National Institute for Health and Care Excellence

Draft for consultation

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[F] Inhaled therapies

NICE guideline <number>

Evidence reviews

July 2018

Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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ISBN:

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Inhaled therapy combinations

Review question

In people with stable COPD, what is the clinical and cost effectiveness of a long-acting muscarinic antagonist (LAMA) plus a long-acting beta-adrenoceptor agonist (LABA) compared with:

- a LAMA alone
- a LABA alone
- a LABA plus an inhaled corticosteroid (ICS)?

Introduction

COPD management is aimed at reducing the symptoms of the disease, preventing exacerbations and slowing disease progression. It consists of a number of components that may include a self-management strategy, vaccinations, smoking cessation treatment and support, pulmonary rehabilitation, oxygen therapy and non-invasive ventilation, and the use of inhaled medicines. Inhaled drugs can be grouped into short-acting bronchodilators, that aim to provide rapid relief of acute symptoms, long-acting bronchodilators that are taken by people with moderate to very severe COPD as a maintenance therapy, and inhaled corticosteroids (ICS).

The long-acting bronchodilators can be taken as single or fixed-dose combined inhalers. The possible combinations of drugs include: long-acting muscarinic antagonist (LAMA); long-acting beta-adrenoceptor agonist (LABA); LABA/inhaled corticosteroid (LABA/ICS) and LAMA/LABA. Treatment with ICS aims to reduce inflammation and ICS may act synergistically when combined with a LABA. LAMA and LABA combinations may also lead to synergistic effects.

This review aims to determine the comparative effectiveness of different drug classes for managing stable COPD. This review was carried out as a collaboration with the Cochrane Airways Group. The protocol used by the Cochrane Group is summarised in Table 1 and detailed in appendix A, with any additions noted in the methods section below. The review does not consider the comparative effectiveness of different drugs within a given class, or the comparative effectiveness of different inhaler devices.

Table 1 PICO for the comparative effectiveness of combinations of inhaled therapies

Population	• Patients aged > 35 years • Diagnosis of COPD in accordance with American Thoracic Society-European Respiratory Society (ATS/ERS 2004), GOLD report (GOLD 2017) or equivalent criteria. • Obstructive ventilator defect should be at least moderate, with a baseline FEV1 less than 80% of predicted.
Interventions	• LAMA • LABA • LAMA + LABA • LABA + ICS
Comparator	Each other
Outcomes	• COPD exacerbation (moderate to severe and severe)

	• St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score ≥ 4 units (responder) • Transition Dyspnoea Index (TDI) • Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropouts due to adverse event • Trough FEV1 • Pneumonia • Resource use and costs

Methods and process

This review was carried out as a collaboration with the Cochrane Airways Group. The published review protocol (Oba et al 2017) contains details of the methodology the Cochrane group planned to use to carry out their review and network meta-analysis (NMA).

The evidence presented here is the work of the Cochrane group, with the exception of any alterations made to reflect the methodology used by the NICE Guideline Updates Team, that are stated in the relevant sections. Any errors introduced by these changes are the responsibility of the NICE Guideline Updates Team alone. The sections of the review carried out by the NICE Guideline Updates Team were developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. The search strategies used in this review are detailed in appendix C.

In particular, the following definitions, key outcomes and methods have been adopted:

1. The Cochrane review divided exacerbations into moderate to severe and severe categories. A moderate exacerbation is defined as worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics; a severe exacerbation is defined as a rapid deterioration that requires hospitalisation.
2. Data for the St George's Respiratory Questionnaire (SGRQ) were presented in 2 ways, depending on the format of data in the included studies: as changes in SGRQ total score and as the number of responders (decrease in SGRQ score of ≥4 units).
3. End of study data was reported for dichotomous outcomes, while continuous outcomes were reported for the end of the study and at 3, 6 and 12 months where possible. Data that did not fit into these categories was assigned to the closest category.
4. The Cochrane group reported change in trough FEV1 in litres (L). This was not converted to millilitres (ml) as used in the other reviews carried out by the NICE Guideline Updates Team for the COPD guideline update to prevent the introduction of rounding errors in the data.
5. Resource use and costs were not included in the Cochrane review, but were addressed by the economic searches carried out by the NICE reviewers.
6. This review only includes drugs and doses licenced in the USA and EU.
7. The following inhaled bronchodilators were included in the review:
    - LAMA monotherapy (aclidinium, glycopyrronium, tiotropium and umeclidinium).

- LABA monotherapy (formoterol, olodaterol, salmeterol, vilanterol).
- LABA/ICS (formoterol/beclomethasone, formoterol/budesonide, formoterol/ciclesonide, formoterol/fluticasone, formoterol/mometasone, indacaterol/ mometasone, salmeterol/fluticasone, vilanterol/fluticasone).
- LABA/LAMA (formoterol/aclidinium, indacaterol/glycopyrronium, indacaterol/tiotropium, olodaterol/tiotropium, vilanterol/umeclidinium).

8. The Cochrane group NMA models allowed analysis of the drugs at the class level and at the individual drug level within and between classes. However, this review was limited to comparisons between drug classes. Please refer to the Cochrane review for additional information.
9. For data analysis, the Cochrane group divided the studies into low and high risk groups, based on the previous exacerbation history of the participants. Studies that specifically recruited people with a history of hospital admission due to COPD exacerbation within 12 months of study entry (or contained subgroup data on these people) were classed as high risk and those that didn't mention this as an entry criteria or actively recruited people without an exacerbation requiring hospitalisation in this time frame were classed as low risk. Data was presented for both low and high risk groups in the forest plots. Only the pooled effects from combining both groups was presented in the GRADE tables for the pair-wise comparisons because the use of these subgroups was not prespecified by the committee.
10. PINNACLE 3 (Hanania 2017) is an extension of the PINNACLE 1 and 2 (Martinez 2017 a and b) trials. Data were extracted for PINNACLE 3 in preference to PINNACLE 1 and 2 where possible. If data were included for all 3 studies, the PINNACLE 3 data were for the period of the extension trial only to prevent double counting.
11. The minimally important differences (MIDs) used in this review are summarised in Table 15 in appendix B. These were selected based on the literature with input from the committee.
12. Evidence tables, individual domain risk of bias judgements and reasons for study exclusion were extracted directly from the Cochrane review. However, overall study risk of bias and applicability assessments were carried out by the NICE Guideline Updates Team based on the information provided in the Cochrane review.
13. Publication bias was assessed using the funnel plots shown in appendix F, but in the absence of a clear risk of bias, was not incorporated into the GRADE tables.
14. The planned subgroup analyses were not carried out for this review because the included studies did not report data for the categories of interest in an accessible format.
15. The NMA models and data were provided by the Cochrane review authors. The models included fixed and random effect models with/without fixed or random class effects. These models were run according to the Cochrane group methods and choice of burn in, with priors specified by them. However, the NICE Guideline Updates Team used a larger burn in of 100,000 iterations to allow convergence of chains for the Cardiac SAEs low and high risk models.
16. Cochrane group did not write and test all possible models for each outcome. They started with the simplest model (fixed effect and fixed class) and then moved to more complex models as needed to achieve a good model fit to the data. If a simpler model was a good fit, then more complex models were not always tested. The Guideline updates team chose which of these models to use based on the rules in appendix B.

17. In cases where the data contained a large number of zero events, the Cochrane group used a continuity correction. This involved adding 0.5 to the zero event arm and its matching comparator arm.
18. Data were extracted for the mean effect and 95% credible intervals from the NMA model with the best fit to the data based on the NICE Guideline Updates team criteria for model choice detailed in appendix B. The data was extracted as mean differences (MD) or Relative Risks (RR).
19. The Cochrane group presented dichotomous outcomes, apart from exacerbations, as odds ratios (OR). These were converted to RR by the NICE Guideline Updates Team using the event rate in the reference or control arm for each outcome from sources used in the health economics model or, if this was not available, based on LABA arm data for the largest trial for a particular outcome.
20. The Cochrane group used hazard ratio (HR) models to look at exacerbations in their NMAs. The HR data obtained from these models cannot be compared to the pair wise RR data and, as a result, the pairwise data section of the tables for exacerbations are left blank (Table 27, Table 28, Table 29, Table 30).
21. Although there were studies at high risk of bias included in the NMA, a sensitivity analysis excluding these studies was not carried out because the sensitivity analysis carried out on the pair wise data did not alter the interpretation of the effects of the treatments.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Protocol deviation

From the methods in appendix B, sensitivity analysis should be carried out to examine the effects of removing studies at high risk of bias from all relevant outcomes. Based on discussion with the committee, it was agreed to prioritise the outcomes that would be of most use for decision making, namely exacerbations, change in TDI score, SGRQ score and the number of SGRQ responders.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the 2010 NICE COPD guideline (CG101). It covers three questions that were last updated in 2010 (see appendix A). The evidence for this review was provided as part of a collaboration with the Cochrane Airways Group. They searched for and identified relevant studies. Please refer to the Cochrane review for details of the numbers of papers retrieved by the searches and for the PRISMA diagram for this process.

The Cochrane group carried out a second search for references at the end of the COPD guideline update process. One hundred and fifty references were screened by the Guideline Updates Team at the title and abstract stage and 12 of these were ordered for full text screening. Four of the references were included (Buhl 2017, Hanania 2017, Ichinose 2017, Vogelmeier 2017). However, as they did not refer to new trials, but were published versions of studies that had already been included based on other published papers or clinical trial reports, they were added to the existing references and any additional data was extracted under the original study name.

One additional reference (Ferguson 2017) was identified in the search update for the LAMA monotherapy question. This was added to the RISE trial record as the published version of an included AstraZeneca clinical trial. (Please refer to the LAMA monotherapy review below for the details of this search.)

The evidence tables for the included studies are presented in appendix E and the studies are referenced in full in appendix M.

Excluded studies

The excluded studies are listed in appendix K with reasons for their exclusion, and as full references in appendix M.

Summary of clinical studies included in the evidence review

The evidence tables for the included studies are presented in appendix E and the studies referenced in full in appendix M.

Quality assessment of clinical studies included in the evidence review

The included studies were assessed for risk of individual biases and applicability by the Cochrane group. Overall study level risk of bias and applicability was judged by the Guideline Updates Team and both sets of information are presented in appendix E.

Please refer to appendix F for forest plots, appendix G for the NMA data and appendix H for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. The search returned 16,299 records, of which 16,198 were excluded on title and abstract for this review question. The remaining 101 papers were screened using a review of the full text and 5 were found to be relevant to the question. A number of relevant UK-based analyses were identified by the review, so only studies using an NHS perspective were included.

Excluded studies

Details of the studies excluded at full text review are given in Appendix K.

Summary of studies included in the economic evidence review

Gani et al. (2010) conducted a cost–utility analysis with a 1-year time horizon comparing tiotropium (LAMA) with salmeterol (LABA) and with ipratropium (SAMA) in UK COPD patients with FEV1 of < 80% predicted. This study was funded by 2 manufacturers of tiotropium. The evaluation used a Markov structure based on GOLD stages 2, 3 and 4 (50%–80% FEV1 predicted, 30%–49% FEV1 predicted, and < 30% FEV1 predicted, respectively). In each cycle of the model patients could remain the same GOLD state or progress to a different GOLD state. In each cycle patients were also at risk of either a severe or non-severe exacerbation.

Treatment effects were implemented as a relative risk of exacerbations and treatment-specific probabilities of moving between GOLD stages in each cycle

(determined by patients' change in FEV1 over time). These data were taken from RCTs comparing tiotropium 18 micrograms once-daily with either salmeterol 50 micrograms twice-daily (described in Brusasco 2003), ipratropium 40 micrograms four-times daily (not included in the clinical review), or placebo (described in Casaburi 2002).

The model included 3 categories of cost: (1) maintenance costs, which were estimated based on disease severity by a Delphi Panel of GPs and secondary care consultants; (2) exacerbation costs, which were calculated by estimating the proportion of patients managed in primary or secondary care for each type of exacerbation and weighting the appropriate NHS reference costs by these proportions; and (3) drug costs, which were calculated based on the list prices and recommended dosage of each treatment.

Baseline utility scores stratified by GOLD stage were taken from a study which measured EQ-5D scores of a sample of 1,235 COPD patients, with a utility reduction of 50% or 15% applied over the course of a month for severe or non-severe exacerbations, respectively.

Base-case results showed that, compared with salmeterol, tiotropium is associated with a cost saving of £126 and generates an additional 0.014 QALYs, and therefore dominates salmeterol. Probabilistic sensitivity analysis indicated that tiotropium was the cost-effective option in 97% of iterations. A subgroup analysis showed that tiotropium continues to dominate salmeterol when patients are stratified by baseline GOLD stage.

This study was classified as being partially applicable as it only considered 2 of the interventions of interest. It was categorised as having potentially serious limitations as it uses a short time horizon, does not include treatment-related adverse events, estimates costs via a Delphi Panel rather than using empirical data, and is subject to a potential conflict of interest.

Hertel et al. (2012) conducted a cost–utility analysis with a lifetime horizon of various combinations of LAMA, LABA, ICS and roflumilast in UK COPD patients with severe and very severe COPD, with ICS-tolerant and ICS-intolerant patients analysed as 2 separate cohorts. This study was funded by a manufacturer of roflumilast. The evaluation used a Markov structure based on GOLD stages 3 and 4 (30%–50% predicted FEV1 and < 30% predicted FEV1 respectively). In each cycle of the model, patients could remain in the same GOLD state, progress to a more severe GOLD state or die. In each cycle patients were also at risk of exacerbation, which could be community- or hospital-treated. The model also allowed treatment switching to a second line regimen: LAMA + LABA/ICS for ICS-tolerant patients and LAMA + LABA for ICS intolerant patients.

Patients' probability of progressing to a more severe GOLD stage was modelled based on the mean rate of FEV1 decline in COPD patients. Mortality was incorporated by applying the standardised mortality ratio for COPD to the background mortality rate for the UK population, and also by including a probability of death associated with hospital-treated exacerbations. Treatment effects were incorporated as relative differences in exacerbation rates derived from a network meta-analysis.

The analysis included three categories of cost: (1) maintenance costs, which were estimated using resource use data from a tiotropium and unit cost data from NHS reference costs; (2) exacerbation costs, which were estimated using resource usage data from the GOLD strategy group, and unit costs from NHS reference costs; and (3) drug costs, which were sourced from the BNF. Baseline utility scores according to GOLD stage were obtained from clinical trials of roflumilast, and utility decrements

associated with exacerbations were obtained from a previous study evaluating holistic preferences of a variety of COPD health states.

Relevant base-case results of the evaluation are shown in Table 2 and Table 3, which excludes interventions not relevant to the review question (ICERs have been manually calculated as were not reported by the authors). These results show that LAMA+LABA produces the greatest number of QALYs and is associated with an ICER of less than £20,000 per QALY, and is therefore the most cost-effective option at this threshold.. The authors' sensitivity analyses addressed a comparison which is not relevant to the review question.

Table 2: Incremental results for treatments of interest in Hertel et al. (2012) in ICS-tolerant patients

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
LABA	£22,342	5.39	-	-	-
LAMA	£22,370	5.42	£28	0.03	£933
LABA+ICS	£22,468	5.43	£98	0.01	£9,800
LAMA+LABA	£22,687	5.45	£219	0.02	£10,950

Table 3: Incremental results for treatments of interest in Hertel et al. (2012) for ICS-intolerant patients

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
LABA	£21,477	5.13	-	-	-
LAMA	£21,500	5.17	£23	0.04	£575
LAMA+LABA	£21,814	5.19	£314	0.02	£15,700

This analysis was categorised as being partially applicable as it is conducted in a population of patients with severe or very severe COPD. It was classified as having potentially serious limitations as it relies on assumed exacerbation rates with no empirical basis, does not conduct a probabilistic sensitivity analysis for the comparisons of interest, does not include treatment-related adverse events, and is subject to a potential conflict of interest.

Price et al. (2013) conducted a cost–utility analysis with a 3-year time horizon comparing indacaterol (LABA) with tiotropium (LAMA), and indacaterol (LABA) with salmeterol (LABA) in patients with COPD in the UK. This study was funded by a manufacturer of indacaterol. The evaluation used a Markov structure with states based on GOLD stages 1, 2, 3 and 4 (FEV1 ≥ 80% predicted, 50%-80% predicted, 30%-50% predicted, and <30% predicted, respectively). In each cycle of the model, patients could remain in the same GOLD stage, change GOLD stage, or die. Patients could also experience a mild or severe exacerbation in each cycle.

Effects of treatment on FEV1 and exacerbation rates were incorporated using data from the INLIGHT-2 and INHANCE trials (reported in Donohue 2010 and Kornmann 2011). Improvement in patients' FEV1 was implemented via empirical transition probabilities in the first 12-week cycle of the model. After this initial period the assumption was made that all patients experienced a uniform decline in FEV1 regardless of treatment received. Differences in exacerbation rates were implemented by applying rate ratios for each treatment versus placebo to the number of exacerbations experienced in the placebo arms of the trials.

Resource use data were obtained from the Optimum Patient Care Research Database and were validated with 'a UK clinician with expertise in COPD management'. Unit costs were taken from standard NHS sources. Baseline utility scores for each GOLD state were taken from indacaterol clinical trials, and utility decrements associated with exacerbations were obtained from a previous study evaluating holistic preferences of a variety of COPD health states.

Results were presented as pairwise comparisons, rather than as a fully incremental analysis. Base-case results indicate that, compared with tiotropium 18 micrograms daily, indacaterol 150 micrograms daily produces a cost saving of £248 and generates 0.008 additional QALYs and therefore dominates tiotropium. Similarly, indacaterol 300 micrograms produces a saving of £259 and generates 0.008 additional QALYs compared with tiotropium 18 micrograms daily, and therefore also dominates tiotropium. The authors report that this result is primarily due to a substantially larger 12-week improvement in FEV1 produced by indacaterol compared with tiotropium.

One-way sensitivity analyses showed that indacaterol (at both dosages) dominates tiotropium regardless of the time horizon. Probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, indacaterol is cost effective compared with tiotropium 18 micrograms in 84% of iterations (although the authors do not state which dosage of indacaterol this comparison relates to).

This study was classified as being partially applicable, as it only considers 2 of the interventions of interest. It was categorised as having potentially serious limitations, as it uses a short time horizon in the base case, and does not include treatment-related adverse events, and is subject to a potential conflict of interest.

Punekar et al. (2015) conducted a cost–utility analysis with a lifetime horizon comparing umeclidinium/vilanterol combination therapy (LAMA + LABA) with tiotropium monotherapy (LAMA) in patients with COPD in the UK. The study was funded by a manufacturer of umeclidinium/vilanterol. The evaluation used a linked-equation model of COPD, which consisted of a series of regression equations to describe how patients' baseline variables and disease characteristics (cough/sputum, exacerbations, and FEV1) affected their disease progression and final outcomes (resource usage, HRQoL and mortality) over time. These equations were estimated from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.

Treatment effect was implemented in the model through the difference in change from baseline in FEV1 at 24 weeks between umeclidinium/vilanterol and tiotropium in four umeclidinium/vilanterol phase 3 clinical trials. Three of these trials are described in the clinical evidence review (Decramer 2014a, Decramer 2014b, and Donohue 2013), and one (Celli 2014) was excluded due to using a umeclidinium dose not licensed in the UK.

Resource use was predicted from a linked equation, based on patients' intermediate outcomes. Unit costs were taken from standard NHS sources (National Schedule of Reference Costs and PSSRU Unit Costs of Health and Social Care). Cost of treatment with tiotropium was obtained from the BNF (£33.50 for a 30 day supply), and the assumption was made in the base case that the cost of umeclidinium/vilanterol was equivalent to this (although the BNF reports its cost as £32.50 for a 30 day supply). HRQoL was predicted from a regression equation in the form of a Saint George's Respiratory Questionnaire (SGRQ) score, which was converted to an EQ-5D score via a mapping algorithm.

Base-case results showed that umeclidinium/vilanterol produces an ICER of £2,088 per QALY compared with tiotropium monotherapy. Umeclidinium/vilanterol remained cost effective at a threshold of £20,000 per QALY in scenario analyses using 1- and 5-year time horizons, and in which the benefit of treatment was assumed to only persist for 12 months. Probabilistic sensitivity analysis showed that umeclidininum/vilanterol was cost effective in 85% of iterations.

This study was classified as being partially applicable, as it only assesses 2 of the interventions of interest, and is partly informed by clinical data on a dose of umeclidinium not licensed in the UK. It was categorised as having potentially serious limitations, as it only implements treatment effect via improvement in FEV1, implicitly makes the assumptions that all intermediate and final outcomes of treatment can be explained by change in FEV1, and is subject to a potential conflict of interest.

Ramos et al. (2016) conducted a cost–utility analysis with a 5-year time horizon comparing aclidinium bromide/formoterol (LAMA + LABA) with aclidinium bromide alone in patients with COPD in the UK. This study was funded by a manufacturer of aclidinium bromide. The evaluation used a Markov model with states based on GOLD stages 1, 2, 3, and 4 (FEV1 ≥ 80% predicted, 50%–80% predicted, 30%–50% predicted, and <30% predicted, respectively). In each cycle of the model, patients could remain in the same GOLD stage, change GOLD stage or die. Patients could also experience a hospitalised or non-hospitalised exacerbation or a pneumonia adverse event in each cycle.

Treatment effect was implemented via improvement in FEV1 at 24 months from the ACLIFORM and AUGMENT studies (described in Singh 2014 and D'Urzo 2014), which was incorporated in the model via probabilities of changing GOLD state. After this initial period the assumption was made that all patients experienced a uniform decline in FEV1 regardless of treatment received. Exacerbation rates stratified by disease severity were taken from previous trials of tiotropium, ipratropium, and salmeterol, but were assumed not to be directly affected by treatment.

The analysis included four categories of cost: (1) maintenance costs, for which resource use data were taken from a trial of tiotropium conducted in the Netherlands, stratified by disease severity, with unit costs taken from standard NHS sources; (2) exacerbation costs, which were taken from a previous economic analysis; (3) drug costs, which were taken from the BNF; and (4) cost of a pneumonia adverse event, which was based on HRG data. Baseline utility scores according to severity were taken from a previous quality of life study of COPD patients from the UPLIFT trial, with utility reductions of 15% and 50% for moderate and severe exacerbations respectively, as per the methods of previous economic analyses. A disutility of 50% was also assumed for a pneumonia event.

Results showed that aclidinium bromide/formoterol produces an ICER of £2,976 per QALY compared with aclidinium bromide alone. Aclidinium bromide/formoterol remained cost effective at a threshold of £20,000 per QALY in scenario analyses in which alternative lower values were used to inform patients' baseline FEV1, and in which 1- and 15-year time horizons were used. Probabilistic sensitivity analysis showed that aclidinium bromide/formoterol was cost effective in 79% of iterations.

This study was classified as being partially applicable, as it only includes 2 of the interventions of interest. It was categorised as having potentially serious limitations, as it did not incorporate the effect of treatment on exacerbations in the analysis (only the effect of treatment on FEV1), did not incorporate treatment-related adverse events other than pneumonia, and is subject to a potential conflict of interest.

Economic model

This section summarises the de novo economic modelling conducted for this review question. For a full, comprehensive description of methods, results and conclusions please refer to the model report in Chapter H.

Patient population:

Adults with COPD whose symptoms are not adequately controlled using short-acting bronchodilators.

Comparators:

Four classes of treatment were assessed by the economic model: LABA monotherapy, LAMA monotherapy, LABA+ICS, and LAMA+LABA. However, since the model simulates the long-acting bronchodilator treatment pathway over patients' lifetime rather than just the initial treatment, 6 mutually exclusive treatment strategies are possible when options for stepping up from monotherapy to dual therapy are accounted for:

1. **LABA -to- LABA+ICS** – start treatment on LABA, and step up to LABA+ICS if required
2. **LABA -to- LAMA+LABA** – start treatment on LABA, and step up to LAMA+LABA if required
3. **LAMA -to- LABA+ICS** – start treatment on LAMA, and change to LABA+ICS if stepping up of treatment is required
4. **LAMA -to- LAMA+LABA** - start treatment on LAMA, and step up to LAMA+LAMA if required
5. **LABA+ICS** – start treatment on LABA+ICS without first prescribing a monotherapy
6. **LAMA+LABA** – start treatment on LAMA+LABA without first prescribing a monotherapy

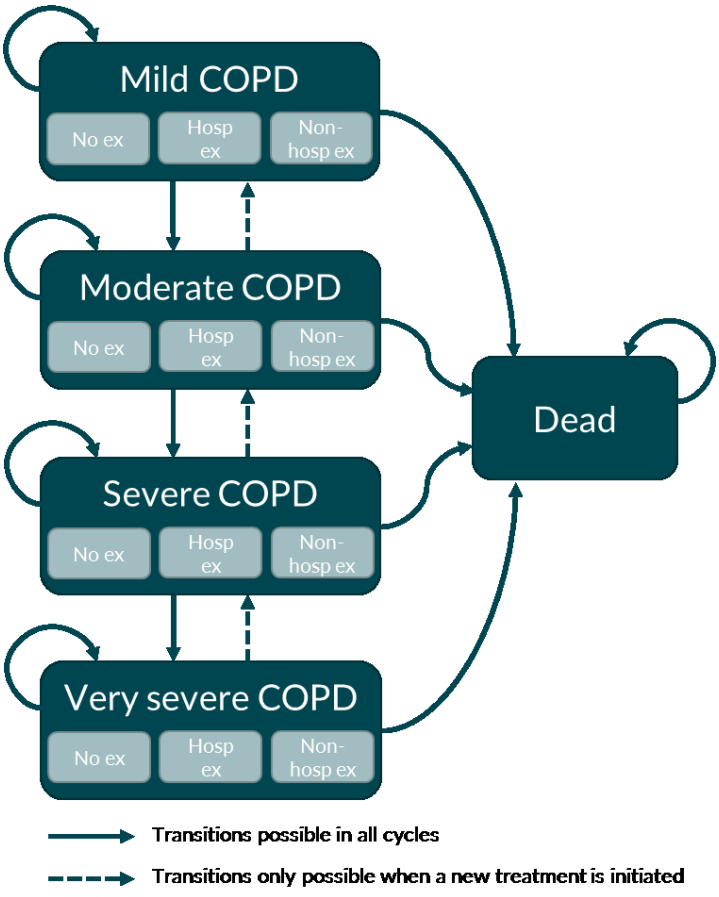
Methods

Model structure

In order to represent the natural history of COPD over time, the model uses a Markov structure, with states based on GOLD severity stages defined by FEV1 percent predicted (shown in Figure 1). In each cycle of the model, patients have a probability of moving to a more severe GOLD stage (defined by the natural rate of FEV1 decline over time), and a probability of death (defined by stage-specific mortality rates). In the first cycle of the model, patients may move to a less severe GOLD stage, in order to reflect the initial FEV1 benefit from initiating long-acting bronchodilator therapy.

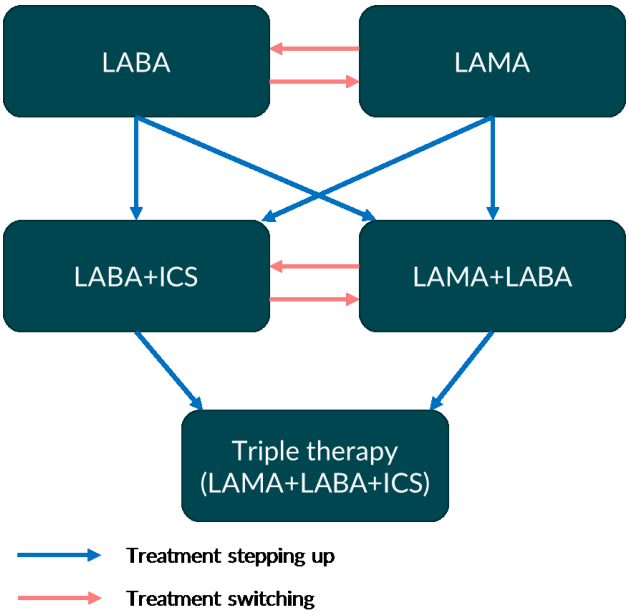
In each cycle, patients can also experience a hospitalised or non-hospitalised exacerbation, or an adverse event. The model uses a 3-month cycle length, which was deemed an appropriate period of time to capture progression between states, as well as interfacing well with clinical trial data on long-acting bronchodilators, which typically use 3-, 6-, or 12-month endpoints.

Figure 1 – overall structure of the model



The model also simulates patients' treatment progression over time. In each cycle, patients have a probability of either stepping up their treatment (adding in another drug) or switching their treatment (changing to a regimen of the same number of drugs). The pathway for treatment progression is shown in Figure 2. While triple therapy (LAMA+LABA+ICS) was outside of scope of the guideline update, this regimen is typically provided for patients whose symptoms are not adequately controlled by dual therapy (as per the recommendations in the 2010 update of this guideline), and is therefore included as a final step in the modelled pathway.

Figure 2 – treatment progression pathway in the model



Incorporating treatment effects

Treatment benefits

The network meta-analysis (NMA) conducted for this review question provided a number of outcomes which could be used to model treatment benefit: exacerbations, SGRQ, FEV1, and TDI. However, independently incorporating all of these outcomes simultaneously in the model would introduce double-counting of benefits. Therefore, a number of scenarios were modelled, using the following combinations of outcomes from the NMA:

- **Scenario 1: Exacerbations alone**
- **Scenario 2: SGRQ and exacerbations**
- **Scenario 3: FEV1 and exacerbations** – this scenario was modelled by allowing differences in transition probabilities in the first cycle of the model, with more effective treatments associated with a greater probability of moving to a less severe GOLD stage
- **Scenario 4: TDI and exacerbations** – this scenario was modelled using coefficients from a regression analysis in order to predict the effect of breathlessness on SGRQ score
- **Scenario 5: FEV1, TDI and exacerbations** – as above, this scenario used coefficients from a multiple regression analysis in order to predict the independent effect of FEV1, breathlessness and exacerbations in the previous year on SGRQ

Effect on treatment progression

Differences in the probability of stepping up treatment were implemented by assuming an inverse relationship with treatment effect on TDI, since breathlessness provides a reasonable indication of how well patients' disease symptoms are managed. Differences in the probability of treatment switching were implemented using the discontinuation due to adverse events outcome from the NMA.

Treatment effect on mortality and adverse events

Treatment effect on mortality was applied directly to the baseline mortality rate for each GOLD stage.

Adverse events were categorised as either cardiac, pneumonia, or 'other' events. Treatment effects from the NMA for the appropriate adverse event category were applied to these, using total serious adverse events as a proxy for the 'other' events category.

Since the mortality and adverse event outcomes from the NMA were generally associated with a high degree of uncertainty, results were presented both with and without treatment-specific differences in these outcomes in 3 scenarios:

- **Option A:** Treatment-specific differences in adverse events and mortality excluded
- **Option B:** Treatment-specific differences in adverse events, but not mortality, included
- **Option C:** Treatment-specific differences in adverse events and mortality included

Costs

Five categories of cost were used in the model

1. **Drug costs** – acquisition costs of long-acting bronchodilators
2. **Maintenance costs** – routine healthcare resource use for each GOLD severity stage
3. **Exacerbation costs** – resource use associated with a hospitalised or non-hospitalised exacerbation
4. **Adverse event costs** – costs associated with treating acute and chronic adverse events
5. **Treatment progression costs** – healthcare costs associated with switching or stepping up treatment

Health-related quality of life

Patients' stable quality of life (QoL) initially depended upon their GOLD stage, with disutilities applied depending on whether patients experienced an exacerbation or adverse event within each cycle.

SGRQ values were used to inform patients' baseline QoL. These were converted to EQ-5D scores via a mapping algorithm in line with the NICE Reference case.

Subgroups

As well as modelling the overall population, results were also produced for patient subgroups stratified by high and low risk of exacerbations. These subgroups differed from the overall population in two ways:

1. NMA outcomes for high- and low-risk subgroups were used to model treatment effect, rather than combined outcomes for the overall population
2. Baseline exacerbation rate was stratified according to patients who had experienced one or more exacerbations in the previous year, versus patients who had experienced no exacerbations, for the high- and low-risk subgroups respectively

Results

Results presented in this section are means of 1,000 probabilistic iterations. Structural uncertainty in the model is also addressed stochastically, by randomly selecting 1 of the 5 scenarios for implementing treatment benefit in each iteration. Individual results for these scenarios are presented in Chapter H.

Overall population

Table 4 shows results for the overall population, when treatment effects on adverse events and mortality are excluded. These results indicate that starting treatment on LAMA+LABA is the most cost-effective option, with a relatively high degree of certainty.

Table 4 – Mean probabilistic results for the overall population. Option A: treatment-specific differences in adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£27,554	5.44	-	-	-	11.7%
LAMA - to - LABA+ICS	£27,747	5.41	£192	-0.029	dominated	0.0%
LAMA+LABA	£27,825	5.52	£271	0.079	£3,428	86.3%
LABA - to - LAMA+LABA	£27,912	5.42	£86	-0.100	dominated	0.1%
LABA - to - LABA+ICS	£28,102	5.39	£276	-0.128	dominated	0.0%
LABA+ICS	£28,113	5.48	£287	-0.039	dominated	1.9%

Table 5 shows results when the effect of treatment on adverse events is included. These results show that LAMA+LABA still has the highest probability of being cost effective, but this result is somewhat less certain than in the previous scenario.

Table 5 – Mean probabilistic results for the overall population. Option B: treatment-specific differences in adverse events but not mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,170	5.40	-	-	-	21.7%
LABA - to - LAMA+LABA	£28,306	5.39	£136	-0.009	dominated	7.3%
LAMA - to - LABA+ICS	£28,341	5.37	£171	-0.029	dominated	0.2%
LABA - to - LABA+ICS	£28,472	5.36	£302	-0.038	dominated	0.1%
LAMA+LABA	£28,577	5.47	£407	0.073	£5,546	57.2%
LABA+ICS	£28,765	5.44	£188	-0.037	dominated	13.5%

Table 6 shows results when treatment effects on both adverse events and mortality are included. These results show that LABA+ICS is now the strategy which generates the highest number of QALYs, but is associated with a mean ICER in excess of £20,000 per QALY. Probabilistic sensitivity analysis also shows that there is now a high degree of uncertainty surrounding results.

Table 6 – Mean probabilistic results for the overall population. Option C: treatment-specific differences in adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£26,712	5.22	-	-	-	9.9%
LABA - to - LAMA+LABA	£27,034	5.24	£322	0.018	ext. dom.	7.5%
LAMA - to - LABA+ICS	£27,209	5.24	£497	0.015	dominated	2.6%
LAMA+LABA	£27,388	5.33	£675	0.108	£6,256	37.8%
LABA - to - LABA+ICS	£27,526	5.25	£139	-0.075	dominated	5.5%
LABA+ICS	£28,004	5.35	£617	0.025	£24,432	36.7%

High-risk population

Table 7 shows results for the high-risk population, when treatment effects on mortality and adverse events are not included. These results show that LAMA+LABA produces a lower mean ICER for the higher risk population than in the overall population, and has a high probability of being the most cost-effective treatment.

Table 7 – Mean probabilistic results for the high-risk subgroup. Option A: treatment-specific differences in adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,922	5.36	-	-	-	6.0%
LAMA+LABA	£28,959	5.45	£37	0.091	£404	93.6%
LAMA - to - LABA+ICS	£29,173	5.32	£214	-0.128	dominated	0.0%
LABA+ICS	£29,341	5.40	£382	-0.050	dominated	0.4%
LABA - to - LAMA+LABA	£29,581	5.31	£622	-0.132	dominated	0.0%
LABA - to - LABA+ICS	£29,830	5.28	£871	-0.169	dominated	0.0%

Table 8 shows results for the high-risk population when the effect of treatment on adverse events is included. These results show that, despite slightly higher uncertainty, there is still a high probability that LAMA+LABA is the most cost-effective treatment.

Table 8 – Mean probabilistic results for the high-risk subgroup. Option B: treatment-specific differences in adverse events but not mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£29,332	5.46	-	-	-	75.0%
LAMA - to - LAMA+LABA	£29,337	5.36	£5	-0.098	dominated	19.2%
LAMA - to - LABA+ICS	£29,658	5.31	£326	-0.141	dominated	0.3%
LABA - to - LAMA+LABA	£29,819	5.33	£487	-0.130	dominated	2.0%
LABA+ICS	£29,873	5.39	£541	-0.064	dominated	3.4%
LABA - to - LABA+ICS	£30,136	5.28	£804	-0.173	dominated	0.1%

Table 9 shows results for the high-risk population when treatment effects on mortality and adverse events are included. Results show that uncertainty increases

substantially when mortality effects are included, but LAMA+LABA still shows a considerably higher probability of being the most cost-effective treatment than any other strategy.

Table 9 – Mean probabilistic results for the high-risk subgroup. Option C: treatment-specific differences in adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£28,255	5.20	-	-	-	11.2%
LAMA+LABA	£28,527	5.33	£272	0.133	£2,047	64.1%
LABA - to - LAMA+LABA	£28,687	5.16	£159	-0.171	dominated	1.5%
LAMA - to - LABA+ICS	£28,854	5.19	£327	-0.140	dominated	2.6%
LABA - to - LABA+ICS	£29,278	5.15	£751	-0.178	dominated	0.4%
LABA+ICS	£29,448	5.32	£921	-0.014	dominated	20.2%

Low-risk subgroup

Table 10 shows results for the low-risk population, when treatment effects on mortality and adverse events are not included. LAMA+LABA is associated with the highest probability of being the most cost-effective treatment, although there is substantially more uncertainty in the probabilistic results than in the equivalent scenario for the overall population and high risk subgroup.

Table 10 – Mean probabilistic results for the low-risk subgroup. Option A: treatment-specific differences in adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA - to - LAMA+LABA	£26,205	5.77	-	-	-	20.3%
LAMA - to - LAMA+LABA	£26,332	5.77	£127	-0.001	dominated	21.9%
LABA - to - LABA+ICS	£26,433	5.75	£228	-0.024	dominated	0.1%
LAMA - to - LABA+ICS	£26,564	5.75	£359	-0.024	dominated	0.0%
LAMA+LABA	£26,900	5.84	£695	0.068	£10,200	48.5%
LABA+ICS	£27,271	5.82	£371	-0.027	dominated	9.2%

Table 11 shows the results for the low-risk population, when treatment effect on adverse events is included. In this scenario, the mean ICER for LAMA+LABA exceeds £20,000 per QALY, and LABA -to- LAMA/LABA shows the highest probability of being cost effective, but no one strategy is clearly the optimal choice.

Table 11 – Mean probabilistic results for the low-risk subgroup. Option B: treatment-specific differences in adverse events but not mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA - to - LAMA+LABA	£26,869	5.48	-	-	-	29.2%
LABA - to - LABA+ICS	£26,924	5.46	£55	-0.021	dominated	4.8%
LAMA - to - LAMA+LABA	£27,037	5.46	£168	-0.018	dominated	13.3%
LAMA - to - LABA+ICS	£27,101	5.44	£232	-0.040	dominated	0.8%

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA+ICS	£27,654	5.50	£785	0.021	ext. dom.	27.6%
LAMA+LABA	£27,712	5.52	£843	0.038	£22,348	24.3%

Table 12 shows the results for the low-risk population when treatment effects on mortality and adverse events are included. Results show that, in this scenario, strategies containing LABA and LABA+ICS have a higher probability of being cost effective than other strategies, although no one strategy is clearly the optimal choice.

Table 12 – Mean probabilistic results for the low-risk subgroup. Option C: treatment-specific differences in adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LAMA - to - LAMA+LABA	£24,355	5.07	-	-	-	2.3%
LAMA - to - LABA+ICS	£24,914	5.12	£559	0.053	ext. dom.	0.6%
LABA - to - LAMA+LABA	£24,957	5.21	£602	0.140	£4,293	17.9%
LAMA+LABA	£25,349	5.17	£391	-0.034	dominated	10.7%
LABA - to - LABA+ICS	£25,528	5.26	£571	0.055	£10,317	35.9%
LABA+ICS	£25,976	5.26	£448	0.002	£256,979	32.6%

Evidence statements

Clinical evidence statements

The format of the evidence statements is explained in the methods in appendix B. All of the results described below are based on pooled data collected for the final time point of each included study, apart from FEV1, SGRQ resonders and total scores, and TDI scores. In these cases, results were analysed at 3, 6 and 12 months and where no time points are stated then the evidence statement applies to all time points examined.

Pair-wise analysis

LABA/LAMA versus LABA/ICS

- Moderate quality evidence from 8 RCTs with 8,753 people found a reduction in the number of people experiencing pneumonia who were offered LAMA/LABA compared to LABA/ICS.
- Very low to moderate quality evidence from up to 7 RCTs with up to 6,446 people found an improvement in trough FEV1 at 3 and 6 months in people offered LAMA/LABA compared to LABA/ICS, but the point estimates were less than the defined individual minimal clinically important differences.
- Very low to high quality evidence from up to 9 RCTs with up to 8,796 people found no meaningful difference in the change in FEV1 at 12 months; TDI score at 3 and 6 months; SGRQ score at 3, 6 and 12 months; the numbers of SGRQ responders at 3 and 12 months; or in the numbers of people experiencing moderate to severe exacerbations and SAEs in people offered LAMA/LABA compared to LABA/ICS.
- Low to moderate quality evidence from up to 9 RCTs with up to 8,796 people could not differentiate between people offered LAMA/LABA compared to LABA/ICS with regards to the number of people experiencing severe

exacerbations, cardiac SAEs, COPD SAEs, the numbers of SGRQ responders at 6 months, all-cause mortality and dropouts due to adverse events.

LABA/LAMA versus LAMA

- Very low to moderate quality evidence from up to 26 RCTs with up 21,877 people found no meaningful difference in the change in FEV1, TDI or SGRQ score or the number of SGRQ responders at 3, 6 and 12 months; or in the numbers of people experiencing SAEs, COPD SAEs or dropouts due to adverse events in people offered LAMA/LABA compared to LAMA.
- Very low to high quality evidence from up to 24 RCTs with up 20,683 people could not differentiate people offered LAMA/LABA compared to LAMA with regards to the number of people experiencing moderate to severe or severe exacerbations, cardiac SAEs, pneumonia and all-cause mortality.

LABA/LAMA versus LABA

- Low quality evidence from 10 RCTs with 8,252 people found an increase in the number of people experiencing pneumonia in people offered LAMA/LABA compared to LABA.
- Very low to low quality evidence from up to 5 RCTS with up to 2,488 people found an improvement in trough FEV1 at 3 months and a reduction in the numbers of people experiencing moderate to severe exacerbations in people offered LAMA/LABA compared to LABA, but the point estimates were less than the defined individual minimal clinically important differences.
- Very low to moderate quality evidence from up to 11 RCTs with up 8,699 people found no meaningful difference in the change in FEV1, TDI score, SGRQ score or the number of SGRQ responders at 6 and 12 months and TDI score at 3 months; or in the numbers of people experiencing SAEs in people treated with LAMA/LABA compared to LABA.
- Very low to low quality evidence from up to 13 RCTs with up 9,202 people could not differentiate people offered LAMA/LABA compared to LABA for change in SGRQ score at 3 months, the number of people experiencing severe exacerbations, cardiac SAEs, COPD SAEs, dropouts due to adverse events and all-cause mortality.

LABA/ICS versus LAMA

- Low to moderate quality evidence from up to 5 RCTs with up to 2,395 people found a reduction in all-cause mortality and cardiac SAEs, and an increase in the number of people experiencing pneumonia in people offered LABA/ICS compared to LAMA.
- Low quality evidence from up to 5 RCTs with up to 2,590 people found increased numbers of SGRQ responders at 2 years and SAEs in people offered LABA/ICS compared to LAMA, but the point estimates were less than the defined individual minimal clinically important differences.
- Very low to moderate quality evidence from up to 7 RCTs with up 2,327 people found no meaningful difference in the change in FEV1, TDI score and SGRQ score at 3 months, 6 months, 12 months and 2 years; or in the numbers of people experiencing moderate to severe exacerbations in people offered LABA/ICS compared to LAMA.
- Very low to low quality evidence from up to 6 RCTs with up 2,657 people could not differentiate people offered LABA/ICS compared to LAMA in the numbers of

SGRQ responders at 3 months, 6 months and 12 months; people experiencing severe exacerbations, COPD SAEs and dropouts due to adverse events.

LABAICS versus LABA

- High quality evidence from 20 RCTs with 19,291 people found an increase in the number of people experiencing pneumonia in people offered LABA/ICS compared to LABA.
- Low to high quality evidence from up to 21 RCTs with up 19,713 people found no meaningful difference in the change in FEV1 at 3, 6 and 12 months, SGRQ score at 3 months, 6 months, 12 months and 3 years; TDI score at 3 and 6 months; the number of SGRQ responders at 3 and 6 months; or in the numbers of people experiencing moderate to severe or severe exacerbations, SAEs, COPD SAEs, cardiac SAEs and dropouts due to adverse events in people offered LABA/ICS compared to LABA.
- Very low to moderate quality evidence from up to 21 RCTs with up to 19,681 people could not differentiate people offered LABA/ICS compared to LABA for change in FEV1 at 3 years, all-cause mortality and the number of SGRQ responders at 12 months and 3 years.

LAMA versus LABA

- Low to moderate quality evidence from up to 13 RCTS with up to 22,789 people found a reduction in the numbers of people experiencing severe exacerbations and COPD SAEs in people offered LAMA compared to LABA, but the mean values were less than the defined individual minimal clinically important differences.
- Very low to high quality evidence from up to 15 RCTs with up 23,844 people found no meaningful difference in the change in FEV1, SGRQ score and TDI score at 3, 6 and 12 months; the number of SGRQ responders at 6 and 12 months; or in the numbers of people experiencing moderate to severe exacerbations, SAEs and dropouts due to adverse in people offered LAMA compared to LABA.
- Very low to moderate quality evidence from up to 13 RCTs with up 22,844 people could not differentiate people offered LAMA compared to LABA for the number of SGRQ responders at 3 months, all-cause mortality and the number of people experiencing cardiac SAEs or pneumonia.

Sensitivity analyses and publication bias assessment

Sensitivity analyses were carried out to remove studies at high risk of bias from the prioritised outcomes. These analyses did not lead to any meaningful changes in the interpretation of the evidence.

There was no evidence identified that publication bias influenced the results of any of the drug combinations and comparisons.

Network meta-analysis

The format of the evidence statements is explained in the methods in appendix B.

Please refer to the summary of the NMA results shown in Table 65 and Table 66 in appendix N.

Based on the NMA, the following differences in effectiveness were obtained:

- Low to moderate quality data from 3 NMAs with up to 10,962 participants found improvements in trough FEV1 at 3, 6 and 12 months for the high risk group offered LABA/LAMA versus LABA.
- Moderate quality data from 1 NMA with 23,874 participants found a reduction in the rates of moderate to severe exacerbations for the low risk group offered LABA/LAMA versus LABA.
- Moderate quality data from 1 NMA with 23,575 participants found a reduction in the rates of moderate to severe exacerbations for the high risk group offered LAMA, LABA/ICS or LABA/LAMA versus LABA.
- High quality data from 1 NMA with 16,830 participants found a reduction in the rates of severe exacerbations for the high risk group offered LAMA or LABA/LAMA versus LABA and LABA/LAMA versus LABA/ICS.
- Low to moderate quality data from 2 NMAs with up to 61,157 participants found an increase in the rates of pneumonia for both the high and low risk groups offered LABA/ICS versus LABA or LAMA, and for the low risk group offered LABA/ICS versus LABA/LAMA.

The remaining NMAs found no differences, could not differentiate between interventions or found statistically significant differences that were below the MID.

Economic evidence statements

One partially applicable study with potentially serious limitations (Hertel 2012) assessed the cost-effectiveness of LAMA, LABA, LABA+ICS and LAMA+LABA in patients with severe or very severe COPD. LAMA+LABA was found to be the most costly and most effective option, with an ICER of £10,950 per QALY in ICS tolerant patients an ICER of £15,700 per QALY in ICS intolerant patients.

Two partially applicable studies with potentially serious limitations assessed the cost-effectiveness of a LAMA compared with a LABA. One study (Gani 2010) found that tiotropium (LAMA) dominates (is both less costly and generates more QALYs than) salmeterol (LABA), with probabilistic sensitivity analysis (PSA) indicating a 97% probability that tiotropium is the more cost-effective option. One study (Price 2013) found that indacaterol (LABA) dominates tiotropium (LAMA), with PSA indicating an 84% probability that indacaterol is more cost-effective.

Two partially applicable studies with potentially serious limitations assessed the cost-effectiveness of LAMA+LABA compared with LAMA monotherapy. One study (Punekar 2015) found that umeclidinium/vilanterol (LAMA+LABA) produced an ICER of £2,088 per QALY compared with tiotropium (LAMA), with PSA analysis indicating an 85% probability that umeclidinium/vilanterol is the more cost-effective option. One study (Ramos 2016) found that aclidinium bromide/formoterol (LAMA+LABA) produced an ICER of £2,967 per QALY compared with aclidinium bromide monotherapy (LAMA), with PSA indicating a 79% probability that aclidinium bromide is more cost-effective.

A directly applicable original model with minor limitations found that starting treatment on LAMA+LABA has a high probability (86%) of being optimal in the base case. Introducing treatment effects on adverse events and mortality increased the amount of uncertainty in results, but, for the overall population, LAMA+LABA remained the option with the highest probability of being cost effective (38%-57%).

The committee's discussion of the evidence

The committee used the evidence for this question, the new economic model and the evidence from the LAMA monotherapy review below to make a number of related recommendations for the use of inhaled therapies in people with COPD. Their discussion and recommendations for both reviews are contained in the section on LAMA monotherapy.

LAMA monotherapy

Review question

Which is the most clinically and cost-effective long-acting anticholinergic (LAMA) for managing stable COPD, and which subgroups of people should receive treatment with it?

Introduction

Breathlessness is one of the main problems associated with COPD and one approach to treatment is the use of bronchodilators, such as LAMAs and long-acting beta agonists (LABAs), with some use of inhaled corticosteroids (ICS). However, although these drugs may provide some symptomatic relief, they do not prevent disease worsening over time.

In people with COPD, airflow obstruction increases the resistance to expiratory flow, causing the airways to close prematurely and incomplete expiration of air, which in turn leads to hyperinflation of the lungs. LAMAs work by blocking acetylcholine from binding at the muscarinic acetylcholine receptors, thereby preventing messages going to the parasympathetic nervous system. This leads to smooth muscle relaxation and dilation of the airways, which can help improve exercise tolerance and improve symptoms in people with COPD. However, to date, treatment with any pharmacological agent has not been reflected in a reduction in mortality.

LAMAs are also known as long-acting anti-muscarinic agents. There are currently 4 LAMAs that are licenced for use in the UK: aclidinium, glycopyrronium, tiotropium and umeclidinium. They are all available as dry powder inhalers and licensed for COPD, with the exception of tiotropium, which also has an alternative device (Respimat).

This review aims to determine the comparative effectiveness of different LAMAs for managing stable COPD, and to identify which subgroups of people benefit from treatment. The review protocol is summarised in Table 13 and detailed in appendix A. The outcomes in the PICO were adapted to match the Cochrane review earlier in this evidence review that focused on combinations of LAMA, LABA and LABA/ICS.

Table 13 PICO for examining the comparative effectiveness of different LAMAs.

Population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)
Interventions	Specific drug from LAMA class including: • Aclidinium • Glycopyrronium (also known as glycopyrrolate) • Tiotropium • Umeclidinium
Comparator	• Alternative drug from LAMA class • Placebo
Outcomes	• COPD exacerbations (moderate to severe and severe) • St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score ≥ 4 units (responder) • Transition Dyspnoea Index (TDI)

	• Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropout due to adverse event • Trough FEV1 • Pneumonia • Exercise tolerance/ capacity (6MWD) • Resource use and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. The search strategies used in this review are detailed in appendix C.

To facilitate comparison with the Cochrane review and network meta-analysis in the preceding section, this review has adopted the following definitions, key outcomes and methods:

1. Exacerbations were divided into moderate to severe and severe categories. A moderate exacerbation is defined as worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics; a severe exacerbation is defined as a rapid deterioration that requires hospitalisation.
2. Data for the St George's Respiratory Questionnaire (SGRQ) was presented in 2 ways, depending on the format of data in the included studies: as changes in SGRQ total score and as the number of responders (decrease in SGRQ score of ≥4 units).
3. End of study data was reported for dichotomous outcomes, while continuous outcomes will be reported for the end of the study and at 3, 6 and 12 months where possible. Data that does not fit into these categories will be assigned to the closest category.
4. Breathlessness was only measured using the Transition Dyspnoea Index (TDI).
5. The original review protocol developed with the committee is shown in appendix A. The outcomes listed there were adapted to match the Cochrane review outcomes, which are shown in the PICO in Table 13 to facilitate comparison with the Cochrane review chapter.
6. To prevent formatting issues introducing confusion, drug doses are written as micrograms, apart from in the forest plots where they are abbreviated to mcg. This review only includes drugs and doses that are licenced in the UK. Where multiple doses are presented, data was collected for all licenced doses. However, trials using doses of up to 20% more or less than the licenced UK dose were also included. The following drugs are currently licenced for LAMA monotherapy in the UK: aclidinium, glycopyrronium, tiotropium and umeclidinium. The following doses were used in the included clinical trials:
    a. Aclidinium: 400 micrograms twice daily
    b. Glycopyrronium: 50 micrograms daily
    c. Tiotropium 18 micrograms once daily or 5 micrograms daily (2 doses of 2.5 micrograms using the Respimat device)
    d. Umeclidinium: 62.5 micrograms daily

    In each case, the dose can be written in a number of ways, depending on whether the delivered or pre-dispensed dose, and the corresponding salt or active component alone is presented. For simplicity, in our analyses we have

used the format listed above, which may not refer to the same formulation, but matches the doses referred to in the included clinical trials.

7. The devices used to deliver the LAMAs were not investigated here as they outside the scope of this review.
8. This review question aimed to look at the effect of LAMA monotherapy on people with stable COPD. To try to ensure that any effects on outcomes could be attributed to treatment with a LAMA, included trials were required to recruit people who were not taking routine concomitant medication at the start of the trial that could complicate this interpretation (in particular, Long-Acting Beta agonists (LABAs)). Studies were included if trial participants who were taking a LABA/ICS combination were switched to the same dose of ICS, with access to rescue medication as required. Rescue medication including short-acting bronchodilators, such as albuterol (salbutamol), and ipratropium was allowed. Inhaled corticosteroids (ICS) were allowed providing they were only used in participants who had been prescribed them prior to entering the trial and were on a stable dose.
9. In cases where primary studies were included in a Cochrane review that was judged to be of high quality and fully or partially applicable, evidence tables were not compiled and the reader is referred to the Cochrane review for study information. Risk of bias and applicability assessments are reported in appendix E. The exceptions to this are studies that had already been extracted before the Cochrane reviews were examined. Trials that have been reported in multiple papers are grouped under the author of the first published paper or, if they are reported in an included Cochrane review, under the name used in that review. Studies that were not published in English are included if the data is accessible from an included Cochrane review (e.g. Beeh et al, 2006).
10. The included Cochrane reviews were also used as a source of data in cases where data was inaccessible or not available in the published papers. However, studies were excluded if they were used in an included Cochrane review, but there was no peer-reviewed primary publication available.
11. In cases where the data extracted by the Guideline Updates Team disagreed substantially with those reported in the included Cochrane reviews and there was no obvious explanation, then the data in the Cochrane review was assumed to be correct as they may include data (for example, on sample sizes) supplied by the study authors.
12. In cases where the judgement of risk of bias of studies differed between the Cochrane review authors and the Guideline Updates Team, the risk of bias reported in the evidence tables in appendix E was based on the Cochrane review judgements. This decision was made because it was assumed that these differences were based on additional information available to the Cochrane review authors following contact with the authors of the primary studies. However, the risk of bias judgements were also adjusted by the Guideline Updates Team to maintain consistency across the studies included from the 3 Cochrane reviews and the remaining primary studies that were extracted separately.
13. Attrition bias was a particular issue in some of these trials. To simplify the assessment of attrition bias, the following rules were used.
    a. A gap of ≥ 10% in the number of drop-outs between trial arms was considered to be uneven drop out.
    b. High risk of attrition bias- if ≥ 20% of the participants for either trial arm dropped out **or** if the trial had a high drop-out (≥ 20%) and the rate was uneven between arms.
    c. Unclear risk of bias- if the trial had a high drop-out and the rate was even between arms **or** if the trial had a relatively high drop-out

(between 15-20%) and the rate was uneven or even between arms **or** if the trial had a low drop-out and the rate was uneven between arms.

d. Low risk of bias- if the trial had a low drop-out and the rate was even between arms.

14. For the overall risk of bias for the study,1 domain with high risk of bias was associated with a moderate risk of bias overall and ≥ 2 domains was a high risk of bias. Large numbers of unclear risks of bias judgements could also cause a study to move to moderate or high risk of bias overall. This decision was based on the potential impact of the particular domains on the outcome and likelihood that they were at high risk of bias given the judgement for other domains. For example, if information about allocation concealment was not provided (unclear risk of bias), but a study statistician carried out randomisation using an acceptable method then it is likely that allocation concealment occurred even if it was not described. A lack of information leading to unclear risk of bias in both the randomisation and allocation concealment domains would be judged to be more serious than the former example.
15. The minimally important differences (MIDs) used in this review are summarised in Table 15 in appendix B. These were selected based on the literature with input from the committee.
16. Within trial subgroup analyses were not carried out for this review because the majority of included studies did not report data for the categories of interest in an accessible format. Within the trials reporting subgroup analyses, the outcomes were limited to trough FEV1 in 6 trials, SGRQ total score in 2 trials and 1 trial looked at exacerbations per year.
17. Between trial subgroup analysis was carried out for background ICS use where data was available. Twenty two trials allowed ICS use, 2 did not and 1 was unclear as the paper was not in English. Since all of the trials involving aclidinium, glycopyrronium or umeclidinium allowed concomitant ICS use, only trials with tiotropium versus placebo were included in the subgroup analysis. This was presented in forest plots, but not included in GRADE tables as a meaningful difference was not identified between subgroups.
18. Where there was uncertainty regarding the number of people included in a particular outcome, data was only presented graphically or was not in an extractable format for our analyses, the study authors were contacted and asked to supply the missing information. If no data was forthcoming, then it was extracted from the graphs or calculated using estimated sample sizes based on either the intention to treat population or numbers of people completing the study as deemed appropriate from the study methods. This was footnoted in relevant the forest plots.
19. The published NMAs were not used as a source of data for this review as a new NMA was carried out to combine all the existing evidence and look at the outcomes of interest identified by the committee. Instead, the published NMAs were used to provide evidence to support or contrast with the findings of this review.
20. The NMA models used in this review were based on models from the NICE Decision Support Unit (DSU) technical support document 2. Models 5 and 6 were used for continuous outcomes and models 1c and 1d for dichotomous outcomes.
21. Data was extracted for the mean effect and 95% credible intervals from the NMA model with the best fit to the data based on the NICE Guideline Updates team criteria for model choice detailed in appendix B.
22. The DSU code presents the results of dichotomous outcomes as OR. These were converted to RR by the NICE Guideline Updates Team using data for each outcome from the placebo arm versus tiotropium from the largest trial for

that particular outcome. This was Bateman 2010b for most outcomes and Dusser 2006 otherwise.

23. Where the data for the NMA for a particular outcome (for example mortality) included trials with 0 events in both arms, these trials were not included as part of the analysis.
24. Based on discussions with the committee, certain outcomes were prioritised for the NMA and data is only presented for these outcomes. These outcomes were: respiratory health- related quality of life measured by the St George's Respiratory Questionnaire (SGRQ) total score, SGRQ responders, breathlessness assessed using TDI, moderate to severe and severe exacerbations, dropouts due to adverse events, mortality and serious adverse events.
25. Although there were studies at high risk of bias included in the NMA, a sensitivity analysis excluding these studies was not carried out because the sensitivity analysis carried out on the pair wise data did not alter the interpretation of the effects of the treatments.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Protocol deviation

Based on discussion with the committee, it was agreed to prioritise the outcomes that would be of most use for decision making, namely exacerbations, change in TDI score, SGRQ score and the number of SGRQ responders. These outcomes were also prioritised for the NMA for this review question.

Summary of studies included in the economic evidence review

Eklund 2016 conducted a cost–utility analysis with a lifetime time horizon comparing tiotropium with glycopyrronium in patients with moderate to very severe COPD in the UK. This study was funded by a manufacturer of tiotropium. It used a Markov model with states based on GOLD stages 2, 3 and 4 (FEV1 50%–80% predicted, 30%–50% predicted, and <30% predicted, respectively). In each cycle of the model, patients could remain in the same GOLD stage, change GOLD stage or die. Patients could also experience a severe or non-severe exacerbation in each cycle.

Baseline transition probabilities and exacerbation rates (stratified by disease severity) were obtained from the UPLIFT trial of tiotropium. Treatment effect was implemented via a relative risk of exacerbations for tiotropium versus glycopyrronium taken from the SPARK trial (Wedzicha 2013 – excluded from the clinical review due to a lack of blinding in the tiotropium arm). The analysis assumes that both treatments are equivalent in their effect on FEV1.

Costs per cycle of the model, stratified by disease severity and patients' exacerbation status were taken directly from a previous economic analysis, which estimated resource use via a Delphi panel and unit costs from HRG groups and standard NHS sources. Drug costs were taken from the Monthly Index of Medical Specialities. Baseline utilities, stratified by disease severity, were taken from a HRQoL study of patients in the UPLIFT trial. Disutilities associated with moderate and severe exacerbations were taken from a previous economic analysis, which used EQ-5D scores and estimates of the length of exacerbations to calculate QALY loss.

Results showed that tiotropium generates a cost saving of €169 (~£147) and 0.23 additional QALYs compared with glycopyrronium and is therefore dominant. One-way sensitivity analyses showed that tiotropium remained the cost-effective option when

key parameters were set to high and low plausible values. Subgroup analyses stratifying patients by disease severity at baseline found that tiotropium remained dominant in all scenarios.

This study was classified as being partially applicable, as it considered only 2 of the comparators of interest. It was categorised as having very serious limitations as it only included effect of treatment on exacerbations, and did not conduct a probabilistic sensitivity analysis. Furthermore, the treatment effect for tiotropium compared with glycopyrronium was taken from a study in which tiotropium was prescribed on an open-label basis. The authors also note that this treatment effect is not consistent with previous studies or meta-analyses of within-class LAMA comparisons.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the 2010 NICE COPD guideline (CG101). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews (SRs) was conducted and this returned 4,324 references. No date limits were used for the search as this is a new question, based on evidence identified during routine surveillance. Additional references were added from the old guideline (6) and from the surveillance report (40) to give 4,254 references after duplicated were removed.

These were screened on title and abstract, with 238 papers ordered as potentially relevant Systematic Reviews (SRs), Network Meta-analyses (NMAs) or RCTs. RCTs were excluded if they did not meet the criteria specified in the review protocol (appendix A). Thirty-four papers were included after full text screening: 6 SRs, 3 NMAs and 25 RCTs. This process is presented in a PRISMA diagram in appendix D.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches returned 3,100 references in total for all the questions included in the update, and these were screened on title and abstract. No additional relevant references were found for this review question.

The process of study identification is summarised in the diagram in appendix D.

The included studies are presented in full evidence tables in appendix E and are referenced in appendix M.

Excluded studies

Studies which allowed concomitant use of other LAMAs or LABAs (such as the UPLIFT trial) were excluded (please refer to the methods and processes section above for details).Trials with open-label interventions were also excluded. In addition, individual papers were excluded if they contained no outcomes of interest, even if they referred to an included clinical trial, as were studies reporting analyses of pooled trial data if this data was available elsewhere.

The excluded studies are listed in appendix K with reasons for their exclusion, and as full references in appendix M.

Summary of clinical studies included in the evidence review

This review identified a number of trials for each type of LAMA versus placebo, but very few trials comparing different types of LAMA. The studies are summarised below with full details provided in the evidence tables in appendix E.

- Two SRs, and 11 papers covering 15 RCTs with 8,275 people comparing tiotropium to placebo. These trials were mainly tiotropium versus placebo alone, but in some cases (OTEMTO 1 and 2) there were other, non-LAMA, treatment arms that were excluded from the analysis.
- Two SRs, and 6 RCTs with 2,784 people comparing aclidinium to placebo. These included the AUGMENT, ACLIFORM, ATTAIN, ACCORD COPD I and ACCORD COPD II trials.
- One SR and 4 RCTs with 2,774 people comparing glycopyrronium to placebo. These included the SHINE, GLOW 1, GLOW 2 and GLOW 7 trials.
- One SR, and 2 RCTs with 888 people comparing umeclidinium versus placebo.
- One RCT (GLOW 5) with 657 people comparing glycopyrronium to tiotropium.
- One RCT comparing umeclidinium to tiotropium with 1,017 people.

The Guideline Updates Team would like to acknowledge additional information about the number of people with moderate to severe and severe exacerbations provided by Professor Bateman for the SHINE trial.

Data from another 3 trials were requested from trial authors and provided, but received too late to be included in the consultation version of this guideline. Specifically, additional data or clarification of effect and sample sizes for Bateman 2010 and Casaburi 2002 were provided by Boehringer Ingelheim (BI). Data for the UPLIFT trial were also provided by BI for the group of participants who were not taking a LABA during the trial.

Quality assessment of clinical studies included in the evidence review

The included studies were assessed for risk of bias and applicability as detailed in the methods in appendix B. Some of the included studies are also included in the inhaled therapy combinations Cochrane review and may have a different risk of bias rating for that review compared to this one. One reason for this difference is because the inhaled therapy combinations review included open label LAMAs (and other drugs) whilst this review excluded them. In other cases, there were different ratings of attrition bias as a result of the inclusion of different trial arms in each review.

Please refer to appendix H for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which 16,198 were excluded on title and abstract for this review question. The remaining 101 papers were screened using a review of the full text and 1 was found to be relevant to the question. A relevant UK-based cost-utility analysis was identified by the review, so only studies using an NHS perspective were included.

Excluded studies

Details of the studies excluded at full text review are given in Appendix K.

Evidence statements

Clinical evidence statements

The format of the evidence statements is explained in the methods in appendix B. All of the results described below are based on pooled data collected for the final time point of each included study, apart from SGRQ and TDI scores. In these cases, results were analysed at 3, 6 and 12 months and where no time points are stated then the evidence statement applies to all time points examined.

Pair-wise analysis

The following outcomes were not included in the analysis due to a lack of data: exercise capacity as measured by the 6MWD, COPD SAE and cardiac SAE.

Tiotropium bromide (18micrograms or 5micrograms in total) versus placebo

- Very low to moderate quality evidence from up to 10 RCTs with up to 5,421 people showed a reduction in drop-outs due to adverse events, improvement in TDI and trough FEV1, and an increase in SGRQ responders in people offered tiotropium compared to placebo.
- Very low to low quality evidence from up to 8 RCTs with up to 6,013 people found a reduction in the number of people having moderate to severe exacerbation and an improvement in SGRQ score in people offered tiotropium compared to placebo, but the point estimates were less than the defined individual minimal clinically important differences.
- Low quality evidence from 10 RCTs with 5,421 people found no meaningful difference in the numbers of people with serious adverse events in people offered tiotropium compared to placebo.
- Low quality evidence from up to 12 RCTS with up to 8,275 people could not differentiate the numbers of people with severe exacerbations, all-cause mortality and sessions of pneumonia in people offered tiotropium compared to placebo.

Publication bias: tiotropium versus placebo

There was no evidence identified that publication bias influenced the results of any of the drug combinations and comparisons.

Sensitivity analysis (removing studies at high risk of bias)

The following differences were found:

- Low quality evidence from 1 RCT with up to 90 people could not differentiate the TDI or SGRQ score at 3 months in people offered tiotropium compared to placebo.

The remaining sensitivity analyses did not result in any meaningful change in results.

Aclidinium bromide (400 micrograms twice daily) versus placebo

- Very low to low quality evidence from up to 6 RCTS with up to 2,782 people found improvements in trough FEV1, an increase in the numbers of SGRQ responders

and a reduction in the number of people with moderate to severe exacerbations in people offered aclidinium compared to placebo.

- Low to high quality evidence from 3 RCTs with up to 1,522 people found improvements in TDI scores, and SGRQ scores at 3 months in people offered aclidinium compared to placebo, but the point estimates were less than the defined individual minimal clinically important differences.
- Very low to low quality evidence from up to 6 RCTs with up to 2,784 people could not differentiate the numbers of people with severe exacerbation, non-fatal serious adverse events, sessions of pneumonia, drop-outs due to adverse events, all-cause mortality or SGRQ scores at 6 months in people offered aclidinium compared to placebo.

Glycopyrronium bromide (50 micrograms once daily) versus placebo

- Very low to moderate quality evidence from up to 4 RCTS with up to 2,670 people found improvements in trough FEV1 at all time points and SGRQ score at 3 months, and a reduction in the numbers of people with moderate to severe or severe exacerbations in people offered glycopyrronium compared to placebo.
- Very low to low quality evidence from up to 4 RCTs with up to 2,485 people found improvements in SGRQ score at 6 months and TDI scores in people offered glycopyrronium compared to placebo, but the point estimates were less than the defined individual minimal clinically important differences.
- Moderate quality evidence from 4 RCTs with 2,427 people found no meaningful difference in the numbers of SGRQ responders in people offered glycopyrronium compared to placebo.
- Low quality evidence from up to 4 RCTs with up to 2,779 people could not differentiate the numbers of people with serious adverse events, sessions of pneumonia, drop-outs due to adverse events and all-cause mortality in people offered glycopyrronium compared to placebo.

Sensitivity analysis (removing studies at high risk of bias)

The following differences were found:

- Low quality evidence from 1 RCT with 758 people found an improvement in SGRQ at 3 months in people offered glycopyrronium compared to placebo, but the point estimate was less than the defined individual minimal clinically important difference.
- Low quality evidence from 3 RCTs with 2,320 people found a decrease in dropouts due to adverse events in people offered glycopyrronium compared to placebo.

The remaining sensitivity analyses did not result in any meaningful change in results.

Umeclidinium bromide (62.5 micrograms once daily) versus placebo

- Low to high quality evidence from up to 2 RCTs with up to 835 people found improvements in TDI and SGRQ scores, trough FEV1 and the numbers of SGRQ responders, with an increase in the numbers of people with serious adverse events and drop-outs due to adverse events in people offered umeclidinium compared to placebo.
- Low to moderate quality evidence from up to 2 RCTs with up to 904 people could not differentiate the numbers of people with moderate to severe or severe exacerbations and all-cause mortality in people offered umeclidinium compared to placebo.

Glycopyrronium bromide (50 micrograms once daily) versus Tiotropium bromide (5 micrograms or 18 micrograms in total)

- High quality evidence from 1 RCT with 630 people found no difference in SGRQ and TDI scores, trough FEV1 and the number of SGRQ responders in people offered glycopyrronium compared to tiotropium.
- Low quality evidence from 1 RCT with up to 657 people could not differentiate the numbers of people with moderate to severe or severe exacerbations, non-fatal serious adverse events, sessions of pneumonia or drop-outs due to adverse events in people offered glycopyrronium compared to tiotropium.

Umeclidinium bromide (62.5 micrograms once daily) versus Tiotropium bromide (5 micrograms or 18 micrograms in total)

- High quality evidence from 1 RCT with up to 1,012 people found no meaningful difference in SGRQ and TDI scores, trough FEV1, and the number of SGRQ responders in people offered umeclidinium compared to tiotropium.
- Low to moderate quality evidence from 1 RCT with up to 1,017 people could not differentiate the numbers of people with moderate to severe exacerbations, non-fatal serious adverse events, drop-outs due to adverse events and all-cause mortality in people offered umeclidinium compared to tiotropium.

ICS subgroup analyses

- Between trial subgroup analyses for background ICS use did not show any meaningful differences in outcomes for people using ICS compared to those not using ICS in the tiotropium versus placebo trials. The aclidinium, glycopyrronium and umeclidinium trials all allowed background ICS use.

Network meta-analyses

The format of the evidence statements is explained in the methods in appendix B.

Please refer to the summary of the NMA results shown in Table 67 in appendix N.

- Very low to moderate-quality evidence from 5 network meta-analyses containing up to 11,137 participants could not differentiate SGRQ scores or responders, TDI score, moderate to severe exacerbations or mortality between people offered tiotropium, aclidinium, glycopyrronium or umeclidinium.
- Moderate to high quality and partially applicable evidence from 3 published network meta-analyses did not detect any meaningful differences in FEV1, SGRQ and TDI score, exacerbations or use of rescue medication between people offered tiotropium, aclidinium, glycopyrronium or umeclidinium.
- Moderate quality evidence from 3 network meta-analyses containing up to 23,477 participants found higher rates of severe exacerbations, dropouts due to adverse events and serious adverse events in people offered umeclidinium compared to other LAMAs, but could not detect differences between tiotropium, aclidinium or glycopyrronium.

Economic evidence statements

One partially applicable cost-utility analysis with potentially serious limitations found that tiotropium dominates glycopyrronium in patients with moderate to very severe COPD. This finding was robust to one-way sensitivity analyses, although no probabilistic sensitivity analysis was conducted.

Recommendations

Inhaled combination therapies

Recommendations shaded in grey were not within the scope of the update. Evidence for these was not reviewed and changes were made only to bring the wording in line with current NICE style or to link the existing recommendation to a new one if the treatment pathway changed.

F1. Do not assess the effectiveness of bronchodilator therapy using lung function alone. Include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. **[2004]**

F2. Offer LAMA+LABA[1] to people who:

- have spirometrically confirmed COPD **and**
- do not have asthmatic features/features suggesting steroid responsiveness[2] **and**
- remain breathless or have exacerbations despite:
  - treatment for tobacco dependence if they smoke **and**
  - optimised non-pharmacological management and relevant vaccinations **and**
  - using a short-acting bronchodilator. **[2018]**

F3. Consider LABA+ICS for people who:

- have spirometrically confirmed COPD **and**
- have asthmatic features/features suggesting steroid responsiveness[2] **and**
- remain breathless or have exacerbations despite:
  - treatment for tobacco dependence if they smoke **and**
  - optimised non-pharmacological management and relevant vaccinations **and**
  - using a short-acting bronchodilator. **[2018]**

F4. For guidance on managing asthma in people with COPD and asthma see the NICE guideline on asthma. **[2018]**

F5 Offer LAMA+LABA+ICS[1] to people with COPD with asthmatic features/features suggesting steroid responsiveness[2] who remain breathless or have exacerbations despite taking LABA+ICS. **[2010, amended 2018]**

F6. Base the choice of drugs and inhalers on:

- how much they improve symptoms
- the person's preferences and ability to use the inhalers
- the drugs' potential to reduce exacerbations, and their side effects and cost.

Minimise the number of inhalers and the number of different types of inhaler used by each person as far as possible. **[2018]**

F7. When prescribing long-acting drugs, ensure people receive inhalers they have been trained to use (for example, by specifying the brand and inhaler in prescriptions). **[2018]**

[1] The MHRA has published advice on the risk for people with certain cardiac conditions when taking tiotropium delivered via Respimat or Handihaler (2015).

[2] This includes any previous, secure diagnosis of asthma or of atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).

Research recommendations

F8. What features predict inhaled corticosteroid responsiveness most accurately in people with COPD?

F9. What is the clinical and cost effectiveness of inhaled therapies (bronchodilators and/or inhaled corticosteroids) in people with both stable COPD and asthma?

Rationale and impact

Why the committee made the recommendations

The evidence showed that, compared with other dual therapy combinations and with monotherapy, LAMA+LABA:

- provides the greatest benefit to overall quality of life
- is better than other inhaled treatments for many individual outcomes (such as reducing the risk of moderate to severe exacerbations)
- is the most cost-effective option.

The committee did not recommend a particular LAMA because they were not convinced that the evidence showed any meaningful differences in effectiveness between the drugs in this class. Instead, they updated the existing recommendation on drug and inhaler choice, based on their experience of what factors should be taken into account. In particular, minimising the number and types of inhalers prescribed will make it easier for people to use their inhalers correctly.

Most of the trials specifically excluded people with COPD and asthma, so there was no direct evidence for this group. The committee recommended LABA+ICS based on their clinical experience and knowledge of the likely benefit of inhaled corticosteroids in certain specific COPD phenotypes.

Because most of the trials excluded people with asthma, there is a lack of evidence on the most clinically and cost-effective treatments for people with COPD and asthma. There is also no evidence on how to predict steroid responsiveness in people with COPD. The committee made research recommendations to address these points.

Impact of the recommendations on practice

The recommendation on LAMA+LABA dual therapy is likely to increase the number of people with COPD who are having this treatment. The higher cost of dual therapy compared with monotherapy may result in a significant resource impact, but cost savings are also likely from a reduction in treatments needed for exacerbations (including hospitalisation).

Using LABA+ICS for people with features of asthma/features suggesting steroid responsiveness is in line with current practice.

The recommendation on how to choose drugs and inhalers covers factors that prescribers routinely consider, so is not a change in practice. However, minimising the number and type of inhaler devices and avoiding unnecessary within-class switching may produce cost savings through lower upfront spending and better symptom control.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that a key outcome for people with COPD was breathlessness. The Transition Dyspnoea Index was the most commonly reported measure of breathlessness in the inhaled therapy trials. They also agreed the quality of life outcomes such as the SGRQ, and risk of exacerbations and adverse events would also be of particular importance for these review questions. They noted that although FEV1 is an important measure of the effect of bronchodilator medication it was not an outcome that was as important for people with COPD as symptoms. They commented that it was still important to capture FEV1 as a prognostic marker of severity.

The quality of the evidence

The committee noted that triple therapy (LAMA+LABA+ICS) was outside of the scope of this guideline update and that they were thefore unable to make any recommendations for this part of the pathway during this update.

The committee noted that these questions were focused on choices of drug, and comparisons between individual devices were not within the scope. The committee agreed that the evidence from the Handihaler and Respimat devices used to deliver tiotropium could be merged as they had very similar effects in head to head trials (Calverley 2016). They also agreed that open-label tiotropium should be excluded from the review looking at the within class effects of LAMAs that included data on LAMAs versus placebo. This was because the use of open-label drugs results in a greater risk of reporting bias due to the lack of blinding of participants when compared to placebo. They noted that this was not as much of a problem for the inhaled therapy combinations review as this question excluded placebo comparisons and just focused on drug to drug comparisons, where all participants knew they were on an active treatment. As a result, open-label drugs were not excluded from the latter review, but the studies were marked as being at high risk of bias and a sensitivity analysis was carried out for the pairwise data.

There was lack of evidence for people with COPD and comorbidities as these people were usually excluded from trials. In particular, people with COPD and asthma were excluded from the majority of included studies. The committee commented that this could impact the generalisability of the recommendations to these groups of people. They agreed that where both asthma and COPD are current diagnoses, asthma guidance for inhaled therapy is likely to be the most salient.

The committee agreed that although the Cochrane review restricted their included trials to studies that recruited people over 35 years old, this approach was not inconsistent with that of the Guideline Updates Team for the LAMA monotherapy review for the following reasons. Firstly, the vast majority of people in the UK are diagnosed with COPD at over 51 years old[3], with very few people being diagnosed under 40 years old. It would therefore be hard to recruit people <35 years old due to their small numbers and this is presumably the case in other countries too. Secondly, not all of the LAMA montherapy trials and the Cochrane review trials specified a minimum inclusion age, but the trials that did frequently used a cut off of over 40 years. It is likely therefore, that even if the Cochrane group had not used a date cut

[3] British Lung Foundation. Chronic obstructive pulmonary disease (COPD) statistics [online; accessed 23 April 2018]

off that a large number of trials would have recruited people ≥ 40 years anyway. Thirdly, the mean ages of study populations for trials in both reviews was around the mid 60s, which is likely to be representative of the population of people with COPD in the UK. Taking these factors into consideration, the committee agreed that restricting the population to > 35 year olds was was unlikely to have resulted in the exclusion of relevant trials from the evidence base for the Cochrane review. Inhaled therapy combinations

The Cochrane review used as the basis of the evidence for this question stratified the included studies by risk of exacerbation based on the previous exacerbation history of the study participants. The committee agreed that this was a potentially useful way to explain heterogeneity in the data. They noted that high risk studies specifically recruited people with a history of hospital admission due to COPD exacerbation within 12 months of study entry, but the low risk category was less well defined. Since all other studies were classified as low risk by default this meant that the low risk group would probably also include studies where previous exacerbations were not an entry criteria, but may include many individuals who had had an exacerbation, as well as studies that specifically recruited people without exacerbations requiring hospitalisation within this time frame.

The committee agreed that there was no evidence that publication bias was a problem for any of the drug combinations and comparisons. They also agreed that since a sensitivity analysis of the pairwise data removing studies at high risk of bias did not lead to a meaningful change in interpretation of the evidence, it was not necessary to perform a sensitivity analysis on the NMA data.

The committee noted that the NMA results were presented at the class level to match this review question and so they were unable to recommend individual drugs within a class in comparison to each other. This is in comparison to the LAMA monotherapy question that specifically looked at within class differences between drugs.

The committee noted that there was a discrepancy between the pairwise and NMA data for certain outcomes, namely mortality, cardiac SAEs and pneumonia for LABA+ICS compared to LAMA. For the low risk group, the mortality data for LABA+ICS compared to LAMA has a RR point estimate of 0.44, but this is a non-significant result as the 95% CI crosses 1. This is much lower than the RR for the other treatment comparisons. The data underlying this result comes from 2 studies with only 4 events for 815 people in total across both trials. As a result, the effect estimate is associated with a large 95% CI that crosses 1 and reflects the uncertain effect of LABA/ICS compared to LAMA on mortality. The NMA model has taken this into account and included data from indirect comparisons, resulting in an increase in the RR point estimate so it is more in line with the other treatment comparisons and has a tighter 95% CrI (credible interval). The committee agreed that the results of the NMA were likely to be more accurate for these reasons.

Similar issues were noted for the low risk group with LABA+ICS versus LAMA for cardiac SAEs and pneumonia. Here the RR point estimates were particularly small (0.14) or large (5.83) respectively compared to the other treatment comparisons and both 95% CI crossed 1. The RR for both outcomes were also based on relatively few events and were brought into line with the other comparisons by the NMA using additional information from the indirect comparisons.

In the case of the high risk group, the RR for mortality with LABA+ICS compared to LAMA was significantly different and there were inconsistencies in the data between comparisons. The majority of the weight in the pairwise meta-analysis for this outcome came from the Wedzicha 2008 trial, which had nearly double the number of

deaths in the LAMA arm compared to the LABA+ICS arm. The committee discussed the characteristics of this study in detail, but were unable to identify a reason for this finding only appearing in this individual study (this issue is discussed in more detail in the cost effectiveness and resource use section below.) As above, the NMA model used indirect data to resolve the inconsistency in the pairwise data. Based on their discussions and the evidence, the committee decided that it was unlikely that the risk of mortality was reduced by nearly 50% in people treated with LABA+ICS versus LAMA and the committee agreed to accept the NMA result over the pairwise data.

For cardiac SAEs and pneumonia, the high risk group comparison of LABA+ICS versus LAMA also showed inconsistency between the pairwise (from Wedzicha 2008) and NMA data. The low RR point estimate from the pairwise data was overwritten in the NMA using indirect evidence.

LAMA monotherapy

The committee commented that ideally the trial population would be treatment naïve as this would be closest to the situation in real life where LAMA monotherapy was a treatment choice for people with COPD. However, they noted that in most trials a large proportion of the participants were also on ICS too and/or had been on LABA+ICS at baseline. They agreed that trials where participants remained on LABA or LABA+ICS during the trial should be excluded as this would complicate interpretation of the data, making it hard to attribute any effects observed to the LAMA. This decision is supported by the results of another LAMA monotherapy NMA, Oba (2015), which showed that trials where LABA was prohibited had a greater reductions in hazard ratios for exacerbations than trials where background LABA was allowed.

The majority of trials allowed background ICS use. The committee agreed to include these trials and this decision was supported by the whole trial subgroup analysis for tiotropium that did not identify meaningful differences in outcomes for people using ICS compared to those not using ICS. They also agreed to include trials with background theophylline use as they did not expect this to affect the outcomes.

The committee agreed to exclude papers with more complex interventions (e.g. Ambrosino 2008 using inhalers and pulmonary rehabilitation in same trial) as there may be an interaction between these interventions that results in a different outcome or degree of effect to inhalers alone.

The committee commented that the smoking rates were very high in some studies (for example, Lee 2015) and greater than seen in clinical practice in UK. This has issues for generalisability and affects exacerbation rates.

Despite its importance to people with COPD, the committee noted that most trials did not include exercise capacity/tolerance as an outcome and, as a result, this outcome was not included in the analysis.

Benefits and harms

Inhaled therapy combinations

The committee noted that LAMA+LABA had the highest probability of being ranked best for outcomes where there were meaningful difference between treatment alternatives, which included increased FEV1 and reductions in moderate to severe, and severe exacerbation rates for the high risk stratified group (see summary Table 65 and Table 66). They also noted that LAMA+LABA showed benefits over other treatments across a range of domains, and that even if outcomes in the individual

domains were below the defined MIDs, these were likely to add up to a meaningful difference overall. The committee agreed therefore that it was important not to consider these individual outcomes in isolation, but to consider the overall impact on quality of life, as estimated in the economic model. The committee also agreed there was a clear pattern of dual therapies being better than monotherapy across a range of outcomes.

Based on this clinical data and the results of the economic modelling which showed that LAMA+LABA was the most cost effective choice for the majority of scenarios, the committee felt able to make a strong recommendation for the use of LAMA+LABA as first line inhaled treatment for people with COPD who fell into the high risk group (i.e. had an hospital admission for an exacerbation of COPD in the last year) and did not have comorbid asthma.

The results for the low risk group showed a similar pattern but with smaller absolute differences between treatments. The NMAs showed a number of outcomes where there were differences between comparators, but these were less than the MID and so not considered to be clinically meaningful in isolation, and again the committee agree it was important to consider the overall impact on quality of life estimated from combining these outcomes in the model. The exception to this was moderate to severe exacerbations, where LAMA+LABA was meaningfully better than LABA at reducing the risk of exacerbations. If the outcomes with differences between comparators that were less than the MID were considered, then LAMA+LABA had the highest probability of being ranked best for the majority of these outcomes. As a result, the committee decided to combine these results into 1 recommendation irrespective of previous exacerbation history.

The exclusion criteria for most trials meant that people with common COPD comorbidities such as asthma were not recruited. As a result, the committee were able to make a strong recommendation for people with COPD without asthmatic features/features suggesting steroid responsiveness[4] based on the NMA and cost effectiveness evidence, but were forced to rely on their clinical expertise to make a recommendation for people with COPD and asthmatic features/features suggesting steroid responsiveness. The committee decided to use the term asthmatic features/ features suggesting steroid responsiveness rather than simply asthma to take into account issues around the diagnosis of asthma in people with COPD and that some people without clinically defined asthma may also have features that could lead them to benefit from treatment with LABA+ICS instead of LAMA+LABA. They defined this term in the recommendations based on their clinical experience.

The committee decided to recommend LABA+ICS as the first line treatment for people with COPD who had asthmatic features/features suggesting steroid responsiveness for the following reasons. Firstly, they decided that it was clinically inapropriate to treat people with COPD and asthma as though they just had asthma as they have different underlying disease mechanisms. As a result , the committee decided against making a recommendation to treat people with COPD and asthmatic features/features suggesting steroid responsiveness for breathlessness according to the asthma guideline. Secondly, the committee felt that people with COPD who meet criteria for long acting bronchodilators will need this therapy irrespective of whether they have comorbid asthma and so ICS alone would not be a relevant treatment option for this population. Thirdly, to treat the COPD symptoms, the committee agreed that the same drug combinations that were effective for people with just

[4] This includes any previous, secure diagnosis of asthma or of atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).

COPD should be considered. Based on the results of the NMAs, dual therapy was more effective than monotherapy for most outcomes, even though the point estimates of effect were often less than the MID. However, the committee thought that for people with asthmatic features/features suggesting steroid responsiveness LABA+ICS was likely to be a better initial treatment combination than LAMA+LABA, as they agreed it would be clinically inappropriate for people with these features not to be on an inhaled steroid since they are likely to benefit from the use of ICS in a similar manner to people with diagnosed asthma. Finally, the committee agreed that due to the lack of evidence in this population group, weaker wording should be used for this recommendation.

The committee also agreed that people with COPD and asthma should be managed taking both guidelines into account where relevant and they included a reference to the asthma guideline to ensure that people with both COPD and asthma have their asthma managed appropriately.

The committee noted the 2010 guideline contains a separate recommendation to add a LAMA to LABA+ICS for people who remain breathless or have exacerbations despite taking LABA+ICS, and therefore these people would reach a stage of being on dual bronchodilator therapy, if this was needed to control their symptoms. The committee amended the recommendation for triple therapy to include reference to asthmatic features/features suggesting steroid responsiveness to match the format of the new recommendations and the new treatment pathway.

They wrote a research recommendation to investigate which features could be used to predict inhaled steroid responsiveness in people with COPD to help with the identification of people who could benefit from following the LABA+ICS pathway.

The committee noted that for both low and high risk groups, the risk of pneumonia was increased in people taking LABA+ICS compared to other treatments, but they agreed the benefits for people with COPD and asthmatic features/features suggesting steroid responsiveness outweighed the harms.

The committee noted the absence of any evidence looking at the optimal treatments for people with both COPD and asthma, and therefore agreed it was appropriate to make a research recommendation on this topic.

LAMA monotherapy

The majority of the included trials compared individual LAMAs to placebo and in all cases the LAMAs showed improvements in some of the outcomes of interest versus placebo. The committee noted, however, that the focus of this question was not the effectiveness of LAMAs themselves, but differences between different LAMAs. Only 2 trials directly compared one LAMA to another LAMA and these looked at glycopyrronium or umeclidinium versus tiotropium. In both studies, the pairwise data found no differences or could not differentiate between the drugs. These findings are supported by the NMA results for TDI scores, SQRQ scores and probability of being a responder, and the risk of moderate to severe exacerbations and all-cause mortality. However, the NMA results for severe exacerbations, dropouts due to adverse events and serious adverse events were worse for umeclidinium compared to the other LAMAs (see summary Table 67).

The committee discussed these findings in detail. They noted that the data for these NMA findings came predominantly from 1 particular study (Donahue 2013) that was carried out across 163 centres in 13 countries with 698 participants. The committee noted that there were many more people with severe exacerbation events in the umeclidinium arm in the Donahue 2013 study, compared to Trivedi 2014, which had

none in either arm of the trial. In addition, for SAEs and dropouts due to adverse events, the Trivedi 2014 study had very few or no events in each arm, but the small study size resulted in very wide 95% CI.

The committee also noted that severe exacerbations were by definition serious adverse events and that these were also common reasons for participants to drop out of the trial. They thus concluded that there was likely to be overlap between the outcomes. As a result, they decided that there was likely to be one negative finding for umeclidinium rather than 3 and that this could have occurred by random chance.

The committee looked at data in the Ni (2017) Cochrane review, which also includes trials using higher doses of umeclidinium (125 micrograms), as well as the 62.5 micrograms dose examined here, and noted these studies did not show an elevated number of people with serious adverse events or discontinuations due to adverse events at the higher doses compared to placebo. They commented that it was biologically implausible that there would be more adverse effects with lower doses of umeclidinium compared to higher doses.

In addition, the results of a published NMA did not detect any differences in FEV1, SGRQ and TDI score, or use of rescue medication between people taking tiotropium, aclidinium, glycopyrronium or umeclidinium.

Based on these discussions, the committee decided that there was insufficient evidence to make a negative recommendation for umeclidium for the following reasons:

- There was likely to be an overlap between the negative outcomes.
- There were no meaningful differences between the LAMAs for TDI score, SQRQ score and responders, moderate to severe exacerbations or mortality.
- There was a lack of biological plausibility that there would be more adverse effects with lower doses of umeclidinium compared to higher doses.
- The adverse events were not seen to the same extent in other comparable umeclidinium trials.

Taking all of this information into account, the committee decided that there was insufficient evidence to conclude that any LAMA was better or worse than another. Instead, the evidence supported the view that there was probably no meaningful difference between aclidinium, glycopyrronium, tiotropium and umeclidinium for the outcomes of interest. As a result, the committee did not make a recommendation favouring one drug over another, but rather recommended that a number of factors be taken into consideration when making a choice of drug, including patient preference regarding inhaler device and the ability to use it. However, since the review question comparing inhaled therapy combinations led to recommendations to start treatment with dual therapy rather than monotherapy, this recommendation was kept as a general recommendation relevant to all stages of the inhaled therapy decision making process. In particular, the committee wanted to make sure that people were not being switched between drugs and devices without ensuring that they are able to use the devices correctly. They noted that having fewer devices or types of devices was likely to be less confusing for people and lead to better adherence to treatment regimens.

Cost effectiveness and resource use

The committee were presented with economic evidence on the relative cost effectiveness of different classes of long-acting bronchodilators, both from the existing literature and from the economic model developed for this guideline. Overall,

the committee were confident in prioritising the evidence from the original model over that in the literature for a number of reasons. First, evidence from the literature generally compares 2 specific products, rather than evaluating the entire decision problem. Second, published economic analyses are generally informed by relatively few clinical trials, whereas the *de novo* analysis uses outcomes from a network meta-analysis which synthesises a large number of studies. Third, evidence from the literature is commonly associated with limitations in terms of duration of analysis, limited sensitivity analysis, lack of inclusion of adverse events, and opacity of sources for model parameters. Finally, all of the included economic evaluations from the literature were funded by manufacturers of long-acting bronchodilators and, as such, were subject to a potential conflict of interest.

The committee considered the economic evidence from the *de novo* model and noted that, when treatment effects on adverse events and mortality are not included, starting patients on a LAMA+LABA is the most cost-effective option in the model base case, and in all 5 individual treatment effect scenarios. Probabilistic sensitivity analysis also showed that there is a high degree of certainty behind this result in most cases. The committee noted that the reason for this is the favourable treatment effect of LAMA+LABA on exacerbations, FEV1, TDI, and SGRQ compared to other options. These treatment benefits mean that LAMA+LABA generally produces the highest number of QALYs, and also generates cost savings through the reduction in hospitalised and non-hospitalised exacerbations.

The committee noted that including treatment effects on adverse events and mortality substantially increases the uncertainty in results. This is particularly due to the effect on mortality, as this outcome is an important determinant of QALYs, and is associated with wide confidence intervals which, in turn, causes greater uncertainty in model results. It was also noted that the point estimates for mortality effects are most favourable towards LABA+ICS, which reduces the probability that LAMA+LABA is the most cost-effective strategy. The committee carefully considered the plausibility of this mortality effect. It was observed that this result was largely produced by a single trial – Wedzicha et al. (2008) – which reported a significant reduction in mortality for LABA+ICS compared with LAMA monotherapy. This result also affects the relative mortality effect between LAMA+LABA and LABA+ICS, as it provides indirect evidence in the network meta-analysis. However, the committee observed that the pairwise evidence comparing LAMA+LABA to LABA+ICS found no difference in mortality between these 2 treatments. Moreover, none of the other studies used in the network meta-analysis found a significant mortality effect for any of the pairwise comparisons. The committee also noted that there is no evidence that LAMA treatment has an effect on mortality *per se*, as the network meta-analysis results for the LAMA monotherapy review do not show an effect on mortality compared to placebo for any of the individual LAMA agents.

For these reasons, the committee agreed that the mortality benefit associated with LABA+ICS is likely to be generated by an outlying result, and agreed that scenarios which did not include a treatment-specific effect on mortality were a more accurate representation of the true relative health benefits and costs of the treatments assessed.

