events/number of patients
Buhl 2015[19]	**5162**	**52**	No	No	Yes	No	No	Yes
Celli 2014 [20]	**1489**	**24**	No	No	Yes	No	No	Yes
Decramer 2014a [21]	**843**	**24**	No	No	Yes	No	No	Yes
Decramer 2014b [21]	**869**	**24**	No	No	Yes	No	No	Yes
D'Urzo 2014[22]	**1669**	**24**	No	No	Yes	No	No	Yes
Maleki-Yazdi 2014[22]	**905**	**24**	No	No	Yes	No	No	Yes
Singh 2014[24]	**1729**	**24**	No	No	No	No	No	Yes
ZuWallack 2014[26]	**2267**	**12**	No	No	Yes	No	No	Yes
Donohue 2013 [29]	**1532**	**24**	No	No	Yes	No	No	Yes
Donohue 2014 [31]	**562**	**52**	No	No	Yes	No	No	Yes
DB2114417 2012 [32]	**641**	**12**	No	No	Yes	No	No	Yes
DB2114418 2012 [33]	**554**	**12**	No	No	No	No	No	Yes
Vincken 2014 [25]	**447**	**12**	No	No	Yes¶	No	No	Yes
Bateman 2013 [27]	**2135**	**26**	No	No	Yes	No	No	Yes
Dahl 2013 [28]	**338**	**52**	No	Yes	Yes	No	No	Yes
Wedzicha 2013 [30]	**2205**	**64**	No	No	Yes	No	No	Yes
Novartis A1301 2012 [35]	**158**	**52**	No	No	Yes	No	No	Yes
Mahler 2012a [34]	**1131**	**12**	No	No	Yes	No	No	Yes
Mahler 2012b [34]	**1142**	**12**	No	No	Yes	No	No	Yes
Tashkin 2009 [36]	**243**	**12**	No	No	Yes¶	No	No	No
Vogelmeier 2008 [37]	**847**	**24**	No	No	Yes	No	No	No
Aaron 2007 [38]	**304**	**52**	No	No	Yes	No	No	Yes

† Number of patients included in this study. ¶ No fatal events. HR= hazard ratio; AE= adverse event; No.= number; SE= standard error

Table S10. Summary effects of LABA/LAMA combination therapy with pairwise and network meta-analyses.

Outcome	vs. placebo	vs. LABA	vs. LAMA
CFB in FEV1 (L) WMD RE at 3 mo	0.21(0.20, 0.24)	0.11(0.09, 0.12)	0.06(0.05, 0.07)
CFB in FEV1 (L) WMD FE at 3 mo	0.21(0.20, 0.23)	0.11(0.09, 0.12)	0.06(0.05, 0.07)
CFB in FEV1 (L) Network MD RE at 3 mo	0.21(0.19, 0.23)	0.10(0.07, 0.12)	0.06(0.05, 0.08)
CFB in FEV1 (L) WMD RE at 6 mo	0.17(0.12, 0.21)	0.08(0.06, 0.10)	0.07(0.04, 0.10)
CFB in FEV1 (L) WMD FE at 6 mo	0.16(0.14, 0.18)	0.08(0.06, 0.09)	0.06(0.05, 0.07)
CFB in FEV1 (L) MD Network RE at 6 mo	0.17(0.12, 0.21)	0.08(0.06, 0.10)	0.05(0.03, 0.07)
CFB in FEV1 (L) WMD RE at 12 mo	0.24(0.17, 0.30)	NA	0.08(0.02, 0.13)
CFB in FEV1 (L) WMD FE at 12 mo	0.24(0.17, 0.30)	NA	0.07(0.04, 0.10)
CFB in FEV1 (L) MD Network RE at 12 mo	0.24(0.14, 0.35)	NA	0.07(0.04, 0.15)
CFB in SGRQ WMD RE at 3 mo	-4.4(-5.8, -3.0)	-2.1(-3.2, -1.0)	-2.3(-2.9, -1.7)
CFB in SGRQ WMD FE at 3 mo	-4.4(-5.8, -3.0)	-2.1(-3.2, -1.0)	-2.3(-2.9, -1.7)
CFB in SGRQ MD Network FE at 3 mo	-4.6(-5.9, -3.3)	-2.3(-3.3, -1.3)	-2.3(-2.9, -1.7)
CFB in SGRQ WMD RE at 6 mo	-3.6(-5.0, -2.2)	-1.5(-2.4, -0.6)	-1.6(-2.3, -0.8)
CFB in SGRQ WMD FE at 6 mo	-3.6(-4.6, -2.6)	-1.5(-2.3, -0.7)	-1.6(-2.2, -0.9)
CFB in SGRQ MD Network RE at 6 mo	-3.6(-4.9, -2.4)	-1.5(-2.5, -0.3)	-1.5(-2.4, -0.6)
Proportion of SGRG responders OR RE at 6 mo	1.62(1.37, 1.92)	1.12(0.98, 1.28)	1.22(1.12, 1.34)
Proportion of SGRG responders OR FE at 6 mo	1.62(1.40, 1.88)	1.12(0.98, 1.28)	1.23(1.12, 1.34)
Proportion of SGRG responders OR Network OR RE at 6 mo	1.66(1.41, 1.95)	1.23(1.06, 1.39)	1.24(1.11, 1.36)
TDI WMD RE at 3 mo	1.21(0.93, 1.48)	0.34(0.13, 0.54)	0.39(0.20, 0.57)
TDI WMD FE at 3 mo	1.21(0.93, 1.48)	0.34(0.13, 0.54)	0.39(0.20, 0.57)
TDI Network MD FE at 3 mo	1.21(0.95, 1.48)	0.37(0.16, 0.57)	0.41(0.23, 0.59)

TDI WMD RE at 6 mo	1.19(0.96, 1.41)	0.40(0.26, 0.53)	0.34(0.22, 0.46)
TDI WMD FE at 6 mo	1.19(0.96, 1.41)	0.40(0.26, 0.53)	0.34(0.22, 0.46)
TDI Network MD FE at 6 mo	1.17(0.96, 1.38)	0.40(0.26, 0.53)	0.35(0.24, 0.47)
Proportion of TDI responders OR RE at 6 mo	2.11(1.73, 2.58)	1.34(1.19, 1.51)	1.29(1.16, 1.44)
Proportion of TDI responders OR FE at 6 mo	2.16(1.83, 2.45)	1.34(1.19, 1.50)	1.31(1.18, 1.46)
Proportion of TDI responders OR FE Network at 6 mo	2.12(1.76, 2.50)	1.34(1.16, 1.56)	1.30(1.13, 1.48)
Moderate-to-severe exacerbations OR RE	0.60(0.45, 0.79)	0.74(0.61, 0.88)	0.90(0.81, 1.00)
Moderate-to-severe exacerbations OR FE	0.60(0.50, 0.74)	0.74(0.62, 0.89)	**0.90(0.82, 0.99)**
Moderate-to-severe exacerbations Network HR RE	0.66 (0.57, 0.77)	0.82 (0.73, 0.93)	0.92(0.84, 1.00)
Severe exacerbations OR RE	0.72(0.46, 1.13)	0.94(0.72, 1.22)	0.94(0.77, 1.14)
Severe exacerbations OR FE	0.75(0.48, 1.16)	0.95(0.74, 1.23)	0.97(0.83, 1.13)
Severe exacerbations Network HR FE	0.74(0.50, 1.10)	0.97(0.77, 1.24)	0.92(0.79, 1.08)
Mortality OR RE	1.08(0.37, 3.18)	0.96(0.56, 1.65)	0.81(0.60, 1.08)
Mortality OR FE	1.13(0.43, 2.95)	0.94(0.56, 1.58)	0.81(0.60, 1.08)
Mortality Network HR FE	1.95(0.73, 7.71)	0.99(0.61, 1.66)	0.87(0.64, 1.16)
Total SAEs OR RE	1.03(0.82, 1.31)	0.96(0.83, 1.12)	1.04(0.94, 1.15)
Total SAEs OR FE	1.04(0.81, 1.31)	0.96(0.83, 1.12)	1.04(0.94, 1.15)
Total SAEs Network HR FE	1.10(0.89, 1.38)	0.96(0.84, 1.10)	1.04(0.95, 1.14)
Cardiac SAEs OR RE	1.25(0.63, 2.48)	0.82(0.46, 1.48)	0.90(0.70, 1.17)
Cardiac SAEs OR FE	1.42(0.74, 2.70)	0.86(0.57, 1.29)	0.89(0.70, 1.14)
Cardiac SAEs Network HR RE	1.65(0.81, 3.35)	0.82(0.46, 1.35)	0.87 (0.59, 1.27)
Dropouts due to AE OR RE	0.92(0.68, 1.25)	0.87(0.62, 1.22)	0.98(0.82, 1.16)
Dropouts due to AE OR FE	0.94(0.73, 1.21)	0.83(0.68, 1.03)	0.98(0.84, 1.14)
Dropouts due to AE Network HR RE	0.96(0.71, 1.28)	0.92(0.71, 1.19)	**1.03**(0.84, 1.26)

Abbreviations: AE=adverse event; CFB=change from baseline; FE=fixed effects; FEV1= forced expiratory volume in 1 second; HR= hazard ratio; LABA= long-acting beta-agonist; LAMA=long-acting muscarinic antagonist; MD=mean difference; mo=months; NA=not applicable (no direct comparison); OR=odds ratio; RE=random effects; SAE=serious adverse event; SGRQ=St. George's Respiratory Questionnaire; TDI=Transitional Dyspnea Index; WME=weighted mean difference. **Bold type** font indicates inconsistency between network and pairwise meta-analyses.

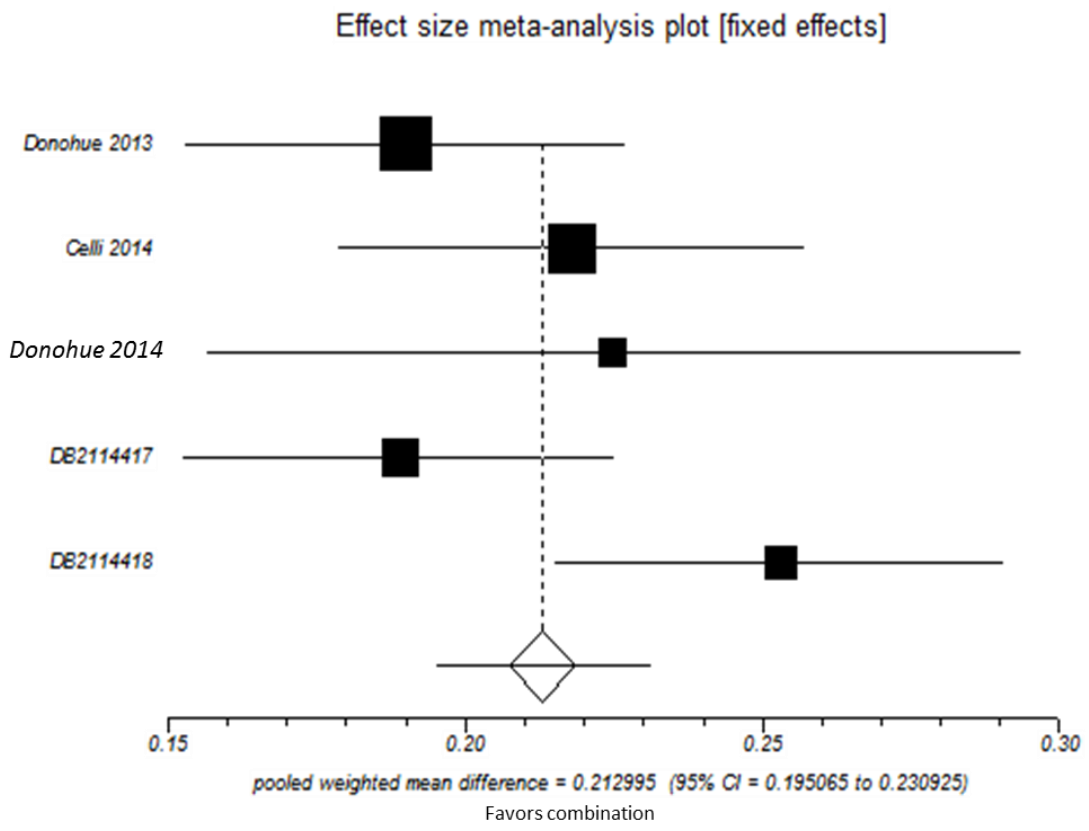

Figure S1-1. Summary effects of LABA/LAMA combination vs. placebo on changes in trough FEV1 from baseline at 3 months. Cohran Q = 7.641004 (df = 4) P = 0.1056 Moment-based estimate of between studies variance = 0.000391. I^2 (inconsistency) = 47.7% (95% CI = 0% to 79.1%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

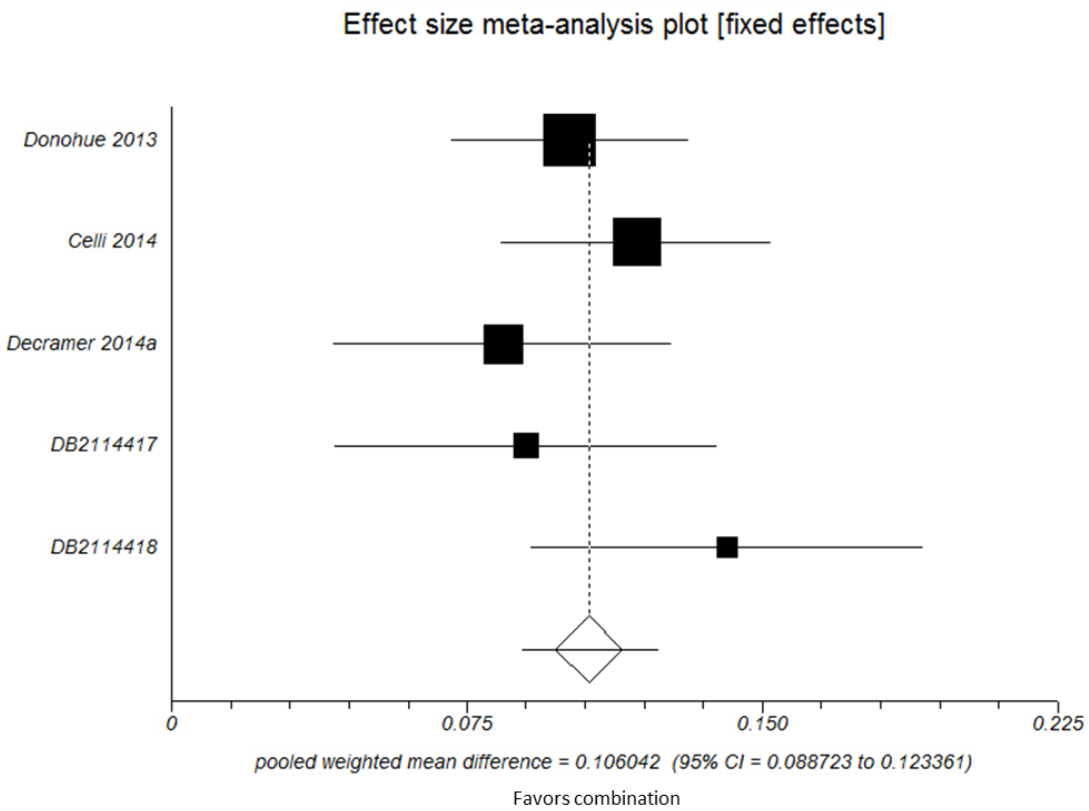

Figure S1-2. Summary effects of LABA/LAMA combination vs. LABA on changes in trough FEV1 from baseline at 3 months. Cohran Q = 3.904884 (df = 4) P = 0.419 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 64.1%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

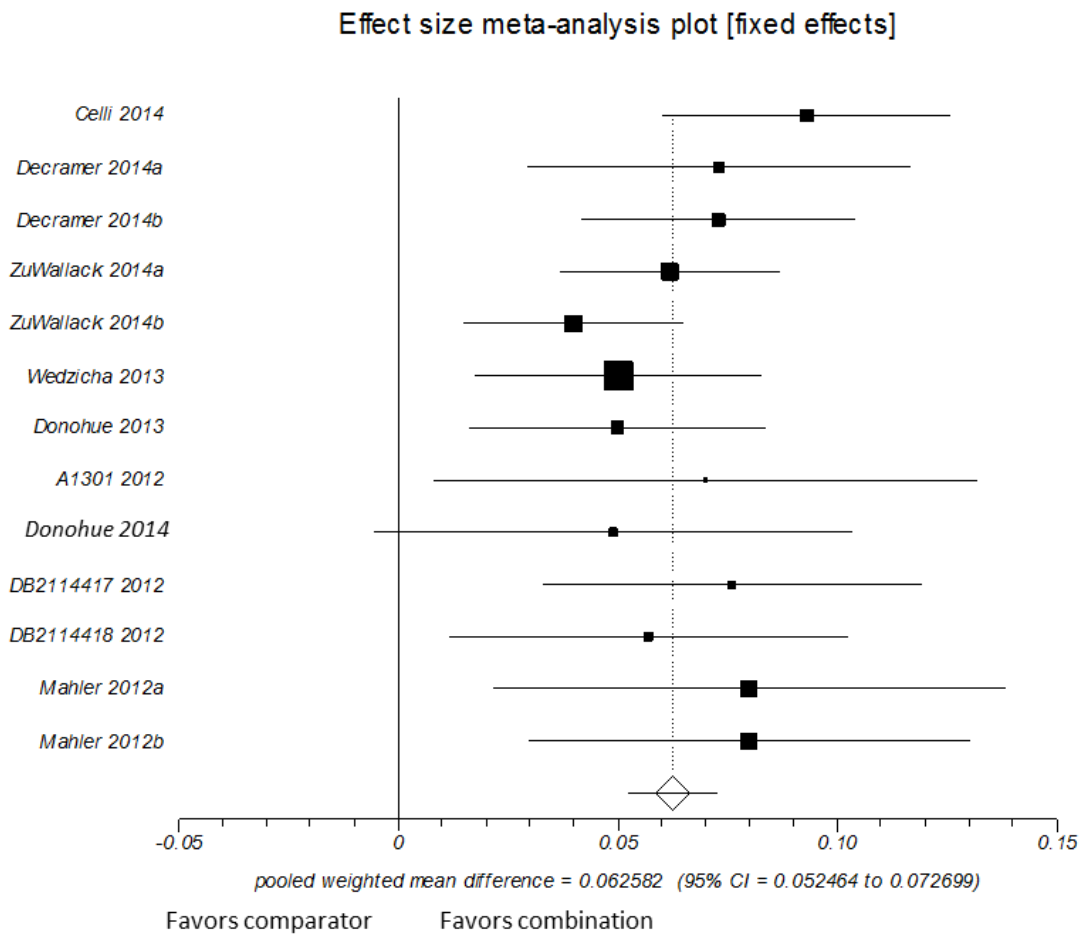

Figure S1-3. Summary effects of LABA/LAMA combination vs. LAMA on changes in trough FEV1 from baseline at 3 months. Cohran Q = 9.720337 (df = 12) P = 0.6405 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 48.6%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA=long-acting muscarinic antagonist

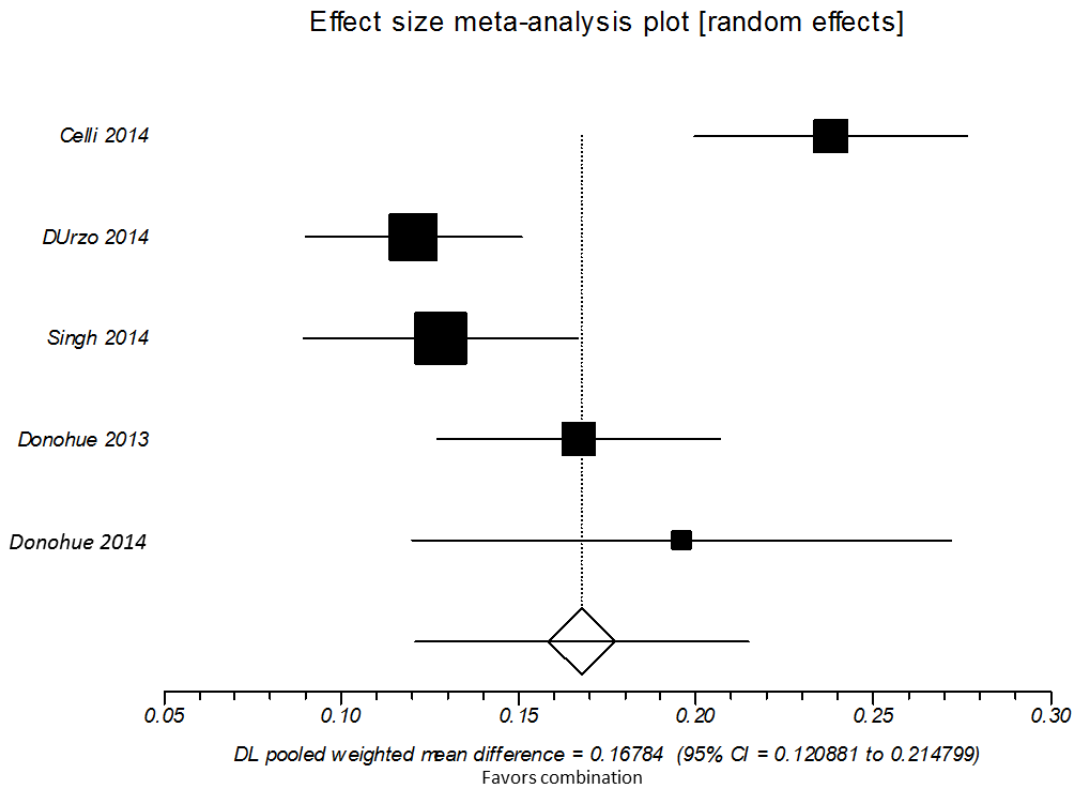

Figure S1-4. Summary effects of LABA/LAMA combination vs. placebo on changes in trough FEV1 from baseline at 6 months. Cohran Q = 26.286847 (df = 4) P < 0.0001Moment-based estimate of between studies variance = 0.002349. I^2 (inconsistency) = 84.8% (95% CI = 59.7% to 91.7%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

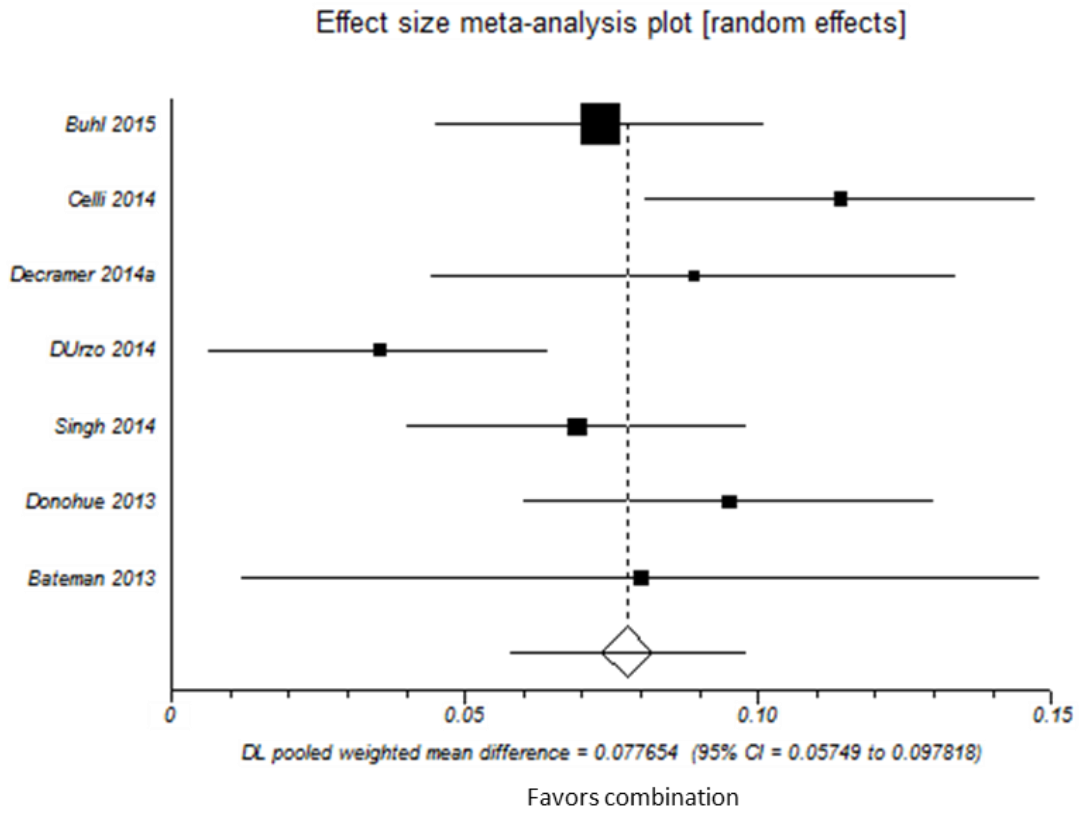

Figure S1-5. Summary effects of LABA/LAMA combination vs. LABA on changes in trough FEV1 from baseline at 6 months. Cohran Q = 14.375251 (df = 6) P = 0.0257. Moment-based estimate of between studies variance = 0.00041. I^2 (inconsistency) = 58.3% (95% CI = 0% to 80%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