The committee also considered model subgroup results for patients at high- and low-risk of exacerbations. It was noted that, for the high-risk population, LAMA+LABA is associated with a lower ICER and a higher probability of being cost-effective than in the overall population across all scenarios. This is primarily due to a higher baseline exacerbation rate for this subgroup, meaning that more effective treatments achieve a larger absolute reduction in exacerbations, and are therefore associated with greater QALY gains and cost reductions. For the low-risk subgroup, the opposite is

true; a lower baseline exacerbation rate results in higher ICERs and more uncertainty that LAMA+LABA is the most cost-effective treatment. The committee noted that, for this subgroup, LAMA+LABA retained the highest probability of being cost effective when treatment effects on adverse events and mortality were excluded. However, this ceased to be the case when either or both of these effects were included. A strategy of LABA -to- LAMA+LABA had the highest probability of being cost effective when adverse event effects were included, and a strategy of LABA -to- LABA+ICS had the highest probability when both adverse event and mortality effects were included. Despite these findings, the committee were still confident that LAMA+LABA is likely to be the optimal strategy overall. This was firstly because the scenario in which treatment effects on adverse events and mortality were excluded was deemed to be the most plausible, due to the level of uncertainty in these outcomes. Secondly, the patient population eligible for long-acting bronchodilator therapy is, by definition, more akin to the high-risk population than to the low-risk population, as these treatments are only offered to patients who remain breathless or have exacerbations despite using short-acting bronchodilators. Therefore, if anything, LAMA+LABA is likely to be more cost-effective than in the model base case, which is based on a population containing both high- and low-risk patients.

For these reasons, the committee were confident in recommending LAMA+LABA as first-line long-acting bronchodilator therapy for patients with stable COPD on both economic and clinical grounds.

The committee discussed the implications of recommending LAMA+LABA as the initial long-acting bronchodilator therapy on the rest of the treatment pathway. It was noted that, as a result, an existing recommendation on triple therapy (LAMA+LABA+ICS) for patients whose symptoms are not controlled with a LAMA alone would become obsolete, since the treatment pathway no longer includes LAMA monotherapy as an option. The committee considered evidence from the economic model for a scenario in which progression from dual to triple therapy was not permitted. It was observed that this scenario resulted in LAMA+LABA becoming more cost effective than in the model base case, and so the committee remained confident in their recommendations. It was agreed that it may be appropriate to revisit the place of triple therapy in the treatment pathway in a future guideline update, especially given recent evidence on the effectiveness of triple therapy fixed-dose combination inhalers.

The committee noted that there was no economic or clinical evidence on inhaled therapy for patients with COPD and features of asthma. However, it was observed that inhaled corticosteroids are a mainstay of treatment for asthma and, as such, it is logical that any recommended regimen should contain an ICS. The committee discussed the possibility of recommending triple therapy (LAMA+LABA+ICS) for patients with symptoms of both COPD and asthma, given that LAMA+LABA was found to be cost effective in the *de novo* economic analysis, and that adding an ICS to this regimen would be a logical step to address the asthma component. However, it was decided that, given the uncertainty in the cost-effectiveness of triple therapy in general, and the lack of evidence for patients with features of asthma, it would be more appropriate to make a more conservative recommendation for LABA+ICS, considering that patients with COPD and features of asthma whose symptoms remain uncontrolled can be later stepped up to triple therapy.

The committee discussed choice of specific drugs and devices, and agreed that giving regard to patient response, preferences, and ability to use the device would generally be cost effective, given that these factors are likely to improve patients' use of medication and hence disease control, and therefore are likely to result in downstream cost savings. Similarly, the committee agreed that minimising the

number and type of inhaler devices would also be cost effective, as prescribing a single fixed-dose combination product is typically cheaper than prescribing both components individually, and also reduces clinician time in demonstrating how to use inhalers. Furthermore the committee noted that patients' adherence would, on average, be improved by using fewer devices.

The committee discussed the clinical evidence for the relative effectiveness of individual LAMAs, and determined that there is no strong evidence for differential effectiveness of treatments within the class. However, it was noted that there are some differences in costs of different drugs and inhalers. The committee agreed that this point was captured in their recommendation to base drug choice on a drug's cost (as well as other factors). Given the lack of evidence for within-class treatment differences, the committee recommended that medication switching within a class should be avoided where possible, in order to minimise treatment disruption, drug wastage, and use of clinicians' time, given the opportunity costs involved.

The committee considered the potential resource impact of their recommendations. It was determined that prescribing of LAMA+LABA is likely to increase as a result, and this may have a significant impact on resource use, given that dual therapy is typically more expensive than monotherapy. However, the committee were confident in this recommendation, given the robust economic and clinical evidence supporting it. Furthermore, many of the modelled scenarios show a downstream reduction in costs due to prevented exacerbations, which may (partially or totally) mitigate the total resource impact.

The committee agreed that the recommendation regarding the use of LABA+ICS for patients with COPD with asthmatic features would be unlikely to result in a significant resource impact, because LABA and ICS are common treatments for COPD and asthma, respectively. Furthermore, this recommendation is a weaker 'consider' recommendation, and is therefore anticipated to have a less pronounced effect on practice.

The committee agreed that the recommendations relating to the choice of specific drugs and inhaler devices represented good clinical practice and, if anything, would result in cost savings due to reduced waste in inhaler prescription, more effective delivery of inhaled medication, and better control of symptoms.

Other factors the committee took into account

These reviews did not include consideration of the effectiveness of the delivery device. The committee noted that it was important that people with COPD were assessed for their ability to manage a specific inhaler device, its acceptability was assessed and they were trained to use their inhaler device by healthcare professionals competent to do so. They noted that since the inhaler devices were different they may suit different people. In particular, some devices may be less suited to older and elderly people who have problems with dexterity and/ or cognition. As a result, the committee recommended that the choice of inhaler device and ability to use it should also be taken into account when making decisions on inhaled therapies. The committee also noted that in clinical practice the availability of each LAMA in a different device would impact on medication choice.

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for combinations of inhaled therapies

4 This review was carried out as a collaboration with the Cochrane Airways Group. The
5 following table is based on the published review protocol (Oba et al 2017).

Field (based on PRISMA-P)	Content
Review question	In people with stable COPD, what is the clinical and cost effectiveness of a LAMA plus a LABA compared with: • a LAMA alone • a LABA alone • a LABA plus an inhaled corticosteroid (ICS)
Type of review question	Intervention
Objective of the review	To determine the comparative effectiveness of different drug classes for managing stable COPD
Eligibility criteria – population	People diagnosed with COPD Inclusion criteria from Cochrane Review: • Patients aged > 35 years • Diagnosis of COPD in accordance with American Thoracic Society-European Respiratory Society (ATS/ERS 2004), GOLD report (GOLD 2017) or equivalent criteria. • Obstructive ventilator defect should be at least moderate, with a baseline FEV1 less than 80% of predicted.
Eligibility criteria – interventions	• LAMA • LABA • LAMA + LABA • LABA + ICS
Eligibility criteria – comparators	Each other

Outcomes	• COPD exacerbation (moderate to severe and severe) • St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score ≥ 4 units (responder) • Transition Dyspnoea Index (TDI) • Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropout due to adverse event • Trough FEV1 • Pneumonia • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other inclusion exclusion criteria	• Trials with a follow-up of less than 12 weeks
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Disease severity • Treatment duration • Smoking status • Type of each arm (intraclass comparison) • Dose of ICS component for pneumonia • Publication status
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic

	reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C Cochrane Airways Group Specialised Register (CAGR): searches for inhaled therapy combinations The searches will be undertaken by the Cochrane Airways Group using the following databases: • AMED (EBSCO) • CINAHL (EBSCO) • Cochrane Central Register of Controlled Trials – CENTRAL (the Cochrane Library) • EMBASE (Ovid) • MEDLINE (Ovid) • PsycINFO (Ovid) • ClinicalTrials.gov • World Health Organization (WHO) trials portal All databases will be searched from their inception to present. Hand searches: core respiratory conference abstracts • American Academy of Allergy, Asthma and Immunology (AAAAI) • American Thoracic Society (ATS) • Asia Pacific Society of Respirology (APSR) • British Thoracic Society Winter Meeting (BTS) • Chest Meeting • European Respiratory Society (ERS) • International Primary Care Respiratory Group Congress (IPCRG) • Thoracic Society of Australia and New Zealand (TSANZ) NICE economic search:

	• NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017
Identify if an update	Update of 2010 COPD guideline questions: What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists compared to long-acting beta2 agonists in the management of people with stable COPD? What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD? What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists compared to long-acting beta2 agonists plus inhaled corticosteroids in the management of people with stable COPD?
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).

Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson initially, then Andrew Molyneux from September 2017 onwards in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.

Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

1 **Review protocol for the choice of long-acting anticholinergics (LAMAs)**

Field (based on PRISMA-P)	Content
Review question	Which is the most clinically and cost-effective long-acting anticholinergic (LAMA) for managing stable COPD, and which subgroups of people should receive treatment with it?
Type of review question	Intervention
Objective of the review	To determine the comparative effectiveness of different LAMAs for managing stable COPD, and to identify which subgroups of people benefit from treatment.
Eligibility criteria – population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)
Eligibility criteria – interventions	• Specific drug from LAMA class including: • Tiotropium • Glycopyrronium (sometimes called glycopyrrolate) • Aclidinium (Eklira brand name) • Umeclidinium
Eligibility criteria – comparators	• Alternative drug from LAMA class • Placebo
Outcomes	• Mortality • Hospital admissions and readmissions • Exacerbations • Gas trapping (Residual Volume, RV)

	• Gas transfer (carbon monoxide diffusion capacity and arterial oxygen partial pressure, PaO2) • Exercise capacity/ exercise tolerance (e.g. 6 minute walking distance, 6MWD, or the shuttle walk test) • Symptoms including breathlessness (e.g. Borg dyspnoea score, Modified MRC scale for dyspnoea) and orthopnoea • Change in FEV1, rate of change in FEV1 • Adverse events including: • Renal problems • Cardiac problems • Falls • Quality of life (e.g. St. George's respiratory questionnaire, SGRQ, overall score) • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other inclusion exclusion criteria	• Trials of less than 12 weeks duration (to ensure trials looking at acute effects (e.g. on exercise) are excluded and confine search to trials looking at longer term effects of interventions). • Non-English language publications
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Multimorbidities (including COPD with asthma, bronchiectasis, anxiety or depression) • Smoking status (smokers versus non-smokers or, data permitting, never smoked, ex-smokers and current smokers). • Polypharmacy (defined as taking ≥ 4 medicines; stratify by ≥5, ≥ 8, ≥ 10 medicines as per NICE multi-morbidity guideline NG56) • Trials that recruited patients with at least one COPD exacerbation in the 12 months before study entry

	• People with cognitive decline Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C Main Searches: • Cochrane Database of Systematic Reviews – CDSR (Wiley) • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley) • •Database of Abstracts of Reviews of Effects – DARE (Wiley) • Health Technology Assessment Database – HTA (Wiley) • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The search will not be date limited due to additional terminology to that in the searches carried out in the 2010 guideline update.

	Economics: • NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017.
Identify if an update	This is a new question for the 2017 COPD guideline. It was derived from the 2004 questions: Which patients with stable COPD should be treated with long-acting anticholinergics? How should the effects of this intervention be assessed?
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B

Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson initially, then Andrew Molyneux from September 2017 in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

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Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 14. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 14: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Incorporating published Network Meta-Analyses (NMAs)

Quality assessment

Individual NMA studies were quality assessed using a modified version of the PRISMA-NMA checklist specified below. The modified version of the checklist includes only the subset of items in the full checklist that are specifically applicable to reporting the results of network meta-analysis. The full PRISMA-NMA statement with elaborations on each item is reported in the following publication:

Hutton B, Salanti G, Caldwell DM et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-784.

The checklist was adapted to allow 'yes' or 'no' answers for the provision of information in the NMA. This checklist was used to provide an overall quality rating based on the number of 'no' answers and the relative importance of the different questions for study quality in the opinion of the Guideline Updates Team.

Modified PRISMA-NMA checklist (reproduced and modified with permission)

1. Has the rationale for the review been described in the context of what is already known, including mention of why a network meta-analysis has been conducted?
2. Have the study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility been specified, with rationale given for the choices made? Have eligible treatments included in the treatment network been clearly described, and has it been noted whether any have been clustered or merged into the same node (with justification)?
3. Have the methods used to explore the geometry of the treatment network and potential biases related to it been described? This should include how the evidence base has been graphically summarised for presentation, and what characteristics were compiled and used to describe the evidence base to readers.
4. Have the principal summary measures (e.g., risk ratio, difference in means) been described? Also have the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses been described?
5. Have the methods of handling data and combining results of studies for each network meta-analysis been described? This should include, but not be limited to:
    a. Handling of multi-arm trials;
    b. Selection of variance structure;
    c. Selection of prior distributions in Bayesian analyses; and
    d. Assessment of model fit
6. Have the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied been described? Were efforts taken to address inconsistency when found?
7. Have the methods of additional analyses been described if done, indicating which were pre-specified. This may include, but not be limited to, the following:
    a. Sensitivity or subgroup analyses;
    b. Meta-regression analyses;
    c. Alternative formulations of the treatment network; and
    d. Use of alternative prior distributions for Bayesian analyses (if applicable).

8. Has a network graph of the included studies been provided to enable visualisation of the geometry of the treatment network?
9. Has a brief overview of characteristics of the treatment network been provided? This may include commentary on the abundance of trials and randomised patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure (for example, publication bias).
10. Have the results, including confidence/credible intervals, of each meta-analysis carried out been presented? In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care). League tables and forest plots may be considered to summarise pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.
11. Have the results from investigations of inconsistency been described? This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.
12. Have the results of additional analyses been presented, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth)?
13. Do the authors discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias)? Do they comment on the validity of the assumptions, such as transitivity and consistency and discuss any concerns regarding network geometry (e.g., avoidance of certain comparisons)?

Using published NMAs as a source of data

If the NMAs were judged to be sufficiently applicable and high quality, they could be used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 14. Data from these published NMAs was presented in GRADE tables as described below. The quality of the systematic review used as a basis for the NMA was assessed using ROBIS before data was extracted. However, if the published NMA was only used in comparison to a new NMA being carried out to address the review question, then ROBIS was not required.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.

- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 15. For other mean differences where no MID is given below the line of no effect is used.

Table 15: Identified MIDs

Outcome	MID	Source
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.
Change in Transition Dyspnoea Index (TDI)	1 point (-1, +1)	Witek TJ, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. The European respiratory journal 2003; 21:267-272.
Change in FEV1	100ml (-100, +100)	Cazzola M, MacNee W, Martinez M et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. For relative risks where no other MID was available, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

In cases where the point estimate of effect fell on an MID boundary, it was taken as being within the MID and therefore not being a clinically meaningful effect. If the 95% CI of the point estimate fell on either or both of the MID boundaries it was taken as being within/inside the MID.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 16

Table 16: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (1 corresponding to meaningful benefit; 1 corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed 1 MID, and twice if it crossed both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following five conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.

- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology 'up to' in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement.

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Conventional 'pairwise' meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from two or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following three criteria were met:

- At least three treatment alternatives.
- A sufficiently connected network to enable valid estimates to be made.
- The aim of the review was to produce recommendations on the most effective option, rather than simply an unordered list of treatment alternatives.

Synthesis

Two separate frameworks and software packages were used for undertaking network-meta analyses in this guideline, with the chosen method dependent on the specifics of the question (for certain datasets, it may be possible to run the preferred analysis in one program but not the other, or it may be particularly more efficient to use one package over another):

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

Results were reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned N (0, 1000) priors, and the between-trial standard deviations used in random-effects models were given U (0, 5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed- and random-effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model (or 6 points lower if the model contained 2 random effects terms), it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more parsimonious analysis, and was preferred.

Because different approaches and software had been applied, sensitivity analysis have previously been undertaken to establish whether this might have led to any substantive differences in output. Specimen dichotomous and continuous NMAs from the Bayesian analysis were rerun in the frequentist framework and generated results that were materially indistinguishable from the Bayesian version.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis. Where sufficient studies were available, meta-regression was undertaken to explore the effect of study level covariates.

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 17: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded.

GRADE criteria	Reasons for downgrading quality
	Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for a random-effects model was lower than the DIC for a fixed-effects model. In addition, under both frameworks, the direct and indirect treatment estimates were compared as a check on the consistency of the network.
Imprecision	The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or statistical significance if MIDs were not available.

Evidence statements

In contrast to the pair-wise data, the NMA evidence statements for the inhaled therapy combinations review only described drug combinations and outcomes where there was an effect that was greater than a defined MID. For simplicity, where the NMA found no difference, could not differentiate or found statistically significant differences that were below the MID no evidence statements were presented. However, to aid in the visualisation of results, the summary tables in appendix N included both drug combinations and outcomes where there was an effect greater than the MID and those where the effect was less than the MID. (Please see the pair-wise evidence statements descriptions for an explanation of the different categories of evidence statement referred to above.)

Since the LAMA monotherapy review was less complex, the NMA evidence statements followed the pair-wise evidence statement format and all 4 categories of evidence statement were reported where relevant. The NMA results showing an effect (greater or less than the MID) were summarised in Table 67. An evidence statement was included to summarise the results of the published NMAs.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel

clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 18.

Table 18 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 19.

Table 19 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Cochrane Airways Group Specialised Register (CAGR): Sources and search methods for the Inhaled therapy combinations

Review question search strategy

In people with stable COPD, what is the clinical and cost effectiveness of a LAMA plus a LABA compared with:

- a LAMA alone
- a LABA alone
- a LABA plus an inhaled corticosteroid (ICS)

Electronic searches: core databases

Database	Frequency of search	Search dates
CENTRAL (the Cochrane Library)	Monthly	Inception to March 2017
MEDLINE (Ovid)	Weekly	1946 to March 2017
Embase (Ovid)	Weekly	1974 to March 2017
PsycINFO (Ovid)	Monthly	1967 to March 2017
CINAHL (EBSCO)	Monthly	1937 to March 2017
AMED (EBSCO)	Monthly	All years to March 2017
ClinicalTrials.gov		
World Health Organization (WHO) trials portal		

Top- up searches were carried out from March 2017 to February 2018.

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards

British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Search strategy to identify relevant trials from the CAGR

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 mometasone* AND formoterol*

#8 fluticasone* AND salmeterol*

#9 budesonide* AND formoterol*

#10 beclomethasone* AND formoterol*

#11 fluticasone* AND formoterol*

#12 Flutiform or Fostair or Simplyone

#13 fluticasone* AND vilanterol*

#14 mometasone* AND indacaterol*

#15 formoterol* and ciclesonide*

#16 QMF149

#17 GW685698 AND GW642444

#18 steroid* OR corticosteroid* or ICS

#19 (long-acting* or long NEXT acting*) NEAR beta*

#20 #18 AND #19

#21 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #20

#21 formoterol* AND aclidinium*

#22 indacaterol* AND glycopyrronium*

#23 indacaterol* AND tiotropium*

#24 olodaterol* AND tiotropium*

#25 vilanterol* AND umeclidinium*

#26 QVA149

#27 Ultibro or Stiolto or Duaklir Genuair

#28 Muscarinic* Next Antagonist*

#29 #19 AND #28

#30 #21 or # 22 or #23 or #24 or #25 or #26 or #27 or # 29

#31 combin* NEAR inhaler*

#32 FDC:ti,ab

#33 #21 or #30 or #31 or #32

#34 #6 AND #33

[In search line #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD]

Further information on the CAGR can be found: http://airways.cochrane.org/sites/airways.cochrane.org/files/public/uploads/Search%20strategies%20document_2013_0.pdf

NICE search methods for the LAMA monotherapy review question

Main searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence

The population terms have been updated from the original guideline to include potential co-morbidities such as asthma, bronchopulmonary dysplasia and bronchiectasis. These were excluded in the original strategy.

In this update, several lines of the strategy have been focused with the use of the term ‘chronic’ to reduce retrieval of articles focusing on acute signs or symptoms.

Additional acronyms for COPD have been included and on recommendation from the guideline committee, terms around ‘breathlessness’ have been added.

Searches were re-run in February 2018 and also included searching Medline epub ahead of print.

Review question search strategy

- Which is the most clinically and cost-effective long-acting anticholinergic (LAMA) for managing stable COPD, and which subgroups of people should receive treatment with it?

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases.

Search strategy

Medline Strategy, searched 14th September 2017 **Database: Ovid MEDLINE(R) 1946 to September Week 1 2017** **Search Strategy:**
1 lung diseases, obstructive/
2 exp pulmonary disease, chronic obstructive/
3 (copd or coad or cobd or aecb).tw.
4 emphysema*.tw.
5 (chronic* adj4 bronch*).tw.
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
7 (pulmonum adj4 (volumen or pneumatosis)).tw.
8 pneumonectasia.tw.
9 *Dyspnea/
10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12 or/1-11
13 Muscarinic Antagonists/
14 (long act* adj4 muscarinic*).tw.
15 (muscarinic* adj1 antagonist*).tw.
16 LAMA*.tw.
17 (anticholinergic* or antimuscarinic* or anti-muscarinic*).tw.
18 Tiotropium Bromide/
19 (tiotropium* or ba 679 br or ba679 br or spiriva* or handihaler* or braltus).tw.

Medline Strategy, searched 14th September 2017 Database: Ovid MEDLINE(R) 1946 to September Week 1 2017 Search Strategy:
20 (tiova adj2 rotacap*).tw.
21 Glycopyrrolate/
22 (glycopyrronium* or glycopyrrolate* or seebri* or nva237 or nva 237 or dimethylpyrrolidinium* or ad237 or ad 237 or ahr504 or ahr 504 or asecryl or cuvposa or drm04 or "drm 04" or enurev or gastrodyn or glersa or mobinul or nodapton or robinal or robinol or robinul or sialanar or sroton or strodin or tarodyl or tarodyn or tovanor).tw.
23 (aclidinium or bretaris or eklira or las34273 or las 34273 or tudorza).tw.
24 (umeclidinium or ellipta or gsk573719* or gsk 573719* or incruse).tw.
25 (GSK233705 or BEA2180 or BEA 2180).tw.
26 or/13-25
27 12 and 26
28 animals/ not humans/
29 27 not 28
30 limit 29 to english language
31 limit 30 to (letter or historical article or comment or editorial or news or case reports)
32 30 not 31

1 *Note: In-house RCT and systematic review filters were appended and crossover studies removed*

2 **Study design filters and limits**

3 The MEDLINE systematic review (SR) and Randomized Controlled Trial (RCT) filters were
4 appended to the review question above and are presented below. They were translated for
5 use in the MEDLINE In-Process and Embase databases.

6 **Study design filters**

The MEDLINE SR and RCT filters are presented below.
Systematic Review
1. Meta-Analysis.pt.
2. Meta-Analysis as Topic/
3. Review.pt.
4. exp Review Literature as Topic/
5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
6. (review$ or overview$).ti.
7. (systematic$ adj5 (review$ or overview$)).tw.
8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
9. ((studies or trial$) adj2 (review$ or overview$)).tw.

The MEDLINE SR and RCT filters are presented below.
10. (integrat$ adj3 (research or review$ or literature)).tw. 11. (pool$ adj2 (analy$ or data)).tw. 12. (handsearch$ or (hand adj3 search$)).tw. 13. (manual$ adj3 search$).tw. 14. or/1-13 15. animals/ not humans/ 16. 14 not 15
RCT 1 Randomized Controlled Trial.pt. 2 Controlled Clinical Trial.pt. 3 Clinical Trial.pt. 4 exp Clinical Trials as Topic/ 5 Placebos/ 6 Random Allocation/ 7 Double-Blind Method/ 8 Single-Blind Method/ 9 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. 10 (random$ adj3 allocat$).tw. 11 placebo$.tw. 12 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. 13 or/1-12 14 animals/ not humans/ 15 13 not 14 *Note: analysts requested cross-over studies to be removed.*

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

The search is not date limited due to additional terminology to that in the searches carried out in the 2010 guideline update.

Health Economics search strategy

Economic evaluations and quality of life data

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and EMBASE to identify relevant evidence and can be seen below. Searches were carried out on 5th May 2017 with a

date limit from the previous search of January 2009 – May 2017. Searches were re-run in February 2018.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations
1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

1

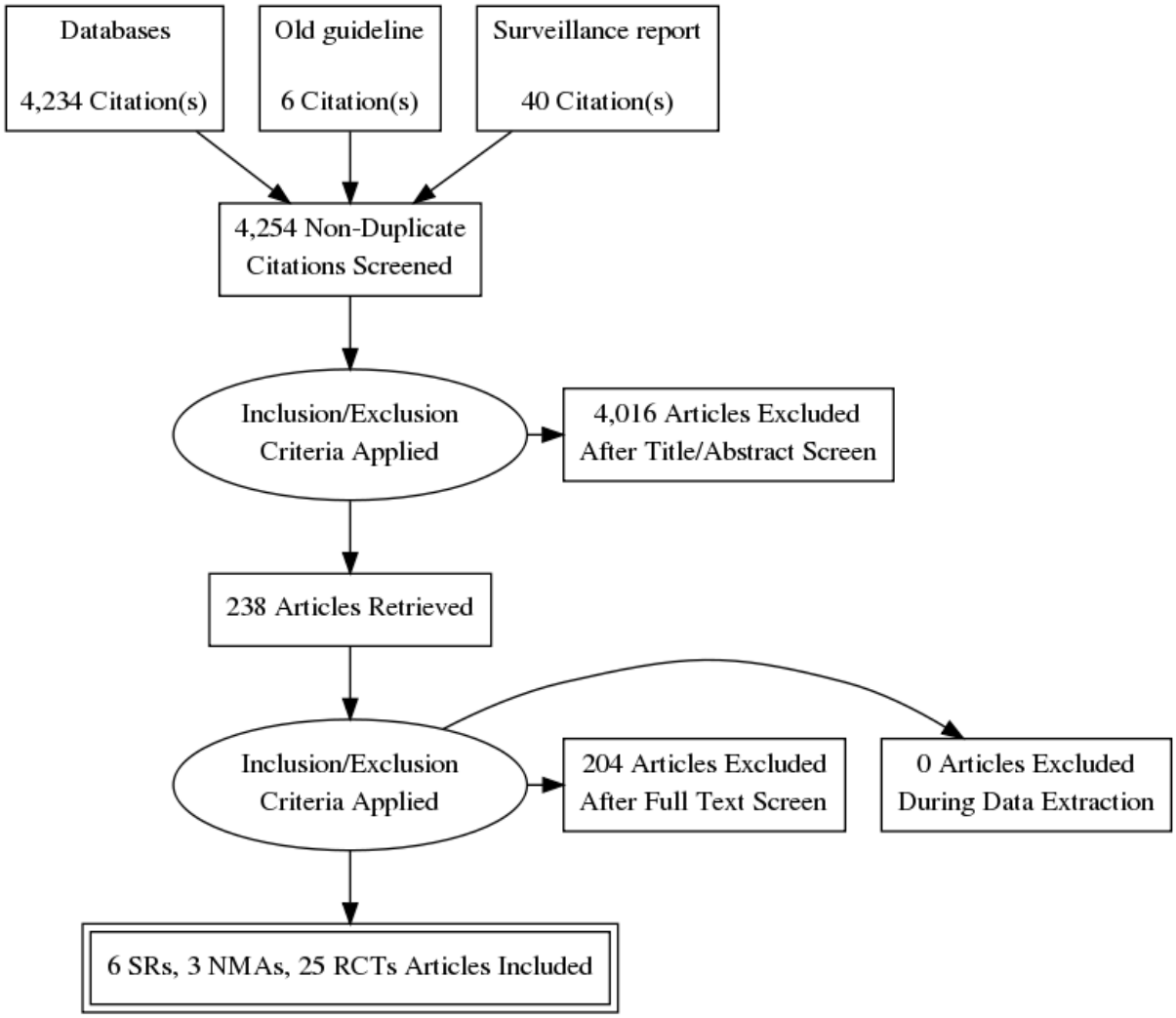
1 Appendix D – Clinical evidence study selection

2 Inhaled therapy combinations

3 Please refer directly to the Cochrane review for the PRISMA diagram.

1 **LAMA monotherapy**

2



3

Appendix E – Clinical evidence tables

Inhaled therapy combinations

Randomised Controlled Trials (RCTs)

The following tables were taken directly from the updated Cochrane review and are based on the work of the Cochrane Airways Group.

Characteristics of studies

Characteristics of included studies

205.137 2003

Methods	See Brusasco 2003
Participants	**Population:** 385 participants were randomised to salmeterol (192) and tiotropium (193) See Brusasco 2003
Interventions	See Brusasco 2003
Outcomes	See Brusasco 2003
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02173691

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Brusasco 2003
Allocation concealment (selection bias)	Low risk	See Brusasco 2003
Blinding of participants and personnel (performance bias)	Low risk	See Brusasco 2003
Blinding of outcome assessment (detection bias)	Low risk	See Brusasco 2003
Incomplete outcome data (attrition bias)	Low risk	See Brusasco 2003
Selective reporting (reporting bias)	Low risk	See Brusasco 2003

205.264 2004

Methods	**Design:** randomized, double-blind, double-dummy, parallel design **Duration:** 12 weeks **Location:** Multicenter Study, Finland, Greece, Italy, Portugal, Sweden, Turkey, United Kingdom, United States
Participants	**Population:** Tiotropium: entered: 328 treated: 328 analysed (for primary endpoint): 308 Salmeterol: entered: 325 treated: 325 analysed (for primary endpoint): 300 **Baseline Characteristics:** Not described **Inclusion Criteria:** Outpatients of either sex, 40 years or older, with a diagnosis of COPD (FEV1 ≤ 60% and FEV1/FVC ≤ 70%) and a smoking history of ≥ 10 pack-years. **Exclusion Criteria:** Not provided.
Interventions	**Inhaler Device:** Tiotropium Inhalation Capsules via the Handihaler **Allowed Co-Medications:** Salmeterol Inhalation Aerosol
Outcomes	FEV1 AUC0-12, peak FEV1, trough FEV1, FVC AUC0-12, trough and peak FVC, individual FEV1 and FVC measurements, COPD exacerbations, use of rescue medication. Adverse events.
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT00274560

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Withdrawal was low and even between two groups (7.7% SAL, 6.1% TIO)
Selective reporting (reporting bias)	High risk	Study was prospectively registered but exacerbation outcomes were not reported in detail.

A3401 2016

Methods	**Design:** A Prospective, Multicenter, Randomized Open-label Study **Duration:** 12-weeks **Location:** 673 centers in 23 countries: Belgium(40), Estonia(6), Slovenia(4), Greece(5), Germany(236), United Kingdom(50), Lithuania(9), Slovakia (Slovak Republic)(16), Spain(50), Latvia(7), Hungary(18), Russia(18), Austria(12), Ireland(6), Italy(72), Czech Republic(35), Sweden(12), Denmark(5), Norway(12), Romania(8), France(32), Portugal(11), Poland(9)
Participants	**Population:** 274 in group C1 (LABA/ICS) and 822 in group C2 (IND/Glyco) **Baseline Characteristics:** age 64.4 (SD 9) in grp C1, 64.7 (SD 8.7) in grp C2, Female/male: 106/168 in grp C1, 286/536 in grp C2. **Inclusion Criteria:** Inclusion Criteria:Male and female adults aged ≥ 40 years Patients with moderate COPD according to the GOLD criteria 2013 Current or ex-smokers who have a smoking history of at least 10 pack years Patients with airflow limitation indicated by a postbronchodilator FEV1 ≥ 50% and <80% of the predicted normal value and a post-bronchodilator FEV1/FVC <0.7 at Visit 2. Patients with an mMRC score ≥ 1 at Visit 1. **Exclusion Criteria:** narrow-angle glaucoma or urinary retention, severe renal impairment, including those with end-stage renal disease requiring dialysis, asthma, malignancy of any organ system, a documented history of >1 COPD exacerbation requiring treatment with systemic corticosteroids or antibiotics and/or hospitalization in the previous 12 months, clinically significant condition such as (but not limited to): *Unstable ischemic heart disease, left ventricular failure (NYHA Class III & IV), history of myocardial infarction,arrhythmia (excluding chronic stable atrial fibrillation), and a body mass index (BMI) of more than 40 kg/m2.

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Interventions	**Inhaler Device:** Glycopyrronium 50 µg capsule for inhalation via SDDPI Indacaterol maleate and glycopyrronium bromide fixed dose combination (110/50 µg) capsule for inhalation via SDDPI Short-acting β2-adrenergic agonist (SABA) Long Acting Beta Agonist (LABA) Short-acting muscarinic antagonist (SAMA) Inhaled corticosteroid (ICS) **Allowed Co-Medications:** Not described. The list of prohibited medication (Table 5-2) not available.
Outcomes	Primary Outcome: Trough FEV1 at week 12 for group: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC)
Notes	**Funding:** Novartis **Identifiers:** NCT01985334, CQVA149A3401

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively low and even between groups (14.6% in grp C1 and 19% in grp C2).
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Aaron 2007

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 52 weeks **Location:** 27 Canadian medical centres
Participants	**Population:** 304 adults, with a clinical history of moderate or severe COPD as defined by ATS and GOLD guidelines, were randomised to tiotropium + salmeterol (148 participants) and tiotropium (156 participants) **Baseline Characteristics:** mean age 68 years. COPD severity moderate to severe with mean FEV1 predicted of 38%. 57% men **Inclusion Criteria:** at least 1 exacerbation of COPD that required treatment with systemic corticosteroids or antibiotics within the 12 months before randomisation; age >35 years; a history of ≥ 10 pack-years of cigarette smoking; documented

1

	chronic airflow obstruction, with an FEV1/FVC ratio < 0.70 and a post-bronchodilator FEV1 < 65% of the predicted value **Exclusion Criteria:** history of physician-diagnosed asthma before 40 years of age; history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction; people receiving oral prednisone; people with a known hypersensitivity or intolerance to tiotropium, salmeterol, or fluticasone-salmeterol; history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery, or diffuse bilateral bronchiectasis; and people who were pregnant or were breastfeeding.
Interventions	**Inhaler Device:** ● tiotropium + salmeterol: tiotropium 18 μg once daily using a HandiHaler + salmeterol 25 μg/puff, 2 puffs twice daily using a pressurised metered-dose inhaler using a spacer device ● tiotropium + placebo: tiotropium, 18 μg once daily, + placebo inhaler, 2 puffs twice daily **Allowed Co-Medications:** as needed albuterol, antileukotrienes, and methylxanthines
Outcomes	Primary: proportion of participants with ≥ 1 exacerbation of COPD Secondary: mean number of COPD exacerbations per patient-year; total number of exacerbations that resulted in urgent visits to a healthcare provider or emergency department; the number of hospitalisations for COPD; the total number of hospitalisations for all causes; changes in health-related quality of life, dyspnoea, lung function
Notes	**Funding:** Canadian Institutes of Health Research and OntarioThoracic Society **Identifiers:** ISRCTN29870041

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done through central allocation of a randomisation schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site
Allocation concealment (selection bias)	Low risk	Randomisation was done through central allocation of a randomisation schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site
Blinding of participants and personnel (performance bias)	Low risk	double-blind
Blinding of outcome assessment (detection bias)	Low risk	The assembled data from the visit for the suspected exacerbation were presented to a blinded adjudication committee for review, and the committee confirmed whether the encounter met the study definition of COPD exacerbation. The statistician who performed the analysis was initially

1

		blinded to patient group assignments.
Incomplete outcome data (attrition bias)	Low risk	The number of people who stopped drug therapy was high but even in both groups. 74 (47%) participants withdrew from the tiotropium + placebo group and 64 (43%) participants on LABA + tiotropium group but the breakdown for withdrawal was similar between TIO vs TIO+SAL arms.
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported.

Agusti 2014

Methods	**Design:** a randomized, double-blind, double-dummy, multi-centre parallel group study **Duration:** 12 weeks **Location:** Belgium, France, Germany, Italy, Philippines, Poland, Russian Federation, Spain, Ukraine
Participants	**Population:** FP/SAL (500/50) 262, FF/VI(100/25) 266 **Baseline Characteristics:** age 62.9 (SD 8.59) F:M 95:433 **Inclusion Criteria:** ● Signed and dated written informed consent ● Male or females ≥ 40 years of age ● Established clinical history of COPD by ATS/ERS definition ● Females are eligible to enter and participate if of non-childbearing potential, or if of child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the acceptable contraceptive methods listed in protocol, used consistently and correctly ● Former or current smoker > 10 pack years ● Post-albuterol spirometry criteria: FEV1/FVC ratio ≤ 0.70 and FEV1 ≤ 70% of predicted normal (NHANES III) ● have been hospitalised or have been treated with oral corticosteroids or antibiotics for their COPD within the last 3 years prior to Screening (Visit 1) **Exclusion Criteria:** ● Current diagnosis of asthma ● Subjects with other respiratory disorders including active tuberculosis, α1-antitrypsin deficiency, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases ● Lung volume reduction surgery within previous 12 months ● Clinically significant abnormalities not due to COPD by chest x-ray ● Hospitalized for poorly controlled COPD within 12 weeks of Screening ● Poorly controlled COPD 6 weeks prior to Screening, defined as acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician ● Lower respiratory infection requiring antibiotics 6 weeks prior to Screening ● Uncontrolled or clinically significant (in opinion of PI) cardiovascular, hypertension, neurological, psychiatric, renal, hepatic, immunological, endocrine, peptic ulcer disease, or hematological abnormalities ● Carcinoma not in complete remission for at least 5 years ● Subjects with history of hypersensitivity to study medications (e.g.,

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	beta-agonists, corticosteroid) or components of inhalation powder (e.g., lactose, magnesium stearate) ● Subjects with history of severe milk protein allergy that, in opinion of study physician, contraindicates subject's participation - Known/suspected history of alcohol or drug abuse in the last 2 years ● Women who are pregnant or lactating or plan to become pregnant ● Subjects medically unable to withhold albuterol and/or ipratropium 4 hours prior to spirometry testing at each study visit ● Use of certain medications such as bronchodilators and corticosteroids for the protocol-specific times prior to Visit 1 (the Investigator will discuss the specific medications) ● Long Term Oxygen Therapy (LTOT) or nocturnal oxygen therapy >12 hours a day ● Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening or during the study - Non-compliance or inability to comply with study procedures or scheduled visits ● Affiliation with investigator site
Interventions	Fluticasone Furoate 100mcg/Vilanterol 25mcg Fluticaosne Propionate 500mcg/Salmeterol 50mcg **Inhaler Device:** ELLIPTA dry powder inhaler **Allowed Co-Medications:** Salbutamol as needed, Ipratropium, mucolytics
Outcomes	Primary Outcome Measures: Change From Baseline Trough in 24-hour Weighted-mean FEV1 on Treatment Day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01342913, 113107

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response system using RandAll and RAMOS
Allocation concealment (selection bias)	Low risk	Interactive voice response system using RandAll and RAMOS
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	The investigator and treating physician were blinded till an emergency arouse.
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (6.1 % in SAL/FP and 8.65 in FF/VI group).
Selective reporting (reporting bias)	Low risk	Trial registration located. Outcomes well reported.

1

Anzueto 2009

Methods	**Design**: Randomised, double-blind, parallel-group, multicenter study **Duration**: 52 weeks (+ 4 week run-in) **Location**: 98 centres in the USA and Canada
Participants	**Population**: 797 participants were randomised to salmeterol alone (403) and salmeterol/fluticasone combination therapy (394) **Baseline characteristics** Age (mean years): sal 65.3, sal/flut 65.4 % Male: sal 57, sal/flut 51 % FEV1 predicted (pre BD): sal 33.9, sal/flut 34.1 Pack-years (mean): sal 56.5, sal/flut 57.8 **Inclusion criteria**: >40 years of age with a diagnosis of COPD, a cigarette smoking history 10 pack-years, a pre-albuterol FEV1/FVC0.70, a FEV150%of predicted normal and a documented history of at least 1 COPD exacerbation the year prior to the study that required treatment with antibiotics, oral corticosteroids, and/or hospitalisation. **Exclusion criteria**: current diagnosis of asthma, a respiratory disorder other thanCOPD, historical or current evidence of a clinically significant uncontrolled disease, or had a COPD exacerbation that was not resolved at screening
Interventions	**Inhaler Device:**1. Salmeterol 50 bid (LABA) 2. Salmeterol/fluticasone 50/250 bid (LABA/ICS) Inhaler device: Diskus **Allowed Co-Medications:** As-needed albuterol was provided for use throughout the study. As needed ipratropium was not provided; however, it could be used during the study. The use of concurrent inhaled long-acting bronchodilators (beta2-agonist and anticholinergic), ipratropium/albuterol combination products, oral beta-agonists, inhaled corticosteroids (ICS), leukotriene modifiers, inhaled nedocromil and cromolyn, theophylline preparations, ritonavir and other investigational medications were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of a COPD exacerbation
Outcomes	Annual rate of moderate/severe exacerbations, time to firstmoderate/severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and pre-dose FEV1.Diary records and health status measured on the StGeorge's Respiratory Questionnaire (SGRQ)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT00115492, GSK NCT00115492

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	an interactive voice response system (IVRS) was used as a means for central allocation of drug in accordance with the randomization schedule

1

Allocation concealment (selection bias)	Low risk	an interactive voice response system (IVRS) was used as a means for central allocation of drug in accordance with the randomization schedule
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind [assumed participants and personnel/investigators]
Blinding of outcome assessment (detection bias)	Low risk	The investigator and treating physician were blinded till an emergency arouse.
Incomplete outcome data (attrition bias)	High risk	The withdrawal rates were very high , 39% discontinued in salmeterol arm and 32% in FPS arm. More patients were withdrawn due to lack of efficacy and exacerbation with FPS arm compared with SAL arm (8.2% vs 5.3%).
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported and could be included

Asai 2013

Methods	**Design:** multi-center, randomized, open label, parallel group study **Duration:** 52 weeks **Location:** 35 centers in Japan
Participants	**Population:** 119 in QVA 149 group, 39 in Tio group. **Baseline Characteristics:** age 69.3 (SD 6.8), M/F 95.6/4.4%, **Inclusion Criteria:** severe stable COPD (Stage II or Stage III), a smoking history of at least 10 pack years, postbronchodilator forced expiratory volume in one second (FEV1) ≥ 30% and < 80% of the predicted normal, and postbronchodilator FEV1/forced vital capacity (FVC) < 0.7 at Visit 2. **Exclusion Criteria:** Pregnant women or nursing mothers, concomitant pulmonary disease, a history of asthma, malignancy of any organ system, certain cardiovascular comorbid conditions, alpha-1 antitrypsin deficiency, etc.
Interventions	**Inhaler Device:** QVA149 (110 mcg indacaterol / 50 mcg glycopyrrolate o.d. delivered via Concept1 tiotropium (18 mcg o.d.) **Allowed Co-Medications:** Not described.
Outcomes	Primary Outcome: Number of participants with adverse events, serious adverse events or death
Notes	**Funding:** Novartis **Identifiers:** NCT01285492, CQVA149A1301, ARISE

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described

1

Blinding of participants and personnel (performance bias)	High risk	open label
Blinding of outcome assessment (detection bias)	High risk	open label
Incomplete outcome data (attrition bias)	High risk	Dropout was relatively low but uneven between two groups (14.0% in QVA and 2.6 % in Tio group).
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

B1303 2011

Methods	**Design:** Multi-center, Randomized, Open Label, Parallel Group Study **Duration:** 52 weeks **Location:** Japan
Participants	**Population:** Indacaterol 300 μg 125, Salmeterol 50 μg 61 **Baseline Characteristics:** age 69.1 (SD 7.97) F:M 10:176 **Inclusion Criteria:** ● Diagnosis of COPD (moderate-to-severe as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines) and: ● Smoking history of at least 20 pack-years ● Post-bronchodilator FEV1 <80% and ≥ 30% of the predicted normal value ● Post-bronchodilator FEV1/FVC (forced vital capacity) <70% **Exclusion Criteria:** a COPD exacerbation in the 6 weeks prior to Visit 1 or during the run-in period, concomitant pulmonary disease, asthma,diabetes Type I or uncontrolled diabetes Type II, lung cancer or a history of lung cancer, certain cardiovascular comorbid conditions
Interventions	**Inhaler Device:** Indacaterol 300 µg once daily (od) via SDDPI Salmeterol 50 µg twice daily (bid) via Diskus **Allowed Co-Medications:** Salbutamol as rescue
Outcomes	long term safety and tolerability (particularly with regard to ECG, laboratory tests, vital signs and adverse events) of indacaterol
Notes	**Funding:** Novartis **Identifiers:** NCT00876694, CQAB149B1303

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	open label

1

Blinding of outcome assessment (detection bias)	High risk	open label
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively low and even between two groups (16.8% in IND, 19.7% in SAL group).
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Bateman 2013

Methods	**Design:** multi-centre, randomised, double-blind, parallel-group, placebo- and activecontrolled trial **Duration:** 26 weeks (+ 2 week run-in) **Location:** academic and clinical research centres inEurope,NorthAmerica, SouthAmerica, Asia (Philippines, Japan, India), Australia, China, Taiwan and South Africa
Participants	**Population:** 2144 participants were randomised to indacaterol (477), glycopyrronium (475), open-label tiotropium (483), placebo (234), and one other arm that was not included in this review (QVA149 combination, 475) **Baseline Characteristics:** Age (mean years): ind 63.6, gly 64.3, tio 63.5, pbo 64,4 % Male: ind 74.4, gly 77.2, tio 75.0, pbo 72.8 % FEV1 predicted: ind 54.9, gly 55.1, tio 55.1, pbo 55.2 **Inclusion Criteria:** Participants were aged 40 years, had moderate-to-severe stable COPD (Stage II or III according to GOLD 2008 criteria), and a smoking history of 10 pack-years. At screening, they were required to have a post-bronchodilator forced expiratory volume in 1 second (FEV1) 30% and <80% of predicted normal and postbronchodilator. FEV1/forced vital capacity (FVC) <0.70. **Exclusion Criteria:** respiratory tract infection within 4 weeks prior to Visit 1; concomitant pulmonary disease; history of asthma; lung cancer or a history of lung cancer; history of certain cardiovascular co-morbid conditions; known history and diagnosis of alpha-1 antitrypsin deficiency; in the active phase of a supervised pulmonary rehabilitation program; contraindicated for inhaled anticholinergic agents and 2 agonists; other protocol-defined inclusion/exclusion criteria may apply
Interventions	1. Indacaterol 150 qd (LABA) 2. Glycopyrronium 50 qd (LAMA) 3. Tiotropium 18 qd (LAMA) - open label 4. Placebo (PBO) **Inhaler Device:** All medications were administered once daily in the morning via the Breezhaler® device except for tiotropium, which was administered open-label via the Handihaler® device. **Allowed Co-Medications:** Participants remained on a stable dose of inhaled corticosteroid (ICS) and salbutamol/albuterol was available for use as rescuemedication throughout the study
Outcomes	Trough FEV1, dyspnoea, health status measured on the SGRQ, rescue medication use and safety

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Notes	**Funding:** Novartis **Identifiers:** NCT01202188

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No specific details of sequence generation but done electronically and presumed valid
Allocation concealment (selection bias)	Low risk	Eligible patients were assigned a randomisation number via Interactive Response Technology (IRT), linking the patient to a treatment arm and specific unique medication number for the study drug. The randomisation number was not communicated to the investigator contacting the IRT
Blinding of participants and personnel (performance bias)	High risk	Blinding procedures were sound, but tiotropium was delivered open label which introduced bias for these comparisons. Blinding of patients, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, and schedule of administration, appearance, taste and odour. Unblinding occurred in the case of emergencies and at the conclusion of the study
Blinding of outcome assessment (detection bias)	High risk	Same as above.
Incomplete outcome data (attrition bias)	Low risk	Dropout was between 9% and 20% across the five groups, and over 99% were included in the analysis
Selective reporting (reporting bias)	Low risk	Prospectively registered and well reported with additional online supplemental material available

BI1237.22 2014

Methods	**Design:** A Randomised, Double-blind, Parallel-group Study **Duration:** 52 weeks **Location:** Japan
Participants	**Population:** Olodaterol (5 μg) 41, Tiotropium + Olodaterol (2.5 / 5 μg) 40, Tiotropium + Olodaterol (5 / 5 μg) 41 **Baseline Characteristics:** age 69.9 (SD7.3), F:M 5:117 **Inclusion Criteria:** 1. Diagnosis of chronic obstructive pulmonary disease. 2. Relatively stable airway obstruction with post FEV1< 80% predicted normal and post FEV1/FVC <70%. 3. Male or female Japanese patients, 40 years of age or older. 4. Smoking history of more than 10 pack years. **Exclusion Criteria:**

	Significant disease other than COPD, Clinically relevant abnormal lab values, History of asthma.significant co-morbidities, known active tuberculosis. malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years, other pulmonary diseases, regular use of daytime oxygen therapy for more than one hour per day, pregnant or nursing women.women of childbearing potential not using a highly effective method of birth control, narrow-angle glaucoma or micturition disorder due to prostatic hyperplasia etc.
Interventions	**Inhaler Device:** Tiotropium and Olodaterol FDC once daily inhalation: Respimat Olodaterol once daily inhalation: Respimat Tiotropium and Olodaterol FDC once daily inhalation: Respimat **Allowed Co-Medications:**
Outcomes	Primary Outcome Measures :Number (%) of Patients With Drug-related AEs
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01536262, 1237.22

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	Dropout was high with olodaterol 5 (19.5%) uneven compared with Tio/Olo 5/5 (4.9%)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Bogdan 2011

Methods	**Design:** Randomised, Double-blind, Placebo-controlled, Parallel-group, Multi-national, Phase III, Efficacy and Safety Study **Duration:** 12 weeks **Location:** Bulgaria, Japan, Romania, Russian Federation, Ukraine
Participants	**Population:** FM 4.5 bid 206 subjects, FM 9 bid 199 subjects **Baseline Characteristics:** age 66.75 (SD 9.4), F:M 74:539 **Inclusion Criteria:** ● Males or females aged above 40 with a clinical diagnosis of COPD and current COPD symptoms ● Current or previous smoker with a smoking history of 10 or more pack years ● Lung function parameters: FEV1/FVC < 70%, post-bronchodilator and

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	post-bronchodilator FEV1 < 80% of predicted normal value **Exclusion Criteria:** ● History and/or current clinical diagnosis of asthma or atopic diseases such as allergic rhinitis ● Use of inhaled glucocorticosteroids within 4 weeks prior to Visit 2 ● Any relevant cardiovascular disorder as judged by the investigator or any current respiratory tract disorder other than COPD.
Interventions	**Inhaler Device:** Formoterol Turbuhaler 4.5mg Formoterol Turbuhaler 9 mg Turbuhaler placebo **Allowed Co-Medications:** Salbutamol as rescue, short-acting anticholinergics
Outcomes	Primary Outcome Measures: Forced Expiratory Volume in 1 Second (FEV1; L) 60 Minutes Post-dose
Notes	**Funding:** AstraZeneca **Identifiers:** NCT00628862, D5122C00001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and even between two groups (5.3% in FM 4.5 and 8.5% in FM 9 group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Briggs 2005

Methods	**Design:** randomised, double-blind, double-dummy, parallel-group study **Duration:** 12 weeks **Location:** 50 centres located in 8 countries, including Finland, Greece, Italy, Portugal, Sweden, Turkey, the United Kingdom and the United States
Participants	**Population:** n = 653 (tiotropium: 328, salmeterol: 325) **Baseline Characteristics:** mean age (tiotropium: 64.2 years, salmeterol 64.6 years); gender (tiotropium 65%male, salmeterol 68%male); mean%predicted FEV1 (tiotropium 37. 7, salmeterol 37.7%);mean smoking pack year history (tiotropium55.6 years, salmeterol 56.1 years)

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	Inclusion Criteria: patients who were ≥ 40 years of age, with a cigarette smoking history of ≥ 10 pack years, and a clinical diagnosis of COPD, were eligible for inclusion in the study if they had a FEV1 % predicted ≤ 60% and FVC ≤ 70% **Exclusion Criteria:** patients with a history of asthma, allergic rhinitis, atopy or a total (absolute) blood eosinophil count ≥ 600 mm were excluded from the study, as were those with any significant medical condition that could preclude participation for the full duration of the trial or interfere with the interpretation of the study results. Patients were also excluded from the study if they took systemic corticosteroids at unstable doses or in daily doses of ≥ 10 mg (or its equivalent), if they were using beta-blockers, cromones, or anti-leukotrienes prior to enrolment in the trial, or if they had experienced a respiratory tract infection or a COPD exacerbation within 30 days of randomisation. Patients using oxygen for more than 1 h per day and who were unable to refrain from its use during pulmonary function testing were also excluded. Additionally, patients were excluded who were actively participating in a rehabilitation programme or had completed such a programme during the previous 30 days
Interventions	1. Tiotropium, 18 μg once daily via the HandiHaler device; or 2. Salmeterol, 2 actuations of 25 μg each, twice daily via a metered dose inhaler **Inhaler Device:** HandiHaler device for tiotropium, MDI for salmeterol. **Allowed Co-Medications:** As-needed albuterol, Inhaled corticosteroid
Outcomes	Primary outcome(s): the co-primary efficacy outcomes were average post-dose FEV1 over 12 h and peak FEV1 after 12 weeks of treatment. Average FEV1 was estimated from the area under the curve from 0 to 12 h (AUC 0– 12). Secondary outcome(s): secondary outcomes including morning pre-dose FEV1, FEV1 at each time point over 12 h, corresponding FVC parameters, incidence and frequency of COPD exacerbations (the number or percentage of patients with at least one COPD exacerbation, time to first exacerbation, number of exacerbations, and exacerbation days), rescue medication use, and incidence of serious adverse events
Notes	**Funding:** Boehringer Ingelheim and Pfizer **Identifiers:** 205.264

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated by Boehringer Ingelheim using a validated system, which involved a pseudo-random number generator so that the resulting treatment sequence was both reproducible and non-predictable
Allocation concealment (selection bias)	Low risk	All investigational medication for each patient was identified by a uniquemedication number. Each eligible patient was assigned the lowest medication number available to the investigator at the time of randomisation

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Blinding of participants and personnel (performance bias)	Low risk	Boehringer Ingelheim was responsible for preparing and coding study medication in a blinded fashion (Boehringer Ingelheim study drug and control were indistinguishable). Patients, investigators and study personnel remained blinded with regard to the treatment assignments up to database lock
Blinding of outcome assessment (detection bias)	Low risk	In all studies, a selection of standard respiratory endpoints like pulmonary function, SGRQ, TDI, treadmill, exacerbations, etc. were used. Outcome assessors remained blinded with regard to the treatment assignments up to database lock
Incomplete outcome data (attrition bias)	Low risk	The withdrawal rates were relatively samll and even between the groups (tiotropium 8.8%, salmeterol 12.6%)
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol.

Brusasco 2003

Methods	**Design:** pooled results from two randomised, double-blind, double-dummy, parallelgroup studies **Duration:** 6 months (+ 2 weeks run-in period) **Location:** The studies were performed in 18 countries The only difference in the two studies was the duration of serial spirometry in the clinic (12 hours in one study, 3 hours in the second)
Participants	**Population:** 805 participants were randomised to salmeterol (405) and placebo (400) **Baseline Characteristics:** Age (mean years): sal, 64.1; pbo, 64.6 % Male: sal, 75.1; pbo, 76.3 % FEV1 predicted: sal 37.7; pbo, 38.7 Pack-years (mean): sal, 44.8; pbo, 42.4 **Inclusion Criteria:** Participants were required to have relatively stable airway obstruction with FEV1 < 65% of predicted normal and < 70% of FVC, > 40 years of age, with a smoking history of > 10 pack-years **Exclusion Criteria:** Patients with a history of asthma, allergic rhinitis or atopy or with an increased total eosinophil count were excluded. Other exclusion criteria included use of supplemental oxygen or an upper respiratory tract infection in the six weeks before screening. Patients with a significant disease other than COPD were not enrolled.Significant disease was defined as a disease that, in the opinion of the investigator, would put the patient at risk because of participation in the study, or a disease that would influence the results of the study.
Interventions	1. Salmeterol 50 bid (LABA) 2. Tiotropium 18 qd (LAMA) 3. Placebo (PBO) **Inhaler Device:** metered dose **Allowed Co-Medications:** Participants were allowed to continue previously prescribed regular inhaled steroids or regular oral steroids, not exceeding a dose equivalent to approximately 10 mg prednisone daily. The number of participants taking these medications during the study was not located.

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Outcomes	Mean change from baseline on the SGRQ and number whose score decreased by at least 4 units; exacerbations (number, time to first etc.), hospital admissions, FEV1, FVC, dyspnoea (evaluated using the Baseline Dyspnoea Index (BDI) and the TDI), diary card data
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02172287, NCT02173691, 205.130, and 205.137

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated by Boehringer Ingelheim using a validated system, which involved a pseudo-random number generator so that the resulting treatment sequence was both reproducible and non-predictable
Allocation concealment (selection bias)	Low risk	All investigational medication for each patient was identified by a unique medication number. Each eligible patient was assigned the lowest medication number available to the investigator at the time of randomisation
Blinding of participants and personnel (performance bias)	Low risk	Boehringer Ingelheim was responsible for preparing and coding study medication in a blinded fashion (Boehringer Ingelheim study drug and control were indistinguishable). Patients, investigators and study personnel remained blinded with regard to the treatment assignments up to database lock. Double dummy technique was used to blind different application devices
Blinding of outcome assessment (detection bias)	Low risk	In all studies, a selection of standard respiratory endpoints like pulmonary function, SGRQ, TDI, treadmill, exacerbations, etc. were used. Outcome assessors remained blinded with regard to the treatment assignments up to database lock.
Incomplete outcome data (attrition bias)	Low risk	The withdrawal rates were relatively even between groups (salmeterol [18.8%], tiotropium [15.4%])
Selective reporting (reporting bias)	Low risk	Results for all expected and specified outcomes were reported (except FEV1 [secondary outcome] was not reported in a way that could be included in the qualitative synthesis.

Buhl 2011

Methods	**Design:** randomised, placebo controlled, double blind, double dummy **Duration:** 12 weeks **Location:** 223 centres in 22 countries: Austria, Belgium, Canada, Colombia, Denmark, Finland, France, Germany, Greece,Hungary, Israel, Italy,Mexico, Norway, Poland, Russia, Slovakia, Spain, Switzerland, Turkey, UK and USA

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Participants	**Population:** n = 1598 (tiotropium: 797, indacaterol: 801) **Baseline Characteristics:** mean age (tiotropium: 63.6 years, indacaterol 63.4 years); gender (tiotropium 70% male, indacaterol 67%); mean% predicted FEV1 (tiotropium 54.3%, indacaterol 54.6%); mean smoking pack year history (tiotropium 41.8 years, indacaterol 43.2 years) **Inclusion Criteria:** patients with a diagnosis of COPD, smoking history of at least 10 pack years, post-bronchodilator FEV1 < 80% and ≥ 30%of the predicted normal value, post-bronchodilator FEV1/FVC < 70% **Exclusion Criteria:** patients who have received systemic corticosteroids or antibiotics and/or was hospitalised for a COPD exacerbation in the 6 weeks prior to screening, respiratory tract infection within 6 weeks prior to screening, concomitant pulmonary disease, history of asthma, diabetes Type I or uncontrolled diabetes Type II, lung cancer or history of lung cancer, history of certain cardiovascular comorbid conditions.
Interventions	**Inhaler Device:** 1. Tiotropium, 18 μg once daily via the HandiHaler device 2. Indacaterol 150 μg delivered via a SDDPI (single-dose dry powder inhaler) **Allowed Co-Medications:** As-needed albuterol, Inhaled corticosteroid
Outcomes	Primary outcome(s): trough FEV1 24h post-dose after 12 weeks of treatment. Secondary outcome(s): FEV1 AUC 5 min to 4 hours post-dose on day 1, week 4 and week 12. Rescue medication use over 12 weeks. Safety and tolerability
Notes	**Funding:** Novartis **Identifiers:** NCT00900731, CQAB149B2350

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System
Allocation concealment (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System
Blinding of participants and personnel (performance bias)	Low risk	double blind, double dummy
Blinding of outcome assessment (detection bias)	Low risk	Investigators, study staff performing the assessments and data analysts were blinded
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rates were low and even (tiotropium 7.6%, indacaterol 7.5%)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

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Buhl 2015

Methods	**Design:** randomised, double-blind, parallel-group, multicentre **Duration:** 52 weeks **Location:** 25 countries including US, Canada, UK, EU coutries, Australia, South Africa, Brazil etc.
Participants	**Population:** 5162 patients **Baseline Characteristics:** See Buhl 2015a&b **Inclusion Criteria:** outpatients aged > 40 years with a history of moderate-to-very severe COPD(GOLDstage 2-4); post-bronchodilator FEV1 < 80%of predicted normal; postbronchodilator FEV1/FVC < 70%; current or ex-smokers with a smoking history of >10 pack-years **Exclusion Criteria:** clinically relevant abnormal baseline laboratory parameters or a historyof asthma; MI within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known activeTB; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if people were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening)
Interventions	**Inhaler Device:** ● tiotropium 5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily ● tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily ● Olodaterol μg Respimat once daily ● tiotropium 5 μg Respimat once daily ● tiotropium 2.5 μg Respimat once daily **Allowed Co-Medications:** as needed albuterol, inhaled corticosteroid, theophylline
Outcomes	Primary: ● FEV1 AUC (0-3 h) response on day 169 ● Trough FEV1 response on day 170 ● SGRQ total score on day 169 from the 2 twin trials, Buhl 2015a (NCT01431274) and Buhl 2015b (NCT01431287) These outcomes were also measured at days 85 and 365
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01431274, NCT01431287, 1237.5, 1237.6

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was assigned via an Interactive Voice Response System/Interactive Web Response System
Allocation concealment (selection bias)	Low risk	Treatment was assigned via an Interactive Voice Response System/Interactive Web Response System

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Blinding of participants and personnel (performance bias)	Low risk	Double-blind for all arms
Blinding of outcome assessment (detection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias)	High risk	Withdrwal was uneven among comparators of interest (18.3% in olo 5, 13.7% in tio 5 and 10.7% in tio/olo 5/5 arms.
Selective reporting (reporting bias)	Low risk	Prospectively registered and well reported.

Buhl 2015a

Methods	**Design:** randomised, double-blind, parallel-group, multicentre **Duration:** 52 weeks **Location:** See Buhl 2015
Participants	**Population:** 2624 participants with moderate-to-very severe COPD **Baseline Characteristics:** mean age 64.2 years. COPD severity was GOLD stage 2 (FEV1 50-80% predicted) in 50% of participants, stage 3 (30-50% predicted) in 39% of participants, and stage 4 (< 30% predicted) in 11% of participants, with mean FEV1 of 50% predicted. 74% were men. 38% were current smokers. 48% were taking ICS. 86% had co-morbidity at baseline **Inclusion Criteria:** outpatients aged > 40 years with a history of moderate-to-very severe COPD(GOLDstage 2-4); post-bronchodilator FEV1 < 80%of predicted normal; postbronchodilator FEV1/FVC < 70%; current or ex-smokers with a smoking history of >10 pack-years **Exclusion Criteria:** clinically relevant abnormal baseline laboratory parameters or a historyof asthma; MI within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known activeTB; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if people were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening)
Interventions	**Inhaler Device:** ● tiotropium 5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily ● tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily ● Olodaterol μg Respimat once daily ● tiotropium 5 μg Respimat once daily ● tiotropium 2.5 μg Respimat once daily **Allowed Co-Medications:** as needed albuterol, inhaled corticosteroid, theophylline
Outcomes	Primary: ● FEV1 AUC (0-3 h) response on day 169 ● Trough FEV1 response on day 170 ● SGRQ total score on day 169 from the 2 twin trials, Buhl 2015a

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	(NCT01431274) and Buhl 2015b (NCT01431287) These outcomes were also measured at days 85 and 365
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01431274, 1237.5

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Buhl 2015
Allocation concealment (selection bias)	Low risk	See Buhl 2015
Blinding of participants and personnel (performance bias)	Low risk	See Buhl 2015
Blinding of outcome assessment (detection bias)	Unclear risk	See Buhl 2015
Incomplete outcome data (attrition bias)	High risk	See Buhl 2015
Selective reporting (reporting bias)	Low risk	See Buhl 2015

Buhl 2015b

Methods	**Design:** randomised, double-blind, parallel-group, multicentre **Duration:** 52 weeks **Location:** See Buhl 2015
Participants	**Population:** 2539 participants with moderate-to-very severe COPD **Baseline Characteristics:** mean age 63.8 years.COPDseveritywasGOLDstage 2 (FEV1 50-80%predicted) in 50%of participants, stage 3 (30-50%predicted) in 38%, and stage 4 (< 30% predicted) in 12% of participants, with mean FEV1 of 50% predicted. 72% were men. 36% were current smokers. 47% were taking ICS. 87% had co-morbidity at baseline **Inclusion Criteria:** outpatients aged > 40 years with a history of moderate-to-very severe COPD(GOLDstage 2-4); post-bronchodilator FEV1 < 80%of predicted normal; postbronchodilator FEV1/FVC < 70%; current or ex-smokers with a smoking history of >10 pack-years **Exclusion Criteria:** clinically relevant abnormal baseline laboratory parameters or a historyof asthma; MI within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known activeTB; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if people were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening)
Interventions	**Inhaler Device:** ● tiotropium 5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily ● tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily ● Olodaterol μg Respimat once daily ● tiotropium 5 μg Respimat once daily

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	• tiotropium 2.5 μg Respimat once daily **Allowed Co-Medications:** as needed albuterol, inhaled corticosteroid, theophylline
Outcomes	Primary: • FEV1 AUC (0-3 h) response on day 169 • Trough FEV1 response on day 170 • SGRQ total score on day 169 from the 2 twin trials, Buhl 2015a (NCT01431274) and Buhl 2015b (NCT01431287) These outcomes were also measured at days 85 and 365
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01431287, 1237.6

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Buhl 2015
Allocation concealment (selection bias)	Low risk	See Buhl 2015
Blinding of participants and personnel (performance bias)	Low risk	See Buhl 2015
Blinding of outcome assessment (detection bias)	Unclear risk	See Buhl 2015
Incomplete outcome data (attrition bias)	High risk	See Buhl 2015
Selective reporting (reporting bias)	Low risk	See Buhl 2015

Buhl 2015c

Methods	**Design:** Multicenter, Randomized, Parallel Group, Blinded Study **Duration:** 26 weeks **Location:** Germany
Participants	**Population:** IND/Glyco (110/50) 476, Tio (18)+FM (12) 458 **Baseline Characteristics:** age 62.9 (SD 8.29) F:M 319:615 **Inclusion Criteria:** ● Male or female adults aged ≥ 40 yrs ● Patients with moderate to severe chronic obstructive pulmonary disease (GOLD 2010 guidelines) ● Smoking history of at least 10 pack years ● Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC (forced vital capacity) <70% **Exclusion Criteria:** ● Pregnant women or nursing mothers or women of child-bearing potential not using adequate contraception ● Patients with a history of long QT syndrome ● Patients with Type I or uncontrolled Type II diabetes ● Patients who have had a COPD exacerbation or respiratory tract infection within 6 weeks prior to screening ● Patients with any history of asthma ● Patients with pulmonary lobectomy, lung volume reduction surgery, or lung transplantation ● Patients with concomitant pulmonary disease

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	● Patients requiring long term oxygen therapy (>15 h a day)
Interventions	**Inhaler Device:** QVA149 110/50µg a single-dose dry powder inhaler tiotropium proprietary inhaler (Handihaler). formoterol capsules Aerolizer device **Allowed Co-Medications:**
Outcomes	Primary Outcome Measures: St. George's Respiratory Questionnaire (SGRQ-C) Total Score After 26 Weeks of Treatment (Non-inferiority Analysis).
Notes	**Funding:** Novartis **Identifiers:** NCT01574651, CQVA149ADE01

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio.
Allocation concealment (selection bias)	Low risk	a validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	investigator staff, personnel performing assessments, and data analysts remained blinded from randomisation until database lock.
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (12.8 % in QVA149 and 11.4% in Tio+FM)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Calverley 2003

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 12 months (+ 2 weeks run-in) **Location:** 109 centres in 15 countries or regions
Participants	**Population:** 1022 participants were randomised to formoterol (255), budesonide (257), formoterol/budesonide combination (254) and placebo (256) **Baseline Characteristics:** Mean age (years): form 63, bud 64, form/bud 64, pbo 65 % Male: form 75, bud 74, form/bud 78, pbo 75 % FEV1 predicted: form 36, bud, form/bud, pbo 36 Pack-years: form 38, bud 39, form/bud 39, pbo 39 **Inclusion Criteria:** Males and females > 40 years old; history of at least 10 pack-years; COPD for at least 2 years; < 70% FEV1/FVC, FEV1 < 50% predicted; 1+ COPD exacerbations requiring medication in previous 2 to 12

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	months **Exclusion Criteria:** history of asthma or seasonal allergic rhinitis before age 40; any relevant cardiovascular disorders or other disease
Interventions	1. Formoterol 9 bid (LABA) 2. Budesonide 400 bid (ICS) 3. Formoterol/budesonide 9/320 bid (LABA/ICS) 4. Placebo (PBO) **Inhaler Device:** dry powder inhaler **Allowed Co-Medications:** terbutaline (0.5 mg) as needed; maximum 3-week course of oral corticosteroids and antibiotics were allowed in the event of exacerbations; parenteral steroids and/or nebulised treatment were allowed at emergency visits. Medications excluded during the study period were oxygen therapy; beta-blocking agents; inhaled corticosteroids; disodium cromoglycate; leukotriene antagonists or 5-lipoxygenase inhibitors; other bronchodilators; antihistamines and medications containing ephedrine.
Outcomes	St Georges Respiratory Questionnaire (SGRQ), COPD exacerbations, FEV1, FVC, morning and evening PEF, diary card data
Notes	**Funding:** AstraZeneca **Identifiers:** SD-039-0670

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment.No details of sequence generationmethods but assumed to adhere to usual AstraZeneca methods
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	Low risk	Study reported as double-blind (patient and investigators)
Blinding of outcome assessment (detection bias)	Low risk	No subjective assessor-rated outcomes were reported
Incomplete outcome data (attrition bias)	High risk	Withdrawal was high and uneven in the arms of interest (formoterol, 43.5%; BUD/FM 29.1%). An intention-to-treat analysis was used and all hypothesis testing but no information regarding method of imputation was provided
Selective reporting (reporting bias)	Low risk	Protocol could not be located but all relevant outcomes were reported.

Calverley 2003 TRISTAN

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group design **Duration:** 12 months (+ 2 weeks run-in period) **Location:** 196 centres in 25 countries

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Participants	**Population:** 1466 participants were randomised to salmeterol (372), fluticasone (375), salmeterol/fluticasone combination (358) and placebo (361) **Baseline Characteristics:** Mean age (years): salm 63.2, flut 63.5, salm/flut 62.7, pbo 63.4 % Male: salm 70, flut 69.5, salm/flut 75.4, pbo 75 % FEV1 predicted: salm 44.3, flut 45.0, salm/flut 44.8, pbo 44.2 Pack-years: salm 43.7, flut 41.5, salm/flut 42.0, pbo 43.4 **Inclusion Criteria:** 10-Pack-year history of cigarette smoking; a history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years; documented history of COPD exacerbations each year for the previous 3 years, including at least one exacerbation in the last year that required oral corticosteroids and/or antibiotics; a baseline (pre-bronchodilator) FEV1 25%to 70%of predicted normal; poor reversibility of airflowobstruction (defined as an increase < 10%of predicted normal FEV1 value 30 minutes after inhalation of 400 μg salbutamol) and FEV1/forced vital capacity (FVC) ratio 70% **Exclusion Criteria:** respiratory disorders other than COPD. Patients were also excluded if they had received systemic corticosteroids, high doses of inhaled corticosteroids or antibiotics in the 4 weeks before the 2 weeks run-in
Interventions	1. Salmeterol 50 bid (LABA) 2. Fluticasone 500 bid (ICS) 3. Salmeterol/fluticasone 50/500 bid (LABA/ICS) 4. Placebo (PBO) **Inhaler Device:** multi-dose dry powder **Allowed Co-Medications:** Inhaled salbutamol was used as relief medication throughout the study, and regular treatment with anticholinergics, mucolytics and theophylline was allowed. Medications not allowed during the study period were inhaled corticosteroids and LABAs.
Outcomes	St George's Respiratory Questionnaire (SGRQ), COPD exacerbations, FEV1 (at least 6 hours after medication), pretreatment FVC and post-bronchodilator FEV1 and FVC, morning PEF, diary card data
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SFCB3024

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We used a randomisation schedule generated by the patient allocation for clinical trials (PACT) programto assign patients to study treatment groups
Allocation concealment (selection bias)	Low risk	Every participating centre was supplied with a list of patient numbers (assigned to patients at their first visit) and a list of treatment numbers. Patients who satisfied the eligibility criteria were assigned the next sequential treatment number from the list
Blinding of participants and personnel (performance bias)	Low risk	Study drugswere labelled in away to ensure that both the patient and the investigator were unaware of the allocated treatment

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Blinding of outcome assessment (detection bias)	Low risk	No subjective assessor-rated outcomes and investigators remained blind
Incomplete outcome data (attrition bias)	Unclear risk	Withdrawal relatively even but high in both groups (salmeterol 32.0%, placebo 38.8%) but the Intent-to-Treat (ITT) population, consisting of all subjects who were randomised to treatment and received at least one dose of the study medication, was used for all analyses of efficacy and safety. Unclear what method of imputation was used for each outcome
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported in detail

Calverley 2007

Methods	**Design:** multi-centre, randomised, double-blind, parallel-group, placebo-controlled study **Duration:** 3 years (+ 3 weeks run-in period) **Location:** 466 centres in 42 countries comprising 190 centres in USA, 134 centres in Western Europe, 46 centres in Eastern Europe, 37 centres in Asia Pacific, and 59 centres in other regions
Participants	**Population:** 6184 participantswere randomised to salmeterol (1542), fluticasone (1551), salmeterol/fluticasone combination (1546) and placebo (1545) **Baseline Characteristics:** Mean age (years): salm 65.1, flut 65.0, salm/flut 65.0, pbo 65.0 % Male: salm 76.3, flut 75.4, salm/flut 75.1, pbo 76.3 % FEV1 predicted: salm 43.6, flut 44.1, salm/flut 44.3, pbo 44.1 Pack-years: salm 49.3, flut 49.2, salm/flut 47.0, pbo 48.6 **Inclusion Criteria:** male or female current or former smokers; history of at least 10 packyears; clinical diagnosis of COPD; aged 40 to 80 years inclusive, with pre-bronchodilator FEV1 < 60% predicted at entry to the study **Exclusion Criteria:** current diagnosis of asthma; current respiratory disorders other than COPD; lung volume reduction surgery and/or transplant; serious uncontrolled disease; evidence of alcohol, drug or solvent abuse, hypersensitivity to ICS, bronchodilators or lactose; deficiency of alpha1-antitrypsin; exacerbation during run-in period
Interventions	1. Salmeterol 50 bid (LABA) 2. Fluticasone 500 bid (ICS) 3. Salmeterol/fluticasone 50/500 bid (LABA/ICS) 4. Placebo (PBO) **Inhaler Device:** multi-dose dry powder **Allowed Co-Medications:** Ventolin as relief, inhaled long-acting bronchodilators and long-term oral corticosteroids (theophyllines long- and short-acting, SABAs and shortacting anticholinergic agents allowed).Medications not allowed during the study period were inhaled corticosteroids, inhaled long-acting bronchodilators, long-term oral corticosteroids and long-term oxygen therapy
Outcomes	St. George's Respiratory Questionnaire (SGRQ), COPD exacerbations, adjusted mean change FEV1

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Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT0026821, GSK SCO30003, TORCH

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	[Fromprotocol] Subjectswill be assigned to study treatment in accordancewith the randomisation schedule, which will be generated using the GWcomputer program Patient Allocation for Clinical Trials (PACT)
Allocation concealment (selection bias)	Low risk	From protocol] Subjects will be centrally randomised to one of the four treatment groups via the System for Central Allocation of Drug (SCAD) and will be stratified by smoking status
Blinding of participants and personnel (performance bias)	Low risk	[From protocol] Once the database has been frozen, the treatment allocations will be unblinded and all of the analyses detailed in this document will be performed. The treatment allocations will be unblinded using standard GSK systems. The database will be frozen by BDS Respiratory Data Management, GSK
Blinding of outcome assessment (detection bias)	Low risk	An independent clinical end point committee, whose members were unaware of the treatment assignments, determined the primary cause of death and whether death was related to COPD. No other outcomes were assessor-rated
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rates quite similar but both high by the end of the 36 month treatment period. Acceptable methods of imputation used in all cases. For any subject who withdraws prematurely fromthe study, all available data up to the time of discontinuation were included in the analyses. Mortality data were collected for subjects who withdrew early
Selective reporting (reporting bias)	Low risk	All relevant outcomes stated in the protocol were reported in detail

Calverley 2010

Methods	**Design**: double-blind, double-dummy, randomised, active-controlled, parallel-group study **Duration**: 11 months (+ 4 week run-in) **Location**: Conducted at 76 centres in 8 countries across Europe
Participants	**Population**: 718 participants were randomised to formoterol (239) and formoterol/budesonide combination (242), and one other treatment arm which was not eligible for this review (237) **Baseline characteristics** Age (mean years): bud/form 64.1, form 63.7 % Male: bud/form 81.5, form 81.1 % FEV1 predicted: bud/form 42.3, form 42.5 Pack-years (mean): bud/form 37.8, form 39.7

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	Inclusion criteria: Hospital outpatients with severe stable COPD according to the GOLD guidelines; aged 40 years with a diagnosis of symptomatic COPD for >2 years, at least a 20 pack-years smoking history, a post-bronchodilator FEV1 between 30% and 50%of the predicted normal and at least 0.7 L absolute value and a pre-dose FEV1/forced vital capacity (FVC) of 0.7; at least one exacerbation requiring medical intervention (oral corticosteroid and/or antibiotic treatment and/or need for a visit to an emergency department and/or hospitalisation) within 2-12 months before the screening visit and to be clinically stable for the 2 months before study entry; change in FEV1 <12% of predicted normal value 30 min following inhalation of 200 mg of salbutamol pMDI **Exclusion criteria**: History of asthma, allergic rhinitis or other atopic disease, variability of symptoms from day to day and frequent symptoms at night and early morning (suggestive of asthma); receiving long term oxygen therapy or they had a lower respiratory tract infection or had been hospitalised for an acute COPD exacerbation within two months before screening or during the run-in period. Treatment with oral, injectable or depot corticosteroids and antibiotics, long-acting antihistamines or changes in the dose of an oral modified release theophylline in the two months preceding screening and during the run-in period were excluded
Interventions	1. Formoterol 12 bid (LABA) 2. Formoterol/budesonide 12/400 bid (LABA/ICS) **Inhaler device**: Dry powder **Allowed co-medications**: not described
Outcomes	Change in pre-dose morning FEV1 and mean rate of COPD exacerbations per patient per year, FVC, PEF, SGRQ total score, six-minute walking test, BMI, BODE index, safety evaluations including ECG
Notes	**Funding**: Chiesi Farmaceutici **Identifier(s)**: NCT00476099

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation scheme followed a balanced-block centre-stratified design and was prepared via a computerised system
Allocation concealment (selection bias)	Low risk	Patients were centrally assigned, in each centre, to one of the three treatment arms at the end of the run-in period through an Interactive Voice/Web Response System (IXRS)
Blinding of participants and personnel (performance bias)	Low risk	On each study day, patients took both active medications and matched placebo twice daily, in order to maintain blinding
Blinding of outcome assessment (detection bias)	Low risk	On each study day, patients took both active medications and matched placebo twice daily, in order to maintain blinding. In case of emergency, un-blinding of the treatment code was done through IXRS

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Incomplete outcome data (attrition bias)	Low risk	12.3% withdrew from the combination group and 14.2% from the formoterol group. Judged to be relatively low and even between groups, and the intention-to-treat populationwere used using last observation carried forward
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Chapman 2014

Methods	**Design:** a randomized, blinded, double-dummy, parallel-group study **Duration:** 12 weeks **Location:** Canada, Croatia, Czech Republic, Estonia, France, Germany, Guatemala, India, Korea, Republic of, Latvia, Lithuania, Philippines, Poland, South Africa, Taiwan
Participants	**Population:** Glyco (50) 123 subjects, Tio (18) 40 subjects **Baseline Characteristics:** age 63.5 (SD8.0), F:M 172:485 **Inclusion Criteria:** ● Patients with moderate to severe stable COPD (Stage II or Stage III) according to the current GOLD Guidelines (GOLD 2010). ● Patients with a post-bronchodilator Forced Expiratory Volume in 1 second (FEV1) ≥ 30% and < 80% of the predicted normal, and a post-bronchodilator FEV1/ Forced Vital Capacity (FVC) < 0.70 at screening ● Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack/day x 10 yrs, or ½ pack/day x 20 yrs). ● Symptomatic patients, according to daily electronic diary data between Visit 2 (Day -14) and Visit 3 (Day 1), with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3. **Exclusion Criteria:** ● Pregnant or nursing (lactating) women ● Patients who, in the judgment of the investigator, or the responsible Novartis personnel, have a clinically relevant laboratory abnormality or a clinically significant condition before Visit 1. ● Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. (BPH patients who are stable on treatment can be considered). ● Patients receiving medications in the classes listed in the protocol as prohibited
Interventions	**Inhaler Device:** NVA237 (glycopyrronium) 50 μg inhalation capsules once a day, delivered via SDDPI Tiotropium 18 μg once a day delivered via HandiHaler device **Allowed Co-Medications:** salbutamol/albuterol as rescue.
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in 1 Second (FEV1) After 12 Weeks of Treatment
Notes	**Funding:** Novartis **Identifiers:** NCT01613326, CNVA237A2314

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An automated, interactive, voice-response technology was used
Allocation concealment (selection bias)	Low risk	An automated, interactive, voice-response technology was used
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone involved in the conduct of the study.
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and even between two groups (4.0% in NVA237 and 4.2% in Tio group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

COMBINE 2017

Methods	**Design:** randomized, open-label, parallel group, 2-treatment arm, active controlled, fixed dose, phase IV, clinical study **Duration:** 24 weeks **Location:** Argentina, Brazil, Chile, Dominican Republic, Ecuador, Honduras, Mexico, Panama
Participants	**Population:** FP+SAL 133, BUD+IND 109 **Baseline Characteristics:** age 67.2 (SD 8.7) F:M 95:127 **Inclusion Criteria:** Inclusion Criteria: ● Written informed consent must be obtained before any assessment is performed ● Outpatients with stable COPD groups C and D according to the 2011 GOLD Guidelines. ● Current or ex-smokers who have a smoking history of at least 10 pack years ● Patients with a history of at least one exacerbation. ● Patients able to read and complete **Exclusion Criteria:** ● Use of other investigational drugs within 30 days ● Patients with a history of hypersensitivity to any of the study drugs ● History or current diagnosis of ECG abnormalities ● Patients with diabetes Type I or uncontrolled diabetes Type II including patients with a history of blood glucose levels consistently outside the normal range ● Patients who have not achieved an acceptable spirometry result at Visit 1 ● Patients with a body mass index (BMI) of more than 40 kg/m2 ● Patients with lung cancer or a history of lung cancer ● Patients with a history of malignancy of any organ system

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	● Pregnant or nursing (lactating) women ● Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment ● Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers) ● Patients that are uncontrolled or unstable on permitted therapy, who in the opinion of the investigator, have clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or haematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment ● Patients requiring oxygen therapy for chronic hypoxemia ● Patients who have had a respiratory tract infection within 6 weeks prior to Visit 1 ● Patients with concomitant pulmonary disease, e.g. pulmonary tuberculosis, bronchiectasis, sarcoidosis, interstitial lung disorder or pulmonary hypertension ● Patients with a known diagnosis of Alpha-1 Antitrypsin deficiency. ● Patients with history of lung surgery ● Patients who are participating in the active phase of a supervised pulmonary rehabilitation program.
Interventions	Budesonide + Indacaterol Fluticasone + Salmeterol **Inhaler Device:** Budesonide 400 mcg twice a day via Breezhaler device, Fluticasone 250 mcg twice daily via Accuhaler device, Indacaterol 150 mcg once daily via Breezhaler® device,Salmeterol 50 mcg twice daily via Diskus device **Allowed Co-Medications:** "rescue medication" as needed
Outcomes	Primary Outcome Measures: Change From Baseline in Trough Forced Expiratory Volume in 1 Second (Non-inferiority Analysis).
Notes	**Funding:** Novartis **Identifiers:** NCT02055352, CQAB149BAR01

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	High risk	Dropout relatively low but uneven between two groups (5.5% in BUD/FM and 15% in FP/SAL).

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Selective reporting (reporting bias)	Unclear risk	Located trial registration - outcomes well reported

COSMOS-J 2016

Methods	**Design:** a multi-center, randomized, double-dummy, study **Duration:** 24 weeks **Location:** 39 sites in Japan.
Participants	**Population:** FP/SAL (250/50) 136, Tio (18) 126 **Baseline Characteristics:** age 68.3 (SD 7.02), F:M 20:385 **Inclusion Criteria:** 1. Male or female aged 40 - 80 years inclusive 2. Has an established clinical history of COPD (defined as per the GOLD definition) 3. The subject achieves a grade of ≥ 1 on mMRC at Visit 1 4. A signed and dated written informed consent is obtained from the subject prior to study participation 5. The subject has a post-bronchodilator FEV1 of ≥ 30% to ≤ 80% of predicted normal 6. The subject has a post-bronchodilator FEV1 / FVC ratio < 70% 7. The subject is a current or ex-smoker with a smoking history of > 10 pack-years Ex-smokers are required to have stopped smoking for at least 6 months prior to visit 1. Ex-smokers who stopped smoking less than 6 months ago will be defined as current smokers. 8. QTc < 450 msec at Visit 1; or for patients with bundle branch block QTc should be < 480 msec. **Exclusion Criteria:** 1. Has a predominant asthma (comorbid asthma is not an exclusion criteria) 2. Has a medical diagnosis of narrow-angle glaucoma, prostatic hyperplasia or bladder neck obstruction that in the opinion of the investigator should prevent them from entering the study Note: As with other anticholinergic drugs, subjects with narrow-angle glaucoma, prostatic hyperplasia or bladder neck obstruction should only be entered into the study at the Investigator's discretion 3. Has known respiratory disorders other than COPD (e.g. lung cancer, sarcoidosis, tuberculosis or lung fibrosis) 4. Has undergone lung surgery e.g., lung transplant and/or lung volume reduction 5. Had a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at Visit 1, if subject has not had one and/or CT image taken within 3 months of Visit 1) 6. Requires regular (daily) or long term oxygen therapy (LTOT). (LTOT is defined as ≥ 12 hours oxygen use per day) 7. Has plan to start or to change the pulmonary rehabilitation program during the study period 8. Requires regular treatment with oral, parenteral, or depot corticosteroids 9. Has serious, uncontrolled disease likely to interfere with the study (e.g. Left Ventricular failure, anaemia, renal or hepatic disease or serious psychological disorders) 10. Received any other investigational drugs within 4 weeks (or 5 half lives) prior to Visit 1

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	11. Has, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse 12. Has a known or suspected hypersensitivity to β2-agonists, steroids, anticholinergic treatments or any components of the formulations 13. Has previously been enrolled to this study and investigational drugs has been administered 14. Is not eligible to participate this study in the opinion of the investigator/subinvestigator
Interventions	**Inhaler Device:** Salmeterol xinafoate / fluticasone propionate 50/250 DISKUS, Tiotropium bromide capsule **Allowed Co-Medications:** salbutamol as rescue
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in 1 Second (FEV1) After 12 Weeks of Treatment
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01762800, SCO116717

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and even between two groups (9.4% in Tio and 10.2 % in FP/SAL group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Covelli 2016

Methods	**Design:** a randomized, double-blind, double-dummy, multi-center, parallel-group study **Duration:** 12 weeks **Location:** Canada, Czechia, Germany, Poland, Romania, United States
Participants	**Population:** FF/VI (100/25) 310, TIO (18) 313 **Baseline Characteristics:** age 62.6 (SD 8.03), F:M 221:402 **Inclusion Criteria:** ● Signed and dated written informed consent ● Male or females ≥ 40 years of age ● Females must be post-menopausal or using a highly effective method for avoidance of pregnancy

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	● Established clinical history of COPD by ATS/ERS definition ● Post-albuterol spirometry criteria: FEV1/FVC ratio ≤ 0.70 and FEV1 ≥ 30 to ≤ 70% of predicted normal (NHANES III) ● Former or current smoker ≥ 10 pack years ● A history of diagnosed cardiovascular disease or a prior cardiovascular event including any of the following: ● Established (i.e., by clinical signs or imaging studies) coronary artery disease (CAD) ● Established (i.e., by clinical signs or imaging studies) peripheral vascular (i.e., arterial) disease (PVD) ● Previous stroke ● Objectively confirmed transient ischemic attack (TIA) (i.e., transient neurological deficit documented by a health-care professional) ● Previous myocardial infarction (MI) (Note: An MI within 6 months prior to Visit 1 is exclusionary) OR ● Presence of one of the following cardiovascular risk factors (in addition to being a former/current smoker): ● Current diagnosis of hypertension ● Current diagnosis of hypercholesterolemia ● Diabetes mellitus treated with pharmacotherapy **Exclusion Criteria:** ● Current diagnosis of asthma ● Subjects with other respiratory disorders including α1-antitrypsin deficiency as the underlying cause of COPD, active tuberculosis, lung cancer, bronchiectasis (Note: focal bronchiectasis is not exclusionary), sarcoidosis, pulmonary fibrosis (Note: focal fibrotic pulmonary lesions are not exclusionary), pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases ● Lung volume reduction surgery within previous 12 months ● Clinically significant abnormalities not due to COPD by chest X-ray or CT scan ● Hospitalized for poorly controlled COPD within 12 weeks of Screening ● Poorly controlled COPD 6 weeks prior to Screening, defined as acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician ● Lower respiratory infection requiring antibiotics 6 weeks prior to Screening ● A moderate or severe COPD exacerbation and/or a lower respiratory tract infection (including pnuemonia) during the Run-In Period ● An abnormal, clinically significant finding in any liver chemistry, biochemical, or haematology tests at Screening (Visit 1) or upon repeat prior to randomization ● An abnormal, clinically significant ECG finding at Screening (Visit 1) or upon repeat prior to randomization ● An abnormal, clinically significant Holter finding at Screening (Visit 1) or upon repeat prior to randomization (sub-set of subjects) ● Historical or current evidence of clinically significant (in opinion of the Investigator) and unstable disease such as cardiovascular (e.g., patients requiring ICD, pacemaker requiring a ventricular pace rate set at >60 bpm,

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	uncontrolled hypertension, New York Heart Association Class IV (New York Heart Association,1994), known left ventricular ejection fraction <30%), neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), peptic ulcer disease, or haematological abnormalities ● Carcinoma not in complete remission for at least 5 years ● History of allergy or hypersensitivity to any of the study medications (e.g., anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid) or components of the inhalation powder (e.g., lactose, magnesium stearate) or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the study physician contraindicates study participation or use of an inhaled anticholinergic. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded ● Known/suspected history of alcohol or drug abuse in the last 2 years ● Women who are pregnant or lactating or plan to become pregnant ● Subjects medically unable to withhold albuterol /salbutamol for 4 hours prior to spirometry testing at each study visit ● Use of certain medications such as bronchodilators and corticosteroids for the protocol-specific times prior to Visit 1 (the Investigator will discuss the specific medications) ● Long Term Oxygen Therapy (LTOT) or nocturnal oxygen therapy >12 hours a day ● Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening or during the study ● Failure to demonstrate adequate compliance defined as completion of the Diary Card (completed all diary entries on at least 4 of the last 7 consecutive days), the ability to withhold COPD medications and to keep clinic visit appointments ● Non-compliance or inability to comply with study procedures or scheduled visits ● History of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study ● Affiliation with investigator site ● Women who are pregnant or lactating or are planning on becoming pregnant during the study
Interventions	**Inhaler Device:** fluticasone furoate/vilanterol 100/25mcg inhalation powder tiotropium bromide 18mcg inhalation powder **Allowed Co-Medications:** rescue medication (albuterol) and mucolytics at a constant dosage.
Outcomes	Primary Outcome Measures: Change From Baseline Trough in 24-hour Weighted Mean FEV1 on Treatment Day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01627327, HZC115805

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central randomization schedule was generated using a validated computerized system (RandAll; GSK) and communicated with a validated computerized voice response system, the Registration and Medication Ordering System (RAMOS; GSK)
Allocation concealment (selection bias)	Low risk	A central randomization schedule was generated using a validated computerized system (RandAll; GSK) and communicated with a validated computerized voice response system, the Registration and Medication Ordering System (RAMOS; GSK),
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arouse.
Incomplete outcome data (attrition bias)	High risk	Dropout was uneven between two groups. (FF/VI 6.1% and Tio 12.4%).
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported.