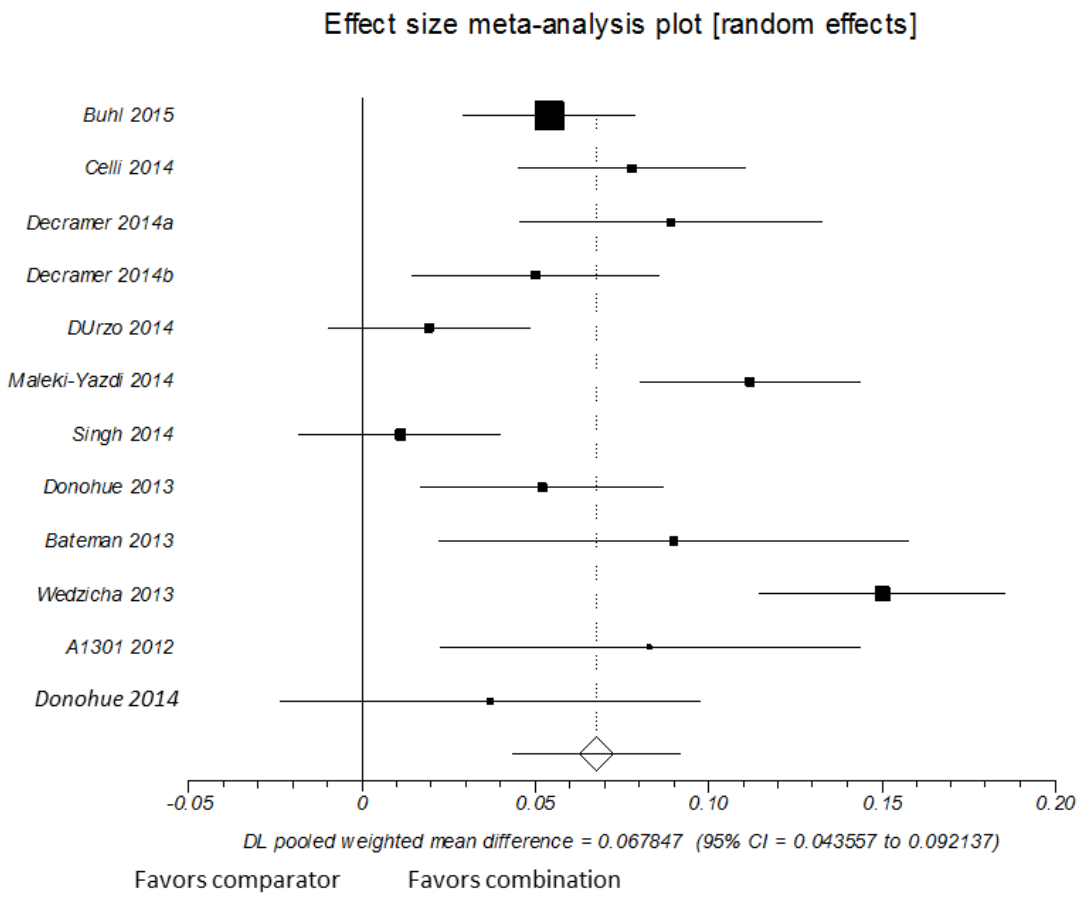

Figure S1-6. Summary effects of LABA/LAMA combination vs. LAMA on changes in trough FEV1 from baseline at 6 months. Cohran Q = 57.726416 (df = 10) P < 0.0001. Moment-based estimate of between studies variance = 0.001736. I^2 (inconsistency) = 82.7% (95% CI = 68.9% to 88.7%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

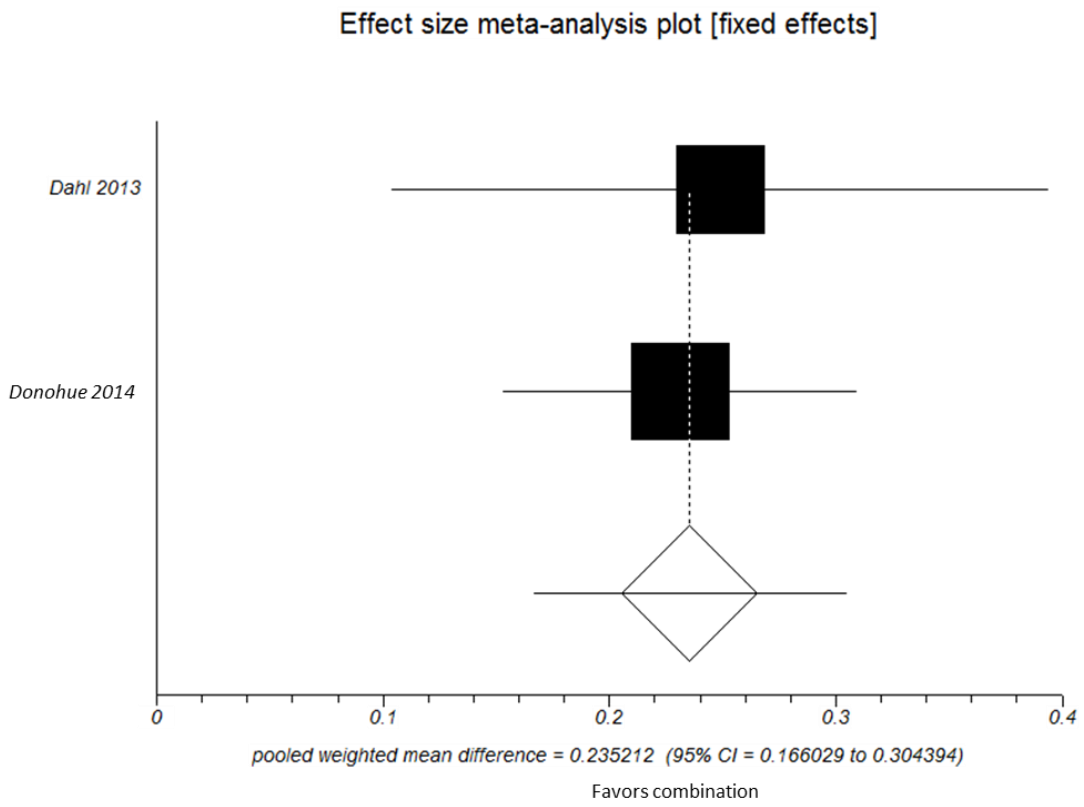

Figure S1-7. Summary effects of LABA/LAMA combination vs. placebo on changes in trough FEV1 from baseline at 12 months. Cohran Q = 0.046609 (df = 1) P = 0.8291 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = *% (95% CI = *% to *%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

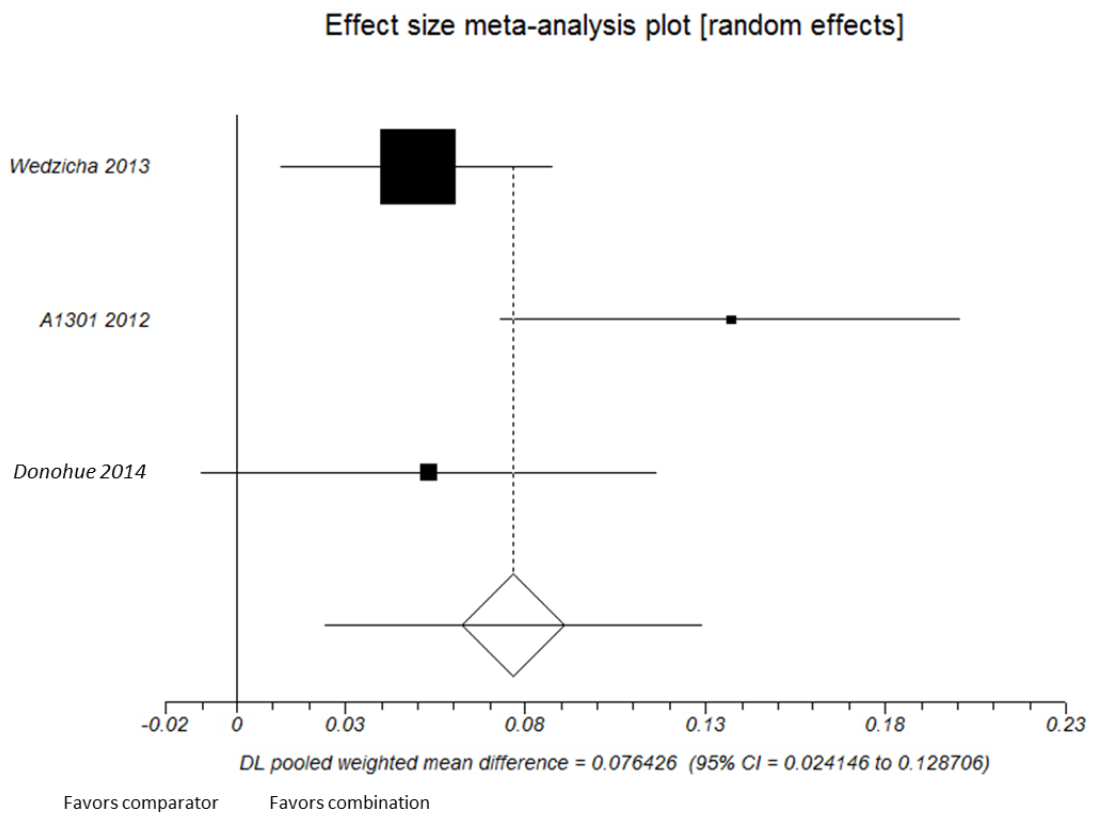

Figure S1-8. Summary effects of LABA/LAMA combination vs. LAMA on changes in trough FEV1 from baseline at 12 months. Cohran Q = 5.593655 (df = 2) P = 0.061 Moment-based estimate of between studies variance = 0.001365. I^2 (inconsistency) = 64.2% (95% CI = 0% to 87.7%) Note: Difference in change from baseline in liters (95% CI) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

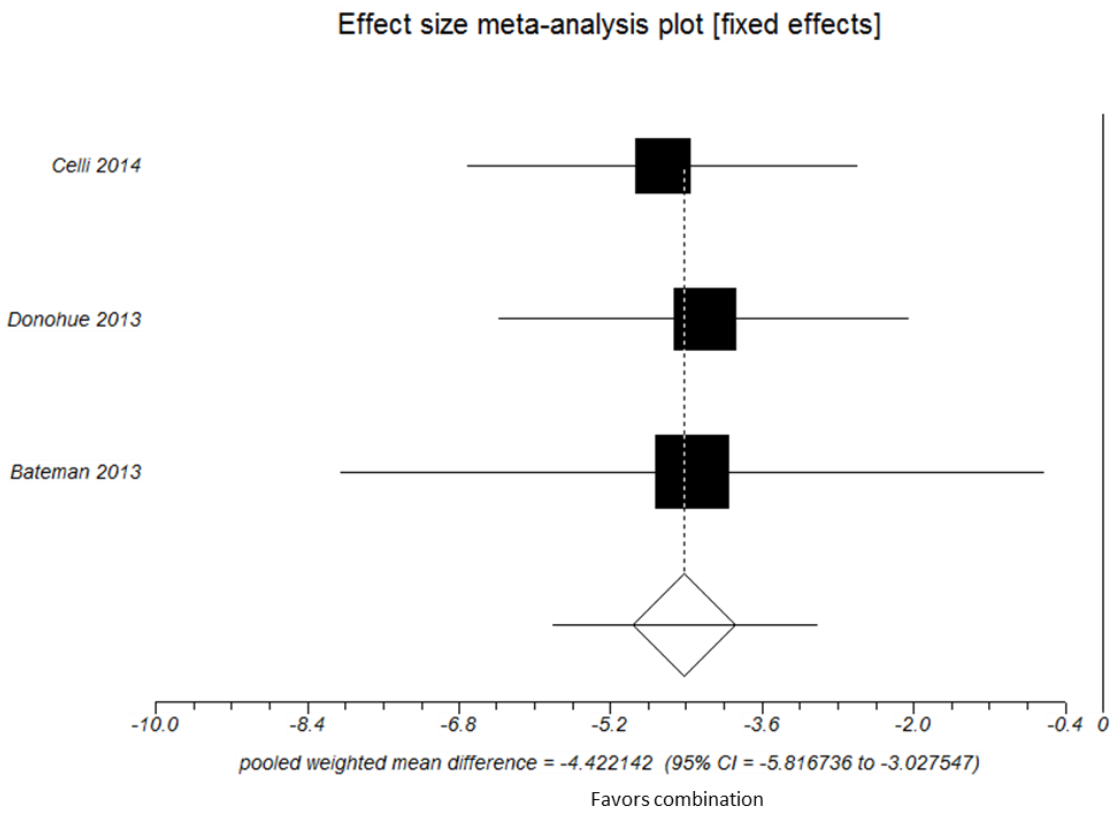

Figure S2-1. Summary effects of LABA/LAMA combination vs. placebo on changes in St. George's Respiratory Questionnaire at 3 months. A difference of at least four units is considered clinically significant. Cohran Q = 0.083782 (df = 2) P = 0.959 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 72.9%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

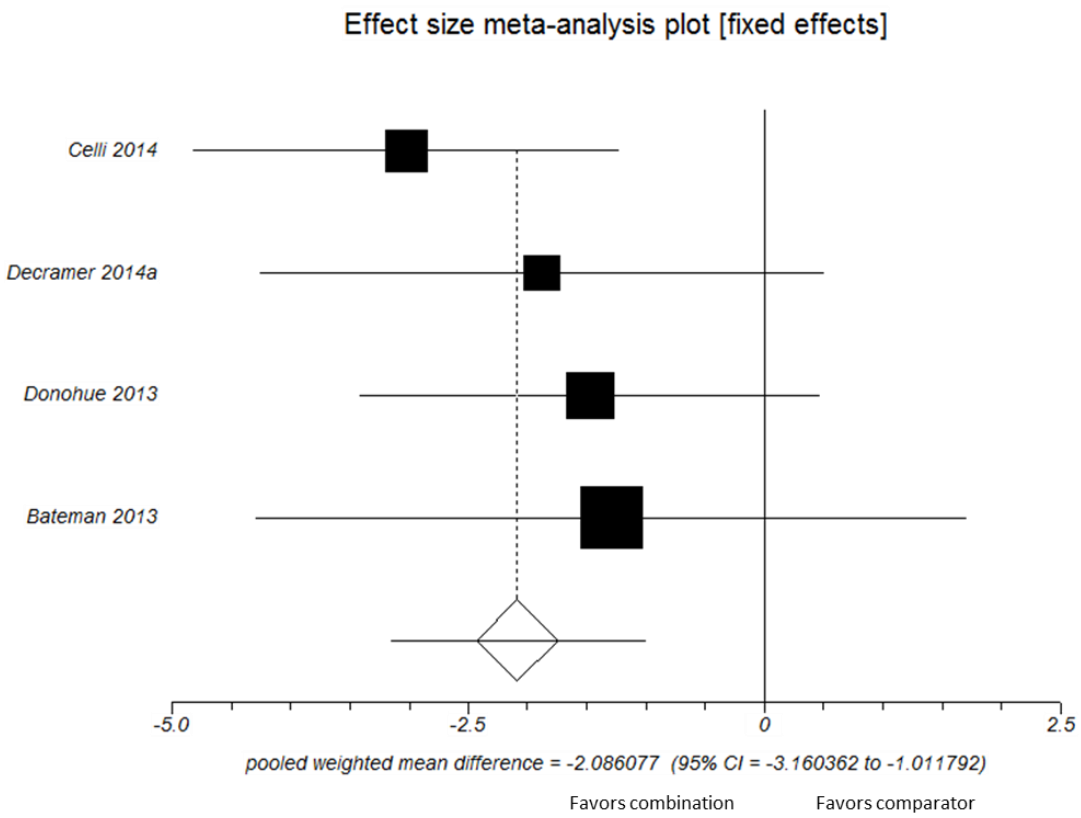

Figure S2-2. Summary effects of LABA/LAMA combination vs. LABA on changes in St. George's Respiratory Questionnaire at 3 months. A difference of at least four units is considered clinically significant. Cohran Q = 1.721374 (df = 3) P = 0.6322 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 67.9%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

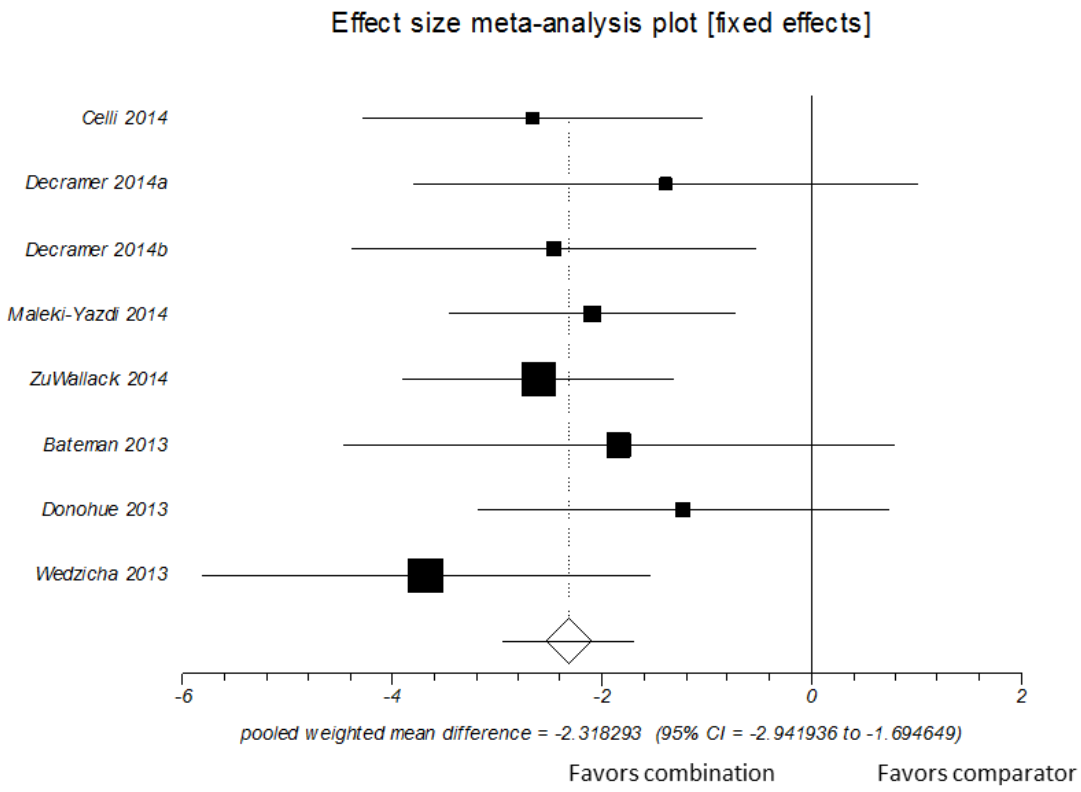

Figure S2-3. Summary effects of LABA/LAMA combination vs. LAMA on changes in St. George's Respiratory Questionnaire at 3 months. A difference of at least four units is considered clinically significant. Cohran Q = 3.612398 (df = 5) P = 0.6065 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 61%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

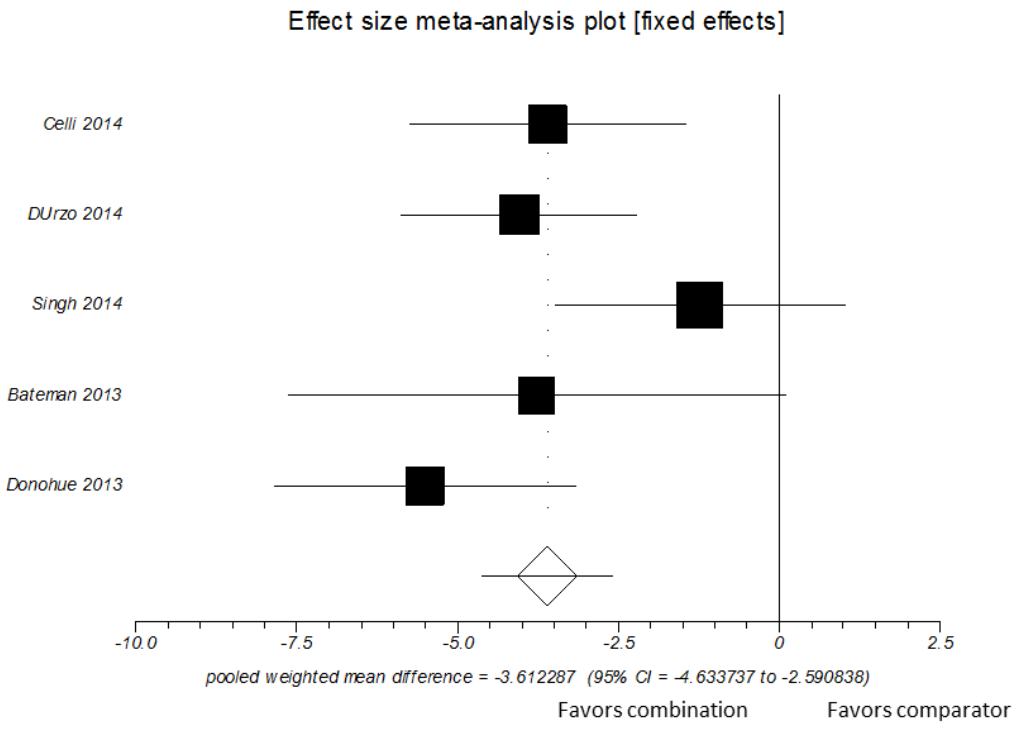

Figure S2-4. Summary effects of LABA/LAMA combination vs. placebo on changes in St. George's Respiratory Questionnaire at 6 months. A difference of at least four units is considered clinically significant. Cohran Q = 7.013603 (df = 4) P = 0.1352. Moment-based estimate of between studies variance = 1.060528. I^2 (inconsistency) = 43% (95% CI = 0% to 77.7%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

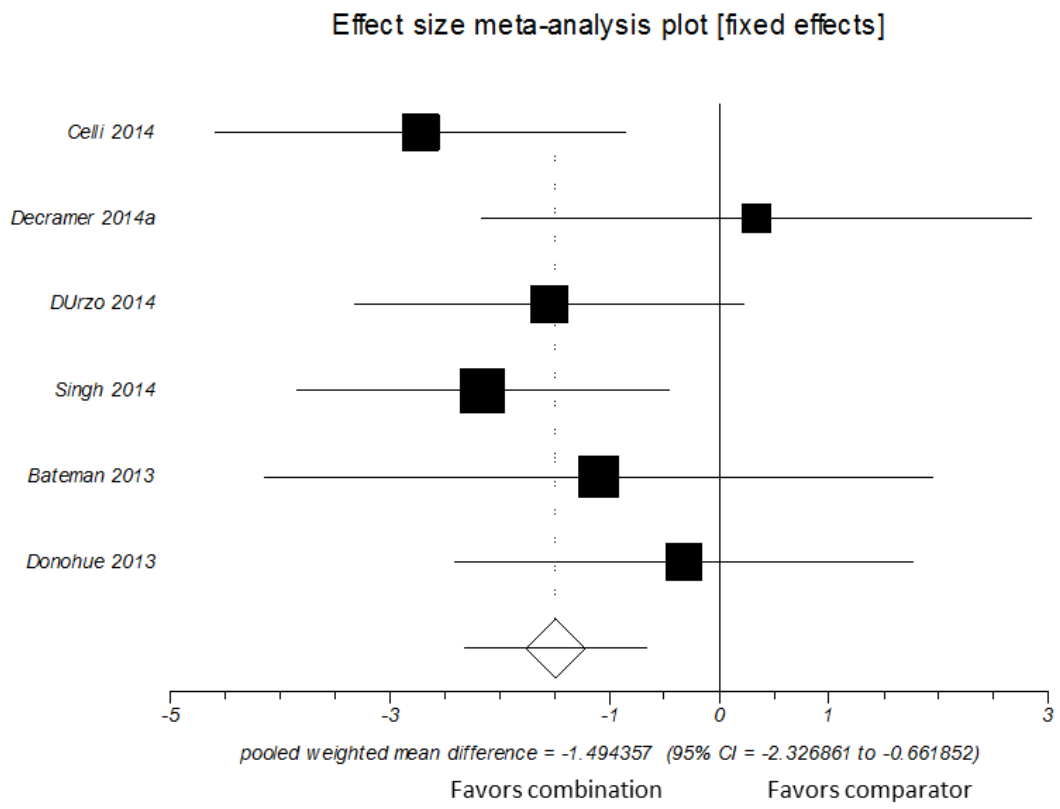

Figure S2-5. Summary effects of LABA/LAMA combination vs. LABA on changes in St. George's Respiratory Questionnaire at 6 months. A difference of at least four units is considered clinically significant. Cohran Q = 5.54226 (df = 5) P = 0.3533. Moment-based estimate of between studies variance = 0.120466. I^2 (inconsistency) = 9.8% (95% CI = 0% to 64.7%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

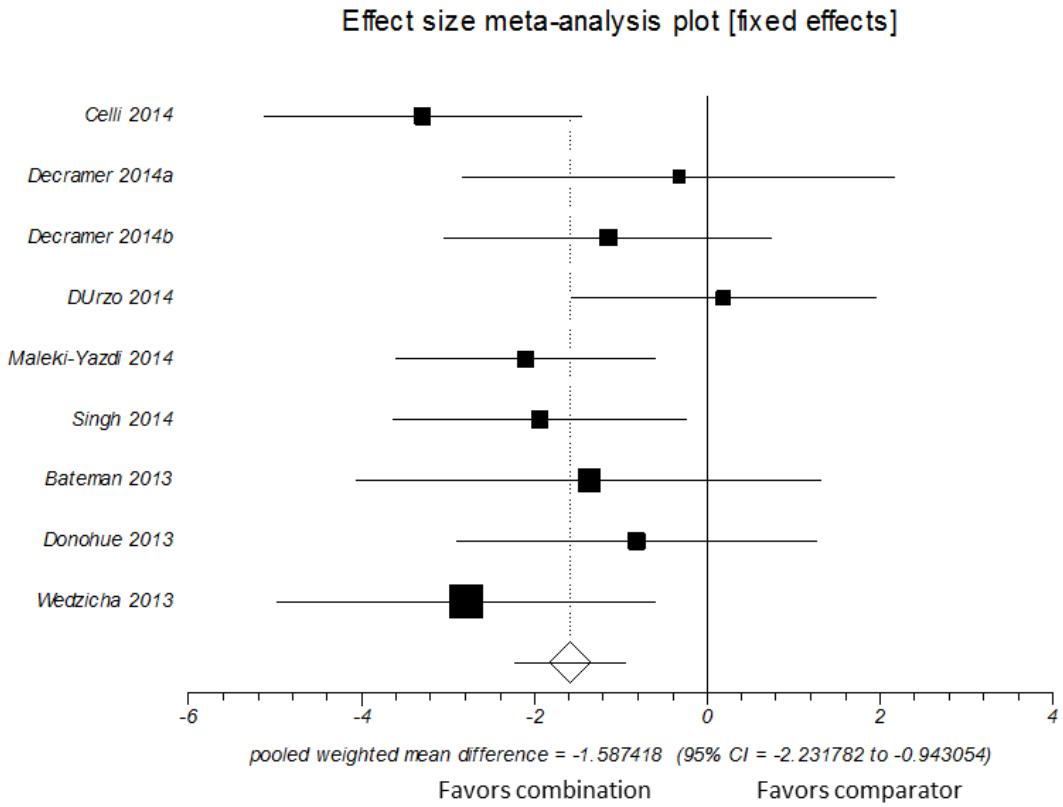

Figure S2-6. Summary effects of LABA/LAMA combination vs. LAMA on changes in St. George's Respiratory Questionnaire at 6 months. A difference of at least four units is considered clinically significant. Cohran Q = 10.594719 (df = 8) P = 0.2257. Moment-based estimate of between studies variance = 0.320115. I^2 (inconsistency) = 24.5% (95% CI = 0% to 64.8%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

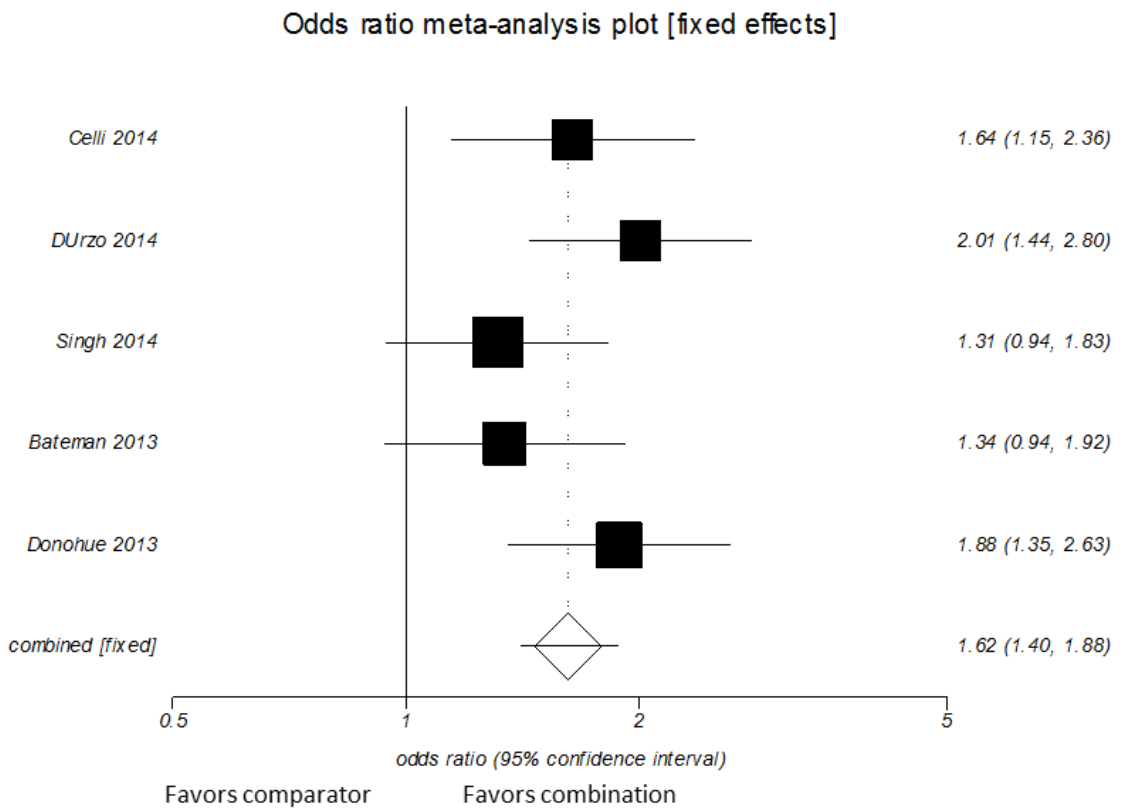

Figure S2-7. Summary effects of LABA/LAMA combination vs. placebo on proportion of SGRQ responders at 6 months. Cochran Q = 5.425332 (df = 4) P = 0.2464. Moment-based estimate of between studies variance = 0.009988. I^2 (inconsistency) = 26.3% (95% CI = 0% to 72.7%) Note: A responder was defined as a subject with an improvement of at least four units in SGRQ total score. Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; SGRQ= St. George's Respiratory Questionnaire

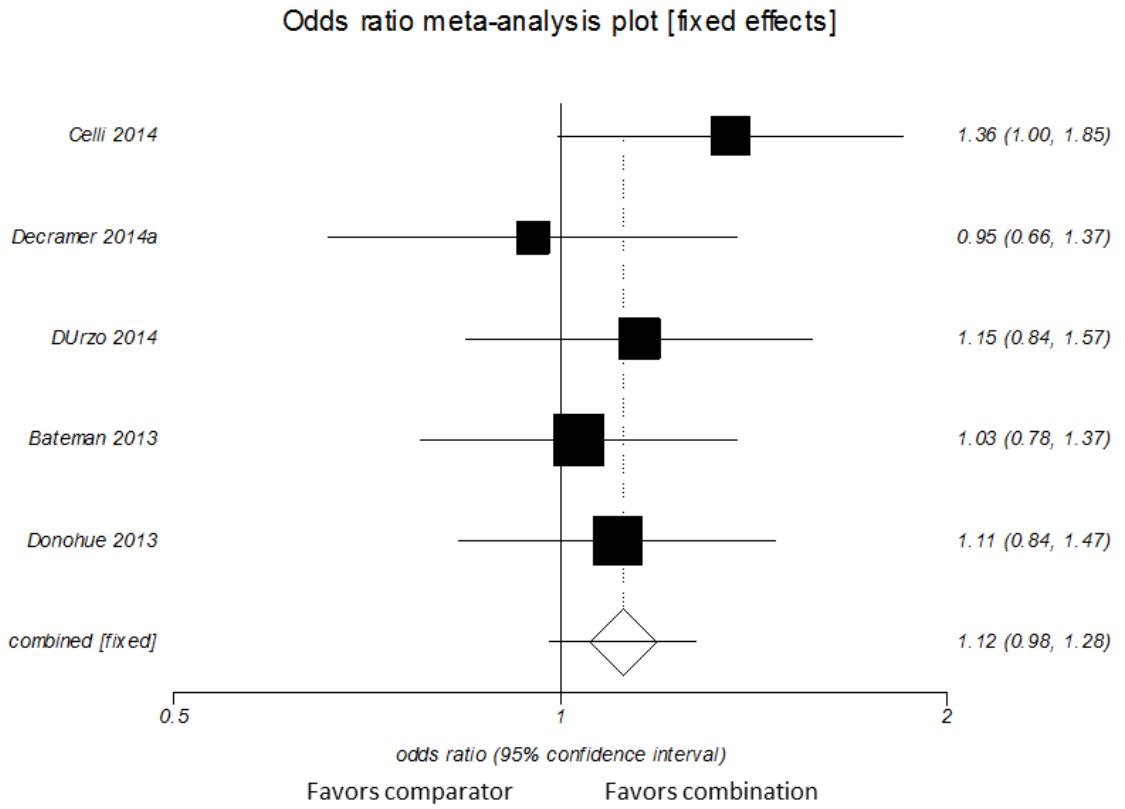

Figure S2-8. Summary effects of LABA/LAMA combination vs. LABA on proportion of SGRQ responders at 6 months. Cochran Q = 2.796806 (df = 4) P = 0.5924. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 64.1%) Note: A responder was defined as a subject with an improvement of at least four units in SGRQ total score. Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; SGRQ= St. George's Respiratory Questionnaire

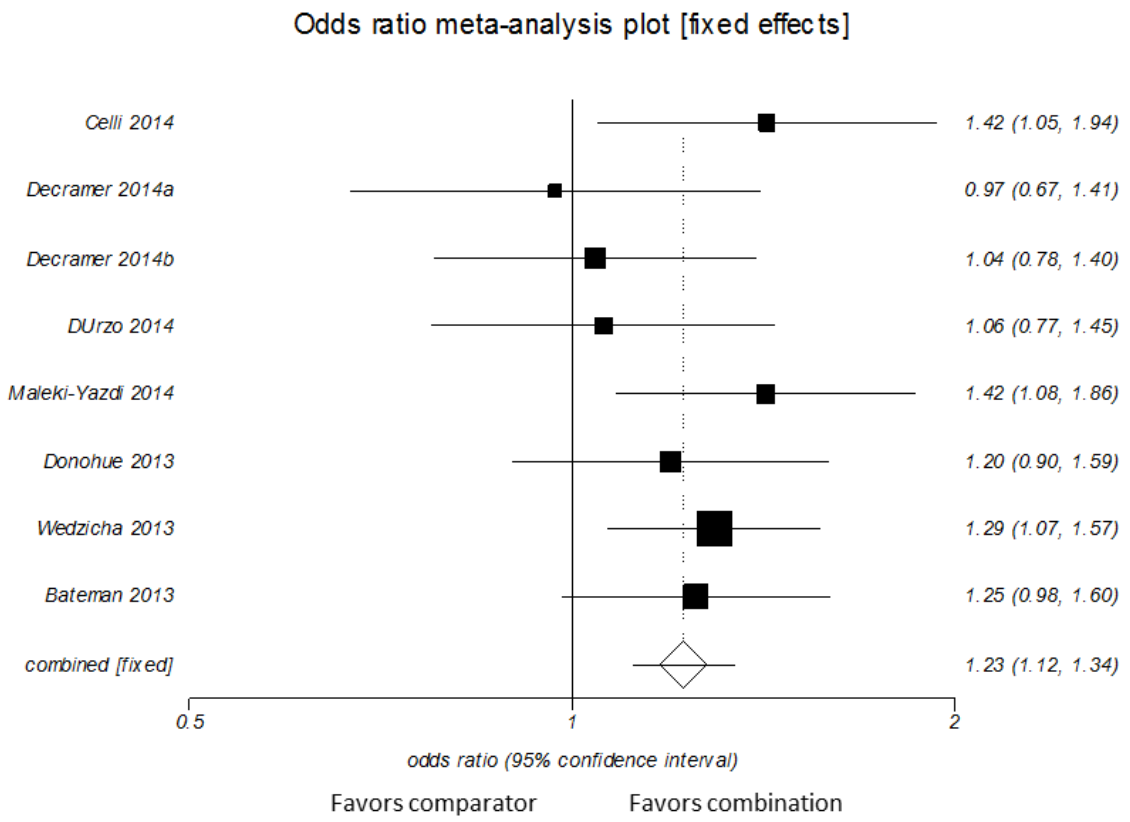

Figure S2-9. Summary effects of LABA/LAMA combination vs. LAMA on proportion of SGRQ responders at 6 months. Cochran Q = 6.434125 (df = 7) P = 0.4901. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 56.3%) Note: A responder was defined as a subject with an improvement of at least four units in SGRQ total score. Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; SGRQ= St. George's Respiratory Questionnaire

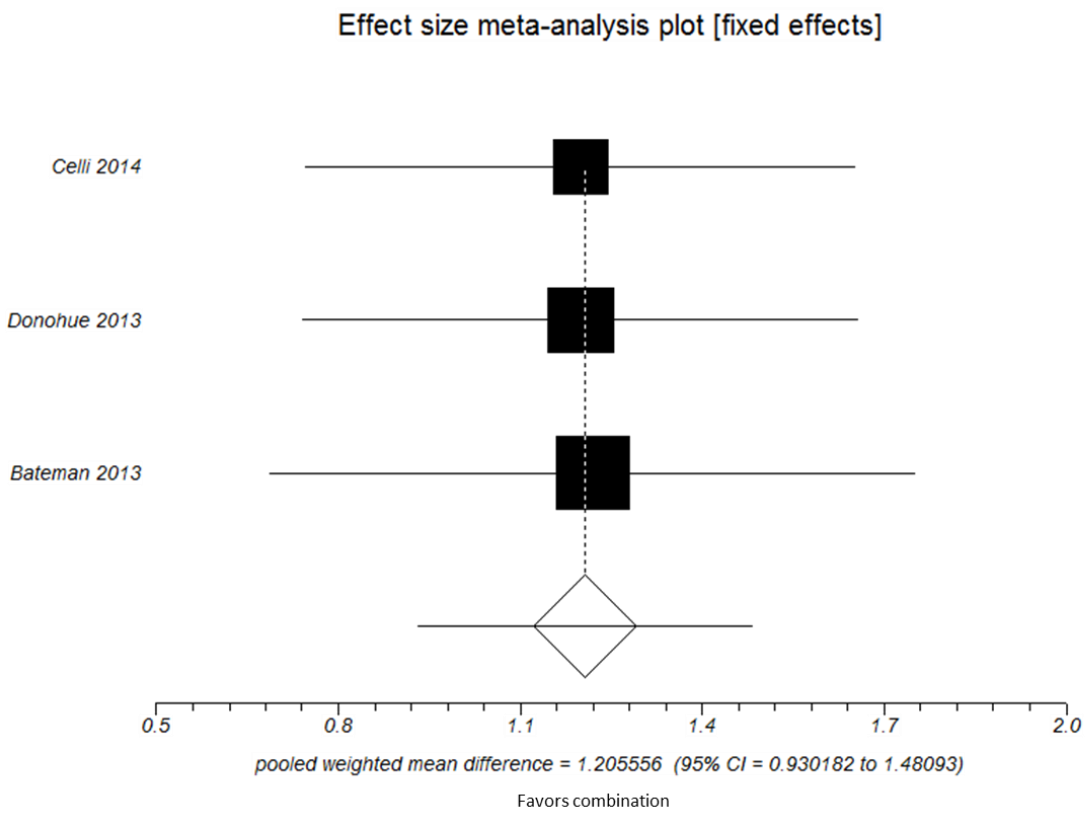

Figure S3-1. Summary effects of LABA/LAMA combination vs. placebo on changes in Transition Dyspnea Index at 3 months. A difference of at least one unit is considered clinically significant. Cohran Q = 0.004065 (df = 2) P = 0.998 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 72.9%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

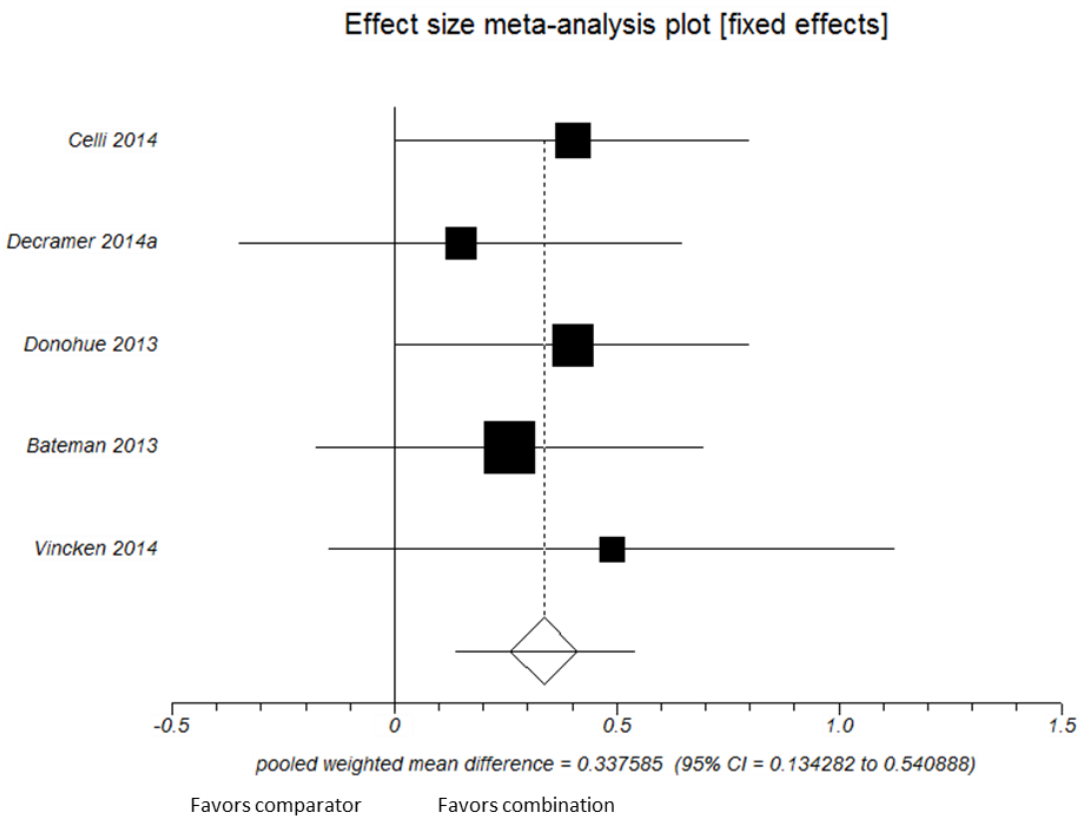

Figure S3-2. Summary effects of LABA/LAMA combination vs. LABA on changes in Transition Dyspnea Index at 3 months. A difference of at least one unit is considered clinically significant. Cohran Q = 1.066918 (df = 4) P = 0.8995 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 64.1%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

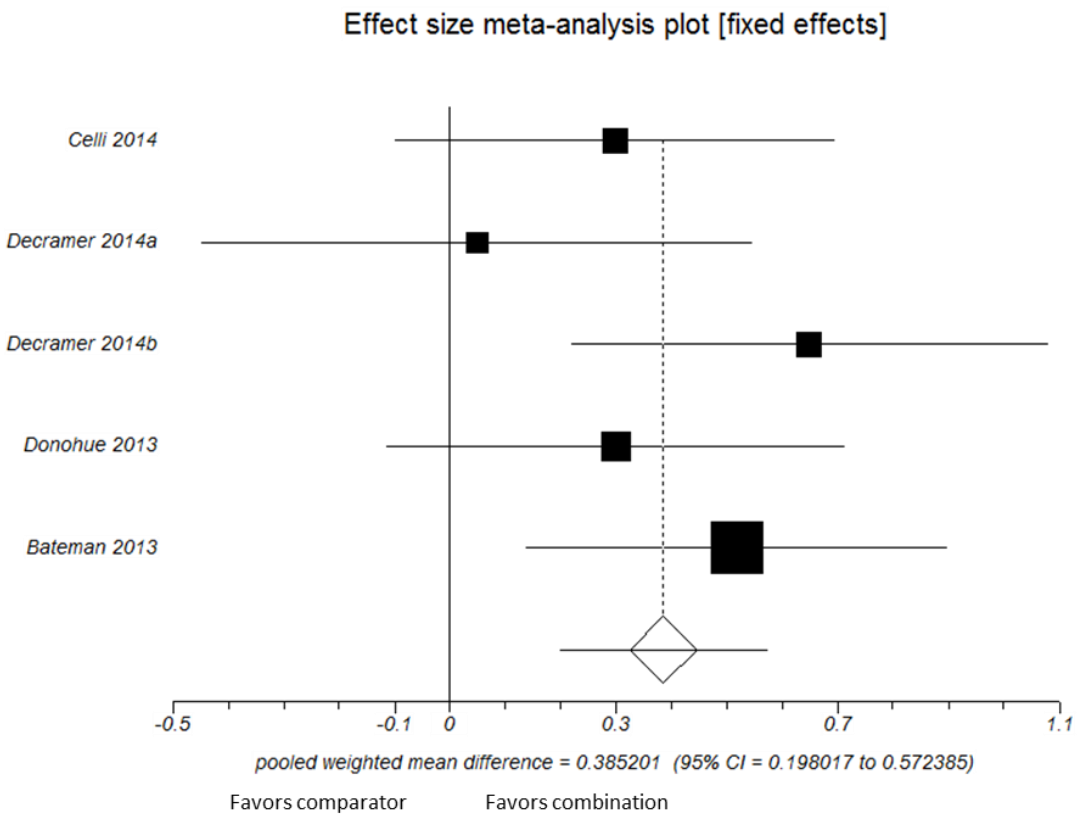

Figure S3-3. Summary effects of LABA/LAMA combination vs. LAMA on changes in Transition Dyspnea Index at 3 months. A difference of at least one unit is considered clinically significant. Cohran Q = 4.00438 (df = 4) P = 0.4054 Moment-based estimate of between studies variance = 0.00005. I^2 (inconsistency) = 0.1% (95% CI = 0% to 64.1%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