D'Urzo 2014

Methods	**Design:** A Phase III, Randomized, Double-blind, Placebo-Controlled Study **Duration:** 24 weeks **Location:** Australia, Canada, New Zealand, United States
Participants	**Population:** ACL/FM (400/12) 325, ACL (400) 337, FM (12) 332 **Baseline Characteristics:** age 63.9 (SD 8.9) F:M 782:887 **Inclusion Criteria:** ● Male or female patients at least 40 years of age ● Current or former cigarette smoker 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 and stable airway obstruction. Patients had to have a postbronchodilator FEV1/FVC ratio < 70% at Visit 1 (GOLD, 2010) ● Post-albuterol/salbutamol FEV1 values ≥ 30% and < 80% of predicted value. FEV1 was measured at the Screening Visit (Visit 1) 10 to 15 minutes after inhalation of albuterol/salbutamol. Predicted normal used for calculation purposes were based on National Health and Nutrition Examination Survey III predicted values (Hankinson et al, 1999) ● Able to perform acceptable and repeatable pulmonary function testing for FEV1 according to ATS/ERS criteria (Miller et al, 2005) at Screening Visit (Visit 1) and throughout their participation in the trial ● Negative serum β-human chorionic gonadotropin pregnancy test at Visit 1

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	and must have been using hormonal contraceptives or a barrier method plus a spermicidal agent; otherwise at least 1-year postmenopausal or surgically sterile, defined as having a hysterectomy or tubal ligation (applied to female patients only) ● Judged by the Principal Investigator to be in otherwise good stable health based on medical history, physical examination, ECGs, and routine laboratory data evaluations ● Patients previously randomized in an aclidinium monotherapy trial were permitted as long as it had been at least 6 months since the completion of their previous trial participation ● Able to understand the study procedures and be willing to participate in the study as indicated by signing the informed consent **Exclusion Criteria:** ● Hospitalization for an acute COPD exacerbation within 3 months before Visit 1 ● Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before Visit 1. Patients who developed a respiratory tract infection or COPD exacerbation during the washout or run-in period were discontinued from the study before randomization ● Any clinically significant respiratory conditions other than COPD, including active tuberculosis, history of interstitial lung disease, pulmonary thromboembolic disease, history of α1-antitrypsin deficiency, pulmonary resection, lung volume surgery, or any other thoracic surgery during the past 12 months, history of bronchiectasis secondary to respiratory diseases other than COPD (eg, cystic fibrosis, Kartagener syndrome), post organ transplantation, or expected to require thoracotomy or other lung surgery during the study ● Clinical history suggesting that the patient had asthma as opposed to COPD (Study Physician was to be contacted to discuss eligibility, if necessary) ● Chronic use of oxygen therapy ≥ 15 hours/day ● Body mass index(BMI) ≥ 40 kg/m2 ● Patients who intended to start a pulmonary rehabilitation program during the trial were excluded, as well as those who finished or started it within 3 months prior to Screening Visit ● Clinically significant cardiovascular conditions including: myocardial infarction within the previous 6 months; newly diagnosed arrhythmia within the previous 3 months; unstable angina; unstable arrhythmia that had required changes in pharmacological therapy or other intervention within the previous 6 months; the presence of an automated implantable cardioverter-defibrillator; history of thoracic surgery within the past year before screening; hospitalization within the previous 12 months for heart failure of New York Heart Association functional class III (marked limitation of physical activity and only comfortable at rest, less than ordinary activity causes fatigue, palpitation or dyspnea), or class IV (unable to carry out any physical activity without discomfort) (Criteria Committee of the New York Heart Association criteria, 1994) ● Any uncontrolled infection that may have placed the patient at risk resulting from human immunodeficiency virus, active hepatitis and/or patients with diagnosed active tuberculosis

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	● QTcB > 470 msec in the resting ECGs performed at Screening (Visit 1), as indicated in the centralized ECG vendor generated report. Patients who were on a stable dose of medication that may prolong the QTc, but had a documented, stable, and normal QTc, could have been considered ● QTcB > 470 msec in the resting ECGs performed before randomization at Visit 2, as indicated in the paper tracing generated by the Sponsor-provided ECG equipment ● Clinically relevant abnormalities in the results of the clinical laboratory tests, in ECG parameters other than QTc, or in the physical examination or vital signs at Visit 1 except for those related to COPD ● History of drug or alcohol abuse within the previous 5 years ● Any other serious or uncontrolled physical or mental condition/disease that, as judged by the Investigator, could have placed the patient at higher risk derived from his/her participation in the study, could have confounded the results of the study, or would be likely to have prevented the patient from complying with the requirements of the study or completing the study. If there was a history of such disease, but the condition had been stable for more than 1 year and was judged by the Investigator not to interfere with the patient's participation in the study, the patient may have been included, with the documented approval of the Study Physician ● History of hypersensitivity reaction to inhaled anticholinergics, beta-2 agonists, sympathomimetic amines, or inhaled medication or any component thereof (including report of paradoxical bronchospasm) or a history of acute urinary retention, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or narrow-angle glaucoma. (Note: Patients who had well controlled, stable, asymptomatic benign prostatic hyperplasia were not to be excluded) ● Sitting, resting systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 100 mm Hg at Visit 1 and Visit 2 ● Unable to use a multidose dry-powder inhaler or a pressurized metered-dose inhaler ● Treatment with any other investigational product within 30 days (or 6 half-lives, whichever was longer) before Visit 1 ● Previous participation in a clinical trial with aclidinium bromide in an FDC therapy ● Pregnant or breastfeeding ● Current diagnosis of cancer (present in the patient) other than basal or squamous cell skin cancer. Patients who had a history of cancer must have been cleared before Visit 1 (Screening) on a case-by-case basis ● Patients who did not maintain regular day/night, waking/sleeping cycles (eg, night shift workers) ● Patients who intended to use any concomitant medication not permitted by this protocol or who had not undergone the required washout period for a particular prohibited medication (Appendix III of the protocol, which can be found in Appendix 16.1.1 of this report) ● Patients who were unlikely to be compliant with study requirements (eg, take their medication, complete their electronic diaries, attend clinic at the required times) ● Patients who were employees or relatives of employees of the investigative study center, FRI, Almirall, SA, or Pharmaceutical Product Development (PPD, Inc.)

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	● Patients who had any other conditions that, in the Investigator's opinion, might have indicated the patient to be unsuitable for the study or supported excluding the patient from the study
Interventions	Inhaled Aclidinium/formoterol FDC 400/12μg, twice per day nhaled Aclidinium 400 μg, twice per day Inhaled Formoterol 12 μg, twice per day Inhaled dose-matched placebo, twice per day **Inhaler Device:** multidose dry powder inhaler **Allowed Co-Medications:** albuterol/salbutamol as rescue, theophylline, inhaled corticosteroids (ICS), oral or parenteral corticosteroids (≤ 10 mg/day or 20 mg every other day of prednisone) were allowed if treatment was stable ≥ 4 weeks prior to screening
Outcomes	Primary Outcome Measures: Change From Baseline in 1-hour Morning Post-dose Forced Expiratory Volume in One Second (FEV1), Change From Baseline in Morning Trough Forced Expiratory Volume in One Second (FEV1)
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01437397, LAC-MD-31

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Cardiac adverse events were evaluated by an adjudication committee of independent cardiologists who were not participating in the study and were blinded to treatment.
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even among the arms of interest (19.5% in ACL/FM 400/12, 21.2% in ACL 400 ,and 20.3% in FM 12.)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported.

D'Urzo 2017

Methods	**Design:** A Phase III, Long-term, Randomized, Double-blind, Extension Study **Duration:** 28-52 weeks **Location:** Australia, Canada, New Zealand, United States
Participants	**Population:** ACL/FM (400/12) 338, ACL (400) 340, FM (12) 339 **Baseline Characteristics:** age 63.2 (SD 8.8), F:M 435:483 **Inclusion Criteria:** ● Completion of the treatment phase of the lead-in study, LAC-MD-31

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	● Written informed consent obtained from the patient before the initiation of any study specific procedures ● No medical contraindication as judged by the PI ● Compliance with LAC-MD-31 study procedures and IP dosing. **Exclusion Criteria:** ● No specific exclusion criteria
Interventions	**Inhaler Device:** Inhaled Aclidinium/formoterol FDC 400/12μg, twice per day nhaled Aclidinium 400 μg, twice per day Inhaled Formoterol 12 μg, twice per day Inhaled dose-matched placebo, twice per day **Allowed Co-Medications:**theophylline, inhaled corticosteroids (ICS), oral or parenteral corticosteroids (10 mg/day or 20 mg every other day prednisone) were allowed if treatment was stable within 4 weeks of the lead-in trial start. Albuterol (108 mg/puff) or salbutamol (100 mg/puff) were the only rescue medications permitted during the study
Outcomes	Primary Outcome Measures: Percentage of Patients to Experience Any Treatment-emergent Adverse Event
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01572792, LAC-MD-36

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even among the arms of interest (19.5% in ACL/FM 400/12, 21.2% in ACL 400 ,and 20.3% in FM 12)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported.

Dahl 2010

Methods	**Design**: randomised double-blind double-dummy parallel-group study **Duration**: 12 months (+ 2 weeks run-in period) **Location**: Denmark, UK, Germany, Russia, USA (unclear how many centres)

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Participants	**Population:** 1732 participants were randomised to formoterol (435), two doses of indacaterol (437 and 428) and placebo (432) **Baseline characteristics** Mean age (years): form 64, ind300 64, ind600 63, pbo 63 % Male: form 80.2, ind300 80.3, ind600 76.9, pbo 81.5 % FEV1 predicted: form 52.5, ind300 51.5, ind600 50.8, pbo 52.0 Pack-years: form 40, ind300 40, ind600 40, pbo 43 **Inclusion criteria**: males and females aged 40 and older; clinical diagnosis of moderate to severe COPD; history of at least 20 pack-years **Exclusion criteria**: history of asthma; current respiratory tract infection or hospitalization for COPD exacerbation within the previous 6 weeks
Interventions	1. Formoterol 12 bid (LABA) 2. Indacaterol 300 qd (LABA) 3. Indacaterol 600 qd (LABA) 4. Placebo (PBO) **Inhaler device**: dry powder turbuhaler and single dose dry powder inhaler **Allowed co-medications**: Fixed-dose combinations of inhaled corticosteroids (ICS) plus LABA were replaced by monotherapy ICS at an equivalent dose and regimen plus salbutamol as needed. Participants receiving ICS monotherapy continued treatment at a stable dose throughout the study. Oral corticosteroids were not allowed, or a change in ICS was noted during the previous month
Outcomes	St George's Respiratory Questionnaire (SGRQ), COPD exacerbations, trough FEV1 and PEF, dyspnoea (baseline and transition scores), diary card data, 6-minute walk test, ECG, vital signs and haematology
Notes	**Funding**: Novartis **Identifier(s)**: NCT00393458

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised to treatment (1:1:1:1) with stratification for smoking status (current/ ex-smoker) using an automated interactive system
Allocation concealment (selection bias)	Low risk	Using an automated interactive system [concealment assumed by automatisation]
Blinding of participants and personnel (performance bias)	Low risk	Double-blind double-dummy trial
Blinding of outcome assessment (detection bias)	Low risk	Protocol state double blind for subject, caregiver, investigator and outcomes assessor http://www.clinicaltrials.gov/ct2/show/NCT00393458
Incomplete outcome data (attrition bias)	Low risk	Efficacy results are presented for the modified intention-to-treat (ITT) population including all randomised patients who received at least one dose of study drug Withdrawal relatively high (Indacaterol 300 22.7%; formoterol 25.7%) but reasons for dropout were similar across the active comparators.

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Selective reporting (reporting bias)	Low risk	All stated and expected outcomes reported in detail

Decramer 2013

Methods	**Design:** A Phase IIIb Multicenter, 52 Week Treatment, Randomized, Blinded, Double Dummy, Parallel Group Efficacy Study **Duration:** 52 weeks **Location:** Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, India, Israel, Italy, Latvia, Lithuania, Mexico, Netherlands, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, Venezuela
Participants	**Population:** IND (150) 1721, Tio (18) 1718 **Baseline Characteristics:** age 64.0 (range 40-91) F:M 782:2657 **Inclusion Criteria:** ● Male and female adults aged ≥ 40 years, who have signed an Informed Consent form prior to initiation of any study-related procedure ● Patients diagnosed with COPD at age 40 and over and with a current diagnosis of severe COPD and including:Smoking history of at least 10 pack years, both current and ex-smokers are eligibleA documented history of at least 1 moderate or severe exacerbation in the previous 12 months **Exclusion Criteria:** ● Patients who have received systemic corticosteroids and/or antibiotics for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period ● Patients who have had a respiratory tract infection within 6 weeks prior to screening ● Patients with concomitant pulmonary disease ● Patients with a history of asthma ● Patients with diabetes Type I or uncontrolled diabetes Type II ● Any patient with lung cancer or a history of lung cancer ● Patients with a history of certain cardiovascular comorbid condition
Interventions	**Inhaler Device:** Indacaterol 150 µg o.d. delivered via SDDPI Tiotropium 18 µg o.d. delivered via handihaler **Allowed Co-Medications:** as needed albuterol or salbutamol, ICS.
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in 1 Second (FEV1).
Notes	**Funding:** Novartis **Identifiers:** NCT00845728, QAB149B2348

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomisation sequence was computer-generated by an interactive voice response system (IVRS; Oracle America Inc, Redwood City, CA, USA)
Allocation concealment (selection bias)	Low risk	randomisation sequence was computer-generated by an interactive voice response system (IVRS; Oracle America Inc, Redwood City, CA, USA)
Blinding of participants and personnel (performance bias)	Low risk	Double-blind double-dummy trial
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even among the arms of interest (22.4% in IND, 19.9% in Tio)
Selective reporting (reporting bias)	Unclear risk	All stated and expected outcomes reported in detail.

Decramer 2014a

Methods	**Design:** Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study **Duration:** 24 weeks **Location:** France, Germany, Italy, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine, United States
Participants	**Population:** UMEC/VI (62.5/25) 212 Tio (18) 208 **Baseline Characteristics:** age 62.9 (SD 9), F:M 261:582 **Inclusion Criteria:** ● outpatient ● signed and dated written informed consent ● 40 years of age or older ● male and female subjects ● COPD diagnosis ● at least 10 pack-year smoking history ● post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and post-albuterol/salbutamol FEV1 of less than or equal to 70% predicted normal values ● score of greater than or equal to 2 on the Modified Medical Resarch Council Dyspnea Scale (mMRC) **Exclusion Criteria:** ● women who are pregnant or lactating or are planning on becoming pregnant during the study ● current diagnosis of asthma ● other respiratory disorders other than COPD ● other diseases/abnormalities that are uncontrolled including cancer not in remission for at least 5 years ● chest x-ray or CT scan with clinically significant abnormalities not believed to be due to COPD

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	● hypersensitivity to anticholinergics, beta-agonists, lactose/milk protein or magnesium stearate or medical conditions associated with inhaled anticholinergics ● hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1 ● lung volume reduction surgery within 12 months prior to Visit 1 ● abnormal and clinically significant ECG at Visit 1 ● significantly abnormal finding from laboratory tests at Visit 1 ● unable to withhold albuterol/salbutamol at least 4 hours prior to spirometry at each visit ● use of depot corticosteroids within 12 weeks of Visit 1 ● use of oral or parenteral corticosteroids, antibiotics for lower respiratory tract infection, or cytochrome P450 3A4 inhibitors, within 6 weeks of Visit 1 ● use of long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS) product if LABA/ICS therapy is discontinued withing 30 days of Visit 1 ● use of ICS at a dose of >1000mcg/day of fluticasone propionate or equivalent within 30 days of Visit 1 ● initiation or discontinuation of ICS within 30 days of Visit 1 ● use of tiotropium or roflumilast within 14 days of Visit 1 ● use of theophyllines, oral leukotriene inhibitors, long-acting oral beta-agonists, or inhaled long-acting beta-agonists within 48 hours of Visit 1 ● short-acting oral beta-agonists within 12 hours of Visit 1 ● use of LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy within 48 hours of Visit 1 for the LABA component ● use of sodium cromoglycate or nedocromil sodium within 24 hours of Visit 1 ● use of inhaled short-acting beta-agonists, inhaled short-acting anticholinergics, or inhaled short-acting anticholinergic/short-acting beta-agonist combination products within 4 hours of Visit 1 ● use of any other investigational medication within 30 days or 5 drug half-lives (whichever is longer) ● long-term oxygen therapy prescribed for >12 hours per day ● regular use of nebulized short-acting bronchodilators ● participation in acute phase of pulmonary rehabilitation program ● known or suspected history of alcohol or drug abse within 2 years prior to Visit 1 ● anyone affiliated with the investigator site (e.g., investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member) ● previous exposure to GSK573719, GSK573719/GW642444 combination, GW642444 (vilanterol), or fluticasone furoate/GW642444 combination
Interventions	GSK573719/GW642444 (UMEC/VI) 62.5/25 mcg GW642444 (vilanterol trifenatate) 25 mcg tiotropium bromide 18 mcg **Inhaler Device:** ELLIPTA dry powder inhaler and the HandiHaler dry powder inhaler **Allowed Co-Medications**: albuterol as needed, ICS.
Outcomes	Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)

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Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01316900, DB2113360

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Registration and Medication Ordering System (RAMOS), using an. Interactive Voice Response System (IVRS), was used
Allocation concealment (selection bias)	Low risk	Registration and Medication Ordering System (RAMOS), using an. Interactive Voice Response System (IVRS), was used
Blinding of participants and personnel (performance bias)	Low risk	double-blind
Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arouse.
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even among the arms of interest (14.6% in UMEC/VI 62.5/25, 14.9% in Tio group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported.

Decramer 2014b

Methods	**Design:** a Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study **Duration:** 24 weeks **Location:** Argentina, Australia, Canada, Chile, Germany, Korea, Republic of, Mexico, Romania, South Africa, United States
Participants	**Population:** UMEC/VI (62.5/25) 212 Tio (18) 208 **Baseline Characteristics:** age 64.6 (SD 8.44) F:M 280:589 **Inclusion Criteria:** ● outpatient ● signed and dated written informed consent ● 40 years of age or older ● male and female subjects ● COPD diagnosis ● at least 10 pack-year smoking history ● post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and post-albuterol/salbutamol FEV1 of less than or equal to 70% predicted normal values ● score of greater than or equal to 2 on the Modified Medical Resarch Council Dyspnea Scale (mMRC) **Exclusion Criteria:** ● women who are pregnant or lactating or are planning on becoming pregnant during the study

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	● current diagnosis of asthma ● other respiratory disorders other than COPD ● other diseases/abnormalities that are uncontrolled including cancer not in remission for at least 5 years ● chest x-ray or CT scan with clinically significant abnormalities not believed to be due to COPD ● hypersensitivity to anticholinergics, beta-agonists, lactose/milk protein or magnesium stearate or medical conditions associated with inhaled anticholinergics ● hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1 ● lung volume reduction surgery within 12 months prior to Visit 1 ● abnormal and clinically significant ECG at Visit 1 ● significantly abnormal finding from laboratory tests at Visit 1 ● unable to withhold albuterol/salbutamol at least 4 hours prior to spirometry at each visit ● use of depot corticosteroids within 12 weeks of Visit 1 ● use of oral or parenteral corticosteroids, antibiotics for lower respiratory tract infection, or cytochrome P450 3A4 inhibitors, within 6 weeks of Visit 1 ● use of long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS) product if LABA/ICS therapy is discontinued withing 30 days of Visit 1 ● use of ICS at a dose of >1000mcg/day of fluticasone propionate or equivalent within 30 days of Visit 1 ● initiation or discontinuation of ICS within 30 days of Visit 1 ● use of tiotropium or roflumilast within 14 days of Visit 1 ● use of theophyllines, oral leukotriene inhibitors, long-acting oral beta-agonists, or inhaled long-acting beta-agonists within 48 hours of Visit 1 ● short-acting oral beta-agonists within 12 hours of Visit 1 ● use of LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy within 48 hours of Visit 1 for the LABA component ● use of sodium cromoglycate or nedocromil sodium within 24 hours of Visit 1 ● use of inhaled short-acting beta-agonists, inhaled short-acting anticholinergics, or inhaled short-acting anticholinergic/short-acting beta-agonist combination products within 4 hours of Visit 1 ● use of any other investigational medication within 30 days or 5 drug half-lives (whichever is longer) ● long-term oxygen therapy prescribed for >12 hours per day ● regular use of nebulized short-acting bronchodilators ● participation in acute phase of pulmonary rehabilitation program ● known or suspected history of alcohol or drug abse within 2 years prior to Visit 1 ● anyone affiliated with the investigator site (e.g., investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member) ● previous exposure to GSK573719, GSK573719/GW642444 combination, GW642444 (vilanterol), or fluticasone furoate/GW642444 combination
Interventions	GSK573719/GW642444 62.5/25 mcg GW642444 (vilanterol trifenatate) 25 mcg tiotropium bromide 18 mcg **Inhaler Device:** ELLIPTA dry powder inhaler and the HandiHaler dry powder

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	inhaler **Allowed Co-Medications:** albuterol as needed, ICS.
Outcomes	Primary Outcome Measures: Change From Baseline in Clinic Visit Trough Forced Expiratory Volume in One Second (FEV1) at Day 169
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01316913, DB2113374

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Registration and Medication Ordering System (RAMOS), using an. Interactive Voice Response System (IVRS), was used
Allocation concealment (selection bias)	Low risk	Registration and Medication Ordering System (RAMOS), using an. Interactive Voice Response System (IVRS), was used
Blinding of participants and personnel (performance bias)	Low risk	double-blind
Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arouse.
Incomplete outcome data (attrition bias)	High risk	Dropout was relatively high and uneven among the arms of interest (24.9% in UMEC/VI 62.5/25, 18.1% in Tio group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported.

Donohue 2010

Methods	**Design**: This study was performed in two stages in an adaptive seamless design. In stage 1, patients were randomized to receive indacaterol 75, 150, 300, or 600 mg once daily,formoterol 12 mg twice daily, or placebo, all double-blind, or open-label tiotropium 18mg once daily. An independent committee used predefined efficacy criteria to select two indacateroldoses based on 2-week efficacy and safety data. As reported elsewhere, the two indacaterol doses selected were 150 and 300 mg (18). In stage 2, the four treatment groups were the two selected doses of indacaterol, tiotropium, and placebo. Treatment continued to 26 weeks, with additional patients recruited and randomized **Duration**: 26 weeks (+ 2 week run-in) **Location**: 345 centres in 12 countries
Participants	**Population**: 1683 participants were randomised to indacaterol at two doses (416 and 416), open-label tiotropium (415), and placebo (418) **Baseline characteristics** Age (mean years): ind150 63.4, ind300 63.3, tio 64.0, pbo 63.6 % Male: ind150 62.3, ind300 63.2, tio 64.8, pbo 61.0 % FEV1 predicted: ind150 56.1, ind300 56.3, tio 53.9, pbo 56.1 Pack-years (mean): ind150 48.3, ind300 50.8, tio 50.0, pbo 49.7

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	Inclusion criteria: Male and female adults aged _ 40 years, who have signed an Informed Consent Form prior to initiation of any study-related procedure. Co-operative outpatients with a diagnosis of COPD (moderate to severe as classified by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Guidelines, 2005) and smoking history of at least 20 pack yearsPost-bronchodilator FEV1 < 80% and _ 30% of the predicted normal value. Post-bronchodilator FEV1/FVC < 70% (Post refers to within 30 min of inhalation of 400 μg of salbutamol) **Exclusion criteria**: lactating females; hospitalised for a COPD exacerbation in the 6 weeks prior to Visit 1 or during the run-in period; requiring long termoxygen therapy (> 15 h a day); respiratory tract infection 6 weeks prior to V1; concomitant pulmonary disease, pulmonary tuberculosis, or clinically significant bronchiectasis; history of asthma; Type I or uncontrolled Type II diabetes; contraindications for tiotropium; clinically relevant laboratory abnormalities or a clinically significant abnormality; active cancer or a history of cancer with less than 5 years disease free survival time; history of long QT syndrome or whose QTc interval is prolonged; hypersensitivity to any of the study drugs or drugs with similar chemical structures; treatment with the investigational drug (with further criteria); live attenuated vaccinations within 30 days prior to visit 1, or during run-in period; known history of non compliance to medication; unable to satisfactorily use a dry powder inhaler device or perform spirometry measurements
Interventions	1. Indacaterol 150 qd (LABA) 2. Indacaterol 300 qd (LABA) 3. Tiotropium 18 qd (LAMA) - open-label 4. Placebo (PBO) **Inhaler device**: 1, 2, and 4 via single-dose dry powder inhaler, open-label tiotropium via HandiHaler **Allowed co-medications**: Patients could continue inhaled corticosteroid (ICS) monotherapy if stable for 1 month before screening; dose and regimen were to remain stable throughout the study. Before the start of the run-in period, treatment with anticholinergic bronchodilators or with 2-agonists was discontinued with appropriate washout, and patients receiving fixed-combination 2-agonist/ICS were switched to ICS monotherapy at an equivalent dose. All patients were supplied with albuterol for use as needed
Outcomes	The primary efficacy outcome was trough FEV1 at 12 weeks. Additional analyses (not adjusted for multiplicity) included transition dyspnoea index (TDI), health status (St George's Respiratory Questionnaire [SGRQ]), and exacerbations. Serum potassium, blood glucose, and QTc interval were measured
Notes	**Funding**: Novartis **Identifier(s)**: NCT00463567 and CQAB149B2335S

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using an automated interactive voice response system, and was stratified by smoking status (current or ex-smoker)

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Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias)	High risk	Blinding procedures were sound, but tiotropium was delivered open label which introduced bias for these comparisons. On completion of stage 1, the independent dose selection committee had access to unblinded data. The only information communicated with the sponsor and investigators was the two selected indacaterol doses, and personnel involved in the continuing clinical study remained blinded for the remainder of the study. The blinding of indacaterol and placebo continued until the study database was locked at the end of stage 2
Blinding of outcome assessment (detection bias)	High risk	Blinding procedures were sound, but tiotropium was delivered open label which introduced bias for these comparisons. Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) [clinicaltrials.gov]
Incomplete outcome data (attrition bias)	Low risk	Efficacy was evaluated for the intention-totreat population, comprising all randomized patients who received at least one dose of study drug. Dropout was variable and generally high across groups (ranging from 18 to 31%). 98.9% were included in the analysis.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Donohue 2013

Methods	**Design:** a phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study **Duration:** 24 weeks **Location:** Bulgaria, Canada, Chile, Czechia, Greece, Japan, Mexico, Poland, Russian Federation, South Africa, Spain, Thailand, United States
Participants	**Population:** UMEC/VI (62.5/25) 413, UMEC (62.5) 418 **Baseline Characteristics:** age 63.1 (SD 8.86) F:M 449: 1083 **Inclusion Criteria:** ● Diagnosis of COPD ● 10 pack-year or greater history of cigarette smoking ● Post-bronchodilator FEV1/FVC of <0.7 ● Predicted FEV1 of 70% of normal or less ● Modified Medical Research Council (mMRC) dyspnea score of 2 or greater **Exclusion Criteria:** ● Women who are pregnant, lactating, or planning to become pregnant ● Respiratory disorders other than COPD, including a current diagnosis of asthma ● Clinically significant non-respiratory diseases or abnormalities that are not adequate controlled ● Significant allergy or hypersensitivity to anticholinergics, beta-agonist, or the excipients of magnesium stereate or lactose used in the inhaler delivery device

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	● Hospitalization for COPD or pneumonia within 12 weeks prior to screening ● Lung volume reduction surgery within 12 weeks prior to screening ● Abnormal and clinically significant ECG findings at screening ● Clinically significant laboratory findings at screening ● Use of systemic corticosteroids, antibiotics for respiratory tract infections, strong cytochrome P450 3A4 inhibitors, high dose inhaled steroids (>1000mcg fluticasone propionate or equivalent), PDE4 inhibitors, tiotropium, oral beta2-agoinists, short- and long-acting inhaled beta2-agonists, ipratropium, inhaled sodium cromoglycate or nedocromil sodium, or investigational medicines for defined time periods prior to the screening visit ● Use of long-term oxygen therapy (12 hours or greater per day) ● Regular use of nebulized treatment with short-acting bronchodilators ● Participation in the acute phase of a pulmonary rehabilitation program ● A know or suspected history of alcohol or drug abuse ● Affiliation with the investigational site ● Previous use of GSK573719 or GW642444 alone or in combination, including the combination of fluticasone furoate and GW64244
Interventions	GSK573719/GW64244 62.5/25mcg (umeclidinium/vilanterol) GSK573719 62.5mcg (umeclidinium) **Inhaler Device:** a dry powder inhaler (DPI) **Allowed Co-Medications:** salbutamol (albuterol) as rescue medication was allowed. Inhaled corticosteroids (ICS) were allowed at a stable dose of 1000 mcg/day of fluticasone propionate or equivalent
Outcomes	Primary Outcome Measures: Change From Baseline (BL) in Trough Forced Expiratory Volume in One Second (FEV1) on Day 169 (Week 24)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01313650, DB2113373

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central randomisation schedule was generated using a validated computerised system (RandAll). Patients were randomised using an automated, interactive telephone based system that registered and randomised medication assignment.
Allocation concealment (selection bias)	Low risk	A central randomisation schedule was generated using a validated computerised system (RandAll). Patients were randomised using an automated, interactive telephone based system that registered and randomised medication assignment.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind

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Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arouse.
Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even between the arms of interest (22.5% in UMEC 62.5 , 19.6 % in UMEC/BI 62.5/25 group)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov.

Donohue 2015a

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 7 countries (US and European countries).63 centres. **Location:** 12 weeks.
Participants	**Population:** UMEC/VI 353, FP/SAL 353 **Baseline Characteristics:** Age: 62.8 (SD 9.0) years. Male/female: 497/209. %pred FEV1: 49.4% (SD 10.9). **Inclusion Criteria:** %pred FEV1 30% to 70%, mMRC ≥ 2, no recent exacerbation **Exclusion Criteria:** Pregnancy/breast feeding, asthma, other respiratory disorders, clinically significant co-morbidities, hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid, history of COPD Exacerbation: A documented history of at least one COPD exacerbation in the 12 months prior to Visit 1, recent lung resection <12 months, long-term oxygen therapy > 12 hours a day, drug or alcohol abuse.
Interventions	umeclidinium/vilanterol (62.5/25 μg) once daily.LAMA/LABA salmeterol/fluticasone (50/250 μg) twice daily. LABA/ICS Placebo **Inhaler Device:** Dry white powder delivered via NDPI (UMEC/VI), Dry white powder delivered via ACCUHALER/DISKUS (FP/SAL) **Allowed Co-Medications:** short-acting inhaled beta-agonists as rescue
Outcomes	Primary endpoint: change from baseline in 24-h weighted-mean serial FEV1 on day 84.
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01817764, DB2114930

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Allocation concealment (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)

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Blinding of participants and personnel (performance bias)	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias)	Low risk	The site personnel involved in making study assessment was aware of a subject's treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rate was low and even between active comparators, 9.6% in umeclidinium/vilanterol arm and 10.8% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Donohue 2015b

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled **Duration:** 12 weeks. **Location:** 7 countries (US and European countries and Russia) and 71 centres.
Participants	**Population:** UMEC/VI 349, FP/SAL 348 **Baseline Characteristics:** Age: 63.6 (SD 8.9) years. Male/female: 528/169. %pred FEV1: 49.5% (SD 10.9). **Inclusion Criteria:** %pred FEV1 30% to 70%, mMRC ≥ 2, no recent exacerbation **Exclusion Criteria:** Pregnancy/breast feeding, asthma, other respiratory disorders, clinically significant co-morbidities, hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid, history of COPD Exacerbation: A documented history of at least one COPD exacerbation in the 12 months prior to Visit 1, recent lung resection <12 months, long-term oxygen therapy > 12 hours a day, drug or alcohol abuse.
Interventions	umeclidinium/vilanterol (62.5/25 μg). LAMA/LABA salmeterol/fluticasone (50/250 μg) twice daily. LABA/ICS **Inhaler Device:** Dry white powder delivered via NDPI (UMEC/VI), Dry white powder delivered via ACCUHALER/DISKUS (FP/SAL) **Allowed Co-Medications:** short-acting inhaled beta-agonists as rescue
Outcomes	Primary endpoint: Change from baseline in 24-h weighted-mean serial FEV1 on treatment day 84.
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01879410, DB2114951

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Allocation concealment (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)

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Blinding of participants and personnel (performance bias)	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias)	Low risk	The site personnel involved in making study assessment was aware of a subject's treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rate was low and relatively even between active comparators, 6.9% in umeclidinium/vilanterol arm and 10.9% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Donohue 2016

Methods	**Design:** Phase III randomized, double-blind, parallel-group, active-control study **Duration:** 52 weeks. **Location:** 127 centers in the US
Participants	**Population:** ACL/FM (400/12) 392, FM (12) 384 **Baseline Characteristics:** age 64.2 (SD 9.4) F:M 265:325 **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 Global Initiative for Chronic Obstructive Lung Disease guidelines and stable airway obstruction. **Exclusion Criteria:** ● Patients who have been hospitalized 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. ● Patients with any clinically significant respiratory conditions other than COPD ● Clinical history that suggests that the patient has asthma as opposed to COPD ● Chronic use of oxygen therapy ≥ 15 hours/day ● Patients with clinically significant cardiovascular conditions ● Patients with uncontrolled infection that may place the patient at risk resulting from human immunodeficiency virus (HIV), active hepatitis and/or patients with diagnosed active tuberculosis ● Patients with a history of hypersensitivity reaction to inhaled anticholinergics, ● Patients with Stage II hypertension, defined as systolic pressure of 160 and above, and/or diastolic pressure of 100 and above ● Current diagnosis of cancer other than basal or squamous cell skin cancer
Interventions	**Inhaler Device:** a multidose dry powder inhaler, Aclidinium Bromide/Formoterol Fumarate Formoterol Fumarate **Allowed Co-Medications:** as needed albuterol, ICS and oral or parenteral corticosteroids at doses 10 mg/day, theophylline and H1-antihistamine were permitted

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Outcomes	Primary Outcome Measures: Percentage of Patients to Experience at Least One Treatment-emergent Adverse Event (TEAE)
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01437540, LAC-MD-32

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was carried out by assigning patient identification numbers via an interactive web response system
Allocation concealment (selection bias)	Low risk	Randomization was carried out by assigning patient identification numbers via an interactive web response system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Major adverse cardiac events (MACE) were evaluated and classified according to the criteria prespecified by three blinded independent expert cardiologists not participating in the study
Incomplete outcome data (attrition bias)	High risk	Dropout was relatively high (32.6%) and breakdown for dropouts was uneven.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports

Dransfield 2014

Methods	**Design:** randomized, multi-center, double-blind, double-dummy, parallel-group, comparative studies **Duration:** 12 weeks **Location:** Study 1: 51 centers in six countries (Czech Republic, Germany, Poland, Romania, Russia, United States). Study 2: 48 centers in five countries (Italy, South Africa, Spain, Ukraine, United States) Study 3: 68 centers in five countries (Germany, Romania, Russia, Ukraine, United States).
Participants	**Population:** FP/SAL (250/50) 927, FF/VI (100/25) 931 **Baseline Characteristics:** age 61 (SD 9), F:M 582:1276 **Inclusion Criteria:** ● Signed and dated written informed consent ● Male or females ≥ 40 years of age ● Established clinical history of COPD by ATS/ERS definition ● Females are eligible to enter and participate if of non-childbearing potential, or if of child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the acceptable contraceptive methods listed in protocol, used consistently and correctly ● Former or current smoker > 10 pack years ● Post-albuterol spirometry criteria: FEV1/FVC ratio ≤ 0.70 and FEV1 ≤ 70% of predicted normal (NHANES III) **Exclusion Criteria:**

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	● Current diagnosis of asthma ● Subjects with other respiratory disorders including active tuberculosis, α1-antitrypsin deficiency, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases ● Lung volume reduction surgery within previous 12 months ● Clinically significant abnormalities not due to COPD by chest x-ray ● Hospitalized for poorly controlled COPD within 12 weeks of Screening ● Poorly controlled COPD 6 weeks prior to Screening, defined as acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician ● Lower respiratory infection requiring antibiotics 6 weeks prior to Screening ● Uncontrolled or clinically significant (in opinion of PI) cardiovascular, hypertension, neurological, psychiatric, renal, hepatic, immunological, endocrine, peptic ulcer disease, or hematological abnormalities ● Carcinoma not in complete remission for at least 5 years ● Subjects with history of hypersensitivity to study medications (e.g., beta-agonists, corticosteroid) or components of inhalation powder (e.g., lactose, magnesium stearate) ● Subjects with history of severe milk protein allergy that, in opinion of study physician, contraindicates subject's participation ● Known/suspected history of alcohol or drug abuse in the last 2 years ● Women who are pregnant or lactating or plan to become pregnant ● Subjects medically unable to withhold albuterol and/or ipratropium 4 hours prior to spirometry testing at each study visit ● Use of certain medications such as bronchodilators and corticosteroids for the protocol-specific times prior to Visit 1 (the Investigator will discuss the specific medications) ● Long Term Oxygen Therapy (LTOT) or nocturnal oxygen therapy >12 hours a day ● Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening or during the study ● Non-compliance or inability to comply with study procedures or scheduled visits
Interventions	**Inhaler Device:** Fluticasone Furoate/Vilanterol (FF/VI) Inhalation Powder 100/25 mcg Fluticasone Propionate/Salmeterol Inhalation Powder 250/50 mcg **Allowed Co-Medications:** as needed albuterol, ipratropium and mucolytics
Outcomes	Primary Outcome Measures: Change From Baseline Trough in 24-Hour Weighted Mean FEV1 on Treatment Day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01323621; NCT01323634;NCT01706328, HZC112352; HZC113109; RLV116974

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system.
Allocation concealment (selection bias)	Low risk	a validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	The investigator and treating physician were blinded till an emergency arouse.
Incomplete outcome data (attrition bias)	Low risk	Dropout low in both included groups (9.3% in FF/VI and 9.1% in FP/SAL group).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Feldman 2016

Methods	**Design:** a multicentre, randomized, blinded, double dummy, parallel group study **Duration:** 12 weeks. **Location:** Argentina, Canada, Chile, Denmark, France, Germany, Italy, Korea, Republic of, Romania, Russian Federation, South Africa, Ukraine, United States.
Participants	**Population:** UMEC(62.5) 509 Tio (18) 508 **Baseline Characteristics:** age 64.2 (SD 8.2), F: M 282:735 **Inclusion Criteria:** ● Type of subject: outpatient. ● Informed Consent: A signed and dated written informed consent prior to study participation. ● Age: Subjects 40 years of age or older at Visit 1. ● Gender: Male and female subjects are eligible to participate in the study. A female is eligible to enter and participate in the study if she is of: **Exclusion Criteria:** ● Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study. ● Asthma: A current diagnosis of asthma. ● Other Respiratory Disorders: Known Alpha-1 antitrypsin deficiency, active lung infections (such as tuberculosis), and lung cancer are absolute exclusionary conditions. A subject who, in the opinion of the investigator, has any other significant respiratory conditions in addition to COPD should be excluded. Examples may include clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease. ● Other Diseases/Abnormalities: Any subject who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any

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	subject who has any condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study. ● Severe Hepatic Impairment: Patients with severe hepatic impairment (Child-Pugh class C) should be excluded unless, in the opinion of the investigator, the benefit is likely to outweigh the risk. ● Moderate to severe Renal Impairment: Patients with moderate to severe renal impairment (e.g., end-stage renal disease requiring dialysis) should be excluded, unless in the opinion of the investigator, the benefit is likely to outweigh the risk. ● Unstable or life threatening cardiac disease: Long-acting muscarinic antagonists (LAMAs) should be used with caution in subjects with severe cardiovascular disease. In the opinion of the investigator, use should only be considered if the benefit is likely to outweigh the risk in conditions such as: Myocardial infarction or unstable angina in the last 6 months; Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months; New York Heart Association Class IV heart failure ● Contraindications: Any history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate. ● Antimuscarinic effects: Subjects with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk. ● Hospitalization: Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1. ● Lung Resection: Lung volume reduction surgery within the 12 months prior to Visit 1. ● 12-Lead electrocardiogram (ECG): Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. Subjects with the following abnormalities are excluded from participation in the study: Atrial fibrillation with rapid ventricular rate >120 beats per minute; Sustained or nonsustained ventricular tachycardia; Second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted) ● Medication Prior to Spirometry: Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit. ● Medications Prior to Screening: Use of the following medications according to the following defined time intervals prior to Visit 1: Depot corticosteroids-12 weeks; Systemic, oral or parenteral corticosteroids- 6 weeks; Antibiotics (for lower respiratory tract infection)- 6 weeks ; long-acting beta2-agonists/inhaled corticosteroids (LABA/ICS) combination products if LABA/ICS therapy is discontinued completely-30 days; LABA/ICS combination products only If discontinuing ICS/LABA therapy and switching to ICS monotherapy- 48 hours for the salmeterol or formoterol component, 14 days for the vilanterol component [The dose of ICS must be a dose of fluticasone propionate (FP) or equivalent but not to exceed 1000 mcg/day] ; Use of ICS at a dose >1000 mcg/day of FP or equivalent- 30 days; Initiation or discontinuation of ICS use-30 days (Use of

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	ICS is permitted provided the dose does not exceed 1000mcg of FP or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1, except for subjects on LABA/ICS therapy who may discontinue the ICS/LABA product as indicated in the table above and switch to ICS monotherapy); Phosphodiesterase 4 (PDE4) Inhibitor (roflumilast)- 14 days; Inhaled long acting beta2 agonists (LABAs): salmeterol, formoterol-48 hours, olodaterol, indacaterol, vilanterol- 14 days; LAMAs: tiotropium, aclidinium, glycopyrronium, umeclidinium- 7 days; LAMA/LABA combination products if LAMA/LABA therapy is discontinued completely- Apply whichever mono component has the longest washout; Theophyllines- 48 hours; Oral beta2-agonists: Long-acting- 48 hours, Short-acting 12 hours; Inhaled short acting beta2-agonists- 4 hours (Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing) ; Inhaled short-acting anticholinergics- 4 hours; Inhaled short-acting anticholinergic/short-acting beta2-agonist combination products- 4 hours; Any other investigational medication - 30 days or within 5 drug half lives (whichever is longer). ● Oxygen: Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e. <=12 hours per day) is not exclusionary. ● Nebulized Therapy: Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g. albuterol/salbutamol) via nebulized therapy. ● Pulmonary Rehabilitation Program: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded. ● Drug or Alcohol Abuse: A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1. ● Affiliation with Investigator Site: Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study. ● Inability to read: In the opinion of the investigator, any subject who is unable to read and/or write would not be able to complete a questionnaire
Interventions	**Inhaler Device:** Umeclidinium nDPI Tiotropium HANDIHALER inhaler **Allowed Co-Medications:** albuterol/salbutamol for use as a rescue medication, inhaled corticosteroids
Outcomes	Primary Outcome Measures: Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) on Day 85
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT02207829, GSK201316

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized using RAMOS interactive voice technology
Allocation concealment (selection bias)	Low risk	Patients were randomized using RAMOS interactive voice technology
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arouse.
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and even between two groups.(8.3% in UMEC 6.7% in Tio group)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports

Ferguson 2008

Methods	**Design**: Randomized, double-blind, parallel-group study **Duration**: 12 months (+ 4 week run-in) **Location**: 94 research sites in the United States and Canada
Participants	**Population:** 782 people were randomised to salmeterol (388) and fluticasone/salmeterol combination (394) **Baseline characteristics** Age (mean years): salm 65.0, flut/salm 64.9 % Male: salm 52, flut/salm 58 % FEV1 predicted: salm 32.8, flut/salm 32.8 Pack-years (mean): salm 54.4, flut/salm 58.5 **Inclusion criteria**: 40 years of age or olderwith a diagnosis of COPDa cigarette smoking history of greater than or equal to 10 pack-years, a pre-albuterol FEV1/FVC of 0.70 or less, a FEV1 of 50% of predicted normal or less and a history of 1 or more exacerbations of COPDin the year prior to the study that required treatment with oral corticosteroids, antibiotics, or hospitalisation. **Exclusion criteria**: diagnosis of asthma, a significant lung disease other than COPD, a clinically significant and uncontrolled medical disorder including but not limited to cardiovascular, endocrine or metabolic, neurological, psychiatric, hepatic, renal, gastric, and neuromuscular diseases, or had a COPD exacerbation that was not resolved at screening
Interventions	1. Salmeterol 50 bid (LABA) 2. Salmeterol/fluticasone 50/250 bid (LABA/ICS) **Inhaler Device:** Diskus dry powder **Allowed Co-Medications:** As-needed albuterol was provided for use throughout the study. The use of concurrent inhaled long-acting bronchodilators (beta2-agonist and anticholinergic), ipratropium/albuterol combination products, oral beta-agonists, inhaled corticosteroids, and theophylline preparations were not allowed during the treatment period.

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	Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations
Outcomes	COPDexacerbations, pre-dose FEV1, diary records of dyspnoea, night-time awakenings due to COPD, and use of supplemental albuterol
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT00144911, GSK SCO40043

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centre based randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind [presumed participants and personnel/investigators]
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	Dropout high and fairly even (30% vs.38%). More patients in salmeterol arm compared with salmeterol/fluticasone group were discontinued from the study due to lack of efficacy and exacerbation.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Ferguson 2016

Methods	**Design:** multicenter, randomized, double-blind, parallel-group study **Duration:** 52 weeks **Location:** 88 centers in 6 countries: Bulgaria (5), Finland (4), Hungary (10), Romania (10), Spain (8), and the United States (51)
Participants	**Population:** 615 patients randomized to indacaterol/gycopyrrolate 27.5/15.6 bid (204), indacaterol/gycopyrrolate 27.5/31.2 bid (204), indacaterol 75 daily (207) groups. **Baseline Characteristics:** Age (mean): IND/GLY27.5/15.6 (64.7), IND/GLY27.5/31.2 (63.9), IND75 (62.8) Male (%): IND/GLY27.5/15.6 (64.2), IND/GLY27.5/31.2 (60.3), IND75 (72) FEV_1 L (pre BD): IND/GLY27.5/15.6 (1.254), IND/GLY27.5/31.2 (1.232), IND75 (1.278) Current Smokers (%):IND/GLY27.5/15.6 (49.5), IND/GLY27.5/31.2 (51.5), IND75 (51.7) **Inclusion Criteria:** Male and female patients aged ≥ 40 years who had stable COPD according to the 2011 Global initiative for chronic Obstructive Lung Disease (GOLD) criteria. Patients were included if they had moderate-to-severe airflow limitation, as indicated by post-bronchodilator forced expiratory volume in 1 second (FEV1)

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	≥ 30% and <80% of the predicted normal and a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio <0.70 at run in. The patients were either current or ex-smokers, with a smoking history of at least 10 pack years, and were symptomatic, as defined by a modified Medical Research Council (mMRC) dyspnea scale, Grade ≥ 2. **Exclusion Criteria:** Patients with any history of asthma or concomitant pulmonary disease or with a significant disease other than COPD that could significantly confound the trial results or preclude trial completion (including cardiovascular [CV], neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities) were excluded. Patients were also excluded if they had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1.
Interventions	1. IND/GLY (27.5/15.6mcg bid); 1 capsule (between 0700-1100) and (between 1900-2300) 2. IND/GLY (27.5/31.2mcg bid); 1 capsule (between 0700-1100) and (between 1900-2300) 3. IND (75mcg daily). **Inhaler Device:** All treatments delivered via Neohaler device. **Allowed Co-Medications:** Each patient was provided with salbutamol/albuterol inhaler, which was permitted for use as rescue medication throughout study. Nebulized salbutamol/albuterol was not permitted. Patients had to use electronic diary to capture use of the rescue inhaler.
Outcomes	Adverse events, bronchodilator effect on mean trough FEV_1 pre-dose 15 minutes and 45 minutes at week 52 and on FEV_1 and FVC at all post-baseline time points, vital signs, electrocardiogram (ECG), laboratory evaluations and time to first moderate or severe exacerbation, COPD symptoms reported and number of puffs/day of rescue medication during 52 week treatment.
Notes	**Funding**: Novartis Pharmaceuticals Corp. **Identifiers**: NCT01682863

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated to treatment group in a 1:1:1 ratio (with stratification for smoking status, ICS use, and severity of airflow limitation) using Interactive Response Technology.
Allocation concealment (selection bias)	Low risk	All eligible patients were randomized via Interactive Response Technology [concealment assumed by automatization].
Blinding of participants and personnel (performance bias)	Low risk	Described as double blind; (Participant, Care Provider, Investigator, Outcomes Assessor)
Blinding of outcome assessment (detection bias)	Low risk	Described as double blind; (Participant, Care Provider, Investigator, Outcomes Assessor)

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Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even in the included arms, 13.2% in IND/GLY group and 11.6% in the IND group. Efficacy was assessed in the Full Analysis set (FAS) which included all randomized patients who received at least one dose of the study drug; patients in the FAS were analyzed according to the treatment to which they were randomized.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the results Summary on clinicaltrials.gov.

Fukuchi 2013

Methods	**Design:** double-blind, parallel-group, active-controlled, phase III study **Duration:** 12 weeks **Location:** 163 centers in nine countries (Japan, Korea, Taiwan, Philippines, Vietnam, India, Russia, Poland and Ukraine).
Participants	**Population:** 1293 randomized to Budesonide/Formoterol (636) and Formoterol only (657) groups. **Baseline Characteristics:** Age (mean): Budesonide/Formoterol (64.5), Formoterol (65.6) Male (%): Budesonide/Formoterol (87.6), Formoterol (90.3) FEV_1 L (post BD): Budesonide/Formoterol (1.14), Formoterol (1.11) Current Smokers (%): Budesonide/Formoterol (33.8), Formoterol (34.8) **Inclusion Criteria:** Male and female patients aged ≥ 40 years with a diagnosis of moderate to severe COPD for at least 2 years (pre-bronchodilator forced expiratory volume in 1s (FEV1) 50% of predicted normal, post-bronchodilator FEV1/forced vital capacity (FVC) < 70%), a current or previous smoking history of 10 pack-years, and having at least one COPD exacerbation in the 12 months prior to study entry were eligible to participate in the study. **Exclusion Criteria:** Patient with a history or current clinical diagnosis of asthma or atopic disease such as allergic rhinitis; significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, uncontrolled hypertension or any other relevant cardiovascular disorder; experiencing a COPD exacerbation during the run-in period or within 4 weeks prior to randomization that required hospitalization and/or a course of oral or parenteral steroids and requiring regular oxygen therapy were excluded from the surgery.
Interventions	1. Budesonide/Formoterol 160/4.5mcg two inhalations twice daily. 2. Formoterol 4.5mcg two inhalations twice daily. **Inhaler Device:** All treatments delivered via Turbuhaler device. **Allowed Co-Medications:** Salbutamol 100 mg/actuation was available as reliever medication through the treatment period. In the case of a COPD exacerbation, patients were permitted any medication considered necessary for the patient's safety and wellbeing at the discretion of the investigator.
Outcomes	Change in pre-dose FEV_1 from baseline to the treatment period, 1 hour post-dose, pre-dose and 1 hour post-dose FVC, COPD symptoms (breathlessness, cough, nighttime awakenings due to symptoms, time to first COPD exacerbation, number of COPD exacerbations (defined as a worsening in

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	symptoms requiring treatment with a course of systemic steroid or hospitalization), health related quality of life (SGRQ; St. George's Respiratory Questionairre) and morning and evening peak expiratory flow.
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01069289

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized 1:1 ratio to either treatment group. [sequence generation not described, but industry funded so presumed electronic]
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	Low risk	Described as double blind (Participant, Care Provider, Investigator, Outcomes Assessor)
Blinding of outcome assessment (detection bias)	Low risk	Described as double blind (Participant, Care Provider, Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and relatively even in the included groups (8.5% in the formoterol group and 6.6% in the Budesonide/Formoterol group). The analysis set for efficacy was based on the Full Analysis Set (FAS). Available data represent patients who had both baseline and on treatment data which is required to be included in the analysis.
Selective reporting (reporting bias)	Low risk	Full results were available from the published report and on clinicaltrials.gov in accordance with the protocol.

GLOW4 2012

Methods	**Design:** a multi-center, randomized, open label, parallel group study **Duration:** 52 weeks **Location:** Japan
Participants	**Population:** Glyco (50) 525, Tio (18) 267 **Baseline Characteristics:** age 68.7 (SD 7.32), F:M 4:159 **Inclusion Criteria:** ● Patients with moderate to severe stable COPD (Stage II or Stage III) according to the Gold Guideline 2008. ● Current or ex-smokers who have a smoking history of at least 10 pack years. ● Patients with a post-bronchodilator FEV1 ≥ 30% and < 80% of the predicted normal, and postbronchodilator FEV1/FVC < 0.7 at Visit 2 (day -7) **Exclusion Criteria:** ● Pregnant women or nursing mothers or women of child-bearing potential not using an acceptable method of contraception ● Patients requiring long term oxygen therapy ● Patients who have had a lower respiratory tract infection within 6 weeks

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	prior to Visit 1 ● Patients with concomitant pulmonary disease ● Patients with a history of asthma ● Any patient with lung cancer or a history of lung cancer ● Patients with a history of certain cardiovascular comorbid conditions ● Patients with a known history and diagnosis of alpha-1 antitrypsin deficiency ● Patients in the active phase of a supervised pulmonary rehabilitation program ● Patients contraindicated for tiotropium or ipratropium treatment or who have shown an untoward reaction to inhaled anticholinergic agents ● Other protocol-defined inclusion/exclusion criteria may apply
Interventions	**Inhaler Device:** NVA237 Breezhaler Powder for inhalation Tiotropium Handihaler **Allowed Co-Medications:** as needed albuterol
Outcomes	Primary Outcome Measures: Number of Participants With Adverse Events, Serious Adverse Events or Death.
Notes	**Funding:** Novartis **Identifiers:** NCT01119937, CNVA237A1302

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low and even in both included groups (tio 17.5%, Glyco 15.4%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Hagedorn 2013

Methods	**Design:** randomized, open-label, parallel-group study **Duration:** 52 weeks **Location:** Germany
Participants	**Population:** FP/SAL (500/50) 108, FP (500)+SAL(50) 105 **Baseline Characteristics:** age 64.9 (SD 8.6) F:M 62:180 **Inclusion Criteria:** ● Subject must have a diagnosis of COPD based on the American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria. ● Male or female subjects, aged >=40 years. Females must be of Non Child

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	Bearing Potential. The definition of Non Child Bearing Potential is as following: Females, regardless of their age, with functioning ovaries and who have a current documented tubal ligation or hysterectomy, or females who are post-menopausal. ● Have diagnosed COPD stage III or IV according to GOLD criteria: a baseline post-bronchodilator Forced Expiratory Volume, measured at 1 second (FEV1) <50% of predicted normal and a baseline post-bronchodilator FEV1/Inspiratory Vital Capacity (IVC) ratio <70%. ● Have experienced at least 2 moderate or severe COPD exacerbations leading to medical consultation (requiring oral corticosteroids or increasing dosage of oral corticosteroids and/or antibiotics or hospitalization) within the 12 months preceding Visit 1. ● Have stable COPD medication within 4 weeks prior to Visit 1 (no new medication added and no dosage changes in medication). ● Current or ex-smokers with a smoking history of at least 10 pack years (number of pack years = [number of cigarettes per day / 20] x number of years smoked, e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years). ● Are currently managed at home (outpatients), are ambulatory and able to travel to the clinic. Subjects can be treated with all relevant COPD medication. This includes vaccines, inhaled short-acting beta-2-agonists as needed, short-acting or long-acting anticholinergics (tiotropium), systemic beta-2-agonists, theophylline, mucolytics, antioxidants, beta-1-agonists (for cardiovascular indication), non-invasive ventilation, long term oxygen therapy and can have Cor Pulmonale. ● A signed and dated written informed consent is obtained prior to participation. ● Able to comply with the requirements of the protocol and be available for study visits over 52 weeks. **Exclusion Criteria:** ● Known other respiratory disorders or signs for other respiratory disorders (e.g. asthma, lung cancer, sarcoidosis, tuberculosis, lung fibrosis, cystic fibrosis, bronchoectasis). ● Known history of significant inflammatory disease, other than COPD (e.g. rheumatoid arthritis and systemic lupus erythematosus). ● Known to be severely alpha-1-antitrypsin deficient (PI SZ or ZZ) ● Having undergone lung surgery (e.g. lung resection including lung volume reduction surgery, lung transplant) or subjects scheduled for surgery. ● Concurrent medication from Visit 1 and for the duration of the study with any of the prohibited medications: monoamine oxidase inhibitors and tricyclic antidepressants, and ritonavir (a highly potent cytochrome P450 3A4 inhibitor). ● Subjects receiving chronic or prophylactic antibiotic therapy. ● Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study or impact on subject safety. ● Have, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse. ● History of depression. ● History or presence of clinically significant drug sensitivity or clinically significant allergic reaction to corticosteroids or salmeterol.

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	● Moderate or severe COPD exacerbation (requiring corticosteroids or increased dosage of corticosteroids and/or antibiotics or hospitalization) within the 4 weeks prior to Visit 1 ● Lower respiratory tract infection within the 4 weeks prior to Visit 1 . ● Pregnant or lactating female and female of childbearing potential. ● Subject is a participating investigator, sub-investigator, study coordinator, or other employee of a participating investigator, or is an immediate family member of the before mentioned. Subject is an employee of GlaxoSmithKline (GSK). ● Subject participated in an investigational drug study within 30 days prior to Visit 1
Interventions	**Inhaler Device:** Salmeterol / Fluticasone (50/500 µg) BID fixed combination Salmeterol / Fluticasone (50/500 µg) BID separate Inhalers comparator **Allowed Co-Medications:**
Outcomes	Primary Outcome Measures: Mean Number of Exacerbations Per Year: Negative Binomial Model [Time Frame: Baseline through Week 52], Mean Number of Exacerbations Per Year: Poisson Model [Time Frame: Baseline through Week 52]
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT00527826, SCO107227

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Open-label
Blinding of outcome assessment (detection bias)	High risk	Open-label
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively high but even in both included groups (SAL/FP fixed 19.4% and 24.5% in SAL/FP free combo)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Hanania 2003

Methods	**Design**: double-blind, placebo-controlled, parallel-group, multicenter trial **Duration:** 24 weeks **Location:** 76 investigative sites in the United States.

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Participants	**Population:** 723 patients were randomized to following groups; FP (250 µg FLOVENT DISKUS) (n=183), SM (50 µg SEREVENT DISKUS) (n=177); FP plus SM in combination (FSC) (ADVAIR DISKUS) (n=178) and Placebo group (n=185) **Baseline Characteristics:** Age (mean): Placebo (65), SM (64), FP (63), FSC (63) Male (%): Placebo (68), SM (58), FP (66), FSC (61) FEV_1 L: Placebo (1.289), SM (1.245), FP (1.313), FSC (1.252) Current Smokers (%): Placebo (47), SM (51), FP (48), FSC (43) **Inclusion Criteria:** Patients were ≥ 40 years of age, were current or former smokers with a ≥ 20 pack-year history, and had received a diagnosis of COPD, as defined by the American Thoracic Society. Baseline FEV1/FVC ratio of ≤ 70% and a baseline FEV1 of <65% of predicted normal, but >0.70 L (or if ≤ 0.70 L, then >40% of predicted normal). Patients were required to have symptoms of chronic bronchitis and moderate dyspnea. **Exclusion Criteria:** Patients with current diagnosis of asthma; use of oral corticosteroids within the past 6 weeks; abnormal clinically significant ECG; long-term oxygen therapy; moderate or severe exacerbation during the run-in period; and any significant medical disorder that would place the patient at risk, interfere with evaluations, or influence study participation.
Interventions	**Inhaler Device:** 250 µg FLOVENT DISKUS; GlaxoSmithKline, Inc) 50 µg SEREVENT DISKUS; GlaxoSmithKline, Inc 250 µg /50 µg ADVAIR DISKUS; GlaxoSmithKline, Inc) Placebo Diskus (GlaxoSmithKline, Inc; Research Triangle Park, NC) **Allowed Co-Medications:** (VENTOLIN Inhalation Aerosol or VENTOLIN Nebules; GlaxoSmithKline, Inc)
Outcomes	Two different FEV1 time points were measured to determine treatment efficacy: predose FEV1; and 2-h postdose FEV1. Decreases in airway obstruction due to reduced inflammation (ie, the contribution of FP in the combination) were assessed by comparing changes in predose FEV1 between FSC and SM. Bronchodilation (ie, the contribution of SM) was assessed by comparing the changes in the 2-h postdose FEV1 between FSC and FP. Other efficacy parameters included morning peak expiratory flow (PEF), dyspnea (assessed by the transition dyspnea index [TDI]41), supplemental albuterol use, health status (as assessed by the chronic respiratory disease questionnaire [CRDQ]42) symptoms of chronic bronchitis (assessed by the chronic bronchitis symptom questionnaire[CBSQ]43,44), and exacerbations (defined by treatment, with moderate exacerbations requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations requiring hospitalization).
Notes	**Funding:** GlaxoSmithKline, Inc, **Identifiers:** SFCA3007

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was stratified by reversibility(defined as a 12% and 200 mL increase in FEV1 from baseline following the administration of 400 g albuterol) and investigative site [sequence generation not described but study was industry sponsored]
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	Low risk	Described as double blind [presumed subject and investigator]
Blinding of outcome assessment (detection bias)	Low risk	Described as double blind [presumed subject and investigator] Reported outcomes not subject to detection bias [exacerbations, all-cause mortality, adverse events and withdrawal]
Incomplete outcome data (attrition bias)	Low risk	A total of 218 patients (placebo group, 32%; SM group, 32%; FP group, 27%; and FSC group, 30%) were discontinued from the study. The breakdown of discontinuation were similar between FSC and SM groups (GSK Clinical Study Report). In order to account for patient withdrawals, endpoint was used as the primary time point and was defined as the last on-treatment post baseline assessment excluding any data from the discontinuation visit.
Selective reporting (reporting bias)	Low risk	All expected and stated outcomes were meticulously reported on the manufacturer's website as Clinical Study Report. [https://www.gsk-clinicalstudyregister.com/files2/sfca3007-clinical-study-report-redact-v02.pdf]

Hoshino 2013

Methods	**Design:** A randomized, open-label, 4-way study. **Duration:** 16 weeks **Location:** Shizuoka Japan
Participants	**Population:** FP/SAL(250/50) 16, Tio (18) 15, SAL (50) 14 **Baseline Characteristics:** age 71.2 F:M 8/52 **Inclusion Criteria:** The subjects were patients >40 years of age with a diagnosis of COPD, a cigarette smoking history >10 pack-years, a postbronchodilator FEV 1 <70% of the predicted value and ratio of FEV 1 to forced vital capacity (FVC) <0.70. **Exclusion Criteria**:a current diagnosis of asthma, a clinically significant medical disorder (other than COPD), supplemental use of oxygen for exertion or current use of some respiratory medications (including ICS, LABAs, Tio, theophylline or systemic corticosteroids).

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Interventions	**Inhaler Device:** FP/SAL 250/50 mcg bid Tio 18 mcg qd Handihaler SAL 50 mcg bid **Allowed Co-Medications**: Salbutamol was permitted when necessary to relieve symptoms. Inhaled corticosteroids, theophylline and systemic corticosteroids were not allowed.
Outcomes	Airway dimensions, as assessed by CT scans, the mean change in pulmonary function and St. George's Respiratory Questionnaire at 16 weeks.
Notes	**Funding:** Not described. **Identifiers:** None provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Only airway dimensions were assessed in a blinded fashion.
Incomplete outcome data (attrition bias)	Low risk	68 patients were randomized and 60 of them completed the study (12% dropout rate).
Selective reporting (reporting bias)	Unclear risk	We could not locate a prospectively registered protocol to check all outcomes were reported

Hoshino 2014

Methods	**Design:** randomized, open-label, three-way clinical trial **Duration:** 16 weeks **Location:** Shizuoka Japan
Participants	**Population:** 54 patients were randomized to receive tiotropium 18µg once daily (n=16), indacaterol 150 µg once daily (n=20) or tiotropium plus indacaterol once daily (n=18) **Baseline Characteristics:** Age (mean): Tiotropium (73), Indacaterol (69), Tiotropium plus Indacaterol (71) Male (%): Tiotropium (100), Indacaterol (90), Tiotropium plus Indacaterol (88) FEV_1 L: Tiotropium (1.48), Indacaterol (1.63), Tiotropium plus Indacaterol (1.46) Smoking Hx (Pack yrs): Tiotropium (63.4), Indacaterol (62.8), Tiotropium plus Indacaterol (57.8) **Inclusion Criteria:** The subjects were all ex-smoker patients >40 years of age with a diagnosis of COPD, a cigarette smoking history of >10 pack-years, a post-bronchodilator forced expiratory volume in 1 second (FEV1) <70% of the predicted value, and

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	an FEV1/FVC (ratio of FEV1 to forced vital capacity (FVC)) <0.70. **Exclusion Criteria:** Patients with a current diagnosis of asthma, supplemental use of oxygen for exertion or current use of some respiratory medications.
Interventions	1. Tiotropium 18µg once daily 2. Indacaterol 150 µg once daily 3. Tiotropium plus Indacaterol once daily **Inhaler Device:** Tiotropium Handihaler (Boehringer Ingelheim Pharma, Ingelheim, Germany) Indacaterol Breezhaler (Novartis, London, UK) **Allowed Co-Medications:** Concurrent use of salbutamol was permitted when necessary to relieve symptoms
Outcomes	The primary objective was to evaluate the superiority of tiotropium plus indacaterol treatment over tiotropium alone or indacaterol alone in its effect on airway dimensions. The important secondary objectives were the mean change in FEV1 and QoL from baseline to week 16. Pulmonary function, CT and assessment of quality of life (QoL)
Notes	**Funding:** Unknown **Identifiers:** UMIN000006724

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not decribed
Allocation concealment (selection bias)	Unclear risk	Not decribed
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Only CT interpretation was blinded.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rate was relatively low and even. 62 patients were randomized and 54 of them completed the study (13% dropout rate).
Selective reporting (reporting bias)	Low risk	Trial registration was located.

Hoshino 2015

Methods	**Design:** randomized, open-label, parallel-group treatment study **Duration:** 16 weeks **Location:** Shizuoka Japan
Participants	**Population:** 46 patients were randomized to receive tiotropium (18 mg once daily) plus indacaterol (150 mg once daily) (n=24) or Advair® (50/250 mg twice daily) (n=22) **Baseline Characteristics:** Age (mean): Tiotropium plus Indacaterol (72), Advair (69)

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	Male (%): Tiotropium plus Indacaterol (81), Advair (86) FEV1 L: Tiotropium plus Indacaterol (1.38), Advair (1.36) Smoking Hx (Pack yrs): Tiotropium plus Indacaterol (56.2), Advair (60.4) **Inclusion Criteria:** The subjects were all ex-smoker patients >40 years of age with a diagnosis of COPD; a cigarette smoking history >10 pack-years; a post-bronchodilator FEV1 between 30% and 80% of predicted value, and FEV1/FVC (ratio of FEV1 to forced vital capacity <0.70). **Exclusion Criteria:** Patients with a current diagnosis of asthma; clinically significant medical disorder other than COPD; supplemental use of oxygen for exertion; or exacerbation needing treatment with antibiotics, systemic glucocorticosteroids.
Interventions	1. Tiotropium (18 mg once daily) plus Indacaterol (150 mg once daily) 2. Advair® (50/250 mg twice daily) **Inhaler Device:** Tiotropium Handihaler (Boehringer Ingelheim Pharma, Ingelheim, Germany) Indacaterol Breezhaler (Novartis, London, UK) Advair (Glaxo Smith Kline, London, UK). **Allowed Co-Medications:** Rescue inhaler short-acting b2-adrenergic receptor agonist-salbutamol 200 mg by Ventolin (Glaxo Smith Kline, London, UK) was permitted when necessary to relieve symptoms throughout study.
Outcomes	The primary objective was to demonstrate superiority of tiotropium plus indacaterol compared with Advair® for the effect on airway dimensions. The important secondary objectives were also compared the effect of tiotropium plus indacaterol versus Advair® on bronchodilator effect and health status during the treatment period. Pulmonary function, CT and assessment of quality of life.
Notes	**Funding:** Not described. **Identifiers:** None provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Only airway dimensions were assessed in a blinded fashion.
Incomplete outcome data (attrition bias)	Low risk	54 patients were randomized and 46 of them completed the study (15% dropout rate).
Selective reporting (reporting bias)	High risk	We could not locate a prospectively registered protocol to check all outcomes were reported. SGRQ oputcomes not decribed in detail.

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Jones 2011

Methods	**Design:** Pooled data from three RCTs (Donohue 2010, Dahl 2010, and Kornmann 2011) **Duration:** 6 months. **Location:** NCT00393458: Argentina, Chile, Colombia, Czech Republic, Denmark, Ecuador, Egypt, Estonia, France, Germany, Hungary, Israel, Italy, Korea, Republic of, Latvia, Lithuania, Netherlands, Peru, Romania, Russian Federation, Slovakia, Spain, Switzerland, Turkey, United Kingdom NCT00463567: Argentina, Canada, Germany, India, Italy, Korea, Republic of, Puerto Rico, Spain, Sweden, Taiwan, Turkey, United States NCT00624286: Belgium, New Zealand, United States
Participants	**Population:** Tio (18) 345, FM (12) 385, SAL (50) 284, IND (150) 620, IND (300) 671. **Baseline Characteristics:** age 64 (SD 9), M:F 69/31% **Inclusion/exclusion Criteria: See** Donohue 2010, Dahl 2010, and Kornmann 2011
Interventions	Tio 18 qd FM 12 bid SAL 50 bid IND 150 qd IND 300 qd **Inhaler Device:** dry powder turbuhaler and single dose dry powder inhaler (IND) **Allowed Co-Medications:** As needed albuterol, ICS.
Outcomes	SGRQ responder at 6 months
Notes	**Funding:** Novartis **Identifiers:** NCT00393458, NCT00463567, and NCT00624286

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised to treatment (1:1:1:1) with stratification for smoking status (current/ ex-smoker) using an automated interactive system
Allocation concealment (selection bias)	Low risk	Using an automated interactive system [concealment assumed by automatisation]
Blinding of participants and personnel (performance bias)	Low risk	Double-blind double-dummy trial
Blinding of outcome assessment (detection bias)	Low risk	Protocol state double blind for subject, caregiver, investigator and outcomes assessor http://www.clinicaltrials.gov/ct2/show/NCT00393458
Incomplete outcome data (attrition bias)	Low risk	Efficacy results are presented for the modified intention-to-treat (ITT) population including all randomised patients who received at least one dose of study drug Withdrawal relatively high but reasons for dropout were

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		similar across the active comparators.
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes reported in detail

Kalberg 2016

Methods	**Design:** multicenter, randomized, blinded, triple-dummy, parallel-group study **Duration:** 14 weeks **Location:** 86 centers across Argentina, Chile, Estonia, France, Germany, Hungary, Italy, Peru, Poland, Romania, the Russian Federation and Slovakia.
Participants	**Population:** 967 patients were randomized into two treatment groups; Umeclidinium/Vilanterol (n=482) and Tiotropium and Indocaterol (n=479) **Baseline Characteristics:** Age (mean): UMEC/VI (64), TIO+IND (64) Male (%): UMEC/VI (74), TIO+IND (71) FEV1 L (pre BD): UMEC/VI (1.369), TIO+IND (1.357) Current Smokers (%): UMEC/VI (41), TIO+IND (46) **Inclusion Criteria:** Patient were ≥ 40 years of age; had an established clinical history of COPD, were current or former cigarette smokers with a history of smoking of ≥ 10 pack-years; had pre- and post-bronchodilator forced expiratory volume in 1 s (FEV1) values of ≤ 70 % predicted; had pre- and postbronchodilator FEV1/FVC ratios of <0.70; had a score of ≥ 2 on the modified Medical Research Council Dyspnea Scale; and had a corrected QT (QTc) interval (corrected for the heart rate, according to Fridericia's formula) of <450 or <480 ms for patients with bundle branch block. **Exclusion Criteria:** Patients were excluded from the study if they were of childbearing potential (unless they were practicing acceptable birth control methods); had a current diagnosis of asthma; had alpha-1 antitrypsin deficiency, an active lung infection (such as tuberculosis), lung cancer, or another clinically significant disease/abnormality; abnormal ekg; had a history of allergy or hypersensitivity to specific medications, had been hospitalized for COPD or pneumonia within 12 weeks prior to visit 1; had undergone lung volume reduction surgery within 12 months prior to visit 1; were receiving long-term oxygen therapy; or were enrolled actively in pulmonary rehab.
Interventions	1. Umeclidinium/Vilanterol 62.5/25 mcg once daily + Placebo (HandiHaler) + Placebo (Breezehaler) 2. Tiotropioum 18 mcg once daily via a HandiHaler +Indocaterol 150 mcg once daily via a Breezhaler + Placebo (ELLIPTA inhaler) **Inhaler Device:** ELLIPTA®, the HandiHaler®, and theBreezhaler®. **Allowed Co-Medications:** All patients had albuterol provided for as-needed use.
Outcomes	The primary objective of the study was to determine whether the efficacy of UMEC/VI was non-inferior to that of TIO+ IND as assessed by the trough FEV1. The secondary endpoint of the study was the weighted mean (WM) FEV1 over 0–6 h postdose at day 84, calculated from the predose FEV1 values (obtained 30 and 5 min before dosing) and the postdose FEV1 measurements at 1, 3, and 6 h.

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Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT02257385; GSK116961.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized in accordance with a centralized randomization schedule, using a randomization code generated by a validated computerized system (RandAll Version NG, GSK). Patients were randomized using an interactive voice recognition system.
Allocation concealment (selection bias)	Low risk	Computer generated randomization
Blinding of participants and personnel (performance bias)	Unclear risk	All patients and investigators were blinded to the assigned treatment during the study. However, exact physical placebo matches for the TIO and INDcapsules and for the IND blister packs were not available, although they were closely matched in color.
Blinding of outcome assessment (detection bias)	Low risk	Safeguards were in place to prevent the unblinding of study personnel, and study blinding coordinators independent of other clinical trial procedures were involved in the preparation and administration of treatment to patients.
Incomplete outcome data (attrition bias)	Low risk	In total, 917 patients (95 %) completed the study. The most common reason for study withdrawal was AEs, which accounted for a similar proportion of patients withdrawing from each treatment group.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Kardos 2007

Methods	**Design:** Randomized, double-blind, parallel-group study **Duration:** 44 weeks **Location:** 95 respiratory centers in Germany
Participants	**Population:** 998 patients were randomized into two treatment groups; 50mcg/500mcg Salmeterol/Formoterol (SFC) twice daily (507) or 50mcg Salmeterol (SAL) twice daily (487) **Baseline Characteristics:** Age (mean): SFC (63.8), SAL (64) Male (%): SFC (74), SAL (77.6) FEV_1 L (pre BD): SFC (1.13), SAL (1.12) Current Smokers (%): SFC (40.6), SAL (44.4) **Inclusion Criteria:** Outpatients with severe COPD, defined according to GOLD stages III and IV, FEV1/FVC of ≤ 70%, age of ≥ 40 years, smoking history of ≥ 10 pack-years, History ≥ 2 exacerbations in the last year before the study.

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	Exclusion Criteria: COPD exacerbations, hospital admissions, or change in COPD therapy during the 4 wk before Visit 1 or run in period. Asthma, need for long-term oxygen therapy or chronic systemic steroid.
Interventions	**Inhaler Device:** Diskus (GlaxoWellcomeGmbH&Co, BadOldesloe, Germany) **Allowed Co-Medications:** Inhaled salbutamol was used as reliever medication, and regular treatment with short-acting bronchodilators, antioxidants/mucolytics, short-acting oral β2-agonists, and theophylline.
Outcomes	The primary endpoint was the number of moderate and severe exacerbations in each treatment group. Secondary endpoints included time to first exacerbation, prebronchodilator peak flo (PEF), post-bronchodilator FEV1, and disease-specific quality of life as evaluated by the St. George's Respiratory Questionnaire (SGRQ), which investigated three different domains consisting of activity, symptom, and impact scores.
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SCO30006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Consecutive numbers were assigned to patients that determined the blinded treatment based on a centrally generated list with blocks of six. industry funded.
Allocation concealment (selection bias)	Low risk	Consecutive numbers were assigned to patients that determined the blinded treatment based on a centrally generated list with blocks of six.
Blinding of participants and personnel (performance bias)	Low risk	Described as double blind [presumed subject and investigator]
Blinding of outcome assessment (detection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias)	Low risk	In the study population, there were 99 withdrawals (19.5%) in the SFC group and 103 (21.1%) in the SAL group, both mainly due to adverse events that were primarily linked to COPD deterioration.
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol to check outcome reporting

Kerwin 2012

Methods	**Design:** Randomized, Double-blind, Placebo-controlled, With Open-label Tiotropium, Parallel-group Study **Duration:** 52 weeks **Location:** 170 centers in 18 countries: Argentina, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Mexico, Netherlands, New Zealand, Peru, Poland, Russia, United States

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Participants	**Population:** 1,066 patients were randomized to one of three study groups; Glycopyrronium bromide(NVA237) 50 mcg (n=529), Placebo (n=269), Tiotropium 18mcg (n=268) daily **Baseline Characteristics:** Age (mean): NVA237 (63.5±9.1), Placebo (63.6±9.1), Tiotropium (63.9±8.2) Male (%): NVA237 (64.6), Placebo (64.6), Tiotropium (62.9) FEV_1 L (pre BD): NVA237 (1.3±0.5), Placebo (1.4±0.5), Tiotropium (1.3±0.5) Current Smokers (%): NVA237 (45.3), Placebo (46.3), Tiotropium (44.2) **Inclusion Criteria:** ≥ 40 yrs of age, with a smoking history of ≥ 10 pack-yrs, a diagnosis of moderate-to-severe stable COPD, post-bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and postbronchodilator FEV1/forced vital capacity (FVC) <0.70 were enrolled **Exclusion Criteria:** Lower respiratory tract infection in the 6 weeks prior to screening; concomitant pulmonary disease, history of asthma, malignancy of any organ system, long QT syndrome at screening, symptomatic prostatic hyperplasia, bladder-neck obstruction, moderate/severe renal impairment, urinary retention, narrow-angle glaucoma, a known history of α_1-antitrypsin deficiency; participation in the active phase of a supervised pulmonary rehabilitation program; and contraindications for tiotropium or ipratropium or history of adverse reactions to inhaled anticholinergics.
Interventions	**Inhaler Device:** 1. Glycopyrronium bromide(NVA237) via Breezhaler® device 2. Placebo via Breezhaler® device 3. Tiotropium via HandiHaler® device **Allowed Co-Medications:** Inhaled or Intranasal corticosteroids and H1 antagonists were permitted in patients who had been stabilized on a recommended and constant dose prior to study entry. Patients were provided with a salbutamol/albuterol inhaler to be used as rescue medication during the study.
Outcomes	Trough FEV1 in 1 Second at Week 12, dyspnea, quality of life, exacerbations
Notes	**Funding:** Novartis **Identifiers:** NCT00929110

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised 2:1:1 ratio [sequence generation not described, but industry funded so presumed electronic]
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study

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Incomplete outcome data (attrition bias)	Low risk	Dropout was relatively high but even between included groups (22.3% in Glyco and 23.1% in Tio group). Efficacy was assessed in the full analysis set (FAS) which included all randomised patients who received at least one dose of the study drug; patients in the FAS were analysed according to the treatment to which they were randomised.
Selective reporting (reporting bias)	Low risk	Full results in the published report and on clinicaltrials.gov in accordance with the protocol.

Kerwin 2017

Methods	**Design:** Randomized, Double-blind, Placebo-controlled, With Open-label Tiotropium, Parallel-group Study **Duration:** 52 weeks. **Location:** Argentina, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Republic of, Mexico, Netherlands, New Zealand, Peru, Poland, Russian Federation, United States
Participants	**Population:** Glyco (50) 525, Tio (18) 267 **Baseline Characteristics:** age 63.8 (SD 8.87), F:M 380:680 **Inclusion Criteria:** 1. Male or female adults aged ≥ 40 years, who have signed an Informed Consent Form prior to initiation of any study-related procedure. 2. Patients with moderate to severe stable chronic obstructive pulmonary disease (COPD, Stage II or Stage III) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines 2008. 3. Current or ex-smokers who have a smoking history of at least 10 pack years. 4. Patients with a post-bronchodilator forced expiratory volume in 1 second (FEV1) ≥ 30% and < 80% of the predicted normal, and post-bronchodilator FEV1/forced vital capacity (FVC) < 0.7 at Visit 2 (Day -14). 5. Patients, according to daily electronic diary data between Visit 2 (Day -14) and Visit 3 (Day 1), with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3 (Day 1). **Exclusion Criteria:** 1. Pregnant women or nursing mothers (pregnancy confirmed by positive urine pregnancy test). 2. Women of child-bearing potential, unless using an approved method of medical or surgical contraception. 3. Patients requiring long term oxygen therapy (> 15 h a day) on a daily basis for chronic hypoxemia, or who have been hospitalized for an exacerbation of their airways disease in the 6 weeks prior to Visit 1 (Day -21) or between Visit 1 (Day -21) and Visit 3 (Day 1). 4. Patients who have had a respiratory tract infection within 6 weeks prior to Visit 1 (Day -21). 5. Patients who, in the judgment of the investigator or the responsible Novartis personnel, have a clinically relevant laboratory abnormality or a clinically significant condition. 6. Patients with any history of asthma indicated by (but not limited to) a blood eosinophil count > 600/mm^3 (at Visit 1, Day -21) and onset of symptoms

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	prior to age 40 years. 7. Patients with a history of long QT syndrome or whose QTc measured at Visit 1 (Day -21) (Fridericia method) is prolonged (> 450 ms for males or > 470 ms for females.
Interventions	**Inhaler Device:** Glycopyrronium bromide was supplied in powder-filled capsules together with a single-dose dry-powder inhaler (SDDPI) device. Tiotropium was supplied in powder-filled capsules together with the Handihaler **Allowed Co-Medications:** as needed albuterol, inhaled or intranasal corticosteroids and H1 antagonists
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 12
Notes	**Funding:** Novartis **Identifiers:** NCT00929110, CNVA237A2303, GLOW2

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Open-label Tiotropium
Blinding of outcome assessment (detection bias)	High risk	Open-label Tiotropium
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively high but even in both included groups (Tio 23.1%, Glyco 22.3%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Koch 2014

Methods	**Design:** Phase III, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group studies **Duration:** 48 weeks. **Location:** Argentina, Brazil, Canada, Croatia, Czech Republic, Denmark, Finland, Germany, Hong Kong, India, Italy, Korea, Republic of, Malaysia, Norway, Philippines, South Africa, Spain, Sweden, Thailand, Ukraine
Participants	**Population:** Olo (5) 227, FM (12) 227 , Olo(5) 232, FM (12) 233 **Baseline Characteristics:** Study 1222.13 age 63.8 (8.7) F:M 198:706. Study 1222.14 age 64.2 (SD 8.7) F:M 176:758 **Inclusion Criteria:** 1. All patients must have a diagnosis of chronic obstructive pulmonary disease and must meet the following spirometric criteria:post-bronchodilator FEV1<80% of predicted normal (ECSC) and a post-bronchodilator FEV1/FVC <70% at Visit 1

	2. Male or female patients, 40 years of age or older 3. Patients must be current or ex-smokers with a smoking history of more than 10 pack years: **Exclusion Criteria:** 1. Patients with clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis; all patients with an SGOT >x2 ULN, SGPT >x2 ULN, bilirubin >x2 ULN or creatinine >x2 ULN 2. Patients with a history of asthma and/or total blood eosinophil count greater than 600/mm3 3. Patients with thyrotoxicosis, paroxysmal tachycardia (>100 beats per minute) 4. Patients with a history of myocardial infarction within 1 year of screening visit, unstable or life-threatening cardiac arrhythmia, hospitalization for heart failure within the past year, known active tuberculosis, a malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years, life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, significant alcohol or drug abuse 5. Patients who have undergone thoracotomy with pulmonary resection 6. Patients being treated with oral beta-adrenergics or oral corticosteroid medication at unstable doses (i.e., less than six weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day. 7. Patients who regularly use daytime oxygen therapy for more than one hour per day. 8. Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit (Visit 1) or patients who are currently in a pulmonary rehabilitation program 9. Pregnant or nursing women 10. Women of childbearing potential not using two effective methods of birth control (one barrier and one non-barrier).
Interventions	**Inhaler Device:** Olodaterol via Respimat Formoterol Aerolizer inhaler **Allowed Co-Medications:** Albuterol as needed. short-acting muscarinic antagonists, LAMAs, inhaled corticosteroids, and xanthines
Outcomes	FEV1, TDI, SGRQ
Notes	**Funding:** Merck **Identifiers:** NCT00793624, NCT00796653, 1222.13, 1222.14

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details

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Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (olo16%, FM 12%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Kornmann 2011

Methods	**Design:** Randomized, Double-blind, Placebo-controlled, Parallel-group Study **Duration:** 26 weeks **Location:** 142 centers in 15 countries (Canada, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, India, Italy, Peru, Russian Federation, Slovakia, Taiwan)
Participants	**Population:** 998 patients were randomized, into three study arms; 150mg Indacaterol daily (n=330), 50mg Salmeterol twice daily (n=333) or Placebo (n=335) **Baseline Characteristics:** Age (mean): Indacaterol (63±8.7), Salmeterol (63±9.2), Placebo (64±8.6) Male (%): Indacaterol (72), Salmeterol (75), Placebo (77) FEV_1 L (pre BD): Indacaterol (1.5±0.49), Salmeterol (1.5±0.49), Placebo (1.5±0.47) Current Smokers (%): Indacaterol (46), Salmeterol (46), Placebo (45) **Inclusion Criteria:** ≥ 40 yrs with clinical diagnosis of moderate-to-severe COPD and smoking history of ≥ 20 pack-yrs. **Exclusion Criteria:** Asthma
Interventions	**Inhaler Device:** Drypowder inhaler **Allowed Co-Medications:** Patients were permitted concomitant medication with inhaled corticosteroids (ICS), if dose and regimen were stable for 1 month prior to screening. Salbutamol was provided for use as needed (but not <6 h before study assessments).
Outcomes	Trough FEV1 after 12 weeks, efficacy outcomes, safety and tolerability.
Notes	**Funding:** Novartis **Identifiers:** NCT00567996

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1:1 ratio (with stratification for smoking status) using an automated system
Allocation concealment (selection bias)	Low risk	Automated system used for randomization.

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Blinding of participants and personnel (performance bias)	Low risk	Triple (Participant, Investigator, Outcomes Assessor)
Blinding of outcome assessment (detection bias)	Low risk	Triple (Participant, Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias)	Low risk	Dropout was relative low and even between active comparators (13.2% in IND and 15.0% in SAL group).
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the results Summary on clinicaltrials.gov.

Koser 2010

Methods	**Design:** Randomized, Double-Blind, Parallel Group study **Duration:** 12 weeks **Location:**16 research sites in the United States
Participants	**Population:** 246 patients were randomized into two study arms; fluticasone propionate/salmeterol (FSC) at a dose of 250/50mcg twice-daily via DISKUS (FSC DISKUS) (n=126) , Fluticasone Propionate/Salmeterol Hydrofluoroalkane MDI 230/42mcg (FSC MDI) (n= 121) **Baseline Characteristics:** Age (mean): FSC DISKUS (63.4), FSC MDI (61.6) Male (%): FSC DISKUS (52), FSC MDI (55) FEV_1 L (pre BD): FSC DISKUS (1.39), FSC MDI (1.47) Current Smokers (%): FSC DISKUS (62), FSC MDI (61) **Inclusion Criteria:** a) Diagnosis of COPD b) Current or former smokers with at least a 10 pack year history c) Aged > 40 years d) Post-bronchodilator FEV1 of > 0.70L and <70% predicted normal (or if FEV1 < 0.70 L, then >40% of predicted normal value), and a post-albuterol FEV1/FVC ratio of < 0.70. **Exclusion Criteria:**Asthma, clinically significant and uncontrolled medical disorder, COPD exacerbation/infection that required corticosteroids and/or antibiotics that did not resolve within 30 days of visit 1, abnormal ekg at screening, Body mass index (BMI) > 40kg/m^2, use of nocturnal positive pressure such as continuous positive airway pressure or bi-level positive airway pressure was exclusionary.
Interventions	**Inhaler Device:** DISKUS, Metered dose inhaler **Allowed Co-Medications:** None
Outcomes	Mean change from baseline in FEV1 2 Hours Post-dose, mean change from baseline in AM pre-dose FEV1 and peak expiratory flow
Notes	**Funding:** GlaxoSmithKline **Identifiers:**NCT00633217, ADC111117

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Allocation concealment (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Blinding of participants and personnel (performance bias)	Low risk	Double blind (participant and investigator)
Blinding of outcome assessment (detection bias)	Low risk	Double blind (participant and investigator)
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rates 12.4% in the HFA and 18.3 %in the DISKUS group. Reasons for dropout were similar between two groups. The primary analysis population was the Intent-to-Treat (ITT) population.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Mahler 2002

Methods	**Design:** Randomized, double-blind, placebo-controlled, parallel group study **Duration:** 24 weeks **Location:** 64 centers in the United States
Participants	**Population:** 674 patients were randomized to four arms; Fluticasone (F) 500 mcg (n=168), Salmeterol (S) 50 mcg (n=150), Fluticasone/Salmeterol (FSC) 500/50 mcg (n=165), Placebo (n=181) **Baseline Characteristics:** Age (mean): Placebo (64), S (63.5), F (64.4), FSC (61.9) Male (%): Placebo (75), S (64), F (61), FSC (62) FEV_1 L (pre BD): Placebo (1.317), S (1.237), F (1.233), FSC (1.268) Current Smokers (%): Placebo (54), S (46), F (46), FSC (46) **Inclusion Criteria:** 40 years of age or older, were current or former smokers with a 20 pack-year or more history, and COPD. Baseline FEV1/FVC of 70% or less and a baseline FEV1 of less than 65% of predicted but more than 0.70 L. Patients were required to have daily cough productive of sputum for 3 months of the year for 2 consecutive years and dyspnea. **Exclusion Criteria:** Asthma, oral corticosteroid use within the past 6 weeks, abnormal clinically significant electrocardiogram, long-term oxygen therapy, moderate or severe exacerbation during the run-in period.
Interventions	**Inhaler Device:** 1. Fluticasone propionate (F) (Flovent Diskus GlaxoSmith-Kline) 2. Salmeterol (S) (Serevent Diskus; Glaxo-SmithKline, Research Triangle Park,NC) 3. AdvairDiskus;Glaxo-SmithKline **Allowed Co-Medications:** Albuterol as needed.

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Outcomes	Change in predose FEV1 values, change in 2-hour postdose FEV1 values, morning peak expiratory flow (PEF), supplemental albuterol use, dyspnea and exacerbations.
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SFCA3006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Allocation concealment (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Blinding of participants and personnel (performance bias)	Low risk	Double blind
Blinding of outcome assessment (detection bias)	Low risk	No details provided but outcomes not subject to detection bias
Incomplete outcome data (attrition bias)	Low risk	A total of 234 patients (38%, 28%, 40%, and 32% for placebo, S, F, and FSC groups, respectively). Reasons for withdrawal were similar across the groups. Dropouts addressed with various methods including multiple imputation, analysis of only completers, and recursive regression imputation.
Selective reporting (reporting bias)	Low risk	Protocol was located. Outcomes were well reported.

Mahler 2012a

Methods	**Design**: Randomized, Double-blind, Controlled, Parallel-group **Duration**: 12 weeks **Location**: 186 centers in 14 countries; Argentina (10), Australia (6), Colombia (5), Denmark (5), Germany (25), Greece (4), Guatemala (5), Mexico (5), Peru (6), Philippines (2), South Africa (6), Spain (13), Turkey (13) and USA (81)
Participants	**Population:** 1131 patients were randomized into two groups; tiotropium 18mcg + Indacaterol 150mcg (n=570), tiotropium 18mcg + Placebo (n=561) daily. **Baseline Characteristics:** Age (mean): Tiotropium+Indacaterol (64), Tiotropium+Placebo (63.4) Male (%): Tiotropium+Indacaterol (70), Tiotropium+Placebo (67) FEV_1 L (pre BD): Tiotropium+Indacaterol (1.15), Tiotropium+Placebo (1.15) Current Smokers (%): Tiotropium+Indacaterol (40), Tiotropium+Placebo (36) **Inclusion Criteria:** Aged ≥ 40 years with moderate to severe COPD with a smoking history ≥ 10 pack-years and postbronchodilator FEV1 ≤ 65% and ≥ 30% of predicted normal, and post-bronchodilator FEV1/forced vital capacity <70% at screening. **Exclusion Criteria:** History of asthma or had experienced a respiratory tract

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	infection or COPD exacerbation within the previous 6 weeks.
Interventions	**Inhaler Device:** 1. Indacaterol/Placebo via a single dose dry powder inhaler (SDDPI) device. 2. Tiotropium via HandiHaler®. **Allowed Co-Medications:** Salbutamol (albuterol in the USA) was available for as-needed use. Patients receiving inhaled corticosteroids (ICS) at baseline continued treatment (or were switched to ICS monotherapy if taken as a fixed combination with a bronchodilator) at equivalent dose and regimen during the study.
Outcomes	FEV1 standardized (with respect to length of time) area under the curve (AUC) from 5 minutes to 8 hours post-dose at the end of treatment. Trough FEV1 24 hours post-dose at the end of treatment.
Notes	**Funding:** Novartis Pharmaceuticals **Identifiers:** NCT00846586

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization (1:1) was performed using an automated interactive voice response system and was stratified by COPD severity (moderate or severe), with balance maintained at country level.
Allocation concealment (selection bias)	Low risk	Balance maintained at country level. Automated randomization
Blinding of participants and personnel (performance bias)	Low risk	Patients and staff at participating centers were unaware of treatment assignment.
Blinding of outcome assessment (detection bias)	Low risk	Patients, investigators, those performing the assessments and data analysts were blinded unless an emergency arose for a patient.
Incomplete outcome data (attrition bias)	Low risk	Completion rates were similar (93-94%) between treatment groups and studies.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Mahler 2012b

Methods	**Design:** Randomized, Double-blind, Controlled, Parallel-group **Duration:** 12 weeks **Location:**182 centers in 11 countries; Argentina (9), Canada (16), Colombia (3), Czech Republic (9), Hungary (4), India (9), Netherlands (6), Philippines (3), Slovakia (10), Spain (11), USA (102)
Participants	**Population:** 1142 patients were randomized into two groups; tiotropium 18mcg + Indacaterol 150mcg (n=572), tiotropium 18mcg + Placebo (n=570) daily. **Baseline Characteristics:** Age (mean): Tiotropium+Indacaterol (63.1), Tiotropium+Placebo (62.8) Male (%): Tiotropium+Indacaterol (63), Tiotropium+Placebo (68)

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	FEV_1 L (pre BD): Tiotropium+Indacaterol (1.14), Tiotropium+Placebo (1.15) Current Smokers (%): Tiotropium+Indacaterol (38), Tiotropium+Placebo (43) **Inclusion Criteria:** Aged ≥ 40 years with moderate to severe COPD with a smoking history ≥ 10 pack-years and postbronchodilator FEV1 ≤ 65% and ≥ 30% of predicted normal, and post-bronchodilator FEV1/forced vital capacity <70% at screening. **Exclusion Criteria:** History of asthma or had experienced a respiratory tract infection or COPD exacerbation within the previous 6 weeks.
Interventions	**Inhaler Device:** 1. Indacaterol/Placebo via a single dose dry powder inhaler (SDDPI) device. 2. Tiotropium via HandiHaler®. **Allowed Co-Medications:** Salbutamol (albuterol in the USA) was available for as-needed use. Patients receiving inhaled corticosteroids (ICS) at baseline continued treatment (or were switched to ICS monotherapy if taken as a fixed combination with a bronchodilator) at equivalent dose and regimen during the study.
Outcomes	FEV1 standardized (with respect to length of time) area under the curve (AUC) from 5 minutes to 8 hours post-dose at the end of treatment.
Notes	**Funding:** Novartis **Identifiers:** NCT00877383.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization (1:1) was performed using an automated interactive voice response system and was stratified by COPD severity (moderate or severe), with balance maintained at country level.
Allocation concealment (selection bias)	Low risk	Balance maintained at country level. Automated randomization
Blinding of participants and personnel (performance bias)	Low risk	Patients and staff at participating centers were unaware of treatment assignment.
Blinding of outcome assessment (detection bias)	Low risk	Patients, investigators, those performing the assessments and data analysts were blinded unless an emergency arose for a patient.
Incomplete outcome data (attrition bias)	Low risk	Completion rates were high and similar (94-95%) between treatment groups
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Mahler 2015a

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Methods	**Design:** Randomized, double-blind, parallel-group, placebo and active-controlled studies **Duration:** 12 weeks **Location:** United States, Canada, Philippines, Poland, Romania, Spain, Ukraine and Vietnam.
Participants	**Population:** Patients were randomized into one of four arms; indacaterol/glycopyrrolate (IND/GLY 27.5/15.6 mcg twice daily) (n=508), indacaterol (IND 27.5 mcg twice daily) (n=511), glycopyrrolate (GLY 15.6 mcg twice daily) (n=511) or placebo (n=508), combined population from Mahler 2015a and 2015b. **Baseline Characteristics (pooled analysis of Mahler 2015a and b):** Age (mean): IND/GLY (63.4), IND (63.7), GLY (63.4), Placebo (63.2) Male (%): IND/GLY (63.4), IND (65.8), GLY (63.8), Placebo (60.2) FEV_1 L (pre BD): IND/GLY (1.264), IND (1.280), GLY (1.258), Placebo (1.250) Current Smokers (%): IND/GLY (50.4), IND (52.1), GLY (52.3), Placebo (51.6) **Inclusion Criteria:** 40 years of age and older, who had stable but symptomatic moderate to severe COPD according to the GOLD 2011 criteria. Smoking history of at least 10 years. **Exclusion Criteria:** COPD exacerbation requiring antibiotics and/or systemic steroids in last 6 weeks prior to visit 1, long qt syndrome, respiratory tract infection within 4 weeks of screening, history of asthma.
Interventions	**Inhaler Device:** All treatments were delivered via the Neohaler device (Novartis Pharma AG, Basel, Switzerland). **Allowed Co-Medications:** Patients continued to use fixed doses of inhaled corticosteroids if they had been previously prescribed. Albuterol metered dose inhaler was allowed as rescue medication throughout the treatment period.
Outcomes	Standardized area under the curve for FEV1 between 0 and 12 hours at end of treatment period, also change in SGRQ total score from baseline and in the percentage of responders.
Notes	**Funding:** Novartis **Identifiers:** NCT 01727141

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All eligible patients were randomized via Interactive Response Technology (IRT) in 1:1:1:1 ratio.
Allocation concealment (selection bias)	Low risk	All eligible patients were randomized via Interactive Response Technology (IRT) in 1:1:1:1 ratio.
Blinding of participants and personnel (performance bias)	Low risk	The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, scheduling of administration, appearance, taste and odor.
Blinding of outcome assessment (detection bias)	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)

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Incomplete outcome data (attrition bias)	Low risk	Completion rates were high and similar (97-99%) among active comparators.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Mahler 2015b

Methods	**Design:** Randomized, double-blind, parallel-group, placebo and active-controlled studies **Duration:** 12 weeks **Location:** United States, Colombia, Egypt, France, Guatemala, Hungary, Panama, Slovakia and Slovenia.
Participants	**Population:** Patients were randomized into one of four arms; indacaterol/glycopyrrolate (IND/GLY 27.5/15.6 mcg twice daily) (n=508), indacaterol (IND 27.5 mcg twice daily) (n=511), glycopyrrolate (GLY 15.6 mcg twice daily) (n=511) or placebo (n=508), combined population from Mahler 2015a and 2015b. **Baseline Characteristics (pooled analysis of Mahler 2015a and b):** Age (mean): IND/GLY (63.4), IND (63.7), GLY (63.4), Placebo (63.2) Male (%): IND/GLY (63.4), IND (65.8), GLY (63.8), Placebo (60.2) FEV_1 L (pre BD): IND/GLY (1.264), IND (1.280), GLY (1.258), Placebo (1.250) Current Smokers (%): IND/GLY (50.4), IND (52.1), GLY (52.3), Placebo (51.6) **Inclusion Criteria:** 40 years of age and older, who had stable but symptomatic moderate to severe COPD according to the GOLD 2011 criteria. **Exclusion Criteria:** COPD exacerbation requiring antibiotics and/or systemic steroids in last 6 weeks prior to visit 1, long qt syndrome, respiratory tract infection within 4 weeks of screening, history of asthma.
Interventions	**Inhaler Device:** All treatments were delivered via the Neohaler device (Novartis Pharma AG, Basel, Switzerland). **Allowed Co-Medications:** Patients continued to use fixed doses of inhaled corticosteroids if they had been previously prescribed. Albuterol metered dose inhaler was allowed as rescue medication throughout the treatment period.
Outcomes	Standardized area under the curve for FEV1 between 0 and 12 hours at end of treatment period, also change in SGRQ total score from baseline and in the percentage of responders.
Notes	**Funding:** Novartis **Identifiers:** NCT01712516

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All eligible patients were randomized via Interactive Response Technology (IRT) in 1:1:1:1 ratio.
Allocation concealment (selection bias)	Low risk	All eligible patients were randomized via Interactive Response Technology (IRT) in 1:1:1:1 ratio.