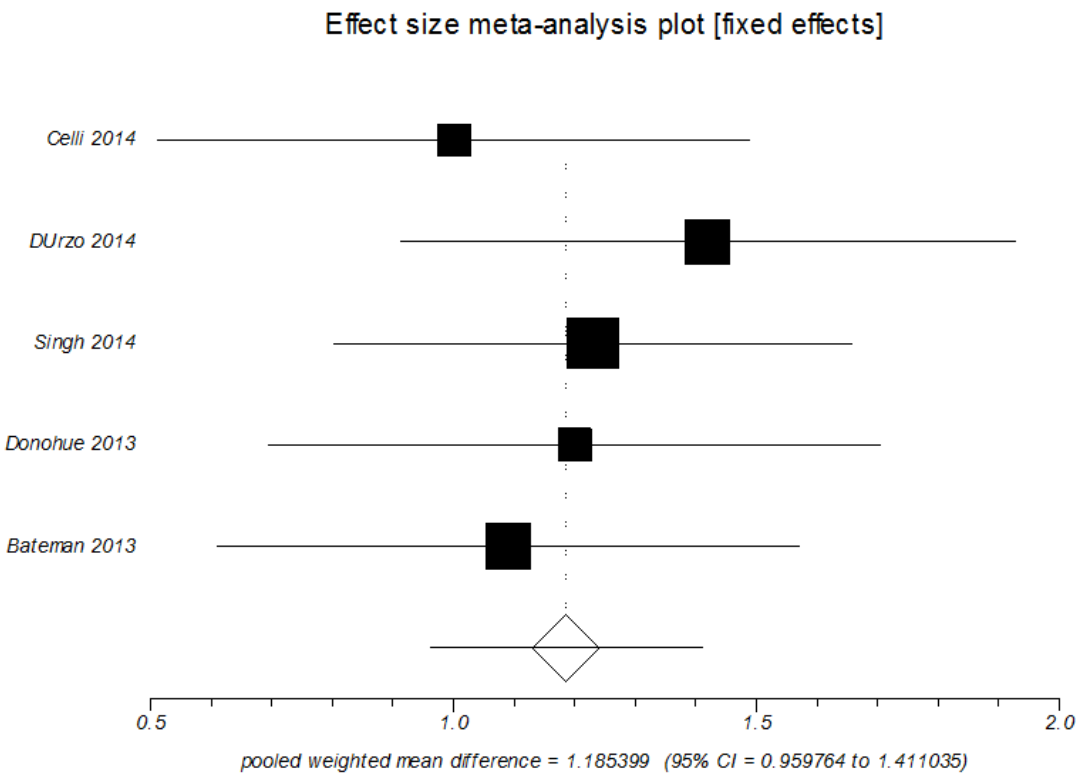

Figure S3-4. Summary effects of LABA/LAMA combination vs. placebo on changes in Transition Dyspnea Index at 6 months. A difference of at least one unit is considered clinically significant. Cohran Q = 1.517231 (df = 4) P = 0.8236. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 64.1%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

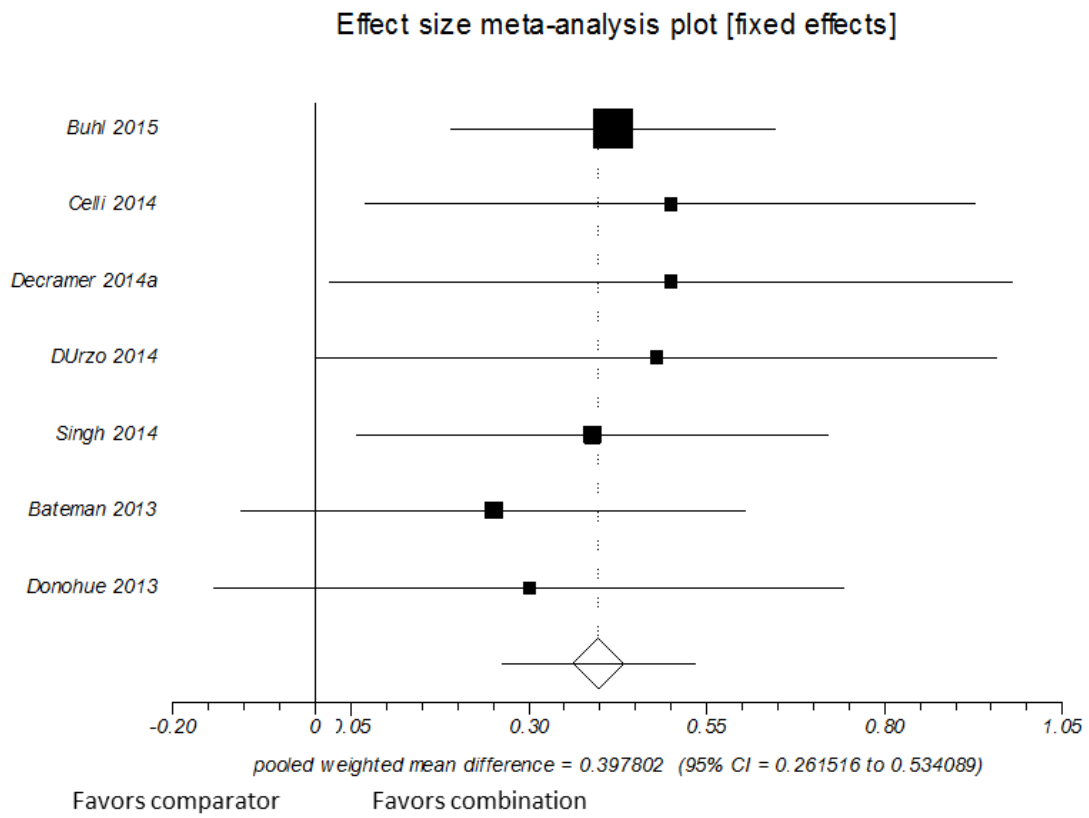

Figure S3-5. Summary effects of LABA/LAMA combination vs. LABA on changes in Transition Dyspnea Index at 6 months. A difference of at least one unit is considered clinically significant. Cohran Q = 1.38496 (df = 6) P = 0.9668. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 58.5%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

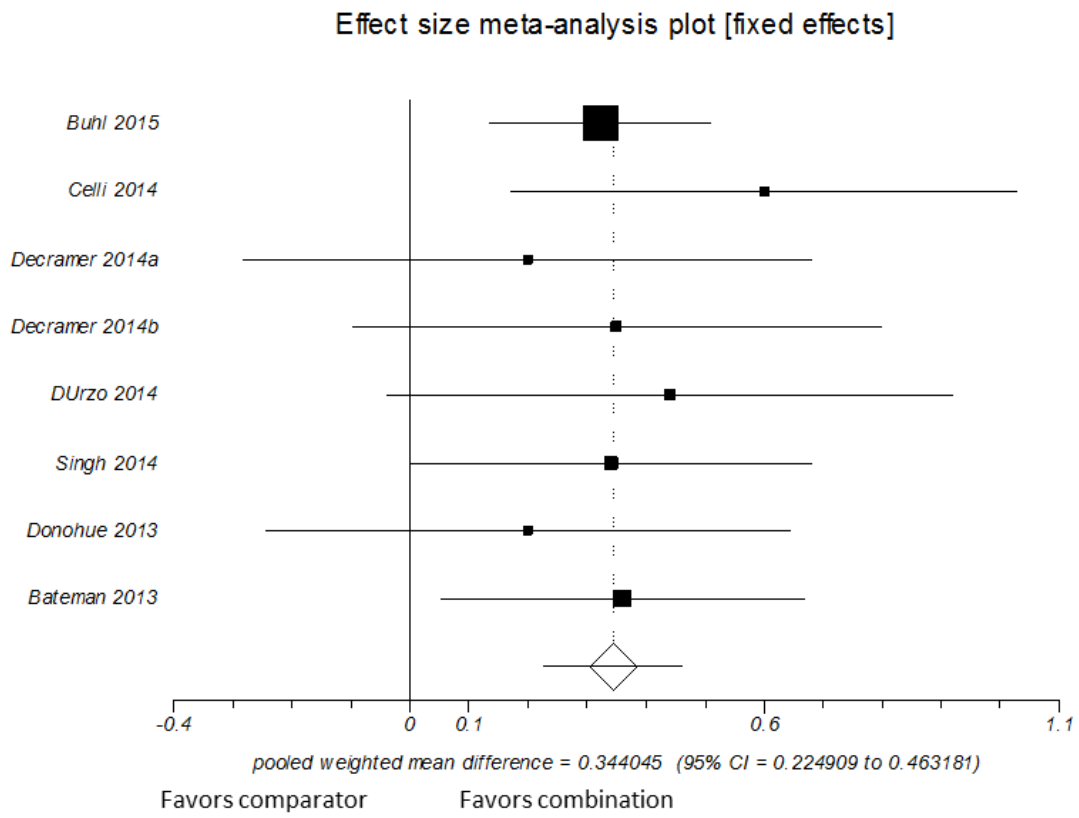

Figure S3-6. Summary effects of LABA/LAMA combination vs. LAMA on changes in Transition Dyspnea Index at 6 months. A difference of at least one unit is considered clinically significant. Cohran Q = 2.327427 (df = 7) P = 0.9395 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 56.3%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist

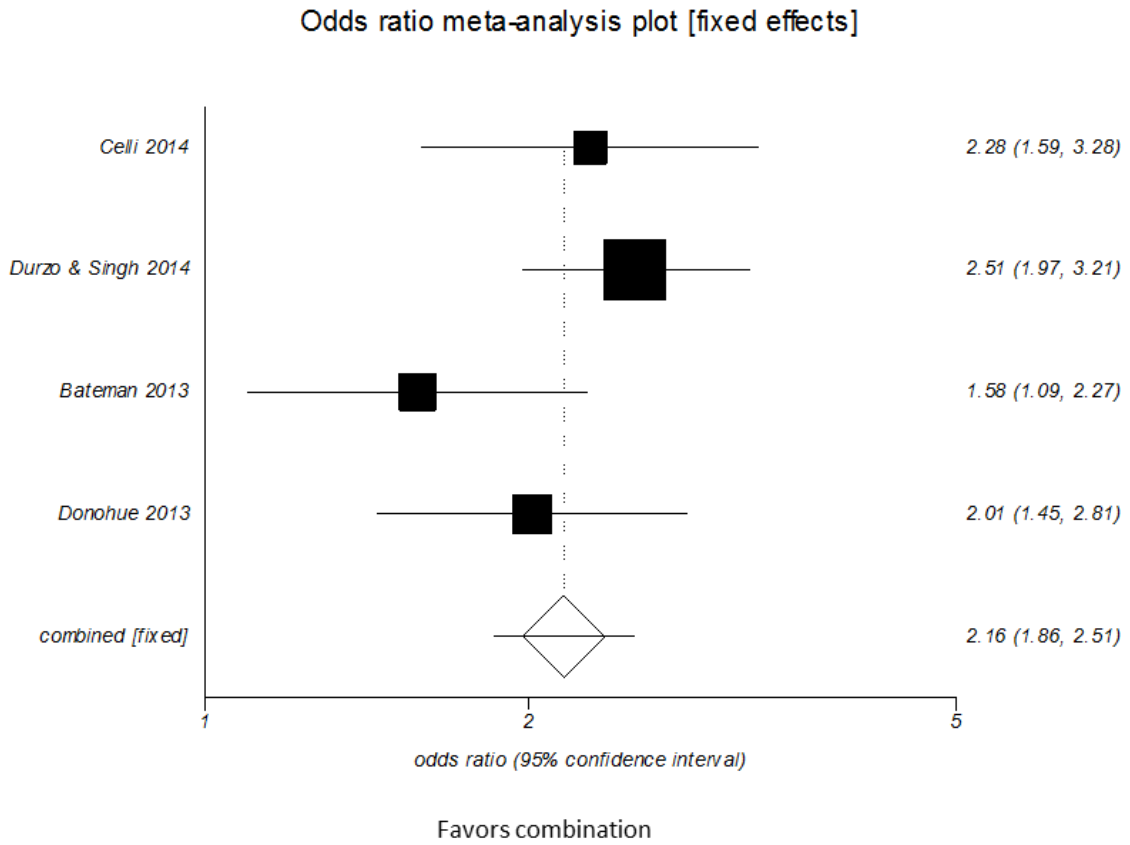

Figure S3-7. Summary effects of LABA/LAMA combination vs. placebo on proportion of TDI responders at 6 months. Cochran Q = 4.986952 (df = 3) P = 0.1728 Moment-based estimate of between studies variance = 0.016264. I^2 (inconsistency) = 39.8% (95% CI = 0% to 79.2%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; TDI= Transition Dyspnea Index

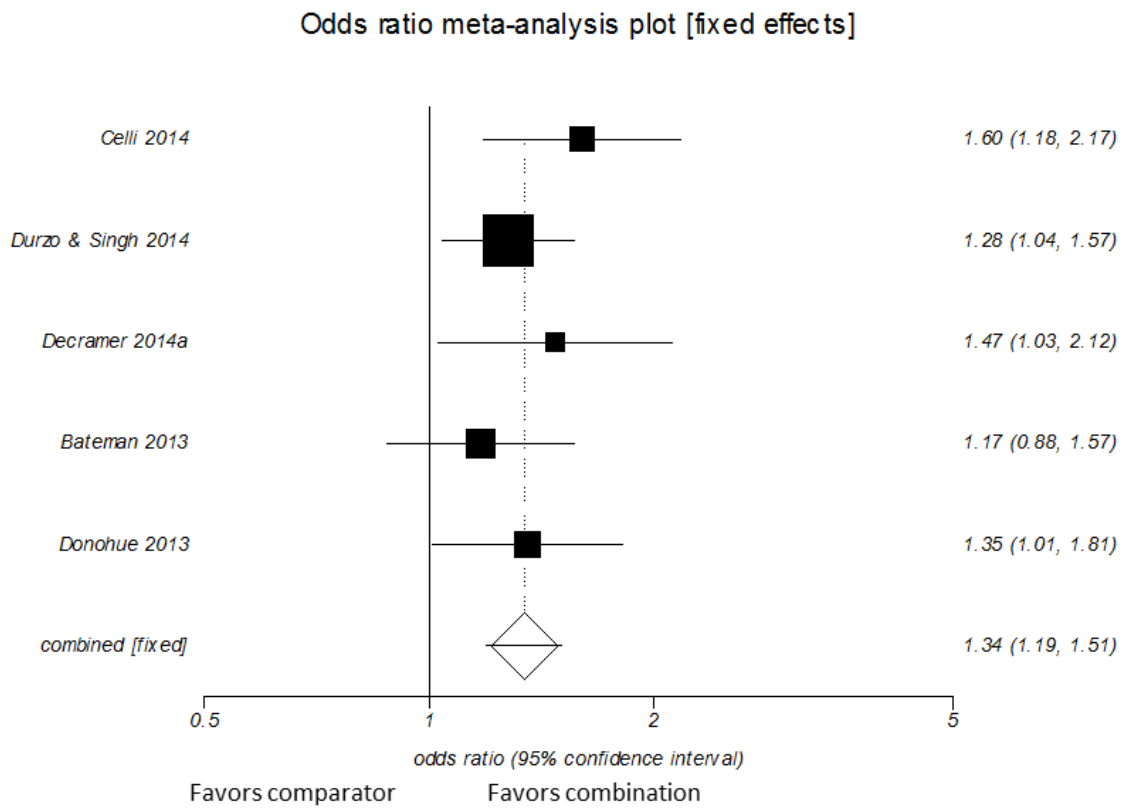

Figure S3-8. Summary effects of LABA/LAMA combination vs. LABA on proportion of TDI responders at 6 months. Cochran Q = 2.769217 (df = 4) P = 0.5972 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 64.1%) Note: A responder was defined as a subject with an improvement of at least one unit in TDI score. Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; TDI= Transition Dyspnea Index

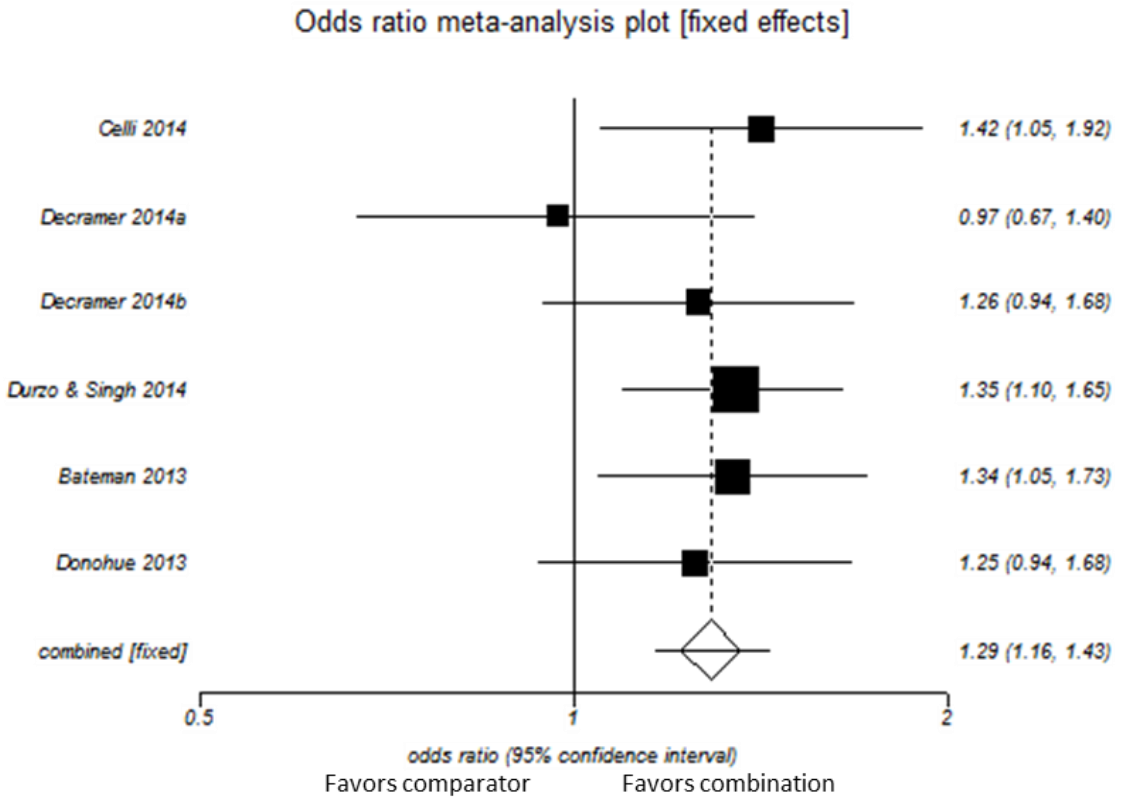

Figure S3-9. Summary effects of LABA/LAMA combination vs. LAMA on proportion of TDI responders at 6 months. Cochran Q = 3.270998 (df = 5) P = 0.6583 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 61%) Note: A responder was defined as a subject with an improvement of at least one unit in TDI score. Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; TDI= Transition Dyspnea Index

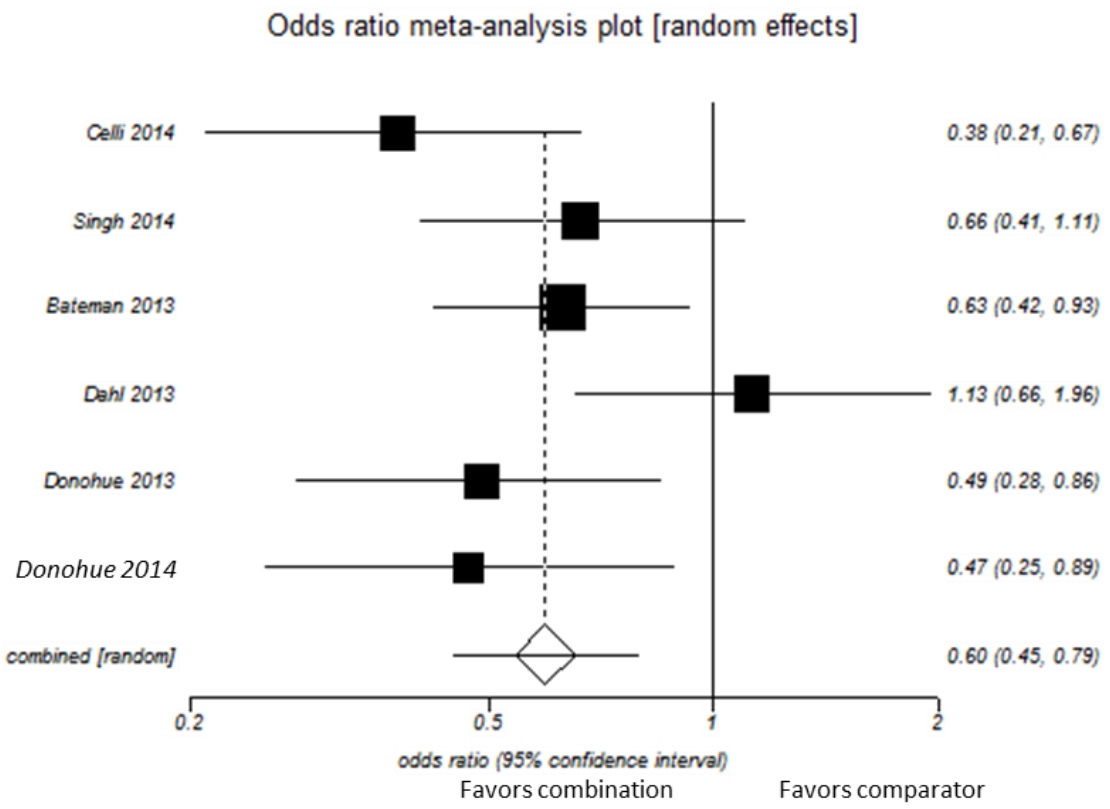

Figure S4-1. Summary effects of LABA/LAMA combination vs. placebo on moderate-to-severe exacerbations. Cochran Q = 10.045685 (df = 5) P = 0.074. Moment-based estimate of between studies variance = 0.063761. I^2 (inconsistency) = 50.2% (95% CI = 0% to 78.3%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