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Blinding of participants and personnel (performance bias)	Low risk	The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, scheduling of administration, appearance, taste and odor.
Blinding of outcome assessment (detection bias)	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias)	Low risk	Completion rates were high and similar (96-98%) among active comparators.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Mahler 2016

Methods	**Design:** Randomized, multicenter, double-blind, parallel-group study **Duration:** 52 weeks **Location:** 65 centers in the US
Participants	**Population:** 511 patients were randomized to one of two study arms; Glycopyrrolate/GLY 15.6 mcg twice daily (n=251) or Indacaterol/IND 75 mcg daily (n=256) **Baseline Characteristics:** Age (mean): GLY (63.3), IND (63.2) Male (%): GLY (56.2), IND (58.2) FEV_1 L (pre BD): GLY (1.24), IND (1.25) Current Smokers (%): GLY (54.2), IND (55.5) **Inclusion Criteria:** Patients aged ≥ 40 years with stable COPD (GOLD 2011 levels 2 and 3), who were current or ex-smokers with a smoking history of at least 10 pack-years, who presented with post-bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and a post-bronchodilator FEV1/forced vital capacity (FVC) < 0.70, and with a modified Medical Research Council (mMRC) Dyspnea Scale grade of at least 2. **Exclusion Criteria:** History of long QT syndrome, clinically significant electrocardiogram (ECG) abnormality, clinically significant cardiovascular disease, renal abnormalities, history of asthma, and COPD exacerbations that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization within the six weeks before the screening or during the screening and run-in periods.
Interventions	**Inhaler Device:** Both treatment arms used low-resistance, single-dose, dry powder inhaler (Neohaler™ device). **Allowed Co-Medications:** Stable background treatment with ICS was permitted to be continued throughout the study. During the study, patients were provided with albuterol as a rescue medication.
Outcomes	Safety and tolerability in terms of the adverse event (AE) reporting rates. Time to first moderate or severe COPD exacerbations. Pre-dose trough FEV1 at Week 52. FEV1 and FVC measurements at all post-baseline time-points, and rescue medication use over 52 weeks of treatment period.
Notes	**Funding:** Novartis **Identifiers:** NCT01697696

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A patient randomization list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. A separate medication list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to study drug packs containing each of the study drugs.
Allocation concealment (selection bias)	Low risk	A patient randomization list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. A separate medication list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to study drug packs containing each of the study drugs.
Blinding of participants and personnel (performance bias)	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias)	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias)	Low risk	18% of patients discontinued the study before the end of treatment period, discontinuation rates and reasons were similar between both groups.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Maleki-Yazdi 2014

Methods	**Design:** Multicenter, randomized, double-dummy, parallel-group study **Duration:** 24 weeks **Location:** 71 centers in 8 countries (Bulgaria, Canada, Germany, Hungary, Romania, Russia, Spain, and the United States)
Participants	**Population:** 905 patients were randomized to treatment with once-daily Umeclidinium bromide+Vilanterol/UMEC/VI 62.5/25 mcg (n=454) or Tiotropium/TIO 18 mcg daily (n=451) **Baseline Characteristics:** Age (mean): UMEC/VI (61.9), TIO (62.7) Male (%): UMEC/VI (68), TIO (67) FEV_1 L (post BD): UMEC/VI (1.41), TIO (1.41) Current Smokers (%): UMEC/VI (59), TIO (54) **Inclusion Criteria:** Patients aged ≥ 40 years with moderate-to-very severe COPD and an established clinical history of COPD as defined by American Thoracic Society/European Respiratory Society guidelines. **Exclusion Criteria:** Hospitalized for COPD or pneumonia within 12 weeks prior to Visit 1.

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Interventions	**Inhaler Device:** 1. UMEC/VI via dry powder inhaler, DPI, ELLIPTA™ DPI; 2. TIO via Handi-Haler® **Allowed Co-Medications:** Use of albuterol/salbutamol provided by GlaxoSmithKline via metered dose inhaler as relief medication was permitted, but was withheld for ≤ 4 h prior to spirometry testing. Inhaled corticosteroids (ICS) at a consistent dose of up to 1000 mcg/day of fluticasone propionate or equivalent were permitted and recorded.
Outcomes	Trough FEV1 at Day 169, weighted mean (WM) FEV1 over 0-6 h post-dose at Day 168
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01777334, ZEP117115

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization code was generated using a GlaxoSmithKline validated computerized system, RandAll.
Allocation concealment (selection bias)	Low risk	Allocation of treatments was controlled using RAMOS (Randomization and Medication Ordering System, GlaxoSmithKline) and the link to the randomization schedule was kept confidential from all staff.
Blinding of participants and personnel (performance bias)	Low risk	Double-dummy design was used for retaining the blinding
Blinding of outcome assessment (detection bias)	Low risk	The investigator and treating physician were blinded till an emergency arouse.
Incomplete outcome data (attrition bias)	Low risk	Most patients completed the study (88%, UMEC/VI group; 86%, TIO group). Reasons for dropout were similar between two groups.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

Martinez 2017a

Methods	**Design:** A Randomized, Double Blind, Chronic Dosing, Placebo-Controlled, Parallel Group, Multi Center Study **Duration:** 24 weeks. **Location:** Australia, New Zealand, United States
Participants	**Population:** Glyco/FM (14.4/9.6) 526, Glyco (14.4) 451, FM (9.6) 452, Tio (18) 451 **Baseline Characteristics:** age 62.8 (SD8.4) F:M 914:1182 **Inclusion Criteria:** ● Male or female subjects at least 40 years of age and no older than 80 at Visit 1. ● Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) ● Current or former smokers with a history of at least 10 pack-years of

	cigarette smoking. ● Average f the -60 and the -30 min pre-dose FEV1 assessments must be < 80% predicted normal value calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations. ● Subjects willing and, in the opinion of the investigator, able to adjust current COPD therapy as required by the protocol **Exclusion Criteria:** ● Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study ● Current diagnosis of asthma or alpha-1 antitrypsin deficiency ● Other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnea ● Hospitalized due to poorly controlled COPD within 3 months prior to screening or during the Screening Period ● Poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to screening or during the Screening Period ● Lower respiratory tract infections that required antibiotics within 6 weeks prior to screening or during the Screening Period ● Unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of enrollment. ● Recent history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft within the past three months ● Congestive heart failure (CHF) New York Heart Association (NYHA) Class III/IV) ● Clinically significant abnormal 12-lead ECG ● Abnormal liver function tests defined as aspartate transaminase (AST), alanine transaminase (ALT), or total bilirubin ≥ 1.5 times upper limit of normal at Visit 1 and on repeat testing ● Cancer not in complete remission for at least five years ● History of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI
Interventions	**Inhaler Device:** GFF MDI, GP MDI, FF MDI, Open-label tiotropium bromide inhalation powder, Placebo MDI **Allowed Co-Medications:** Rescue albuterol, ICS, phosphodiesterase -4 inhibitor.
Outcomes	Primary Outcome Measures: Change From Baseline in Morning Pre-dose Trough FEV1 at Week 24 [Time Frame: Baseline and at Week 24]
Notes	**Funding:** Pearl Therapeutics **Identifiers:** NCT01854645

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Tiotropium was open label
Blinding of outcome assessment (detection bias)	High risk	Tiotropium was open label
Incomplete outcome data (attrition bias)	High risk	Dropout relatively high and uneven among active comparators (GFF 18.6%, GP 23.5%, FF 18.1%, Tio 13.7%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Martinez 2017b

Methods	**Design:** A Randomized, Double Blind, Chronic Dosing, Placebo-Controlled, Parallel Group, Multi Center Study **Duration:** 24 weeks. **Location:** United States
Participants	**Population:** Glyco/FM (14.4/9.6) 510 Glyco (14.4) 439, FM (9.6) 438 **Baseline Characteristics:** age 62.9 (SD 8.3) F:M 723:886 **Inclusion Criteria:** ● Male or female subjects at least 40 years of age and no older than 80 at Visit 1. ● Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) ● Current or former smokers with a history of at least 10 pack-years of cigarette smoking. ● Subjects with FEV1/FVC ratio of <0.70 and FEV1 <80% predicted normal and ≥ 750 mL if FEV1 <30% of predicted normal value. ● Subjects willing and, in the opinion of the investigator, able to adjust current COPD therapy as required by the protocol **Exclusion Criteria:** ● Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study ● Current diagnosis of asthma or alpha-1 antitrypsin deficiency ● Other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnea ● Hospitalized due to poorly controlled COPD within 3 months prior to screening or during the Screening Period

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	● Poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to screening or during the Screening Period ● Lower respiratory tract infections that required antibiotics within 6 weeks prior to screening or during the Screening Period ● Unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of enrollment. ● Recent history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft within the past three months ● Congestive heart failure (CHF NYHA Class III/IV) ● Clinically significant abnormal 12-lead ECG ● Abnormal liver function tests defined as AST, ALT, or total bilirubin ≥ 1.5 times upper limit of normal at Visit 1 and on repeat testing ● Cancer not in complete remission for at least five years ● History of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI
Interventions	**Inhaler Device:** GFF MDI, GP MDI, FF MDI, Open-label tiotropium bromide inhalation powder, Placebo MDI **Allowed Co-Medications:** Rescue albuterol, ICS, phosphodiesterase -4 inhibitor.
Outcomes	Primary Outcome Measures: Change From Baseline in Morning Pre-dose Trough FEV1
Notes	**Funding:** Pearl Therapeutics **Identifiers:** NCT01854658

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Tiotropium was open label
Blinding of outcome assessment (detection bias)	High risk	Tiotropium was open label
Incomplete outcome data (attrition bias)	High risk	Dropout relatively high and uneven among active comparators (GFF 21.2%, GP 17.0%, FF 15.6%, Tio 26.3%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

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Ohar 2014

Methods	**Design**: randomised, parallel-group study **Duration**: 6 months **Location**: unclear
Participants	**Population**: FP/SAL (250/50) 314, SAL (50) 325 **Baseline characteristics:** Age 62.9 (SD 9.22) F:M 291:348 **Inclusion criteria**: >40 years of age and a historical FEV1/FVC<0.7, recent event (within 14 days of randomisation) of: <10-day hospitalisation for an acute COPD exacerbation, or exacerbation requiring treatment with oral corticosteroids (OCS) or OCS+antibiotics in an ER, or during a physician's office visit. If the index event was office-based, a six month history of hospitalizations attributed to AECOPD was also required. **Exclusion criteria**: Diagnosis of pneumonia, congestive heart failure (CHF), or other complicating co-morbidities, previous lung resection surgery (e.g. lobectomy, pneumonectomy, etc) within the year preceding Visit 1 (Screening, asthma as primary diagnosis, Lung cancer, cystic fibrosis, pulmonary fibrosis, active tuberculosis, or sarcoidosis, clinically significant cardiac arrhythmias, current malignancy or a previous history of cancer in remission for < 5yrs (localized basal cell or squamous cell carcinoma of the skin that has been resected is not excluded), preganacy, hypersensitivity to any Beta-agonist, sympathomimetic drug, or corticosteroid, etc.
Interventions	1. Salmeterol 50 bid (LABA) 2. Salmeterol/fluticasone 50/250 bid (LABA/ICS) **Inhaler Device:** Diskus dry powder **Allowed Co-Medications:** Albuterol as needed. Tiotropium.
Outcomes	Pre-dose FEV1, exacerbation outcomes
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01110200, ADC113874

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation of double-blinded study treatments was conducted using RAMOS (GlaxoSmithKline, UK), an interactive voiceresponse system.
Allocation concealment (selection bias)	Low risk	Allocation of double-blinded study treatments was conducted using RAMOS (GlaxoSmithKline, UK), an interactive voiceresponse system.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	No details provided but outcomes not subject to detection bias

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Incomplete outcome data (attrition bias)	Low risk	Dropout rates were high (FSC 250/50 22.7%; SAL 50 25.7%) but the reasons for dropout were similar between two groups. ITT population with Endpoint analysis was used for missing data and premature withdrawal.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the results Summary on clinicaltrials.gov.

Pepin 2014

Methods	**Design:** multicenter, randomized, double-blind, parallel group, chronic dosing, active- and placebo-controlled study **Duration:** 12 weeks **Location:** Argentina, France, Germany, Italy, Norway, Russian Federation, Ukraine
Participants	**Population:** FF/Vl (100/25) 127, Tio(18) 130 **Baseline Characteristics:** age 67.3 (7.28) F:M 37/220 **Inclusion Criteria:** ● Type of subject: Outpatient ● Informed consent: Subjects must give their signed and dated written informed consent to participate. ● Gender: Male or female subjects. ● Age: greater then or equal to 40 years of age at Screening (Visit 1) ● COPD diagnosis: Subjects with a clinical history of COPD in accordance with the following definition by the American Thoracic Society (ATS) /European Respiratory Society(ERS). ● Subjects with a current or prior history ofgreater then or equal to 10 pack-years of cigarette smoking at Screening (Visit 1). ● Subjects with a measured post-albuterol/salbutamol FEV1 less then 70% of predicted at Screening (Visit 1). ● Subjects with a measured post-albuterol/salbutamol FEV1/FVC ratio of less then or equal to 0.70 at Screening (Visit 1). ● Exacerbation History: Subjects who have been hospitalised or have been treated with oral corticosteroids or antibiotics for their COPD within the last 3 years prior to Screening (V1). ● Baseline aPWV: subjects with a measured aPWV greater then 12.0 m/s at Screening (Visit 1). **Exclusion Criteria:** Body Mass Index of less then or equal to 35
Interventions	**Inhaler Device:** fluticasone furoate (FF, GW685698)/vilanterol (Vl, GW642444) 100/25 mcg Novel Dry Powder Inhaler (NDPI) Tiotropium (18 mcg) administered QD via a HandiHaler **Allowed Co-Medications:** Salbutamol/albuterol as needed.
Outcomes	Primary Outcome Measures: Mean Change From Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the End of the 12-week Treatment Period (Day 84)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01395888, HZC115247

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response system
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias)	Low risk	double-blind
Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arouse.
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and even between two groups (11.8% in FF/VI and 13.1% in Tio group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported.

Perng 2009

Methods	**Design:** a randomised (not double blinded) clinical trial **Duration:** 12 weeks **Location:** Taiwan
Participants	**Population:** FP/SAL (500/50) 33, Tio(18) 34 **Baseline Characteristics:** age 73.2. F:M 4/63 **Inclusion Criteria:** Clinical diagnosis of COPD, aged 40–85 yrs; were a current or former smoker (history o20 packyrs);had a post-bronchodilator FEV1 ,80% of the predicted value and FEV1/forced vital capacity (FVC) ,70% **Exclusion Criteria:** no history of asthma, atopy (as defined by a positive reaction to one or more allergen in a fluoroenzyme immunoassay) or any other active lung disease. Subjects were either newly diagnosed or had not taken corticosteroids (either oral or inhaled), or any other bronchodilators or theophylline, for a minimum of 3 months prior to the commencement of the study
Interventions	**Inhaler Device:** SFP 25/250 Evohaler (GlaxoSmithKline) Tio 18 Handihaler (Boehringer Ingelheim) **Allowed Co-Medications:** Not described
Outcomes	Pulmonary function, serum C-reactive protein (CRP), sputum induction and assessment of health-related quality of life
Notes	**Funding:** Unknown **Identifiers:** None

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomisation was performed using a computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and relatively even between two groups (10% in SFP and 14.7 % in Tio group)
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol to check outcome reporting

PINNACLE 3 2017

Methods	**Design:** a multi-center, randomized, double-blind, parallel group, chronic dosing, active-controlled, 28-week safety extension study **Duration:** 52 weeks total **Location:** Australia, New Zealand, United States
Participants	**Population:** GLyco/FM (14.4/9.6) 1036, Glyco (14.4) 890, FM(9.6) 890, Tio (18) 451 **Baseline Characteristics:** age 62.7 (SD 8.3) F:M 1439:1818 **Inclusion Criteria:** ● Participant in/completion of previous 24-week PINNACLE Phase III Trial. ● Male or female subjects at least 40 years of age and no older than 80 at Visit 1. ● Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) ● Current or former smokers with a history of at least 10 pack-years of cigarette smoking. ● Subjects with FEV1/forced vital capacity (FVC) ratio of <0.70 and FEV1 <80% predicted normal and ≥ 750 mL if FEV1 <30% of predicted normal value. ● Subjects willing and, in the opinion of the investigator, able to adjust current COPD therapy as required by the protocol **Exclusion Criteria:** ● Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study ● Current diagnosis of asthma or alpha-1 antitrypsin deficiency ● Other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnea ● Hospitalized due to poorly controlled COPD within 3 months prior to screening or during the Screening Period

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	● Poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to screening or during the Screening Period ● Lower respiratory tract infections that required antibiotics within 6 weeks prior to screening or during the Screening Period ● Unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of enrollment. ● Recent history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft within the past three months ● Congestive heart failure (CHF) New York Heart Association (NYHA) Class III/IV) ● Clinically significant abnormal 12-lead electrocardiogram (ECG) ● Abnormal liver function tests defined as alanine transaminase (ALT), aspartate transaminanse (AST), or total bilirubin ≥ 1.5 times upper limit of normal at Visit 1 and on repeat testing ● Cancer not in complete remission for at least five years ● History of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI
Interventions	**Inhaler Device:** GFF MDI, GP MDI, FF MDI, Open-label tiotropium bromide inhalation powder, Placebo MDI **Allowed Co-Medications:** Rescue albuterol, ICS, phosphodiesterase -4 inhibitor.
Outcomes	Primary Outcome Measures: Change From Baseline in Morning -Pre-dose Trough FEV1 Over 52 Weeks
Notes	**Funding:** Pearl Therapeutics **Identifiers:** NCT01970878, PT003008-00

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Tiotropium was open label.
Blinding of outcome assessment (detection bias)	High risk	Tiotropium was open label.
Incomplete outcome data (attrition bias)	Unclear risk	Dropout relatively high but even among active comparators (GFF 12.8%, GP 12.4%, FF 12.2%, Tio 14.0%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

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RADIATE 2016

Methods	**Design:** A multi-center, randomized, double-blind, parallel-group, placebo and active- controlled study **Duration:** 52 weeks **Location:** Belgium, Bulgaria, Greece, Hungary, Ireland, Russian Federation, Slovakia, Spain, Turkey, United Kingdom
Participants	**Population:** IND/Glyco (110/50) 407 Tio (18) 405 **Baseline Characteristics:** age 6405 (SD 8.14) F:M 318:898 **Inclusion Criteria:** ● Male and female adults aged ≥ 40 years. ● Patients with stable COPD according to GOLD strategy (GOLD 2011). ● Patients with airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and a post-bronchodilator. ● FEV1/FVC < 0.70. ● Current or ex-smokers who have a smoking history of at least 10 pack years. ● Patients with an mMRC ≥ grade 2 **Exclusion Criteria:** ● History of long QT syndrome or prolonged QTc. ● Patients who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1. ● Patients with Type I or uncontrolled Type II diabetes. ● Patients with a history of asthma or have concomitant pulmonary disease. ● Patients with paroxysmal (e.g. intermittent) atrial fibrillation. Only patients with persistent atrial fibrillation and controlled with a rate control strategy for at least six months could be eligible. ● Patients who have clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of safety.
Interventions	**Inhaler Device:** QVA149 IND/Glyco 110/50 µg Novartis Concept1 SDDPI Tiotropium 18 µg HandiHaler SDDPI **Allowed Co-Medications:** Rescue albuterol
Outcomes	Primary Outcome Measures: Number of Patients With Serious Adverse Events
Notes	**Funding:** Novartis **Identifiers:** NCT01610037, CQVA149A2339

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded

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Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (tio 12.6%, QVA (IND/Glyco) 14.5%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Rennard 2009

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group, active- and placebocontrolled, multi-centre study **Duration**: 12 months (+ 2 weeks run-in period) **Location**: 237 sites in the USA, Europe and Mexico
Participants	**Population**: 1964 participants were randomised to formoterol (495), formoterol/budesonide at two doses (494 and 494), and placebo (481) **Baseline characteristics** Age (mean years): form 62.9, form/bud320 63.2, form/bud160 63.6, pbo 62.9 % Male: form 65.3, form/bud320 62.3, form/bud160 62.8, pbo 65.3 % FEV1 predicted: form 39.3, form/bud320 38.6, form/bud160 39.6, pbo 40.8 Pack-years (median): form 40, form/bud320 40, form/bud160 40, pbo 40 **Inclusion criteria**: Males and females aged 40 and older; moderate to severe COPD for 2+ years; history of at least 10 pack-years **Exclusion criteria**: history of asthma or seasonal rhinitis before age 40; significant/unstable cardiovascular disorder; significant respiratory tract disorder other than COPD; homozygous alpha1-antitrypsin deficiency or other clinically significant comorbidities precluding participation.
Interventions	1. Formoterol 12 bid (LABA) 2. Formoterol/budesonide 9/320 (LABA/ICS) 3. Formoterol/budesonide 9/160 (LABA/ICS) 4. Placebo (PBO) **Inhaler device**: dry powder **Allowed co-medications**: Salbutamol was allowed as reliefmedication. Previous inhaled corticosteroids were discontinued, and disallowed medication included long-acting anticholinergics; inhaled LABAs or SABAs (other than salbutamol); oral beta-adrenoreceptor agonists; ephedrine; leukotriene receptor agonists; xanthine derivatives except for shortterm use
Outcomes	St George's Respiratory Questionnaire (SGRQ), COPD exacerbations, pre-dose FEV1, one hour post-dose FEV1, morning and evening PEF
Notes	**Funding**: AstraZeneca **Identifier(s)**: NCT00206167

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized, parallel-group study [no specific details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias)	Low risk	To maintain blinding, patients received both a pressurized metered-dose inhaler (pMDI) and a dry powder inhaler(DPI) containing either active treatment or double-dummy placebo (PL) as appropriate
Blinding of outcome assessment (detection bias)	Low risk	Included outcomes unlikely to be affected by detection bias
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rate was high (BUD/FM 320/9 27.1%, BUD/FM 160/9 28.9%, formoterol 31.7%,) but the reasons for withdrawal were similar across the groups.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published report.

Rheault 2016

Methods	**Design:** multicentre, randomized, open-label, 2-arm, parallel-group study **Duration:** 12 weeks **Location:** Argentina, Chile, Czechia, Germany, Hungary, Norway, Romania, Russian Federation, Spain, Sweden
Participants	**Population:** UMEC(62.5) 516, Glyco (44) 518 **Baseline Characteristics:** age 6401 (SD 8.3) F:M 329:705 **Inclusion Criteria:** ● Type of subject: outpatient ● Informed Consent: a signed and dated written informed consent prior to study participation ● Age: subjects 40 years of age or older at Visit 1. ● Gender: male and female subjects are eligible to participate in the study. A female is eligible to enter and participate in the study if she is of: Non-child bearing potential i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile. Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as being amenorrhoeic for greater than 1 year with an appropriate clinical profile, eg, age appropriate, > 45 years, in the absence of hormone replacement therapy OR child bearing potential, has a negative pregnancy test at screening, and agrees to one of the acceptable contraceptive methods used consistently and correctly i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study - screening to follow-up contact. ● Diagnosis: an established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society

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(ERS)

- Smoking history: current or former cigarette smokers with a history of cigarette smoking of >= 10 pack-years [number of pack years = (number of cigarettes per day / 20) x number of years smoked (eg. 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years both equal 10 pack-years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Pipe and/or cigar use cannot be used to calculate pack-year history
- Severity of Disease: A pre and post-albuterol/salbutamol forced expiratory volume in one second/ forced vital capacity (FEV1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV1 of >=30% and =<70% of predicted normal values at Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative
- Dyspnea: A score of >=2 on the modified medical research council dyspnea scale (mMRC) at Visit 1

Exclusion Criteria:

- Pregnancy: women who are pregnant or lactating or are planning on becoming pregnant during the study.
- Asthma: a current diagnosis of asthma.
- Other respiratory disorders: known alpha-1 antitrypsin deficiency, active lung infections (such as tuberculosis), and lung cancer are absolute exclusionary conditions. A subject who, in the opinion of the investigator, has any other significant respiratory conditions in addition to COPD should be excluded. Examples may include clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease.
- Other diseases/abnormalities: any subject who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any subject who has any condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study.
- Severe hepatic impairment: patients with severe hepatic impairment (Child-Pugh class C) should be excluded unless, in the opinion of the investigator, the benefit is likely to outweigh the risk.
- Severe renal impairment: patients with severe renal impairment (e.g., end-stage renal disease requiring dialysis) should be excluded, unless in the opinion of the investigator, the benefit is likely to outweigh the risk.
- Unstable or life threatening cardiac disease: long-acting muscarinic antagonists (LAMA) should be used with caution in subjects with severe cardiovascular disease. In the opinion of the investigator, use should only be considered if the benefit is likely to outweigh the risk in conditions such as: Myocardial infarction or unstable angina in the last 6 months, Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months, New York Heart Association (NYHA) Class IV heart failure
- Contraindications: Any history of allergy or hypersensitivity to any anticholinergic/ muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.
- Antimuscarinic effects: Subjects with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.

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	● Hospitalization: hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1. ● Lung resection: lung volume reduction surgery within the 12 months prior to Visit 1. ● 12-Lead electrocardiogram (ECG): Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. Subjects with the following abnormalities are excluded from participation in the study: Atrial fibrillation with rapid ventricular rate >120 beats per minute; sustained or nonsustained ventricular tachycardia; second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted) ● Medication prior to spirometry: unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit. ● Medications prior to screening: use of the following medications according to the following defined time intervals prior to Visit 1: depot corticosteroids 12 weeks, systemic, oral or parenteral corticosteroids 6 weeks, antibiotics (for lower respiratory tract infection) 6 weeks, inhaled long acting beta2 agonists/ inhaled corticosteroid (LABA/ICS) combination products if LABA/ICS therapy is discontinued completely 30 days; LABA/ICS combination products only If discontinuing ICS/ LABA therapy and switching to ICS monotherapy 48 hours for the salmeterol or formoterol component 14 days for the vilanterol component (note: the dose of ICS must be a dose of fluticasone propionate (FP) or equivalent but not to exceed 1000 mcg/day), use of ICS at a dose >1000 microgram (mcg)/day of FP or equivalent 30 days (note: use of ICS is permitted provided the dose does not exceed 1000 mcg of FP or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1, except for subjects on LABA/ICS therapy who may discontinue the ICS/LABA product as indicated in the table above and switch to ICS monotherapy); initiation or discontinuation of ICS use 30 days (note: use of ICS is permitted provided the dose does not exceed 1000 mcg of FP or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1, except for subjects on LABA/ICS therapy who may discontinue the ICS/LABA product as indicated in the table above and switch to ICS monotherapy); phosphodiesterase 4 (PDE4) Inhibitor (roflumilast) 14 days; LABA: salmeterol and formoterol 48 hours; olodaterol, indacaterol, and vilanterol 14 days; LAMA: tiotropium, aclidinium, glycopyrronium, umeclidinium 7 days; LAMA/LABA combination products if LAMA/LABA therapy is discontinued completely then apply whichever mono component has the longest washout; theophyllines 48 hours; Oral beta2-agonists: long-acting 48 hours, short-acting 12 hours; inhaled short acting beta2-agonists 4 hours (note: use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing); inhaled short-acting anticholinergics 4 hours; inhaled short-acting anticholinergic/short-acting beta2-agonist combination products 4 hours; any other investigational medication 30 days or within 5 drug half-lives (whichever is longer). ● Oxygen: use of long-term oxygen therapy (LTOT) described as oxygen

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	therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e. =<12 hours per day) is not exclusionary. ● Nebulized therapy: regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g. albuterol/salbutamol) via nebulized therapy. ● Pulmonary rehabilitation program: participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded. ● Drug or alcohol abuse: A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1. ● Affiliation with investigator site: is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study. ● Inability to read: in the opinion of the investigator, any subject who is unable to read and/or would not be able to complete a questionnaire
Interventions	**Inhaler Device:** Umeclidinium 62.5 mcg nDPI Glycopyrronium bromide as inhalation capsules, 44 mcg per capsule, BREEZHALER inhalers **Allowed Co-Medications:**
Outcomes	Primary Outcome Measures: Change From Baseline in Trough FEV1 on Day 85
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT02236611, 201315 (GSK)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Registration And Medication Ordering System (RAMOS; GlaxoSmithKline) interactive response technology
Allocation concealment (selection bias)	Low risk	Registration And Medication Ordering System (RAMOS; GlaxoSmithKline) interactive response technology
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Dropout was low in both included groups (UMEC 5.0%, Glyco 6.6%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

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RISE 2017

Methods	**Design:** A Phase IIIB, 6-Month, Double-blind, Double-dummy, Randomized, Parallel-group, Multicenter Exacerbation Study **Duration:** 26 weeks. **Location:** Argentina, Bulgaria, Chile, Czechia, Germany, Mexico, Poland, Puerto Rico, South Africa, Spain, United States
Participants	**Population:** BUD/FM (320/9) 606 FM (9) 613 **Baseline Characteristics:** age 63.5 (SD 8.67) F:M 521:698 **Inclusion Criteria:** 3. A current clinical diagnosis of COPD with COPD symptoms for more than 1 year, according to the GOLD guidelines. 4. Current or previous smoker with a smoking history equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for 1 year). 5. Post-bronchodilator FEV1/forced vital capacity (FVC) <0.7 (70%) and FEV1 ≤ 70% of predicted normal (PN) value. 6. Documented use of a short-acting inhaled bronchodilator (β2-agonists or anticholinergics) as rescue medication within 6 months prior to study start. 7. A score of ≥ 2 on the modified medical research council (MMRC) dyspnea scale. 8. Documented history of ≥ 1 moderate or severe COPD exacerbation(s) that required treatment with systemic (oral, IM, IV) corticosteroids (a minimum 3 day course of an oral corticosteroid treatment or single depot corticosteroid injection), or hospitalization (defined as an inpatient stay or >24 hour stay in an observation area in the emergency department or other equivalent facility depending on the country and healthcare system) within 2-52 weeks before Visit 1 (i.e., not within the 14 days prior to Visit 1). A history of an exacerbation treated exclusively with antibiotics will not be considered adequate. **Exclusion Criteria:** 1. A history of asthma at or after 18 years of age. 2. Subjects with significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure (including significant cor pulmonale), uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator. 3. Known homozygous alpha-1 antitrypsin deficiency. 4. Any significant disease or disorder (e.g., gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results of the study, or the subject's ability to participate in the study. 5. A history of malignancy (except basal cell carcinoma) within the past 5 years. 6. Active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, or other active pulmonary diseases. 7. Subjects who have needed additions or alterations to their usual maintenance or change in formulation of rescue therapy for COPD due to worsening symptoms within the 14 days prior to Visit 1 and up to Visit 3. 8. CXR (frontal and lateral) with suspicion of pneumonia or other condition/abnormality that will require additional investigation/treatment, or

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	put the subject at risk because of participation in the study. 9. Risk factors for pneumonia: immune suppression (HIV, lupus) or other risk for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson's disease, myasthenia gravis, etc.). 10. Pneumonia not resolved within 14 days of Visit 1. 11. Moderate or severe COPD exacerbation that has not resolved within 14 days prior to Visit 1 or a moderate or severe COPD exacerbation that occurs between Visit 1 and Visit 2. 12. Long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. 13. Subjects who are currently in the intensive rehabilitation phase or scheduled to begin new participation (intensive rehabilitation phase) in a pulmonary rehabilitation program during the study or have started a new pulmonary rehabilitation program within 60 days of Visit 1. Subjects in the maintenance phase of pulmonary rehabilitation program are not excluded. 14. Treatment with oral, parenteral, or intra-articular corticosteroids within 4 weeks prior to Visit 1. 15. Omalizumab or any other monoclonal or polyclonal antibody therapy taken for any reason within 6 months prior to Visit 1.
Interventions	**Inhaler Device:** Budesonide/formoterol pMDI Formoterol turbohaler **Allowed Co-Medications:** albuterol/salbutamol for as-needed rescue, inhaled corticosteroids (ICS) at a dose of <=1000 μg·day
Outcomes	Primary Outcome Measures: The Rate of Moderate and Severe COPD Exacerbations Defined as: Worsening of ≥ 2 Major Symptoms or Worsening of 1 Major Symptom Together With ≥ 1 Minor Symptom for ≥ 2 Consecutive Days
Notes	**Funding:** AstraZeneca **Identifiers:** NCT02157935, D589UC00001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a validated computerized system RandAll version NG. Subjects will be randomized using the RAMOS IRT.
Allocation concealment (selection bias)	Low risk	a validated computerized system RandAll version NG. Subjects will be randomized using the RAMOS IRT.
Blinding of participants and personnel (performance bias)	High risk	open-label
Blinding of outcome assessment (detection bias)	High risk	open-label
Incomplete outcome data (attrition bias)	Unclear risk	Dropout was relatively low but uneven between two groups (BUD/FM 6.4%, FM 10.6%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

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Rossi 2014

Methods	**Design**:A Randomized, Double-blind, Parallel-group Study **Duration**: 26 weeks. **Location**: Argentina, Colombia, Italy, Malaysia, Mexico, Netherlands, Spain, Switzerland, United Kingdom
Participants	**Population:** FP/SAL (500/50) 518, SAL (50) 532 **Baseline Characteristics:** age 66.0 (SD8.49) F:M 180:401 **Inclusion Criteria:** ● Patients with moderate COPD (Stage II) ● Able to perform spirometry assessments ● Current or ex-smokers ● On treatment with the fixed-dose combination of salmeterol 50 µg/fluticasone propionate 500 µg MDDPI b.i.d. for the treatment of COPD for ≥ 3 months directly preceding Visit 1. **Exclusion Criteria:** ● Having had a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the past year. ● Having a history of, or current ECG abnormality ● Asthma
Interventions	**Inhaler Device:** Indacaterol SDDPI Salmeterol/fluticasone MDDPI **Allowed Co-Medications:** Salbutamol as rescue
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in One Second (FEV1) at 12 Weeks (Imputed With LOCF):
Notes	**Funding:** Novartis **Identifiers:** NCT01555138, CQAB149B2401

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Blinding of patients, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding.

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Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (IND 16.0%, SAL/FP 13.2%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Sarac 2016

Methods	**Design:** an open, prospective, randomized trial **Duration:** 52 weeks **Location:** Turkey
Participants	**Population:** FP/SAL (500/50) 22, Tio (18) 22 **Baseline Characteristics:** age 66.6 F:M 2/42 **Inclusion Criteria:** 35-80 years old, they had a smoking history of 10 pack-years or more, their FEV1 level was between 50% and 80% and they reported at least one exacerbation in the preceding year **Exclusion Criteria:** a prior diagnosis of asthma, previous documentation of bronchial hyperreactivity, history of allergy and/or atopy, presence of congestive heart failure or any other cardiopulmonary disease that might interfere with the patient's follow-up.
Interventions	**Inhaler Device:** salmeterol 50 μg/fluticasone 500 μg combination as dry powder inhaler (discus) tiotropium dry powder inhaler (handihaler) **Allowed Co-Medications:** short-acting bronchodilators as needed
Outcomes	COPD exacerbations, CAT score, 6 minute walk distance, adverse events.
Notes	**Funding:** unknown **Identifiers:** none

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Unclear risk	Not clear how many dropped out.
Selective reporting (reporting bias)	Unclear risk	Could not locate protocol to check outcome reporting

SCO100470 2006

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Methods	**Design**: multi-centre, randomised, double-blind, double dummy, parallel group design **Duration**: 6 months (+ run-in of unclear duration) **Location**: Conducted at 135 centres in 20 countries
Participants	**Population**: 1050 people were randomised to fluticasone (532) and fluticasone/salmeterol combination (518) **Baseline characteristics** Age (mean years): salm 63.7, flut/salm 63.5 % Male: salm 77.3, flut/salm 78.4 % FEV1 predicted: not reported Pack-years (mean): not reported **Inclusion criteria**: Male or female, aged 40-80 years with an established history of GOLD stage II COPD; poor reversibility of airflow obstruction (defined as _ 10% increase in FEV1 as a percentage of the normal predicted value); a minimum score of 2 on theModified Medical Research Council Dyspnoea Scale, and a smoking history of at least 10 pack years. In addition, subjects had to achieve a composite symptom score of 120 (out of 400 maximum score, measured using visual analogue scales) on at least 4 of the last 7 days of the run-in period, and to have a Baseline Dyspnoea Index (BDI) score of _ 7 units at Visit 2 **Exclusion criteria**: Subjects would be excluded if they had asthma or atopic disease, had a lung disease likely to confound the drug response other than COPD, had a recent exacerbation (within 4 weeks or screening or during run-in); were receiving long-term oxygen therapy or pulmonary rehabilitation or had taken tiotropium bromide, inhaled corticosteroids or anti-leukotriene medication within 14 days of visit 1
Interventions	1. Salmeterol 50 bid (LABA) 2. Salmeterol/fluticasone 50/250 bid (LABA/ICS) **Inhaler device**: Diskus accuhaler **Allowed co-medications**: Not reported
Outcomes	Transitional Dyspnoea Index (TDI), change frombaseline in trough FEV1, change from baseline in trough FVC and FVC/FEV1 ratio, TDI focal score, change from baseline in post-dose FEV1, FVC and FVC/FEV1 ratio, change from baseline in mean morning PEF, change from baseline in St George's Respiratory Questionnaire
Notes	**Funding**: GlaxoSmithKline **Identifier(s)**: SCO100470 (GSK)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System
Allocation concealment (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System

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Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind (participants and personnel/investigators)
Blinding of outcome assessment (detection bias)	Low risk	Investigators were blInded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias)	Low risk	Dropout low and even between groups (11.4% vs. 13.9%). The ITT (Intent to treat) Population (all subjects randomised and confirmed as having received at least one dose of double-blind study medication) was the primary population for analysis of all efficacy and health outcomes variables; the Safety Population (identical to the ITT Population) was used for analysis of all safety variables
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported and no expected outcomes were missing

SCO40034 2005

Methods	**Design:** randomised, double-blind, double-dummy, multi-centre, parallel-group exploratory study **Duration:** 12 weeks **Location:** 17 centres in the Netherlands
Participants	**Population:** 125 adults with a clinical history of moderate to severe COPD **Baseline Characteristics:** age mean 63.7 (SFC) 65.3 (TIO) F:M 18:43 (SFC), 14:50 (TIO), White 100% **Inclusion Criteria:** aged 40 to 80 years inclusive. Post-bronchodilator FEV1 less than 70% of predicted normal. Participants must have had a smoking history (current or former smokers) of more than 10 pack-years. **Exclusion Criteria:** within 4 weeks prior to visit 1; COPD exacerbation; received oral, parenteral or depot corticosteroids for a COPDexacerbation; received antibiotic therapy and/or been hospitalised for either a lower respiratory tract infection or for COPD exacerbation, or had any changes in their COPD medication
Interventions	**Inhaler Device:** 1. Combination of fluticasone 500 μg and salmeterol 50 μg twice a day via DISKUS inhaler plus placebo capsules to match TIO delivered once daily via the Handihaler inhaler 2. Tiotropium 18 μg once a day via Handihaler plus placebo to match FPS DISKUS combination product delivered twice daily **Allowed Co-Medications:** albuterol as rescue.
Outcomes	Since this study was primarily an exploratory study to compare the effect of SFC with TIO on clinical efficacy, a primary endpoint was not identified
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SCO40034 (GSK)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At randomisation (Visit 2/2A) all eligible subjects were randomly assigned to treatment by use of a Registration and MaterialOrdering System(RAMOS) which utilized an IVRS developed by GSK.
Allocation concealment (selection bias)	Low risk	At randomisation (Visit 2/2A) all eligible subjects were randomly assigned to treatment by use of a Registration and MaterialOrdering System(RAMOS) which utilized an IVRS developed by GSK.
Blinding of participants and personnel (performance bias)	Low risk	Double blind double dummy
Blinding of outcome assessment (detection bias)	Low risk	Someone who was not directly involved in the study received and documented all returned medication in a drug accountability log, a separate accountability log was maintained for each subject and subjects administered their own study medication without the investigator or site personnel being present. Subjects were unblinded only when knowledge of the treatment was essential for the clinical management or welfare of the subject. Cases of unblinding were to be reported and documented immediately.
Incomplete outcome data (attrition bias)	High risk	117/125 (94%) completed the study, but withdrawals were imbalanced with 1 (2%) from the FPS arm and 7 (11%) from the tiotropium arm.
Selective reporting (reporting bias)	High risk	Uable to locate protocol. Clinical Study Report not available through GSK.

SCO40041 2008

Methods	**Design**: Randomized, double-blind parallel group trial **Duration**: 3 years **Location**: 31 centres in the United States
Participants	**Population**: 186 people were randomised to salmeterol (94) and fluticasone/salmeterol combination (92) **Baseline characteristics** Age (mean years): salm 65.9, flut/salm 65.4 % Male: salm 62.8, flut/salm 59.8 % FEV1 predicted: not reported Pack-years (mean): not reported **Inclusion criteria**: Male/female subjects with an established clinical history of COPD (including a history of exacerbations), a baseline (pre-bronchodilator) FEV1 < 70% of the predicted normal value, a baseline (pre-bronchodilator) FEV1 / FVC ratio 70%, have at least one evaluable native hip and have a smoking history of 10 pack-years. **Exclusion criteria**: History of or evidence for metabolic bone diseases other than osteoporosis or osteopenia. Asthma, chronic lung disease other than

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	COPD. LTOT> 12 hours a day. Chronic steroid use.
Interventions	1. Salmeterol 50 bid (LABA) 2. Salmeterol/fluticasone 50/250 bid (LABA/ICS) **Inhaler device: Diskus** **Allowed co-medications:** albuterol/salbutamol, theophyllines, short and long acting anti-cholinergic agents, Combivent.
Outcomes	Change in bone mineral density at the lumbar spine and hip, adverse events, serious adverse events, fatal SAEs
Notes	**Funding**: GlaxoSmithKline **Identifier(s)**: NCT00355342, GSK SCO40041

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System
Allocation concealment (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind (participants and personnel/investigators)
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind (participants and personnel/investigators)
Incomplete outcome data (attrition bias)	Low risk	Withdrawal was very high in both groups (39 and 41%) but breakdown for withdrawals was similar between two groups.
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all outcomes were reported in the GSK Clinical Study Report.

Sharafkhaneh 2012

Methods	**Design**: Randomised, double-blind, double-dummy, parallel-group, multi-centre study **Duration**: 12 months (+ 2 week run-in) **Location**: 180 study sites in the United States, Central and South America, and South Africa
Participants	**Population**: 1219 participants were randomised to formoterol (404) and two doses of formoterol/budesonide combination (407 and 408) **Baseline characteristics** Age (mean years): form 62.5 ,form/bud320 63.8, form/bud160 62.8 % Male: form 56.8 ,form/bud320 64.4, form/bud160 64.7 % FEV1 predicted: form 37.5, form/bud320 37.9, form/bud160 37.6 Pack-years (mean): form 43, form/bud320 46, form/bud160 44 **Inclusion criteria**: Patients were current smokers or ex-smokers with a smoking history of 10 pack-years, aged 40 years, with a clinical diagnosis of COPDwith symptoms for >2 years. Patients were required to have a history of 1 COPD exacerbation requiring treatment with a course of systemic corticosteroids,

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	antibiotics, or both, within 12 months before screening (visit 1) and documented use of an inhaled short-acting bronchodilator as rescue medication. At screening, a pre-bronchodilator FEV1 of 50% of predicted normal and a pre-bronchodilator FEV1/FVC of <70% also were required. **Exclusion criteria**: Current, previous (within past 60 days), or planned enrolment in a COPD pulmonary rehabilitation program, treatment with oral corticosteroids, and incidence of a COPD exacerbation or any other significant medical diagnosis between the screening and randomisation visits
Interventions	1. Formoterol 9 BID (LABA) 2. Formoterol/budesonide 9/320 BID (LABA/ICS) 3. Formoterol/budesonide 9/160 BID (LABA/ICS) **Inhaler device**: 1, dry powder; 2 and 3 pressurized metered dose **Allowed co-medications**: Albuterol pMDI 90 mg 2 inhalations) was provided for as needed use during screening and run-in, and throughout the study
Outcomes	COPD exacerbations, FEV1, FVC, morning and evening PEF, diary card symptoms, rescue medication use, BODE index, exercise capacity, health-related quality of life (SGRQ), adverse events
Notes	**Funding**: AstraZeneca **Identifier(s)**: NCT00419744, D589CC00003 (AstraZeneca)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignments were made sequentially by interactive voice response system following a computer generated allocation schedule produced in advance
Allocation concealment (selection bias)	Low risk	Assignments were made sequentially by interactive voice response system following a computer generated allocation schedule produced in advance
Blinding of participants and personnel (performance bias)	Low risk	To maintain patient and investigator blinding, all active treatments were provided in blinded treatment kits. Patients in the budesonide/formoterol pMDI groups received a placebo DPI and those in the formoterol DPI group received a placebo pMDI
Blinding of outcome assessment (detection bias)	Low risk	Investigators were blInded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias)	High risk	The withdrawal rates were high and relatively uneven (BUD/FM 320/9 28.7% BUD/FM160/9 28.9%, FM 9 32.9%), especially compared to the low event rates for the outcomes of interest.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported in detail

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Singh 2014

Methods	**Design:** double-blind, parallel-group, active- and placebo-controlled, multicentre Phase III study **Duration:** 24 weeks **Location:** Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Korea, Republic of, Netherlands, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Ukraine, United Kingdom
Participants	**Population:** ACL/FM (400/12) 385, ACL (400) 385, FM (12) 384 **Baseline Characteristics:** age 63.2 (SD 8.0), F:M 560:1169 **Inclusion Criteria:** ● Adult male or non-pregnant, non-lactating female aged ≥ 40. Women of childbearing potential are allowed to enter the trial if they show to have a negative serum pregnancy test at the Screening Visit and are using, during the last two months before the Screening Visit, at least one medically approved and highly effective method of birth control defined as those which result in a low failure rate (i.e less than 1% per year) when used consistently and correctly such as implants, injectables, oral contraceptives combined with at least one barrier method, hormonal Intrauterine Devices (IUDs), sexual abstinence or vasectomy of the partner. ● Current or ex-cigarette smoker, with a smoking history of at least 10 pack-years. ● Patient with a clinical diagnosis of stable COPD according to the Global Initiative for Chronic Lung Disease "GOLD" Guidelines at the Screening Visit. ● Patient whose FEV1/FVC (Forced Vital Capacity) at the Screening Visit measured between 10-15 minutes post inhalation of 400 micrograms of salbutamol is < 70% (i.e., 100 x Post-salbutamol FEV1 /FVC < 70%). ● Patient with a diagnosis of moderate to severe COPD according to the GOLD Guidelines classification (stages II and III) at the Screening Visit: FEV1 measured between 10-15 minutes post inhalation of 400 micro grams of salbutamol is 30% < FEV1 < 80% of the predicted normal value (i.e., 100 x Post-salbutamol FEV1/ Predicted FEV1 must be < 80% and ≥ 30%). ● Patient must be able to perform repeatable pulmonary function testing for FEV1 according to American Thoracic Society/European Respiratory Society "ATS/ERS" 2005 criteria at Screening Visit. ● Patient who is eligible and able to participate in the trial and who consent to do so in writing after the purpose and nature of the investigation have been explained. **Exclusion Criteria:** ● 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. ● Patient hospitalised for COPD exacerbation within 3 months prior to Screening Visit. ● Clinically significant respiratory conditions defined as:Known active tuberculosis.History of interstitial lung or massive pulmonary thromboembolic disease.Pulmonary resection or lung volume reduction surgery within 12 months prior to Screening Visit.History of lung

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	transplantation.History of bronchiectasis secondary to respiratory diseases others than COPD (e.g., cystic fibrosis, Kartagener's syndrome, etc).Known a1-antitrypsin deficiency. ● Patients who in the Investigator's opinion might have needed to start a pulmonary rehabilitation program during the study and/or patients who started/finished it within 3 months prior to screening. ● Use of long-term oxygen therapy (≥ 15 hours/day). ● Patients who did not maintain regular day/night, waking/sleeping cycles including night shift workers (eg, history of sleep apnoea syndrome, any condition related to sleep disturbances such as restless-legs syndrome or somnambulism). ● Clinically significant cardiovascular conditions defined as:Myocardial infarction within the 6 months prior to screening.Thoracic surgery within 12 months prior to screening.Unstable angina or unstable arrhythmia which had required changes in the pharmacological therapy or other intervention within 12 months prior to screening, or newly diagnosed arrhythmia within the previous 3 months prior to screening.Hospitalisation within 12 months prior to screening for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity and presence of symptoms at rest) as per the New York Heart Association. ● Patients (with or without pharmacological therapy) with resting systolic blood pressure (SBP)≥ 200 mmHg, a resting diastolic blood pressure (DBP) ≥ 120 mmHg, or a resting heart rate ≥ 105 beats per minute (bpm) at screening and at Visit 1 prior to randomisation. ● Patients with interval corrected for heart rate "QTc" [calculated according to formulae (QTc=QT/RR1/2) > 470 msec as indicated in the centralised reading report assessed at Screening Visit. ● Patients with clinically relevant abnormalities in the clinical laboratory tests, ECG parameters (other than QT interval corrected using Bazett's formula [QTcB]) or in the physical examination at screening, if the abnormality defined a disease state listed as exclusion criteria, except for those related to COPD. ● Patients with a history of hypersensitivity reactions to inhaled anticholinergics, sympathomimetic amines, or inhaled medication or any component thereof (including report of paradoxical bronchospasm). Patients with known narrow-angle glaucoma, symptomatic bladder neck obstruction or acute urinary retention. ● Patients with symptomatic non-stable prostate hypertrophy. (However, patients with well-controlled, stable, asymptomatic benign prostatic hypertrophy were not excluded). ● Patients with known uncontrolled history of infection with human immunodeficiency virus and/or active hepatitis. ● Current diagnosis of cancer other than basal or squamous cell skin cancer. ● Life expectancy of less than 1 year. ● Patients with any other serious or uncontrolled physical or mental dysfunction that, as judged by the Investigator, could have placed the patient at higher risk from his/her participation in the study, could have confounded the results of the study, or is likely to prevent the patient from complying with the requirements of the study, or completing the study. ● Patients with a history (within 2 years prior to screening) of drug and/or

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	alcohol abuse that might have prevented study compliance based on the Investigator judgment. ● Patients unlikely to be cooperative (eg, take the medication, complete the Patient Diaries or attend the clinic at the required times). ● Patients unable to properly use a DPI or pMDI inhaler device or to perform spirometry measurements. ● Patients previously randomised in a study involving aclidinium bromide/formoterol FDC. ● Patients previously randomised in a study involving aclidinium bromide monotherapy except when participation finished at least 6 months before screening. ● Patients treated with any investigational drug within 30 days (or 6 half-lives, whichever is longer) prior to screening. ● Patients who intended to use any concomitant medication not permitted by this protocol or who had not undergone the required washout period for a particular prohibited medication. ● Patients unable to give consent, or patients of consenting age but under guardianship, or vulnerable patients. ● Patients employed, or relatives of employees at the study centre, Almirall or Forest Laboratories. ● Any other conditions that, in the Investigator's opinion, might have indicated the patient to be unsuitable for the study.
Interventions	**Inhaler Device:**breath-actuated, multiple-dose dry powder inhaler Aclidinium Bromide/Formoterol Fumarate Aclidinium Bromide Formoterol Fumarate **Allowed Co-Medications:** as needed salbutamol, inhaled corticosteroids
Outcomes	Primary Outcome Measures: Change From Baseline in 1-hour Morning Post-dose Forced Expiratory Volume in One Second (FEV1), Change From Baseline in Morning Pre-dose (Trough) Forced Expiratory Volume in One Second (FEV1)
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01462942, M/40464/30 (AstraZeneca)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a centralised interactive voice response system
Allocation concealment (selection bias)	Low risk	a centralised interactive voice response system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Major adverse cardiovascular events (MACE;a composite of total cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) were evaluated

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		and classified by an independent, blinded adjudication committee.
Incomplete outcome data (attrition bias)	Low risk	Dropout low and even among the groups of interest (ALC/FM (400/12) 8.8 %, ACL (400) 13.0 %, FM (12) 11.7%).
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported in detail.

Singh 2015 a&b

Methods	**Design:** A Randomised, Double-blind, Placebo- and Active-controlled Parallel Group Study **Duration:** 12 weeks **Location:** See Singh 2015a and 2015b
Participants	**Population:** See Singh 2015a and 2015b **Baseline Characteristics:** See Singh 2015a and 2015b **Inclusion Criteria:** ● Diagnosis chronic obstructive pulmonary disease ● Relatively stable airway obstruction with post FEV1 >=30 and < 80% predicted normal and post FEV1/ FVC < 70% ● Male or female patients, 40 years of age or more ● Smoking history more than 10 pack years **Exclusion Criteria:** ● Significant diseases other than COPD ● History of asthma ● COPD exacerbation in previous 3 months ● Completion of pulmonary rehabilitation program within previous 6 weeks or current participation in pulmonary rehabilitation program. ● Pregnant or nursing women ● Patients unable to comply with pulmonary medication restrictions
Interventions	tiotropium/olodaterol tiotropium **Inhaler Device:** Respimat Inhaler **Allowed Co-Medications:** as needed salbutamol, inhaled corticosteroid
Outcomes	Primary Outcome Measures: FEV1, SGRQ score.
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01964352, 1237.25, NCT02006732, 1237.26

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind

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Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (See Singh 2015a and 2015b).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Singh 2015a

Methods	**Design:** A Randomised, Double-blind, Placebo- and Active-controlled Parallel Group Study **Duration:** 12 weeks **Location:** Belgium, Canada, Czech Republic, Denmark, Finland, Germany, South Africa, Spain, United Kingdom, United States
Participants	**Population:** Tio/Olo (5/5) 203, Tio (5) 203 **Baseline Characteristics:** age 64.8 (SD 8.4) F:M 331:481 **Inclusion Criteria:** ● Diagnosis chronic obstructive pulmonary disease ● Relatively stable airway obstruction with post FEV1 >=30 and < 80% predicted normal and post FEV1/ FVC < 70% ● Male or female patients, 40 years of age or more ● Smoking history more than 10 pack years **Exclusion Criteria:** ● Significant diseases other than COPD ● History of asthma ● COPD exacerbation in previous 3 months ● Completion of pulmonary rehabilitation program within previous 6 weeks or current participation in pulmonary rehabilitation program. ● Pregnant or nursing women ● Patients unable to comply with pulmonary medication restrictions
Interventions	tiotropium/olodaterol tiotropium **Inhaler Device:** Respimat Inhaler **Allowed Co-Medications:** as needed salbutamol, inhaled corticosteroid
Outcomes	Primary Outcome Measures: FEV1, SGRQ score.
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01964352, 1237.25

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind

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Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (tio 5.4%, tio/olo 4.1%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Singh 2015b

Methods	**Design:** A Randomised, Double-blind, Placebo- and Active-controlled Parallel Group Study **Duration:** 12 weeks **Location:** Australia, Austria, Canada, Germany, Greece, New Zealand, Norway, Slovakia, South Africa, Sweden, United States
Participants	**Population:** Tio/Olo (5/5) 202, Tio (5) 203 **Baseline Characteristics:** age 64.6 (SD 8.4) **Inclusion Criteria:** ● Diagnosis chronic obstructive pulmonary disease ● Relatively stable airway obstruction with post FEV1 >=30 and < 80% predicted normal and post FEV1/ FVC < 70% ● Male or female patients, 40 years of age or more ● Smoking history more than 10 pack years **Exclusion Criteria:** ● Significant diseases other than COPD ● History of asthma ● COPD exacerbation in previous 3 months ● Completion of pulmonary rehabilitation program within previous 6 weeks or current participation in pulmonary rehabilitation program. ● Pregnant or nursing women ● Patients unable to comply with pulmonary medication restrictions
Interventions	tiotropium/olodaterol tiotropium **Inhaler Device:** Respimat Inhaler **Allowed Co-Medications:** as needed salbutamol, inhaled corticosteroid.
Outcomes	Primary Outcome Measures: FEV1, SGRQ score.
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02006732, 1237.26

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind

Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low in both included groups (tio 2.0%, tio/olo 5.9%).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Singh 2015c

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 12 weeks **Location:** 8 countries (mainly EU). 79 centers.
Participants	**Population:** UMEC/VI 358 FP/SAL 358 **Baseline Characteristics:** Age: 61.6 years (SD 8.0). Male/female: 515/201. %pred FEV1: 50.6% (SD 10.7%). **Inclusion Criteria:** %pred FEV1 30% to 70%, mMRC ≥ 2, without recent exacerbation. **Exclusion Criteria:** Pregnancy/breast feeding, asthma, other respiratory disorders, clinically significant co-morbidities, hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid, history of COPD Exacerbation: A documented history of at least one COPD exacerbation in the 12 months prior to Visit 1, recent lung resection <12 months, long-term oxygen therapy > 12 hours a day, drug or alcohol abuse.
Interventions	umeclidinium/vilanterol (62.5/25 μg). LAMA/LABA salmeterol/fluticasone (50/500 μg) twice daily. LABA/ICS **Inhaler Device:** Dry white powder NDPI (UMEC/VI) and ACCUHALER/DISKUS (FP/SAL). **Allowed Co-Medications:** short-acting inhaled beta-agonists as rescue.
Outcomes	Primary outcome: change from baseline in 0 to 24 h weighted mean serial FEV1 at day 84.
Notes	**Funding:** GlaxoSmithKline. **Identifiers:** NCT01822899, DB2116134 (GSK)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Allocation concealment (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Blinding of participants and personnel (performance bias)	Low risk	Study was double-blinded

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Blinding of outcome assessment (detection bias)	Low risk	The investigator and treating physician were kept blinded unless an emergency arouse.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rate was low and even between active comparators, 6.7% in umeclidinium/vilanterol arm and 5.0% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Szafranski 2003

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group, multi-centre study **Duration**: 12 months (+ 2 weeks run-in period) **Location**: 89 centres from 11 countries
Participants	**Population**: 812 participants were randomised to formoterol (201), budesonide (198), formoterol/budesonide combination (208), and placebo (205) **Baseline characteristics** Age (mean years): form 63, bud 64, form/bud 64, pbo 65 % Male: form 76, bud 80, form/bud 76, pbo 83 % FEV1 predicted: form 36, bud 37, form/bud 36, pbo 36 Pack-years (mean): form 45, bud 44, form/bud 44, pbo 45 **Inclusion criteria**: males and females aged 40 and older; symptoms for 2+ years; history of at least 10 pack-years **Exclusion criteria**: history of asthma or seasonal rhinitis before 40 years of age; relevant cardiovascular disorders; use of beta-blockers; current respiratory tract disorders other than COPD or any other significant diseases or disorders; requiring regular use of oxygen therapy; exacerbation during run-in
Interventions	1. Formoterol 12 bid (LABA) 2. Budesonide 400 bid (ICS) 3. Formoterol/budesonide 9/320 bid (LABA/ICS) 4. Placebo (PBO) **Inhaler device**: Dry powder turbuhaler **Allowed co-medications**: terbutaline (0.5 mg) as reliever. Disallowed medication included parenteral steroids, oral steroids, antibiotics and nebulised treatment from 4 weeks before; inhaled steroids from 2 weeks before; inhaled long-acting beta2-agonists from 48 hours before; inhaled short-acting beta2-agonists from 6 hours before; other bronchodilators from 6 to 48 hours before
Outcomes	St George's Respiratory Questionnaire (SGRQ), COPD exacerbations, FEV1, vital capacity, morning and evening PEF, diary card data
Notes	**Funding**: AstraZeneca **Identifier(s)**: SD-039-CR-0629 (AstraZeneca)

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A total of 812 patients were randomised [no other details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Double-blind [presumed subject and investigator]
Blinding of outcome assessment (detection bias)	Low risk	Investigators were blinded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias)	High risk	Withdrawal high and uneven between groups (formoterol 32%, formoterol/budesonide 28%). Higher withdrawal rate due to COPD deterioration with fromoterol (14%) vs formoterol/budesonide (10%). An intention-to-treat analysis was used
Selective reporting (reporting bias)	High risk	Quality of life [primary] stated as outcome but not reported in enough detail to include in meta-analysis. Safety and exacerbation outcomes were not reported in enough detail.

Tashkin 2008

Methods	**Design**: randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study **Duration**: 6 months (+ 2 weeks run-in period) **Location**: 194 centres in the USA, Czech Republic, the Netherlands, Poland and South Africa
Participants	**Population**: 1704 participants were randomised to formoterol (284), budesonide (275), three doses of formoterol/budesonide combination (281, 277 and 287, one of which was not included in the review as they were delivered in separate inhalers), and placebo (300) **Baseline characteristics** Age (mean years): form 63.5, bud 63.4, form/bud160 63.6, 1form/bud320 63.1, pbo 63.2 % Male: form 65.5, bud 67.6, form/bud160 64.4, 1form/bud320 67.9, pbo 69 % FEV1 predicted: form 39.6, bud 39.7, form/bud160 39.9, 1form/bud320 39.1, pbo 41.3 Pack-years (median): form 40, bud 41, form/bud160 40, 1form/bud320 40, pbo 40 **Inclusion criteria**: male and female current or former smokers; history of at least 10 pack-years; clinical diagnosis of COPD; 40+ years; symptoms for longer than 2 years; at least one exacerbation treated with oral corticosteroids and/or antibacterials within 1 to 12 months before screening **Exclusion criteria**: history of asthma or seasonal rhinitis before age 40; significant/ unstable cardiovascular disorder; significant respiratory tract disorder other than COPD; homozygous alpha1-antitrypsin deficiency or other clinically significant co morbidities precluding participation

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Interventions	1. Formoterol 12 bid (LABA) 2. Budesonide 320 bid (ICS) 3. Formoterol/budesonide 9/160 bid in one inhaler (LABA/ICS) 4. Formoterol/budesonide 9/320 bid in one inhaler (LABA/ICS) 5. Placebo (PBO) **Inhaler device**: dry powder **Allowed co-medications**: Allowed medications were ephedrine-free antitussives and mucolytics; nasal corticosteroids; stable-dose non-nebulised ipratropium; cardioselective beta-adrenoceptor antagonists; salbutamol as rescue; oral steroids, xanthines, inhaled beta-agonists and ipratropium as medication for exacerbations. Medications disallowed during the study period were long-acting anticholinergics; inhaled LABAs or SABAs (other than salbutamol); oral beta-adrenoreceptor agonists; ephedrine; leukotriene receptor agonists and xanthine derivatives except for short-term use
Outcomes	St George's Respiratory Questionnaire (SGRQ) including number of people reaching threshold for minimal clinically important difference from baseline (4 units), COPD exacerbations per patient year, pre-dose fFEV1 and 1-hour post-dose FEV1, dyspnoea, morning and evening PEF
Notes	**Funding**: AstraZeneca **Identifier(s)**: NCT00206154, D5899C00002 (SHINE)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligable patients were randomized in balanced blocks according to a computer-generated randomisation scheme at each site
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	To maintain blinding, patients received both a pressurized metered-dose inhaler (pMDI) and a dry powder inhaler (DPI) containing either active treatment or placebo (PL), or combinations of active treatment and placebo, as appropriate
Blinding of outcome assessment (detection bias)	Low risk	double-blind, double-dummy. Investigators were blInded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias)	High risk	Withdrawal rates were higher with formoterol (21.5% formoterol, 14.1% BUD/FM 320/9, and 13.5% BUD/FM 160/9) and more patients were discontinue due to adverse event with formoterol (12% formoterol, 7.6% BUD/FM 320/9, and 7.1% BUD/FM 160/9))'The efficacy analysis set included all randomised patients who received at least one dose of study medication and contributed sufficient data for at least one co-primary or secondary efficacy endpoint'
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported in full and included in the quantitative synthesis

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Tashkin 2009

Methods	**Design:** randomised, double-blind, active-control, parallel-group trial **Duration:** 12 weeks **Location:** 35 centres across the US, of which the majority were primary care centres
Participants	**Population:** 255 adults with a clinical history of COPD randomised to tiotropium + formoterol (124 participants) or tiotropium (131 participants) **Baseline Characteristics:** mean age 64 years. COPD severity mild to severe. 67% men **Inclusion Criteria:** men and non-pregnant women aged > 40 years who had a clinical history of COPD. Each participant had a post-bronchodilator FEV1 < 70% and > 30% predicted normal or > 0.75 L, whichever was less, at run-in, and FEV1/FVC < 0.70 at screening and run-in. Daytime or night-time (or both) symptoms of COPD, including dyspnoea, must have been present on ≥ 4 of the 7 days before the baseline visit **Exclusion Criteria:** current or previous history of asthma or other significant medical condition 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 h/day), initiation of pulmonary rehabilitation within the previous 3 months, the requirement for nasal continuous positive airway pressure or bilevel positive airway pressure, clinically significant lung disease other than COPD (i.e. bronchiectasis, sarcoidosis, pulmonary fibrosis, TB), sleep apnoea, chronic narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder neck obstruction, and the need for chronic or prophylactic antibiotic therapy
Interventions	**Inhaler Device:** ● formoterol (Foradil Aerolizer) 12 μg twice daily and tiotropium (HandiHaler) 18 μg once daily in the morning delivered via 2 separate inhalers ● formoterol-matched placebo twice daily and tiotropium 18 μg once daily delivered via 2 separate inhalers **Allowed Co-Medications:** as needed albuterol, inhaled corticosteroid
Outcomes	Primary: normalised AUC for FEV1 measured 0-4 h post-morning dose (FEV1 AUC 0-4 h) at the last visit Secondary: changes frombaseline in trough (mean of values obtained 10 and 30min pre-dose) FEV1 and FVC, weeklymorning and evening PEF, symptom severity scores, TDI, and health related quality of life (SGRQ) scores, number and severity of exacerbations, the global therapeutic response, discontinuations because of worsening COPD, and % participants achieving targeted improvements in the SGRQ and TDI scores, use of rescue albuterol, nocturnal awakenings requiring rescue albuterol, changes in study or concomitant medications, and adverse events
Notes	**Funding:** Schering Corporation **Identifiers:** NCT00139932

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised sequentially as they qualified for the study according to a pre-generated computer code labelled on the medication kit
Allocation concealment (selection bias)	Low risk	Participants were randomised sequentially as they qualified for the study according to a pre-generated computer code labelled on the medication kit
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	The number of withdrawals in the different groups was relatively low but uneven (14.5% with LABA + tiotropium, 6.1% with tiotropium + placebo)
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Tashkin 2012

Methods	**Design**: randomised, double-blind, placebo-controlled trial **Duration**: 6 months (+ 2 weeks run-in period) **Location**: 131 centres located in South America, Asia, Africa, Europe andNorth America
Participants	**Population**: 1055 participantswere randomised to formoterol (209),mometasone (210), two doses of formoterol/mometasone combination (217 and 207), and placebo (212) **Baseline characteristics** Age (mean years): form 59.6, mom 59.8, form/mom 400 59.7, form/mom 200 60.9, pbo 58.8 % Male: form 72.7, mom 78.1, form/mom400 78.8, form/mom200 77.8, pbo 80.2 % FEV1 predicted: not reported Pack-years (mean): form 40.3, mom 40.0, form/mom 400 39.7, form/mom 200 41.7, pbo 40.3 **Inclusion criteria**: males and females aged 40 and older; history of at least 10 packyears; moderate to severe COPD for at least 2 years; predicted FEV1 between 25% and 60% normal **Exclusion criteria**: exacerbation in the four weeks before randomisation; significant medical illness; diagnosis of asthma, lung cancer or alpha1-antitrypsin deficiency, lobectomy, pneumonectomy, lung volume reduction surgery or ocular problems
Interventions	1. Formoterol 10 bid (LABA) 2. Mometasone 400 bid (ICS) 3. Formoterol/mometasone 10/400 bid (LABA/ICS) 4. Formoterol/mometasone 10/200 bid (LABA/ICS)

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	5. Placebo (PBO) **Inhaler device**: metered dose **Allowed co-medications**: Participants were given open-label, short-acting beta2-agonist (SABA)/short-acting anticholinergic fixed-dose combination to use as relief medication throughout the study. All long-acting COPD treatments (LABA, ICS, LABA/ICS FDC or long-acting anticholinergics), supplemental oxygen and beta-blocking agents were not allowed during the study period
Outcomes	St George's Respiratory Questionnaire (SQRQ), reported as both final scores and the number of people experiencing aMCID(improvement or worsening by 4 units), COPD exacerbations, serial FEV1 post-dose, standardised FEV1 area under the curve, systemic and ocular effects
Notes	**Funding**: Merck & Co/Schering-Plough **Identifier(s)**: NCT00383435, NCT00383721, P04229AM4, P04230AM4

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using SAS.Randomisation was stratified according to the subject's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Blinding of participants and personnel (performance bias)	Low risk	Protocol describes the study masking as double-blind (subject, investigator)
Blinding of outcome assessment (detection bias)	Low risk	A prospective statistical analysis plan for evaluation of pooled results was completed before unblinding of the two studies.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rates were relatively low and even among active comparators of interested and even (18.9% in MF/F 400/10, 18.4% in MF/F 200/10, and 17.7% in formoterol)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Tashkin 2012a

Methods	See Tashkin 2012
Participants	See Tashkin 2012
Interventions	See Tashkin 2012
Outcomes	See Tashkin 2012
Notes	**Funding:** Merck & Co/Schering-Plough **Identifiers:** NCT00383435, Merck P04230AM4

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using SAS.Randomisation was stratified according to the subject's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Blinding of participants and personnel (performance bias)	Low risk	Protocol describes the study masking as double-blind (subject, investigator)
Blinding of outcome assessment (detection bias)	Low risk	A prospective statistical analysis plan for evaluation of pooled results was completed before unblinding of the two studies.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rates were relatively low among active comparators of interested and even (18.9% in MF/F 400/10, 18.4% in MF/F 200/10, and 17.7% in formoterol)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Tashkin 2012b

Methods	See Tashkin 2012
Participants	See Tashkin 2012
Interventions	See Tashkin 2012
Outcomes	See Tashkin 2012
Notes	**Funding:** Merck & Co/Schering-Plough **Identifiers:** NCT00383721, Merck P04229AM4

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using SAS.Randomisation was stratified according to the subject's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomized treatment assignment was provided to the investigative site by means of an interactive voice response system at the time subjects were randomized
Blinding of participants and personnel (performance bias)	Low risk	Protocol describes the study masking as double-blind (subject, investigator)
Blinding of outcome assessment (detection bias)	Low risk	A prospective statistical analysis plan for evaluation of pooled results was completed before unblinding of the two studies.

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Incomplete outcome data (attrition bias)	Low risk	Withdrawal rates were relatively low among active comparators of interested and even (18.9% in MF/F 400/10, 18.4% in MF/F 200/10, and 17.7% in formoterol)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

To 2012

Methods	**Design:** Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study **Duration:** 12 weeks **Location:** Hong Kong, India, Japan, Korea, Republic of, Singapore, Taiwan
Participants	**Population:** IND (150) 114, IND(300) 116 **Baseline Characteristics:** age 66.7 (SD 8.38) F:M 12:335 **Inclusion Criteria:** Diagnosis of moderate-to-severe chronic obstructive pulmonary disease (COPD), as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and: 1. Smoking history of at least 20 pack-years. 2. Post-bronchodilator forced expiratory volume in 1 second (FEV1) < 80% and ≥ 30% of the predicted normal value. 3. Post-bronchodilator FEV1/FVC (forced vital capacity) < 70%. **Exclusion Criteria:** ● Patients who have been hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during the 14 day run-in period prior to randomization. ● Patients requiring long-term oxygen therapy (> 15 hours a day) for chronic hypoxemia. ● Patients who have had a respiratory tract infection within 6 weeks prior to screening. ● Patients with concomitant pulmonary disease. ● Patients with a history of asthma. ● Patients with diabetes Type I or uncontrolled diabetes Type II. ● Any patient with lung cancer or a history of lung cancer. ● Any patient with active cancer or a history of cancer with less than 5 years disease-free survival time. ● Patients with a history of long QT syndrome or whose QTc interval (Bazett's) measured at screening or randomization is prolonged. ● Patients who have been vaccinated with live attenuated vaccines within 30 days prior to screening or during the run-in period. ● Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements.
Interventions	**Inhaler Device:** Indacaterol: powder filled capsules with a single dose dry powder inhaler (SDDPI). **Allowed Co-Medications:** as needed salbutamol, ICS.
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in 1 Second (FEV1) 24 Hours Post-dose at the End of Treatment (Week 12 + 1 Day, Day 85)

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Notes	**Funding:** Novartis **Identifiers:** NCT00794157, CQAB149B1302

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized (1:1:1) using a validated automated system
Allocation concealment (selection bias)	Low risk	Patients were randomized (1:1:1) using a validated automated system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low and even in both included groups (8.8% in IND 150 and 8.6% in IND 300 group).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Troosters 2016

Methods	**Design:** Randomised, Partially Double-blinded, Placebo-controlled Parallel Group Trial **Duration:** 12 weeks **Location:** Australia, Austria, Belgium, Canada, Denmark, Germany, New Zealand, Poland, Portugal, United Kingdom, United States
Participants	**Population:** Tio/Olo (5/5) 76, Tio(5) 76 **Baseline Characteristics:** age 64.8 (SD 6.6) F:M 103:200 **Inclusion Criteria:** ● All patients must sign an informed consent consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) - Good Clinical Practice (GCP) guidelines prior to participation in the trial, which includes medication washout and restrictions. ● All patients must have a diagnosis of chronic obstructive pulmonary disease and must meet the following spirometric criteria: Patients must have relatively stable airway obstruction with a post-bronchodilator forced expiratory volume in one second >=30% and <80% of predicted normal; Global Initiative for Chronic Obstructive Lung Disease grade II - III, and a post-bronchodilator Tiffeneau index <70% at Visit 1. ● Male or female patients, aged >=40 years and <=75 years. ● Patients must be current or ex-smokers with a smoking history of more than 10 pack years. Patients who have never smoked cigarettes must be excluded. **Exclusion Criteria:** ● Patients with a significant disease other than chronic obstructive pulmonary

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	disease. ● Patients with clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis. ● Patients with a history of asthma. ● A diagnosis of thyrotoxicosis. ● A diagnosis of paroxysmal tachycardia (>100 beats per minute). ● A history of myocardial infarction within 1 year of screening visit. ● Unstable or life-threatening cardiac arrhythmia. ● Hospitalized for heart failure within the past year. ● Known active tuberculosis. ● A malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years. ● A history of life-threatening pulmonary obstruction and patients with chronic respiratory failure. ● A history of cystic fibrosis. ● Clinically evident bronchiectasis. ● A history of significant alcohol or drug abuse. ● Any contraindications for exercise testing. ● Patients who have undergone thoracotomy with pulmonary resection. ● Patients being treated with any oral ß-adrenergics. ● Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than six weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day. ● Patients who regularly use daytime oxygen therapy for more than one hour per day and in the investigators opinion will be unable to abstain from the use of oxygen therapy during clinic visits. ● Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit or patients who are currently in a pulmonary rehabilitation program. ● Patients who have a limitation of exercise performance as a result of factors other than fatigue or exertional dyspnoea, such as arthritis in the leg, angina pectoris or claudication or morbid obesity. ● Patients who have taken an investigational drug within one month or six half lives (whichever is greater) prior to screening visit. ● Patients with known hypersensitivity to ß-adrenergics drugs, anticholinergic drugs, benzalkonium chloride, disodium edentat, or any other component of the Respimat® inhalation solution delivery system. ● Pregnant or nursing women. ● Women of childbearing potential not using highly effective methods of birth control. ● Patients who have previously been randomized in this study or are currently participating in another study.
Interventions	tiotropium+olodaterol tiotropium **Inhaler Device:** Respimat Inhaler **Allowed Co-Medications:** salbutamol as rescue, inhaled corticosteroids
Outcomes	Primary Outcome Measures:Endurance Time During Endurance Shuttle Walk Test (ESWT) to Symptom Limitation After 8 Weeks

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Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02085161

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	partially double-blinded, as it was not possible to blind the group receiving exercise training
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	High risk	Dropout was relative low but uneven between included arms (Tio 13.2%, Tio/Olo 6.6%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Vincken 2014

Methods	**Design:** Multi-center, Randomized, Double-blind, Parallel Group Study **Duration:** 12 weeks **Location:** Belgium, Bulgaria, Greece, Hungary, Ireland, Russian Federation, Slovakia, Spain, Turkey, United Kingdom
Participants	**Population:** IND + GLyco (110/50) 226, IND (150) 221 **Baseline Characteristics:** age 63.7 (SD 8.07) F:M 81/366 **Inclusion Criteria:** ● Patients with moderate to severe stable Chronic Obstructive Lung Disease (COPD) Stage II or Stage III according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. ● Patients with a post-bronchodilator forced expiratory volume in 1 second (FEV1) ≥ 30 % and/or <80 % of the predicted normal, and a post-bronchodilator FEV1/Forced Vital Capacity (FVC) < 0.70 at screening. ● Current or ex-smokers who have a smoking history of at least 10 pack years ● Symptomatic patients according to daily diary data. **Exclusion Criteria:** ● Pregnant or nursing (lactating) women. ● Women of child-bearing potential unless using adequate contraception. ● Patients with Type I or uncontrolled Type II diabetes. ● Patients with a history of long time interval between start of Q wave and end of T wave in the heart's electrical cycle (QT) syndrome or whose QT corrected for heart rate (QTc) measured at screening (Visit 2) (Fridericia's method) is prolonged ● Patients with paroxysmal (e.g. intermittent) atrial fibrillation ● Patients who have a clinically significant electrocardiogram (ECG) or laboratory abnormality at screening (Visit 2)

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Interventions	**Inhaler Device:** NVA237 (glyco) 50 µg and indacaterol 150 µg supplied as blistered capsules for inhalation. **Allowed Co-Medications:** as needed salbutamol, Inhaled corticosteroids
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume at 1 Second (FEV1) [Time Frame: 12 weeks]
Notes	**Funding:** Novartis **Identifiers:** NCT01604278, CNVA237A2316

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An automated, interactive, voice-response technology
Allocation concealment (selection bias)	Low risk	An automated, interactive, voice-response technology
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Patients, investigators, site staff, persons performing the assessments and data analysts were blind to the identity of the treatment from the time of randomization.
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively low and even in both included groups (6.2% in IND + GLyco and 5.8% in IND group).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Vogelmeier 2008

Methods	**Design**: randomised, partially blinded, placebo-controlled trial **Duration**: 6 months (+ 2 weeks run-in) **Location**: outpatient and specialist clinics at 86 centres in 8 countries
Participants	**Population**: 640 participants were randomised to formoterol (210), tiotropium (221), and placebo (209) **Baseline characteristics** Age (mean years): form 61.8, tio 63.4, pbo 62.5 % Male: form 75.7, tio 79.2, pbo 77.5 % FEV1 predicted: form 51.6, tio 51.6, pbo 51.1 Pack-years (mean): form 35.4, tio 38.6, pbo 40.1 **Inclusion criteria**: males and females aged 40 and older; history of at least 10 packyears; FEV1 < 70% predicted normal; FEV1/FVC < 70% **Exclusion criteria**: respiratory tract infection or hospitalised for an acute exacerbation within the month before screening; clinically significant condition other than COPD such as ischaemic heart disease

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Interventions	1. Tiotropium 18 qd (LAMA) + Formoterol 10 bid (LABA) 2. Formoterol 10 bid (LABA) 3. Tiotropium 18 qd (LAMA) - open-label 4. Placebo (PBO) **Inhaler device**: Multi-dose dry powder inhaler - tiotropium open label **Allowed co-medications**: salbutamol as rescue (but not in the 8 hours before a study visit); inhaled corticosteroids (ICS) were allowed at a stable daily dose. Any participants receiving fixed combinations of ICS and beta2-agonists were switched to receive the same dose of ICS and on-demand salbutamol
Outcomes	St George's Respiratory Questionnaire (SGRQ), COPD exacerbations, FEV1 and FEV measured at 5 minutes, 2 hours and 3 hours post-dose, PEF, 6-minute walk test, haematology, blood chemistry, ECG, diary card data
Notes	**Funding**: Novartis **Identifier(s)**: NCT00134979, CFOR258F2402

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was not stratified [no other information given but assumed to follow convention Novartis sequence generation methods]
Allocation concealment (selection bias)	Low risk	Randomization was not stratified [no other information given but assumed to follow convention Novartis sequence generation methods]
Blinding of participants and personnel (performance bias)	High risk	Tiotropium was delivered open-label
Blinding of outcome assessment (detection bias)	High risk	Tiotropium was delivered open-label
Incomplete outcome data (attrition bias)	Low risk	Withdrawal rate was relatively low (12-13%) and even across active comparators. The intent-to-treat (ITT) population consisted of all randomized patients who received at least one dose of study medication. This population was used for efficacy and safety analyses
Selective reporting (reporting bias)	High risk	FEV1 and SGRQ outcomes only provided in graphical form only with inexact P-value

Vogelmeier 2011

Methods	**Design**: randomized, double-blind, double-dummy, parallel-group trial **Duration**: 1 year (+ 2 week run-in) **Location**: 725 centres in 25 countries
Participants	**Population**: 7376 participants were randomised to tiotropium (3707) and salmeterol (3669) **Baseline characteristics** Age (mean years): salm 62.8, tio 62.9 % Male: salm 74.9, tio 74.4

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	% FEV1 predicted: salm 49.4, tio 49.2 Pack-years (mean): salm 37.8, tio 38.8 **Inclusion criteria**: at least 40 years of age and had a smoking history of 10 pack-yearsor more, a diagnosis of COPD, a forced expiratory volume in 1 second (FEV1) afterbronchodilation of <70% of the predicted value, a ratio of FEV1 to forced vital capacity(FVC) of <70%, and a documented history of at least one exacerbation leading to treatment with systemic glucocorticoidsor antibiotics or hospitalisation within the previous year **Exclusion criteria**: significant disease other thanCOPD; diagnosis of asthma; life-threatening pulmonary obstruction, or a history of CF; active TB; narrow angle glaucoma; myocardial infarction or hospital admission for heart failure within the year prior to visit 1; cardiac arrhythmia requiring medical or surgical treatment; severe CV disorders; hypersensitivity to components of study drugs; respiratory infection or exacerbation in the 4 weeks prior to visit 1
Interventions	1. Salmeterol 50 bid (LABA) - plus HandiHaler placebo 2. Tiotropium 18 qd (LAMA) - plus pMDI placebo **Inhaler device**: HandiHaler and pressurised metered dose inhaler (pMDI) **Allowed co-medications**: Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and long-acting _2-agonists, during the double blind treatment phase
Outcomes	Time to first exacerbation (primary); Secondary and safety end points included time-toevent end points, number-of-event end points, serious adverse events, and death
Notes	**Funding**: Boehringer Ingelheim and Pfizer **Identifier(s)**: NCT00563381

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated by the sponsor using a validated system involving a pseudo-random number generator. Patients were randomized in a 1:1 ratio in blocks of four, with equal allocation of treatment within each block per country site
Allocation concealment (selection bias)	Low risk	Patients were randomized to treatment via an Interactive Voice Response System(Perceptive Informatics Inc., Berlin, Germany)
Blinding of participants and personnel (performance bias)	Low risk	Blinding was maintained by allocation of a dummy placebo MDI to those randomized to the tiotropium arm and a dummy placebo HandiHaler to those in the salmeterol arm.Tiotropiumand placebo capsules were identical in size and colour and were therefore indistinguishable
Blinding of outcome assessment (detection bias)	Low risk	A committee assessing cause of death was blind to treatment group. Authors judged that other outcomes were blind also

Incomplete outcome data (attrition bias)	Low risk	The efficacy and safety analyses included all the patients who underwent randomisation and who received at least one dose of the study medication. Fewer patients in the tiotropium group than in the salmeterol group withdrew from the study prematurely: 585 patients (15.8%) vs. 648 patients (17.7%) but both were judged to be low over a year and considering imputation of missing values
Selective reporting (reporting bias)	Low risk	Outcomes were well reported in the publications and on clinicaltrials.gov

Vogelmeier 2013

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 26 weeks **Location:** 10 countries and 92 centers (mainly EU).
Participants	**Population:** IND/Glyco 258, FP/SAL 264 **Baseline Characteristics:** Age: LAMA/LABA, 63.2 years (SD 8.2); LABA/ICS, 63.4 years (SD 7.7) Male/female: LAMA/LABA, 181/77; LABA/ICS, 189/75. %pred FEV1: LAMA/LABA, 60.5% (SD 10.5%); LABA/ICS, 60.0% (SD 10.7%). **Inclusion Criteria:** COPD stage II/III without recent exacerbation **Exclusion Criteria:** Pregnancy, significant co-morbidities, history of malignancy, COPD exacerbations within the last one year, long-term oxygen therapy, asthma, other concomitant lung disease, lung transplant.
Interventions	indacaterol/glycopyrronium (110/50 μg) once daily. salmeterol/fluticasone (50/500 μg) twice daily. **Inhaler Device:** dry powder inhaler (SDDPI) for IND/Glyco, dry inhalation powder delivered via Accuhaler for FP/SAL. **Allowed Co-Medications:** short-acting inhaled beta-agonists as rescue
Outcomes	Primary outcome: FEV1 AUC (0 to 12 h).
Notes	**Funding:** Novartis **Identifiers:** NCT01315249, CQVA149A2313

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used an automated, interactive response technology to assign randomisation numbers to participants
Allocation concealment (selection bias)	Low risk	Investigators used an automated, interactive response technology to assign randomisation numbers to participants
Blinding of participants and personnel (performance bias)	Low risk	Study was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	Randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone else involved in the study

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Incomplete outcome data (attrition bias)	Low risk	Withdrawal was relatively low and even between active comparators, 17.0% in indacaterol/glycopyrronium arm and 17.0% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Vogelmeier 2016

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 24 weeks **Location:** 14 countries and 126 centers (mainly EU).
Participants	**Population:** ACL/FM 467, FP/SAL 466 **Baseline Characteristics:** Age: 63.4 years (SD 7.8). Male/female: 607/326. **Inclusion Criteria:** %pred FEV1 < 80%, CAT ≥ 10, without recent exacerbation **Exclusion Criteria:** Pregnancy, significant co-morbidities, history of malignancy, COPD exacerbations within the last 3 months, long-term oxygen therapy (>15 hrs a day), asthma, other concomitant lung disease.
Interventions	aclidinium/formoterol (400/12 μg) twice daily. salmeterol/fluticasone (50/500 μg) twice daily. **Inhaler Device:** Genuair/Pressair(ACL/FM), Accuhaler (FP/SAL) **Allowed Co-Medications:** Salbutamol as rescue
Outcomes	Primary outcome: peak FEV1 at week 24.
Notes	**Funding:** Almirall/ AstraZeneca **Identifiers:** NCT01908140, M/40464/39, 2013-000116-14

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry- funded
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	Low risk	double-blind, double-dummy
Blinding of outcome assessment (detection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal was relatively low and even between active comparators, 14.1% in ACL/FM arm and 17.0% in salmeterol/fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described.

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Wedzicha 2008

Methods	**Design**: multicenter, randomized, double-blind, double-dummy controlled trial **Duration**: 2 years (+ 2 week run-in) **Location**: 179 centres from 20 countries
Participants	**Population**: 1323 participants were randomised to tiotropium (665) and salmeterol/fluticasone combination (658) **Baseline characteristics** Age (mean years): tio 65, SFC 64 % Male: tio 84, SFC 81 % FEV1 predicted: tio 39.4, SFC 39.1 Pack-years (mean): tio 39.5, SFC 41.3 **Inclusion criteria**: aged 40 to 80 years, with a smoking history of 10 or more packyears, a clinical history of COPDexacerbations, a post-bronchodilator FEV1 of less than 50% predicted, reversibility to 400 mg salbutamol 10% or less of predicted FEV1, and a score of 2 or more on the Modified Medical Research Council dyspnoea scale. **Exclusion criteria**: any respiratory disorder other than COPD or who required daily long-term oxygen therapy (>12 h/d)
Interventions	1. Tiotropium 18 qd (LAMA) - plus Diskus/Accuhaler placebo 2. Salmeterol/fluticasone 50/500 (LABA/ICS) - plus HandiHaler placebo **Inhaler device**: Diskus/Accuhaler and Handihaler **Allowed co-medications**: After randomisation, in addition to studymedication, patients were allowed short-acting inhaled beta-agonists for relief therapy and standardized short courses of oral systemic corticosteroids and/or antibiotics where indicated for treatment of COPD exacerbations
Outcomes	Primary endpointwas health care utilization exacerbation rate.Other endpoints included health status measured by St. George's Respiratory Questionnaire (SGRQ), mortality, adverse events, and study withdrawal
Notes	**Funding**: GlaxoSmithKline **Identifier(s)**: NCT00361959

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized using a predefined, computer-generated, central randomisation list. Treatment allocation was stratified by centre and smoking status on a 1:1 basis, in line with current guidelines. The block size used was four
Allocation concealment (selection bias)	Low risk	Telephone-based interactive voice response system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias)	Low risk	The investigator and treating physician were kept blinded unless an emergency arouse.

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Incomplete outcome data (attrition bias)	High risk	1,323 were randomized and comprised the intent-to-treat population.Withdrawal was high in both groups and uneven after two years (35.3 and 42%) A higher proportion of patients was withdrawn due to COPD exaerbation and consent withdrawal with tio group comared with SFC group.
Selective reporting (reporting bias)	Low risk	Outcomes were well reported in the publications, and matched the study protocol (although results have not been posted on clinicaltrials.gov)

Wedzicha 2013

Methods	**Design**: randomised, double-blind, parallel-group study **Duration**: 64 weeks **Location**: 345 study locations
Participants	**Population**: 2224 participants were randomised to open-label tiotropium (742), glycopyrronium (741), and a combination therapy not relevant to this review (741) **Baseline characteristics** Age (mean years): gly 63.1, tio 63.6 % Male: gly 73.2, tio 75.0 % FEV1 predicted: not reported Pack-years (mean): not reported **Inclusion criteria**: Male or female adults aged _40 years, who had signed an informed consent form prior to initiation of any study-related procedure; severe to very severe Chronic Obstructive Pulmonary Disease COPD(Stage III or IV) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines 2008; current or ex-smokers with a smoking history of at least 10 pack years (Ten pack-years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years); postbronchodilator Forced Expiratory Volume in one second (FEV1) <50% of the predicted normal value, and post-bronchodilator FEV1/ Forced Vital Capacity (FVC) <0.70 at Visit 2; documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics **Exclusion criteria**: Pregnant women or nursing mothers; women of child-bearing potential; requiring long term oxygen therapy; COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalisation in the 6 weeks prior to visit 1; respiratory tract infection within 4 weeks prior to visit 1; concomitant pulmonary disease; lung lobectomy, or lung volume reduction or lung transplantation; clinically relevant laboratory abnormality or a clinically significant condition; history of asthma, allergic rhinitis, eczema or alpha1 antitrypsin deficiency; contraindication for study drugs.
Interventions	1. QVA149 (IND 110/glyco 50) qd (LABA/LAMA) 2.. Glycopyrronium 50 qd (LAMA) 3. Tiotropium 18 qd (LAMA) - open-label **Inhaler device**: QVA149 110/50 μg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI). Glycopyrronium was delivered via a Novartis single-dose dry powder inhaler, and tiotropium was delivered open-label via the HandiHaler **Allowed co-medications**: Salbutamol could be taken as needed throughout the study

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Outcomes	The primary outcome was rate of moderate/severe COPD exacerbations. Secondary outcomes included pre-dose FEV1 and FVC, rescue medication use, and the St George's Respiratory Questionnaire
Notes	**Funding**: Novartis **Identifier(s)**: NCT01120691

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry funded
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding procedures were sound, but tiotropium was delivered open label which introduced bias for these comparisons. Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Blinding of outcome assessment (detection bias)	High risk	Blinding procedures were sound, but tiotropium was delivered open label which introduced bias for these comparisons. Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias)	Low risk	The full analysis set included over 99% of the randomised population. 25% dropped out overall, and dropout was relatively even across groups (24 and 27%)
Selective reporting (reporting bias)	Low risk	Outcomes were fully reported on clinicaltrials.gov

Wedzicha 2014

Methods	**Design:** a phase III, double-blind, randomised, 2-arm parallel-group study **Duration:** 48 weeks **Location:** United Kingdom
Participants	**Population:** BDP/FM (200/12) 601, FM (12) 596 **Baseline Characteristics:** age 64.3 F:M 372:818 **Inclusion Criteria:** ● Severe COPD ● At least one COPd exacerbation in previous year **Exclusion Criteria:** ● Asthma, allergic rhinitis or other atopic disease ● Unstable concurrent disease: ● Evidence of heart failure
Interventions	**Inhaler Device:** Beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg/per metered dose Formoterol fumarate 12 µg per metered dose

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	Allowed Co-Medications: as needed salbutamol, Theophylline and Tiotropium
Outcomes	Primary Outcome Measures: Exacerbation rate Change in pre-dose FEV1 [Time Frame: 0-4-12-24-36-48 weeks]
Notes	**Funding:** Chiesi Farmaceutici S.p.A **Identifiers:** NCT00929851, CCD-0906-PR-0016, 2009-012546-23 (EudraCT Number)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropout relatively high but even in both included groups (13% in BUD/FM and 16.9% in FM group).
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Wedzicha 2016

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 52 weeks **Location:** 43 countries, 496 centres.
Participants	**Population:** IND/Glyco 1678, FP/SAL 1680 **Baseline Characteristics:** Age: 64.6 years (SD 7.8). Male/female: 2557/805. %pred FEV1: 44.1% (SD 9.5%). **Inclusion Criteria:** COPD %pred FEV1 25% to 60%, mMRC ≥ 2, with recent exacerbation **Exclusion Criteria:** Pregnancy, significant co-morbidities, history of malignancy, long-term oxygen therapy, asthma, other concomitant lung disease, lung transplant.
Interventions	indacaterol/glycopyrronium (110/50 μg) once daily. salmeterol/fluticasone (50/500 μg) twice daily. **Inhaler Device:** dry powder inhaler (SDDPI) for IND/Glyco, dry inhalation powder delivered via Accuhaler for FP/SAL. **Allowed Co-Medications:** Salbutamol as rescue
Outcomes	Primary outcome: rate of COPD exacerbations per year.

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Notes	**Funding:** Novartis. **Identifiers:** NCT01782326, CQVA149A2318

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms
Allocation concealment (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms
Blinding of participants and personnel (performance bias)	Low risk	Study was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients, investigator staff, persons performing the assessments, and data analysts were blinded.
Incomplete outcome data (attrition bias)	Low risk	Withdrawal was relatively low and even between two groups, 16.6% in indacaterol/glycopyrronium arm and 19.0% in salmeterol/ fluticasone arm.
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Wise 2013

Methods	**Design:** Randomized, Active-controlled, Double-blind, Double-dummy, Parallel Group Design, Multi-center Trial **Duration:** 120 weeks **Location:** Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Denmark, Finland, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Ireland, Israel, Italy, Korea, Republic of, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Panama, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Ukraine, United Kingdom, United States
Participants	**Population:** Tio(5) 5705, Tio (18) 5687 **Baseline Characteristics:** age 65.0 (SD 9.1) F;M 4879: 12237 **Inclusion Criteria:** 1. All patients must sign an informed consent consistent with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines prior to participation in the trial, which includes medication washout and restrictions. 2. Male or female patients 40 years of age or older. 3. Patients must be current or ex-smokers with a smoking history of ≥ 10 pack-years. (Patients who have never smoked cigarettes must be excluded) 4. All patients must have a diagnosis of COPD (P06-12085), and must meet the following criteria: Relatively stable airway obstruction with a post-bronchodilator FEV1 ≤ 70% of predicted normal and post-bronchodilator FEV1 / FVC ≤ 70%.Pulmonary function tests (PFTs) were conducted after the inhalation of 400 μg salbutamol / albuterol

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	(preferred), however testing with either 200 μg salbutamol/albuterol or a combination of salbutamol / albuterol with ipratropium bromide (2 to 4 actuations) was acceptable. Other short-acting beta agonists, such as terbutaline, may have been used for the testing. The medication used for the testing was documented. Further, historical data from measurements within the past 6 months either at the site or at a referral site may have been used (see Section 6.2.1 of the CTP, located in Appendix 16.1.1). Subjects were not to have been randomized to the study without the availability of spirometry data at the actual study site.Eligibility for PFT sub-study: For subjects participating in the spirometry sub-study, historical data may not have been used for inclusion. These subjects must have qualified in the clinic at Visit 1 after performing a baseline measurement. These subjects performed a pre-dose PFT which was followed by the administration of 400 μg salbutamol / albuterol only (no other short-acting beta agonist was allowed), followed by a post-dose PFT for qualification. 5. Able to inhale from the HandiHaler® and the Respimat® devices. **Exclusion Criteria:** 1. Significant diseases other than COPD. A significant disease is defined as a disease or condition which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence the patients ability to participate in the study. 2. Patients with a recent history (i.e., six months or less) of myocardial infarction. 3. Patients with any unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year. 4. Hospitalisation for cardiac failure (New York Heart Association (NYHA) Class III or IV) during the past year. 5. Known active tuberculosis. 6. Patients with a history of asthma, cystic fibrosis, clinically evident bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease. 7. History of thoracotomy with pulmonary resection. Subjects with a history of thoracotomy for other reasons were to have been evaluated per exclusion criterion 1. 8. Subject was planning to undergo lung transplant or lung volume reduction surgery (LVRS). 9. Malignancy for which the subject had undergone resection, radiation, chemotherapy or biological treatments within the last 5 years. Subjects with treated basal cell carcinoma were allowed. 10. Known respiratory infection or exacerbation of COPD in the 4 weeks prior to randomization. 11. Known hypersensitivity to anticholinergic drugs, lactose, benzalkonium chloride (BAC), ethylenediaminetetraacetic acid (EDTA), or any other components of the HandiHaler® or Respimat® inhalation solution delivery system. 12. Known moderate to severe renal impairment (as judged by the investigator). 13. Known narrow angle glaucoma. 14. Known significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Subjects whose symptoms were controlled on treatment may have been included.

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	15. Use of systemic corticosteroid medication at unstable doses (i.e., less than 6 weeks on stable dose) or at doses in excess of the equivalent of 10 mg prednisolone per day. 16. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception for at least 3 months prior to and for the duration of the trial. 17. Significant alcohol or drug abuse within the past 12 months. 18. Subjects requiring the use of supplemental oxygen therapy for > 12 hours per day. 19. Subjects who had completed a pulmonary rehabilitation program in the 6 weeks prior to the screening visit or subjects who were currently in a pulmonary rehabilitation program that was not maintained throughout the duration of the study. 20. Subjects who had taken an investigational drug within 30 days prior to the Screening Visit. 21. Previous participation (receipt of randomized treatment) in this study. 22. Subjects who were currently participating in an interventional study
Interventions	**Inhaler Device:** Tiotropium Inhalation Solution Delivered by the Respimat Inhaler Tiotropium Inhalation Capsules 18 µg Delivered by the HandiHaler **Allowed Co-Medications:** as needed salbutamol / albuterol. All classes of maintenance respiratory medications
Outcomes	Primary Outcome Measures: mortality, COPD exacerbations
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01126437

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	an interactive voice or web response system
Allocation concealment (selection bias)	Low risk	an interactive voice or web response system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Scientific Steering Committee met every 6 months to review both the progress and blinded study data.
Incomplete outcome data (attrition bias)	Low risk	Dropout was high but even in both included groups (23.2% in Tio 5 and 23.0% in Tio 18 group).
Selective reporting (reporting bias)	Low risk	Located trial registration and protocol - outcomes well reported

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Yao 2014

Methods	**Design:** Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study **Duration:** 26 weeks **Location:** Hong Kong, India, Japan, Korea, Republic of, Singapore, Taiwan
Participants	**Population:** IND (150) 187, IND (300) 188 **Baseline Characteristics:** age 66.7 (SD 8.38) F:M 12:335 **Inclusion Criteria:** Diagnosis of moderate-to-severe chronic obstructive pulmonary disease (COPD), as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and: 1. Smoking history of at least 20 pack-years. 2. Post-bronchodilator forced expiratory volume in 1 second (FEV1) < 80% and ≥ 30% of the predicted normal value. 3. Post-bronchodilator FEV1/FVC (forced vital capacity) < 70%. **Exclusion Criteria:** ● Patients who have been hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during the 14 day run-in period prior to randomization. ● Patients requiring long-term oxygen therapy (> 15 hours a day) for chronic hypoxemia. ● Patients who have had a respiratory tract infection within 6 weeks prior to screening. ● Patients with concomitant pulmonary disease. ● Patients with a history of asthma. ● Patients with diabetes Type I or uncontrolled diabetes Type II. ● Any patient with lung cancer or a history of lung cancer. ● Any patient with active cancer or a history of cancer with less than 5 years disease-free survival time. ● Patients with a history of long QT syndrome or whose QTc interval (Bazett's) measured at screening or randomization is prolonged. ● Patients who have been vaccinated with live attenuated vaccines within 30 days prior to screening or during the run-in period. ● Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements.
Interventions	**Inhaler Device:** Indacaterol was supplied in powder filled capsules with a single dose dry powder inhaler (SDDPI). **Allowed Co-Medications:** Salbutamol as rescue. inhaled corticosteroids and slow-release theophylline
Outcomes	Primary Outcome Measures: Trough Forced Expiratory Volume in 1 Second (FEV1) 24 Hours Post-dose at the End of Treatment (Week 12 + 1 Day, Day 85)
Notes	**Funding:** Novartis **Identifiers:** NCT00794157, CQAB149B2333

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Dropout was low and even between included arms (8.8% in IND 150 and 9.4% in IND 300 arm)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Zhong 2015

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 26 weeks **Location:** 4 countries and 56 centers (recruited mainly in China).
Participants	**Population:** IND/Glyco 372, FP/SAL 369 **Baseline Characteristics:** Age: LAMA/LABA 64.8 years (SD 7.8); LABA/ICS 65.3 years (SD 7.9) Male/female: 672/69. %pred FEV1: LAMA/LABA 51.6% (SD 12.8%), LABA/ICS 52.0% (SD 12.9%). **Inclusion Criteria:** COPD stage II/III mMRC ≥ 2, without recent exacerbation **Exclusion Criteria:** Pregnancy, significant co-morbidities, COPD exacerbations within the last one year, long-term oxygen therapy (>12 hrs/day), asthma, other concomitant lung disease.
Interventions	indacaterol/glycopyrronium (110/50 μg) once daily. salmeterol/fluticasone (50/500 μg) twice daily. **Inhaler Device:** dry powder inhaler (SDDPI) for IND/Glyco, dry inhalation powder delivered via Accuhaler for FP/SAL. **Allowed Co-Medications:** short-acting inhaled beta-agonists as rescue
Outcomes	Primary outcome: trough FEV1 following 26 weeks of treatment to demonstrate the non-inferiority of indacaterol/glycopyrronium to salmeterol/fluticasone
Notes	**Funding:** Novartis **Identifiers:** NCT01709903, CQVA149A2331

Risk of bias table

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms
Allocation concealment (selection bias)	Low risk	Participants were randomised via Interactive Response Technology to 1 of the treatment arms
Blinding of participants and personnel (performance bias)	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias)	Low risk	Blinding of patients from the investigator staff, people performing the assessments, and data analysts was maintained by ensuring that the randomization data were kept strictly confidential until the time of unblinding
Incomplete outcome data (attrition bias)	Low risk	Withdrawal was low and even between two groups, 7.8% in indacaterol/glycopyrronium arm and 10.4% in salmeterol/fluticasone arm
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

ZuWallack 2014

Methods	**Design:** multi-centre, randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 12 weeks **Location:** 90 centres across the US
Participants	**Population:** 2267 adults, with a clinical history of moderate-to-severe COPD as defined by GOLD guidelines (FEV1 < 80% and ≥ 30% predicted), were randomised to tiotropium + olodaterol (1133 participants) or tiotropium + placebo (1134 participants) **Baseline Characteristics:** mean age 64 years. 50% men. Mean FEV1 1.45 L (54% predicted) **Inclusion Criteria:** men and women aged ≥ 40 years with a clinical diagnosis of COPD, a smoking history ≥ 10 pack-years, and post-bronchodilator FEV1 < 80% and ≥ 30% predicted, with FEV1/FVC < 70% **Exclusion Criteria:** participants who were on prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day, oxygen use > 1 h/day, pulmonary rehabilitation in the last 6 weeks, participants who had significant disease other than COPD (e.g. asthma, history of life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, active TB, previous thoracotomy with resection, thyrotoxicosis, paroxysmal tachycardia, unstable or life-threatening cardiac arrhythmia,MI or hospitalisation for heart failure in the previous year, malignancy requiring treatment in the last 5 years)
Interventions	**Inhaler Device:** ● Olodaterol 5 μg through SDDPI Respimat, once daily + tiotropium 18 μg through SDDPI HandiHaler, once daily ● Placebo to olodaterol + tiotropium 18 μg through SDDPI HandiHaler, once daily **Allowed Co-Medications:** ICS, oral (#10 mg prednisone per day, or equivalent) and injected steroids, cromolyn sodium/nedocromil sodium, antihistamines,

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	antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted.Albuterol as rescue.
Outcomes	Primary: AUC for FEV1 measured 0-3 h post-morning dose (FEV1 AUC 0-3 h) after 12 weeks of treatment. Also trough FEV1 after 12 weeks of treatment Secondary: change in FEV1, SGRQ, FVC AUC 0-3 h, change in peak and trough FVC after 12 weeks' treatment, and rescue medication use over the 12-week period
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01694771, NCT01696058

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Zuwallack 2014a&b
Allocation concealment (selection bias)	Low risk	See Zuwallack 2014a&b
Blinding of participants and personnel (performance bias)	Low risk	See Zuwallack 2014a&b
Blinding of outcome assessment (detection bias)	Low risk	See Zuwallack 2014a&b
Incomplete outcome data (attrition bias)	Low risk	See Zuwallack 2014a&b
Selective reporting (reporting bias)	Low risk	See Zuwallack 2014a&b

ZuWallack 2014a

Methods	**Design:** multi-centre, randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 12 weeks **Location:** 90 centres across the US
Participants	**Population:** 1132 adults, with a clinical history of moderate-to-severe COPD as defined by GOLD guidelines (FEV1 < 80% and ≥ 30% predicted), were randomised to tiotropium + olodaterol (567 participants) or tiotropium + placebo (565 participants) **Baseline Characteristics:** mean age 64 years. 50% men. Mean FEV1 1.45 L (54% predicted) **Inclusion Criteria:** men and women aged ≥ 40 years with a clinical diagnosis of COPD, a smoking history ≥ 10 pack-years, and post-bronchodilator FEV1 < 80% and ≥ 30% predicted, with FEV1/FVC < 70% **Exclusion Criteria:** participants who were on prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day, oxygen use > 1 h/day, pulmonary rehabilitation in the last 6 weeks, participants who had significant disease other than COPD (e.g. asthma, history of life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, active TB, previous thoracotomy with resection, thyrotoxicosis, paroxysmal tachycardia, unstable or life-threatening cardiac arrhythmia,MI or hospitalisation for heart failure in the previous year, malignancy requiring treatment in the last 5 years)
Interventions	**Inhaler Device:** ● Olodaterol 5 μg through SDDPI Respimat, once daily + tiotropium 18 μg through SDDPI HandiHaler, once daily ● Placebo to olodaterol + tiotropium 18 μg through SDDPI HandiHaler, once daily

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	Allowed Co-Medications: ICS, oral (#10 mg prednisone per day, or equivalent) and injected steroids, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted.Albuterol as rescue.
Outcomes	Primary: AUC for FEV1 measured 0-3 h post-morning dose (FEV1 AUC 0-3 h) after 12 weeks of treatment. Also trough FEV1 after 12 weeks of treatment Secondary: change in FEV1, SGRQ, FVC AUC 0-3 h, change in peak and trough FVC after 12 weeks' treatment, and rescue medication use over the 12-week period
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01694771

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An automated and validated randomisation tool (Interactive Response Technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Allocation concealment (selection bias)	Low risk	An automated and validated randomisation tool (Interactive Response Technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Blinding of participants and personnel (performance bias)	Low risk	double-blind
Blinding of outcome assessment (detection bias)	Low risk	People performing the assessments and data analysts were blinded to the identity of the treatment fromthe time of randomisation until database lock
Incomplete outcome data (attrition bias)	Low risk	The number of withdrawals were relatively low and even in each group (40 participants in both groups, 7%)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

ZuWallack 2014b

Methods	**Design:** multi-centre, randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 12 weeks **Location:** 90 centres across the US
Participants	**Population:** 1135 adults, with a clinical history of moderate-to-severe COPD as defined by GOLD guidelines (FEV1 < 80% and ≥ 30% predicted), were randomised to tiotropium + olodaterol (566 participants) or tiotropium + placebo (569 participants) **Baseline Characteristics:** mean age 64 years. 50% men. Mean FEV1 1.45 L (54% predicted) **Inclusion Criteria:** men and women aged ≥ 40 years with a clinical diagnosis of

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	COPD, a smoking history ≥ 10 pack-years, and post-bronchodilator FEV1 < 80% and ≥ 30% predicted, with FEV1/FVC < 70% **Exclusion Criteria:** participants who were on prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day, oxygen use > 1 h/day, pulmonary rehabilitation in the last 6 weeks, participants who had significant disease other than COPD (e.g. asthma, history of life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, active TB, previous thoracotomy with resection, thyrotoxicosis, paroxysmal tachycardia, unstable or life-threatening cardiac arrhythmia,MI or hospitalisation for heart failure in the previous year, malignancy requiring treatment in the last 5 years)
Interventions	**Inhaler Device:** ● Olodaterol 5 μg through SDDPI Respimat, once daily + tiotropium 18 μg through SDDPI HandiHaler, once daily ● Placebo to olodaterol + tiotropium 18 μg through SDDPI HandiHaler, once daily **Allowed Co-Medications:** ICS, oral (#10 mg prednisone per day, or equivalent) and injected steroids, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted.Albuterol as rescue.
Outcomes	Primary: AUC for FEV1 measured 0-3 h post-morning dose (FEV1 AUC 0-3 h) after 12 weeks of treatment. Also trough FEV1 after 12 weeks of treatment Secondary: change in FEV1, SGRQ, FVC AUC 0-3 h, change in peak and trough FVC after 12 weeks' treatment, and rescue medication use over the 12-week period
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01696058

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An automated and validated randomisation tool (Interactive Response Technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Allocation concealment (selection bias)	Low risk	An automated and validated randomisation tool (Interactive Response Technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Blinding of participants and personnel (performance bias)	Unclear risk	double-blind
Blinding of outcome assessment (detection bias)	Low risk	People performing the assessments and data analysts were blinded to the identity of the treatment fromthe time of randomisation until database lock
Incomplete outcome data (attrition bias)	Low risk	The number of withdrawals were relatively low and even in each group (31/569 (5.5%) and 43/566 (7.5%))
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full.

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1 **Overall study risk of bias and directness**

2 This table was compiled by the NICE Guideline Updates Team.

Study name	Risk of bias	Directness
205.137 2003	Low	Directly applicable
205.264 2004	High[1]	Directly applicable
A3401 2016	High[2]	Directly applicable
Aaron 2007	Low	Directly applicable
Agusti 2014	Low	Directly applicable
Anzueto 2009	Moderate[3]	Directly applicable
Asai 2013	High[2]	Directly applicable
B1303 2011	High[2]	Directly applicable
Bateman 2013	High[4]	Directly applicable
BI1237.22 2014	Low	Directly applicable
Bogdan 2011	Moderate[5]	Directly applicable
Briggs 2005	Low	Directly applicable
Brusasco 2003	Low	Directly applicable
Buhl 2011	Low	Directly applicable
Buhl 2015	Moderate[6]	Directly applicable
Buhl 2015a	Moderate[6]	Directly applicable
Buhl 2015b	Moderate[6]	Directly applicable
Buhl 2015c	Low	Directly applicable
Calverley 2003	Moderate[7]	Directly applicable
Calverley 2003 TRISTAN	Low	Directly applicable
Calverley 2007	Low	Directly applicable
Calverley 2010	Low	Directly applicable
Chapman 2014	Low	Directly applicable
COMBINE 2017	High[8]	Directly applicable
COSMOS-J 2016	Moderate[5]	Directly applicable
Covelli 2016	Moderate[9]	Partially directly applicable[24]
D'Urzo 2014	Low	Directly applicable
D'Urzo 2017	Moderate[5]	Directly applicable
Dahl 2010	Low	Directly applicable
Decramer 2013	Low	Directly applicable
Decramer 2014a	Low	Directly applicable
Decramer 2014b	Moderate[10]	Directly applicable
Donohue 2010	High[4]	Directly applicable
Donohue 2013	Low	Directly applicable
Donohue 2015a	Low	Directly applicable
Donohue 2015b	Low	Directly applicable
Donohue 2016	High[3]	Directly applicable
Dransfield 2014	Low	Directly applicable

Feldman 2016	Low	Directly applicable
Ferguson 2008	Moderate[11]	Directly applicable
Ferguson 2016	Low	Directly applicable
Fukuchi 2013	Low	Directly applicable
GLOW 4 2012	Moderate[5]	Directly applicable
Hagedorn 2013	High[2]	Directly applicable
Hanania 2003	Low	Directly applicable
Hoshino 2013	High[12]	Directly applicable
Hoshino 2014	High[12]	Directly applicable
Hoshino 2015	High[13]	Directly applicable
Jones 2011	Low	Directly applicable
Kalberg 2016	Low	Directly applicable
Kardos 2007	Low	Directly applicable
Kerwin 2012	High[14]	Directly applicable
Kerwin 2017	High[14]	Directly applicable
Koch 2014	Moderate[5]	Directly applicable
Kornmann 2011	Low	Directly applicable
Koser 2010	Low	Directly applicable
Mahler 2002	Low	Directly applicable
Mahler 2012a	Low	Directly applicable
Mahler 2012b	Low	Directly applicable
Mahler 2015a	Low	Directly applicable
Mahler 2015b	Low	Directly applicable
Mahler 2016	Low	Directly applicable
Maleki-Yazdi 2014	Low	Directly applicable
Martinez 2017a	High[15]	Directly applicable
Martinez 2017b	High[15]	Directly applicable
Ohar 2014	Low	Directly applicable
Pepin 2014	Low	Directly applicable
Perng 2009	High[2]	Directly applicable
PINNACLE 3 2017	High[2]	Directly applicable
RADIATE 2016	Moderate[5]	Directly applicable
Rennard 2009	Low	Directly applicable
Rheault 2016	High[4]	Directly applicable
RISE 2017	High[16]	Directly applicable
Rossi 2014	Low	Directly applicable
Sarac 2016	High[17]	Directly applicable
SCO100470 2006	Low	Directly applicable
SCO40034 2005	High[18]	Directly applicable
SCO40041 2008	Low	Directly applicable
Sharafkhaneh 2012	Moderate[19]	Directly applicable
Singh 2014	Low	Directly applicable
Singh 2015 a&b	Moderate[5]	Directly applicable

Singh 2015a	Moderate[5]	Directly applicable
Singh 2015b	Moderate[5]	Directly applicable
Singh 2015c	Low	Directly applicable
Szafranski 2003	High[20]	Directly applicable
Tashkin 2008	Moderate[6]	Directly applicable
Tashkin 2009	High[21]	Directly applicable
Tashkin 2012	Low	Directly applicable
Tashkin 2012a	Low	Directly applicable
Tashkin 2012b	Low	Directly applicable
To 2012	Low	Directly applicable
Troosters 2016	High[22]	Partially directly applicable[25]
Vincken 2014	Low	Directly applicable
Vogelmeier 2008	High[23]	Directly applicable
Vogelmeier 2011	Low	Directly applicable
Vogelmeier 2013	Low	Directly applicable
Vogelmeier 2016	Moderate[5]	Directly applicable
Wedzicha 2008	Moderate[3]	Directly applicable
Wedzicha 2013	High[2]	Directly applicable
Wedzicha 2014	Moderate[5]	Directly applicable
Wedzicha 2016	Low	Directly applicable
Wise 2013	Low	Directly applicable
Yao 2014	Moderate[5]	Directly applicable
Zhong 2015	Low	Directly applicable
ZuWallack 2014	Low	Directly applicable
ZuWallack 2014a	Low	Directly applicable
ZuWallack 2014b	Low	Directly applicable

1. Lack of information about allocation concealment and outcome assessor blinding, and poor reporting of the exacerbation outcomes.
2. Lack of information about allocation concealment and the use of open label drugs.
3. High withdrawal rates that were not evenly balanced across study arms.
4. Open label drug use.
5. Lack of information about allocation concealment and outcome assessor blinding.
6. Uneven withdrawal rates across the treatment arms and a lack of information about assessor blinding.
7. High withdrawal rates that were not evenly balanced across relevant study arms and a lack of information about allocation concealment.
8. Open label drug use; low, but uneven withdrawals; and a lack of information about allocation concealment.
9. Uneven withdrawals across the study arms.
10. Relatively high withdrawal rates that were not evenly balanced across study arms.
11. High withdrawal rates that were fairly evenly balanced across relevant study arms, and a lack of information about allocation concealment and outcome assessor blinding.
12. Lack of information about randomisation and allocation concealment, open label drug use and only 1 outcome assessed in a blinded fashion.

13. Lack of information about randomisation and allocation concealment; open label drug use; only 1 outcome assessed in a blinded fashion and SGRQ outcomes were not described in detail.
14. Open label drug use and a lack of information about allocation concealment.
15. Lack of information about allocation concealment; relatively high and uneven withdrawals among active comparators and use of open-label tiotropium.
16. Open label drug use and low, but uneven withdrawals between arms.
17. Lack of information about randomisation, allocation concealment and withdrawals; open-label drug use.
18. Low, but uneven withdrawals across the study arms and the lack of a study protocol or clinical study report. Study is unpublished.
19. High withdrawal rates that were relatively evenly balanced across study arms, but might be an important risk of bias given the low event rates for the outcomes of interest.
20. Lack of information about allocation concealment; relatively high and uneven withdrawals among active comparators and poor reporting of outcomes.
21. Lack of information about blinding of participants, personnel and outcome assessors; and low, but uneven withdrawals among active comparators.
22. Lack of information about allocation concealment and assessor blinding; relatively low, but uneven withdrawals among active comparators.
23. Open label use of tiotropium and issues with data presentation (FEV1 and SGRQ outcomes only provided in graphical form only with inexact P-value).
24. Study inclusion criteria required participants to have a history of diagnosed cardiovascular disease or a prior cardiovascular event.
25. Participants all underwent a behaviour-change self-management programme in parallel with drug treatment.

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1 **LAMA monotherapy**

2 **Systematic Reviews**

Short Title	Title	Study characteristics	Risk of bias and directness
Halpin (2016)	Effect of tiotropium on COPD exacerbations: A systematic review	**Study type** • Systematic review **Study details** • Dates searched *January 2000 to May 2014, with an additional search prior to submission (before September 2015).* • Databases searched *Medline, BIOSIS Previews, EMBASE and EMBASE Alert.* • Sources of funding *One of the authors was an employee of Boehringer Ingelheim at the time of manuscript submission. Writing assistance was funded by Boehringer Ingelheim.* **Study inclusion criteria** • RCTs with a parallel group design *Both placebo and active-controlled (i.e. versus other maintenance therapies) trials were eligible.* • Study duration of ≥ 6 months • Trials presenting exacerbation data • Blinded studies with additional open-label tiotropium *Included if appropriate.* **Study exclusion criteria** • Non-blinded open-label studies • Retrospective studies	**Study eligibility criteria** • Low risk of bias **Identification and selection of studies** • Unclear risk of bias *No information was provided about the number of authors who assessed the studies for inclusion or about additional methods of study identification.* **Data collection and study appraisal** • High risk of bias *No quality assessment was carried out and there is no information on whether accuracy of data extraction was confirmed by a second author.* **Synthesis and findings** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		• Pooled analyses • Pharmacoeconomic studies • Conference findings, conference abstracts and meeting reports **Participant inclusion criteria** • People with COPD **Participant exclusion criteria** • No details provided **Interventions** • Tiotropium bromide *Open-label included if the comparator was blinded.* • Placebo • Another maintenance therapy *Not specified.* **Relevant outcome measures** • Exacerbations *The only outcome of interest for this review.* **Included studies from the systematic review** • Bateman 2010b • Brusasco 2003 • Casaburi 2002 • Dusser 2006 • Tonnel 2008	*Narrative synthesis only with no attempt to meta-analyse data.* **Overall quality** • Moderate **Applicability as a source of data** • Partially applicable *Review only covers exacerbations.*

Short Title	Title	Study characteristics	Risk of bias and directness
		Excluded studies from the systematic review • Aaron 2007 *Multidrug trial that lacks a suitable comparator.* • Abrahams 2013 *Non-UK licenced drug as comparator.* • Bateman 2010a *Concomitant drug issues.* • Chan 2007 *Concomitant drug use issues.* • Decramer 2009 *Concomitant drug use issues.* • Decramer 2011 *Concomitant drug use issues.* • Decramer 2014 *Non-UK licenced drug dose.* • Decramer 2013 *Multidrug trial that lacks a suitable comparator.* • Fukuchi 2011 *Concomitant drug use issues.* • Hanania 2011 *Concomitant drug use issues.* • Hanania 2012 *Multidrug trial that lacks a suitable comparator.* • Maleki-Yazdi 2014 *Multidrug trial that lacks a suitable comparator.* • Morice 2010 *Concomitant drug use issues.* • Niewoehner 2005 *Concomitant drug use issues.* • Powrie 2007	

Short Title	Title	Study characteristics	Risk of bias and directness
		Concomitant drug use issues. • Rice 2008 *Secondary analysis of trial.* • Tashkin 2008 *Concomitant drug use issues.* • Tang 2013 *Concomitant drug use issues.* • Troosters 2010 *Concomitant drug use issues.* • Vogelmeier 2013 *Multidrug trial that lacks a suitable comparator.* • Tashkin 2010 *Concomitant drug issues.* • Wedzicha 2008 *Multidrug trial that lacks a suitable comparator.* • Wedzicha 2013 *Multidrug trial that lacks blinding for the LAMA arm.*	
Karner (2014)	Tiotropium versus placebo for chronic obstructive pulmonary disease	**Study type** • Systematic review **Study details** • Dates searched *Databases were searched from their inception to the present, but the date of the last search is not specified.* • Databases searched *The Cochrane Airways Group's Specialised Register of Trials (CAGR) was used as a source of trials. This is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and hand*	**Study eligibility criteria** • Low risk of bias **Identification and selection of studies** • Low risk of bias **Data collection and study appraisal** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		searching of respiratory journals and meeting abstracts. • Sources of funding *C.K is supported by St George's University of London, UK and the work was funded by a programme grant from the NIHR, UK.* **Study inclusion criteria** • RCTs with a parallel group design • Study duration of ≥ 12 weeks **Study exclusion criteria** • Cross-over trials *Excluded as of the primary outcomes was mortality.* **Participant inclusion criteria** • People with COPD *Diagnosis of COPD, using an external set of criteria (e.g. Global Initiative for Chronic Obstructive Lung Disease (GOLD), American Thoracic Society (ATS), British Thoracic Society (BTS), and Thoracic Society of Australia and New Zealand (TSANZ)).* **Interventions** • Tiotropium bromide *Tiotropium bromide was allowed in any formulation. Participants were allowed inhaled steroids and other concomitant COPD medication, provided they were not part of the randomised treatment.* • Placebo • Co-interventions	**Synthesis and findings** • Low risk of bias **Overall quality** • High **Applicability as a source of data** • Partially applicable *Study does not cover all of the treatments of interest for the LAMA monotherapy review.*

Short Title	Title	Study characteristics	Risk of bias and directness
		Participants were allowed inhaled steroids and other concomitant COPD medication, provided they were not part of the randomised treatment. **Relevant outcome measures** • All-cause mortality *All-cause mortality* • Exacerbations *Exacerbations requiring oral corticosteroids and/or antibiotics and causing hospitalisation.* **Other outcome measures** • COPD specific quality of life *Such as St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Questionnaire (CRQ).* • Hospital admissions *Hospital admissions: all-cause and due to exacerbations.* • Forced expiratory volume in one second (FEV1) • Non-fatal serious adverse events *Non-fatal serious adverse events: all-cause and cardiovascular.* • Withdrawals from study treatment **Included studies from the systematic review** • Bateman 2010b • Beeh 2006 • Brusasco 2003 • Casaburi 2002 • Dusser 2006 • Johansson 2008 • Tonnel 2008	

Short Title	Title	Study characteristics	Risk of bias and directness
		• Trooster 2011 • Verkindre 2006 • Voshaar 2008 **Excluded studies from the systematic review** • Bateman 2010a *Concomitant drug use issues.* • Chan 2007 *Concomitant drug use issues.* • Cooper 2010 *There is no peer-reviewed publication of the results of the trial. There data presented in the systematic review comes from a trial protocol, conference abstract and a publication looking at implementing the exercise protocol.* • Covelli 2005 *Concomitant drug use issues.* • Freeman 2007 *Concomitant drug use issues.* • Magnussen 2008 *Concomitant drug use issues.* • Moita 2008 *Concomitant drug use issues.* • NCT00144326 *This refers to a Clinical trial.gov record and there is no associated peer-reviewed publication of the study results.* • Niewoehner 2005 *Concomitant drug use issues.* • Powrie 2007 *Concomitant drug use issues.* • Sun 2007 *Concomitant drug use issues.*	

Short Title	Title	Study characteristics	Risk of bias and directness
		• Tashkin 2008 *Concomitant drug use issues.*	
Ni (2014)	Aclidinium bromide for stable chronic obstructive pulmonary disease	**Study type** • Systematic review **Study details** • Dates searched *All databases were searched from their inception. The initial search was conducted in March 2013 and it was updated in April 2014.* • Databases searched *Trials were identified from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and hand searching of respiratory journals and meeting abstracts.* • Sources of funding *Cochrane Airways Group, UK.* **Study inclusion criteria** • RCTs with a parallel group design • Trials comparing aclidinium bromide with placebo or a LABA or LAMA • Open-label and blinded studies **Study exclusion criteria** • Cross-over trials • Cluster-randomised trials **Participant inclusion criteria** • People with COPD	**Study eligibility criteria** • Low risk of bias **Identification and selection of studies** • Low risk of bias **Data collection and study appraisal** • Low risk of bias **Synthesis and findings** • Low risk of bias **Overall quality** • High **Applicability as a source of data** • Partially applicable *Study does not cover all of the treatments of interest for the LAMA monotherapy review.*

Short Title	Title	Study characteristics	Risk of bias and directness
		Moderate to severe COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2013), American Thoracic Society (ATS), European Respiratory Society (ERS) (ATS/ERS 2011), Thoracic Society of Australia and New Zealand (TSANZ 2012), UK National Institute for Health and Clinical Excellence (NICE 2010) or the WHO. • People over 18 years old • Trial participants had evidence of airway obstruction *Post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio of < 70% and FEV1 < 80% of predicted value).* • Clinical presentation of breathlessness • Chronic cough or sputum production • With or without a history of smoking **Participant exclusion criteria** • Co-morbidities *Studies enrolling people with bronchial asthma, bronchiectasis, cystic fibrosis or other lung diseases.* **Interventions** • Placebo • Aclidinium bromide • Long-acting beta2-agonist (LABA) • Another long-acting muscarinic antagonist (LAMA) **Relevant outcome measures** • Transitional Dyspnoea Index (TDI) • Serious Adverse Events (SAEs) *Non-fatal serious adverse events.* • All-cause mortality	

Short Title	Title	Study characteristics	Risk of bias and directness
		All-cause and respiratory mortality. • St George's Respiratory Questionnaire (SGRQ) • Exacerbations *Exacerbations requiring a short course of an oral steroid or antibiotic, or both and exacerbations resulting in hospital admission.* • Drop-outs due to adverse events **Other outcome measures** • COPD specific quality of life *Quality of life measured by a validated scale, such as the St George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Disease Questionnaire (CRQ).* • Hospital admissions *Hospital admissions due to exacerbations or from all causes.* • Withdrawals from study treatment *Due to lack of efficacy.* • Changes in lung function *FEV1, FEV1/FVC* • Functional capacity by six-minute walking distance • Adverse events **Included studies from the systematic review** • ACCORD COPD I • ACCORD COPD II • ACLIFORM • ATTAIN • AUGMENT COPD **Excluded studies from the systematic review** • ACCLAIM/ COPD I	

Short Title	Title	Study characteristics	Risk of bias and directness
		Not a UK licenced drug dose or within 20% of a licenced dose. • ACCLAIM/ COPD II *Not a UK licenced drug dose or within 20% of a licenced dose.* • Beier 2013 *Trial duration < 12 weeks.* • Chanez 2010 *Trial duration was < 12 weeks.* • Maltais 2011 *Trial duration is < 12 weeks.* • NCT01572792 *Based on unpublished data only.* • Sliwinski 2010 *Trial duration < 12 weeks.*	
Ni (2017)	Umeclidinium bromide versus placebo for people with chronic obstructive pulmonary disease (COPD)	**Study type** • Systematic review **Study details** • Dates searched *Searches were carried out from inception to April 2017.* • Databases searched *The systematic review authors searched the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE Ovid SP; Embase Ovid SP; PsycINFO Ovid SP; Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.* • Sources of funding	**Study eligibility criteria** • Low risk of bias **Identification and selection of studies** • Low risk of bias **Data collection and study appraisal** • Low risk of bias **Synthesis and findings** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		The review authors declare that no funding was received for this systematic review. **Study inclusion criteria** • RCTs with a parallel group design • Study duration of ≥ 12 weeks • Trials comparing umeclidinium bromide with placebo • Studies reported as full text, those published as abstract only, and unpublished data **Study exclusion criteria** • Cross-over trials • Cluster-randomised trials **Participant inclusion criteria** • People with COPD *Diagnosis of COPD according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD 2017), the American Thoracic Society (ATS), the European Respiratory Society (ERS) (ATS/ERS 2011), the Thoracic Society of Australia and New Zealand (TSANZ) (TSANZ 2014), the UK National Institute for Health and Clinical Excellence (NICE) (NICE 2010), or the World Health Organization (WHO).* • People over 18 years old • Trial participants had evidence of airway obstruction *Post-bronchodilator FEV1/FVC ratio < 70%* • Clinical presentation of breathlessness • Chronic cough or sputum production • With or without a history of smoking • Stable COPD	**Overall quality** • High **Applicability as a source of data** • Partially applicable *Study does not cover all of the treatments of interest for the LAMA monotherapy review.*

Short Title	Title	Study characteristics	Risk of bias and directness
		Participants did not have recent exacerbations requiring a short course of oral steroids, antibiotics, or both, and who were taking stable doses of medications for at least four weeks before screening. **Participant exclusion criteria** • Co-morbidities *Bronchial asthma, bronchiectasis, cystic fibrosis, or other chronic lung diseases.* **Interventions** • Placebo • Umeclidinium bromide • Co-interventions *The systematic review allowed the following co-interventions, provided they were not part of the randomised treatment: salbutamol or albuterol as rescue medication; oral sustained-release theophylline, inhaled corticosteroids, or systemic corticosteroids (oral or parenteral) at stable doses; and oxygen therapy given for less than 15 hours per day.* **Relevant outcome measures** • Transitional Dyspnoea Index (TDI) • Serious Adverse Events (SAEs) *Non-fatal serious adverse events.* • All-cause mortality *Mortality: all-cause and respiratory.* • St George's Respiratory Questionnaire (SGRQ) • Exacerbations *Exacerbations requiring a short course of an oral steroids or antibiotics, or both, and exacerbations leading to hospitalisation.*	

Short Title	Title	Study characteristics	Risk of bias and directness
		Other outcome measures • COPD specific quality of life *Quality of life as measured by a validated scale: St George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRQ).* • Hospital admissions *Due to exacerbations* • Changes in lung function • Adverse events *and side effects* • Use of rescue medications **Included studies from the systematic review** • Donahue 2013 • Trivedi 2014 **Excluded studies from the systematic review** • Celli 2014 *Umeclidinium bromide is used at a non-UK licenced dose (125 micrograms).* • Donohue 2014 *Umeclidinium bromide is used at a non-UK licenced dose (125 micrograms).*	
Ulrik (2012)	Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit	**Study type** • Systematic review *Narrative systematic review with no meta-analysis.* **Study details** • Dates searched *Last search was August 2012.* • Databases searched *PubMed*	**Study eligibility criteria** • Unclear risk of bias *Insufficient information provided.* **Identification and selection of studies** • High risk of bias *The authors only searched one database, although they did*

Short Title	Title	Study characteristics	Risk of bias and directness
		• Sources of funding *None stated.* **Study inclusion criteria** • Peer-reviewed publications relevant to glycopyrronium bromide and COPD **Study exclusion criteria** • Not stated **Participant inclusion criteria** • People with COPD **Participant exclusion criteria** • No details provided **Interventions** • Glycopyrronium bromide **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • Exacerbations • Trough FEV1 **Other outcome measures** • Adverse events • Use of rescue medications • Exercise capacity	*attempt to find extra studies using citation searching. There is only one author, so there was no capacity for study inclusion to be confirmed by a second author.* **Data collection and study appraisal** • High risk of bias *One author only was involved in data collection. There was no attempt to present the characteristics of the studies in a format that allowed comparison and no assessment of risk of bias was performed.* **Synthesis and findings** • High risk of bias *There was no attempt at meta-analysis and minimal evidence synthesis. The studies were presented as sequential descriptive summaries.* **Overall quality** • Low

Short Title	Title	Study characteristics	Risk of bias and directness
		Included studies from the systematic review • D'Urzo 2011 • Kerwin 2012c **Excluded studies from the systematic review** • Beeh 2012 *Trial duration < 12 weeks* • Fogarty 2011 *Trial duration < 12 weeks* • Sechaud 2012 *Treatment duration <12 weeks* • Van de Maele 2010 *Intervention does not include a single LAMA versus an acceptable comparator.* • Verkindre 2010 *Trial duration< 12 weeks.* • Vogelmeier 2010 *Trial duration < 12 weeks*	**Applicability as a source of data** • Partially applicable
Zou (2016)	Efficacy and Safety of an Aclidinium Bromide Treatment for 12 Weeks or Longer in Patients with Moderate-To-Severe COPD: A Meta-Analysis	**Study type** • Systematic review **Study details** • Dates searched *The last search date was March 1st 2015.* • Databases searched *MEDLINE, EMBASE, CINAHL and the Cochrane library databases. In addition, the drug manufacturer's database and Clinical Trials. gov were searched and the authors undertook manual searching of respiratory journals.*	**Study eligibility criteria** • Low risk of bias **Identification and selection of studies** • Low risk of bias **Data collection and study appraisal** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		• Sources of funding *Not stated, but there are no conflicts of interest.* **Study inclusion criteria** • RCTs with a parallel group design *Placebo-controlled and double-blind.* • Study duration of ≥ 12 weeks • Trials comparing aclidinium bromide to placebo **Study exclusion criteria** • Not stated **Participant inclusion criteria** • Stable COPD *Moderate to severe COPD.* **Participant exclusion criteria** • No details provided **Interventions** • Placebo • Aclidinium bromide **Relevant outcome measures** • Transitional Dyspnoea Index (TDI) • Serious Adverse Events (SAEs) • All-cause mortality • St George's Respiratory Questionnaire (SGRQ) • Exacerbations	**Synthesis and findings** • Low risk of bias **Overall quality** • High **Applicability as a source of data** • Partially applicable *The review only covered one of the LAMA drugs of interest.*

Short Title	Title	Study characteristics	Risk of bias and directness
		Including hospitalisation due to a COPD exacerbation. • Cardiac and COPD serious adverse events • Trough FEV1 **Other outcome measures** • Changes in lung function *Trough FVC, peak FEV1 and FVC.* **Included studies from the systematic review** • ACCORD COPD I • ACCORD COPD II • ACLIFORM • ATTAIN • AUGMENT COPD **Excluded studies from the systematic review** • ACCLAIM/ COPD I *Non-UK licenced drug doses used.* • ACCLAIM/ COPD II *Non-UK licenced drug doses used.*	

1 **Network Meta-Analyses**

Short Title	Title	Study characteristics	Risk of bias and directness
Ismaila (2015)	Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic	**Study type** • Network Meta- Analysis (NMA) **Study details** • Dates searched *The searches covered 1946- 2014 Week 15.*	**Rationale for review included?** • Yes

Short Title	Title	Study characteristics	Risk of bias and directness
	review and network meta-analysis	• Databases searched *MEDLINE (Ovid); MEDLINE In-Process (Ovid); EMBASE (Ovid); The Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE); and Health Technology Assessment (HTA) websites, HTA database and National Institute for Health Research (NIHR). The following clinical trial registries were searched: Clinicaltrials.gov; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); Current Controlled Trials; EU Clinical Trials Register (EU-CTR); Klinische Prüfungen PharmNet.Bund; and The International Prospective Register of Systematic Reviews (PROSPERO).* • Sources of funding *The analysis was sponsored by GSK (GSK study number: 201280).* **Study inclusion criteria** • Randomized controlled trials • Studies that compare treatments of interest with placebo or to each other **Study exclusion criteria** • Cross-over studies • Post hoc or retrospective analyses • Cost-effectiveness analyses • Observational studies • Reviews or meta-analyses • Methodology studies or protocols • N of 1 trials (sample size of one patient) • Studies lasting less than 2 weeks • Studies where patients were required to spend time in a sleep laboratory	**Study inclusion/exclusion criteria specified clearly?** • Yes **Description of network and potential biases related to it?** • Yes **Summary measures stated?** • Yes *Mean difference* **Methodology for data handling described?** • Yes **Statistical methods to compare direct and indirect data described?** • Yes **Description of subgroup, sensitivity and meta-regression analyses where applicable?** • Yes **Network diagram available?** • Yes

Short Title	Title	Study characteristics	Risk of bias and directness
		• Studies comparing only double or triple therapies (i.e. LABA, LAMA, ICS as fixed or open combinations) to each other or to placebo **Participant inclusion criteria** • People with COPD as defined by GOLD guidelines (i.e. airflow limitation that is not fully reversible) • Studies that include asthma patients and COPD patients and report data for COPD patients separately • Adults • Studies that include adults and children and report data for adults separately **Participant exclusion criteria** • Studies with patients who have reversible airway or obstructive lung disease • Studies with only patients with asthma • Studies with only healthy patients without COPD • Studies that include asthma patients and COPD patients but do not report data for COPD patients separately • Studies with only patients who have alpha-1-antitrypsin-deficiency-related COPD • Studies that include adults and children but do not report data for adults separately **Interventions** • Umeclidinium *62.5 micrograms once daily* • Tiotropium *18 micrograms once daily only (data for 5 micrograms via a soft mist device was excluded)* • Glycopyrronium *50 micrograms once daily*	**Characteristics of the treatment network described?** • Incomplete description *The description is very brief and does not discuss the number of trials and participants for each outcome examined, or gaps of evidence in the treatment network, and potential biases reflected by the network structure.* **Results of each meta-analysis presented?** • Yes **Investigations of inconsistency carried out?** • Yes *Data is not presented, but the text states that there were no important deviations between direct and indirect evidence observed.* **Results presented for additional analyses?** • No *Scenario analyses were developed to test the impact of*

Short Title	Title	Study characteristics	Risk of bias and directness
		• Aclidinium *400 micrograms twice daily* • LABAs (Indacaterol; salmeterol; olodaterol; formoterol) **Outcomes** • Trough FEV1 • SGRQ total score • TDI focal score • Rescue medication use **Analysis** • NMA methodology *Bayesian WINBUGs v1.4.3. Models were based on those defined by Dias et al (programs 7(b) for a fixed effects normal distribution for difference data and 8(a) for a random effects normal distribution with shared parameters in the Appendix of Dias et al (2014)). Generalised linear model with normal likelihood distribution. Fixed/random effects model selection based in DIC.* **Measures** • Mean Difference (MD)	*certain studies on the relative treatment estimates, but the results were not presented.* **Discussion of study limitations?** • Yes **Overall quality** • Moderate **Applicability as a source of data** • Partially applicable *The NMA does not cover all of the outcomes of interest.*
Karabis (2013)	Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a	**Study type** • Network Meta- Analysis (NMA) **Study details** • Dates searched *The databases were searched from July 1989 to October 2012 and an additional PubMed search was performed restricted to 2012 to capture advance online publications ahead of print.* • Databases searched	**Rationale for review included?** • Yes **Study inclusion/exclusion criteria specified clearly?** • Yes

Short Title	Title	Study characteristics	Risk of bias and directness
	systematic review and network meta-analysis	*MEDLINE, MEDLINE in Process, EMBASE (using OVID), and Cochrane Controlled Trials Registry. Additional targeted searches were performed in clinicaltrials.gov database.* • Sources of funding *Almirall SA (Barcelona, Spain) and Forest Research Institute (FRI; Jersey City, NJ, USA).* **Study inclusion criteria** • Randomized controlled trials • Study duration ≥ 10 weeks • Studies that compare any of the interventions against each other or placebo **Study exclusion criteria** • Studies with high proportions (>30%) of mild and/or very severe patients were excluded. **Participant inclusion criteria** • People with COPD as defined by GOLD guidelines (i.e. airflow limitation that is not fully reversible) • Adults **Participant exclusion criteria** • None stated **Interventions** • Tiotropium *Tiotropium 18 micrograms once daily, or tiotropium 5 micrograms once daily.* • Glycopyrronium *50 micrograms once daily*	**Description of network and potential biases related to it?** • Yes **Summary measures stated?** • Yes **Methodology for data handling described?** • Yes **Statistical methods to compare direct and indirect data described?** • No *No information provided.* **Description of subgroup, sensitivity and meta-regression analyses where applicable?** • Yes **Network diagram available?** • Yes **Characteristics of the treatment network described?**

Short Title	Title	Study characteristics	Risk of bias and directness
		• Aclidinium *400 micrograms twice daily* **Outcomes** • Trough FEV1 • SGRQ total score • SGRQ responders • TDI focal score • TDI responders **Analysis** • NMA methodology *Bayesian WINBUGs v1.4.3. Models were based on those defined by Dias et al. A generalised linear model with normal likelihood distribution and an identity link was used for continuous outcomes. A logit link with binomial likelihood distribution was used for dichotomous outcomes. Fixed/random effects model selection based in DIC.* **Measures** • Mean Difference (MD) • Odds Ratios (ORs)	• Yes **Results of each meta-analysis presented?** • Yes **Investigations of inconsistency carried out?** • No **Results presented for additional analyses?** • Yes **Discussion of study limitations?** • Yes **Overall quality** • Moderate **Applicability as a source of data** • Partially applicable *The NMA does not cover all of the outcomes of interest or all currently licenced LAMAs*

Short Title	Title	Study characteristics	Risk of bias and directness
			(umeclidinium was not included in the analysis).
Oba (2015)	Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression.	**Study type** • Network Meta- Analysis (NMA) **Study details** • Dates searched *1946 to 15 May 2014* • Databases searched *Ovid Medline, Scopus, CINAHL, and the internet including the online trial registries of manufacturers of LAMA products.* • Sources of funding *This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.* **Study inclusion criteria** • Randomized controlled trials *Published and unpublished RCTs* • Studies that compare any of the interventions against each other or placebo • Study duration ≥ 12 weeks **Study exclusion criteria** • Not stated **Participant inclusion criteria** • People with COPD	**Rationale for review included?** • Yes **Study inclusion/exclusion criteria specified clearly?** • Incomplete description *The information on study and participant inclusion/exclusion criteria was limited.* **Description of network and potential biases related to it?** • Incomplete description **Summary measures stated?** • Yes **Methodology for data handling described?** • Yes **Statistical methods to compare direct and indirect data described?** • Yes

Short Title	Title	Study characteristics	Risk of bias and directness
		Participant exclusion criteria • None stated **Interventions** • Tiotropium *18 micrograms and 5 micrograms once daily* • Glycopyrronium *50 micrograms once daily* • Aclidinium *400 micrograms and 200 micrograms twice daily* **Outcomes** • Moderate to severe exacerbations • Severe exacerbations **Analysis** • NMA methodology *Bayesian WINBUGs v1.4.3. A Poisson likelihood model with a log link was used. Fixed/random effects model selection based in DIC.* **Measures** • Hazard ratios (HRs)	**Description of subgroup, sensitivity and meta-regression analyses where applicable?** • Yes **Network diagram available?** • Yes **Characteristics of the treatment network described?** • Yes **Results of each meta-analysis presented?** • Yes **Investigations of inconsistency carried out?** • Yes **Results presented for additional analyses?** • Yes

Short Title	Title	Study characteristics	Risk of bias and directness
			Discussion of study limitations? • Yes **Overall quality** • High **Applicability as a source of data** • Partially applicable *The NMA does not cover all of the outcomes of interest or all currently licenced LAMAs (umeclidinium was not included in the analysis).*

1 **Randomised Controlled Trials (RCTs)**

Short Title	Title	Study characteristics	Risk of bias and directness
Bateman (2010b)	Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies	**Trial Registration number(s)** • NCT00168844 • NCT0016883 **Additional information** • Evidence table in a systematic review *Please refer to Bateman 2010 in Karner et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • ICS use *Trough FEV1 outcome only*	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Whole trial subgroup analysis information • ICS use allowed • Theophylline use allowed	**Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • High risk of bias *The withdrawal rates were relatively large and uneven (tiotropium 10 micrograms 20.4%, placebo 31.4%). However, information on vital status was collected for all patients, including patients who discontinued prematurely.* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the high and uneven withdrawal rates.* **Directness** • Directly applicable
Bateman (2013)	Dual bronchodilation with QVA149 versus	**Trial name** • SHINE	**Random sequence generation** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
	single bronchodilator therapy: the SHINE study	**Trial Registration number(s)** • NCT01202188 **Additional Information:** • Data obtained from the authors: *The study authors kindly provided us with details of exacerbations separated into exacerbation severity groups (moderate to severe and severe) to match our analyses.* • Data extraction information: *Data on Tiotropium was not analysed as this drug was supplied in an open-label format. Data for exacerbations was not extracted as it was unclear whether the numbers referred to all exacerbations or just moderate to severe ones.* **Study type** • Randomised controlled trial **Study details** • Study location(s) *Europe, North America, South America, Asia (Philippines, Japan, India), Australia, China, Taiwan and South Africa.* • Study setting *Academic and clinical research centres* • Study dates *September 2010- February 2012.* • Duration of follow-up *26 weeks* • Sources of funding *The study was funded by Novartis Pharma AG.*	**Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Unclear risk of bias *Only 80.8% of the placebo group completed the trial, compared to 88.8% in the intervention group.* **Selective reporting** • Low risk of bias **Other sources of bias** • Unclear risk of bias *Patients who were, in the opinion of the investigator, unreliable or non-compliant were excluded from enrolment.* **Overall risk of bias** • Moderate

Short Title	Title	Study characteristics	Risk of bias and directness
		Inclusion criteria • Age ≥ 40 years • Post-bronchodilator FEV1, % predicted *≥30% and <80%* • Moderate to severe COPD (GOLD 2-3) • Smoking history *≥10 pack-years.* • FEV1/FVC, % predicted *<0.7* • Symptomatic patients *Based on daily electronic diary data.* **Exclusion criteria** • Asthma • Another significant disease *Uncontrolled hypo-or hyperthyroidism, hypokalemia or hyperadrenergic state any condition which might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.* • Recent COPD exacerbation *That required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalisation in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 3.* • Recent respiratory tract infection *Within 4 weeks prior to Visit 1.* • History of malignancy • Concomitant pulmonary diseases • Long QT syndrome or QTc >450 ms • Pregnancy *Also nursing mothers and women with child-bearing potential.* • Lung volume reduction surgery • Use of long-term oxygen therapy	*Due to the unusual enrolment criteria and relatively high drop-out rate in the placebo arm.* **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		> 15 hours a day • Drug contraindications *Patients contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: • anticholinergic agents • long and short acting β2-agonists • sympathomimetic amines • lactose or any of the other excipients.* • Diabetes • Renal impairment or urinary retention • A known history and/or diagnosis of alpha-1 antitrypsin deficiency • Participation in the active phase of a supervised pulmonary rehabilitation programme • Symptomatic prostatic hyperplasia • Bladder-neck obstruction • Narrow-angle glaucoma • Patients who were, in the opinion of the investigator unreliable or non-compliant • Eczema (atopic), known high immunoglobulin E levels, or a known positive skin prick test in the last 5 years • Patients with allergic rhinitis who used a H1 antagonist or intra-nasal corticosteroids intermittently *Treatment with a stable dose was permitted.* **Sample characteristics** • Sample size *2144* • Split between study groups *Glycopyrronium: 475; Placebo: 234. Other interventions: 1435.* • Loss to follow-up *Glycopyrronium: 422/475 (88.8%) of participants completed the trial; Placebo: 189/234 (80.8%) of participants completed the trial.*	

Short Title	Title	Study characteristics	Risk of bias and directness
		• % female *24.6* • Mean age (SD) *64.0 years (8.8)* • Smoking status and history *Smoking status, mean (SD) Placebo; Glycopyrronium Ex-smoker: 139 (59.9); 284 (60.0) Current smoker: 93 (40.1); 189 (40.0)* • Baseline pulmonary medication *ICS use, mean (SD) Placebo; Glycopyrronium 134 (57.8); 274 (57.9)* **Interventions** • Tiotropium 18 micrograms once daily *Administered using an open-label HandiHaler device.* • Placebo *Administered once daily in the morning via the Breezhaler (Novartis Pharma AG, Stein, Switzerland) device.* • Glycopyrronium 50 micrograms once daily *Administered once daily in the morning via the Breezhaler (Novartis Pharma AG, Stein, Switzerland) device.* • QVA149 (indacaterol 110 micrograms/glycopyrronium 50 micrograms) *Administered once daily in the morning via the Breezhaler (Novartis Pharma AG, Stein, Switzerland) device.* • Indacaterol 150 micrograms *Administered once daily in the morning via the Breezhaler (Novartis Pharma AG, Stein, Switzerland) device.* • Concomitant medication *These included: selective serotonin reuptake inhibitors prior to screening; inactivated vaccines, ICS, intranasal corticosteroids, H1 antagonists. Constant, stable doses (where relevant) were required. Patients receiving fixed-dose combinations of LABA/inhaled corticosteroid (ICS) were switched to an*	

Short Title	Title	Study characteristics	Risk of bias and directness
		equivalent dose of ICS monotherapy. A salbutamol/ albuterol pressurised metered-dose inhaler was provided as rescue medication. **Relevant outcome measures** • Mortality • St George's Respiratory Questionnaire (SGRQ) • St George Respiratory Questionnaire responders • Trough FEV1 • Serious Adverse Events (SAEs) • Drop-outs due to adverse events **Other outcome measures** • All adverse events • Use of rescue medication • Peak FEV1 **Relevant within trial subgroup analyses** • COPD severity *Moderate, severe* • ICS use • Sex **Additional within trial subgroup analysis** • Age *< 65 years, ≥ 65 years* **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded	

Short Title	Title	Study characteristics	Risk of bias and directness
		Multimorbidities excluded • Asthma • Cardiovascular disease • Other significant non-specified/ specified multimorbidities	
Beeh (2006)	Efficacy of tiotropium bromide (Spiriva) in patients with chronic-obstructive pulmonary disease (COPD) of different severities	**Additional information** • Evidence table in a systematic review *Please refer to Beeh et al 2006 in Karner et al 2014 Cochrane review.* • Data taken from a systematic review *As the study is written in German, data was extracted from Karner et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • Unclear as original study not in English **Whole trial subgroup analysis information** • ICS use unclear as trial not in English • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Other significant non-specified/ specified multimorbidities	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Unclear risk of bias *The withdrawal rates were high, but relatively even (tiotropium 17.6%, placebo 22.3%).* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low

Short Title	Title	Study characteristics	Risk of bias and directness
			Directness • Directly applicable
Brusasco (2003)	Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD	**Additional information** • Evidence table in a systematic review *Please refer to Karner et al 2014 Cochrane Review* • Data taken from a systematic review *It was unclear whether the study presented mean difference with SE or SD. The data for the outcomes reported in this way was taken from the Cochrane review and they had access to unpublished information.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Other significant non-specified/ specified multimorbidities	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • High risk of bias *The withdrawal rates were relatively high and uneven (tiotropium 15.4%, placebo 25.8%).* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
			Overall risk of bias • Moderate *Due to the high drop-out rate in the placebo arm compared to the intervention arm.* **Directness** • Directly applicable
Casaburi (2002)	A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease.	**Additional information** • Evidence table in a systematic review *Please refer to the entry for Casaburi et al 2002 in the Karner et al 2014 Cochrane review.* • Data taken from a systematic review *Data was presented as a range of means (SE) over the duration of the trial for FEV1, and SGRQ was shown graphically in the original paper.* **Relevant within trial subgroup analyses** • Exacerbation frequency (<1, ≥ 1) *See Anzueto 2009 for data on SGRQ and trough FEV1* • Exacerbation frequency (<2, ≥ 2) *See Anzueto 2009 for data on SGRQ and trough FEV1* • None **Additional within trial subgroup analysis** • Treatment naive participants *Analysis in Adams 2006.* **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • High risk of bias *The withdrawal rates were high and uneven (tiotropium 18.7%, placebo 27.8%).*

Short Title	Title	Study characteristics	Risk of bias and directness
		• Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the high withdrawal rate in the placebo arm compared to the intervention arm.* **Directness** • Directly applicable
Chapman (2014)	A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study	**Trial name** • GLOW5 **Trial Registration number(s)** • NCT01613326 **Study type** • Randomised controlled trial **Study details** • Study location(s) *Canada.* • Study setting *Not specified, but multiple sites were involved.* • Study dates *Not specified.*	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias *Blinding was achieved by specifying that the study medications be dispensed by a third party not involved in other aspects of the study, and by the use of study drugs that were similar in appearance, with the*

Short Title	Title	Study characteristics	Risk of bias and directness
		• Duration of follow-up *12 weeks* • Sources of funding *The study was sponsored by Novartis Pharma AG.* **Inclusion criteria** • Age ≥ 40 years • Post-bronchodilator FEV1, % predicted *≥ 30% and < 80%.* • Moderate to severe COPD (GOLD 2-3) • Smoking history *Current or ex-smokers with a smoking history of at least 10 pack-years.* • FEV1/FVC, % predicted *<0.7* • Stable COPD **Exclusion criteria** • Asthma *History of asthma* • Recent COPD exacerbation *Requiring treatment with antibiotics and/or oral corticosteroids and/or hospitalization 6 weeks prior to screening.* • Recent respiratory tract infection *Within 4 weeks prior to screening.* • History of malignancy • Clinically significant cardiovascular disease *Such as unstable ischemic heart disease, New York Heart Association class III/IV left ventricular failure, myocardial infarction, arrhythmia (including paroxysmal atrial fibrillation).* • Long QT syndrome or QTc >450 ms	*same schedule of administration. Personnel were also blinded to group allocation.* **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		• Drug contraindications *Contraindications for tiotropium or ipratropium, or history of adverse reactions to inhaled anticholinergics.* • Diabetes • Renal impairment or urinary retention • A known history and/or diagnosis of alpha-1 antitrypsin deficiency • Participation in the active phase of a supervised pulmonary rehabilitation programme • Symptomatic prostatic hyperplasia • Bladder-neck obstruction **Sample characteristics** • Sample size *657* • Split between study groups *Glycopyrronium: 327 Tiotropium: 330* • Loss to follow-up *Glycopyrronium: 314/327 (96.0%) of participants completed the trial. Tiotropium: 316/330 (95.8%) of participants completed the trial.* • % female *Glycopyrronium: 27.5% Tiotropium: 24.8%* • Mean age (SD) *63.5 years (8.0)* • Smoking status and history *Smoking history, n (%): Glycopyrronium; Tiotropium Ex-smoker: 179 (54.7); 182 (55.2) Current smoker: 148 (45.3); 148 (44.8).* *Mean (SD) duration of smoking, pack-years: Glycopyrronium; Tiotropium 39.6 (20.4); 40.2 (21.5).* • Baseline pulmonary medication	

Short Title	Title	Study characteristics	Risk of bias and directness
		ICS use at baseline, n (%): Glycopyrronium; Tiotropium 163 (49.8); 174 (52.7). **Interventions** • Tiotropium 18 micrograms once daily *Delivered via the HandiHaler® device with a placebo delivered via the Breezhaler® device.* • Glycopyrronium 50 mcg once daily *Delivered via the Breezhaler® device with a placebo delivered via the HandiHaler® device.* • Concomitant medication *Patients on fixed-dose LABA/ ICS combinations were switched to an equivalent dose of ICS contained in the fixed-dose combination. Patients were provided with a salbutamol/albuterol (short-acting β2-agonist; SABA) inhaler to be used as rescue medication during the study.* **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • Transition Dyspnoea Index (TDI) • Trough FEV1 • Exacerbations *COPD exacerbations were defined as worsening of two or more major symptoms for at least 2 consecutive days or worsening of any one major symptom together with any minor symptom for at least 2 consecutive days. Exacerbations were considered to be of moderate severity if they required treatment with systemic corticosteroids, antibiotics or both, and were considered severe if they also required hospitalization.* • Serious Adverse Events (SAEs) • Cardiac and COPD serious adverse events • Pneumonia	

Short Title	Title	Study characteristics	Risk of bias and directness
		• Drop-outs due to adverse events **Other outcome measures** • Trough FVC and FVC AUC responses • All adverse events **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	
Donohue (2013a)	Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD	**Trial Registration number(s)** • NCT01313650 **Additional information** • Evidence table in a systematic review *Please refer to Donahue 2013 in Ni et al 2017 Cochrane review* • Data taken from a systematic review *Data for SGRQ total score, exacerbations and for sample sizes for some outcomes were taken from the Ni et al 2017 Cochrane review.* • Data obtained from the authors: *The authors kindly confirmed that the participants were not allowed to take LABAs for the duration of the trial.*	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Relevant within trial subgroup analyses • None **Whole trial subgroup analysis information** • ICS use allowed *But not at doses > 1000mcg/day* • Theophylline use not allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease *Excluded if this was uncontrolled.* • Other significant non-specified/ specified multimorbidities *Excluded if this was uncontrolled.*	**Incomplete outcome data** • Unclear risk of bias *Withdrawal rates and reasons were similar between groups although relatively high (umeclidinium 22%, and placebo 27%) for a short trial duration. Numbers of withdrawals and reasons were clearly stated for both intervention and placebo arms.* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
D'Urzo (2011)	Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial.	**Trial name** • GLOW1 **Trial Registration number(s)** • NCT01005901	**Random sequence generation** • Unclear risk of bias *No details were provided.* **Allocation concealment** • Unclear risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Study type • Randomised controlled trial **Study details** • Study location(s) *USA, Canada, Australia, Japan, Republic of Korea, The Netherlands, Romania, Russia, Singapore, Spain, Turkey.* • Study setting *Novartis Investigative Sites in the participating countries.* • Study dates *Not stated.* • Duration of follow-up *26 weeks* • Sources of funding *The study was sponsored by Novartis Pharma AG.* **Inclusion criteria** • Age ≥ 40 years • Post-bronchodilator FEV1, % predicted *< 80% and ≥ 30%* • Moderate to severe COPD (GOLD 2-3) • Smoking history *≥ 10 pack-years* • FEV1/FVC, % predicted *<0.7* **Exclusion criteria** • Asthma • Recent respiratory tract infection *Within the last 6 weeks*	*No information was provided.* **Blinding of participants and personnel** • Unclear risk of bias *No information was provided, but the intervention and placebo had matching inhaler devices so the participants should have been blind to their group allocation.* **Blinding of outcome assessment** • Unclear risk of bias *No information was provided.* **Incomplete outcome data** • Unclear risk of bias *Only 81.5% of participants taking glycopyrronium and 78.5% taking the placebo completed the study, but the reasons for discontinuation (and the % of people involved) were similar across both arms in most cases.* **Selective reporting** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		• Lung cancer • Concomitant pulmonary diseases • Long QT syndrome or QTc >450 ms • Drug contraindications *Contraindications for tiotropium or ipratropium or had experienced adverse reactions to inhaled anticholinergics.* • Renal impairment or urinary retention • A known history and/or diagnosis of alpha-1 antitrypsin deficiency • Participation in the active phase of a supervised pulmonary rehabilitation programme • Symptomatic prostatic hyperplasia • Narrow-angle glaucoma **Sample characteristics** • Sample size *822* • Split between study groups *Glycopyrronium: 552; Placebo: 270.* • Loss to follow-up *450/552 (81.5%) of the participants on Glycopyrronium completed the study. 212/270 (78.5%) of the participants taking the placebo completed the study.* • % female *18.1* • Mean age (SD) *Glycopyrronium: 63.8 (9.47); placebo: 64.0 (8.96)* • Smoking status and history *Smoking history, n (%) Ex-smoker: glycopyrronium 370 (67.3); placebo 176 (65.9) Current Smoker: glycopyrronium 180 (32.7); placebo 91 (34.1). Mean (SD) duration of smoking, pack years: glycopyrronium 44.9 (28.08); placebo 44.6 (24.80).*	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the lack of information on blinding, randomisation and group allocation, and numbers of people withdrawing from the study.* **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		• Baseline pulmonary medication *ICS use at baseline, n (%): glycopyrronium 301 (54.7); placebo 136 (50.9).* **Interventions** • Placebo *Administered once daily via a low-resistance single- dose dry-powder inhaler (SDDPI; Breezhaler®).* • Glycopyrronium 50 mcg once daily *Administered via a low-resistance single- dose dry-powder inhaler (SDDPI; Breezhaler®).* • Concomitant medication *Inhaled corticosteroids (ICS), intranasal corticosteroids or H1 antagonists were permitted in patients who had been stabilized on a recommended and constant dose prior to study entry. Patients were required to cease taking long-acting bronchodilator therapy before beginning the run-in period and were instructed to use rescue medication. Patients receiving LABA/ICS combinations were switched to an equivalent dose of the ICS contained in the fixed-dose combination product, with rescue medication if required. Patients previously treated with a single-agent ICS continued on their pre-study regimen. Patients were provided with a salbutamol/albuterol inhaler to use as rescue medication throughout the study.* **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • Transition Dyspnoea Index (TDI) • Trough FEV1 • Exacerbations *Time to first moderate or severe COPD exacerbation. Exacerbations were considered to be of moderate severity if they required treatment with systemic corticosteroids or an antibiotic and were considered severe if they also required*	

Short Title	Title	Study characteristics	Risk of bias and directness
		hospitalization. • Serious Adverse Events (SAEs) **Other outcome measures** • All adverse events • Electrocardiogram recordings • Use of rescue medication • Inspiratory capacity **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma	
D'Urzo (2014b)	Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study	**Trial name** • AUGMENT COPD **Trial Registration number(s)** • NCT01437397 **Additional information** • Evidence table in a systematic review *Please refer to the AUGMENT entry in Ni et al 2014 Cochrane review.* • Data taken from a systematic review *Where data was presented graphically, in an inaccessible format or without SE,*	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment**

Short Title	Title	Study characteristics	Risk of bias and directness
		SD or 95% CI, the results were taken from Ni et al 2014 Cochrane review. **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	• Low risk of bias **Incomplete outcome data** • High risk of bias *A larger percentage of participants in the placebo arm withdrew from the trial (30%), compared to 21% in the intervention arm.* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the large and uneven dropout rates between the trial arms.* **Directness** • Directly applicable
Dusser (2006)	The effect of tiotropium on exacerbations and airflow in patients with COPD	**Trial Registration number(s)** • 205.214 **Additional information** • Evidence table in a systematic review	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Please refer to Dusser et al 2006 in Karner et al 2014 Cochrane review. **Relevant within trial subgroup analyses** • COPD severity *Based on FEV1, for the mean number of exacerbations/ patient/ year* • ICS use *For the mean number of exacerbations/ patient/ year* • Exacerbation frequency *For the mean number of exacerbations/ patient/ year in people with 1, 2 or at least 3 exacerbations in the previous year.* **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use not allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Other significant non-specified/ specified multimorbidities	**Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Unclear risk of bias *Withdrawal rates were relatively large but even between arms (tiotropium 23.4%, placebo 28.8%).* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
Feldman (2016)	A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5	**Trial Registration number(s)** • NCT02207829	**Random sequence generation** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
	mug compared with tiotropium 18 mug in patients with COPD	**Study type** • Randomised controlled trial **Study details** • Study location(s) *Canada, Chile, Denmark, France, Germany, Italy, Romania, Korea, South Africa, the Russian Federation, the Ukraine, and the USA.* • Study setting *Unspecified clinics.* • Study dates *September 2014 and June 2015.* • Duration of follow-up *12 weeks* • Sources of funding *This study was funded and conducted by GSK (GSK study number: 201316).* **Inclusion criteria** • Age ≥ 40 years • Diagnosis of COPD *Diagnosis of COPD in accordance with the American Thoracic Society/European Respiratory Society.* • Post-bronchodilator FEV1, % predicted *Post-albuterol/salbutamol FEV1 of 30%–70%.* • Smoking history *Current or former cigarette smokers with ten or more pack-years cigarette smoking history.* • FEV1/FVC, % predicted *Pre- and post-albuterol/salbutamol FEV1/FVC ratio of <0.70* • Breathlessness score *Breathlessness score of ≥2 on the modified Medical Research Council*	**Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias *The participants received 2 different matching inhalers to mask treatment allocation. The study personnel were also blind to allocation.* **Blinding of outcome assessment** • Low risk of bias *The coordinator involved with efficacy and safety assessments was blinded to treatment assignment.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Dyspnoea Scale at Visit 1. **Exclusion criteria** • Asthma *A current diagnosis of asthma.* • Another significant disease *A current diagnosis of a significant respiratory disorder or other condition that may affect respiratory function (e.g. unstable or life-threatening cardiac disease, a neurological condition).* • Recent COPD exacerbation *Hospitalization for COPD/pneumonia within 12 weeks prior to Visit 1.* • Pregnancy • Lung volume reduction surgery • Use of long-term oxygen therapy *Prescribed for >12 hours per day.* • Use of COPD maintenance medications other than study medication or ICS • Use of other prohibited medications within a specified time *These included the phosphodiesterase 4 inhibitor (roflumilast); inhaled LABAs; LAMAs. The exclusion times prior to study visit 1 vary across the drugs.* **Sample characteristics** • Sample size *1,017* • Split between study groups *Umeclidinium: 509 Tiotropium: 508* • Loss to follow-up *Umeclidinium: 467/509 (91.7%) participants completed the trial.* *Tiotropium:474/508 (93.3%) participants completed the trial.* • % female *27.7*	**Overall risk of bias** • Low **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		• Mean age (SD) *64.2 years (8.2)* • Smoking status and history *Current smoker at screening, n (%): 519 (51%)* *Smoking pack-years: 41.6 (21.6)* • Baseline pulmonary medication *ICS use at screening ICS users, n (%): 476 (47)* **Interventions** • Tiotropium 18mcg once daily *Once-daily TIO 18 mcg (delivering 10mcg) administered via the HandiHaler® plus placebo administered via the ELLIPTA™ dry powder inhaler.* • Umeclidinium 62.5mcg *Once-daily UMEC 62.5 mcg (delivering 55 mcg) administered via the ELLIPTA™ dry powder inhaler plus placebo administered via the HandiHaler®.* • Concomitant medication *The use of COPD maintenance medications other than study medication, with the exception of inhaled corticosteroids (ICSs) was not permitted. People on LABA/ICS were included if they switched to ICS monotherapy. Patients were provided albuterol/salbutamol for use as a rescue medication.* **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • St George Respiratory Questionnaire responders *SGRQ responders were defined by a reduction from baseline of ≥4 units in SGRQ total score.* • Transition Dyspnoea Index (TDI) • Trough FEV1 • Exacerbations *A COPD exacerbation was defined as an acute worsening of symptoms of*	

Short Title	Title	Study characteristics	Risk of bias and directness
		COPD requiring the use of any treatment beyond study medication or rescue albuterol/salbutamol. This included the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization. **Other outcome measures** • All adverse events • Trough FCV • COPD Assessment Test (CAT) score *Including the proportion of CAT responders (defined as a reduction from baseline of ≥2 units in CAT score.* • Use of rescue medication *Assessed by the mean number of puffs/day of rescue medication and percentage of rescue-free days over the study duration.* • Inhaler errors and patient inhaler preference **Relevant within trial subgroup analyses** • COPD severity *Global initiative for chronic Obstructive Lung Disease (GOLD) Grade 1/2 and Grade 3/4, and GOLD Groups B and D for trough FEV1 outcome.* • ICS use *+/-ICS and an analysis by GOLD Grade 1/2 and Grade 3/4, each split by ICS use, was also performed for the trough FEV1 outcome.* **Additional within trial subgroup analysis** • FEV1 responder analysis (by GOLD grade) **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use not allowed	

Short Title	Title	Study characteristics	Risk of bias and directness
		• Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	
Johansson (2008)	Bronchodilator efficacy of tiotropium in patients with mild to moderate COPD	**Trial Registration number(s)** • 205.281 **Additional information** • Evidence table in a systematic review *Please refer to Johansson et al 2008 in Karner et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use not allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
			Overall risk of bias • Low **Directness** • Directly applicable
Jones (2012)	Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study.	**Trial name** • ATTAIN **Trial Registration number(s)** • NCT01001494 **Additional information** • Evidence table in a systematic review *Please refer to ATTAIN entry in Ni et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Unclear risk of bias *The number of withdrawals were low, but higher in the placebo group (14.9%) compared to the intervention group (6.3%).* **Selective reporting** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
			Other sources of bias • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
Kerwin (2012b)	Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I).	**Trial name** • ACCORD COPD I **Trial Registration number(s)** • NCT00891462 **Additional information** • Evidence table in a systematic review *Please refer to ACCORD COPD I entry in Ni et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias *Withdrawals were relatively low and balanced across the groups with similar reasons (aclidinium 12.6%, placebo 19.9%).*

Short Title	Title	Study characteristics	Risk of bias and directness
			Selective reporting • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
Kerwin (2012c)	Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study	**Trial name** • GLOW2 **Trial Registration number(s)** • NCT00929110 **Additional information** • Data extraction information *Data was not extracted for tiotropium as it was provided open-label.* **Study type** • Randomised controlled trial **Study details** • Study location(s) *USA, Argentina, Canada, Chile, France, Germany, Hungary, Israel, Italy, Republic of Korea, Mexico, The Netherlands, New Zealand, Peru, Poland, Russia.* • Study setting	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Unclear risk of bias *<80% of the participants completed the trial in both arms. The reasons (and percentages)*

Short Title	Title	Study characteristics	Risk of bias and directness
		Multiple Novartis Investigative Sites in each country. • Study dates *June 2009- April 2011* • Duration of follow-up *52 weeks* • Sources of funding *Novartis* **Inclusion criteria** • Age ≥ 40 years • Post-bronchodilator FEV1, % predicted *< 80% and ≥ 30%* • Moderate to severe COPD (GOLD 2-3) • Smoking history *≥ 10 pack-years* • FEV1/FVC, % predicted *<0.7* **Exclusion criteria** • Asthma • Recent COPD exacerbation *An exacerbation that required hospitalisation within the last 6 weeks prior to screening.* • Recent respiratory tract infection *Within the last 6 weeks.* • History of malignancy *Of any organ system (including lung cancer and with the exception of localised basal cell carcinoma of the skin).* • Concomitant pulmonary diseases *Such as pulmonary tuberculosis (unless confirmed by x-ray to be no longer*	*were comparable across the arms, apart from for adverse events, which was greater in the placebo arm (11.0% versus 7.6%).* **Selective reporting** • Unclear risk of bias *The percentage of people with night-time awakenings and day time symptoms was not reported.* **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the low completion rate and lack of reporting on some of the secondary outcomes mentioned in the clinical trial record.* **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		active) or clinically significant bronchiectasis. • Long QT syndrome or QTc >450 ms • History of myocardial infarction *or arrhythmia, but excluding chronic stable atrial fibrillation.* • Pregnancy *Women of child-bearing potential not using an accepted form of contraception, pregnant women, and nursing mothers were excluded.* • Use of long-term oxygen therapy *> 15 hours a day* • Drug contraindications *For tiotropium/ipratropium or had shown previous untoward reaction to inhaled anticholinergic agents.* • Renal impairment or urinary retention *Moderate to severe* • A known history and/or diagnosis of alpha-1 antitrypsin deficiency • Participation in the active phase of a supervised pulmonary rehabilitation programme • Symptomatic prostatic hyperplasia • Bladder-neck obstruction • Narrow-angle glaucoma • Ischemic heart disease • Left ventricular failure **Sample characteristics** • Sample size *1,066* • Split between study groups *Glycopyrronium: 529; Placebo: 269; Tiotropium: 268.* • Loss to follow-up *411/529 (77.7%) of the participants taking Glycopyrronium completed the trial.*	

Short Title	Title	Study characteristics	Risk of bias and directness
		193/269 (71.7%) of the participants taking the placebo completed the trial. • % female *35.4* • Mean age (SD) *Glycopyrronium: 63.5 (9.1); placebo: 63.6 (9.1).* • Smoking status and history *Smoking history Ex-smoker: glycopyrronium 287 (54.7); placebo 144 (53.7). Current smoker: glycopyrronium 238 (45.3); placebo 124 (46.3). Duration of smoking in pack-yrs, Mean (SD): glycopyrronium 49.0 (25.4); placebo 48.0 (24.0)* • Baseline pulmonary medication *Patients on different COPD medications prior to start of study, glycopyrronium; placebo, n (%). LAMA 134 (25.5); 66 (24.6). LABA 58 (11.0); 38 (14.2). SABA 229 (43.9); 105 (39.2). SAMA 66 (12.6); 36 (13.4). ICS+LABA 194 (37.0); 88 (32.8). Xanthine derivatives 32 (6.1); 15 (5.6). ICS 13 (2.5); 4 (1.5). Leukotriene modifiers 4 (0.8); 7 (2.6).* **Interventions** • Tiotropium 18mcg once daily *Open-label tiotropium 18 mg (delivered via the HandiHaler device; Boehringer Ingelheim).* • Placebo *Delivered via a low-resistance single-dose dry-powder inhaler (the Breezhaler1 device; Novartis).* • Glycopyrronium 50 mcg once daily *Delivered via a low-resistance single-dose dry-powder inhaler (the Breezhaler1 device; Novartis).* • Concomitant medication *Patients were to discontinue taking long-acting bronchodilator therapy before starting the run-in period. Patients using LABA/ICS combinations were switched*	

Short Title	Title	Study characteristics	Risk of bias and directness
		to an equivalent dose of ICS as monotherapy plus rescue medication. Patients were expected to remain on the same dose of ICS throughout the study. Inhaled or intranasal corticosteroids and H1 antagonists were permitted in patients who had been on a stable dose prior to study entry. Patients were provided with a salbutamol/albuterol inhaler to be used as rescue medication during the study. **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • Transition Dyspnoea Index (TDI) • Trough FEV1 *Taken at 12 weeks for primary outcome measure.* • Exacerbations *Number of moderate or severe exacerbations and time to first moderate or severe exacerbation.* • Serious Adverse Events (SAEs) **Other outcome measures** • All adverse events *All treatment-emergent adverse events were recorded.* • Trough FCV *and FVC post-dose.* • Use of rescue medication • Peak FEV1 • Night-time awakenings and daytime symptoms *Percentage of Nights With no Night-time Awakenings and days with no symptoms (such as coughing, sputum, need for rescue medication).* **Relevant within trial subgroup analyses** • None	

Short Title	Title	Study characteristics	Risk of bias and directness
		Whole trial subgroup analysis information • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease • Other significant non-specified/ specified multimorbidities	
Lee (2015)	Efficacy and safety of aclidinium bromide in patients with COPD: A phase 3 randomized clinical trial in a Korean population	**Trial Registration number(s)** • NCT01636401 **Study type** • Randomised controlled trial **Study details** • Study location(s) *South Korea* • Study setting *Not stated.* • Study dates *Participants were randomised between August 2012 and February 2013.* • Duration of follow-up *12 weeks* • Sources of funding *This study was supported by Daewoong Pharmaceutical Company Ltd. Republic of Korea.* **Inclusion criteria** • Age ≥ 40 years • Moderate to severe COPD (GOLD 2-3)	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		• Smoking history *≥ 10 pack-years* • Stable COPD **Exclusion criteria** • Recent COPD exacerbation *Requiring hospitalisation within the last 3 months or any exacerbation ≤ 6 weeks before screening.* • Recent respiratory tract infection *≤ 6 weeks before screening.* • Concomitant pulmonary diseases • Clinically significant cardiovascular disease *Including myocardial infarction within 6 months or newly diagnosed arrhythmia within 3 months before screening.* • Drug contraindications *History of hypersensitivity reactions or contraindications to inhaled anticholinergic drugs.* **Sample characteristics** • Sample size *263* • Split between study groups *Aclidinium: 134; Placebo: 129.* • Loss to follow-up *240/263 (91.3%) of participants completed the trial.* • % female *1.91* • Mean age (SD) *68.0 years (7.3)* • Smoking status and history	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Smoking history, mean (SD), pack-years. Aclidinium: 39.4 (17.3) Placebo: 42.5 (18.3) **Interventions** • Placebo *Inhaler device not specified.* • Aclidinium 400mcg twice daily *Inhaler device not specified.* • Concomitant medication *Theophylline, ICS and oral/parenteral corticosteroids at ≤ 10mcg daily prednisone or its corticosteroid equivalent were permitted if the dose was stable for at least 4 weeks before screening. Other inhaled LAMAs and LABAs were prohibited during the study.* **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • St George Respiratory Questionnaire responders • Transition Dyspnoea Index (TDI) • Trough FEV1 • Exacerbations *Defined as an increase in COPD symptoms lasting ≥ 2 consecutive days. Exacerbations were defined as mild (self-managed using rescue medication or increasing ICS use), moderate (treatment with antibiotics or systemic corticosteroids) or severe (requiring hospitalisation).* **Other outcome measures** • Trough FVC and FVC AUC responses • All adverse events • Electrocardiogram recordings • Trough FCV	

Short Title	Title	Study characteristics	Risk of bias and directness
		• Peak FEV1 **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded **Multimorbidities excluded** • Cardiovascular disease	
Rennard (2013)	ACCORD COPD II: a randomized clinical trial to evaluate the 12-week efficacy and safety of twice-daily aclidinium bromide in chronic obstructive pulmonary disease patients	**Trial name** • ACCORD COPD II **Trial Registration number(s)** • NCT01045161 **Additional information** • Evidence table in a systematic review *Please refer to ACCORD COPD II entry in Ni et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias *The number of withdrawals were relatively low and even across the*

Short Title	Title	Study characteristics	Risk of bias and directness
		Multimorbidities excluded • Cardiovascular disease	*groups with similar reasons (aclidinium 16.9% and placebo 17%).* **Selective reporting** • Low risk of bias **Other sources of bias** • High risk of bias *There was an imbalance in the trial arms as a relatively higher percentage of severe COPD patients were recruited in aclidinium 400mcg arm than placebo.* **Overall risk of bias** • Moderate *Due to the imbalance in participant characteristics between trial arms.* **Directness** • Directly applicable
Singh (2014a)	Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with	**Trial name** • ACLIFORM COPD **Trial Registration number(s)** • NCT01462942	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
	individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study	**Additional information** • Evidence table in a systematic review *Please refer to the ACLIFORM entry in Ni et al 2014 Cochrane review.* • Data taken from a systematic review *Where data is only presented graphically or the mean change is given without SD, SE or 95% CI in the original paper, then the corresponding numbers have been taken from Ni et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias *Withdrawal rates were somewhat higher in the placebo group, but overall low in all groups (aclidinium 13%, placebo 17.5%).* **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
Singh (2015a)	Tiotropium + olodaterol shows clinically meaningful	**Trial name** • OTEMTO 1 • OTEMTO 2	**Random sequence generation** • Unclear risk of bias *No information provided.*

Short Title	Title	Study characteristics	Risk of bias and directness
	improvements in quality of life	**Trial Registration number(s)** • NCT01964352 • NCT02006732 **Study type** • Randomised controlled trial **Study details** • Study location(s) *The trials were multinational with sites in countries including USA, Austria, Germany, UK and Sweden.* • Study setting *Not specified.* • Study dates *Not specified.* • Duration of follow-up *12 weeks* • Sources of funding *This work was supported by Boehringer Ingelheim Pharma GmbH & Co. KG.* **Inclusion criteria** • Age ≥ 40 years • Post-bronchodilator FEV1, % predicted *Between 30% and 80% of predicted normal.* • Moderate to severe COPD (GOLD 2-3) • Smoking history *> 10 pack-years* • FEV1/FVC, % predicted *<0.7*	**Allocation concealment** • Unclear risk of bias *No information provided.* **Blinding of participants and personnel** • Unclear risk of bias *Study states that it is double-blind, but no details are provided. All drugs were supplied to participants used the Respimat® inhaler, which presumably means that they were blind to their group allocation.* **Blinding of outcome assessment** • Unclear risk of bias *No information provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Exclusion criteria • Asthma • Another significant disease *No details provided.* • Recent COPD exacerbation *Within the previous 3 months.* • Recent respiratory tract infection *Within the previous 3 months.* • History of life-threatening pulmonary obstruction • Unstable or life-threatening cardiac arrhythmia • A history of heart failure *Hospitalisation for heart failure within the last year.* • History of myocardial infarction *Within 1 year of screening for the trial.* **Sample characteristics** • Sample size *OTEMTO 1: 812; OTEMTO 2: 809.* • Split between study groups *OTEMTO 1: placebo 204; Tiotropium 5mcg 203; other combined drug doses 405. OTEMTO 2: placebo 202; Tiotropium 5mcg 203; other combined drug doses 404.* • Loss to follow-up *OTEMTO 1: 178/204 (87.3%) completed the trial in the placebo group; 192/204 (94.6%) completed the trial in the tiotropium group. OTEMTO 2: 182/224 (90.1%) completed the trial in the placebo group; 191/203 (94.1%) completed the trial in the tiotropium group.* • % female *OTEMTO 1: 40.8% OTEMTO 2: 37.5%* • Mean age (SD)	**Overall risk of bias** • High *For subjective outcome measures such as SGRQ and TDI, which are more at risk of bias if blinding was insufficient. The lack of information about randomisation also remains a problem.* • Moderate *Due to the lack of information regarding randomisation and blinding of personnel and outcome assessors. However, outcomes such as mortality and number of exacerbations are unlikely to be affected by risk of bias caused by the lack of blinding.* **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		OTEMTO 1: 64.9 years (8.4) OTEMTO 2: 64.6 YEARS (8.4) • Smoking status and history *Smoking status, n (%) OTEMTO 1 Ex-smoker: placebo 116 (56.9); tiotropium 105 (51.7) Current smoker: placebo 88 (43.1); tiotropium 98 (48.3) OTEMTO 2 Ex-smoker: placebo 107 (53.0); tiotropium 112 (55.2) Current smoker: placebo 95 (47.0); tiotropium 91 (44.8)* • Baseline pulmonary medication *OTEMTO 1 Baseline pulmonary medication, placebo n (%); triotropium n (%). Any 156 (76.5); 160 (78.8). ICS 71 (34.8); 77 (37.9). LAMA 83 (40.7); 64 (31.5). SAMA 13 (6.4); 18 (8.9). LABA 78 (38.2); 78 (38.4). SABA 101 (49.5); 112 (55.2). OTEMTO 2 Baseline pulmonary medication, placebo n (%); triotropium n (%). Any 156 (77.2); 158 (77.8). ICS 71 (35.1); 71 (35.0). LAMA 59 (29.2); 77 (37.9). SAMA 16 (7.9); 15 (7.4). LABA 76 (37.6); 81 (39.9). SABA 107 (53.0); 109 (53.7).* **Interventions** • Tiotropium 5mcg *Respimat® inhaler* • Placebo *Respimat® inhaler* • Tiotropium and olodaterol 5/5 mcg *Respimat® inhaler* • Tiotropium and olodaterol 2.5/5 mcg *Respimat® inhaler* • Concomitant medication *Patients were allowed to continue their inhaled corticosteroid therapy (if they were on a stable dose for 6 weeks prior to screening). LAMAs or LABAs other than study medication were prohibited during the screening or treatment periods, and short acting muscarinic antagonists were permitted only during the screening period. Open-label salbutamol was provided as rescue medication for*	

Short Title	Title	Study characteristics	Risk of bias and directness
		use throughout the study. **Relevant outcome measures** • St George's Respiratory Questionnaire (SGRQ) • St George Respiratory Questionnaire responders *People with ≥ 4.0 units improvement.* • Transition Dyspnoea Index (TDI) • Trough FEV1 *Trough FEV1 was defined as the mean of the FEV1 values at 23 h post-dose and 23 h 50 min post-dose.* • Serious Adverse Events (SAEs) **Other outcome measures** • Trough FVC and FVC AUC responses • All adverse events • Electrocardiogram recordings *Abnormalities were reported as adverse events.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	

Short Title	Title	Study characteristics	Risk of bias and directness
Tonnel (2008)	Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD	**Additional information** • Evidence table in a systematic review *Please refer to Tonnel et al 2008 in Karner et al Cochrane review.* • Data taken from a systematic review *Data on trough FEV1 was taken from the Cochrane review as it was presented as a graph in the original paper.* **Relevant within trial subgroup analyses** • COPD severity *Based on FEV1 % predicted- mean change from baseline in SGRQ total score.* • ICS use *Data for mean change from baseline in SGRQ total score* **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • High risk of bias *The withdrawal rates were large and uneven (tiotropium 14.7%, placebo 25.7%)* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the large withdrawal rate in the placebo arm compared to the*

Short Title	Title	Study characteristics	Risk of bias and directness
			intervention arm. **Directness** • Directly applicable
Trivedi (2014)	Umeclidinium in patients with COPD: a randomised, placebo-controlled study	**Trial Registration number(s)** • NCT01387230 **Additional information** • Evidence table in a systematic review *Please refer to Trivedi 2014 in Ni et al 2017 Cochrane review.* • Data taken from a systematic review *Data for the number of SGRQ responders and people with severe exacerbations was taken from the Ni et al 2017 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Other significant non-specified/ specified multimorbidities	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • High risk of bias *The withdrawal rate was uneven, but with similar reasons between the umeclidinium and placebo groups (umeclidinium 62.5mcg 10%, and placebo 26%).* **Selective reporting** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
			Other sources of bias • Low risk of bias **Overall risk of bias** • Moderate *Due to the large withdrawal rate in the placebo arm compared to the intervention arm.* **Directness** • Directly applicable
Troosters (2014)	Tiotropium in patients with moderate COPD naive to maintenance therapy: a randomised placebo-controlled trial	**Trial Registration number(s)** • NCT00523991 **Additional information** • Evidence table in a systematic review *Please refer to Troosters et al 2011 entry in Karner et al 2014 Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use not allowed • Theophylline use not allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Multimorbidities included • Cardiovascular disease included	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
Verkindre (2006)	The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease	**Trial Registration number(s)** • 205.215 **Additional information** • Evidence table in a systematic review *Please refer to Verkindre et al 2006 in Karner et al Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • High risk of bias *The withdrawal rates were relatively low, but uneven (tiotropium 2.2%, placebo 16.7%).*

Short Title	Title	Study characteristics	Risk of bias and directness
			Selective reporting • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Due to the uneven withdrawal rate across the trial arms.* **Directness** • Directly applicable
Voshaar (2008)	A randomized study of tiotropium Respimat Soft Mist inhaler vs. ipratropium pMDI in COPD	**Trial Registration number(s)** • 205.251 • 205.252 **Additional information** • Evidence table in a systematic review *Please refer to Voshaar et al 2008 in Karner et al Cochrane review.* **Relevant within trial subgroup analyses** • None **Whole trial subgroup analysis information** • ICS use allowed • Theophylline use allowed • Multimorbidities excluded	**Random sequence generation** • Low risk of bias **Allocation concealment** • Low risk of bias **Blinding of participants and personnel** • Low risk of bias **Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Multimorbidities excluded • Asthma	**Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable
Wang (2015)	Efficacy and safety of once-daily glycopyrronium in predominantly Chinese patients with moderate-to-severe chronic obstructive pulmonary disease: the GLOW7 study	**Trial name** • GLOW7 **Study type** • Randomised controlled trial **Study details** • Study location(s) *People's Republic of China, Korea, India, and the Philippines.* • Study setting *37 centres in four countries. The majority of centres were in the People's Republic of China (25 centres).* • Study dates *Not stated* • Duration of follow-up *26 weeks* • Sources of funding *The study was funded by Novartis Pharma AG, Basel, Switzerland.*	**Random sequence generation** • Unclear risk of bias *Lack of information regarding method of randomisation.* **Allocation concealment** • Unclear risk of bias *Lack of information regarding method of allocation concealment.* **Blinding of participants and personnel** • Unclear risk of bias *There is no information about whether the study personnel were blinded to allocation, but participants received identical inhalers and so should have been*

Short Title	Title	Study characteristics	Risk of bias and directness
		Inclusion criteria • Age ≥ 40 years • Post-bronchodilator FEV1, % predicted *≥30% and <80* • Moderate to severe COPD (GOLD 2-3) *According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2010) guidelines* • Smoking history *Current or ex-smokers who had a smoking history of at least 10 pack-years.* • FEV1/FVC, % predicted *<0.7* • Stable COPD • Symptomatic patients *According to daily electronic diary data.* **Exclusion criteria** • Asthma • Another significant disease *Such as paroxysmal (e.g. intermittent) atrial fibrillation with persistent atrial fibrillation;* • Recent COPD exacerbation *An exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the last year up to and including visit three or in the 6 weeks prior to visit one or between visit one and visit three.* • Recent respiratory tract infection *Within 4 weeks prior to visit one.* • History of malignancy • Concomitant pulmonary diseases • Clinically significant cardiovascular disease *Unstable ischemic heart disease, left ventricular failure (New York Heart*	*blinded.* **Blinding of outcome assessment** • Unclear risk of bias *No information is provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • High *For subjective outcome measures such as SQRG and TDI, which are more at risk of bias if blinding of personnel and outcome assessors was insufficient. The lack of information about randomisation also remains a problem.* • Moderate *Due to the lack of information regarding randomisation and blinding of personnel and*

Short Title	Title	Study characteristics	Risk of bias and directness
		Association class III or IV), history of myocardial infarction, arrhythmia. • Long QT syndrome or QTc >450 ms • Pregnancy *Also nursing mothers and women of child-bearing potential.* • Lung volume reduction surgery *Lung lobectomy or lung volume reduction or lung transplantation.* • Use of long-term oxygen therapy *> 15 hours a day.* • Drug contraindications *Patients contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: anticholinergic agents, short-acting β2-agonists, sympathomimetic amines, lactose, or any of the other excipients.* • Diabetes *Uncontrolled diabetes* • Renal impairment or urinary retention • A known history and/or diagnosis of alpha-1 antitrypsin deficiency • Participation in the active phase of a supervised pulmonary rehabilitation programme • Symptomatic prostatic hyperplasia • Bladder-neck obstruction • Narrow-angle glaucoma • Patients with allergic rhinitis who used a H1 antagonist or intra-nasal corticosteroids intermittently • Clinically significant abnormality on the ECG **Sample characteristics** • Sample size *460* • Split between study groups	*outcome assessors. However, outcomes such as mortality and number of exacerbations are unlikely to be affected by the lack of blinding.* **Directness** • Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Glycopyrronium: 306; Placebo: 154. • Loss to follow-up *Glycopyrronium: 282/306 (92.2%) of participants completed the trial. Placebo: 143/154 (92.9%) of participants completed the trial.* • % female *4.4%* • Mean age (SD) *64.7 years (8.0)* • Smoking status and history *Smoking history, n (%), Glycopyrronium; placebo. Ex-smoker: 237 (77.7); 120 (77.9). Current smoker: 68 (22.3); 34 (22.1).* • Baseline pulmonary medication *ICS use, n (%) Glycopyronnium; placebo. 198 (64.9); 86 (55.8).* **Interventions** • Placebo *Delivered via the Breezhaler® device.* • Glycopyrronium 50 mcg once daily *Delivered via the Breezhaler® device.* • Concomitant medication *Patients using LAMA/ICS combination therapy were switched to equivalent ICS monotherapy. Salbutamol/albuterol was permitted as rescue medication throughout the study.* **Relevant outcome measures** • Mortality • St George's Respiratory Questionnaire (SGRQ) • Transition Dyspnoea Index (TDI) • Trough FEV1 • Exacerbations	

Short Title	Title	Study characteristics	Risk of bias and directness
		• Serious Adverse Events (SAEs) • Cardiac and COPD serious adverse events **Other outcome measures** • All adverse events • Trough FCV • Use of rescue medication • Peak FEV1 **Relevant within trial subgroup analyses** • Smoking status (ex and non-smoker, current smoker) • COPD severity *Moderate or less, severe or worse.* • ICS use • Sex **Additional within trial subgroup analysis** • Age *< 65 years or ≥ 65 years* • Ethnicity *Chinese or other.* **Whole trial subgroup analysis information** • ICS use allowed • Multimorbidities excluded **Multimorbidities excluded** • Asthma • Cardiovascular disease • Other significant non-specified/ specified multimorbidities	

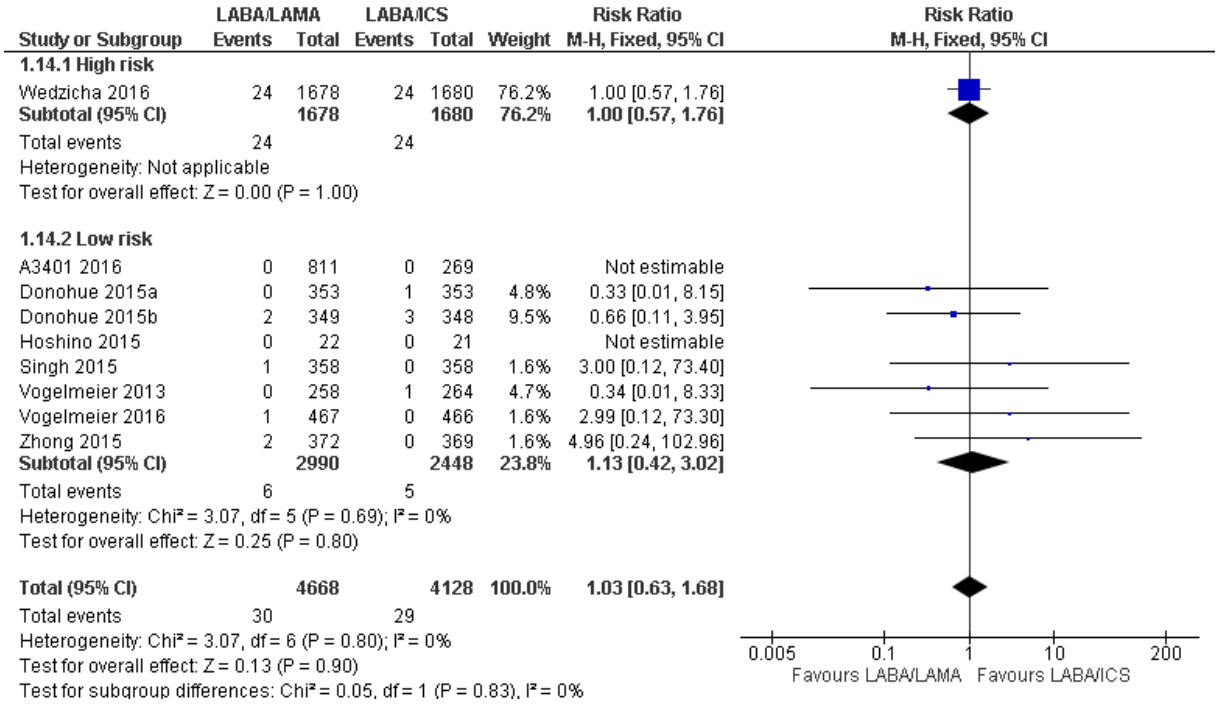
Appendix F – Forest plots

Inhaled therapy combinations

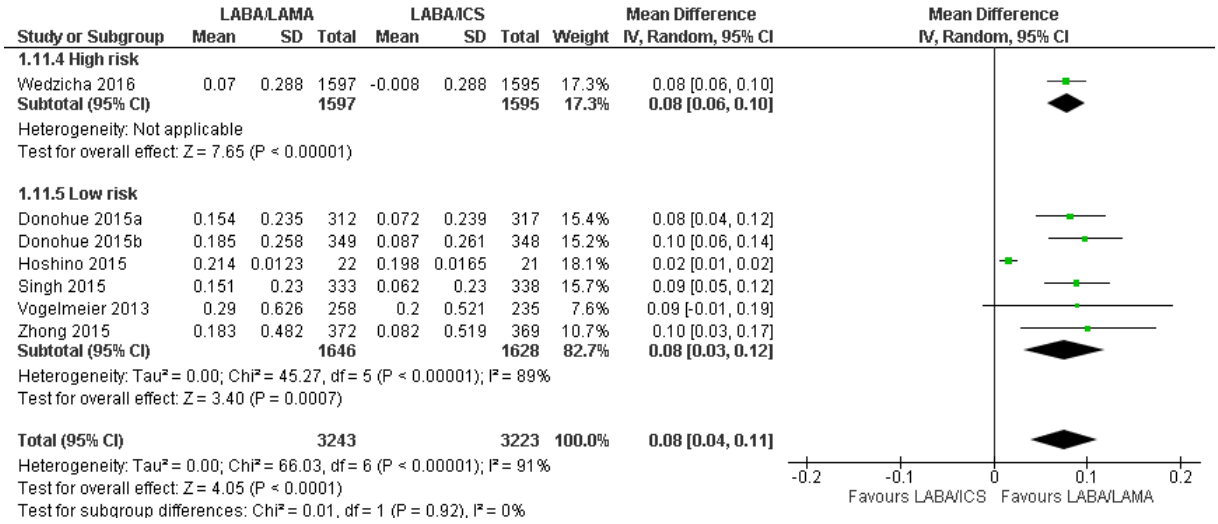
The following plots were based on data from the Cochrane review. However, the dichotomous data plots have been altered to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B. Any sensitivity analyses were carried out by NICE Guideline Updates Team using data from the Cochrane group. In contrast to other reviews carried out by the NICE Guideline Updates Team in this update of the COPD guideline, the Cochrane group reported change in FEV1 in litres (L).