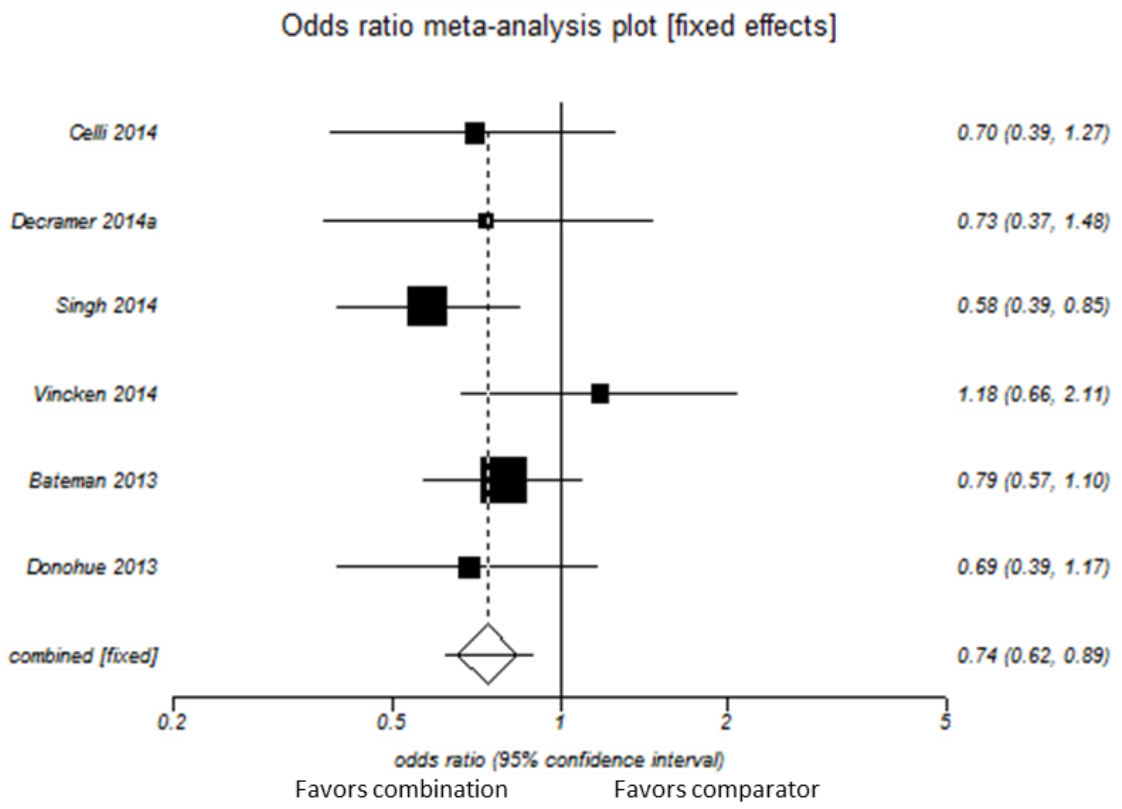

Figure S4-2. Summary effects of LABA/LAMA combination vs. LABA on moderate-to-severe exacerbations. Cochran Q = 4.895821 (df = 5) P = 0.4287. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 61%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

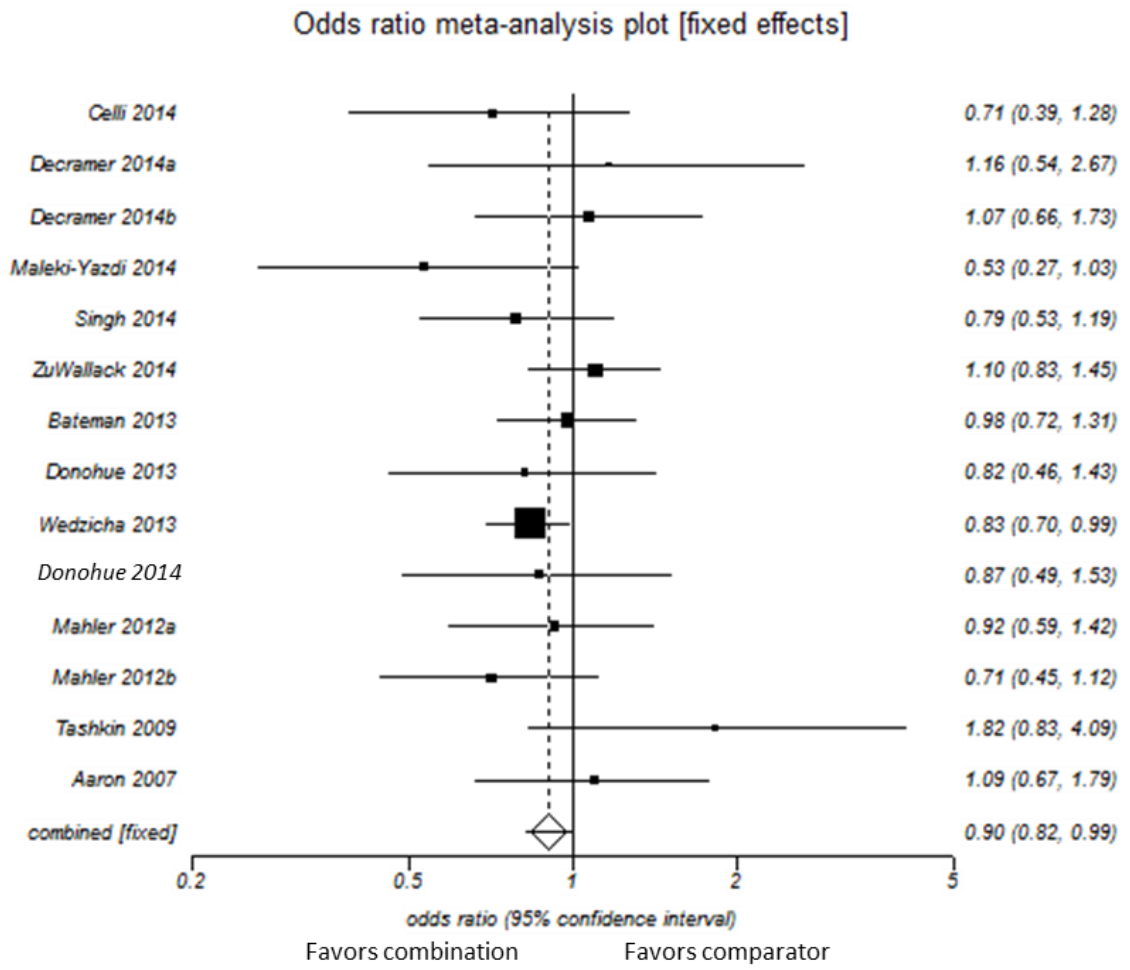

Figure S4-3. Summary effects of LABA/LAMA combination vs. LAMA on moderate-to-severe exacerbations. Cochran Q = 13.67236 (df = 13) P = 0.3973. Moment-based estimate of between studies variance = 0.001999. I^2 (inconsistency) = 4.9% (95% CI = 0% to 50%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

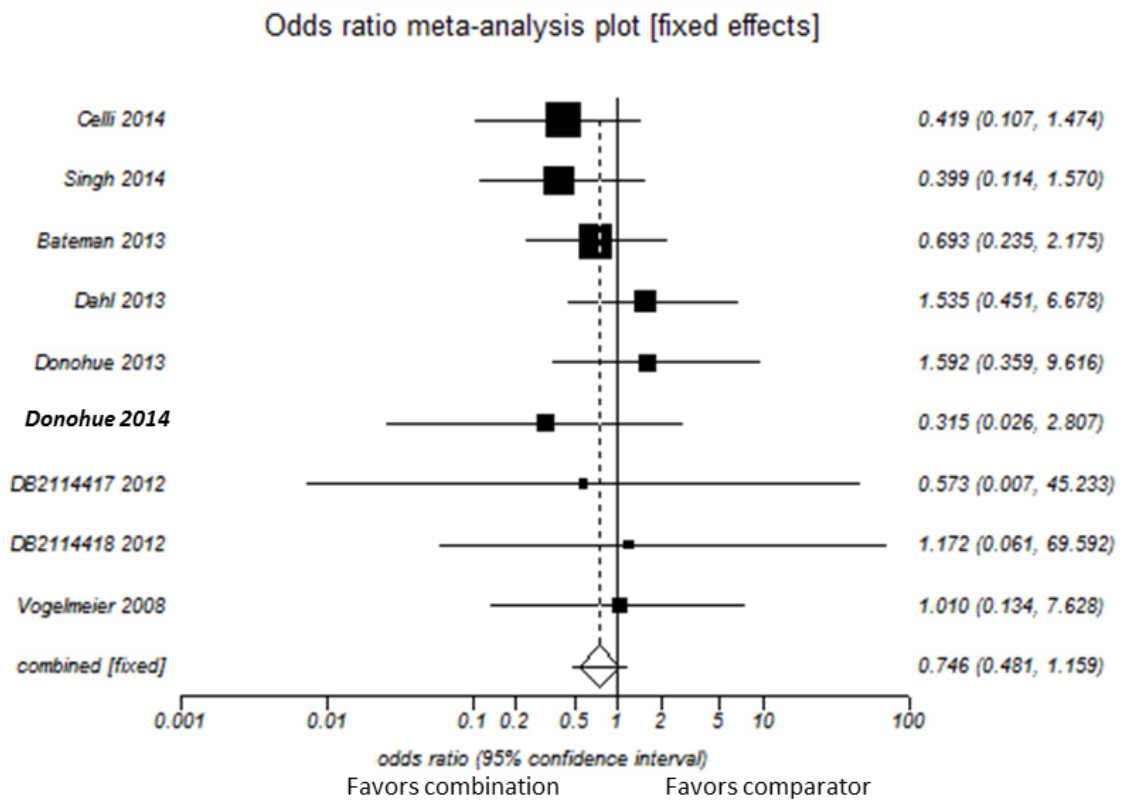

Figure S4-4. Summary effects of LABA/LAMA combination vs. placebo on severe exacerbations. Cochran Q = 6.077237 (df = 8) P = 0.6386. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 54.4%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

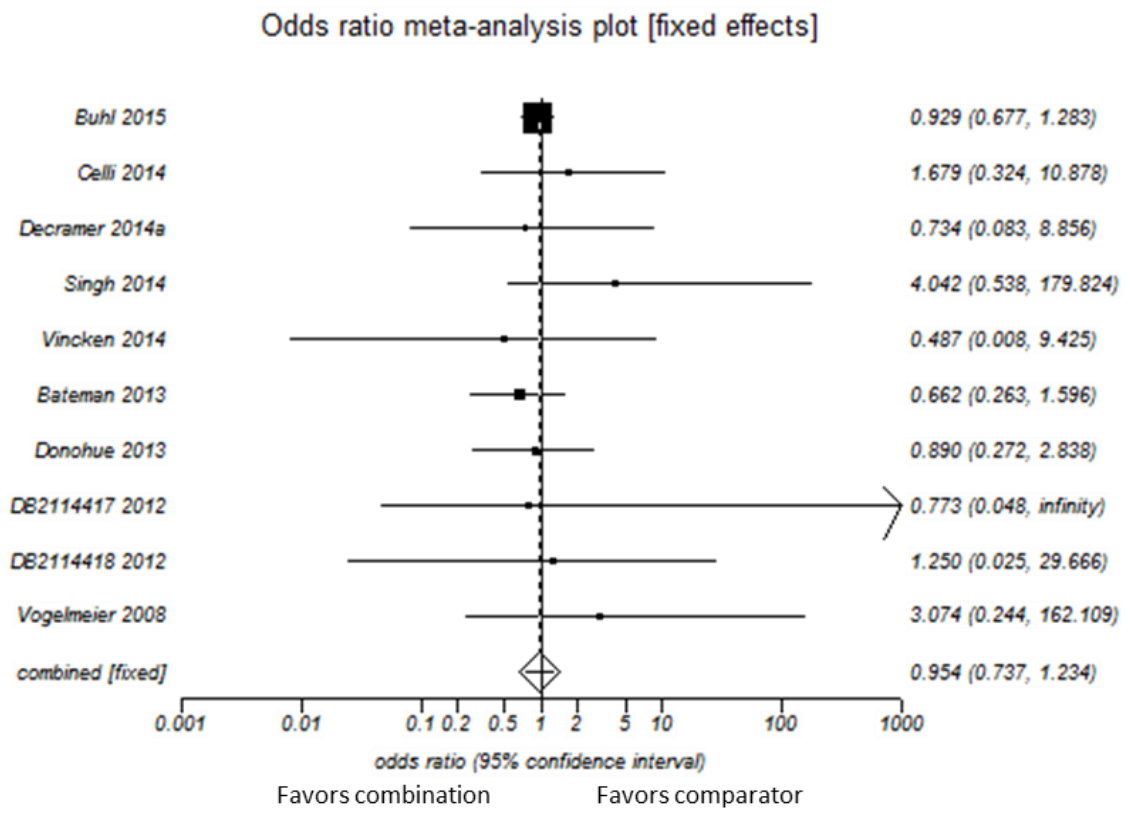

Figure S4-5. Summary effects of LABA/LAMA combination vs. LABA on severe exacerbations. Cochran Q = 4.713351 (df = 9) P = 0.8585. Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 52.7%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

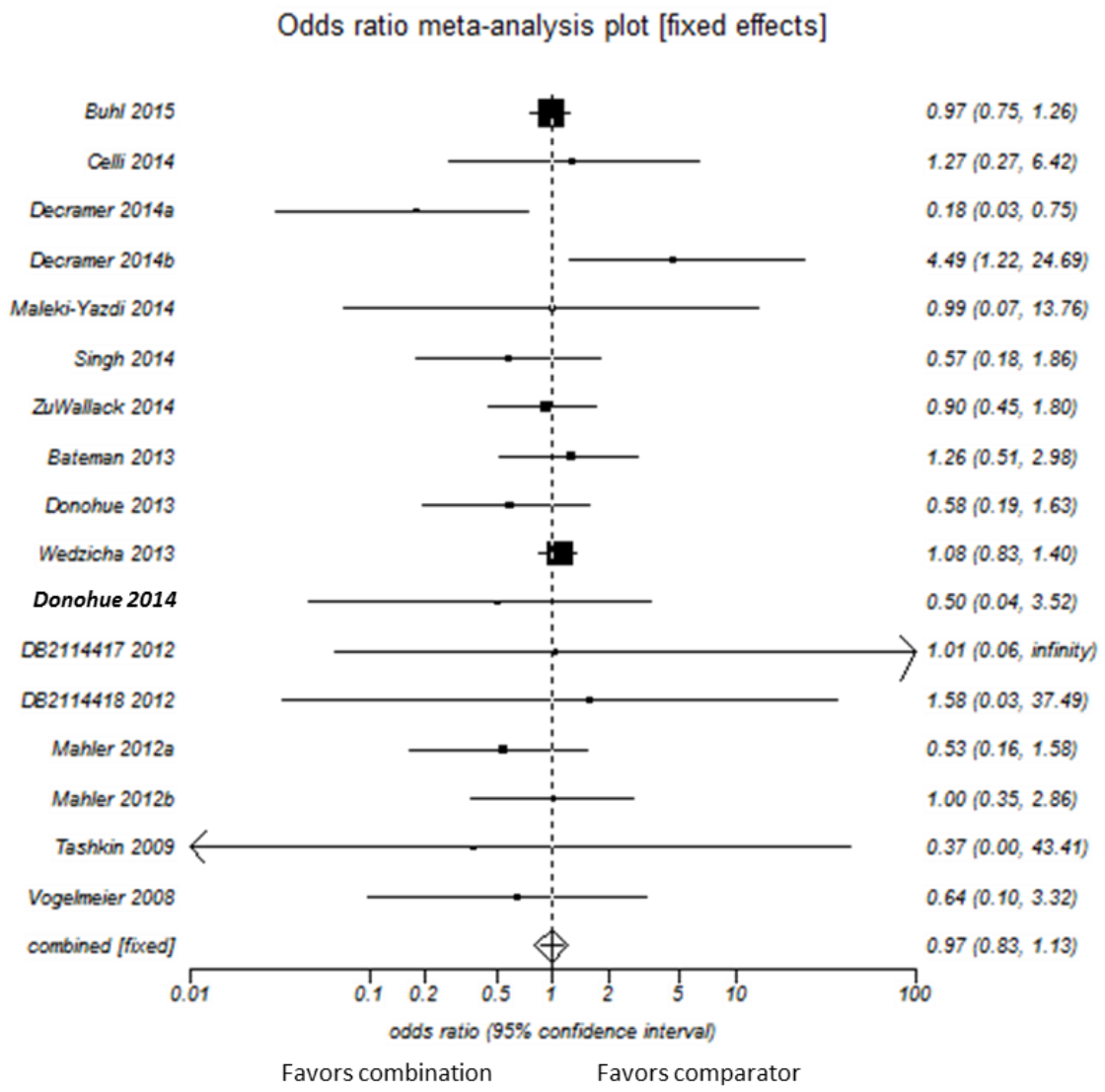

Figure S4-6. Summary effects of LABA/LAMA combination vs. LAMA on severe exacerbations. Cochran Q = 18.074774 (df = 16) P = 0.3195. Moment-based estimate of between studies variance = 0.017593. I^2 (inconsistency) = 11.5% (95% CI = 0% to 50.7%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

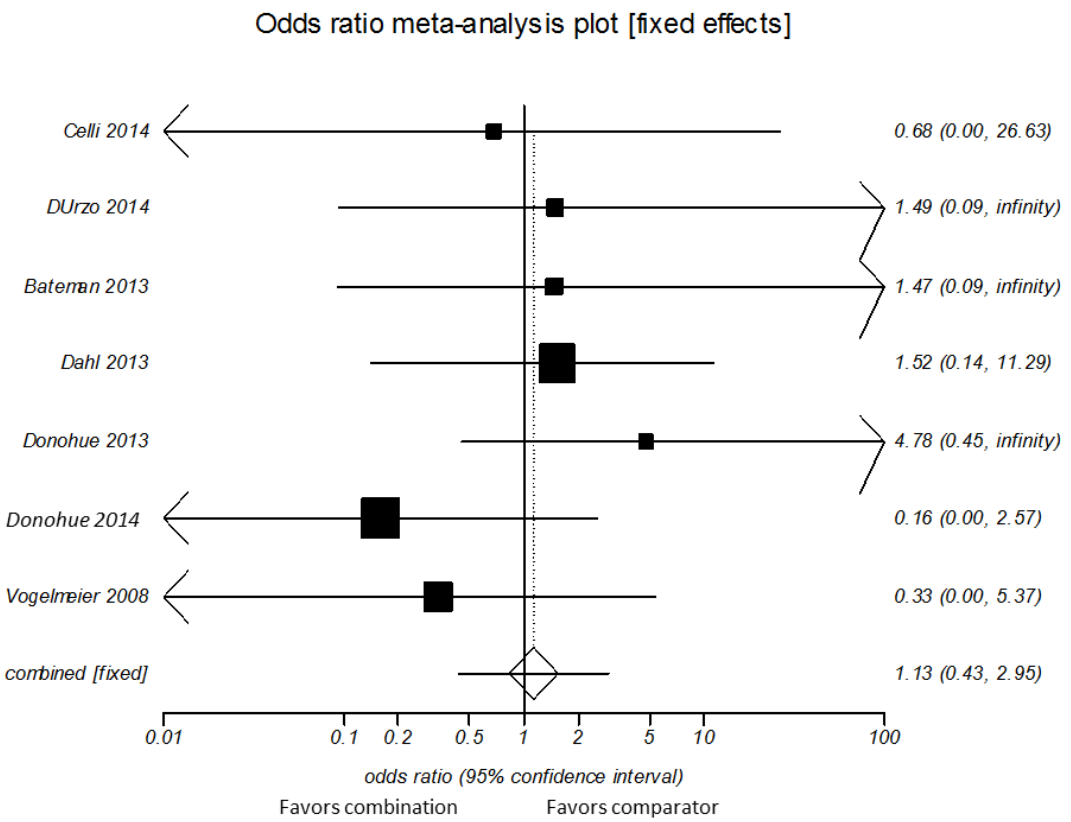

Figure S5-1. Summary effects of LABA/LAMA combination vs. placebo on mortality. Cochran Q = 3.108046 (df = 6) P = 0.7952 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 58.5%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

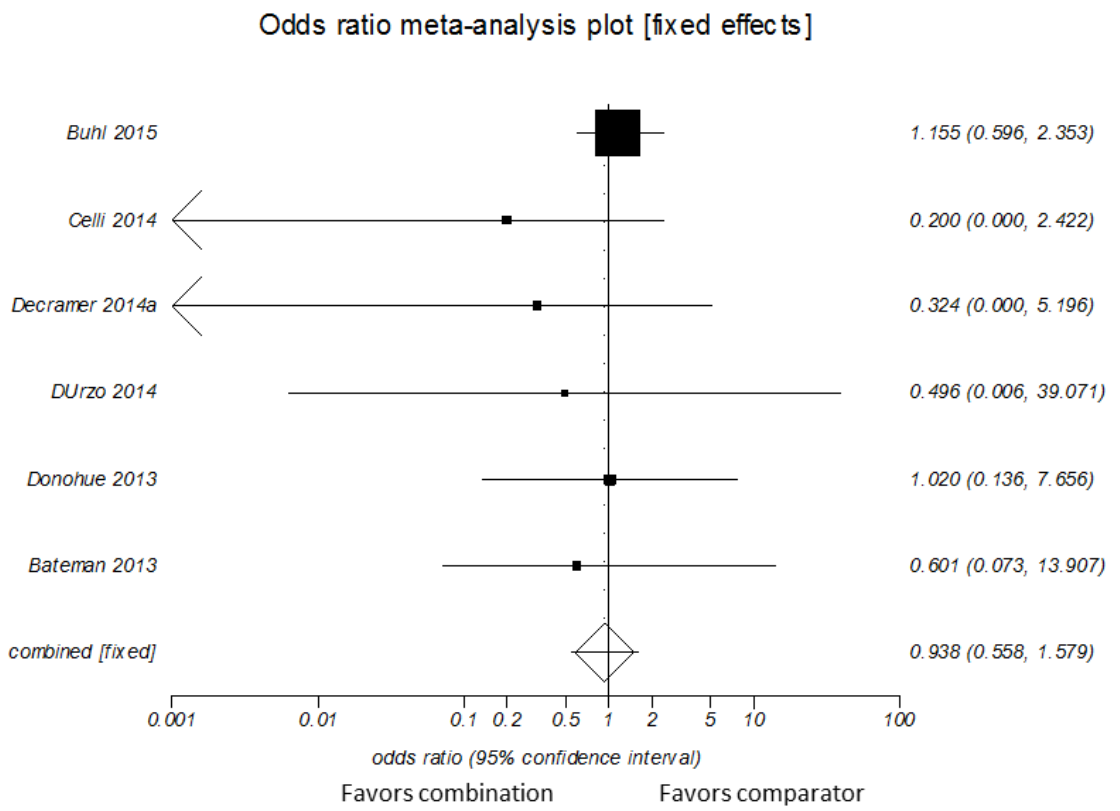

Figure S5-2. Summary effects of LABA/LAMA combination vs. LABA on mortality. Cochran Q = 2.230234 (df = 5) P = 0.8165 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 61%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

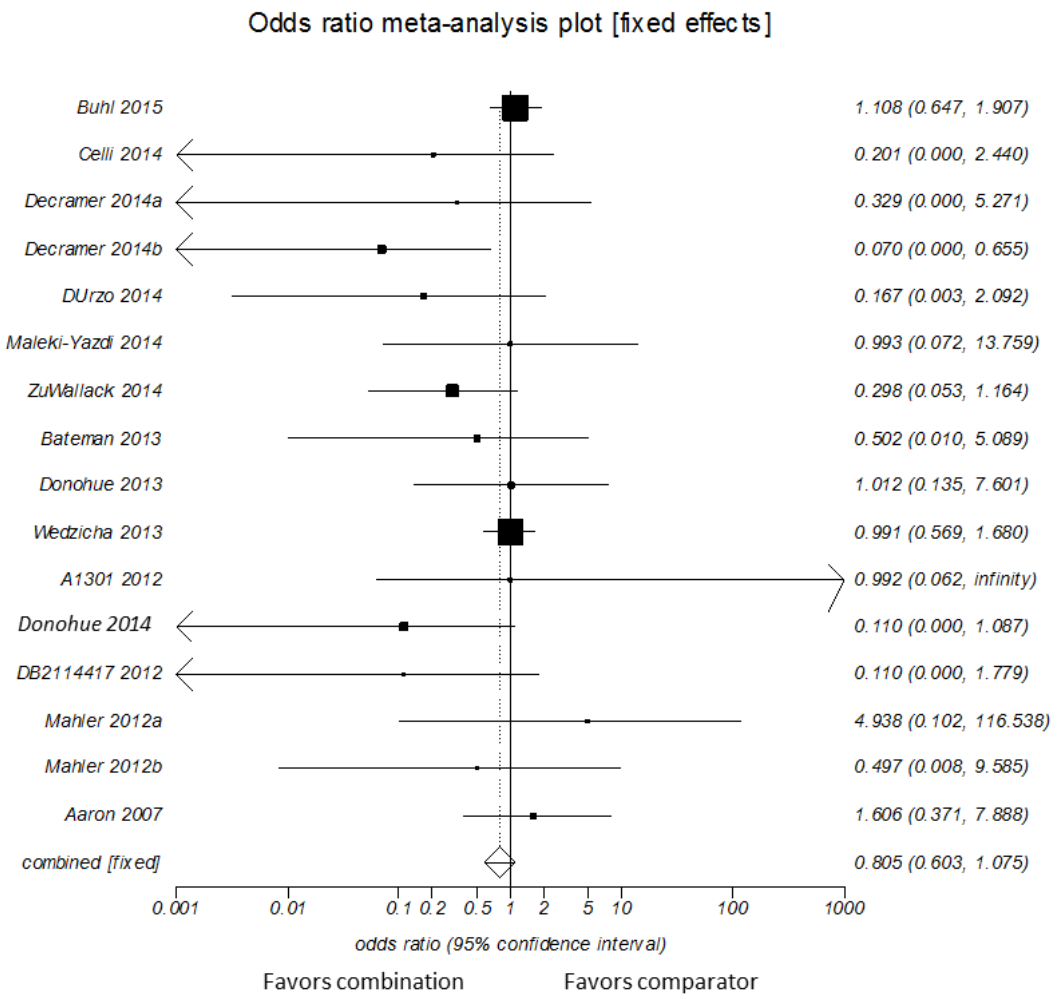

Figure S5-3. Summary effects of LABA/LAMA combination vs. LAMA on mortality. Cochran Q = 16.332396 (df = 15) P = 0.3603 Moment-based estimate of between studies variance = 0.042879. I^2 (inconsistency) = 8.2% (95% CI = 0% to 49.8%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

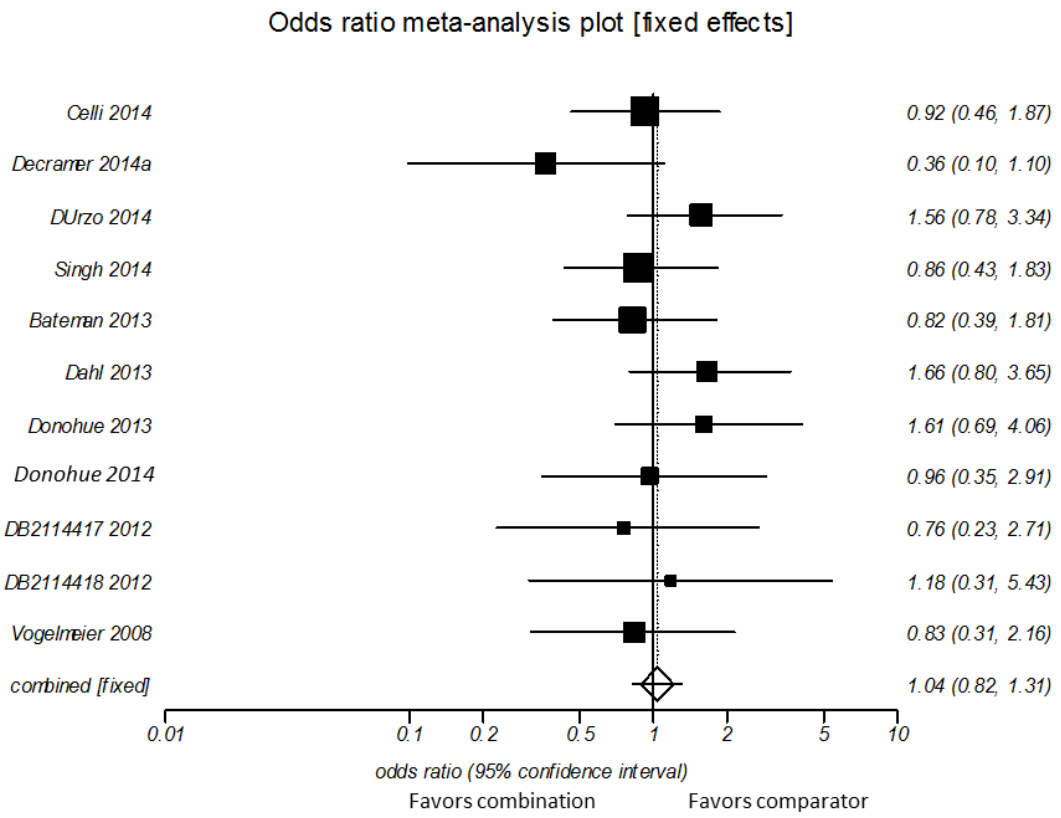

Figure S6-1. Summary effects of LABA/LAMA combination vs. placebo on total serious adverse events. Cochran Q = 9.832963 (df = 10) P = 0.4553 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 51.2%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

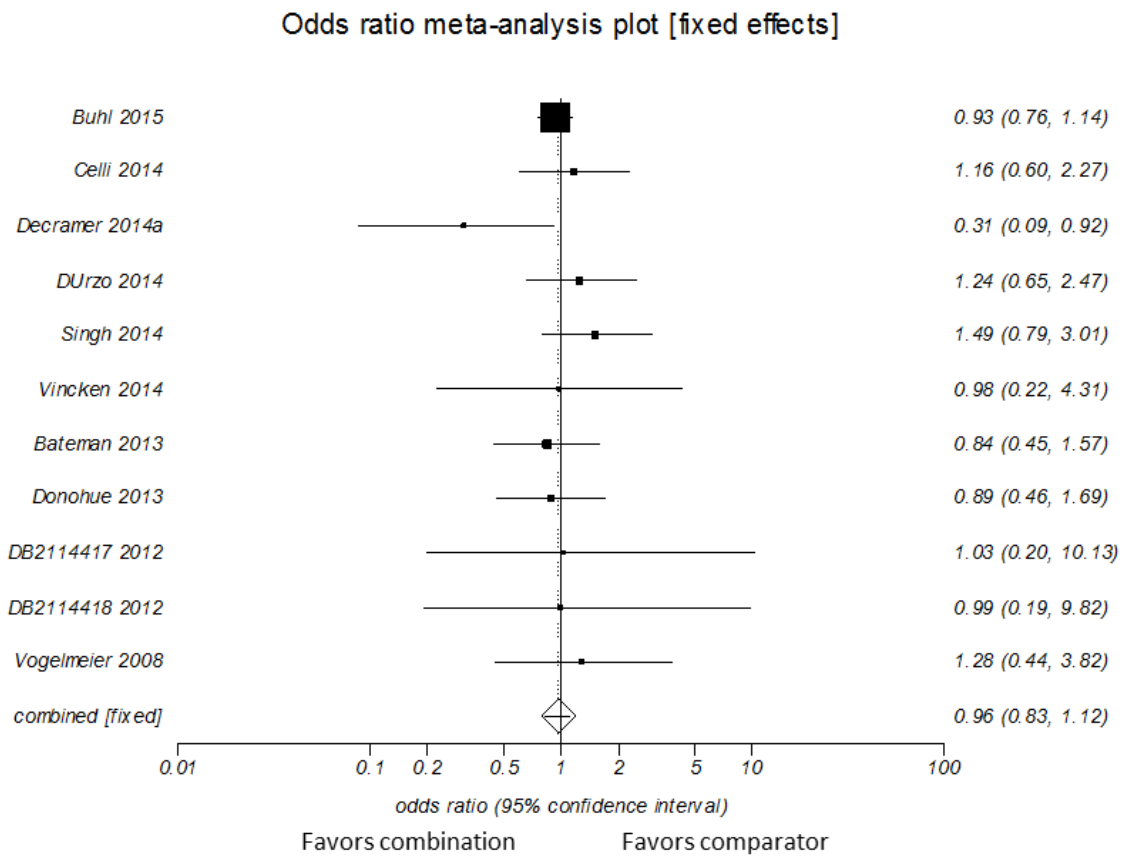

Figure S6-2. Summary effects of LABA/LAMA combination vs. LABA on total serious adverse events. Cochran Q = 8.375787 (df = 10) P = 0.5922 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 51.2%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

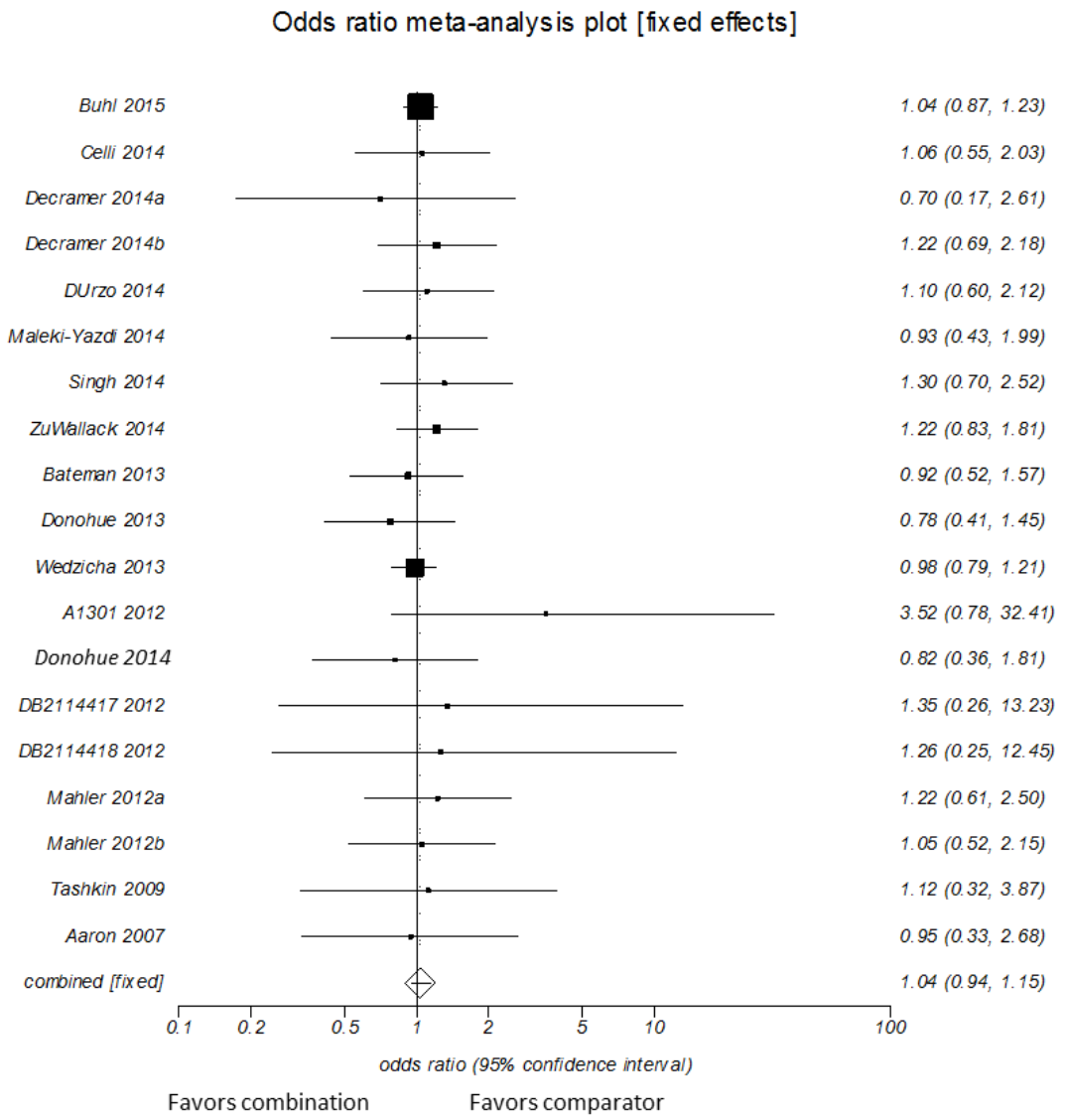

Figure S6-3. Summary effects of LABA/LAMA combination vs. LAMA on total serious adverse events. Cochran Q = 7.104034 (df = 18) P = 0.9892 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 42.9%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

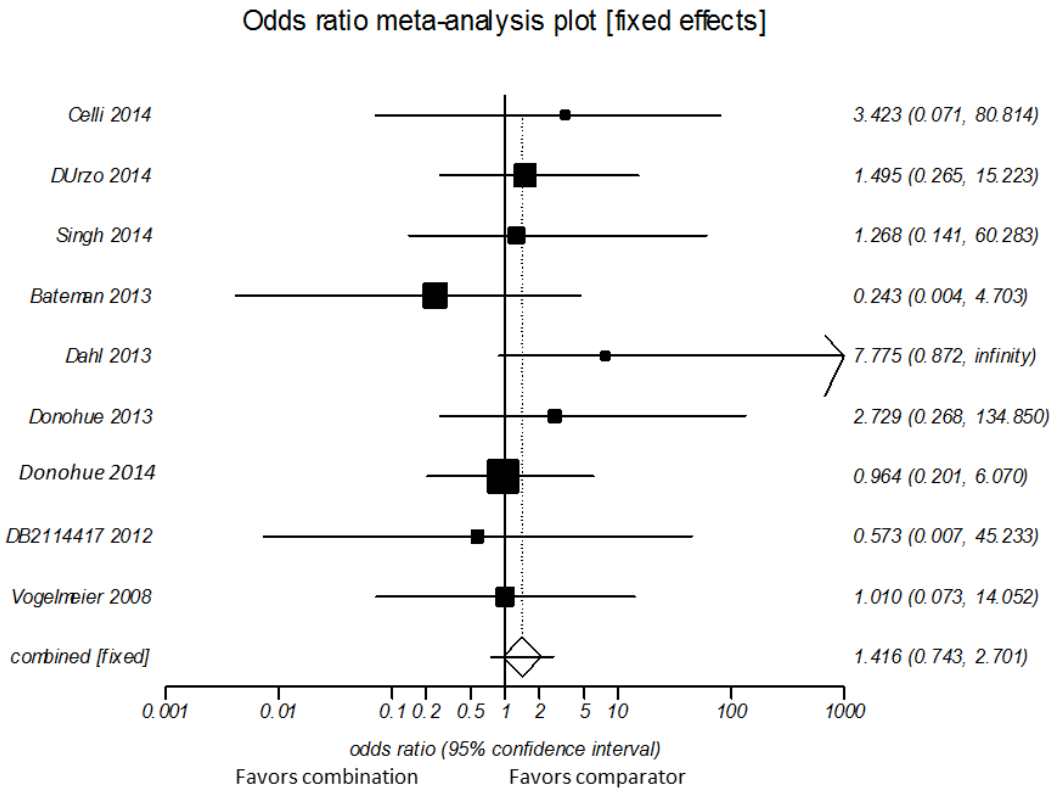

Figure S7-1. Summary effects of LABA/LAMA combination vs. placebo on cardiac serious adverse events. Cochran Q = 4.902434 (df = 8) P = 0.768 Moment-based estimate of between studies variance = 0. I^2 (inconsistency) = 0% (95% CI = 0% to 54.4%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

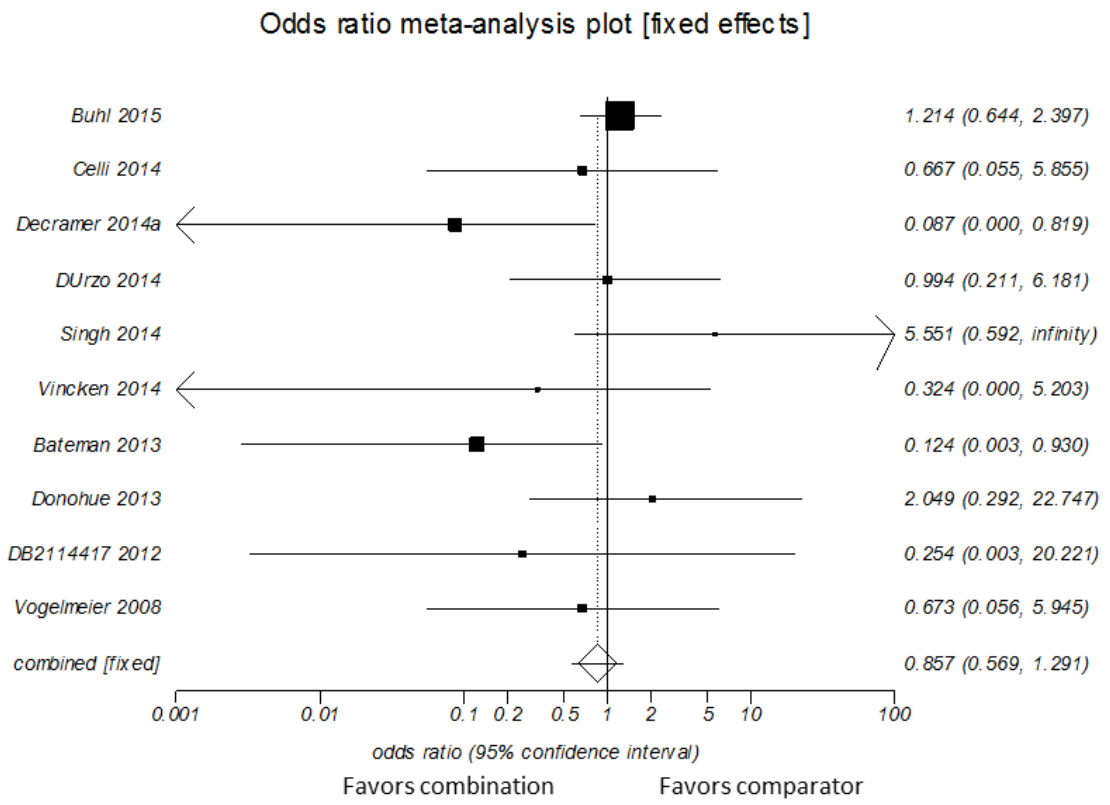

Figure S7-2. Summary effects of LABA/LAMA combination vs. LABA on cardiac serious adverse events. Cochran Q = 10.853717 (df = 9) P = 0.2859 Moment-based estimate of between studies variance = 0.148833. I^2 (inconsistency) = 17.1% (95% CI = 0% to 60.4%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

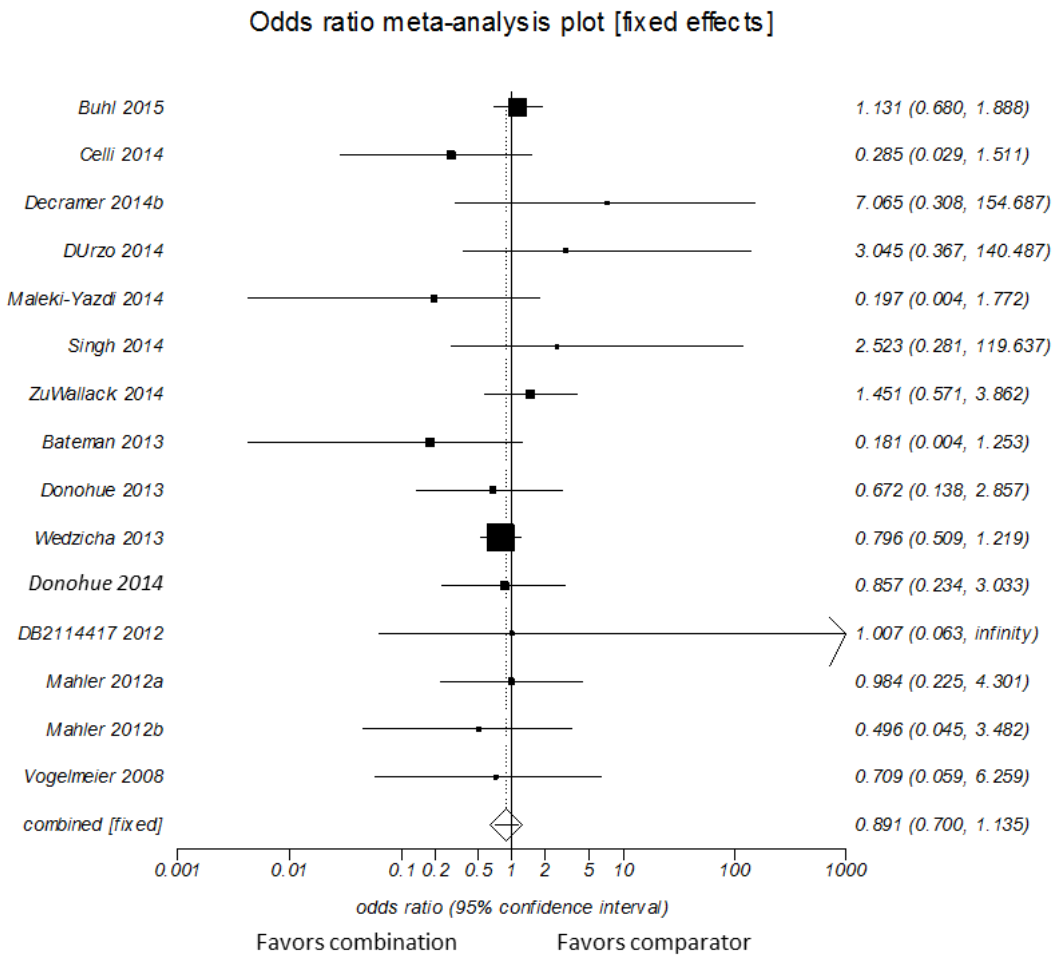

Figure S7-3. Summary effects of LABA/LAMA combination vs. LAMA on cardiac serious adverse events. Cochran Q = 13.557543 (df = 14) P = 0.4832 Moment-based estimate of between studies variance = 0, I^2 (inconsistency) = 0% (95% CI = 0% to 46.4%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