LABA/LAMA versus LABA/ICS

All-cause mortality

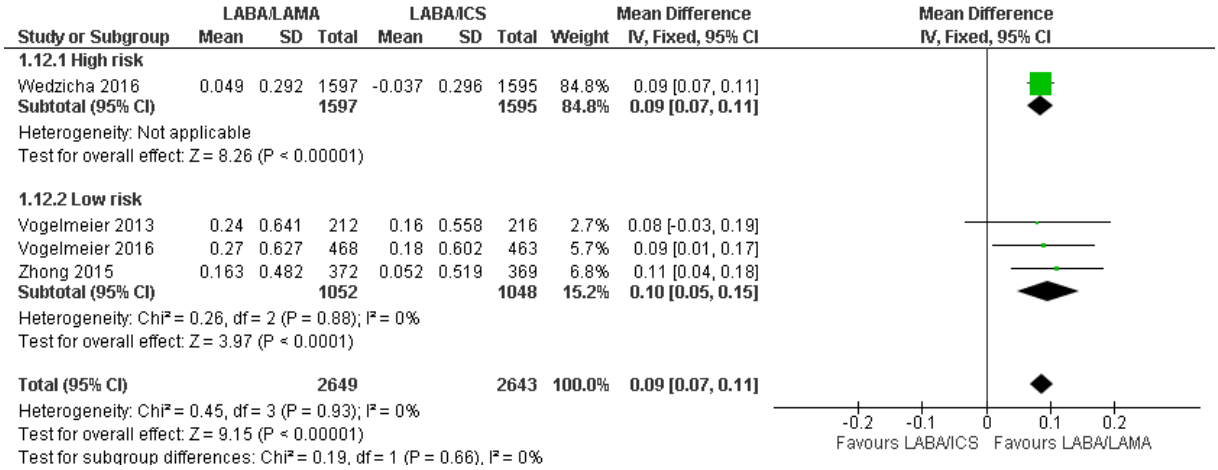


1 ***Change in Trough FEV1 (L) at 3 months***



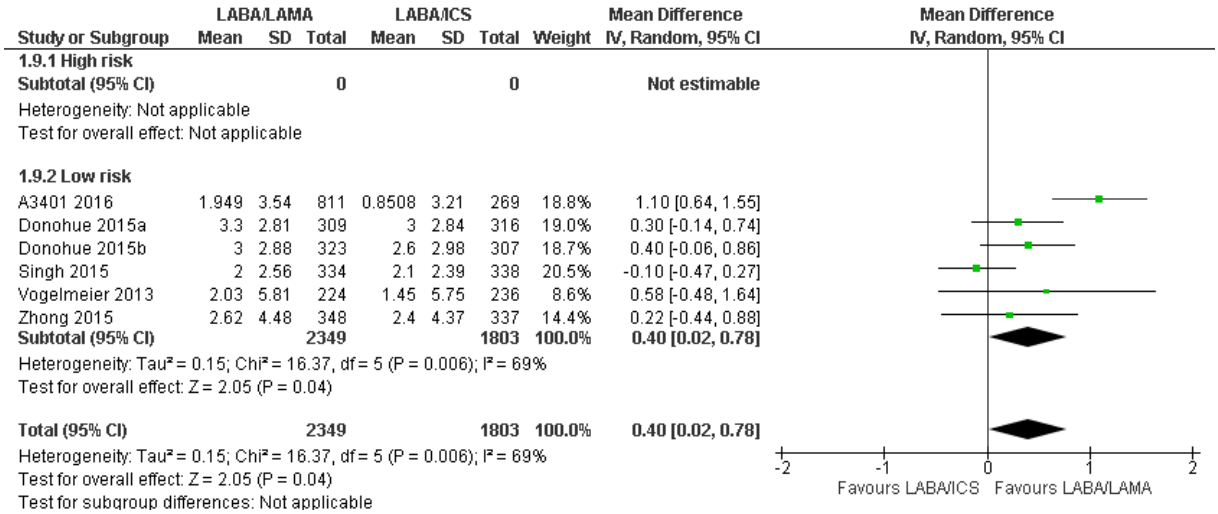
2

3 ***Change in Trough FEV1 (L) at 6 months***



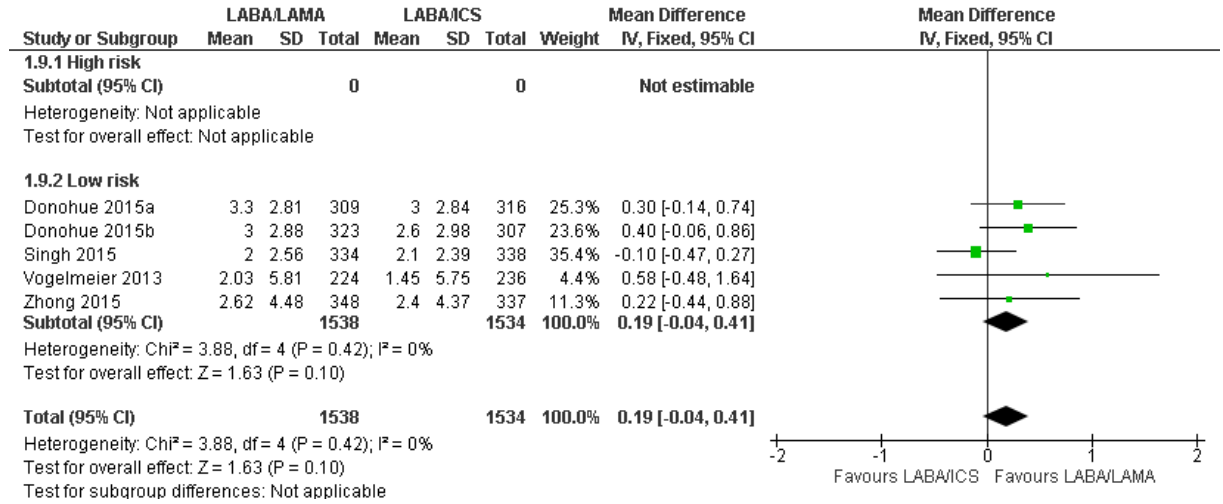
4

5 ***Transition Dyspnoea Index (TDI) focal score at 3 months***

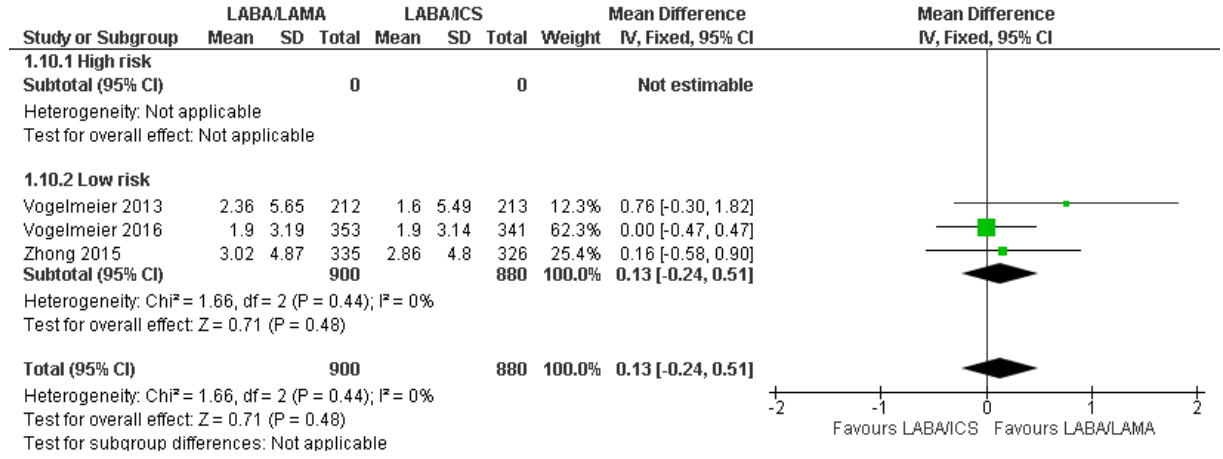


6

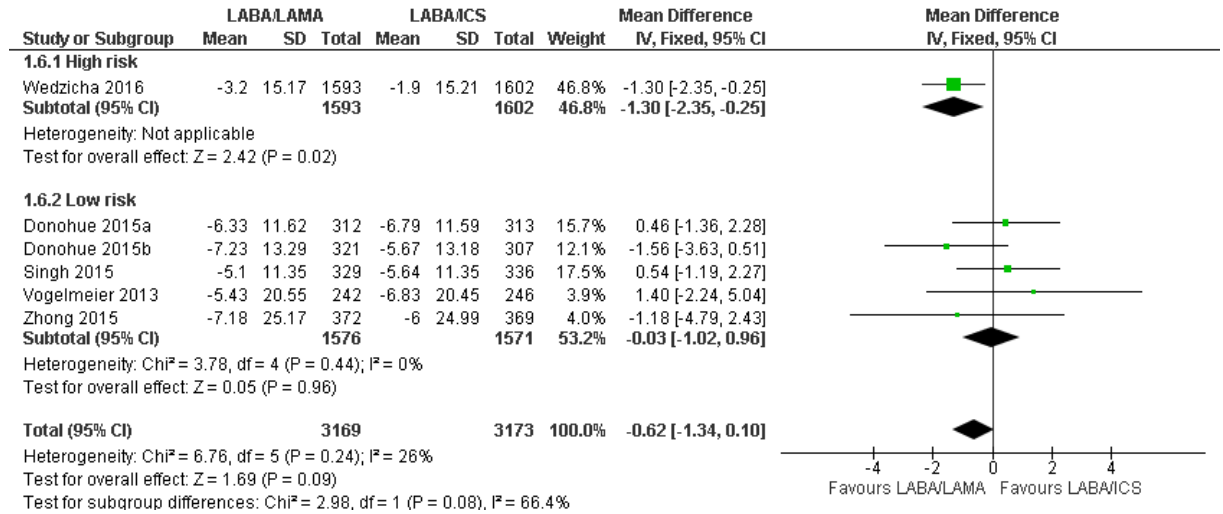
Sensitivity analysis: TDI at 3 months



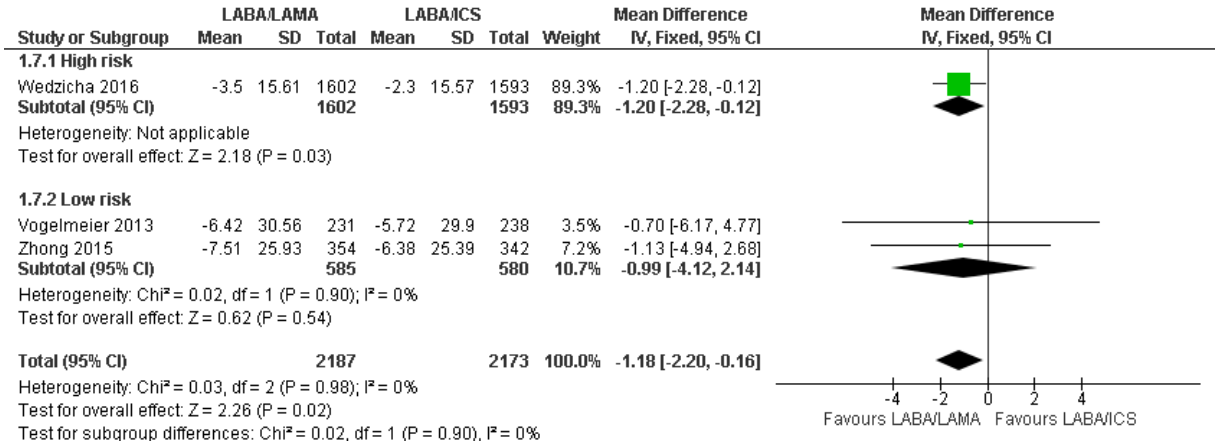
Transition Dyspnoea Index (TDI) focal score at 6 months



St. George's Respiratory Questionnaire (SGRQ), total score at 3 months

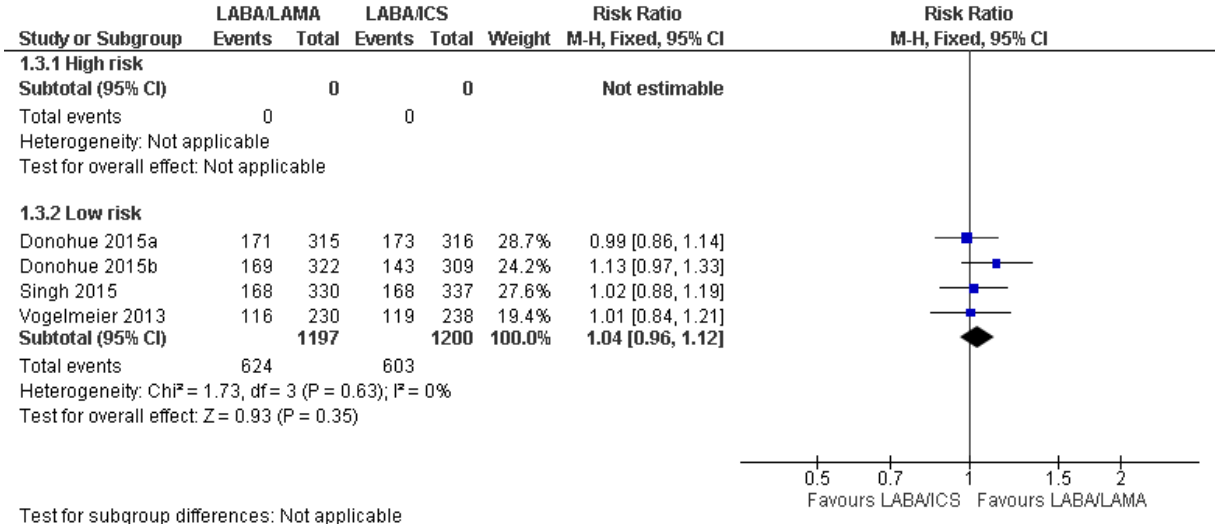


1 ***St. George's Respiratory Questionnaire (SGRQ), total score at 6 months***



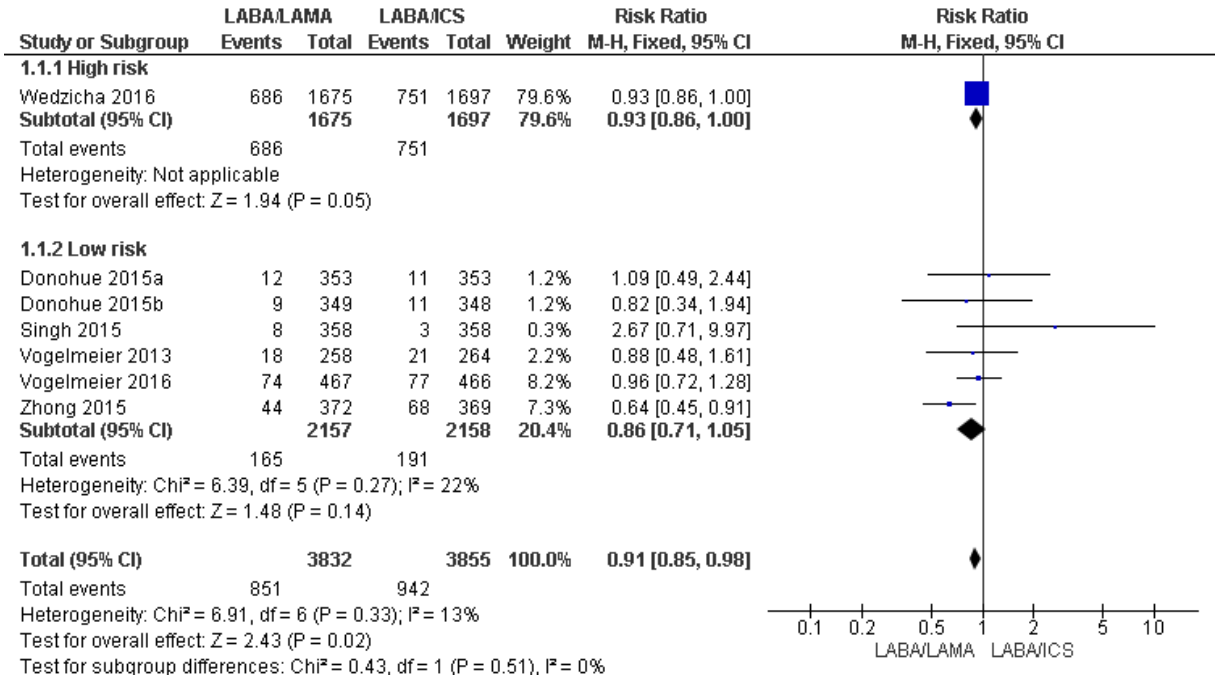
2

3 ***People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months***

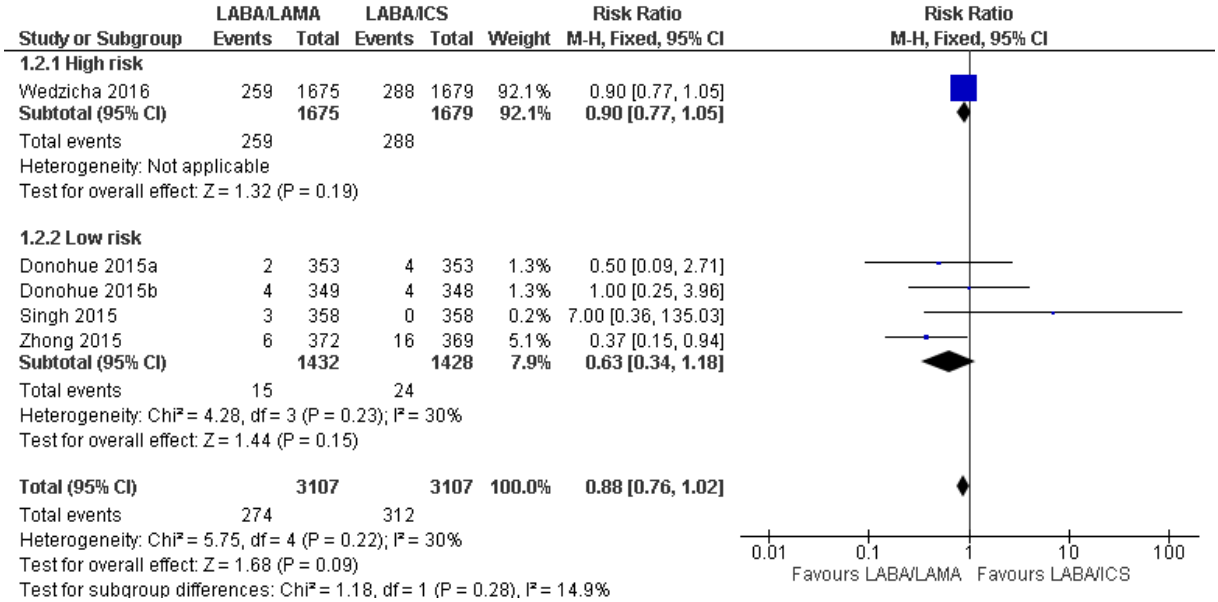


4 Test for subgroup differences: Not applicable

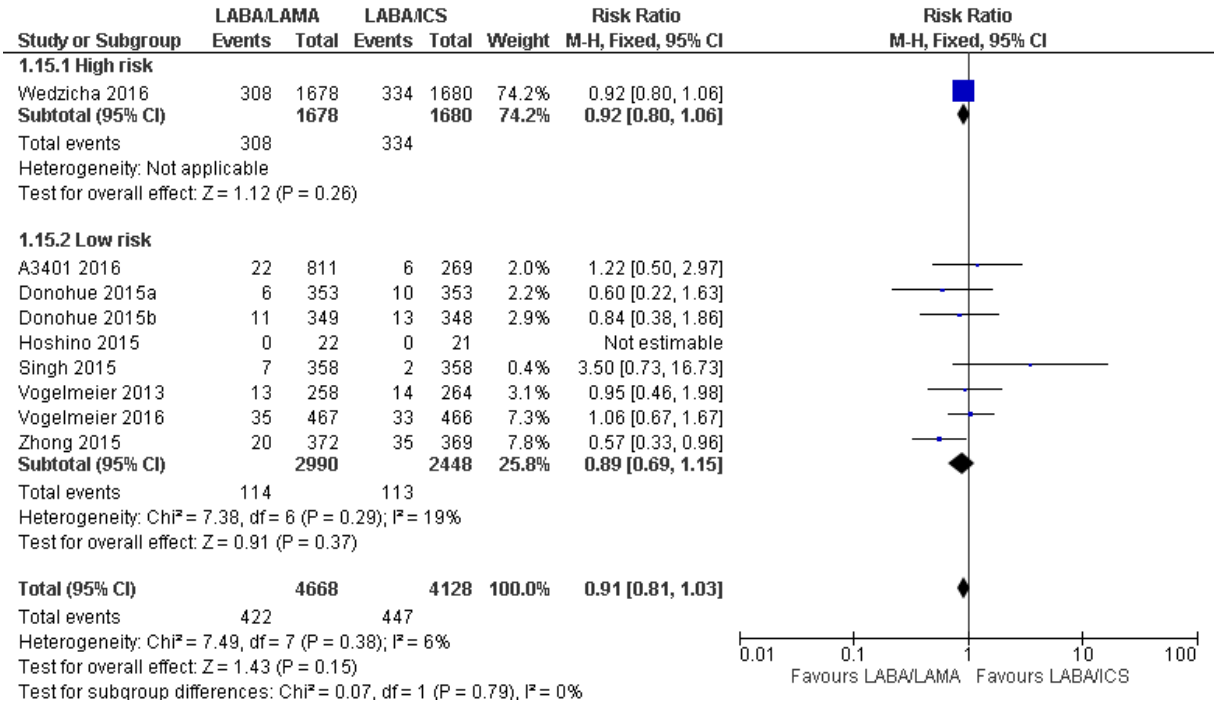
People with ≥ 1 moderate to severe exacerbation



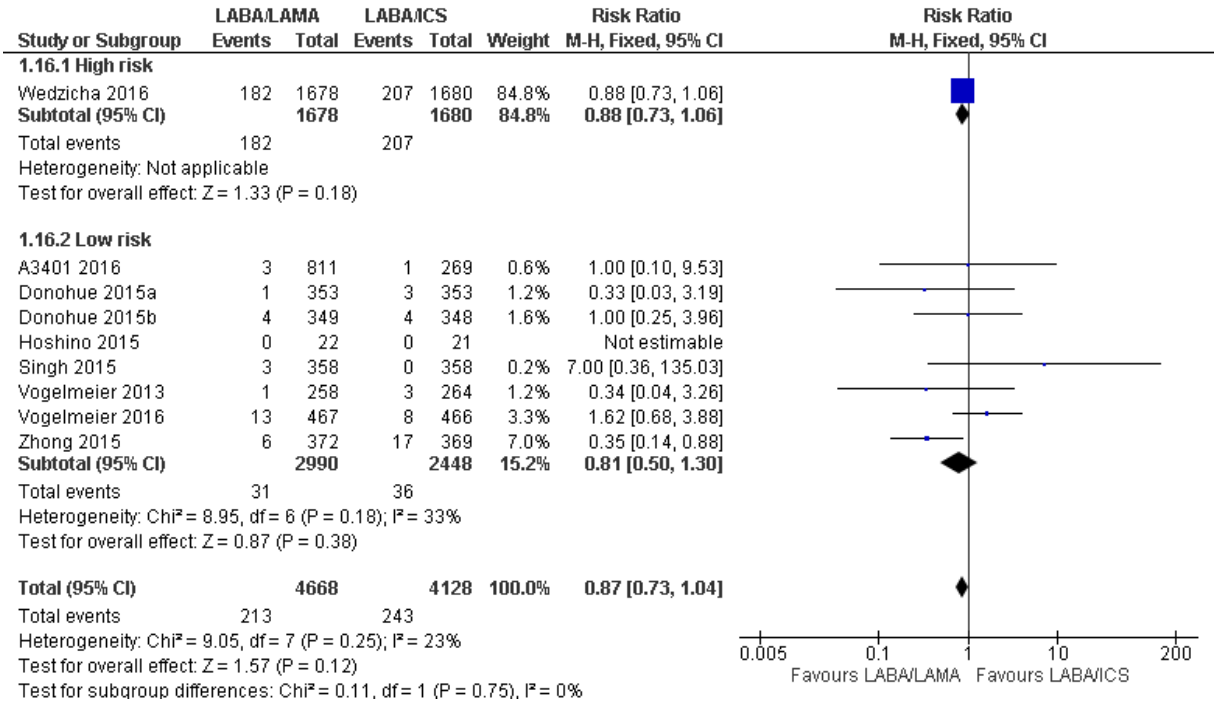
People with ≥ 1 severe exacerbation (requiring hospitalisation)



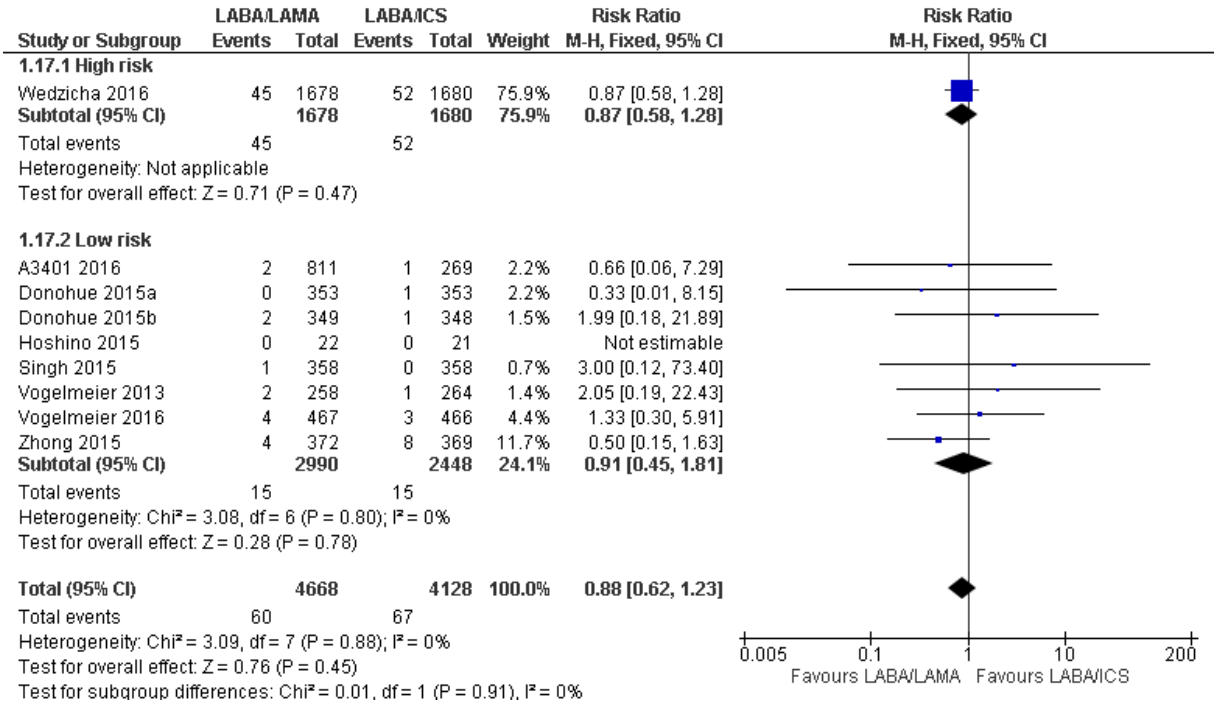
People with ≥ 1 Serious Adverse Event (SAE)



People with ≥ 1 COPD SAE

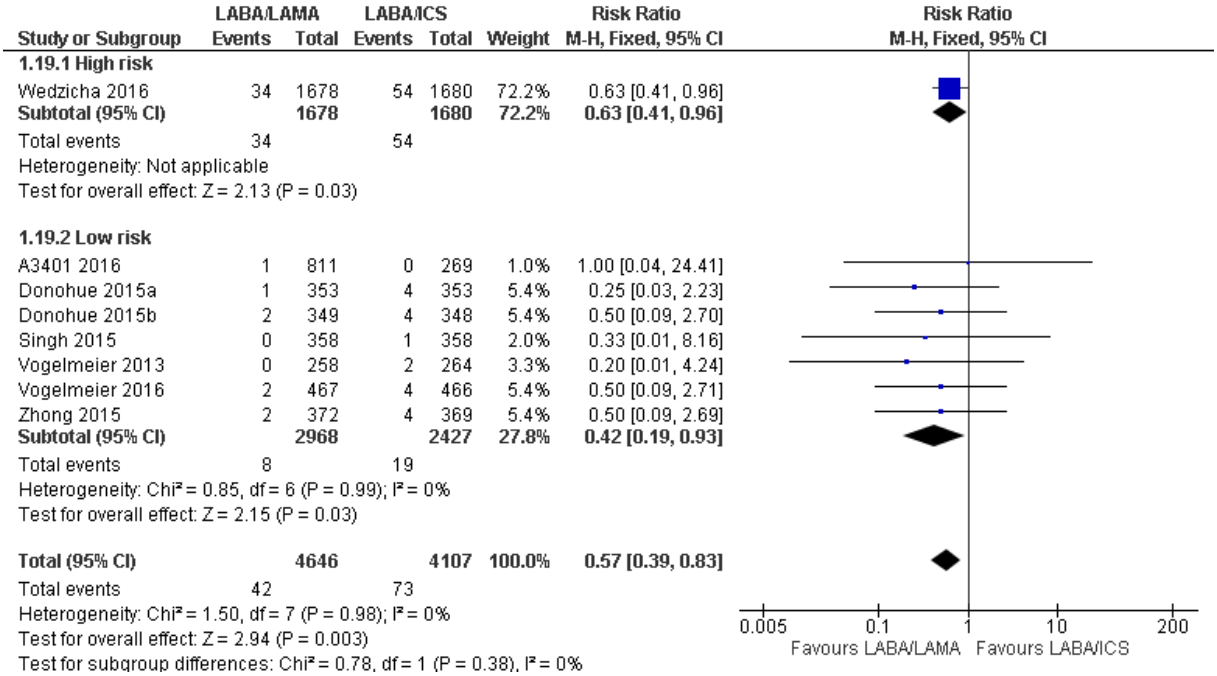


1 ***People with ≥ 1 cardiac SAE***



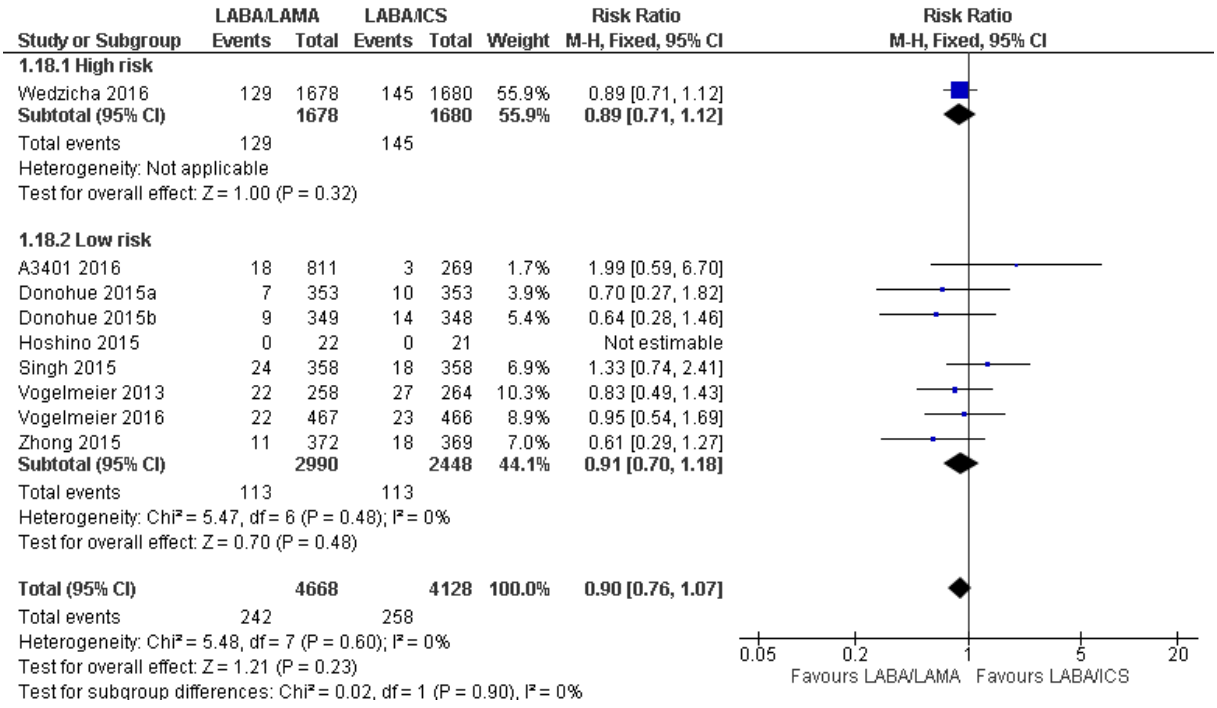
2

3 ***People with ≥ 1 session of pneumonia***



4

1 ***Drop-outs due to adverse events***

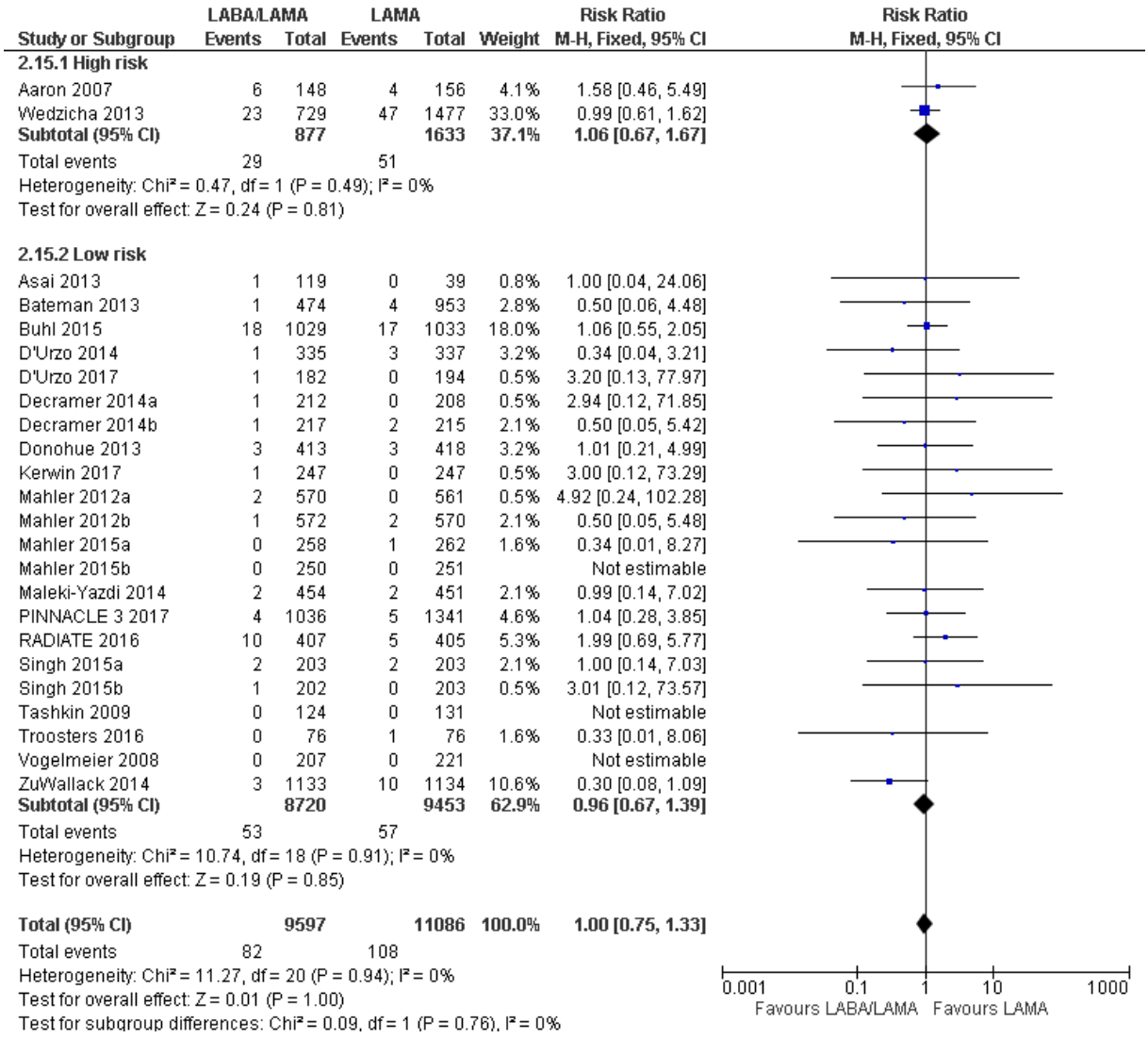


Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LABA/ICS Events	LABA/ICS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 High risk						
Wedzicha 2016	129	1678	145	1680	55.9%	0.89 [0.71, 1.12]
Subtotal (95% CI)		**1678**		**1680**	**55.9%**	**0.89 [0.71, 1.12]**
Total events	129		145			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
1.18.2 Low risk						
A3401 2016	18	811	3	269	1.7%	1.99 [0.59, 6.70]
Donohue 2015a	7	353	10	353	3.9%	0.70 [0.27, 1.82]
Donohue 2015b	9	349	14	348	5.4%	0.64 [0.28, 1.46]
Hoshino 2015	0	22	0	21		Not estimable
Singh 2015	24	358	18	358	6.9%	1.33 [0.74, 2.41]
Vogelmeier 2013	22	258	27	264	10.3%	0.83 [0.49, 1.43]
Vogelmeier 2016	22	467	23	466	8.9%	0.95 [0.54, 1.69]
Zhong 2015	11	372	18	369	7.0%	0.61 [0.29, 1.27]
Subtotal (95% CI)		**2990**		**2448**	**44.1%**	**0.91 [0.70, 1.18]**
Total events	113		113			
Heterogeneity: Chi² = 5.47, df = 6 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**4668**		**4128**	**100.0%**	**0.90 [0.76, 1.07]**
Total events	242		258			
Heterogeneity: Chi² = 5.48, df = 7 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%						

2

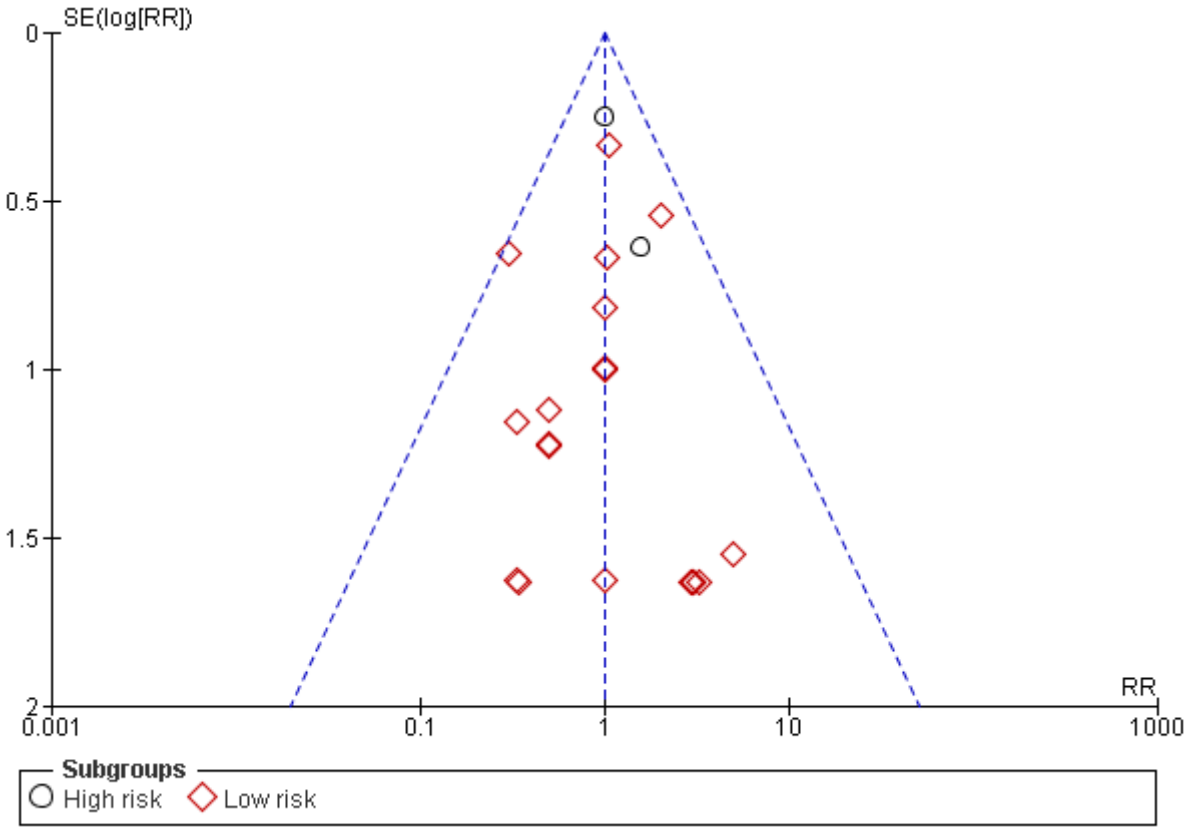
1 LABA/LAMA versus LAMA

2 *All-cause mortality*

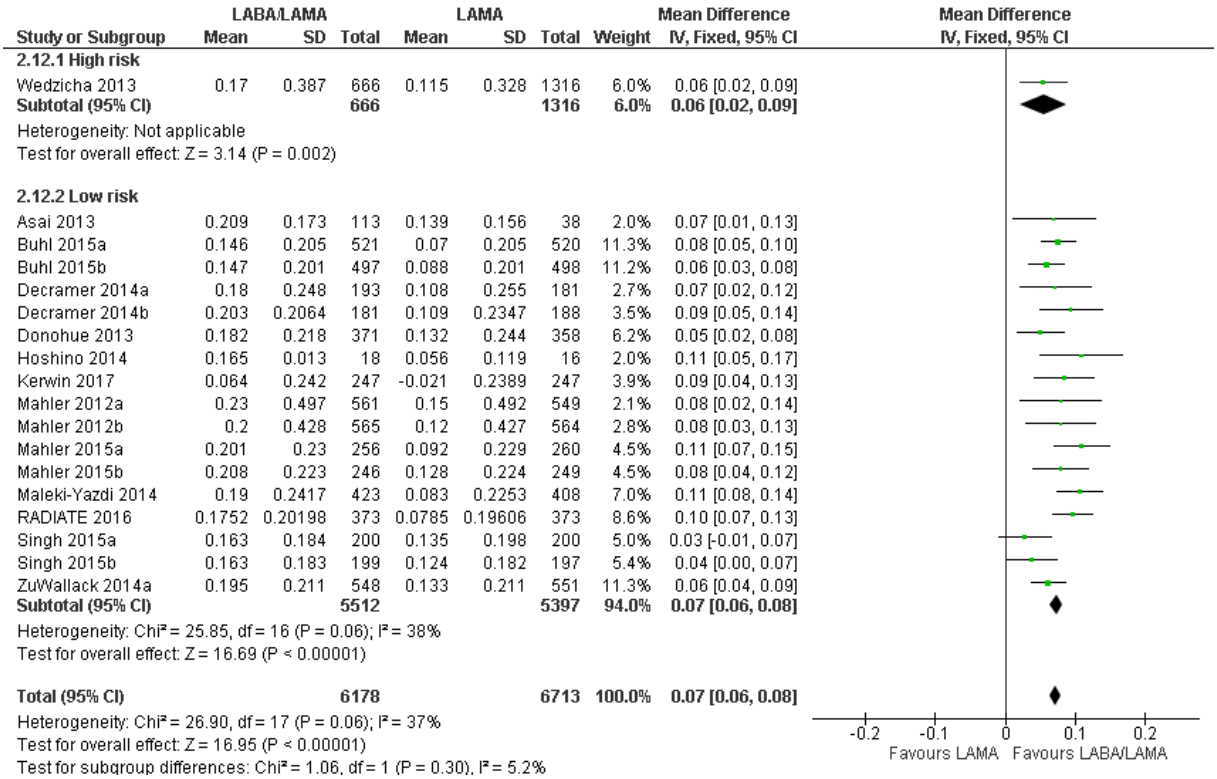


3

Publication bias assessment: funnel plot for all-cause mortality



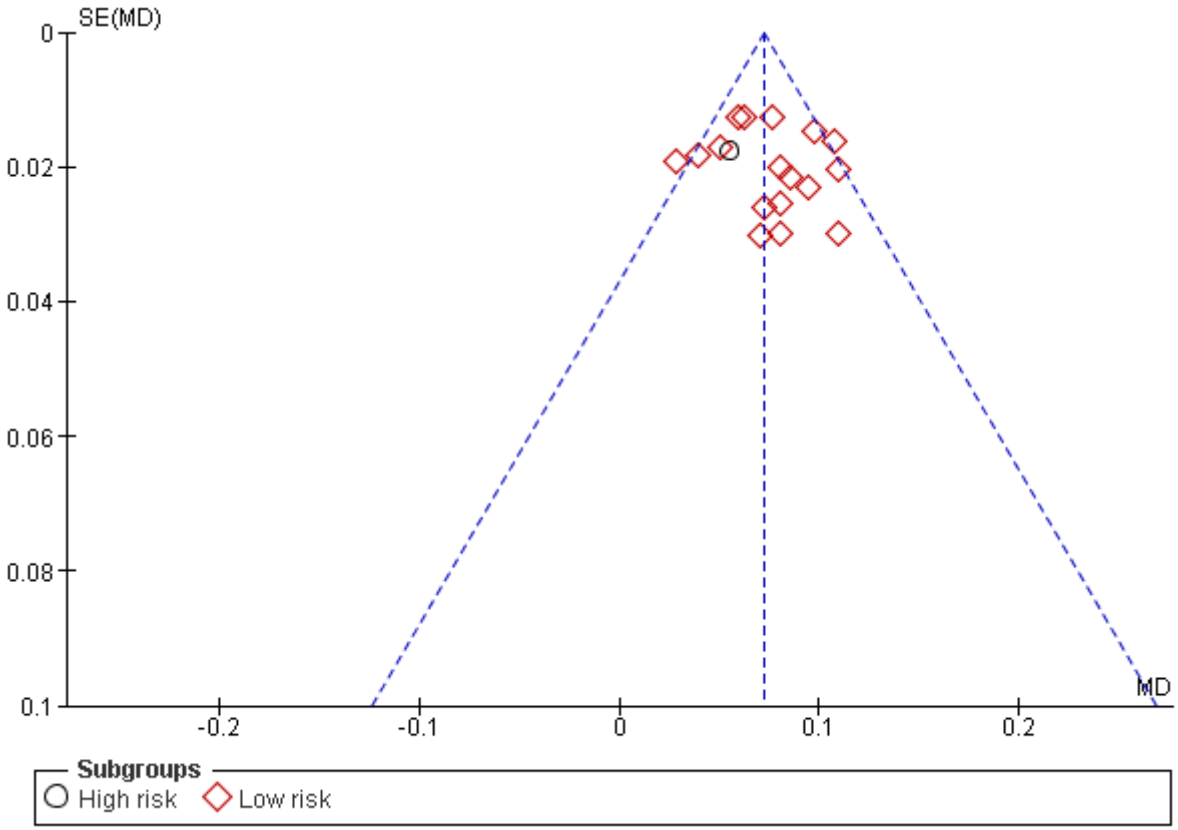
1 ***Change in Trough FEV1 (L) at 3 months***



Study or Subgroup	LABA/LAMA Mean	SD	Total	LAMA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.12.1 High risk								
Wedzicha 2013	0.17	0.387	666	0.115	0.328	1316	6.0%	0.06 [0.02, 0.09]
Subtotal (95% CI)			**666**			**1316**	**6.0%**	**0.06 [0.02, 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.14 (P = 0.002)								
2.12.2 Low risk								
Asai 2013	0.209	0.173	113	0.139	0.156	38	2.0%	0.07 [0.01, 0.13]
Buhl 2015a	0.146	0.205	521	0.07	0.205	520	11.3%	0.08 [0.05, 0.10]
Buhl 2015b	0.147	0.201	497	0.088	0.201	498	11.2%	0.06 [0.03, 0.08]
Decramer 2014a	0.18	0.248	193	0.108	0.255	181	2.7%	0.07 [0.02, 0.12]
Decramer 2014b	0.203	0.2064	181	0.109	0.2347	188	3.5%	0.09 [0.05, 0.14]
Donohue 2013	0.182	0.218	371	0.132	0.244	358	6.2%	0.05 [0.02, 0.08]
Hoshino 2014	0.165	0.013	18	0.056	0.119	16	2.0%	0.11 [0.05, 0.17]
Kerwin 2017	0.064	0.242	247	-0.021	0.2389	247	3.9%	0.09 [0.04, 0.13]
Mahler 2012a	0.23	0.497	561	0.15	0.492	549	2.1%	0.08 [0.02, 0.14]
Mahler 2012b	0.2	0.428	565	0.12	0.427	564	2.8%	0.08 [0.03, 0.13]
Mahler 2015a	0.201	0.23	256	0.092	0.229	260	4.5%	0.11 [0.07, 0.15]
Mahler 2015b	0.208	0.223	246	0.128	0.224	249	4.5%	0.08 [0.04, 0.12]
Maleki-Yazdi 2014	0.19	0.2417	423	0.083	0.2253	408	7.0%	0.11 [0.08, 0.14]
RADIATE 2016	0.1752	0.20198	373	0.0785	0.19606	373	8.6%	0.10 [0.07, 0.13]
Singh 2015a	0.163	0.184	200	0.135	0.198	200	5.0%	0.03 [-0.01, 0.07]
Singh 2015b	0.163	0.183	199	0.124	0.182	197	5.4%	0.04 [0.00, 0.07]
ZuWallack 2014a	0.195	0.211	548	0.133	0.211	551	11.3%	0.06 [0.04, 0.09]
Subtotal (95% CI)			**5512**			**5397**	**94.0%**	**0.07 [0.06, 0.08]**
Heterogeneity: Chi² = 25.85, df = 16 (P = 0.06); I² = 38%								
Test for overall effect: Z = 16.69 (P < 0.00001)								
Total (95% CI)			**6178**			**6713**	**100.0%**	**0.07 [0.06, 0.08]**
Heterogeneity: Chi² = 26.90, df = 17 (P = 0.06); I² = 37%								
Test for overall effect: Z = 16.95 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² = 5.2%								

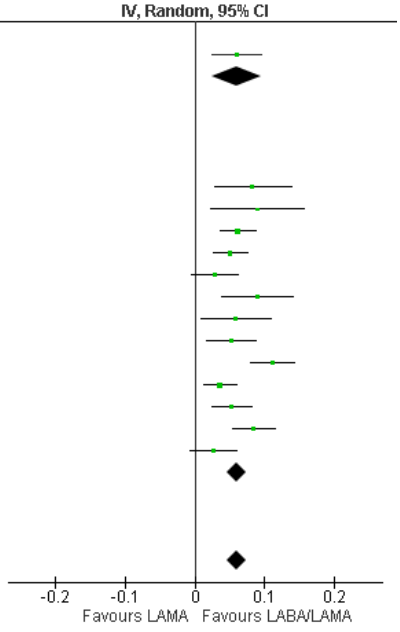
2

Publication bias assessment: funnel plot for change in trough FEV1 at 3 months

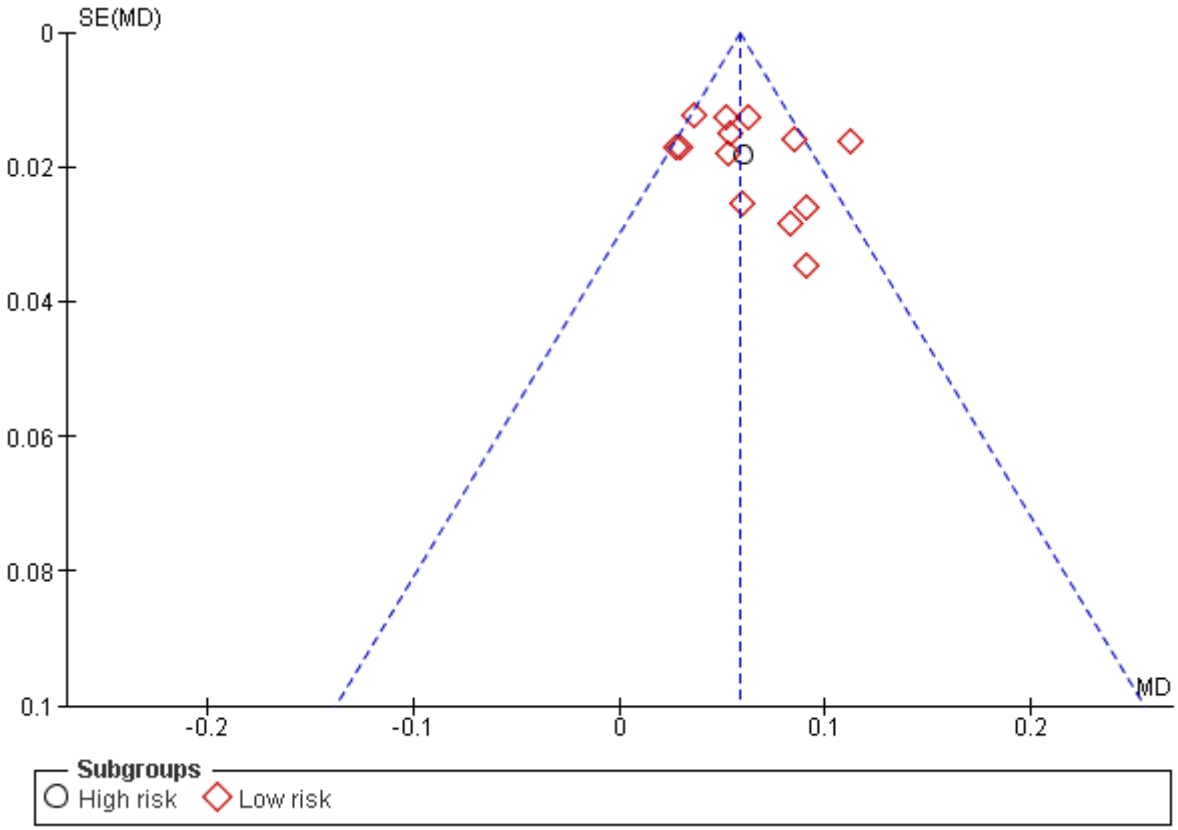


Change in Trough FEV1 (L) at 6 months

Study or Subgroup	LABA/LAMA Mean	SD	Total	LAMA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.13.1 High risk								
Wedzicha 2013	0.16	0.371	604	0.1	0.36	1176	7.0%	0.06 [0.02, 0.10]
Subtotal (95% CI)			**604**			**1176**	**7.0%**	**0.06 [0.02, 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.26 (P = 0.001)								
2.13.2 Low risk								
Asai 2013	0.198	0.174	113	0.115	0.14	37	4.1%	0.08 [0.03, 0.14]
Bateman 2013	0.17	0.544	474	0.08	0.494	424	3.0%	0.09 [0.02, 0.16]
Buhl 2015a	0.112	0.205	521	0.05	0.205	520	9.7%	0.06 [0.04, 0.09]
Buhl 2015b	0.119	0.201	497	0.068	0.201	498	9.6%	0.05 [0.03, 0.08]
D'Urzo 2014	0.095	0.19754	271	0.066	0.196	266	7.6%	0.03 [-0.00, 0.06]
Decramer 2014a	0.211	0.243	177	0.121	0.245	173	4.6%	0.09 [0.04, 0.14]
Decramer 2014b	0.208	0.228394	161	0.149	0.238118	175	4.8%	0.06 [0.01, 0.11]
Donohue 2013	0.171	0.229	330	0.119	0.226	322	7.3%	0.05 [0.02, 0.09]
Maleki-Yazdi 2014	0.205	0.243	454	0.093	0.244	451	8.0%	0.11 [0.08, 0.14]
Martinez 2017a	0.126	0.201	429	0.09	0.2	734	9.9%	0.04 [0.01, 0.06]
Martinez 2017b	0.116	0.21	433	0.063	0.209	367	8.6%	0.05 [0.02, 0.08]
RADIATE 2016	0.1557	0.21754	356	0.0714	0.20358	358	8.2%	0.08 [0.05, 0.12]
Singh 2014	0.083	0.22418	349	0.056	0.219	332	7.6%	0.03 [-0.01, 0.06]
Subtotal (95% CI)			**4565**			**4657**	**93.0%**	**0.06 [0.05, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 27.18, df = 12 (P = 0.007); I² = 56%								
Test for overall effect: Z = 8.27 (P < 0.00001)								
Total (95% CI)			**5169**			**5833**	**100.0%**	**0.06 [0.05, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 27.19, df = 13 (P = 0.01); I² = 52%								
Test for overall effect: Z = 8.88 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%								

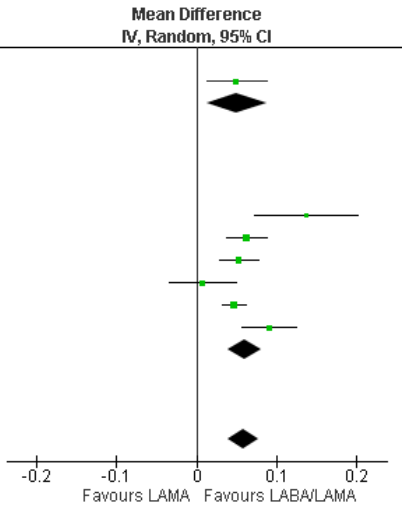


Publication bias assessment: funnel plot for change in trough FEV1 at 6 months

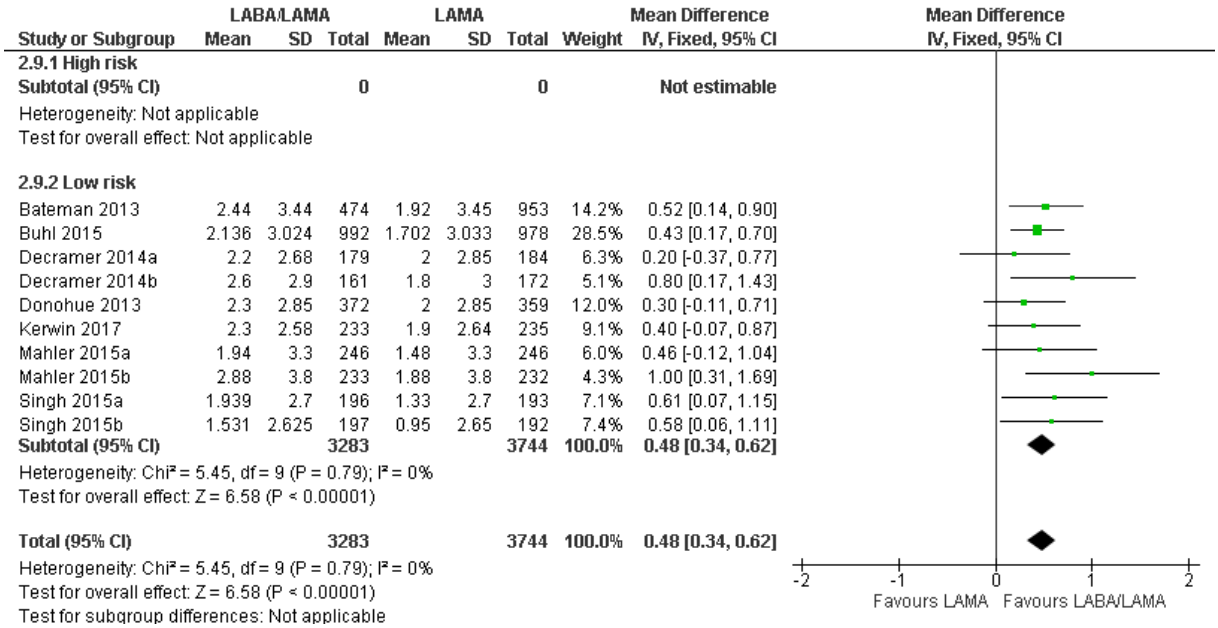


Change in Trough FEV1 (L) at 12 months

Study or Subgroup	LABA/LAMA Mean	SD	Total	LAMA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.14.1 High risk								
Wedzicha 2013	0.14	0.421	729	0.09	0.427	1477	12.6%	0.05 [0.01, 0.09]
Subtotal (95% CI)			**729**			**1477**	**12.6%**	**0.05 [0.01, 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.61 (P = 0.009)								
2.14.2 Low risk								
Asai 2013	0.189	0.173	104	0.052	0.17	37	6.5%	0.14 [0.07, 0.20]
Buhl 2015a	0.099	0.205	521	0.036	0.205	520	17.3%	0.06 [0.04, 0.09]
Buhl 2015b	0.093	0.201	497	0.04	0.201	498	17.2%	0.05 [0.03, 0.08]
D'Urzo 2017	0.038	0.275	335	0.03	0.275	337	11.3%	0.01 [-0.03, 0.05]
PINNACLE 3 2017	0.133	0.179	1021	0.086	0.181	1317	21.4%	0.05 [0.03, 0.06]
RADIATE 2016	0.1468	0.22933	333	0.0559	0.22433	346	13.7%	0.09 [0.06, 0.13]
Subtotal (95% CI)			**2811**			**3055**	**87.4%**	**0.06 [0.04, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 17.00, df = 5 (P = 0.005); I² = 71%								
Test for overall effect: Z = 5.42 (P < 0.00001)								
Total (95% CI)			**3540**			**4532**	**100.0%**	**0.06 [0.04, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 17.05, df = 6 (P = 0.009); I² = 65%								
Test for overall effect: Z = 6.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%								



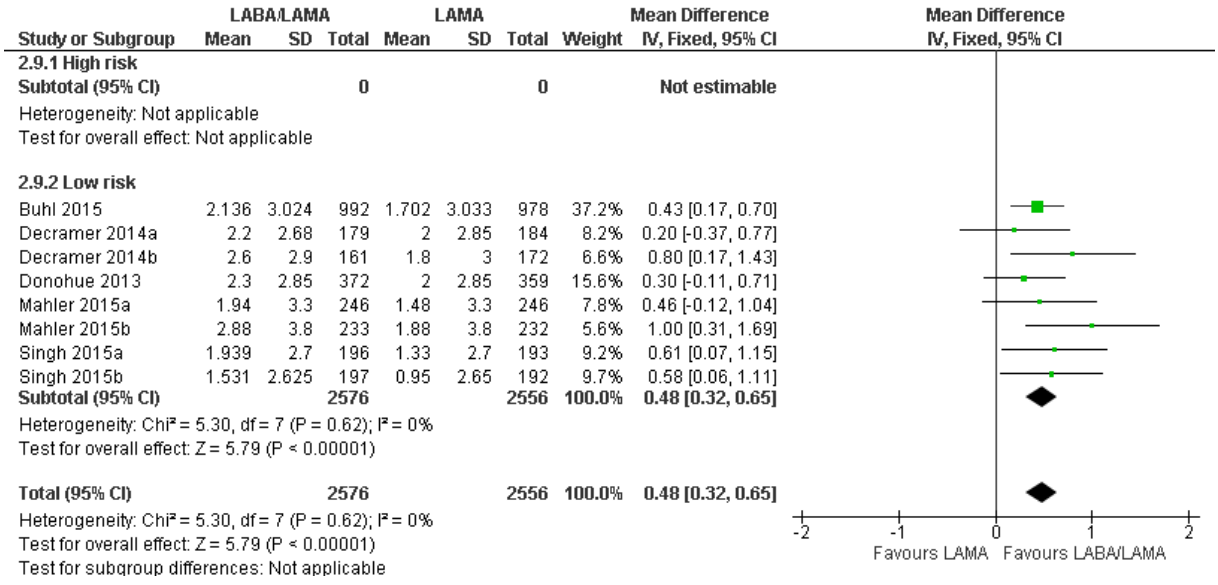
1 ***Transition Dyspnoea Index (TDI) focal score at 3 months***



Study or Subgroup	LABA/LAMA Mean	SD	Total	LAMA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.9.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
2.9.2 Low risk								
Bateman 2013	2.44	3.44	474	1.92	3.45	953	14.2%	0.52 [0.14, 0.90]
Buhl 2015	2.136	3.024	992	1.702	3.033	978	28.5%	0.43 [0.17, 0.70]
Decramer 2014a	2.2	2.68	179	2	2.85	184	6.3%	0.20 [-0.37, 0.77]
Decramer 2014b	2.6	2.9	161	1.8	3	172	5.1%	0.80 [0.17, 1.43]
Donohue 2013	2.3	2.85	372	2	2.85	359	12.0%	0.30 [-0.11, 0.71]
Kerwin 2017	2.3	2.58	233	1.9	2.64	235	9.1%	0.40 [-0.07, 0.87]
Mahler 2015a	1.94	3.3	246	1.48	3.3	246	6.0%	0.46 [-0.12, 1.04]
Mahler 2015b	2.88	3.8	233	1.88	3.8	232	4.3%	1.00 [0.31, 1.69]
Singh 2015a	1.939	2.7	196	1.33	2.7	193	7.1%	0.61 [0.07, 1.15]
Singh 2015b	1.531	2.625	197	0.95	2.65	192	7.4%	0.58 [0.06, 1.11]
Subtotal (95% CI)			**3283**			**3744**	**100.0%**	**0.48 [0.34, 0.62]**
Heterogeneity: $Chi^2 = 5.45$, df = 9 (P = 0.79); $I^2 = 0\%$								
Test for overall effect: Z = 6.58 (P < 0.00001)								
Total (95% CI)			**3283**			**3744**	**100.0%**	**0.48 [0.34, 0.62]**
Heterogeneity: $Chi^2 = 5.45$, df = 9 (P = 0.79); $I^2 = 0\%$								
Test for overall effect: Z = 6.58 (P < 0.00001)								
Test for subgroup differences: Not applicable								

2

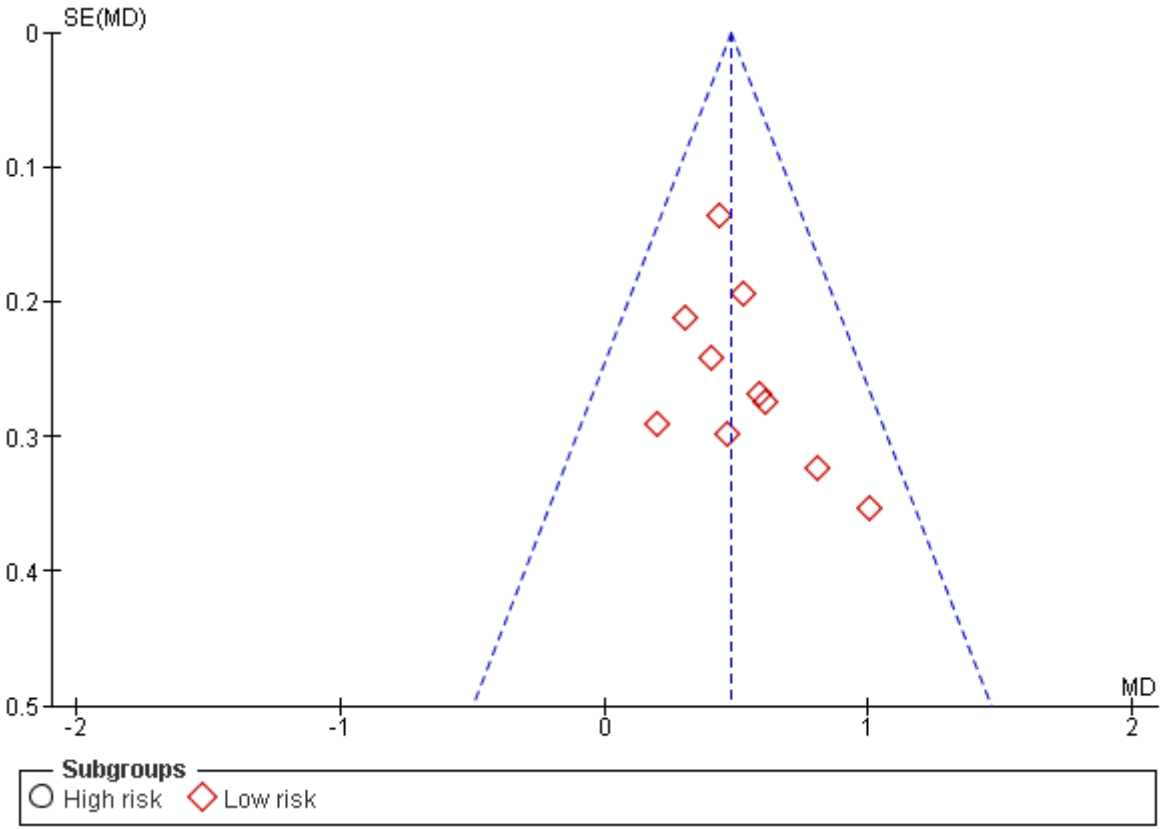
3 *Sensitivity analysis: TDI at 3 months*



Study or Subgroup	LABA/LAMA Mean	SD	Total	LAMA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.9.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
2.9.2 Low risk								
Buhl 2015	2.136	3.024	992	1.702	3.033	978	37.2%	0.43 [0.17, 0.70]
Decramer 2014a	2.2	2.68	179	2	2.85	184	8.2%	0.20 [-0.37, 0.77]
Decramer 2014b	2.6	2.9	161	1.8	3	172	6.6%	0.80 [0.17, 1.43]
Donohue 2013	2.3	2.85	372	2	2.85	359	15.6%	0.30 [-0.11, 0.71]
Mahler 2015a	1.94	3.3	246	1.48	3.3	246	7.8%	0.46 [-0.12, 1.04]
Mahler 2015b	2.88	3.8	233	1.88	3.8	232	5.6%	1.00 [0.31, 1.69]
Singh 2015a	1.939	2.7	196	1.33	2.7	193	9.2%	0.61 [0.07, 1.15]
Singh 2015b	1.531	2.625	197	0.95	2.65	192	9.7%	0.58 [0.06, 1.11]
Subtotal (95% CI)			**2576**			**2556**	**100.0%**	**0.48 [0.32, 0.65]**
Heterogeneity: $Chi^2 = 5.30$, df = 7 (P = 0.62); $I^2 = 0\%$								
Test for overall effect: Z = 5.79 (P < 0.00001)								
Total (95% CI)			**2576**			**2556**	**100.0%**	**0.48 [0.32, 0.65]**
Heterogeneity: $Chi^2 = 5.30$, df = 7 (P = 0.62); $I^2 = 0\%$								
Test for overall effect: Z = 5.79 (P < 0.00001)								
Test for subgroup differences: Not applicable								

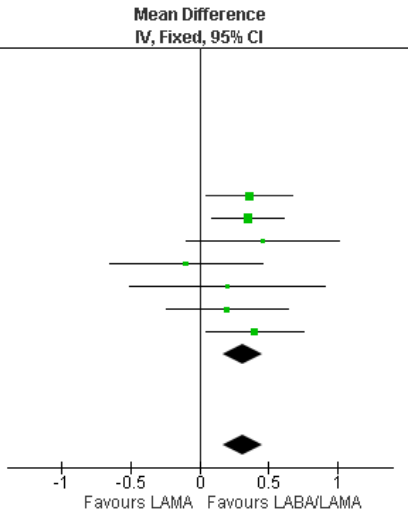
4

Publication bias assessment: funnel plot for TDI at 3 months

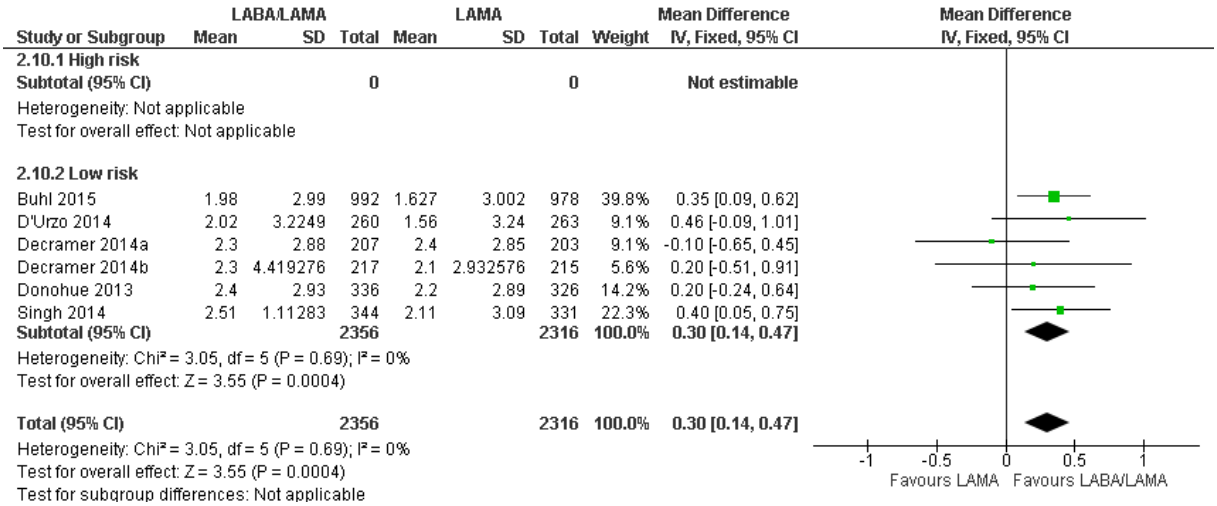


Transition Dyspnoea Index (TDI) focal score at 6 months

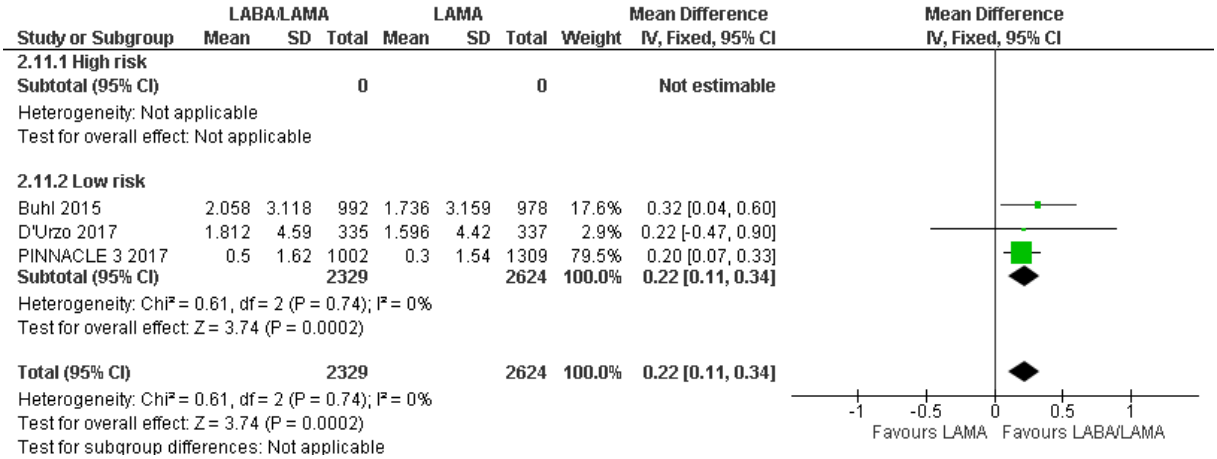
Study or Subgroup	LABA/LAMA Mean	SD	Total	LAMA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.10.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
2.10.2 Low risk								
Bateman 2013	2.72	2.83	474	2.36	2.79	953	22.4%	0.36 [0.05, 0.67]
Buhl 2015	1.98	2.99	992	1.627	3.002	978	30.9%	0.35 [0.09, 0.62]
D'Urzo 2014	2.02	3.2249	260	1.56	3.24	263	7.0%	0.46 [-0.09, 1.01]
Decramer 2014a	2.3	2.88	207	2.4	2.85	203	7.0%	-0.10 [-0.65, 0.45]
Decramer 2014b	2.3	4.419276	217	2.1	2.932576	215	4.3%	0.20 [-0.51, 0.91]
Donohue 2013	2.4	2.93	336	2.2	2.89	326	11.0%	0.20 [-0.24, 0.64]
Singh 2014	2.51	1.11283	344	2.11	3.09	331	17.3%	0.40 [0.05, 0.75]
Subtotal (95% CI)			**2830**			**3269**	**100.0%**	**0.32 [0.17, 0.46]**
Heterogeneity: Chi² = 3.16, df = 6 (P = 0.79); I² = 0%								
Test for overall effect: Z = 4.20 (P < 0.0001)								
Total (95% CI)			**2830**			**3269**	**100.0%**	**0.32 [0.17, 0.46]**
Heterogeneity: Chi² = 3.16, df = 6 (P = 0.79); I² = 0%								
Test for overall effect: Z = 4.20 (P < 0.0001)								
Test for subgroup differences: Not applicable								



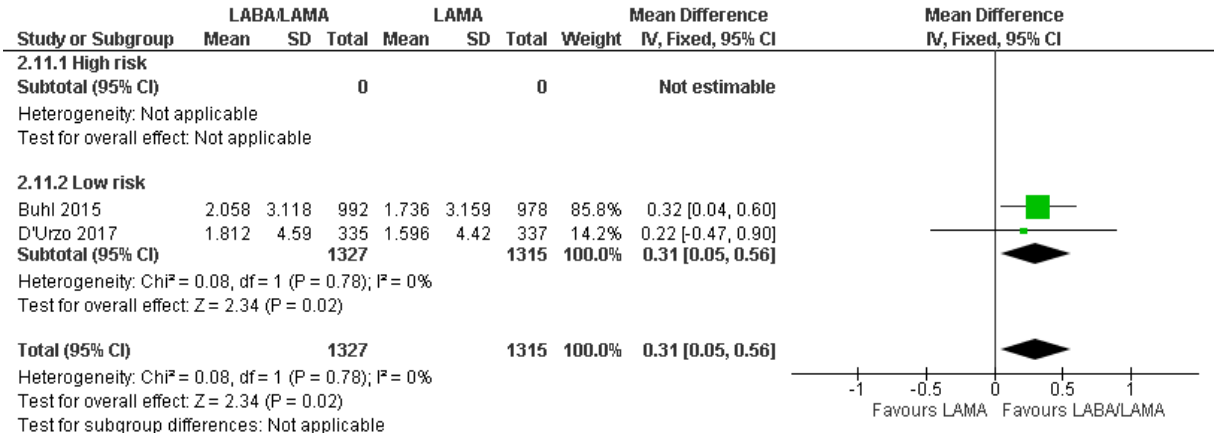
Sensitivity analysis: TDI at 6 months



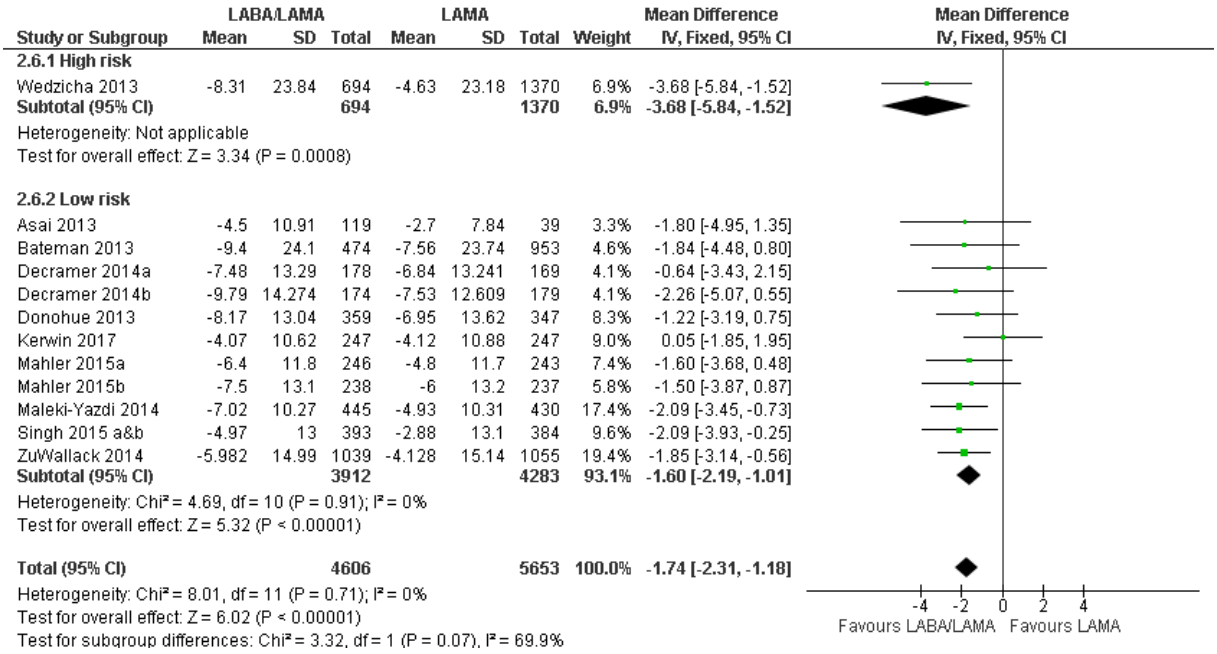
Transition Dyspnoea Index (TDI) focal score at 12 months