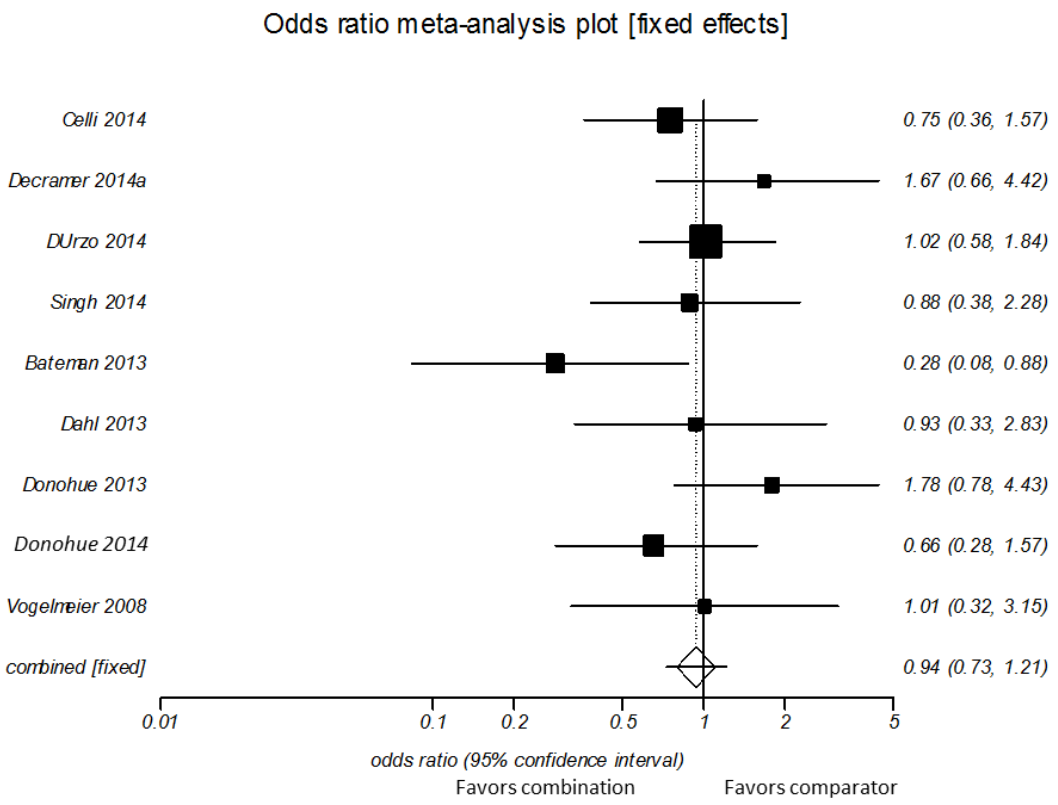

Figure S8-1. Summary effects of LABA/LAMA combination vs. placebo on dropouts due to adverse events. Cochran Q = 10.853898 (df = 8) P = 0.2101. Moment-based estimate of between studies variance = 0.057376. I^2 (inconsistency) = 26.3% (95% CI = 0% to 65.5%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

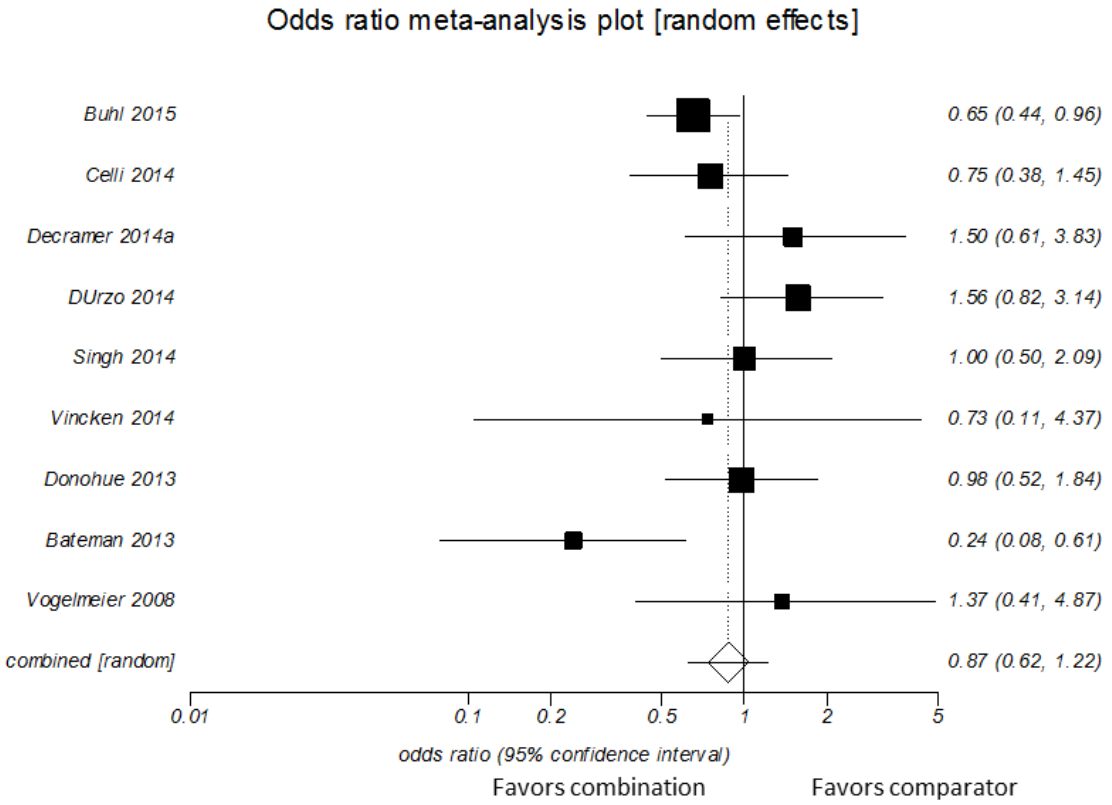

Figure S8-2. Summary effects of LABA/LAMA combination vs. LABA on dropouts due to adverse events. Cochran Q = 16.377109 (df = 8) P = 0.0373 Moment-based estimate of between studies variance = 0.122265. I^2 (inconsistency) = 51.2% (95% CI = 0% to 75.4%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

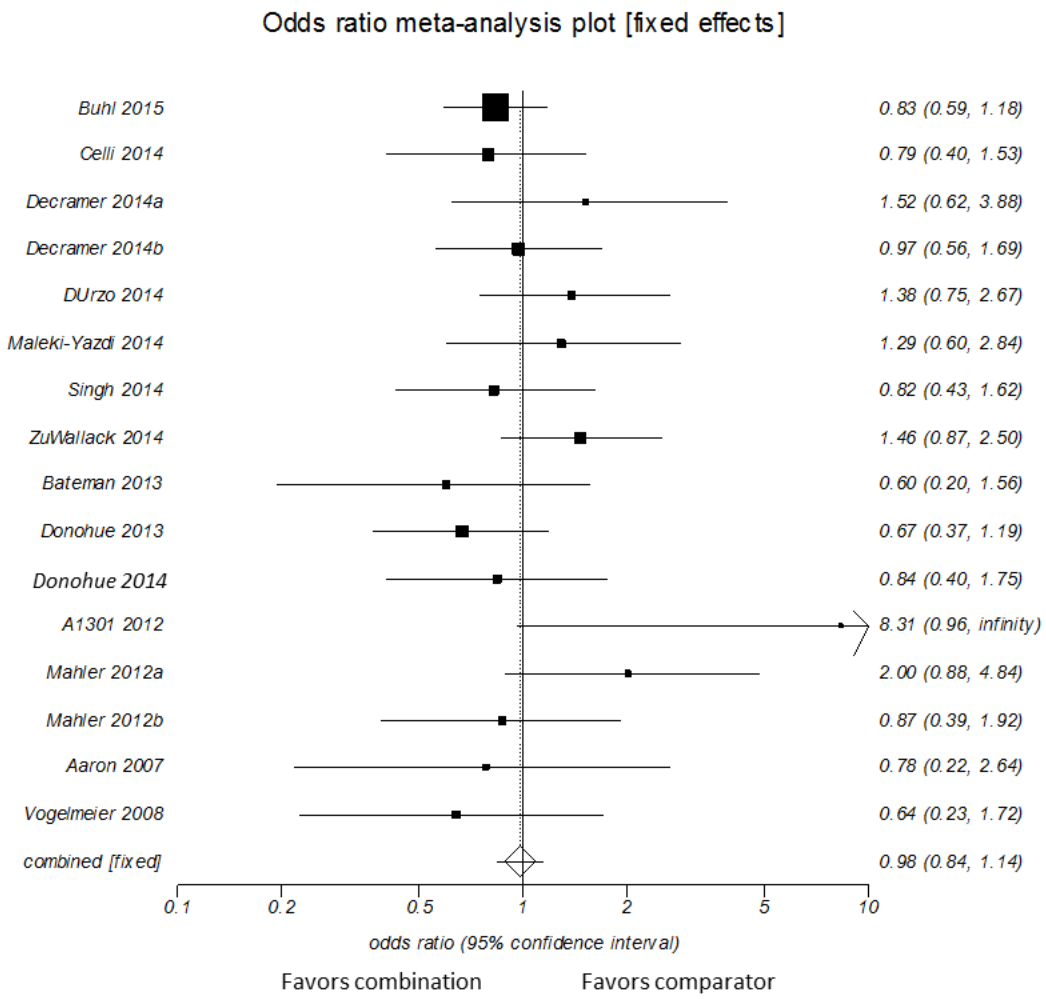

Figure S8-3. Summary effects of LABA/LAMA combination vs. LAMA on dropouts due to adverse events. Cochran Q = 16.949525 (df = 15) P = 0.3219 Moment-based estimate of between studies variance = 0.013753. I^2 (inconsistency) = 11.5% (95% CI = 0% to 51.5%) Abbreviations: CI= confidence interval; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

	Effective head-to-head sample size	Effective indirect sample size	Effective total sample size	Required sample size†	Statistical power*
SGRQ responders					
LABA/LAMA vs placebo	2660	5971	8631	1482	100%
LABA/LAMA vs LABA	3765	3736	7501	1018	100%
LABA/LAMA vs LAMA	7904	3049	10953	1008	100%
TDI responders					
LABA/LAMA vs placebo	2088	2972	5060	1530	100%
LABA/LAMA vs LABA	4772	2955	7727	898	100%
LABA/LAMA vs LAMA	5998	5744	11742	846	100%
Moderate or severe exacerbations					
LABA/LAMA vs placebo	1848	4045	5893	4428	100%
LABA/LAMA vs LABA	4823	4146	8969	6308	95.6%
LABA/LAMA vs LAMA	13747	3470	17217	3714	100%
Severe exacerbations					
LABA/LAMA vs placebo	5001	5319	10320	46428	29.8%
LABA/LAMA vs LABA	9031	5546	14577	32918	55.5%
LABA/LAMA vs LAMA	17128	5510	22638	20638	93.5%

Table S11. Heterogeneity corrected sample sizes and power estimates on patient centered outcomes.
† to detect additional 20% relative efficacy with a power of 90%. * to detect additional 20% relative efficacy with an alpha level of 0.05. LABA= long-acting beta-agonist; LAMA=long-acting muscarinic antagonist; SGRQ=St. George's Respiratory Questionnaire; TDI=Transitional Dyspnea Index.

Outcome	Likelihood	Link Function	Comment(s)
TDI and CFB in FEV1 and SGRQ	Normal	identity	Continuous outcomes. CFB in FEV1 was analyzed at 3, 6, and 12 months and TDI and CFB in SGRQ were analyzed at 3 and 6 months to account for the fact that changes in these outcomes could be time-dependent. There were insufficient data to assess TDI and CFB in SGRQ at 12 months.
COPD exacerbations	Normal	identity	A shared parameter model. Hazard ratio data (Cox regression analysis of time to first COPD exacerbation) were used in preference to dichotomous data (the number of patients with at least one exacerbation out of the total number of patients) when available. Then the trials reporting the hazard ratio were combined with the trials reporting binomial counts.[11] Data on the log hazard ratio were modelled assuming the continuous treatment differences follow a normal distribution with an identity link. Dichotomous outcomes were assumed to follow a binomial distribution with a cloglog link.
	Binominal	cloglog	
Mortality and dropouts due to adverse event	Binominal	cloglog	This model allows for different study durations, since a longer follow-up would likely make a difference in study results for these outcomes
Total and cardiac SAEs	Binominal	cloglog	There might be studies where multiple events are counted per patient, although this could not be confirmed. However, there was no better model to apply due to the lack of appropriate data (i.e., events/person years).
SGRQ and TDI responders	Binominal	logit	Dichotomous outcomes. These outcomes were analyzed at 6 months. There were insufficient data for other time points.

Table S2. Model used in each outcome. CFB= change from baseline; FEV1= forced expiratory volume in 1 second; SAE= severe adverse event; SGRQ= St. George's Respiratory Questionnaire; TDI= Transitional Dyspnea Index

Table S3. Study quality

Study, year	Concealed allocation	ITT analysis	Blinding	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting
Buhl 2015 [19]	Yes	Yes	Yes	Unclear	Yes
Celli 2014 [20]	Yes	Yes	Yes	Yes	Yes
Decramer 2014 a&b [21]	Yes	Yes	Yes	Yes	Yes
D'Urzo 2014 [22]	Yes	Yes	Yes	Yes	Yes
Maleki-Yazdi 2014 [23]	Yes	Yes	Yes	Yes	Yes
Singh 2014 [24]	Yes	Yes	Yes	Yes	Yes
ZuWallack 2014 [26]	Yes	Yes[§]	Yes	Yes	Yes
Donohue 2013 [29]	Yes	Yes	Yes	Yes	Yes
Donohue 2014 [31]	Yes	Yes	Yes	Unclear	Yes
DB2114417 2012 [32]	Yes	Yes	Yes	Unclear	Yes
DB2114418 2012 [33]	Yes	Yes	Yes	Unclear	Yes
Vincken 2014 [25]	Yes	Yes	Yes	Yes	Yes
Bateman 2013 [27]	Yes	Yes	Yes	Yes	Yes
Dahl 2013 [28]	Unclear	Yes	Yes	Unclear	Yes
Wedzicha 2013 [30]	Yes	Yes	Yes[¶]	Yes	Yes
Novartis A1301 2012 [35]	No	Yes	No	Yes	Unclear
Mahler 2012 a&b [34]	Yes	Yes	Yes	Yes	Yes
Tashkin 2009 [36]	Unclear	Yes	Yes	Unclear	Unclear
Vogelmeier 2008 [37]	Unclear	Yes	Yes[¶]	Unclear	Unclear
Aaron 2007 [38]	Yes	Yes	Yes	Unclear	Yes

¶ Except for tiotropium which was open-label §Treated set (TS) was used, which included all randomized patients who receive at least one dose of double-blind study treatment. Two patients out of 1134 and 1137 patients did not receive study treatment in each trial. ITT= intention-to-treat.

Buhl 2015 [19]	**Inclusion criteria**: Diagnosis of chronic obstructive pulmonary disease; 40 years of age or older; Relatively stable airway obstruction with post FEV1< 80% predicted normal and post FEV1/FVC <70%; 40 years of age or older; Smoking history of more than 10 pack years. **Exclusion criteria**: Significant disease other than COPD; History of asthma; Regular use of daytime oxygen therapy for more than one hour per day **Allowed co-medications**: ICS as required, salbutamol/albuterol inhaler as rescue medication. Temporary increases in the dose or addition of oral steroids or theophylline were allowed.
Celli 2014 [20]	**Inclusion criteria**: Diagnosis of COPD, 10 pack-year or greater history of cigarette smoking, Post-bronchodilator FEV1/FVC ratio of <0.7, Predicted FEV1 of 70% of normal or less, mMRC dyspnea score of 2 or greater. 40 years of age or older. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease, an abnormal and significant ECG or 24-h Holter finding. **Allowed co-medications:** Salbutamol rescue medication, and regular use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent)
Decramer 2014 a &b [21]	**Inclusion criteria**: History of COPD as defined by ATS–ERS; current or former cigarette smoker with a smoking history of 10 pack-years or more; a post-salbutamol FEV1/FVC ratio < 0·70 and a post-salbutamol FEV1 of 70% of predicted normal values or less and a score of 2 or higher on the mMRC Dyspnoea score. **Exclusion criteria**: Hospital admission for COPD or pneumonia within the 12 weeks before study visit. Present diagnosis of asthma or other known respiratory disorder. **Allowed co-medications:** Salbutamol rescue medication, and regular use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent)
D'Urzo 2014 [22]	**Inclusion criteria**: Current or former cigarette smokers with a cigarette smoking history of at least 10 pack-years; a diagnosis of stable moderate to severe COPD and stable airway obstruction as defined by the GOLD guidelines with a post-bronchodilator FEV1 = 30 % and < 80% of predicted normal and a post-bronchodilator FEV1/FVC <70%;40 years of age or older. **Exclusion criteria**: Recent hospitalization for an acute COPD exacerbation within three months prior to Visit 1; Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the six weeks before Visit 1; clinically significant respiratory conditions other than COPD; Clinical history of asthma; Chronic use of oxygen therapy ≥ 15 hours/day; clinically significant cardiovascular conditions. **Allowed co-medications**: albuterol/salbutamol as rescue medication. theophylline, ICS, oral or parenteral corticosteroids (≤10 mg/day or 20 mg every other day of prednisone)
Maleki-Yazdi 2014 [23]	**Inclusion criteria**: A pre and post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and a pre and post-albuterol/salbutamol FEV1 of <=70% of predicted; COPD diagnosis defined by ATS/ERS guidelines; 40 years of age or older; a history of cigarette smoking of $\geq$ 10 pack-years. **Exclusion criteria**: a current diagnosis of asthma; Clinically significant

	comorbidity; Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1; home oxygen greater than 12 hours a day. As-needed oxygen use (i.e., ≥ 12 hours per day) was allowed. **Allowed co-medications**: Albuterol/salbutamol rescue medication, and regular use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent).
Singh 2014 [24]	**Inclusion criteria**: Smoking history of at least 10 pack-years; a diagnosis of stable moderate to severe COPD and stable airway obstruction as defined by the GOLD guidelines with a post-bronchodilator FEV1 > 30 % and < 80% of predicted normal and a post-bronchodilator FEV1/FVC <70%; 40 years of age or older. **Exclusion criteria**: Use of long-term oxygen therapy (≥ 15 hours/day).History or current diagnosis of asthma; Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before screening visit; History of interstitial lung or massive pulmonary thromboembolic disease. **Allowed co-medications**: salbutamol as rescue medication. ICS, oral sustained-release methylxanthines, oxygen therapy (<15 hours/day) and oral or parenteral corticosteroids equivalent to ≤10 mg/day of prednisone or 20 mg every other day.
ZuWallack 2014 [26]	**Inclusion criteria**: Diagnosis of chronic obstructive pulmonary disease; relatively stable airway obstruction with a post-bronchodilator FEV1 > 30 % and < 80% of predicted normal and a post-bronchodilator FEV1/FVC <70% at Visit 1; 40 years of age or older; a smoking history of more than 10 pack years. **Exclusion criteria**: A significant disease other than COPD in the opinion of the investigator; history of asthma, cystic fibrosis or bronchiectasis; regular use of daytime oxygen therapy for more than one hour per day. **Allowed co-medications**: albuterol as rescue medicine was allowed. ICS, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, long-term oral steroids, mucolytics, and theophylline were NOT allowed.
Donohue 2013 [29]	**Inclusion criteria**: 40 years of age or older with a clinically established history of COPD ; smoking history of 10 pack-years; a post-salbutamol FEV1/ FVC ratio of <0.70 and a post-salbutamol FEV1 of 70% of predicted normal values ; a score of 2 on the mMRC Dyspnea Scale. **Exclusion criteria**: current diagnosis of asthma or other known respiratory disorders, any clinically significant uncontrolled disease as determined by the study investigators, an abnormal and clinically significant ECG or 24-h Holter ECG (if conducted), or significantly abnormal clinical laboratory finding. **Allowed co-medications**: inhaled salbutamol (albuterol) as rescue medication. ICS were allowed at a stable dose of 1000 mcg/day of fluticasone propionate or equivalent from 30 days prior to screening.
Donohue 2014 [31]	**Inclusion criteria**: 40 years of age or older with a diagnosis of COPD and 10 pack-years smoking history; Post-salbutamol FEV1/ FVC ratio of <0.70, a post-salbutamol FEV1 of >35% and < 80% of predicted normal values. **Exclusion criteria**: Current diagnosis of asthma, alfa1-antitrypsin deficiency, any clinically significant uncontrolled disease, a significant ECG or clinical laboratory finding, or a lower respiratory tract infection or recent COPD exacerbation were excluded.

	Allowed co-medications: Inhaled salbutamol (albuterol) as rescue medication. Concurrent use of ICS at a stable dose. Concurrent use of systemic corticosteroids, long-acting bronchodilators, including theophyllines, was NOT allowed.
DB2114417 2012 [32]	**Inclusion criteria**: 40 years of age or older with a current COPD diagnosis with a post albuterol FEV1/FVC <0.7, 35%-70% FEV1 predicted, >120% forced residual capacity and 2 or more on the mMRC scale. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications**: albuterol/salbutamol for "as-needed" use. Short-acting anticholinergics were permitted during the run-in and washout periods. Concurrent use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent).
DB2114418 2012 [33]	**Inclusion criteria**: 40 years of age or older with a current COPD diagnosis with a post albuterol FEV1/FVC <0.7, 35%-70% FEV1 predicted, >120% forced residual capacity and 2 or more on the mMRC scale. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications**: albuterol/salbutamol for "as-needed" use. Short-acting anticholinergics were permitted during the run-in and washout periods. Concurrent use of ICS at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent).
Vincken 2014 [25]	**Inclusion criteria**: 40 years of age or older with a current COPD diagnosis with a post albuterol FEV1/FVC <0.7, 30%-80% FEV1 predicted; current or ex-smokers with a smoking history of at least 10 pack-years. **Exclusion criteria**: Respiratory tract infection within 6 weeks prior to screening; COPD exacerbation 6 weeks prior to screening; current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications:** Inhaled salbutamol (albuterol) as rescue medication and stable dose of ICS.
Bateman 2013 [27]	**Inclusion criteria**: 40 years of age or older; Smoking history of at least 10 pack years; Diagnosis of COPD (GOLD Guidelines, 2008); Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC <70%. **Exclusion criteria**: a respiratory tract infection within 4 weeks prior to Visit 1. Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications**: Inhaled salbutamol (albuterol) as rescue medication and fixed dose of ICS.
Dahl 2013 [28]	**Inclusion criteria:** 40 years of age or older; Smoking history of at least 10 pack years; Diagnosis of COPD (GOLD Guidelines, 2008); Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC <70%. **Exclusion criteria**: a respiratory tract infection within 4 weeks prior to Visit 1; concomitant pulmonary disease, asthma, alpha-1 antitrypsin deficiency or lung; certain cardiovascular co-morbid conditions. **Allowed co-medications:** Inhaled salbutamol (albuterol) as rescue medication

	and ICS.
Wedzicha 2013 [30]	**Inclusion criteria**: 40 years of age or older; severe to very severe COPD (Stage III or IV GOLD Guidelines 2008).Current or ex-smokers with a smoking history of at least 10 pack years; a post-bronchodilator FEV1 <50% of the predicted normal value, and post-bronchodilator FEV1/FVC <0.70 at Visit 2. A documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics. **Exclusion criteria**: Patients requiring long term oxygen therapy (> 15 h a day) on a daily basis; a COPD exacerbation that required treatment with antibiotics, systemic steroids or hospitalization in the 6 weeks prior to visit 1. Current diagnosis of asthma or other known respiratory disorder; a clinically significant abnormality on the screening or baseline ECG. **Allowed co-medications**: Inhaled salbutamol (albuterol) as rescue medication and fixed dose of ICS.
Novartis A1301 2012 [35]	**Inclusion criteria**: 40 years of age or older; smoking history of at least 10 pack years. Diagnosis of COPD (GOLD Guidelines, 2008). Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC <70%. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant uncontrolled disease. **Allowed co-medications:** Not described.
Mahler 2012a&b [34]	**Inclusion criteria**: patients aged ≥ 40 years with COPD (GOLD 2007 criteria), with a smoking history ≥10 pack-years and postbronchodilator FEV1 ≤ 65% and ≥ 30% of predicted normal, and post-bronchodilator FEV1/FVC <70% at screening. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, certain cardiovascular disease; a respiratory tract infection or COPD exacerbation within the previous 6 weeks. **Allowed co-medications**: Inhaled salbutamol (albuterol) as rescue medication and fixed dose of ICS.
Tashkin 2009 [36]	**Inclusion criteria**: patients aged ≥40 years with a clinical history of COPD. a postbronchodilator FEV1 < 70% and >30% predicted normal or >0.75 L and a FEV1/FVC ratio of <0.70 at screening and run-in. Daytime and/or nighttime symptoms of COPD, including dyspnea, must have been present on ≥4 of the 7 days before the baseline visit. **Exclusion criteria**: Current diagnosis of asthma or other known respiratory disorder, any clinically significant disease that may have interfered with study treatment as assessed by the investigator. Smoking cessation within the previous 3 months, ventilator support for respiratory failure within the previous year, the use of oxygen (≥2 L/min or for >2 hours/day). **Allowed co-medications:** Inhaled salbutamol (albuterol) as rescue medication and a fixed dose of ICS. Ipratropium bromide, leukotriene antagonists, and theophylline were NOT allowed.
Vogelmeier 2008 [37]	**Inclusion criteria**: stable COPD aged ≥40 years with a smoking history of ≥10 pack-years, FEV1 < 70% of patient's predicted normal value (and ≤1.00 L), and FEV1/FVC < 70%. Patients were to be symptomatic on at least 4 of 7 days prior to randomization (symptom score >0 on diary card).