Sensitivity analysis: TDI at 12 months

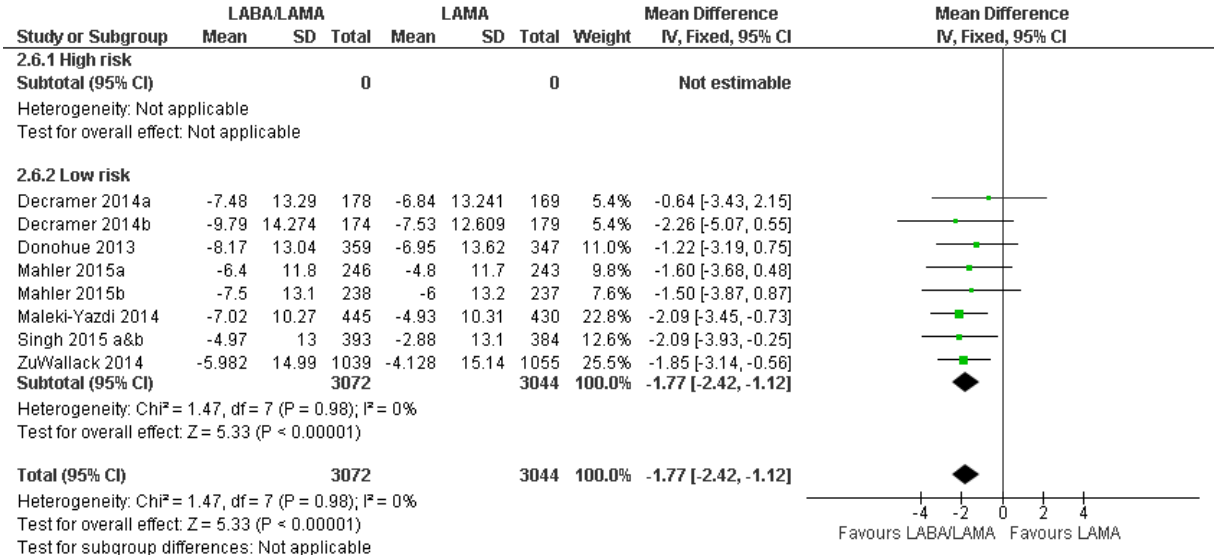


1 ***St. George's Respiratory Questionnaire (SGRQ), total score at 3 months***



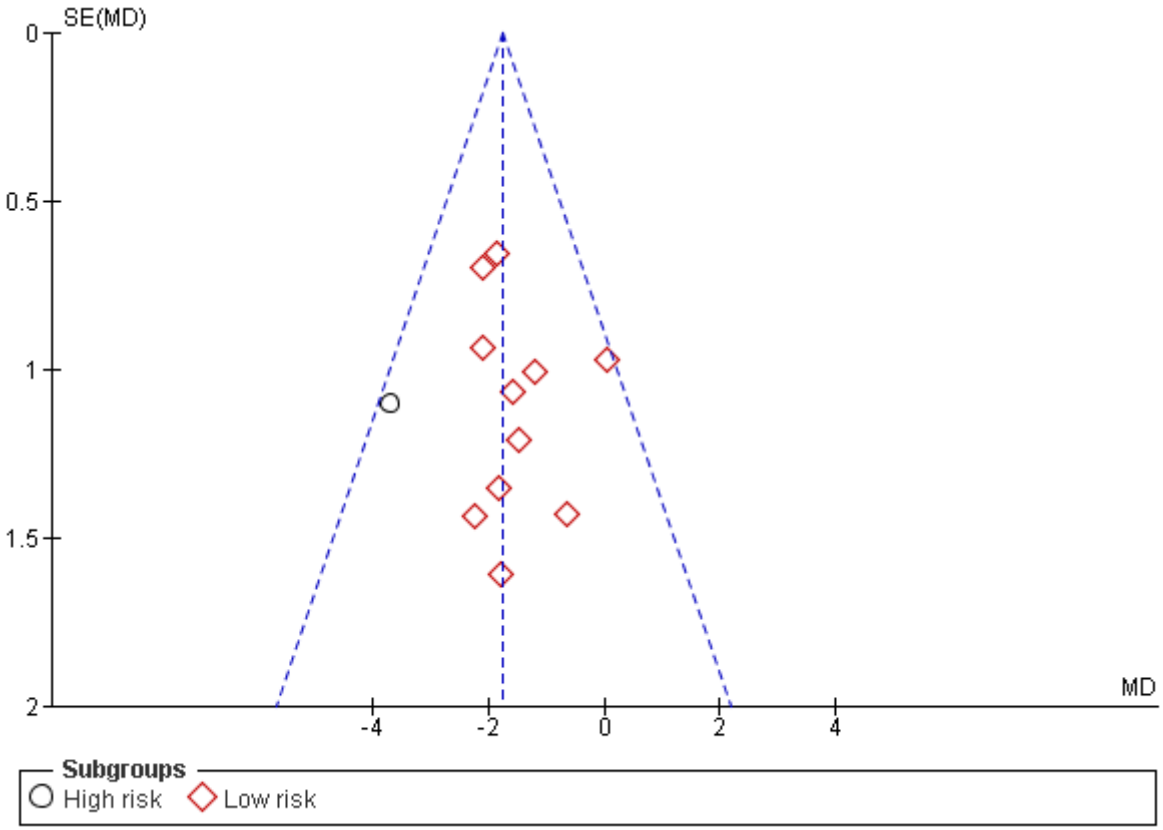
2

3 *Sensitivity analysis: SGRQ at 3 months*

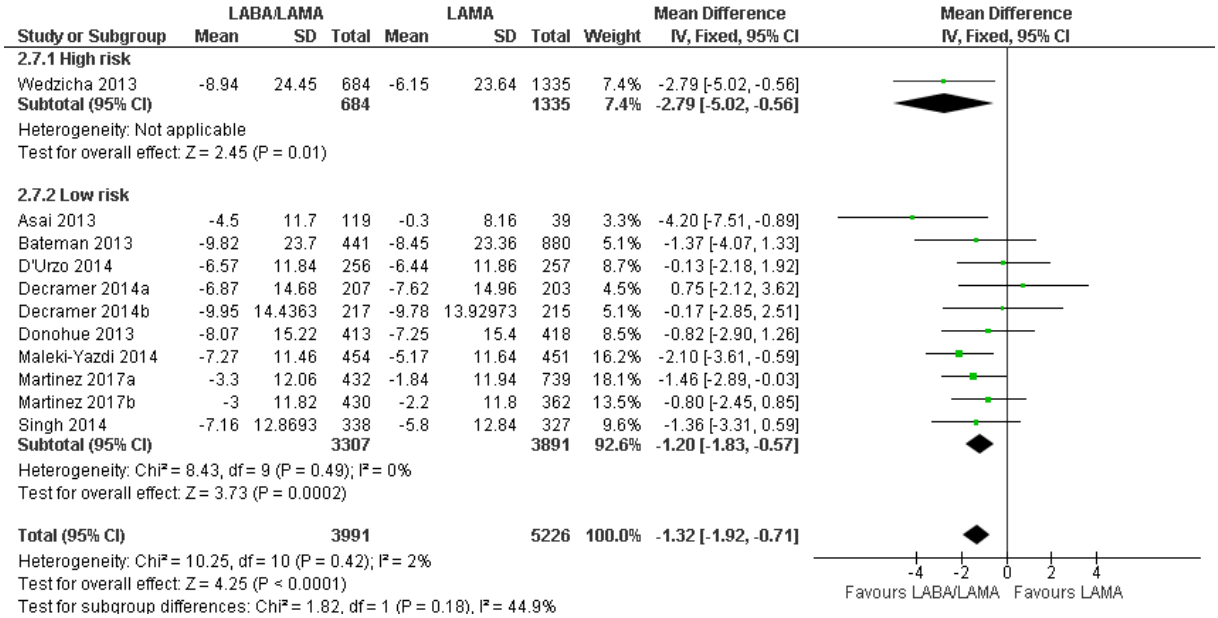


4

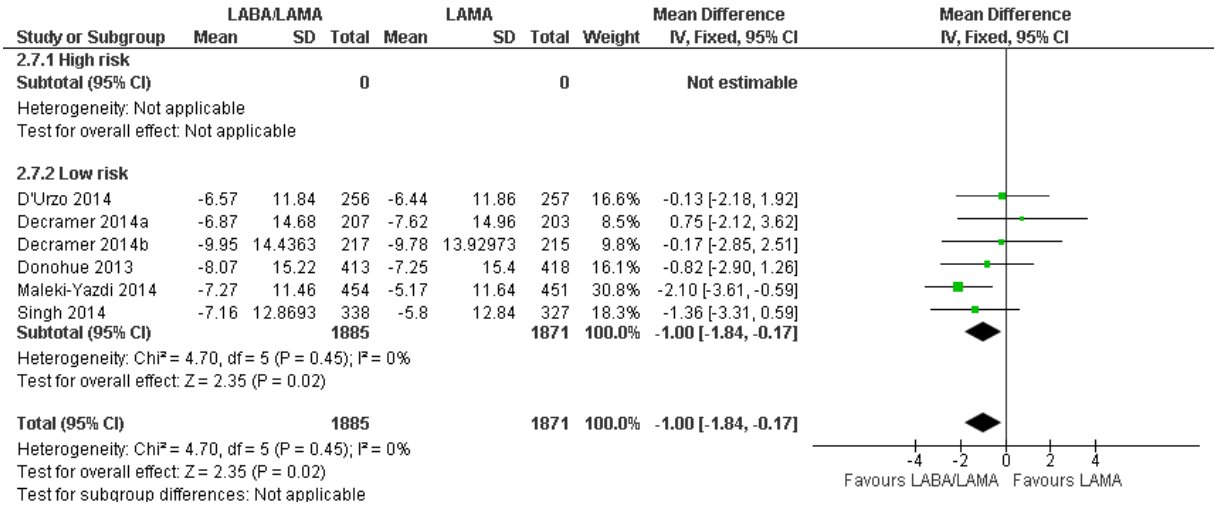
Publication bias assessment: funnel plot for SGRQ at 3 months



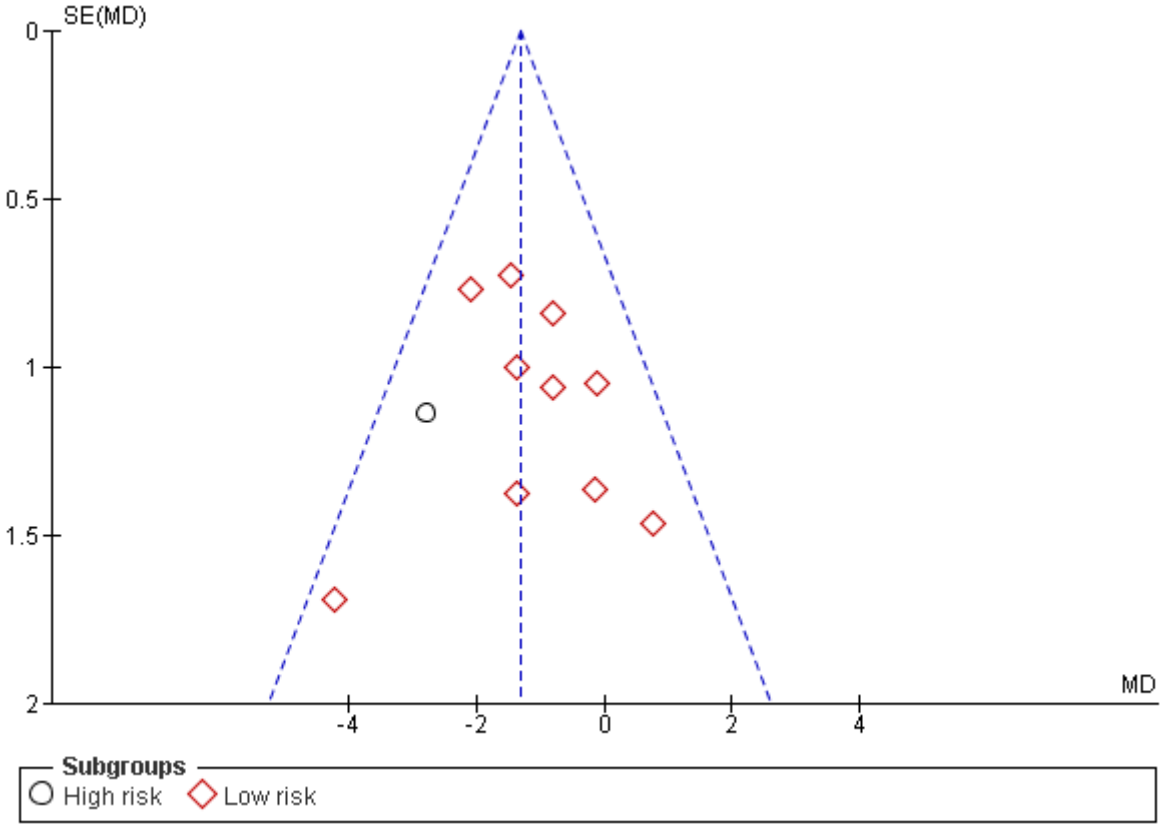
St. George's Respiratory Questionnaire (SGRQ), total score at 6 months



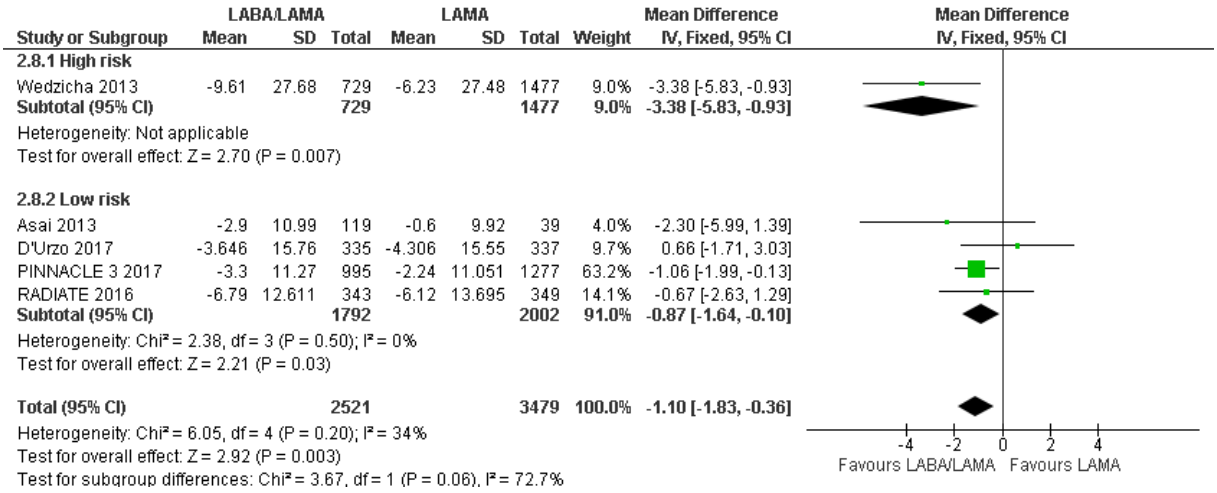
Sensitivity analysis: SGRQ at 6 months



Publication bias assessment: funnel plot for SGRQ at 6 months

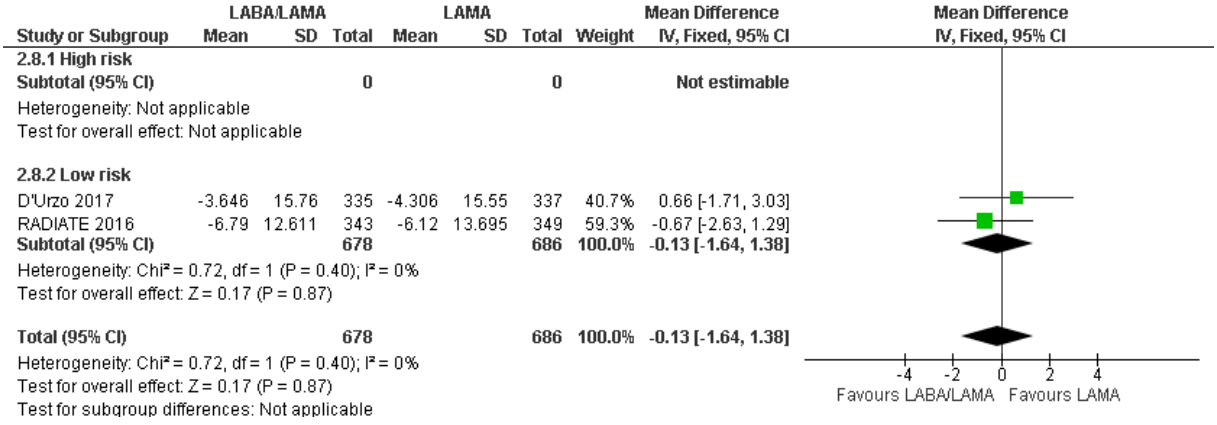


1 ***St. George's Respiratory Questionnaire (SGRQ), total score at 12 months***



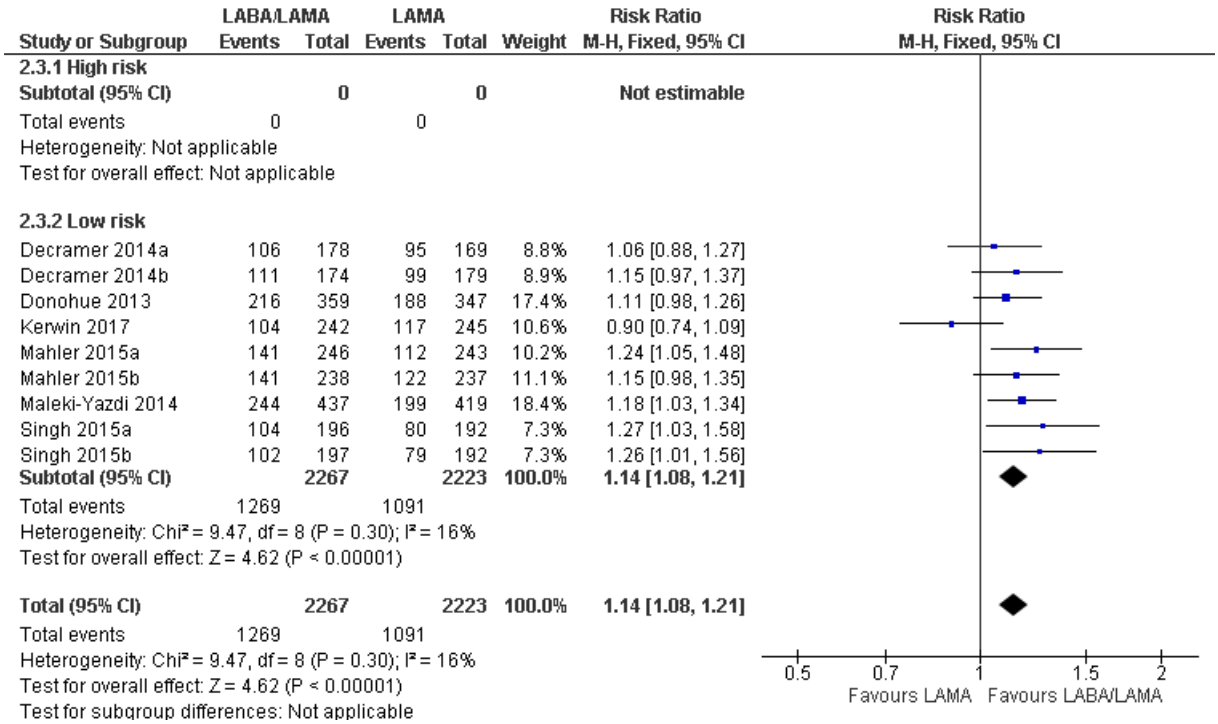
2

3 *Sensitivity analysis: SGRQ at 12 months*



4

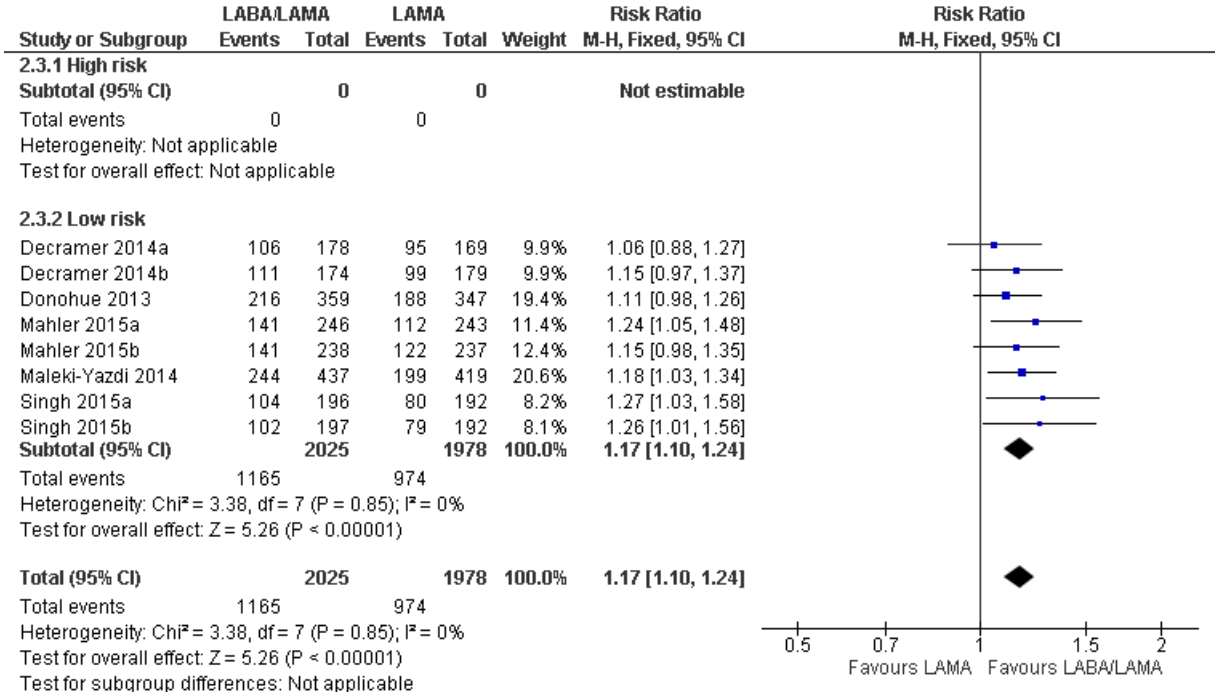
1 ***People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months***



Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LAMA Events	LAMA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.2 Low risk						
Decramer 2014a	106	178	95	169	8.8%	1.06 [0.88, 1.27]
Decramer 2014b	111	174	99	179	8.9%	1.15 [0.97, 1.37]
Donohue 2013	216	359	188	347	17.4%	1.11 [0.98, 1.26]
Kerwin 2017	104	242	117	245	10.6%	0.90 [0.74, 1.09]
Mahler 2015a	141	246	112	243	10.2%	1.24 [1.05, 1.48]
Mahler 2015b	141	238	122	237	11.1%	1.15 [0.98, 1.35]
Maleki-Yazdi 2014	244	437	199	419	18.4%	1.18 [1.03, 1.34]
Singh 2015a	104	196	80	192	7.3%	1.27 [1.03, 1.58]
Singh 2015b	102	197	79	192	7.3%	1.26 [1.01, 1.56]
Subtotal (95% CI)		**2267**		**2223**	**100.0%**	**1.14 [1.08, 1.21]**
Total events	1269		1091			
Heterogeneity: Chi² = 9.47, df = 8 (P = 0.30); I² = 16%						
Test for overall effect: Z = 4.62 (P < 0.00001)						
Total (95% CI)		**2267**		**2223**	**100.0%**	**1.14 [1.08, 1.21]**
Total events	1269		1091			
Heterogeneity: Chi² = 9.47, df = 8 (P = 0.30); I² = 16%						
Test for overall effect: Z = 4.62 (P < 0.00001)						
Test for subgroup differences: Not applicable						

2

3 *Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ) at 3 months*



Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LAMA Events	LAMA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.2 Low risk						
Decramer 2014a	106	178	95	169	9.9%	1.06 [0.88, 1.27]
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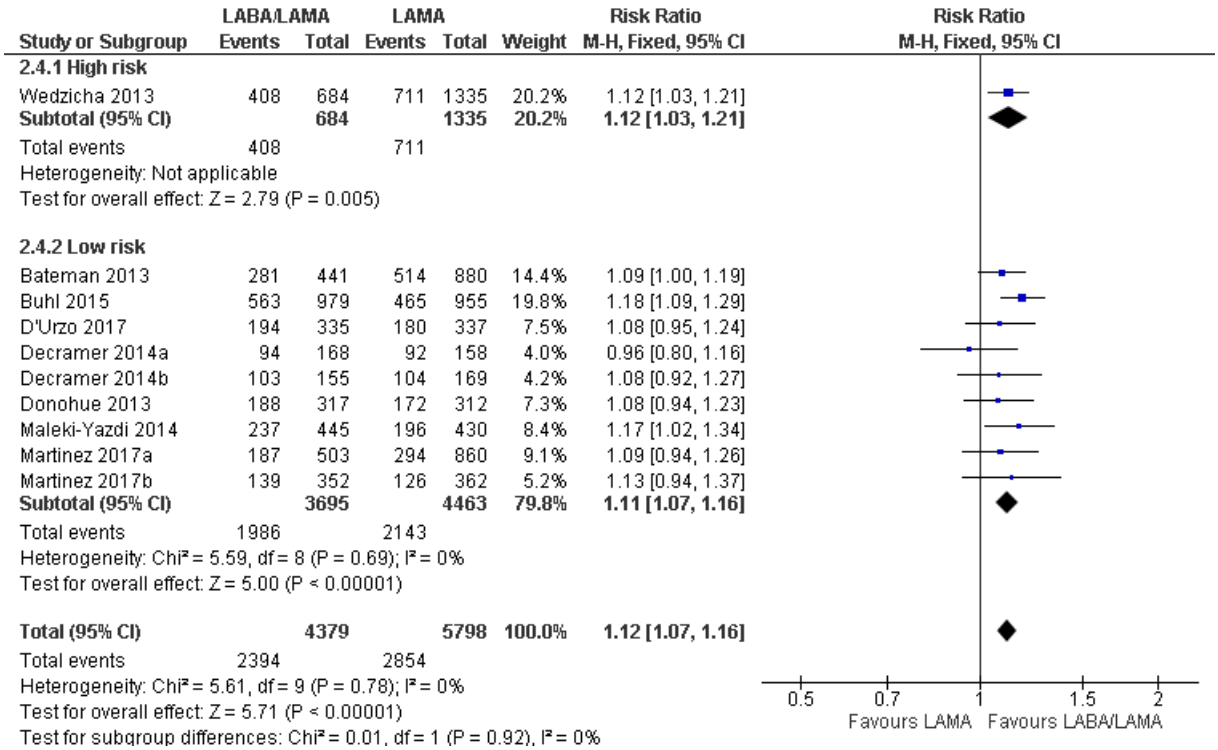
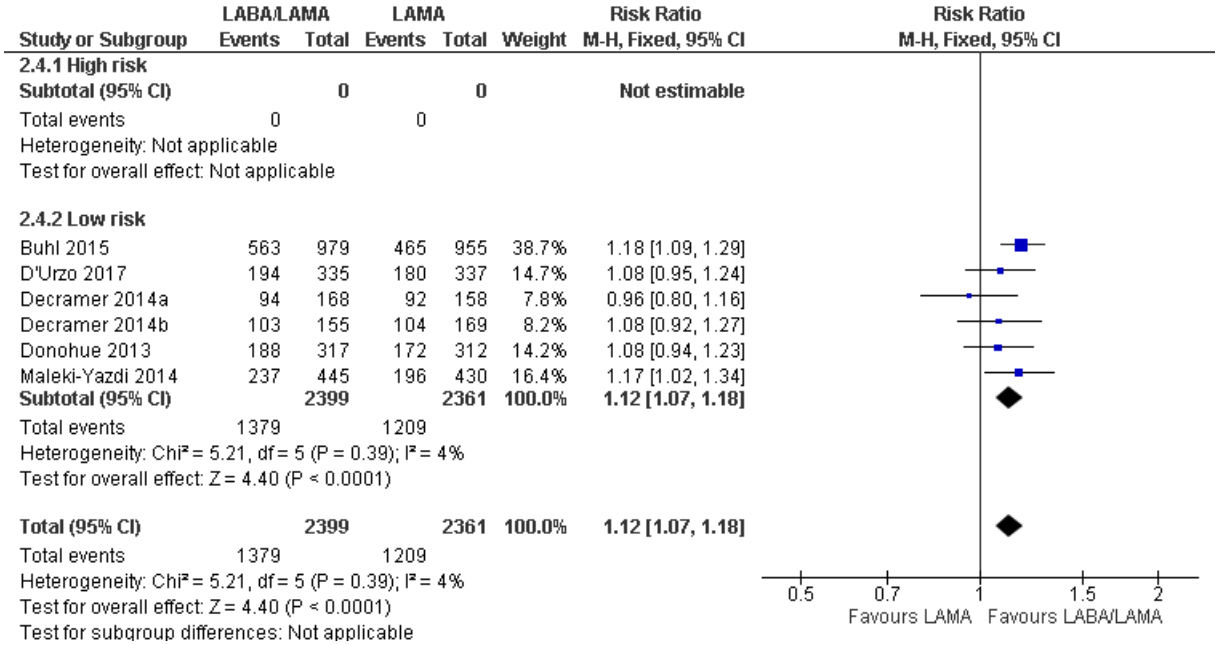
Singh 2015a	104	196	80	192	8.2%	1.27 [1.03, 1.58]
Singh 2015b	102	197	79	192	8.1%	1.26 [1.01, 1.56]
Subtotal (95% CI)		**2025**		**1978**	**100.0%**	**1.17 [1.10, 1.24]**
Total events	1165		974			
Heterogeneity: Chi² = 3.38, df = 7 (P = 0.85); I² = 0%						
Test for overall effect: Z = 5.26 (P < 0.00001)						
Total (95% CI)		**2025**		**1978**	**100.0%**	**1.17 [1.10, 1.24]**
Total events	1165		974			
Heterogeneity: Chi² = 3.38, df = 7 (P = 0.85); I² = 0%						
Test for overall effect: Z = 5.26 (P < 0.00001)						
Test for subgroup differences: Not applicable						

4

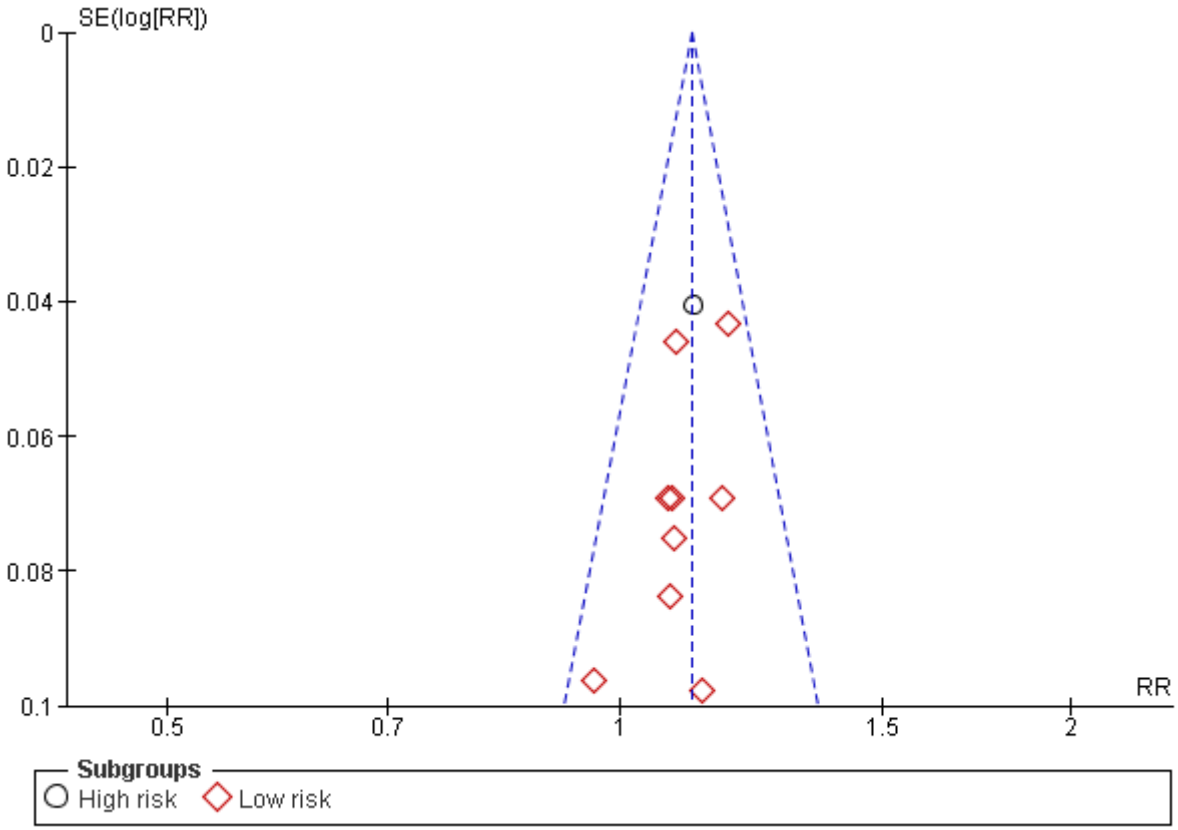
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months



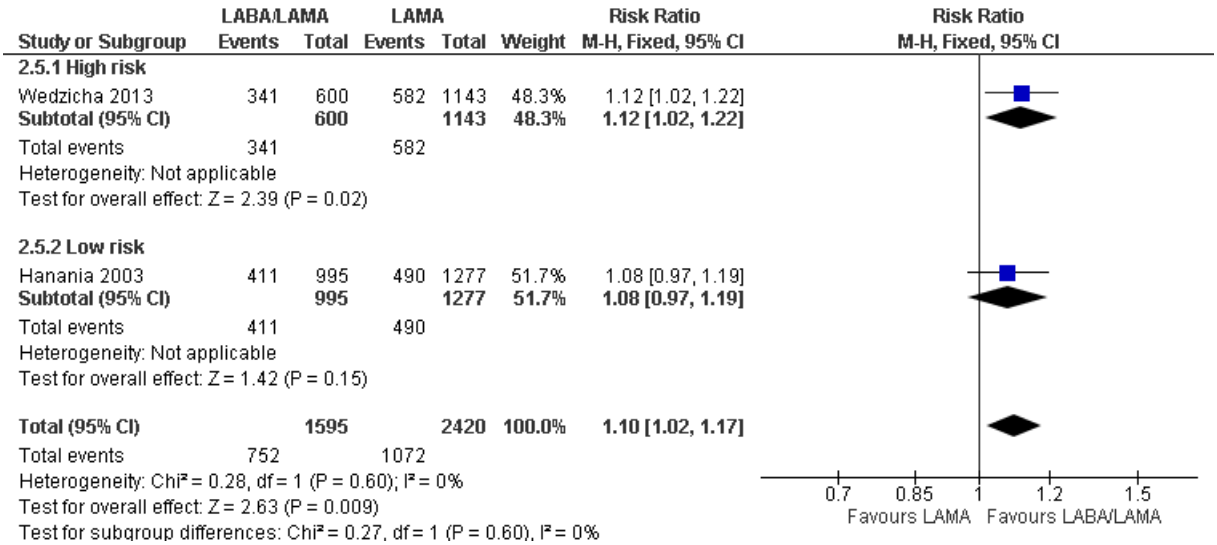
Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ) at 6 months



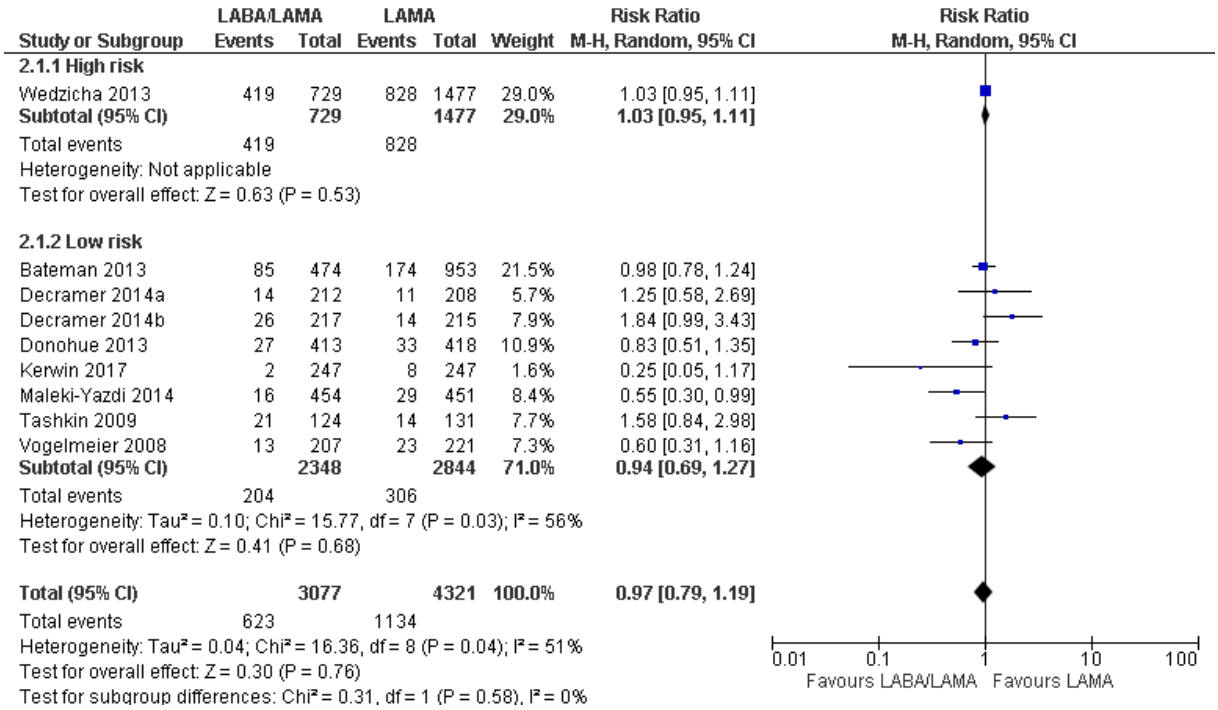
Publication bias assessment: funnel plot for SGRQ responders at 6 months



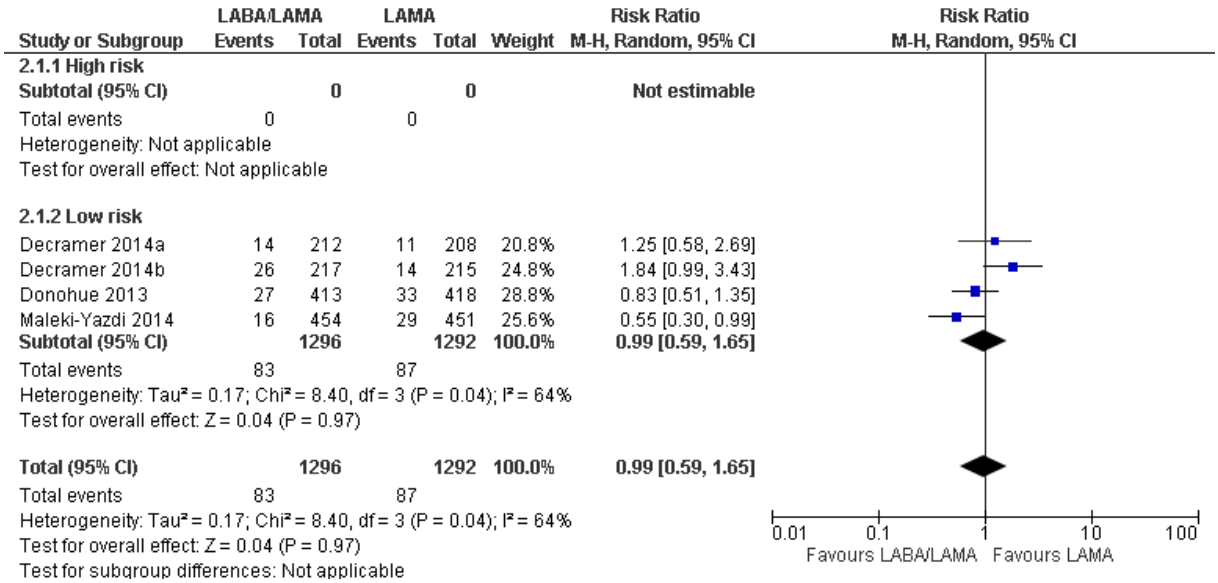
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months



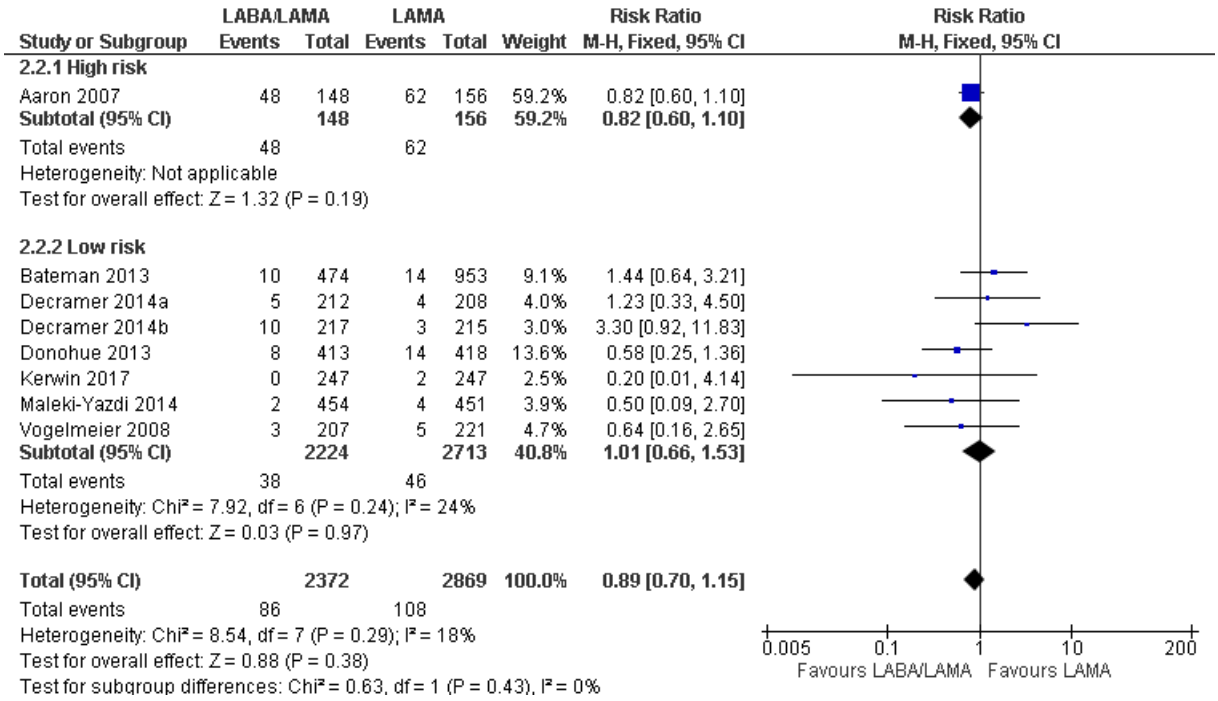
People with ≥ 1 moderate to severe exacerbation



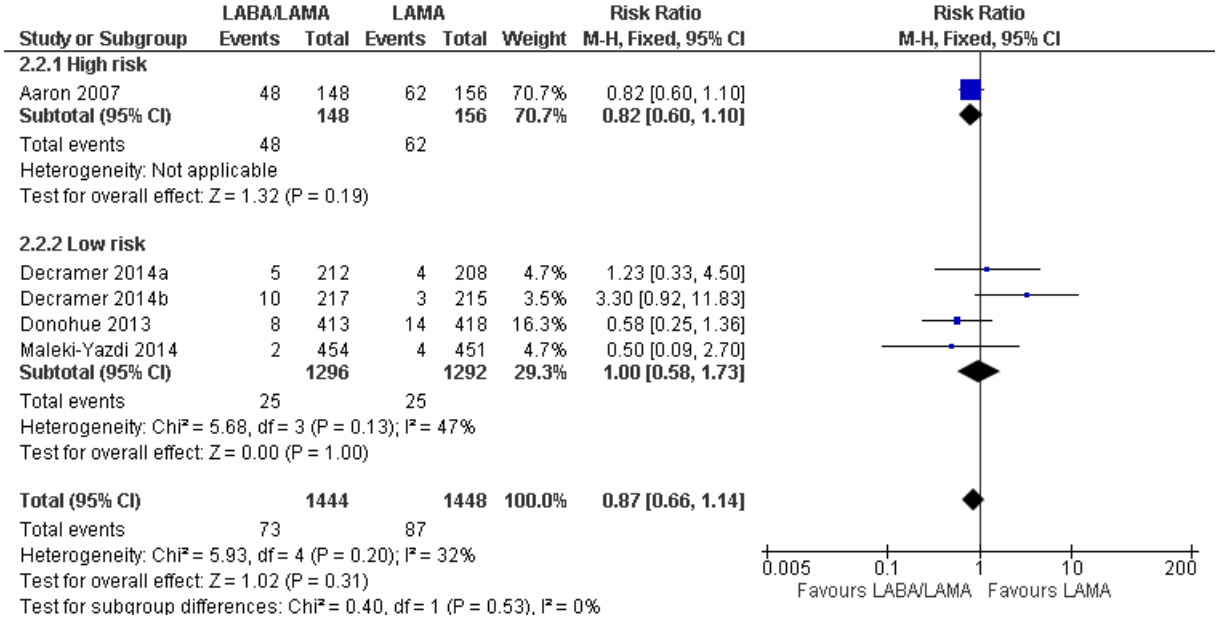
Sensitivity analysis: people with ≥ 1 moderate to severe exacerbation



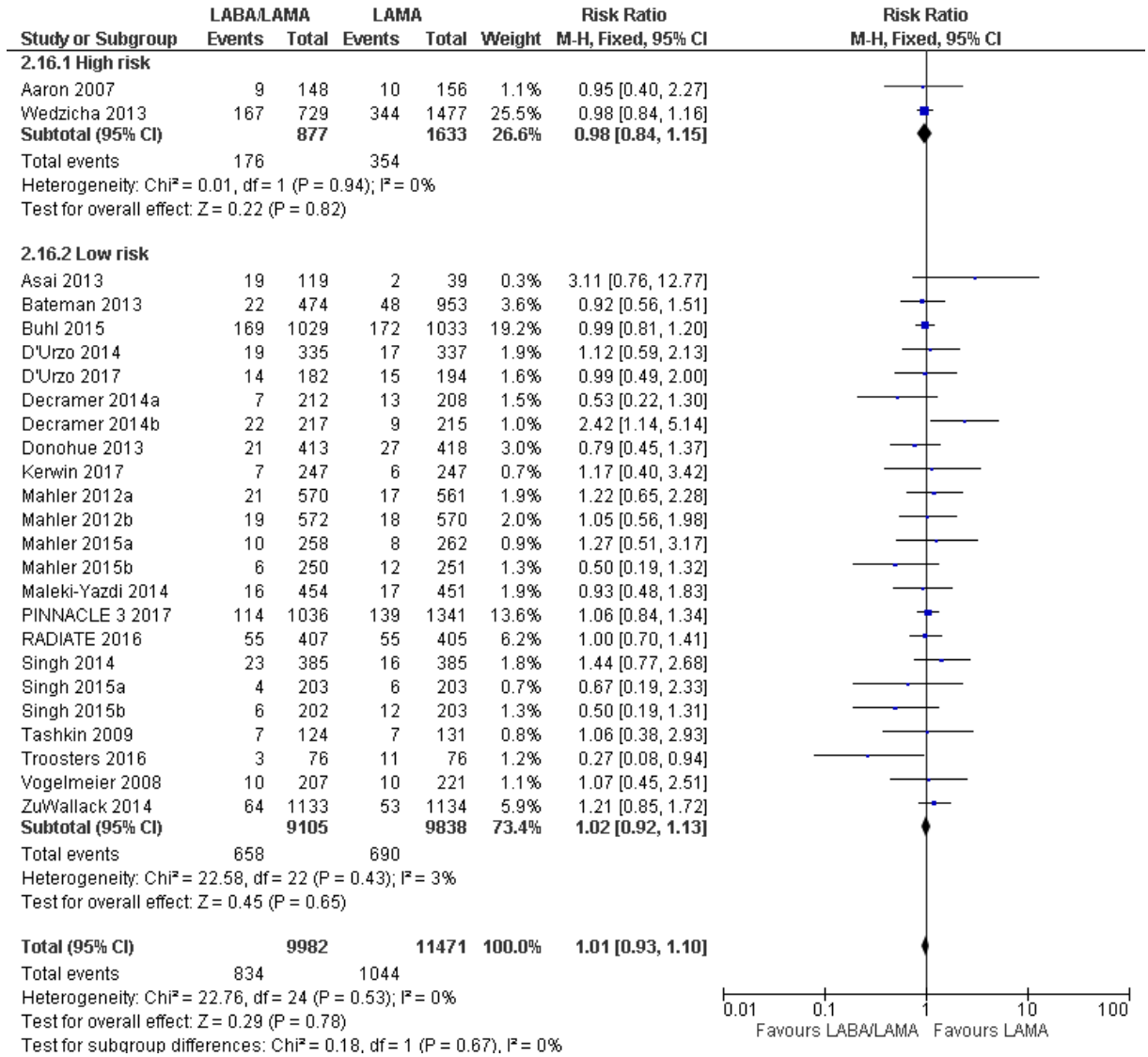
People with ≥ 1 severe exacerbation (requiring hospitalisation)



Sensitivity analysis: people with ≥ 1 severe exacerbation

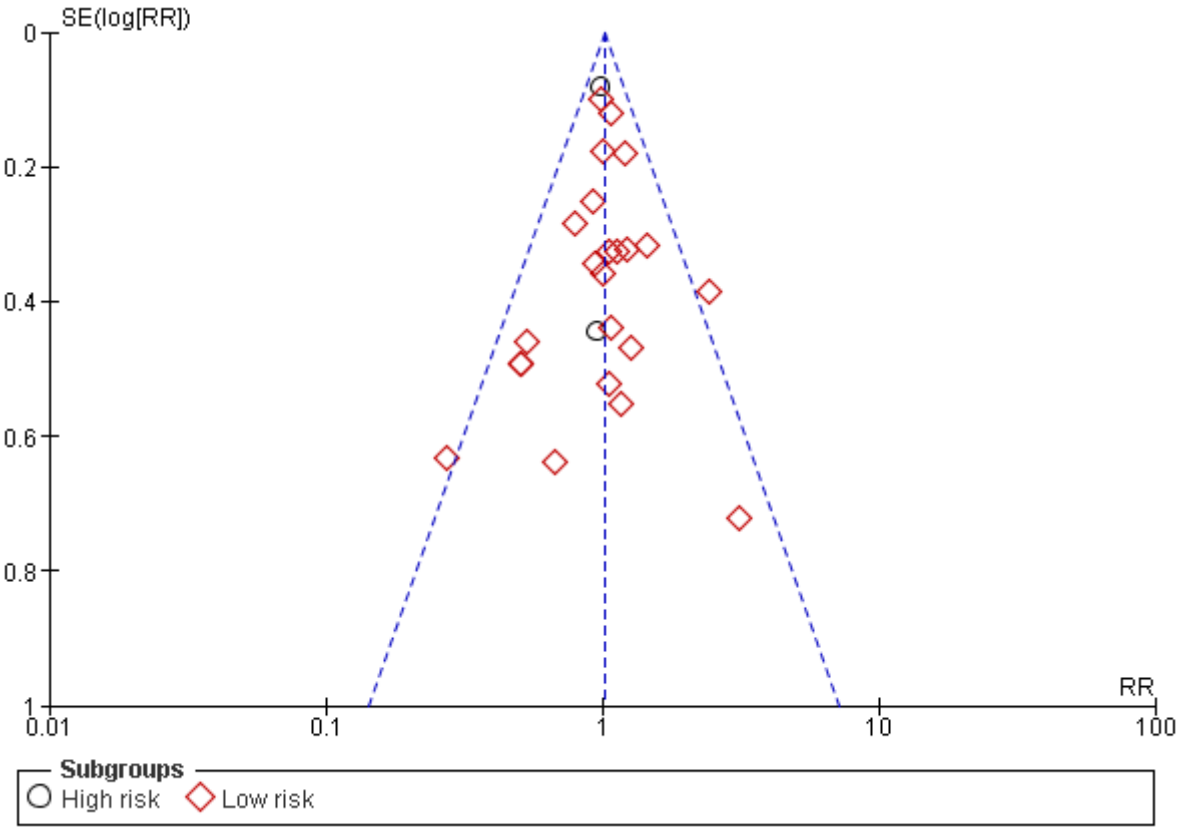


1 ***People with ≥ 1 Serious Adverse Event (SAE)***

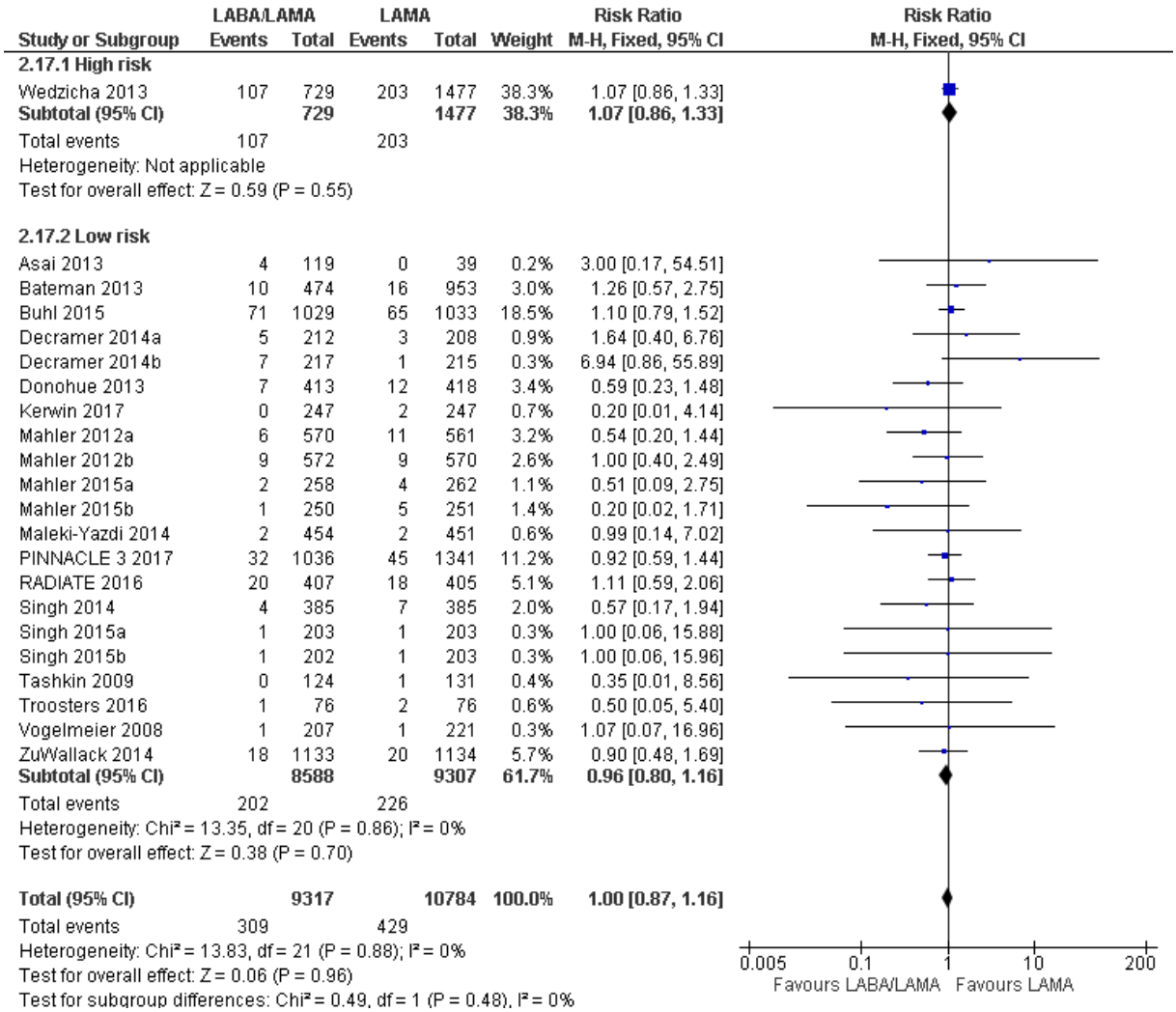


2

Publication bias assessment: funnel plot for SAEs

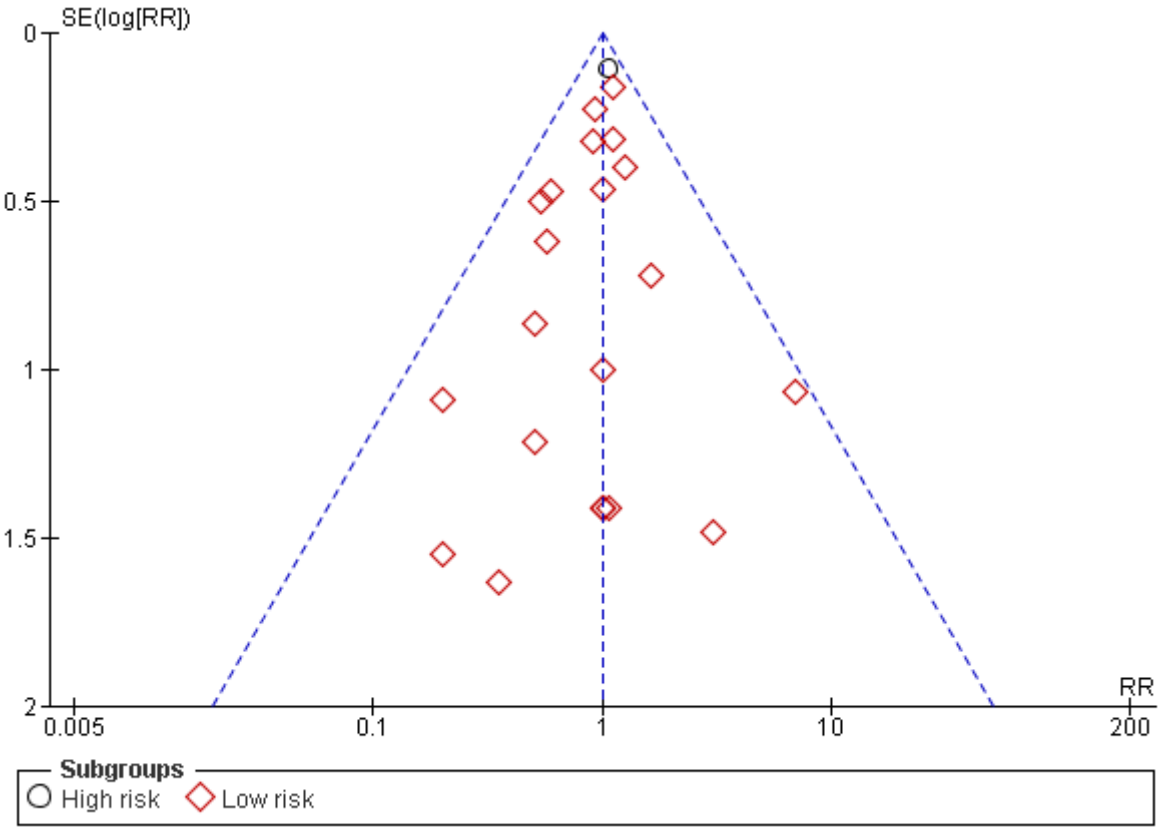


1 ***People with ≥ 1 COPD SAE***

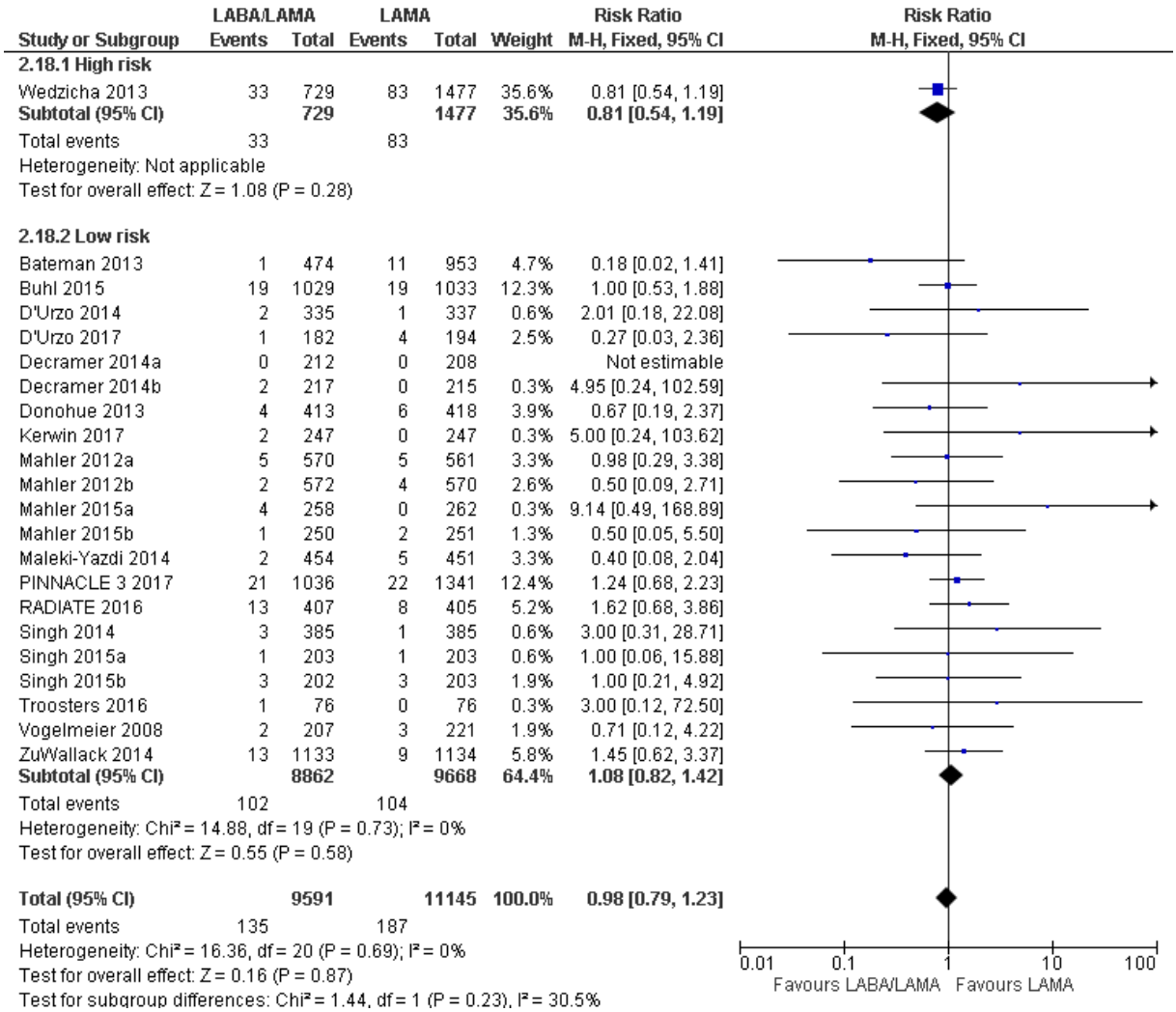


2

Publication bias assessment: funnel plot for COPD SAEs

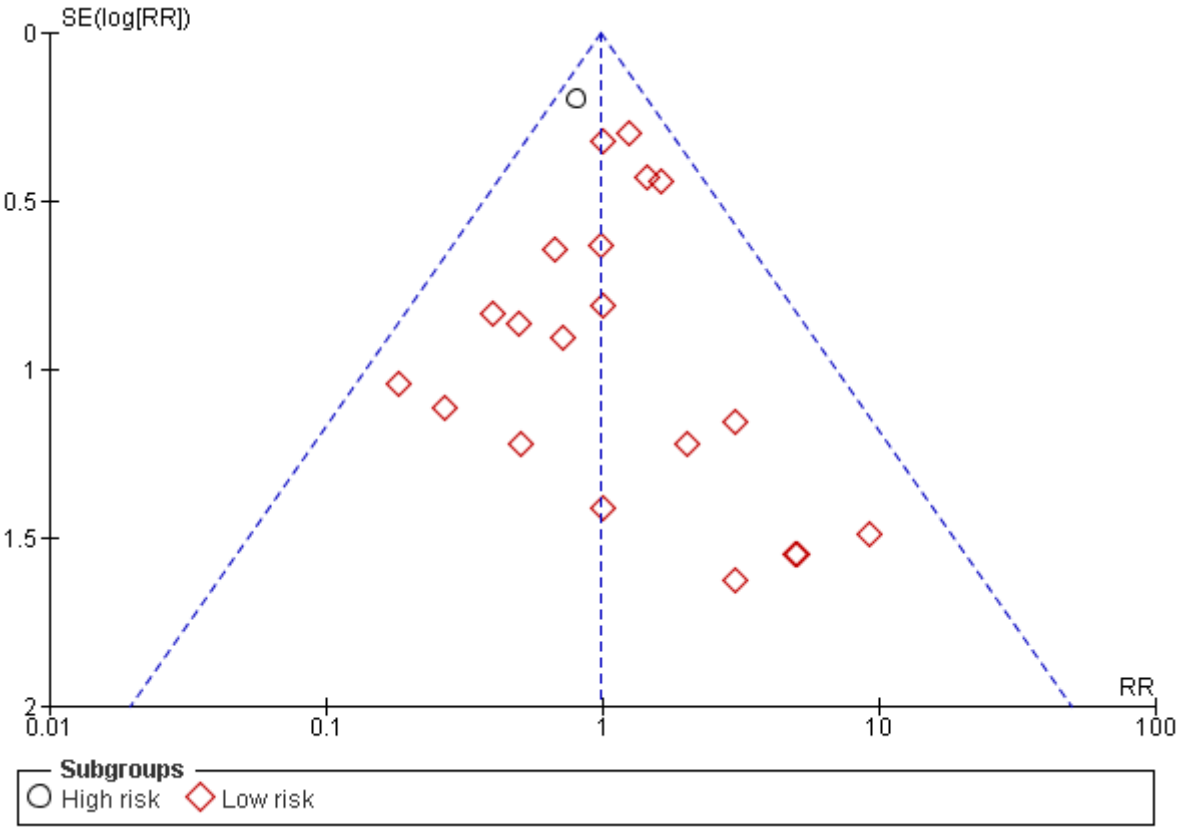


1 ***People with ≥ 1 cardiac SAE***

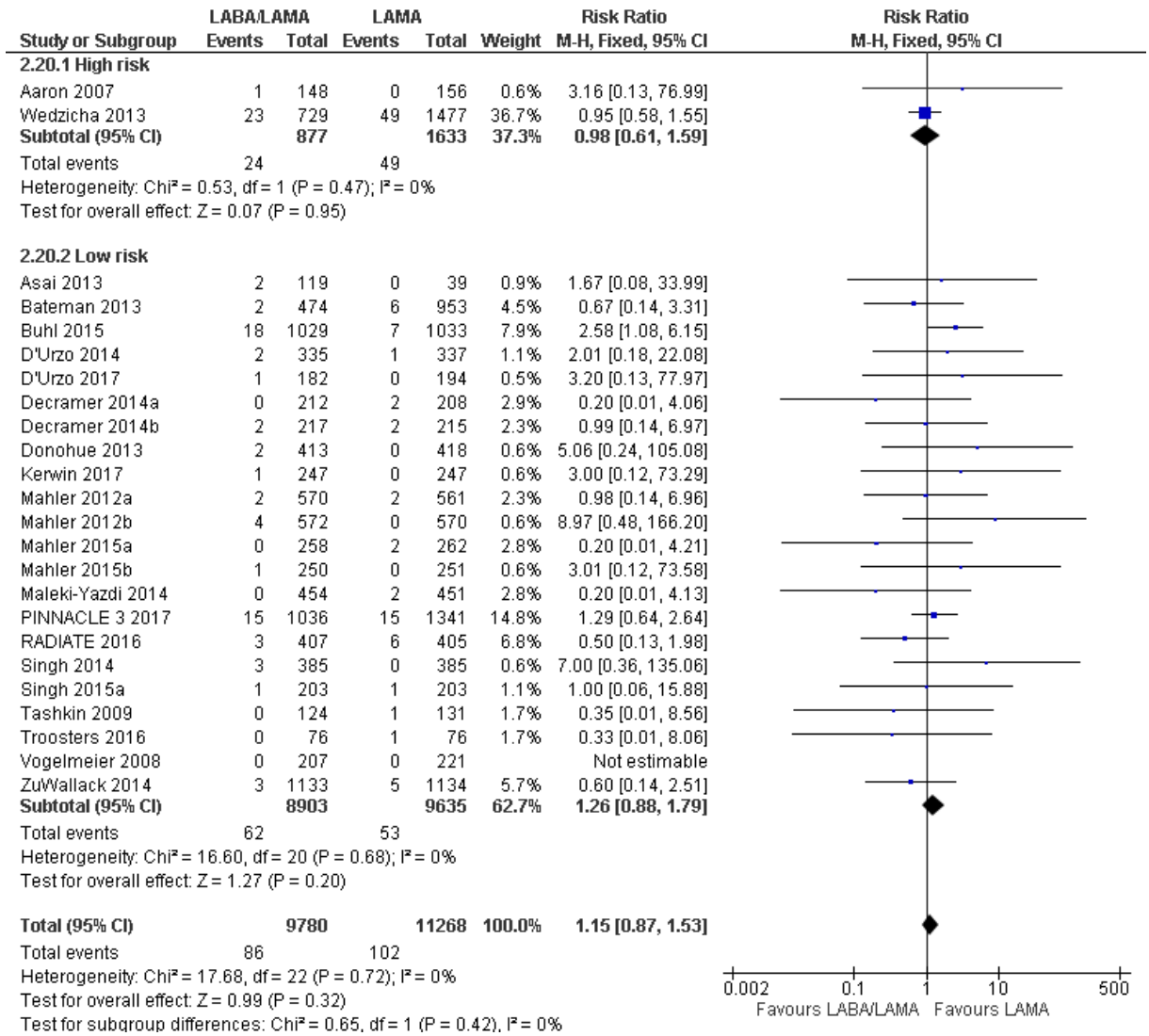


2

Publication bias assessment: funnel plot for Cardiac SAEs

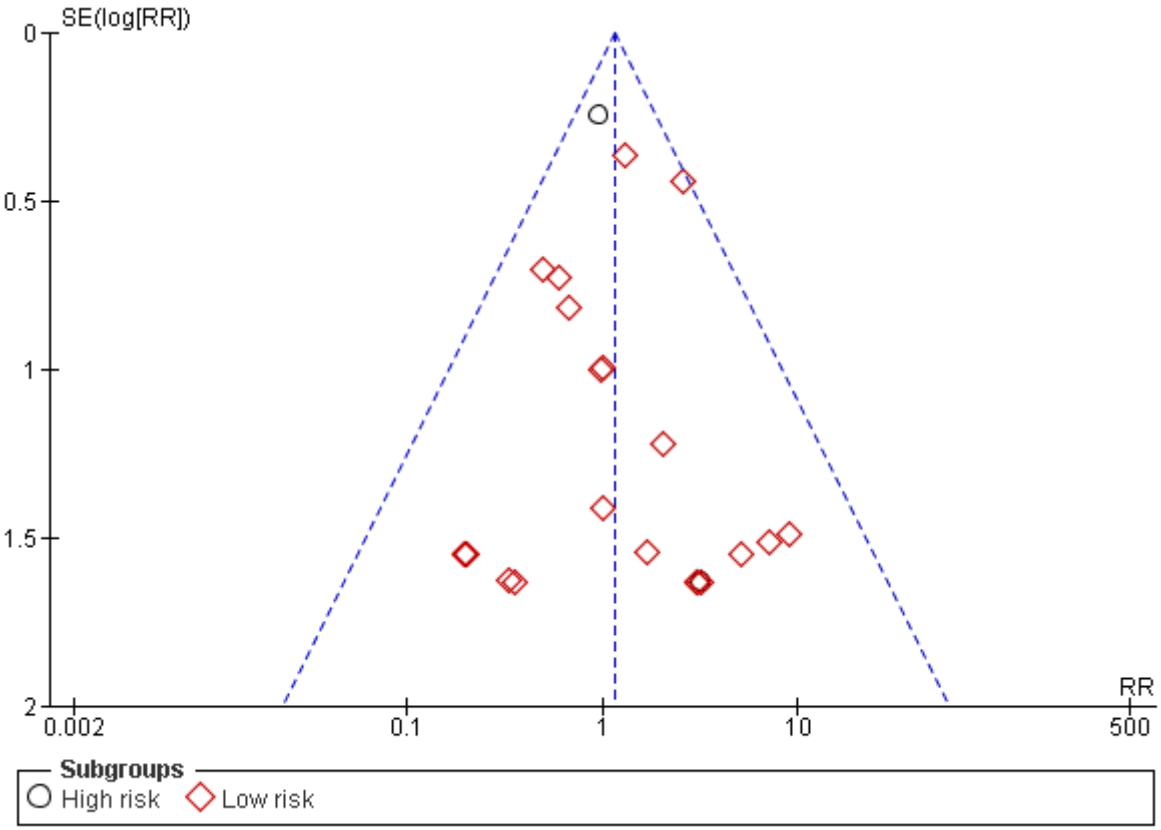


1 ***People with ≥ 1 session of pneumonia***

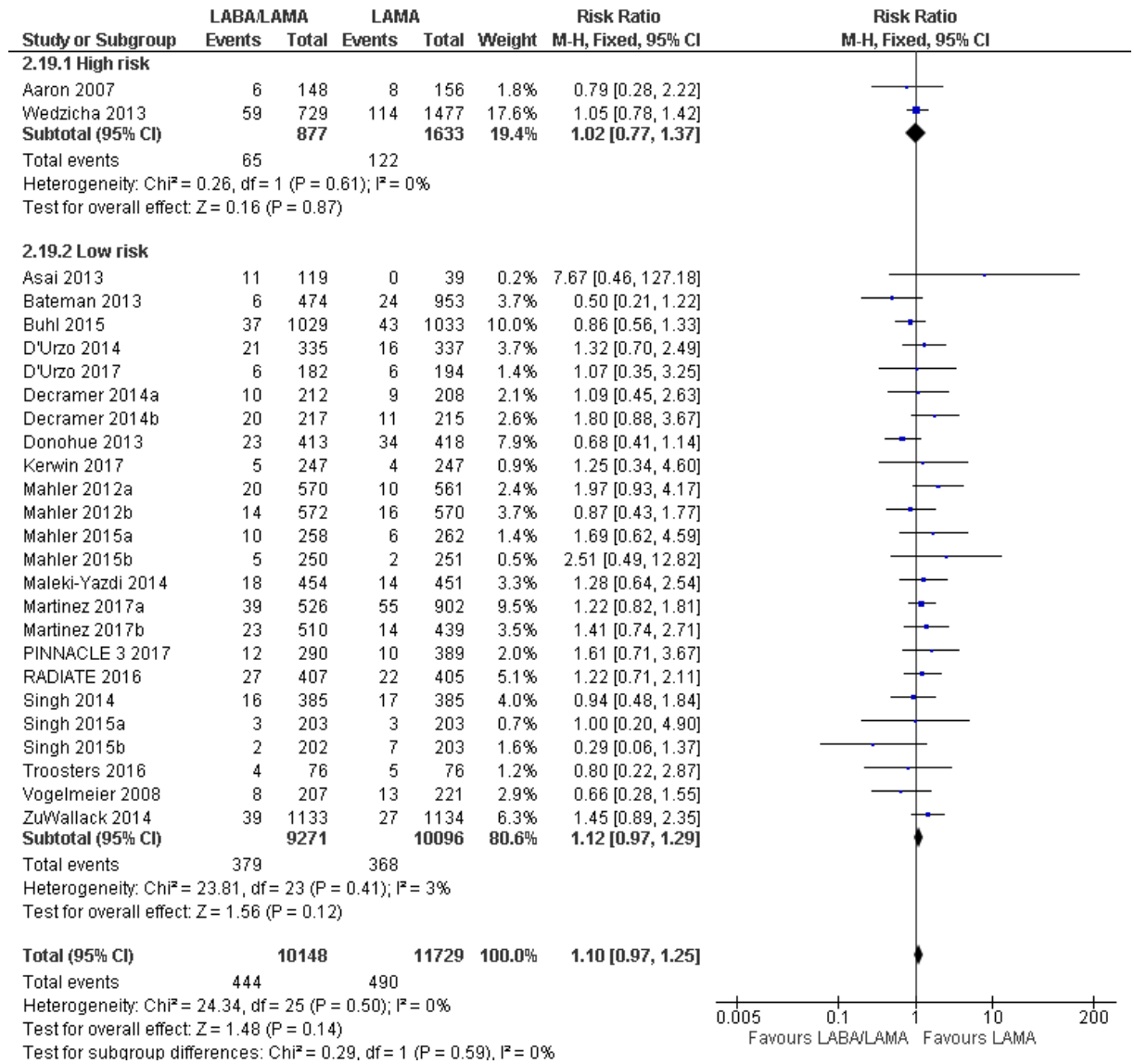


2

Publication bias assessment: funnel plot for pneumonia

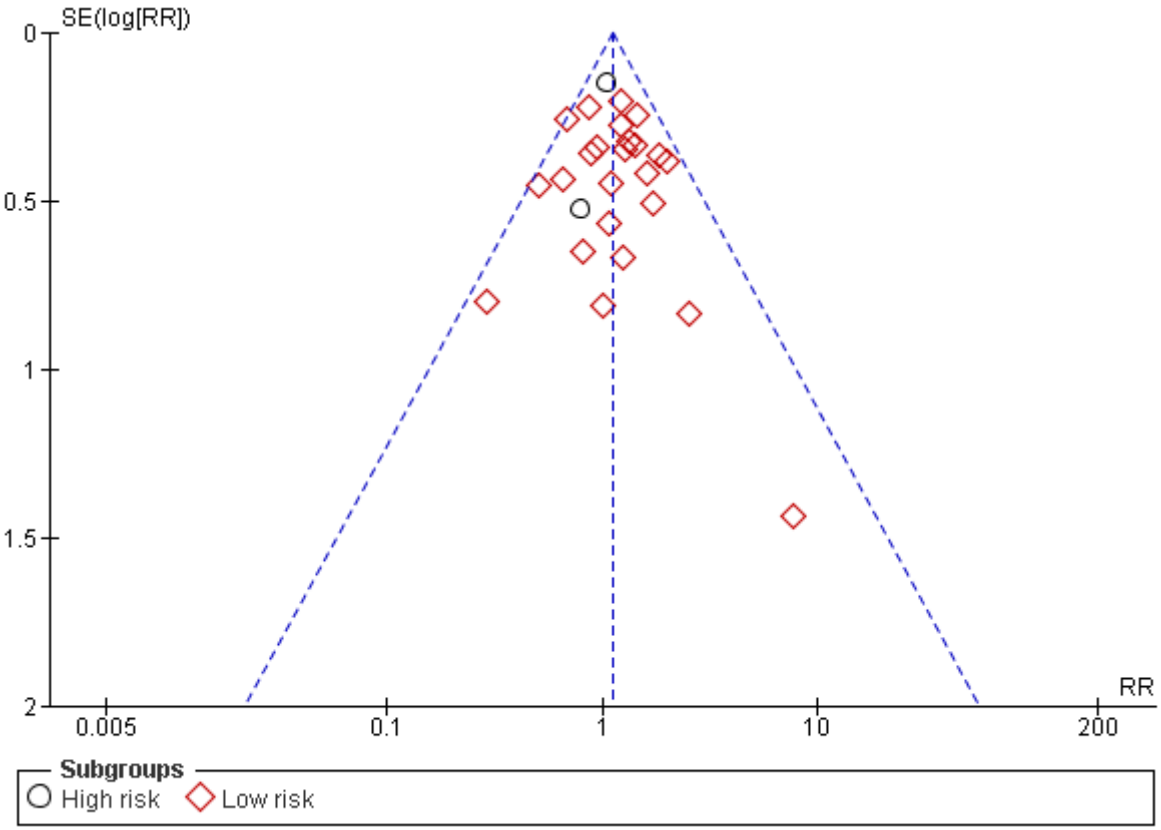


1 ***Drop-outs due to adverse events***



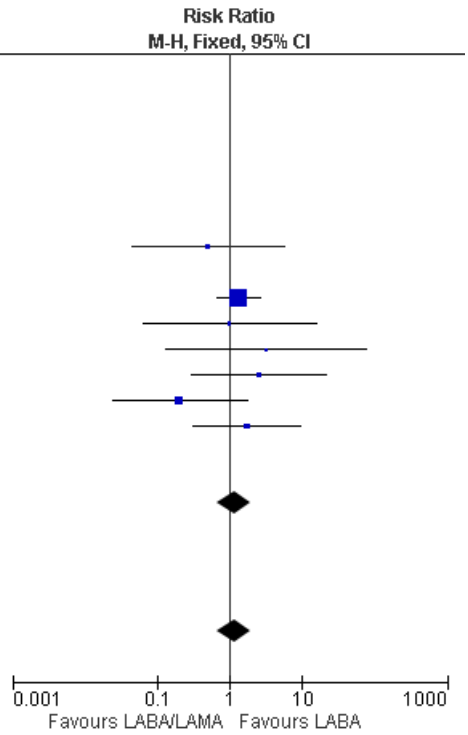
2

Publication bias assessment: funnel plot for drop-outs due to adverse events



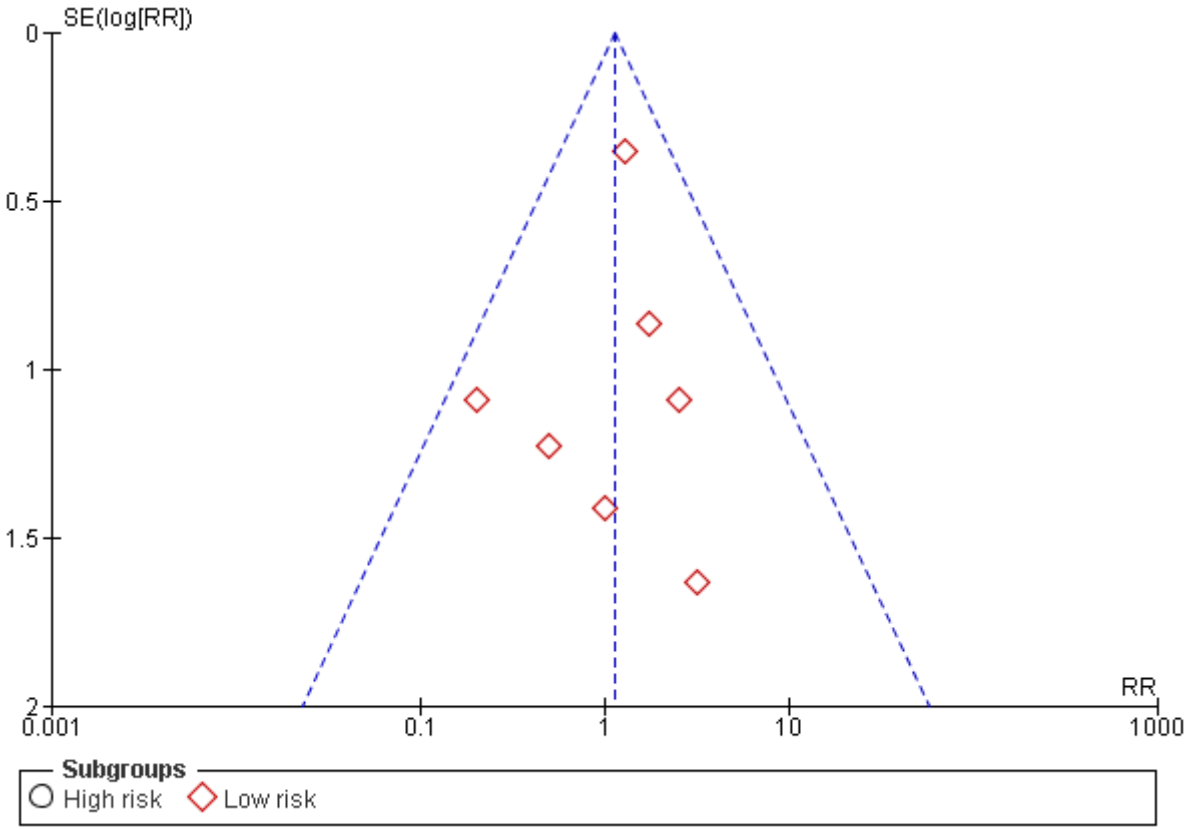
1 **LABA/LAMA versus LABA**

2 ***All-cause mortality***



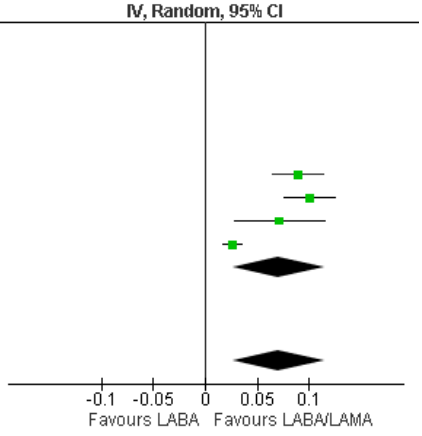
3

Publication bias assessment: funnel plot for all-cause mortality



Change in Trough FEV1 (L) at 3 months

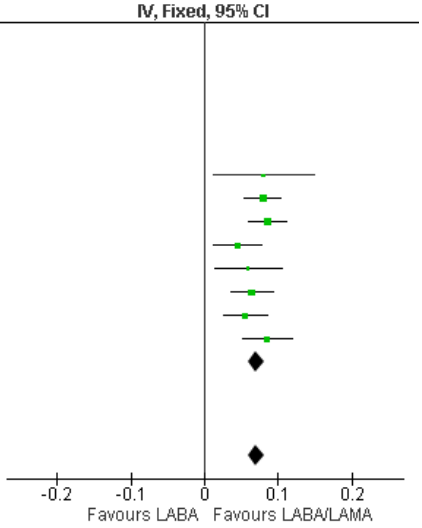
Study or Subgroup	LABA/LAMA Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.11.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.11.2 Low risk								
Buhl 2015a	0.146	0.205	521	0.057	0.205	519	25.4%	0.09 [0.06, 0.11]
Buhl 2015b	0.147	0.201	497	0.047	0.202	503	25.4%	0.10 [0.08, 0.12]
Ferguson 2016	0.166	0.219	192	0.095	0.221	199	21.9%	0.07 [0.03, 0.11]
Hoshino 2014	0.165	0.013	18	0.139	0.0149	20	27.3%	0.03 [0.02, 0.03]
Subtotal (95% CI)			**1228**			**1241**	**100.0%**	**0.07 [0.03, 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 48.48, df = 3 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.10 (P = 0.002)								
Total (95% CI)			**1228**			**1241**	**100.0%**	**0.07 [0.03, 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 48.48, df = 3 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.10 (P = 0.002)								
Test for subgroup differences: Not applicable								



1

2 ***Change in Trough FEV1 (L) at 6 months***

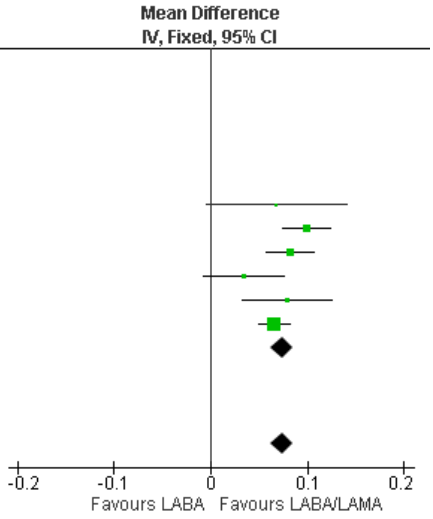
Study or Subgroup	LABA/LAMA Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.12.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.12.2 Low risk								
Bateman 2013	0.17	0.544	474	0.09	0.501	435	2.7%	0.08 [0.01, 0.15]
Buhl 2015a	0.112	0.205	521	0.033	0.205	519	19.8%	0.08 [0.05, 0.10]
Buhl 2015b	0.119	0.201	497	0.034	0.202	503	19.7%	0.08 [0.06, 0.11]
D'Urzo 2014	0.095	0.19754	271	0.05	0.196	268	11.1%	0.04 [0.01, 0.08]
Ferguson 2016	0.138	0.231	192	0.079	0.234	199	5.8%	0.06 [0.01, 0.11]
Martinez 2017a	0.126	0.201	429	0.062	0.203	367	15.5%	0.06 [0.04, 0.09]
Martinez 2017b	0.116	0.21	433	0.061	0.208	350	14.2%	0.06 [0.03, 0.08]
Singh 2014	0.083	0.22418	349	-0.002	0.22	337	11.1%	0.09 [0.05, 0.12]
Subtotal (95% CI)			**3166**			**2978**	**100.0%**	**0.07 [0.06, 0.08]**
Heterogeneity: Chi² = 6.32, df = 7 (P = 0.50); I² = 0%								
Test for overall effect: Z = 12.40 (P < 0.00001)								
Total (95% CI)			**3166**			**2978**	**100.0%**	**0.07 [0.06, 0.08]**
Heterogeneity: Chi² = 6.32, df = 7 (P = 0.50); I² = 0%								
Test for overall effect: Z = 12.40 (P < 0.00001)								
Test for subgroup differences: Not applicable								



3

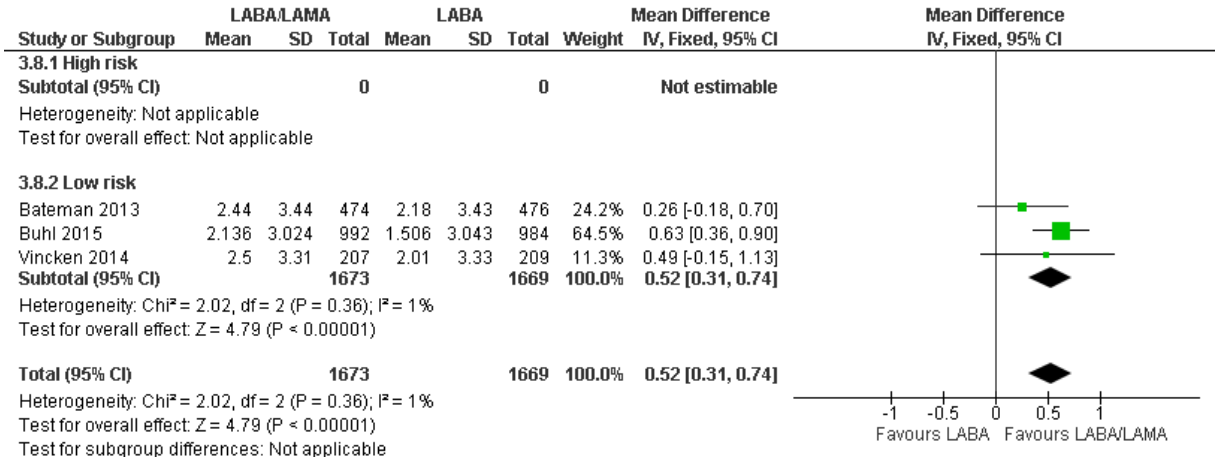
4 ***Change in Trough FEV1 (L) at 12 months***

Study or Subgroup	LABA/LAMA Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.13.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.13.2 Low risk								
BI1237.22 2014	0.143	0.156	39	0.075	0.157	34	2.3%	0.07 [-0.00, 0.14]
Buhl 2015a	0.099	0.205	521	0	0.205	519	19.6%	0.10 [0.07, 0.12]
Buhl 2015b	0.093	0.201	497	0.011	0.202	503	19.5%	0.08 [0.06, 0.11]
D'Urzo 2017	0.038	0.275	335	0.004	0.273	332	7.0%	0.03 [-0.01, 0.08]
Ferguson 2016	0.116	0.234	192	0.037	0.238	199	5.6%	0.08 [0.03, 0.13]
PINNACLE 3 2017	0.133	0.179	1021	0.068	0.181	871	45.9%	0.07 [0.05, 0.08]
Subtotal (95% CI)			**2605**			**2458**	**100.0%**	**0.07 [0.06, 0.08]**
Heterogeneity: Chi² = 9.06, df = 5 (P = 0.11); I² = 45%								
Test for overall effect: Z = 13.08 (P < 0.00001)								
Total (95% CI)			**2605**			**2458**	**100.0%**	**0.07 [0.06, 0.08]**
Heterogeneity: Chi² = 9.06, df = 5 (P = 0.11); I² = 45%								
Test for overall effect: Z = 13.08 (P < 0.00001)								
Test for subgroup differences: Not applicable								

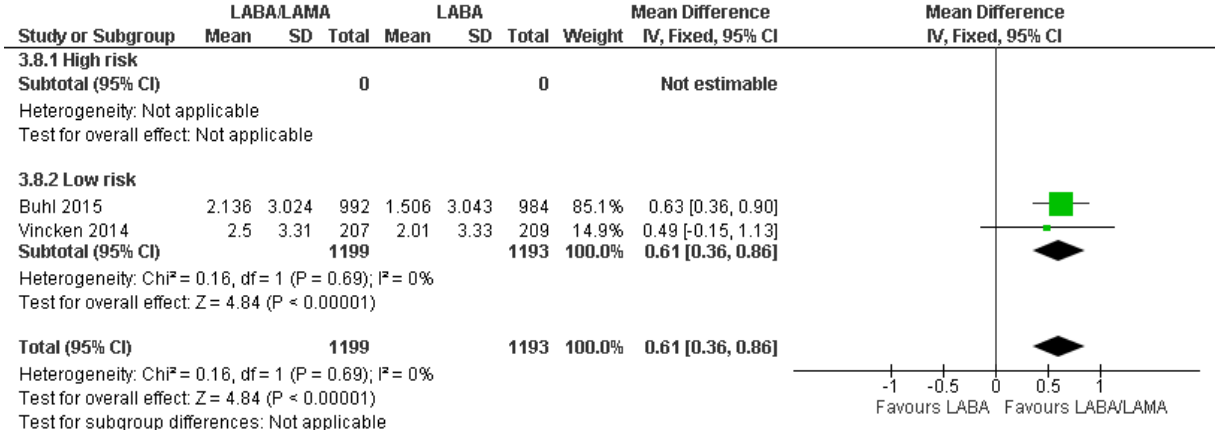


5

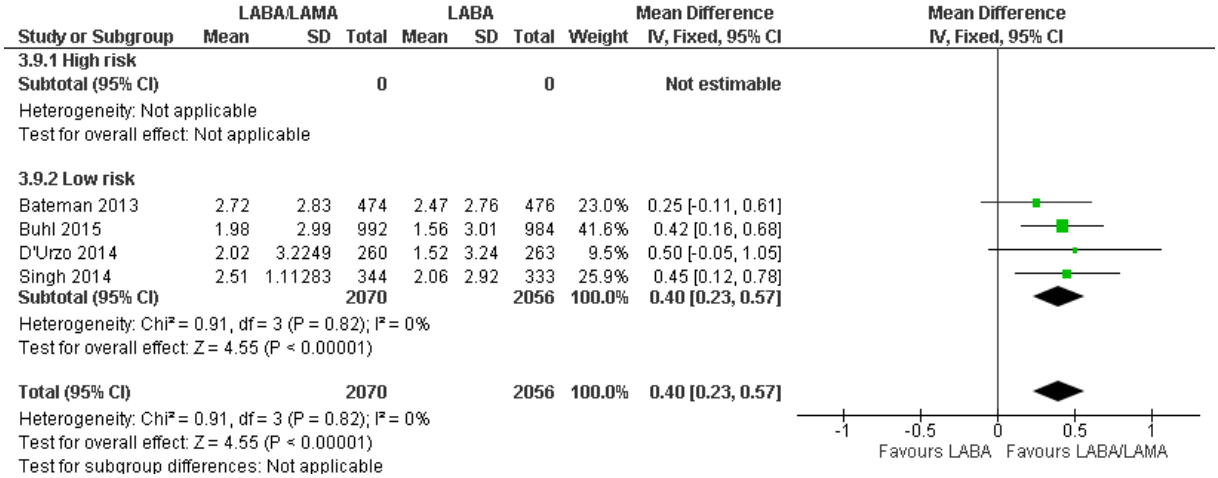
Transition Dyspnoea Index (TDI) focal score at 3 months



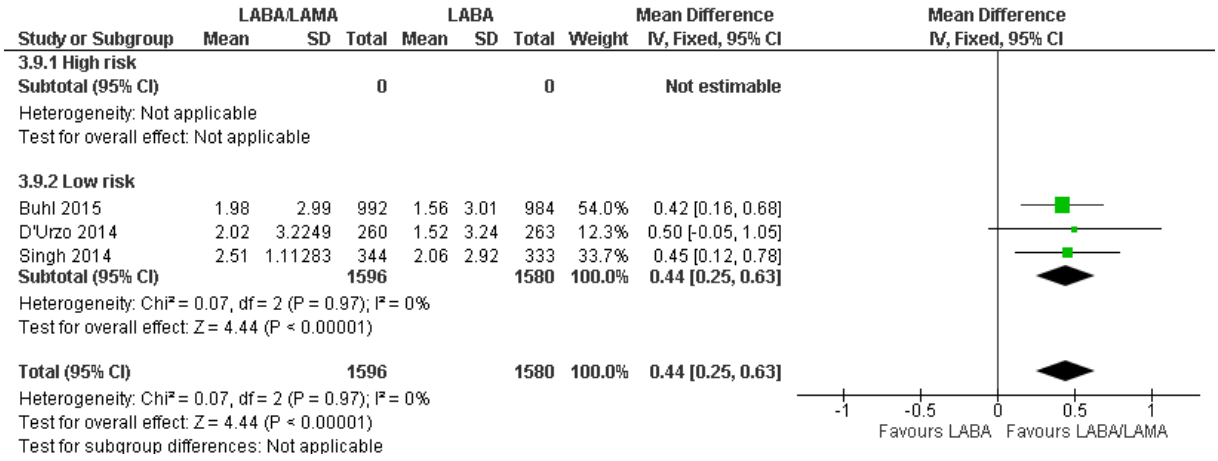
Sensitivity analysis: TDI at 3 months



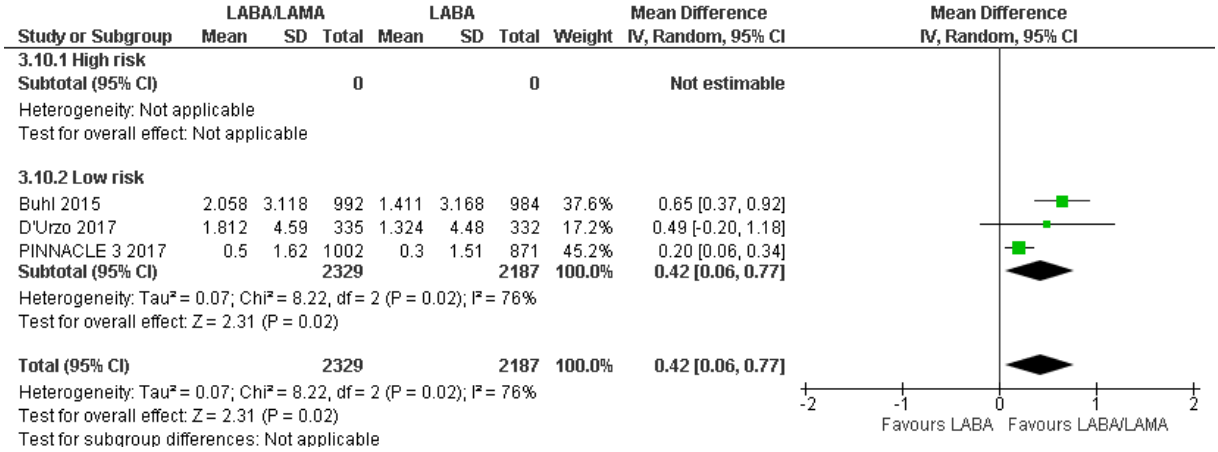
Transition Dyspnoea Index (TDI) focal score at 6 months