	Exclusion criteria: a concomitant pulmonary disease; a respiratory tract infection within a month prior to screening; a clinically significant condition such as ischemic heart disease that might compromise patient safety or compliance. **Allowed co-medications**: On demand salbutamol and a fixed dose of ICS.
Aaron 2007 [38]	**Inclusion criteria**: Age older than 35 years; a history of 10 pack-years or more of cigarette smoking; moderate or severe COPD with an FEV1/FVC ratio < 0.70 and a postbronchodilator FEV1 < 65% of the predicted value; at least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomization; a recent COPD exacerbation requiring antibiotics or steroids were required to wait until treatment with these agents had been discontinued for 28 days before entering the study. **Exclusion criteria**: Physician-diagnosed asthma before 40 years of age; bronchiectasis; lung transplant; lung volume reduction surgery; chronic congestive heart failure with known persistent severe left ventricular dysfunction. **Allowed co-medications**: Inhaled albuterol as rescue medication, antileukotrienes, and methylxanthines. ICS, long-acting beta 2-agonists, and anticholinergics were NOT allowed.

Table S4 Characteristics of included studies. Abbreviations: ATS–ERS= American Thoracic Society-European Respiratory Society; ECG= electrocardiogram; FEV1= forced expiratory volume in one second; FVC= forced vital capacity; GOLD= Global Initiative for Chronic Obstructive Lung Disease; ICS= inhaled corticosteroids; mMRC= Modified Medical Research Council.

Comparison	Comparisons	N	Age	Male %	Baseline FEV1(L)	Current smoker %
LABA vs placebo	8	4,169	62.9	67	1.34	48
LAMA vs placebo	9	5,037	63.3	69	1.34	48
LABA/LAMA vs placebo	9	5,604	63.2	69	1.36	48
LABA vs LAMA	10	8,680	63.6	71	1.29	43
LABA vs LABA/LAMA	11	9,783	63.5	70	1.28	44
LAMA vs LABA/LAMA	20	20,793	63.6	62	1.21	40

Table S5. Study characteristics of class pair-wise comparisons and transitivity assessment. FEV1= forced expiratory volume in 1 second; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; N= number of subjects

Table S6a. Individual study results for death, total serious adverse events and dropouts due to adverse event

Study	N	Death	Total SAE	Dropout due to AE
D'Urzo 2014				
ACL/FM	335	1	19	21
ACL/FM	333	0	18	22
ACL	337	3	17	16
FM	332	1	15	14
Placebo	332	0	12	21
Singh 2014				
ACL/FM	385	NR	23	16
ACL/FM	381	NR	18	12
ACL	385	NR	16	17
FM	384	NR	14	14
Placebo	194	NR	12	8
Donohue 2013				
UMEC/VI	413	3	21	23
UMEC	418	3	27	34
VI	421	3	24	24
Placebo	280	0	9	9
Celli 2014				
UMEC/VI	403	0	23	19
UMEC	407	2	22	24
VI	404	2	20	25
Placebo	275	2	17	17
Decramer 2014a				
UMEC/VI	214	0	5	15
UMEC	212	1	7	10
VI	209	1	15	10
TIO	208	0	13	9
Decramer 2014b				
UMEC/VI	432	2	37	35
UMEC	222	0	15	17
TIO	215	2	9	11
Maleki-Yazdi 2014				
UMEC/VI	454	2	16	18
TIO	451	2	17	14
Donohue 2014				
UMEC/VI	226	0	14	17
UMEC	227	4	17	20
Placebo	109	1	7	12
DB2114417 2012				
UMEC/VI	296	0	8	NR
UMEC	99	1	2	NR
VI	76	0	2	NR
Placebo	170	0	6	NR
DB2114418 2012				
UMEC/VI	258	NR	8	NR
UMEC	81	NR	2	NR
VI	64	NR	2	NR
Placebo	151	NR	4	NR
Wedzicha 2013				
IND/Glyco	729	23	167	NR
Glyco	739	22	179	NR
TIO	737	25	165	NR
Dahl 2013				
IND/Glyco	225	4	37	13
Placebo	113	1	12	7
Bateman 2013				

IND/Glyco	474	1	22	6
IND	476	2	26	24
Glyco	473	1	29	14
TIO	480	3	19	10
Placebo	232	0	13	10
Vincken 2014				
IND/Glyco	226	0	5	3
IND	221	0	5	4
Novartis A1301				
IND/Glyco	119	1	19	11
TIO	39	0	2	0
Buhl 2015				
TIO/OLO	1029	18	169	37
TIO/OLO	1030	14	168	30
TIO	1033	17	172	43
TIO	1032	12	156	37
OLO	1038	14	181	51
ZuWallack 2014				
TIO/OLO	1133	3	64	39
TIO	1134	10	53	27
Aaron 2007				
TIO/SAL	148	6	9	6
TIO	156	4	10	8
Tashkin 2009				
TIO/FM	115	0	7	NR
TIO	128	0	7	NR
Vogelmeier 2008				
TIO/FM	207	0	10	8
FM	210	0	8	6
TIO	221	0	10	13
Placebo	209	1	12	8
Mahler 2012a				
TIO/IND	570	2	21	20
TIO	561	0	17	10
Mahler 2012b				
TIO/IND	572	1	19	14
TIO	570	2	18	16

ACL = aclidinium; AE=adverse event; FM= formoterol; Glyco=glycopyrronium; IND= indacaterol; N=number; NR=not reported; OLO= olodaterol; SAE=serious adverse event; SAL=salmeterol; TIO= tiotropium; UMEC=umeclidinium; VI=vilanterol

Table S6b. Individual study results for Cardiac serious adverse events, SGRQ and TDI responders.

Study	N	Cardiac SAE	SGRQ responders		TDI responders	
D'Urzo 2014			n	N	n	N
ACL/FM	335	2	290	519	756	1202
ACL/FM	333	4				
ACL	337	1	140	257	331	594
FM	332	3	133	254	340	596
Placebo	332	2	87	225	153	380
Singh 2014			n	N	n	N
ACL/FM	385	3	458	766	Data were combined and reported together with D'Urzo's study as shown above.	
ACL/FM	381	2				
ACL	385	1	NR	NR		
FM	384	0	NR	NR		
Placebo	194	1	103	194		
Donohue 2013			n	N	n	N
UMEC/VI	413	4	188	413	226	389
UMEC	418	6	172	418	207	394
VI	421	2	181	421	197	389

Placebo	280	1	86	280	106	260
Celli 2014			n	N	n	N
UMEC/VI	403	2	173	356	183	371
UMEC	407	7	144	361	153	376
VI	404	3	145	353	137	362
Placebo	275	0	80	219	70	234
Decramer 2014a			n	N	n	N
UMEC/VI	214	0	193	379	230	391
UMEC	212	0	92	178	112	188
VI	209	5	97	186	95	193
TIO	208	0	Combined with UMEC		Combined with UMEC	
Decramer 2014b			n	N	n	N
UMEC/VI	432	4	203	387	220	392
UMEC	222	0	201	391	200	397
TIO	215	0				
Maleki-Yazdi 2014			n	N		
UMEC/VI	454	2	237	454	NR	NR
TIO	451	2	196	451	NR	NR
Donohue 2014						
UMEC/VI	226	6	NR	NR	NR	NR
UMEC	227	7	NR	NR	NR	NR
Placebo	109	3	NR	NR	NR	NR
DB2114417						
UMEC/VI	296	1	NR	NR	NR	NR
UMEC	99	0	NR	NR	NR	NR
VI	76	1	NR	NR	NR	NR
Placebo	170	1	NR	NR	NR	NR
DB2114418						
UMEC/VI	258	NR	NR	NR	NR	NR
UMEC	81	NR	NR	NR	NR	NR
VI	64	NR	NR	NR	NR	NR
Placebo	151	NR	NR	NR	NR	NR
Wedzicha 2013			n	N		
IND/Glyco	729	33	404	684	NR	NR
Glyco	739	42	704	1335	NR	NR
TIO	737	41			NR	NR
Dahl 2013						
IND/Glyco	225	7	NR	NR	NR	NR
Placebo	113	0	NR	NR	NR	NR
Bateman 2013			n	N	n	N
IND/Glyco	474	1	281	441	299	439
IND	476	8	279	443	284	440
Glyco	473	8	514	880	531	865
TIO	480	3				
Placebo	232	2	111	196	111	193
Vincken 2014						
IND/Glyco	226	0	NR	NR	NR	NR
IND	221	1	NR	NR	NR	NR
Novartis A1301						
IND/Glyco	119	NR	NR	NR	NR	NR
TIO	39	NR			NR	NR
Buhl 2015			n	N	n	N
TIO/OLO	1029	19	1090	1969	NR	NR
TIO/OLO	1030	17			NR	NR
TIO	1033	19	941	1915	NR	NR
TIO	1032	13			NR	NR
OLO	1038	15	427	954	NR	NR
ZuWallack 2014			n	N	n	N
TIO/OLO	1133	13	556	1128	NR	NR
TIO	1134	9	480	1129	NR	NR
Aaron 2007						
TIO/SAL	148	NR	NR	NR	NR	NR
TIO	156	NR	NR	NR	NR	NR
Tashkin 2009						
TIO/FM	115	NR	NR	NR	NR	NR
TIO	128	NR	NR	NR	NR	NR

Vogelmeier 2008						
TIO/FM	207	2	NR	NR	NR	NR
FM	210	3	NR	NR	NR	NR
TIO	221	3	NR	NR	NR	NR
Placebo	209	2	NR	NR	NR	NR
Mahler 2012a						
TIO/IND	570	5	NR	NR	NR	NR
TIO	561	5	NR	NR	NR	NR
Mahler 2012b						
TIO/IND	572	2	NR	NR	NR	NR
TIO	570	4	NR	NR	NR	NR

ACL = aclidinium; AE=adverse event; FM= formoterol; Glyco=glycopyrronium; IND= indacaterol; N=number; NR=not reported; OLO= olodaterol; SAE=serious adverse event; SAL=salmeterol; SGRQ= St. George's Respiratory Questionnaire; TDI= Transition Dyspnea Index; TIO= tiotropium; UMEC=umeclidinium; VI=vilanterol

Table S7. Individual study results for COPD exacerbations.

Study(duration of treatment)	Total number of patients	Number of patients with at least one exacerbation	
		Moderate-to-severe exacerbation	Severe exacerbation
D'Urzo 2014 (24 weeks)			
ACL/FM	122	NR	NR
ACL	76	NR	NR
FM	61	NR	NR
Placebo	83	NR	NR
Singh 2014 (24 weeks)			
ACL/FM	766	74	8
ACL	385	46	7
FM	384	60	1
Placebo	194	27	5
Donohue 2013 (24 weeks)			
UMEC/VI	413	27	7
UMEC	418	33	12
VI	421	39	8
Placebo	280	35	3
Celli 2014 (24 weeks)			
UMEC/VI	403	23	5
UMEC	407	32	4
VI	404	32	3
Placebo	275	38	8
Decramer 2014a (24 weeks)			
UMEC/VI	426	26	8
UMEC or TIO	208	11	3
VI	209	17	2
Decramer 2014b (24 weeks)			
UMEC/VI	432	42	13
UMEC or TIO	437	40	3
Maleki-Yazdi 2014 (24 weeks)			
UMEC/VI	454	16	2
TIO	451	29	2
Donohue 2014 (52 weeks)			
UMEC/VI	226	29	2
UMEC	227	33	4
Placebo	109	26	3
DB2114417 (12 weeks)			
UMEC/VI	296	NR	1
UMEC	99	NR	0

VI	76	NR	0
Placebo	170	NR	1
DB2114418 (12 weeks)			
UMEC/VI	258	NR	2
UMEC	81	NR	0
VI	64	NR	0
Placebo	151	NR	1
Wedzicha 2013 (64 weeks)			
IND/Glyco	729	419	107
Glyco or TIO	1476	828	203
Dahl 2013 (52 weeks)			
IND/Glyco	225	63	12
Placebo	113	29	4
Bateman 2013 (26 weeks)			
IND/Glyco	474	85	10
Glyco or TIO	953	174	16
IND	476	103	15
Placebo	232	60	7
Vincken 2014 (12 weeks)			
IND/Glyco	226	33	1
IND	221	28	2
Novartis A1301 (52 weeks)			
IND/Glyco	119	NR	NR
TIO	39	NR	NR
Buhl 2015 (52 weeks)			
TIO/OLO	2059	633	124
TIO	2065	692	128
OLO	1038	370	67
ZuWallack 2014 (12 weeks)			
TIO/OLO	1133	126	18
TIO	1134	116	20
Aaron 2007 (52 weeks)			
TIO/SAL	148	96	NR
TIO	156	98	NR
Tashkin 2009 (12 weeks)			
TIO/FM	115	21	0
TIO	128	14	1
Vogelmeier 2008 (24 weeks)			
TIO/FM	207	13	3
TIO	221	23	5
FM	210	17	1
Placebo	209	30	3
Mahler 2012a (12 weeks)			
TIO/IND	570	48	6
TIO	561	51	11
Mahler 2012b (12 weeks)			
TIO/IND	572	38	9
TIO	570	52	9

ACL = aclidinium; AE=adverse event; FM= formoterol; Glyco=glycopyrronium; IND= indacaterol; NR=not reported; OLO= olodaterol; SAE=serious adverse event; SAL=salmeterol; TIO= tiotropium; UMEC=umeclidinium; VI=vilanterol

Table S8. Individual study results for change from baseline in FEV1, Transition Dyspnea Index, and change from baseline in SGRQ

Study	CFB in FEV1 (SE)	TDI (SE)	CFB in SGRQ (SE)
D'Urzo 2014 at 6 mo			
ACL/FM	0.095 (0.012)	2.02 (0.20)	-6.57 (0.74)
ACL/FM	0.076 (0.012)	1.98 (0.20)	-5.94(0.73)
ACL	0.066 (0.012)	1.56 (0.20)	-6.44(0.74)

FM	0.05 (0.012)	1.52 (0.20)	-4.70(0.74)
Placebo	-0.035 (0.012)	0.58 (0.20)	-2.21(0.74)
Singh 2014 at 6 mo			
ACL/FM	0.083 (0.012)	2.51 (0.06)	-7.16 (0.70)
ACL/FM	0.05 (0.012)	2.38 (0.17)	-8.34 (0.71)
ACL	0.056 (0.012)	2.11 (0.17)	-5.8 (0.71)
FM	-0.002 (0.012)	2.06 (0.16)	-5.58 (0.71)
Placebo	-0.061 (0.012)	1.22 (0.24)	-6.51 (1.03)
Donohue 2013 at 6 mo			
UMEC/VI	0.17 (0.013)	2.4 (0.16)	-8.07 (0.75)
UMEC	0.12 (0.013)	2.2 (0.16)	-7.25 (0.75)
VI	0.08 (0.013)	2.1 (0.16)	-7.75 (0.76)
Placebo	0.004 (0.016)	1.2 (0.20)	-2.56 (0.95)
Celli 2014 at 6 mo			
UMEC/VI	0.21 (0.012)	1.8 (0.15)	-7.43 (0.67)
UMEC	0.13 (0.012)	1.2 (0.16)	-4.14 (0.66)
VI	0.09 (0.012)	1.3 (0.16)	-4.71 (0.68)
Placebo	-0.03 (0.015)	0.8 (0.20)	-3.83 (0.88)
Decramer 2014a at 6 mo			
UMEC/VI	0.21 (0.019)	2.9 (0.20)	-9.03 (1.05)
UMEC	0.21 (0.018)	2.3 (0.20)	-6.87 (1.02)
VI	0.12 (0.019)	2.1 (0.20)	-8.29 (1.06)
TIO	0.12 (0.019)	2.4 (0.20)	-7.62 (1.05)
Decramer 2014b at 6 mo			
UMEC/VI	0.22 (0.018)	2.4 (0.20)	-10.52 (0.97)
UMEC/VI	0.21 (0.018)	2.3 (0.30)	-9.95 (0.98)
UMEC	0.19 (0.018)	1.9 (0.20)	-8.40 (0.97)
TIO	0.15 (0.018)	2.1 (0.20)	-9.78 (0.95)
Maleki-Yazdi 2014 at 6 mo			
UMEC/VI	0.205(0.011)	NR	-7.27 (0.54)
TIO	0.093(0.012)	NR	-5.17 (0.55)
Donohue 2014 at 12 mo			
UMEC/VI	0.19 (0.022)	NR	NR
UMEC	0.13 (0.023)	NR	NR
Placebo	-0.05 (0.033)	NR	NR
DB2114417 at 3 mo			
UMEC/VI	0.14 (0.016)	NR	NR
UMEC/VI	0.18 (0.016)	NR	NR
UMEC	0.11 (0.026)	NR	NR
UMEC	0.05 (0.026)	NR	NR
VI	0.07 (0.022)	NR	NR
Placebo	-0.03 (0.015)	NR	NR
DB2114418 at 3 mo			
UMEC/VI	0.22 (0.016)	NR	NR
UMEC/VI	0.20 (0.016)	NR	NR
UMEC	0.21 (0.029)	NR	NR
UMEC	0.10 (0.027)	NR	NR
VI	0.07 (0.022)	NR	NR
Placebo	-0.04 (0.016)	NR	NR
Wedzicha 2013 at 6 mo			
IND/Glyco	0.16 (0.015)	NR	-9.61 (1.03)
Glyco	0.09(0.015)	NR	-6.54 (1.02)
TIO	0.11(0.015)	NR	-5.92 (1.00)
Dahl 2013 at 12 mo			
IND/Glyco	0.18 (0.042)	NR	NR
Placebo	-0.07 (0.060)	NR	NR
Bateman 2013 at 6 mo			
IND/Glyco	0.17 (0.025)	2.72 (0.13)	-9.82 (1.13)
IND	0.09 (0.024)	2.47 (0.13)	-8.72 (1.07)
Glyco	0.08 (0.024)	2.52 (0.13)	-9.61 (1.13)
TIO	NR	2.21 (0.13)	-7.34 (1.10)
Placebo	NR	1.63 (0.23)	-6.05 (1.53)
Vincken 2014 at 3 mo			

IND/Glyco	NR	2.5 (0.23)	NR
IND	NR	2.0 (0.23)	NR
Novartis A1301 at 12 mo			
IND/Glyco	0.19 (0.017)	NR	NR
TIO	0.05 (0.028)	NR	NR
Buhl 2015 at 6mo			
TIO/OLO	0.13 (0.009)	1.98 (0.10)	NR
TIO/OLO		1.98 (0.10)	NR
TIO	0.076 (0.009)	1.63 (0.10)	NR
TIO		1.69 (0.10)	NR
OLO	0.057 (0.009)	1.56 (0.10)	NR
ZuWallack 2014 at 3mo			
TIO/OLO	0.185(0.006)	NR	-6.48 (0.47)
TIO	0.134(0.006)	NR	-3.87 (0.47)
Aaron 2007 at 12 mo			
TIO/SAL	0.07 (NR)	1.40 (0.33)	-6.3 (NR)
TIO	0.03 (NR)	1.78 (0.33)	-4.5 (NR)
Tashkin 2009 at 3 mo			
TIO/FM	0.34 (NR)	1.60 (NR)	-4.81 (NR)
TIO	0.17 (NR)	1.53 (NR)	-3.80 (NR)
Vogelmeier 2008			
TIO/FM	NR	NR	NR
FM	NR	NR	NR
TIO	NR	NR	NR
Placebo	NR	NR	NR
Mahler 2012a at 3 mo			
TIO/IND	0.23 (0.021)	NR	NR
TIO	0.15 (0.021)	NR	NR
Mahler 2012b at 3 mo			
TIO/IND	0.20 (0.018)	NR	NR
TIO	0.12 (0.018)	NR	NR

ACL = aclidinium; CFB= change from baseline; FM= formoterol; Glyco=glycopyrronium; IND= indacaterol; NR=not reported; OLO= olodaterol; SAE=serious adverse event; SAL=salmeterol; SE=standard error; SGRQ= St. George's Respiratory Questionnaire; TDI= Transition Dyspnea Index; TIO= tiotropium; UMEC=umeclidinium; VI=vilanterol

Table S9. Heterogeneity in the relative treatment effects.

	Relative treatment effect of combination therapy vs. comparator (SD)¶	Between-trials standard deviation†
Change from baseline in FEV1 (L) at 3 months (vs. placebo, LABA, and LAMA)	0.21 (0.01) 0.10 (0.01) 0.06 (0.01)	0.01
Change from baseline in (L) FEV1 at 6 months(vs. placebo, LABA, and LAMA)	0.17 (0.01) 0.08 (0.01) 0.05 (0.01)	0.02
Change from baseline in FEV1 (L) at 12 months(vs. placebo and LAMA)	0.24 (0.05) 0.07 (0.04)	0.05
Change from baseline in SGRQ at 3 months(vs. placebo, LABA, and LAMA)	-4.50 (0.69) -2.16 (0.54) -2.12 (0.33)	0.34
Change from baseline in SGRQ at 6 months(vs. placebo, LABA, and LAMA)	-3.63 (0.63) -1.44 (0.55) -1.53 (0.44)	0.82
Proportion of SGRQ responders at 6 months(vs. placebo, LABA, and LAMA)	0.20 (0.07) 0.21 (0.07) 0.21 (0.05)	0.09
TDI at 3 months(vs. placebo, LABA, and LAMA)	1.22 (0.14) 0.37 (0.12) 0.41 (0.10)	0.08
TDI at 6 months(vs. placebo, LABA, and LAMA)	1.18 (0.16) 0.40 (0.13) 0.35 (0.11)	0.05
Proportion of TDI responders at 6 months (vs. placebo, LABA, and LAMA)	0.74 (0.09) 0.29 (0.07) 0.26 (0.07)	0.08
Moderate-to-severe exacerbations(vs. placebo, LABA, and LAMA)	0.66 (0.06) 0.82 (0.05) 0.92 (0.04)	0.06
Severe exacerbations(vs. placebo, LABA, and LAMA)	-0.29 (0.23) 0.07 (0.20) -0.06 (0.13)	0.25
Mortality(vs. placebo, LABA, and LAMA)	0.69 (0.58) -0.07 (0.33) -0.26 (0.24)	0.33
Total serious adverse events(vs. placebo, LABA, and LAMA)	0.10 (0.11) -0.03 (0.08) -0.04 (0.06)	0.07
Cardiac serious adverse events(vs. placebo, LABA, and LAMA)	0.49 (0.36) -0.21 (0.27) -0.14 (0.19)	0.37

Dropouts due to adverse event(vs. placebo, LABA, and LAMA)	-0.04 (0.15) -0.08 (0.13) 0.03 (0.10)	0.22

¶ The results of dichotomous outcomes are presented in log-odds or log-hazard ratio. † If the between-trials SD approximates the size of treatment effect, heterogeneity is likely very high so that a 95% predictive interval of a future trial of infinite size could span zero effect. FEV1= forced expiratory volume in 1 second; SD= standard deviation; SGRQ=St. George's Respiratory Questionnaire; TDI=Transitional Dyspnea Index