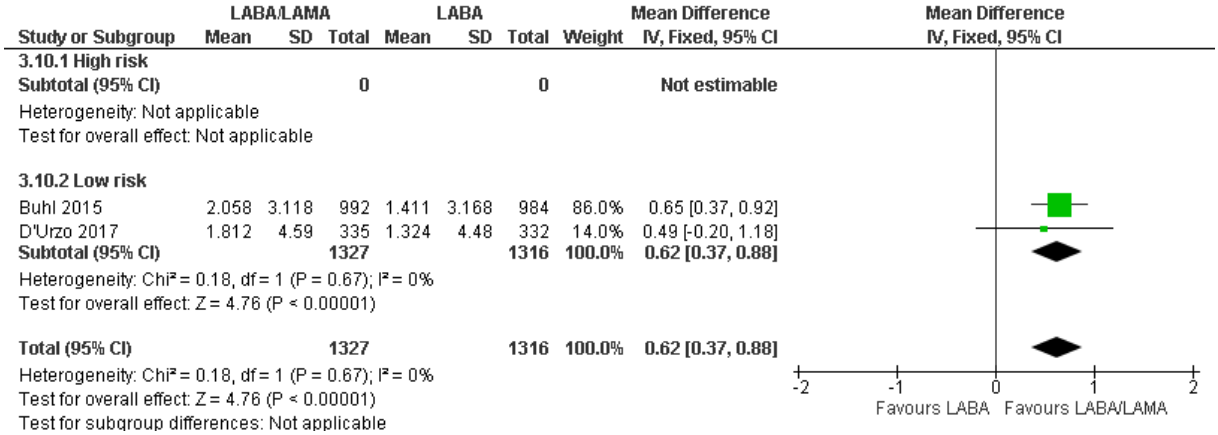
Sensitivity analysis: TDI at 6 months



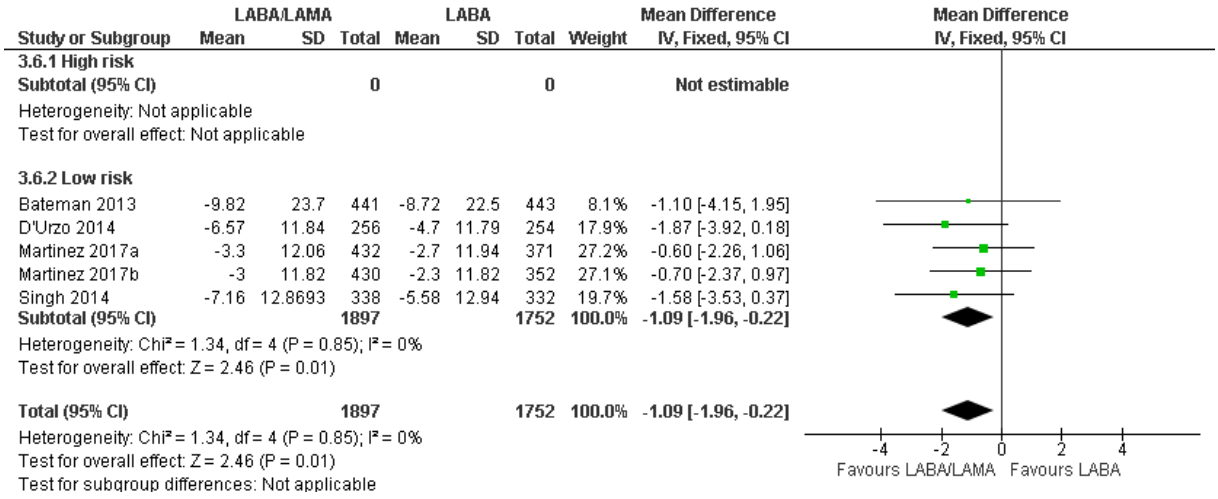
Transition Dyspnoea Index (TDI) focal score at 12 months



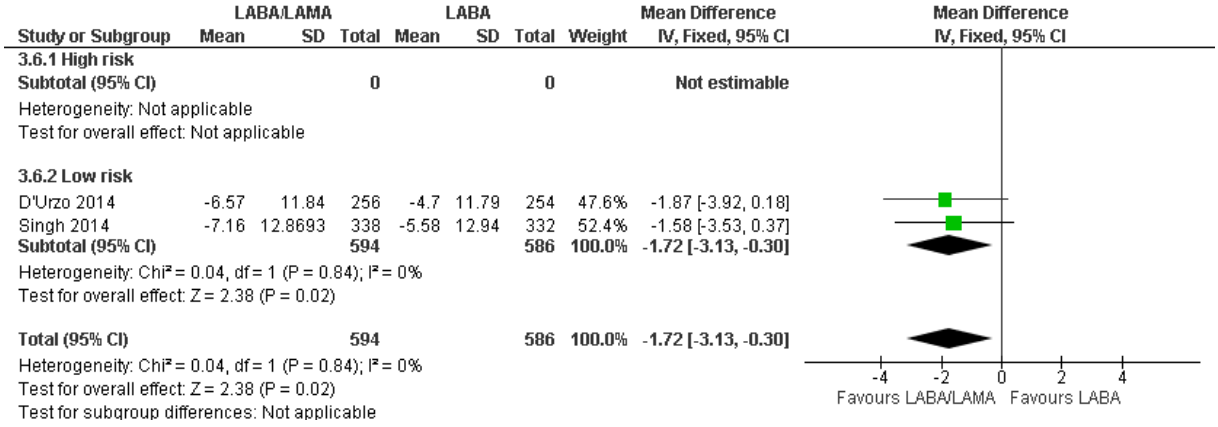
Sensitivity analysis: TDI at 12 months



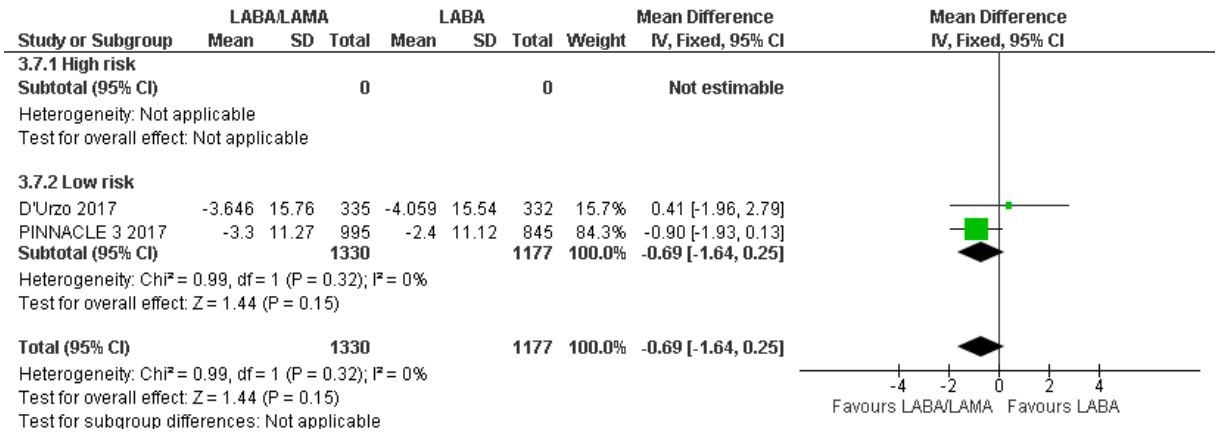
St. George's Respiratory Questionnaire (SGRQ), total score at 6 months



Sensitivity analysis: SGRQ at 6 months

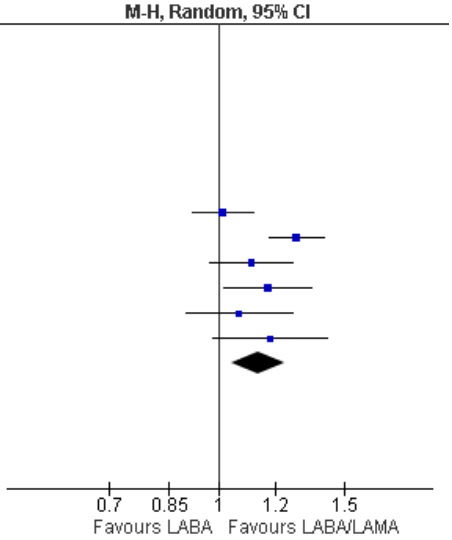


St. George's Respiratory Questionnaire (SGRQ), total score at 12 months



1 ***People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months***

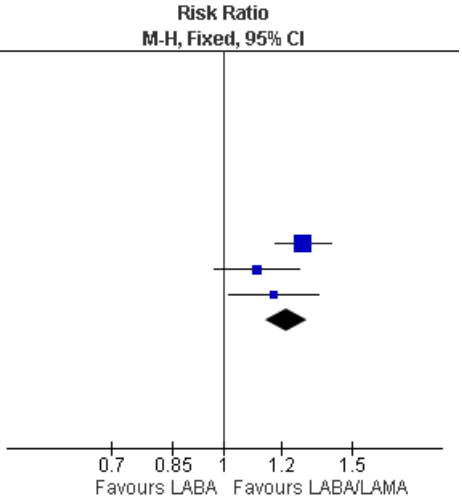
Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.3.2 Low risk						
Bateman 2013	281	441	279	443	20.3%	1.01 [0.92, 1.12]
Buhl 2015	563	979	427	954	21.6%	1.28 [1.18, 1.40]
D'Urzo 2014	195	335	174	332	16.5%	1.11 [0.97, 1.27]
D'Urzo 2017	194	335	164	332	16.0%	1.17 [1.02, 1.35]
Martinez 2017a	187	503	151	434	13.4%	1.07 [0.90, 1.27]
Martinez 2017b	139	352	144	430	12.3%	1.18 [0.98, 1.42]
Subtotal (95% CI)		**2945**		**2925**	**100.0%**	**1.14 [1.04, 1.24]**
Total events	1559		1339			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.44$, df = 5 (P = 0.02); $I^2 = 63\%$						
Test for overall effect: Z = 2.88 (P = 0.004)						



2 Test for subgroup differences: Not applicable

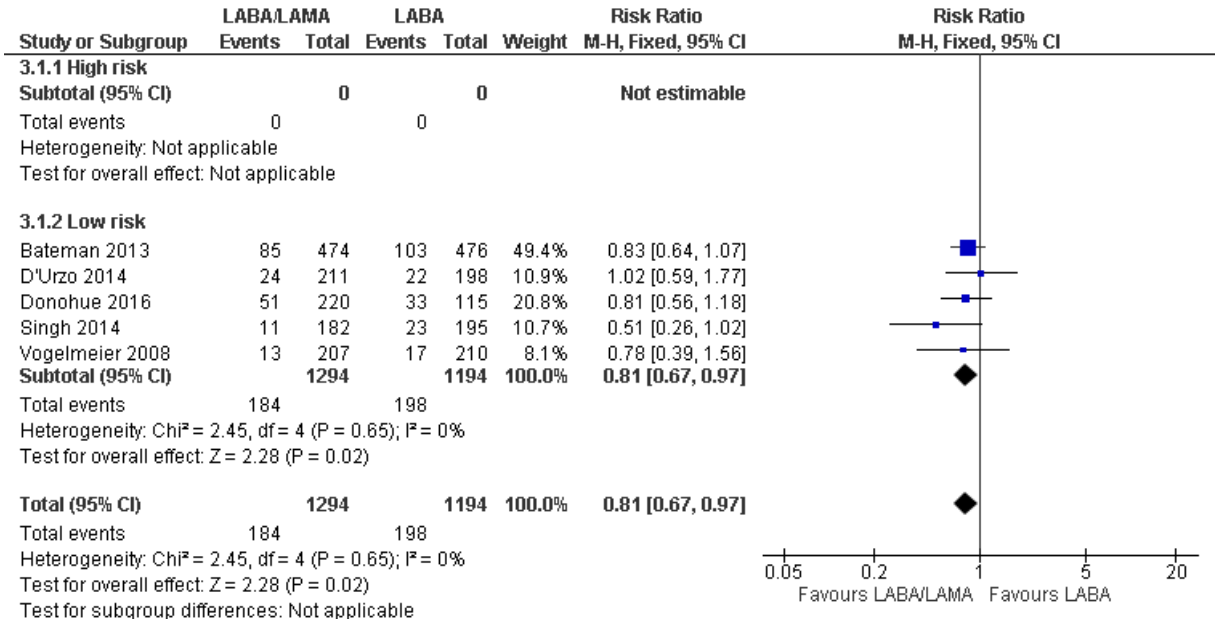
3 *Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ) at 6 months*

Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.3.2 Low risk						
Buhl 2015	563	979	427	954	56.0%	1.28 [1.18, 1.40]
D'Urzo 2014	195	335	174	332	22.6%	1.11 [0.97, 1.27]
D'Urzo 2017	194	335	164	332	21.3%	1.17 [1.02, 1.35]
Subtotal (95% CI)		**1649**		**1618**	**100.0%**	**1.22 [1.14, 1.30]**
Total events	952		765			
Heterogeneity: $Chi^2 = 3.42$, df = 2 (P = 0.18); $I^2 = 42\%$						
Test for overall effect: Z = 5.94 (P < 0.00001)						

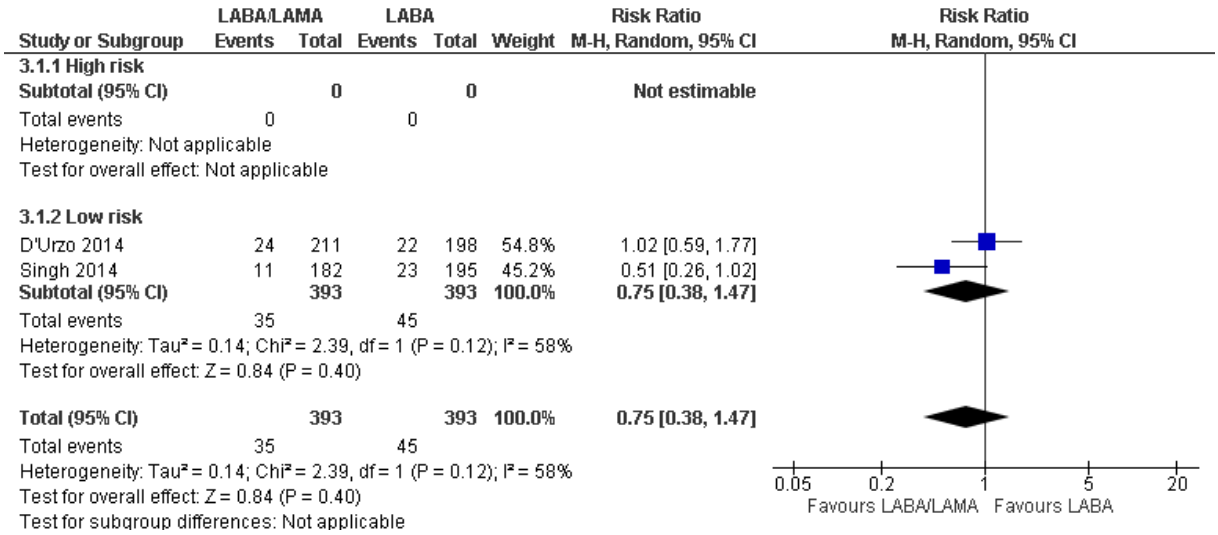


4 Test for subgroup differences: Not applicable

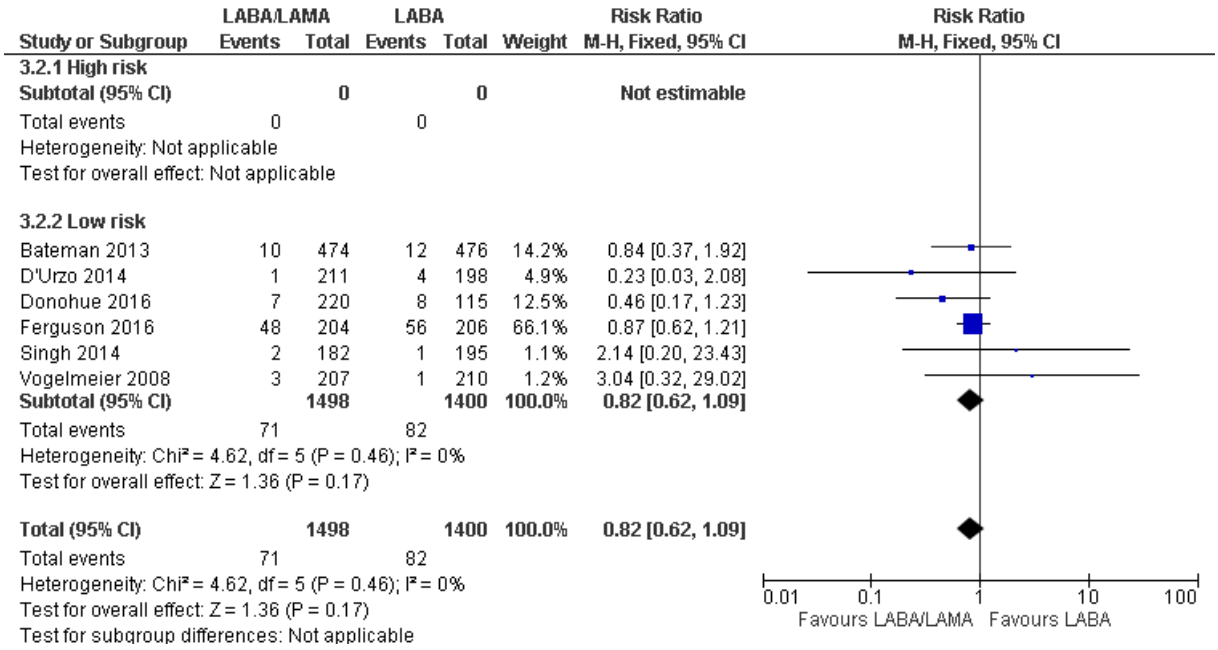
People with ≥ 1 moderate to severe exacerbation



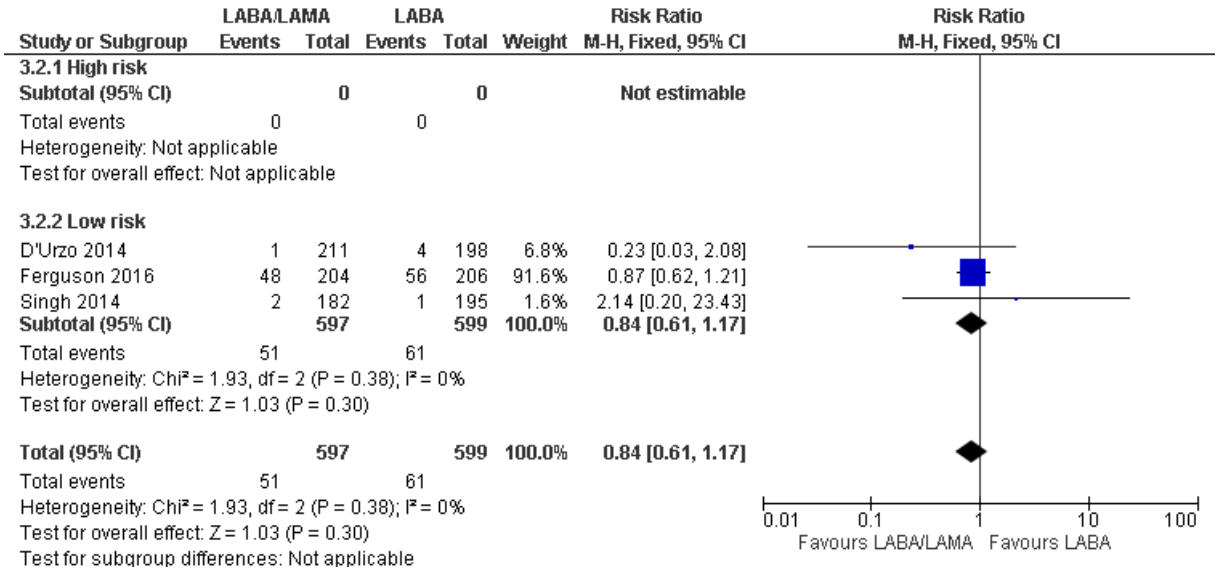
Sensitivity analysis: people ≥ 1 moderate to severe exacerbation



People with ≥ 1 severe exacerbation requiring hospitalisation

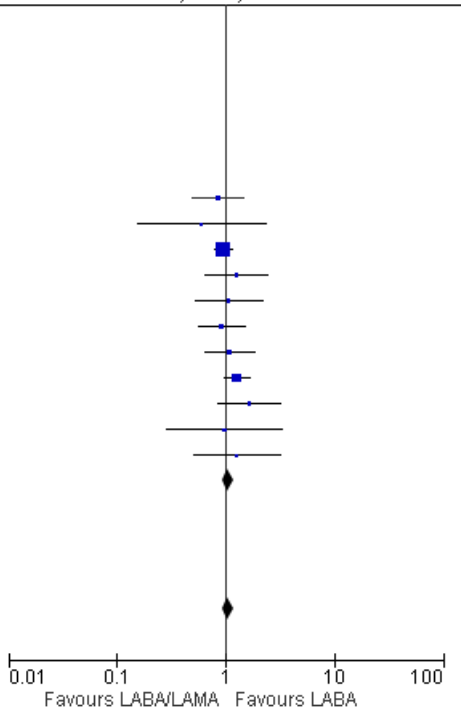


Sensitivity analysis: people ≥ 1 severe exacerbation



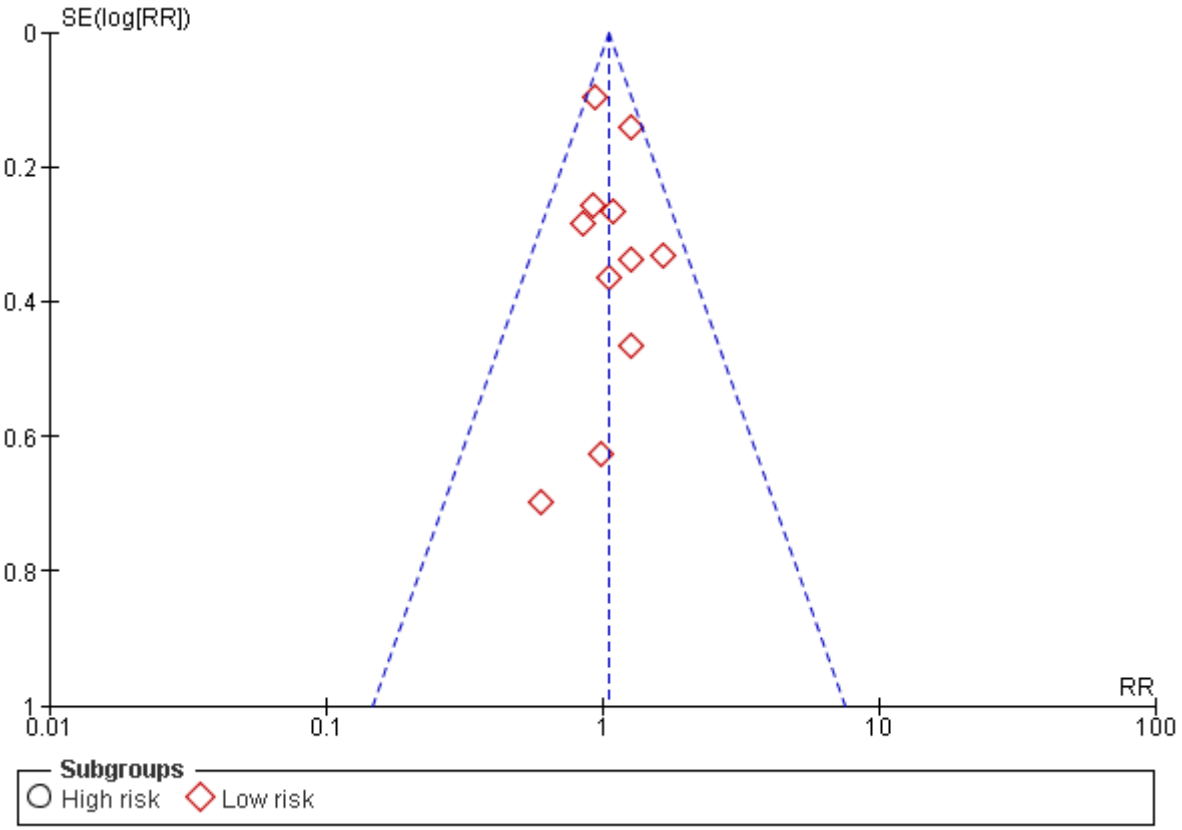
1 ***People with ≥ 1 Serious Adverse Event (SAE)***

Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.15.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.15.2 Low risk						
Bateman 2013	22	474	26	476	6.4%	0.85 [0.49, 1.48]
BI1237.22 2014	3	41	5	41	1.2%	0.60 [0.15, 2.35]
Buhl 2015	169	1029	181	1038	44.8%	0.94 [0.78, 1.14]
D'Urzo 2014	19	335	15	332	3.7%	1.26 [0.65, 2.43]
D'Urzo 2017	14	182	14	192	3.4%	1.05 [0.52, 2.15]
Donohue 2016	38	392	21	198	6.9%	0.91 [0.55, 1.51]
Ferguson 2016	26	204	24	206	5.9%	1.09 [0.65, 1.84]
PINNACLE 3 2017	114	1036	78	890	20.8%	1.26 [0.95, 1.65]
Singh 2014	23	385	14	384	3.5%	1.64 [0.86, 3.14]
Vincken 2014	5	226	5	221	1.3%	0.98 [0.29, 3.33]
Vogelmeier 2008	10	207	8	210	2.0%	1.27 [0.51, 3.15]
Subtotal (95% CI)		**4511**		**4188**	**100.0%**	**1.05 [0.92, 1.19]**
Total events	443		391			
Heterogeneity: Chi² = 6.67, df = 10 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**4511**		**4188**	**100.0%**	**1.05 [0.92, 1.19]**
Total events	443		391			
Heterogeneity: Chi² = 6.67, df = 10 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Not applicable						



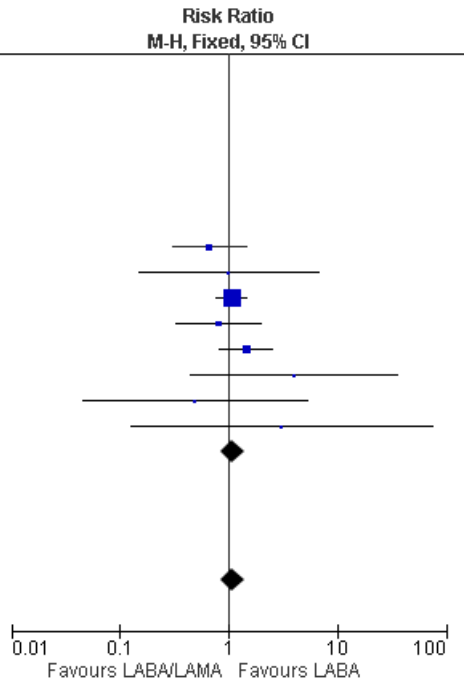
2

Publication bias assessment: funnel plot for SAEs

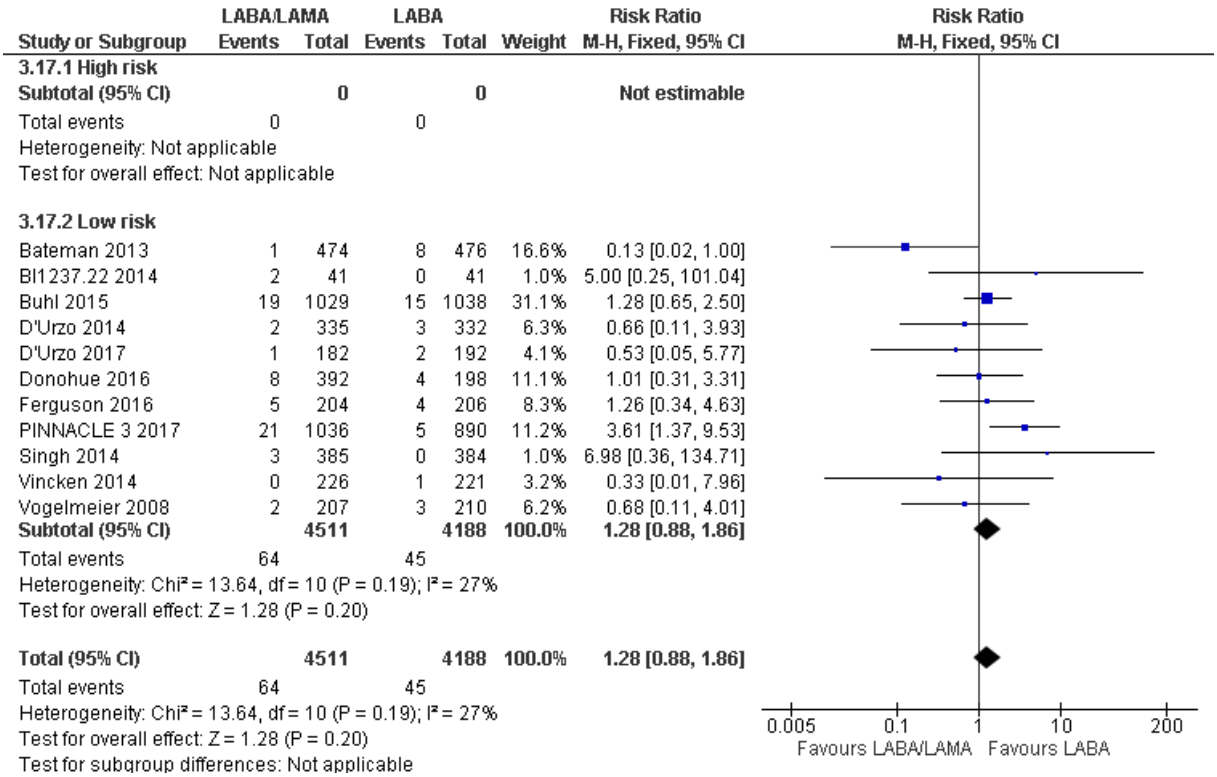


People with ≥ 1 COPD SAE

Study or Subgroup	LABA/LAMA Events	Total	LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.16.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.16.2 Low risk						
Bateman 2013	10	474	15	476	12.7%	0.67 [0.30, 1.48]
BI1237.22 2014	2	41	2	41	1.7%	1.00 [0.15, 6.76]
Buhl 2015	71	1029	67	1038	56.7%	1.07 [0.77, 1.48]
Ferguson 2016	8	204	10	206	8.5%	0.81 [0.33, 2.01]
PINNACLE 3 2017	32	1036	19	890	17.4%	1.45 [0.83, 2.53]
Singh 2014	4	385	1	384	0.9%	3.99 [0.45, 35.53]
Vincken 2014	1	226	2	221	1.7%	0.49 [0.04, 5.35]
Vogelmeier 2008	1	207	0	210	0.4%	3.04 [0.12, 74.28]
Subtotal (95% CI)		**3602**		**3466**	**100.0%**	**1.08 [0.85, 1.38]**
Total events	129		116			
Heterogeneity: Chi² = 5.05, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**3602**		**3466**	**100.0%**	**1.08 [0.85, 1.38]**
Total events	129		116			
Heterogeneity: Chi² = 5.05, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						

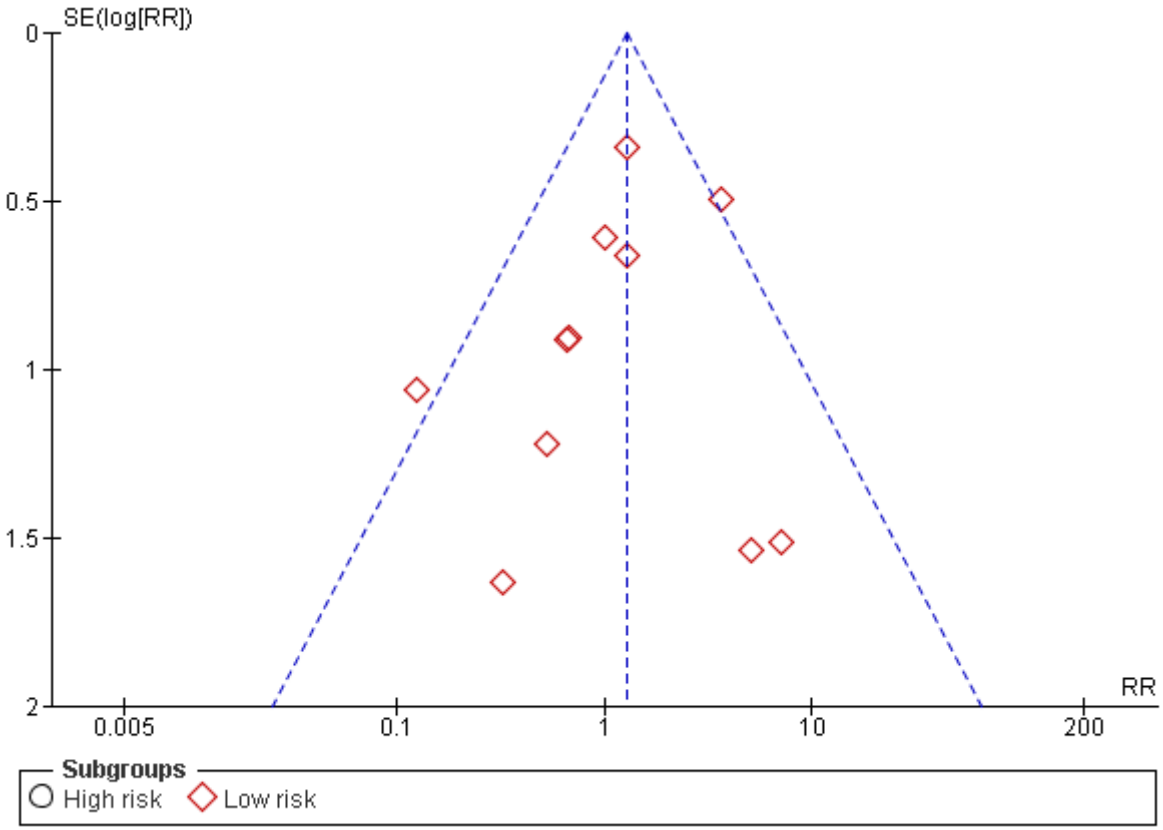


1 ***People with ≥ 1 cardiac SAE***



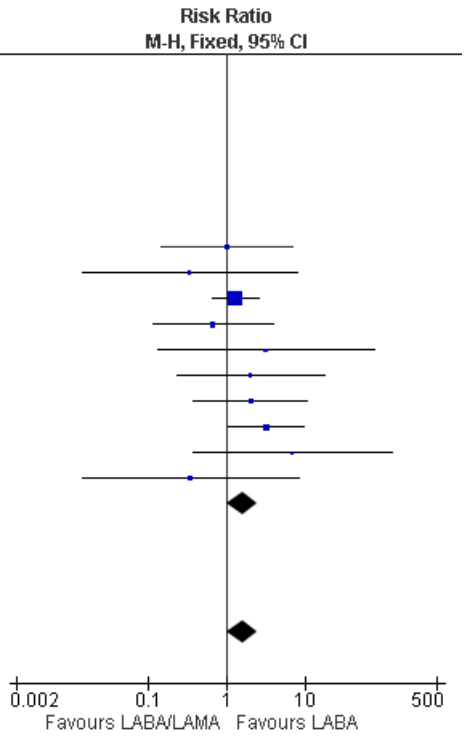
2

Publication bias assessment: funnel plot for cardiac SAEs

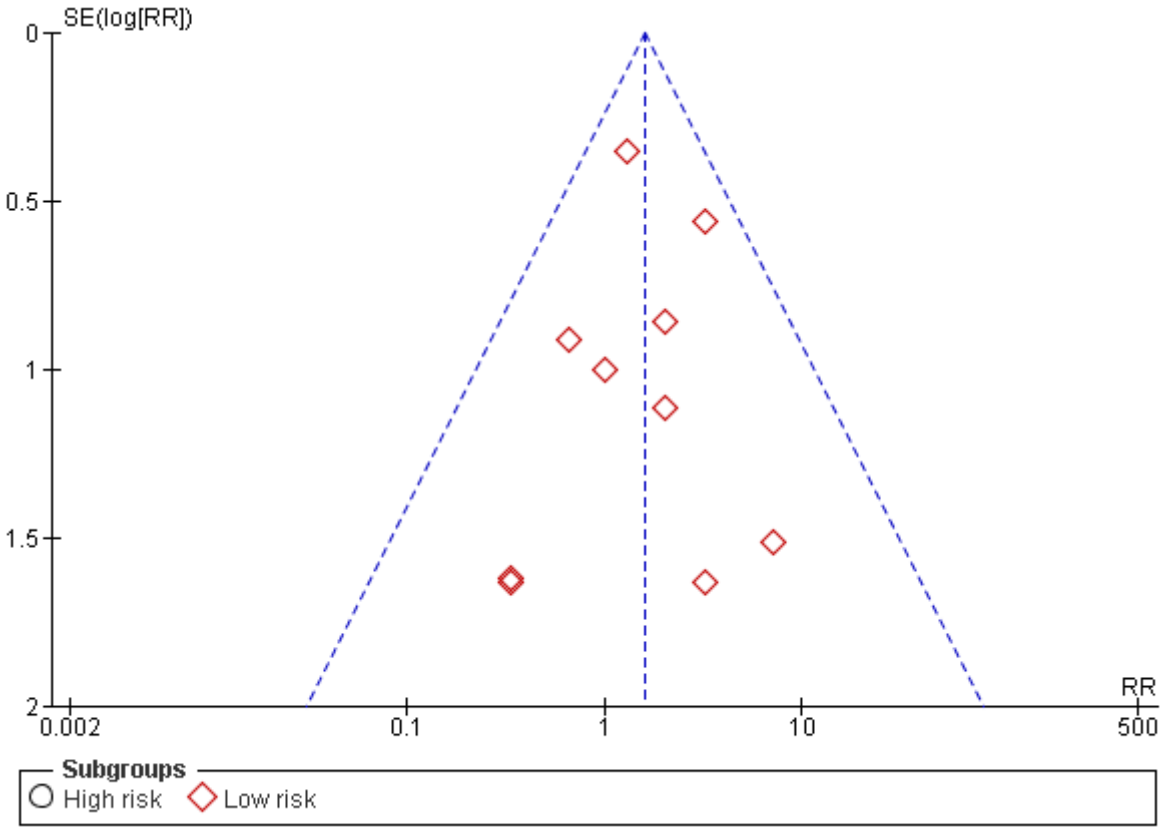


People with ≥ 1 session of pneumonia

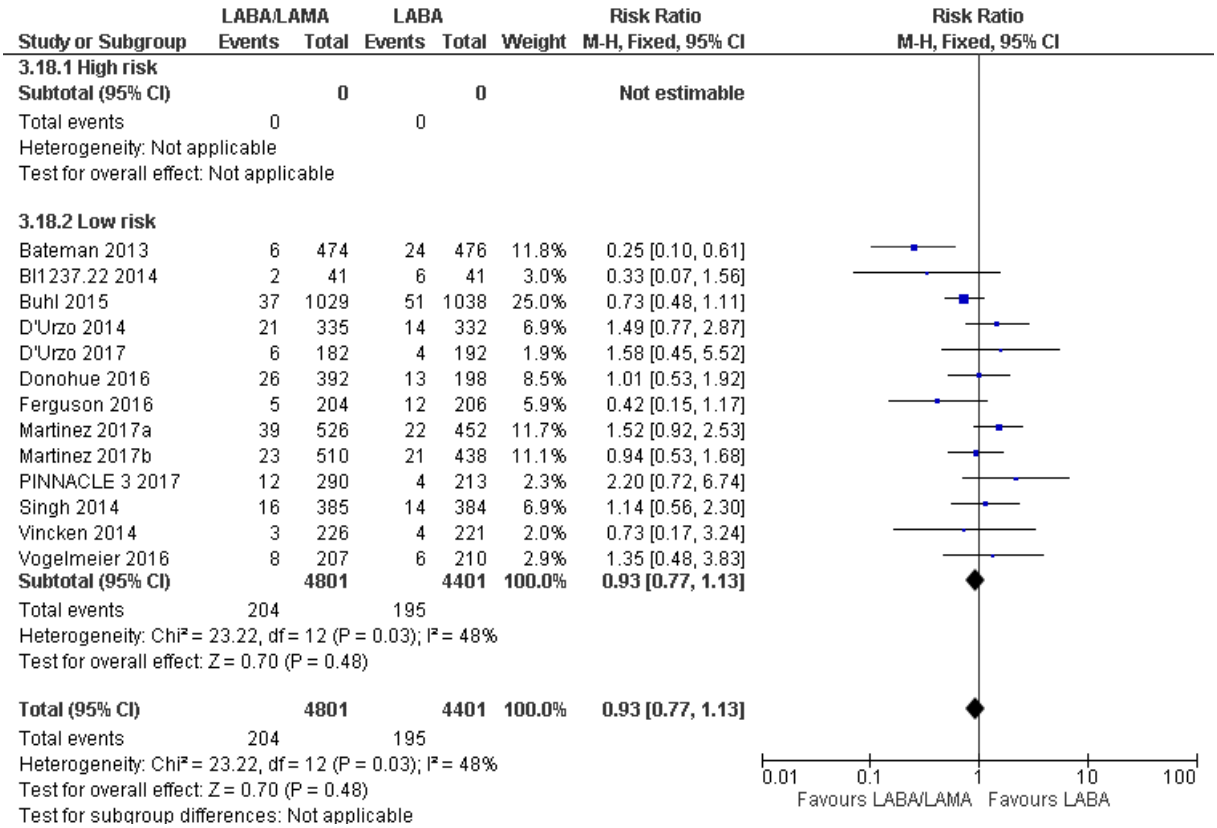
Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.19.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.19.2 Low risk						
Bateman 2013	2	474	2	476	6.5%	1.00 [0.14, 7.10]
BI1237.22 2014	0	41	1	41	4.9%	0.33 [0.01, 7.95]
Buhl 2015	18	1029	14	1038	45.6%	1.30 [0.65, 2.59]
D'Urzo 2014	2	335	3	332	9.9%	0.66 [0.11, 3.93]
D'Urzo 2017	1	182	0	192	1.6%	3.16 [0.13, 77.17]
Donohue 2016	4	392	1	198	4.4%	2.02 [0.23, 17.96]
Ferguson 2016	4	204	2	206	6.5%	2.02 [0.37, 10.90]
PINNACLE 3 2017	15	1036	4	890	14.1%	3.22 [1.07, 9.67]
Singh 2014	3	385	0	384	1.6%	6.98 [0.36, 134.71]
Vogelmeier 2008	0	207	1	210	4.9%	0.34 [0.01, 8.25]
Subtotal (95% CI)		**4285**		**3967**	**100.0%**	**1.59 [1.01, 2.51]**
Total events	49		28			
Heterogeneity: Chi² = 6.16, df = 9 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**4285**		**3967**	**100.0%**	**1.59 [1.01, 2.51]**
Total events	49		28			
Heterogeneity: Chi² = 6.16, df = 9 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Not applicable						



Publication bias assessment: funnel plot for pneumonia



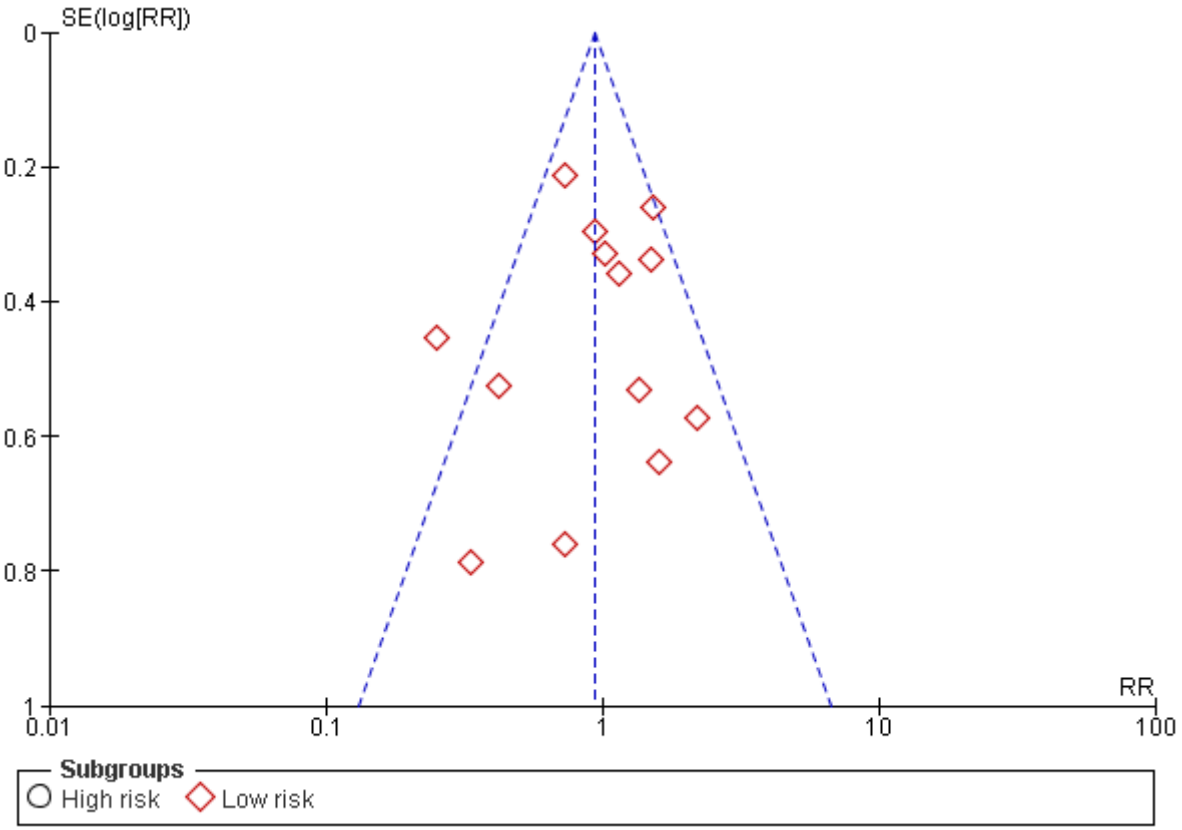
1 ***Drop-outs due to adverse events***



Study or Subgroup	LABA/LAMA Events	LABA/LAMA Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.18.1 High risk						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.18.2 Low risk						
Bateman 2013	6	474	24	476	11.8%	0.25 [0.10, 0.61]
BI1237.22 2014	2	41	6	41	3.0%	0.33 [0.07, 1.56]
Buhl 2015	37	1029	51	1038	25.0%	0.73 [0.48, 1.11]
D'Urzo 2014	21	335	14	332	6.9%	1.49 [0.77, 2.87]
D'Urzo 2017	6	182	4	192	1.9%	1.58 [0.45, 5.52]
Donohue 2016	26	392	13	198	8.5%	1.01 [0.53, 1.92]
Ferguson 2016	5	204	12	206	5.9%	0.42 [0.15, 1.17]
Martinez 2017a	39	526	22	452	11.7%	1.52 [0.92, 2.53]
Martinez 2017b	23	510	21	438	11.1%	0.94 [0.53, 1.68]
PINNACLE 3 2017	12	290	4	213	2.3%	2.20 [0.72, 6.74]
Singh 2014	16	385	14	384	6.9%	1.14 [0.56, 2.30]
Vincken 2014	3	226	4	221	2.0%	0.73 [0.17, 3.24]
Vogelmeier 2016	8	207	6	210	2.9%	1.35 [0.48, 3.83]
Subtotal (95% CI)		**4801**		**4401**	**100.0%**	**0.93 [0.77, 1.13]**
Total events	204		195			
Heterogeneity: $Chi^2 = 23.22$, df = 12 (P = 0.03); $I^2 = 48\%$						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**4801**		**4401**	**100.0%**	**0.93 [0.77, 1.13]**
Total events	204		195			
Heterogeneity: $Chi^2 = 23.22$, df = 12 (P = 0.03); $I^2 = 48\%$						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						

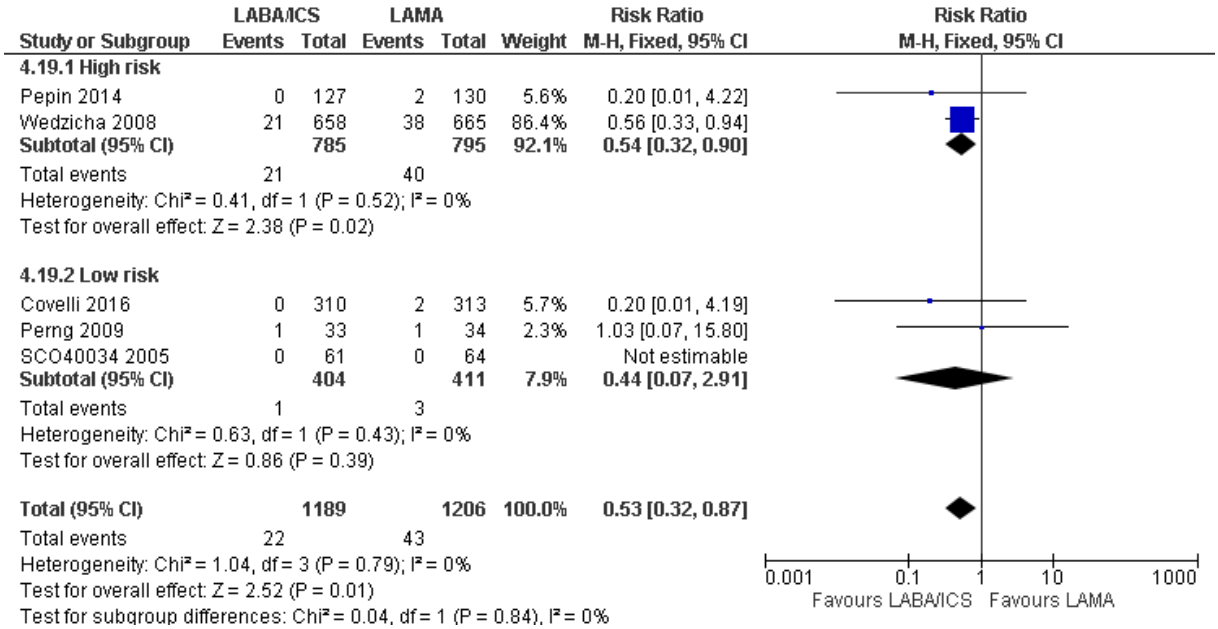
2

Publication bias assessment: funnel plot drop-outs due to adverse events

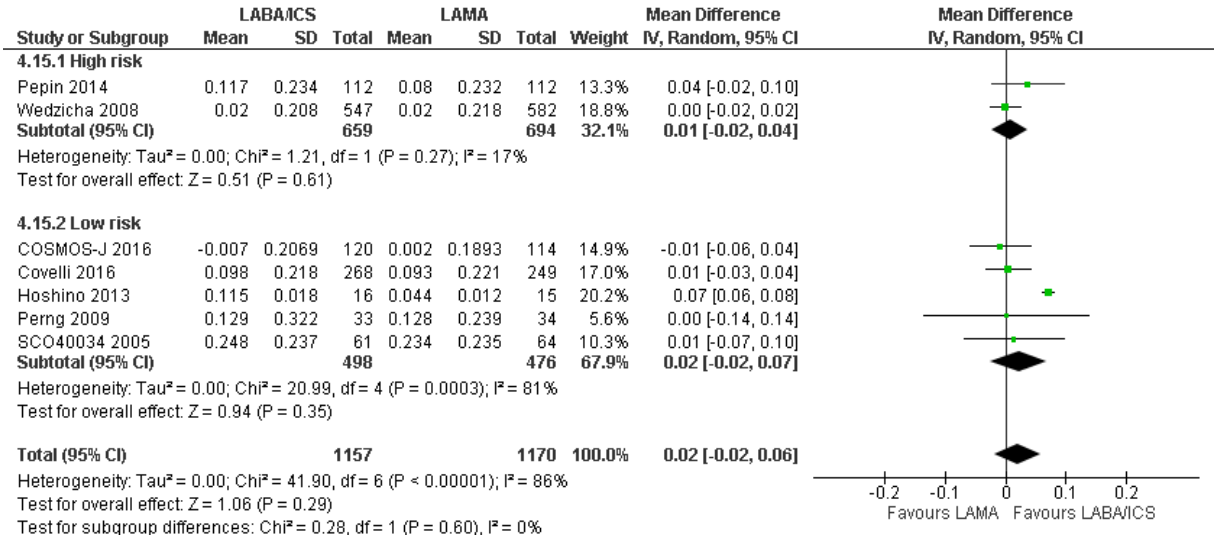


LABA/ICS versus LAMA

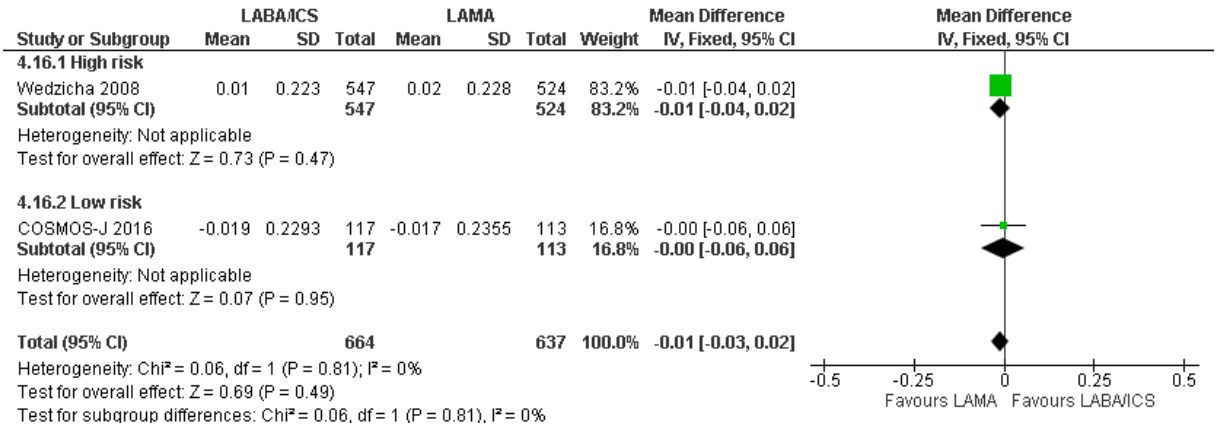
All-cause mortality



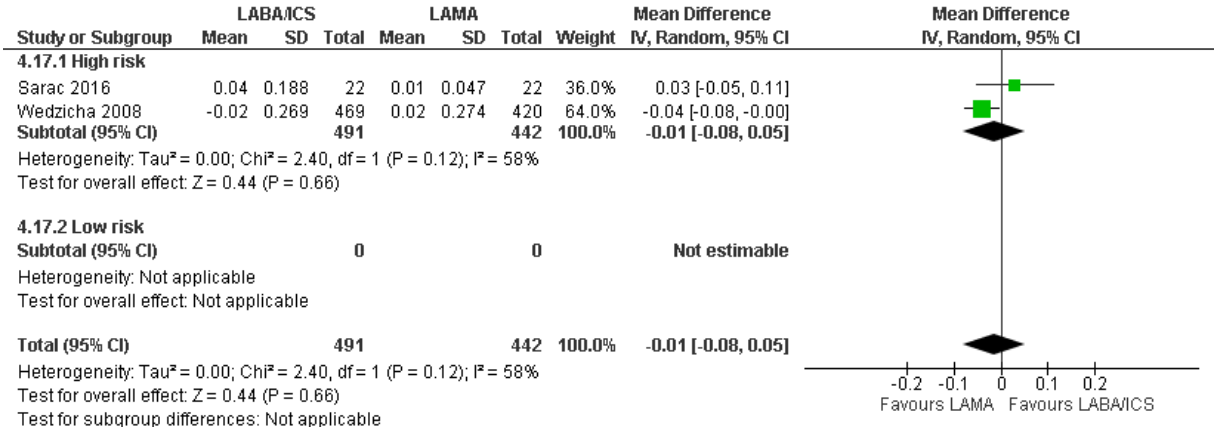
Change in Trough FEV1 (L) at 3 months



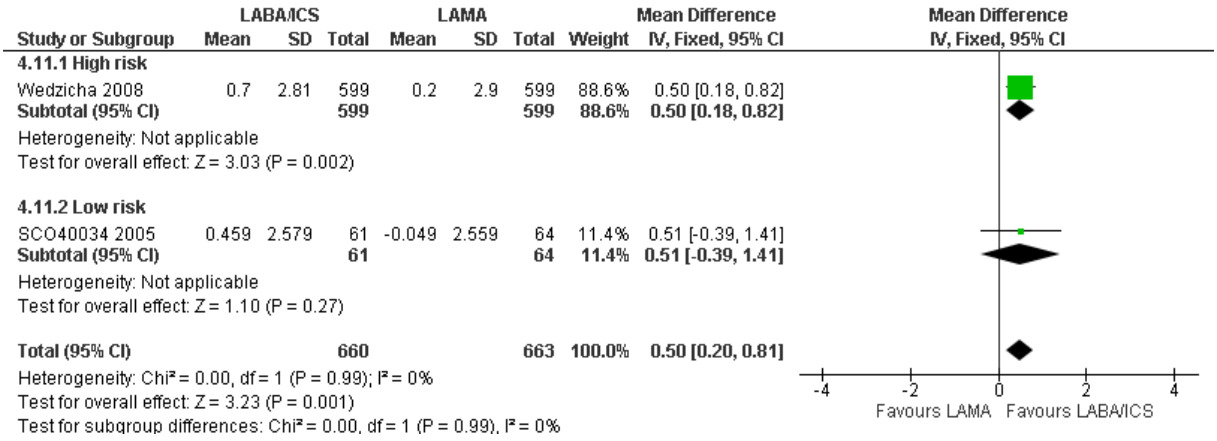
Change in Trough FEV1 (L) at 6 months



Change in Trough FEV1 (L) at 12 months

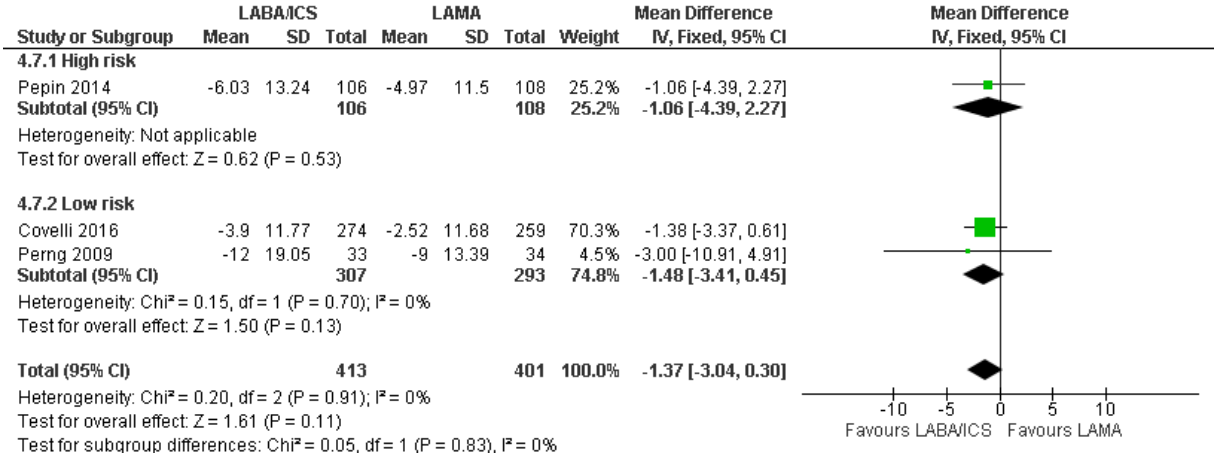


1 ***Transition Dyspnoea Index (TDI) focal score at 3 months***



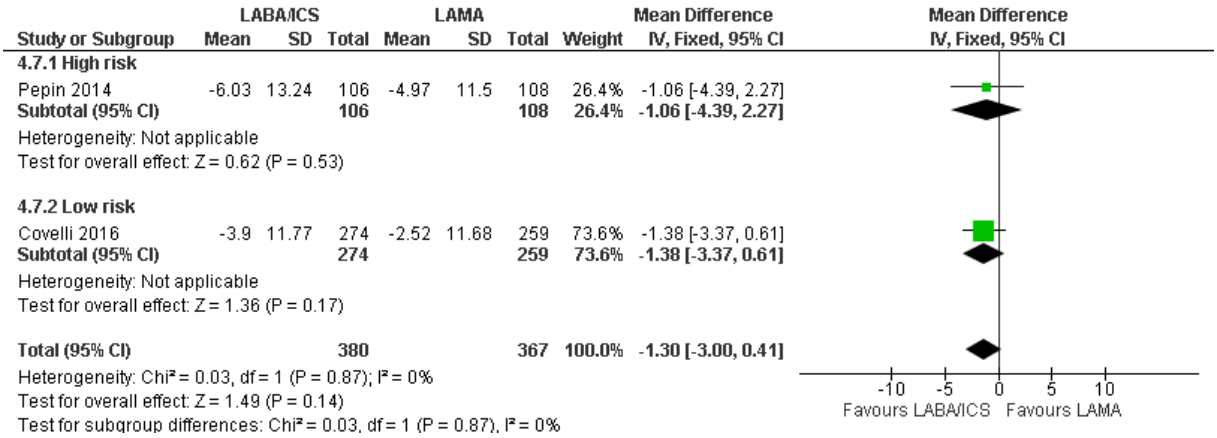
2

3 ***St. George's Respiratory Questionnaire (SGRQ), total score at 3 months***



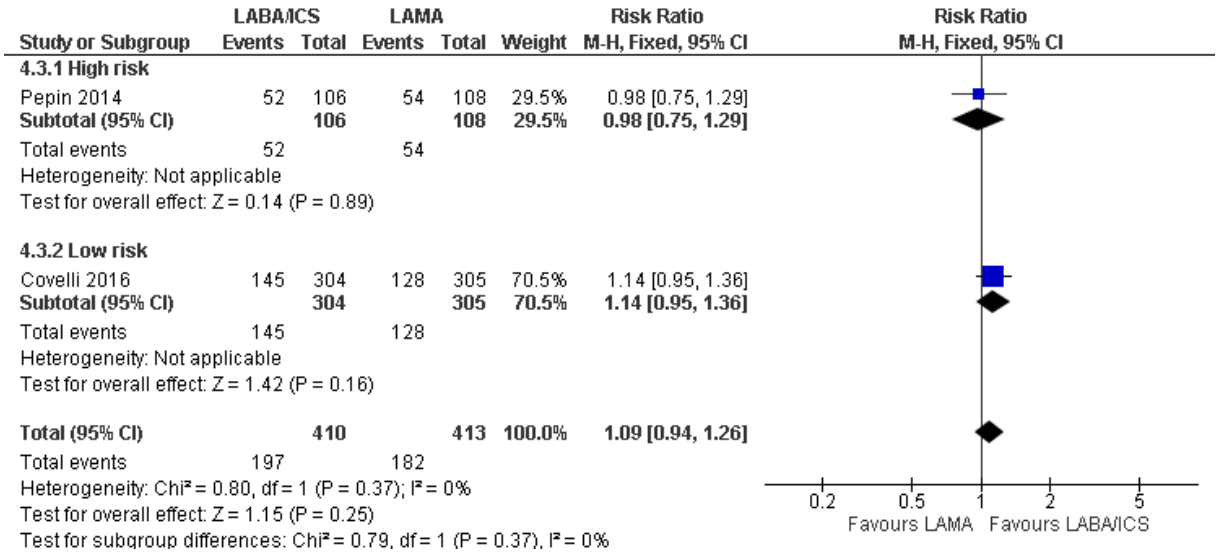
4

5 *Sensitivity analysis: SGRQ at 3 months*

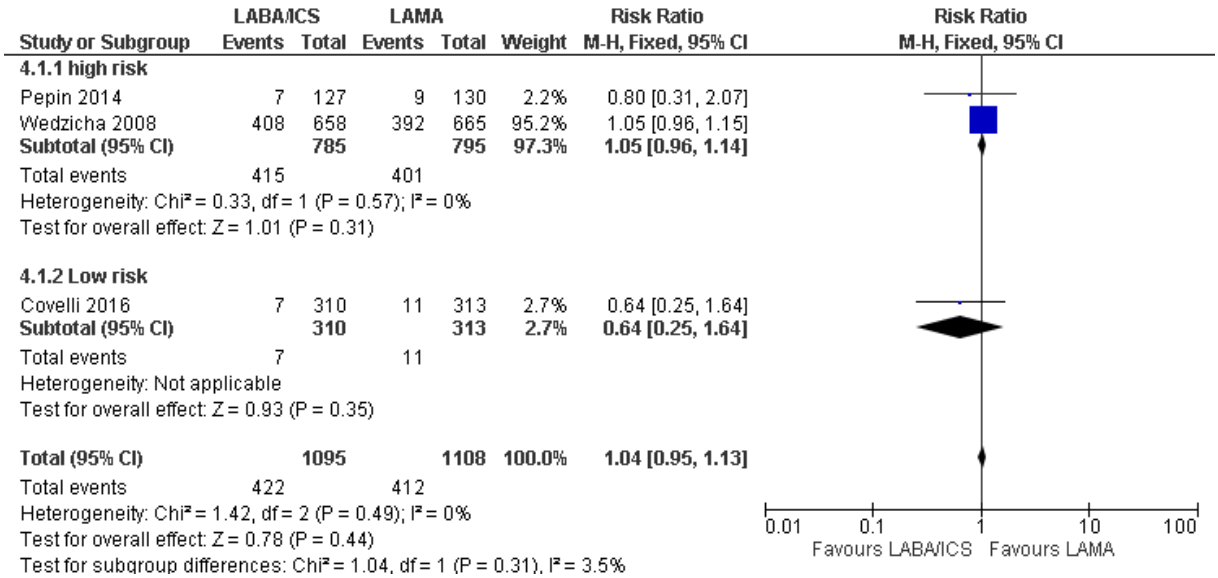


6

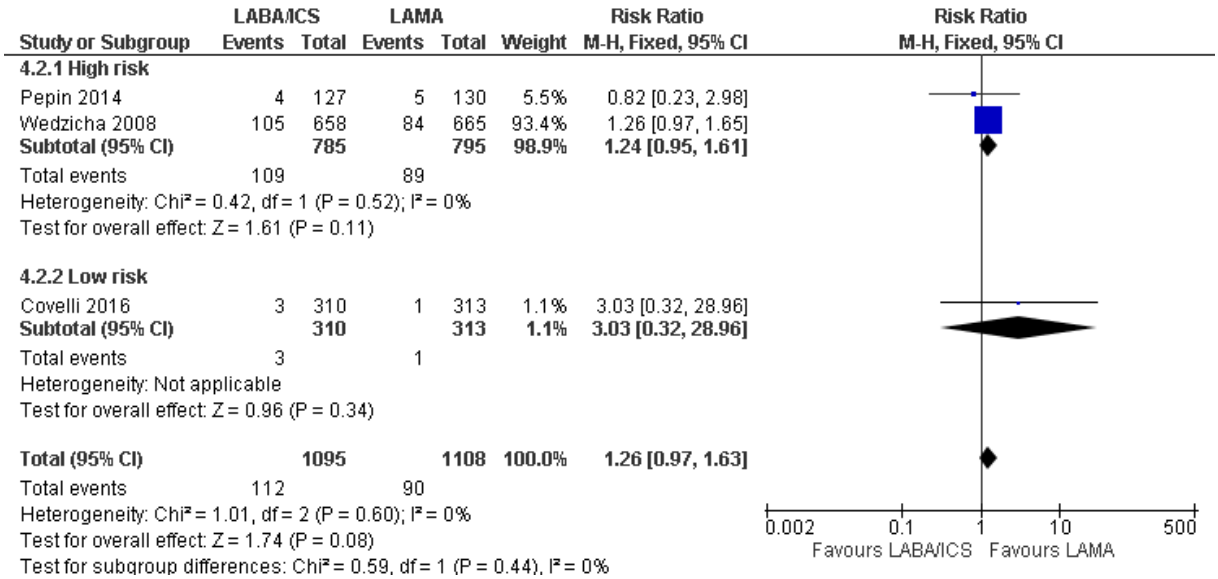
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months



People with ≥ 1 moderate to severe exacerbation

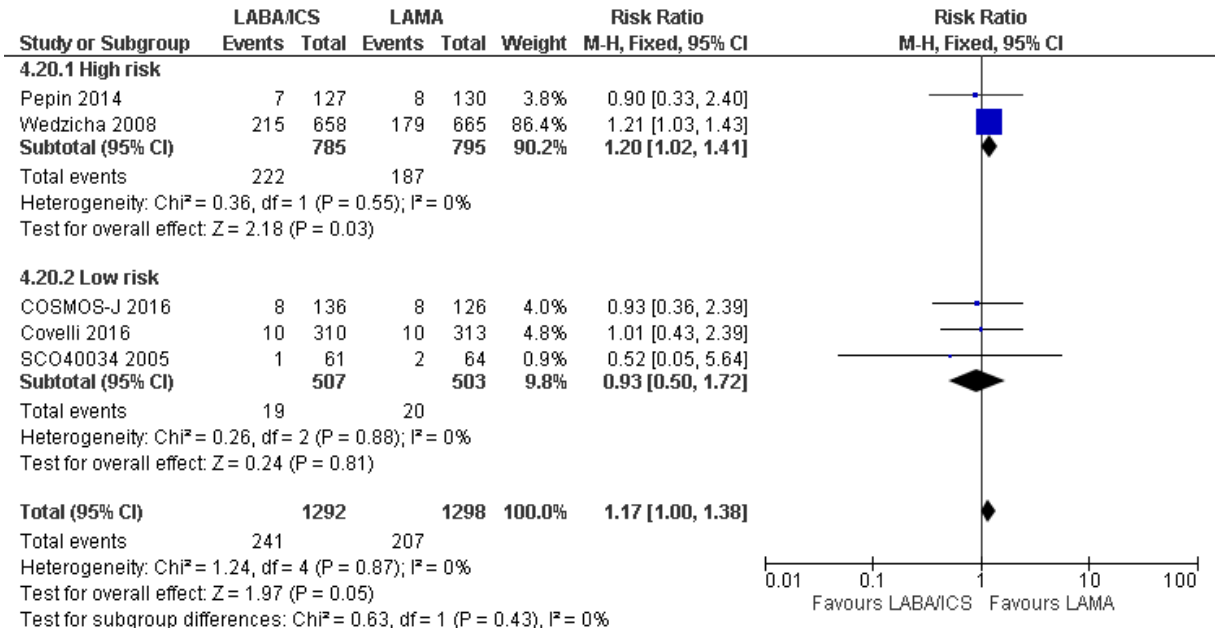


1 ***People with ≥ 1 severe exacerbation (requiring hospitalisation)***



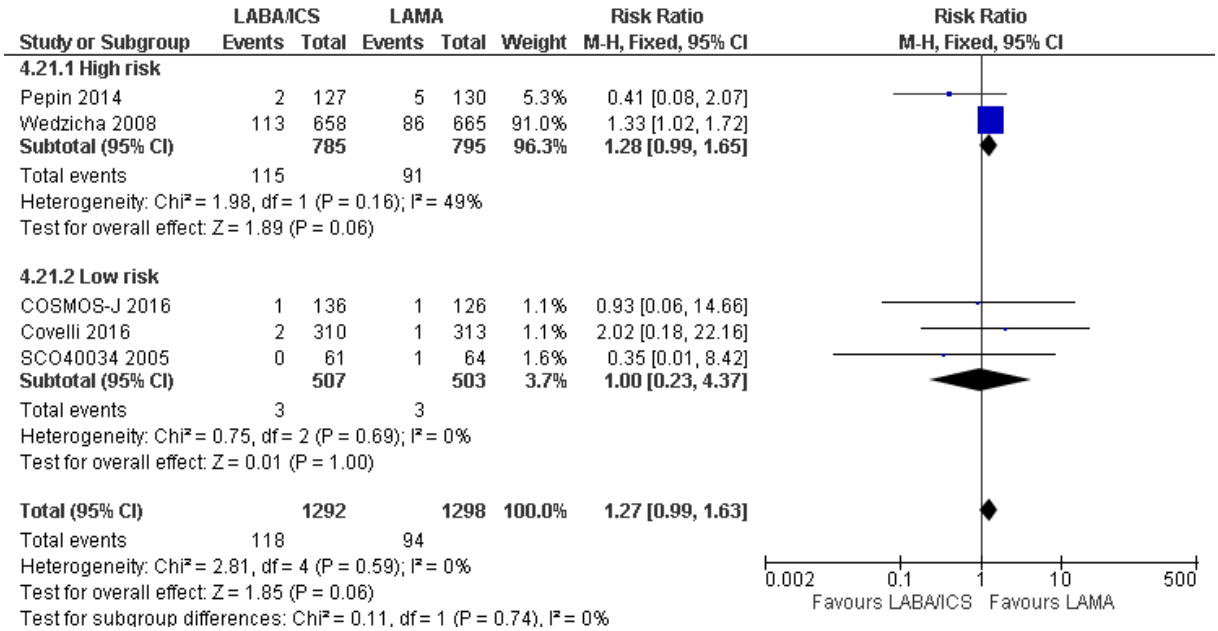
2

3 ***People with ≥ 1 Serious Adverse Event (SAE)***



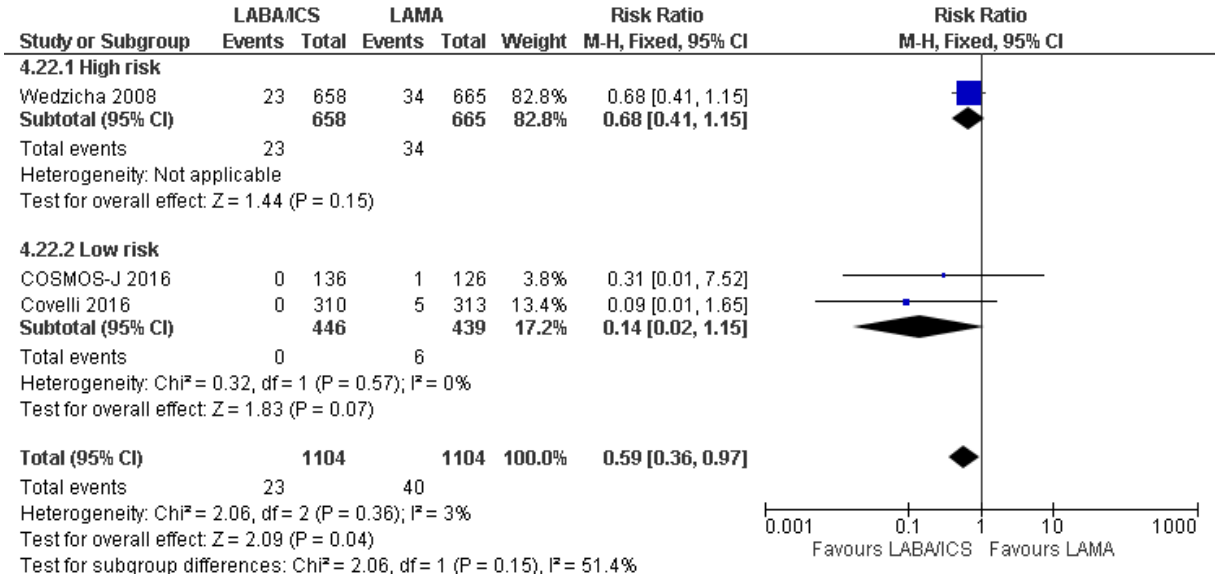
4

1 ***People with ≥ 1 COPD SAE***



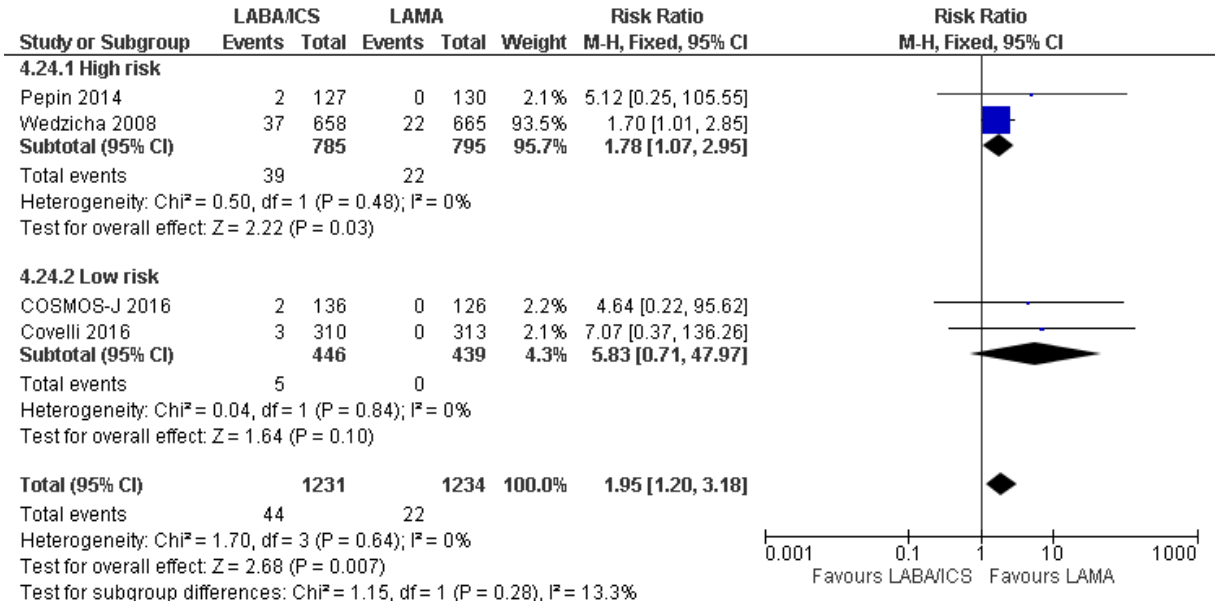
2 Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%

3 ***People with ≥ 1 cardiac SAE***

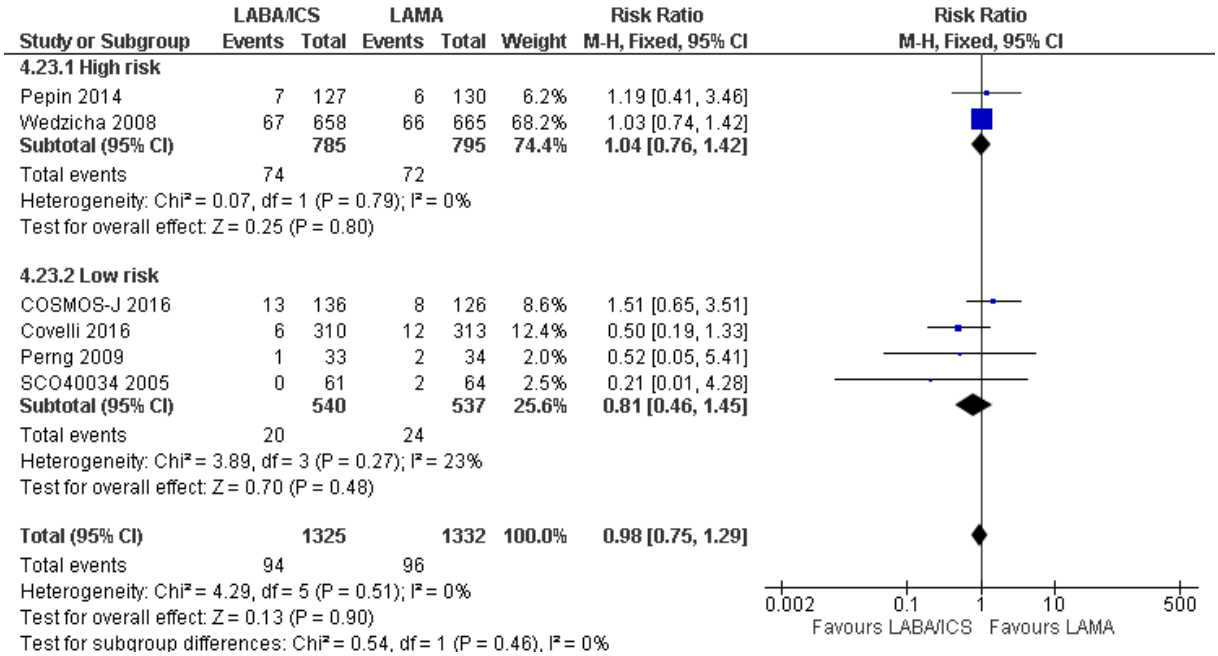


4 Test for subgroup differences: Chi² = 2.06, df = 1 (P = 0.15), I² = 51.4%

People with ≥ 1 session of pneumonia

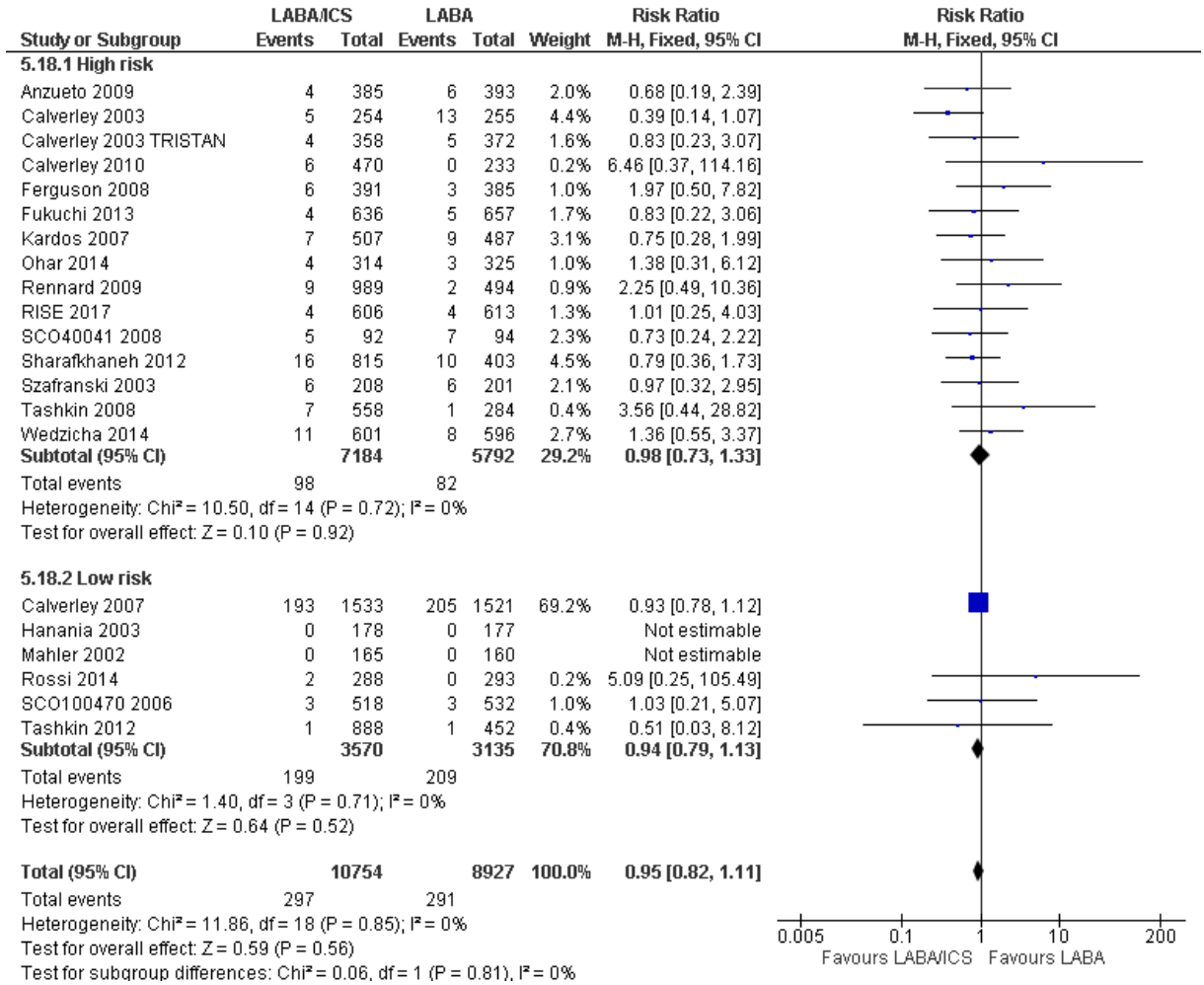


Drop-outs due to adverse events



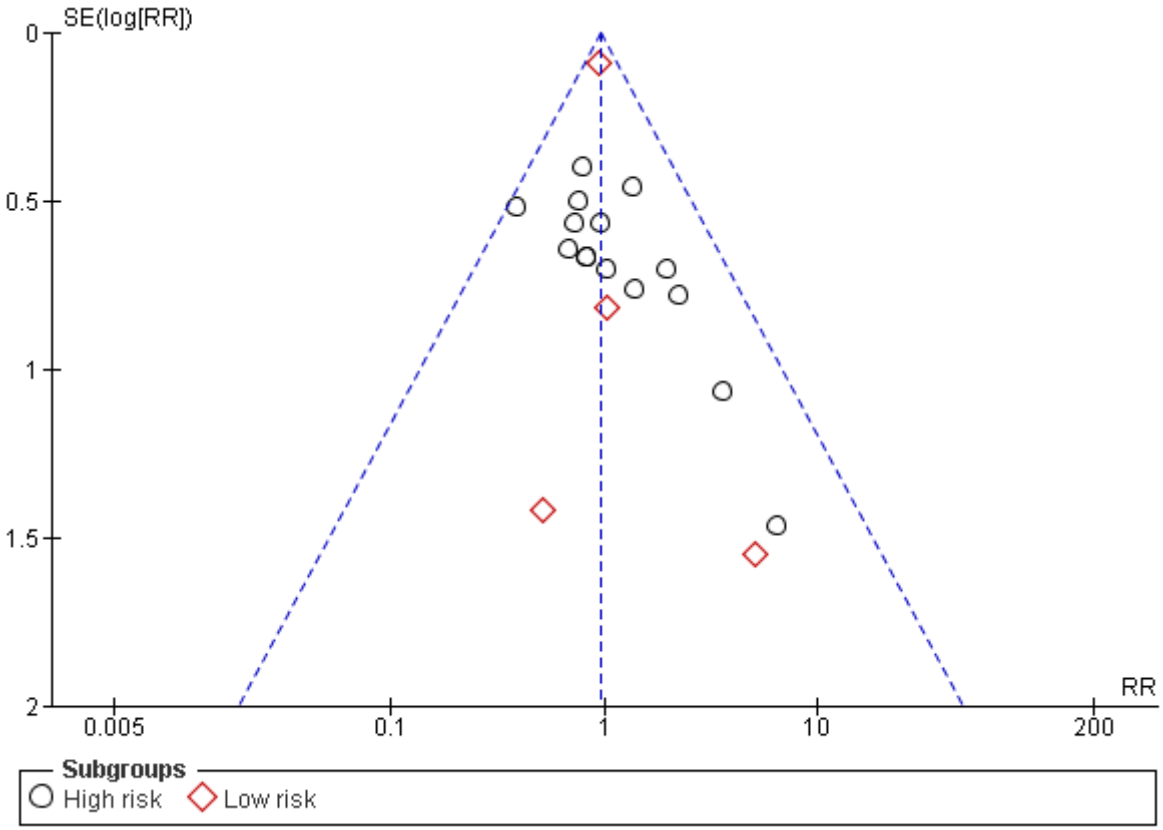
1 **LABA/ICS versus LABA**

2 ***All-cause mortality***



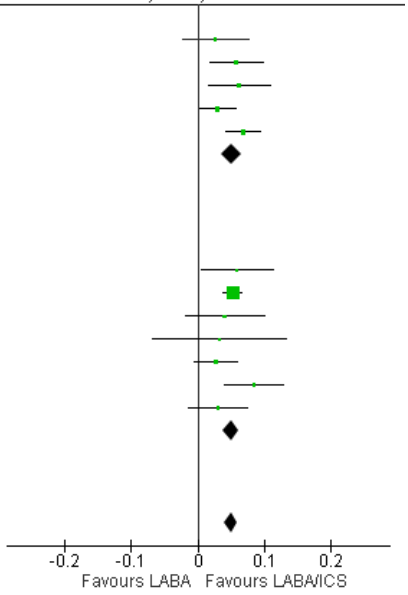
3

Publication bias assessment: funnel plot for all-cause mortality

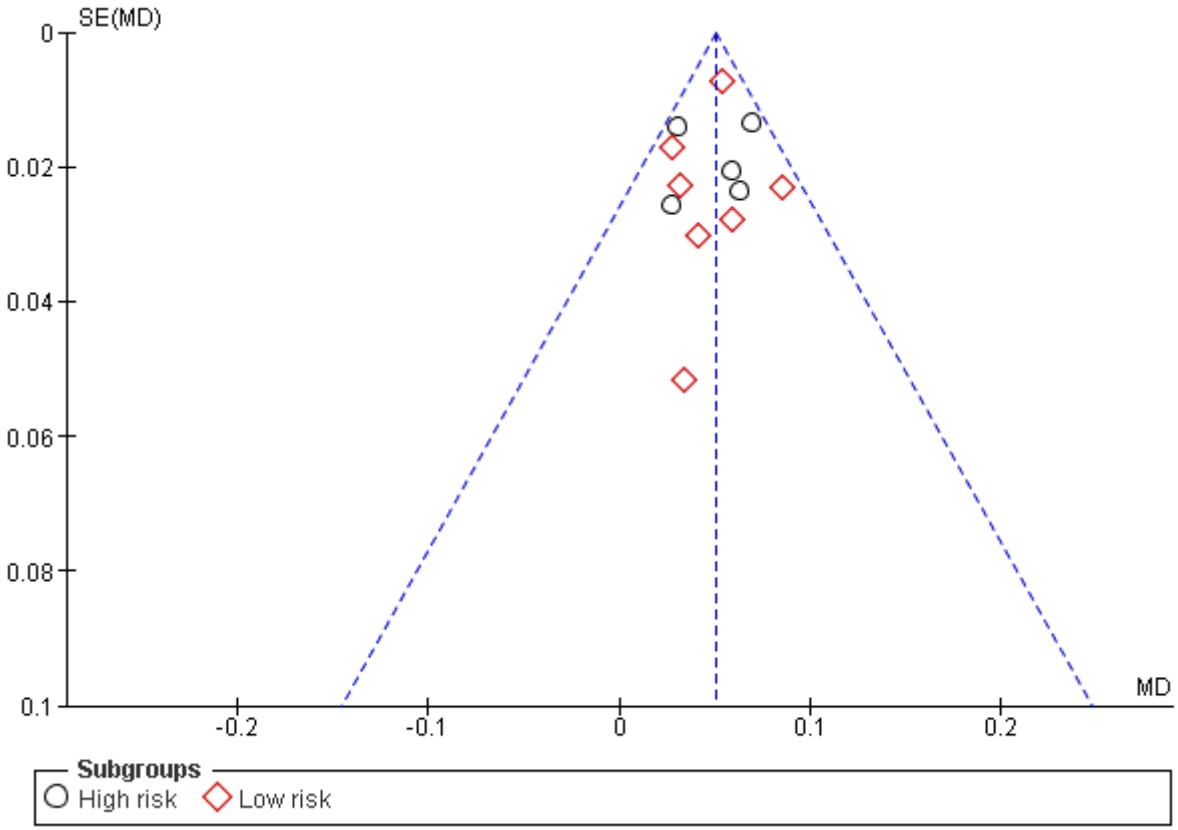


Change in Trough FEV1 (L) at 3 months

Study or Subgroup	LABA/ICS Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.14.1 High risk								
Anzueto 2009	-0.021	0.313	340	-0.048	0.338	314	3.4%	0.03 [-0.02, 0.08]
Calverley 2003 TRISTAN	0.134	0.264	309	0.075	0.258	326	5.1%	0.06 [0.02, 0.10]
Ferguson 2008	0.022	0.326	352	-0.041	0.286	315	3.9%	0.06 [0.02, 0.11]
Fukuchi 2013	0.044	0.252	636	0.014	0.256	657	11.0%	0.03 [0.00, 0.06]
Wedzicha 2014	0.081	0.244	595	0.012	0.219	591	12.1%	0.07 [0.04, 0.10]
Subtotal (95% CI)			**2232**			**2203**	**35.5%**	**0.05 [0.04, 0.07]**
Heterogeneity: Chi² = 5.29, df = 4 (P = 0.26); I² = 24%								
Test for overall effect: Z = 6.46 (P < 0.00001)								
5.14.2 Low risk								
Hanania 2003	0.166	0.246	144	0.107	0.216	135	2.9%	0.06 [0.00, 0.11]
Hoshino 2013	0.115	0.018	16	0.062	0.021	14	42.4%	0.05 [0.04, 0.07]
Mahler 2002	0.137	0.179	86	0.096	0.222	91	2.4%	0.04 [-0.02, 0.10]
Rossi 2014	0.074	0.628	288	0.041	0.616	293	0.8%	0.03 [-0.07, 0.13]
SCO100470 2006	0.074	0.27	508	0.047	0.273	517	7.6%	0.03 [-0.01, 0.06]
Tashkin 2012a	0.085	0.271	416	0	0.27	208	4.2%	0.09 [0.04, 0.13]
Tashkin 2012b	0.08	0.281	443	0.049	0.28	235	4.3%	0.03 [-0.01, 0.08]
Subtotal (95% CI)			**1901**			**1493**	**64.5%**	**0.05 [0.04, 0.06]**
Heterogeneity: Chi² = 5.35, df = 6 (P = 0.50); I² = 0%								
Test for overall effect: Z = 8.59 (P < 0.00001)								
Total (95% CI)			**4133**			**3696**	**100.0%**	**0.05 [0.04, 0.06]**
Heterogeneity: Chi² = 10.64, df = 11 (P = 0.47); I² = 0%								
Test for overall effect: Z = 10.75 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%								

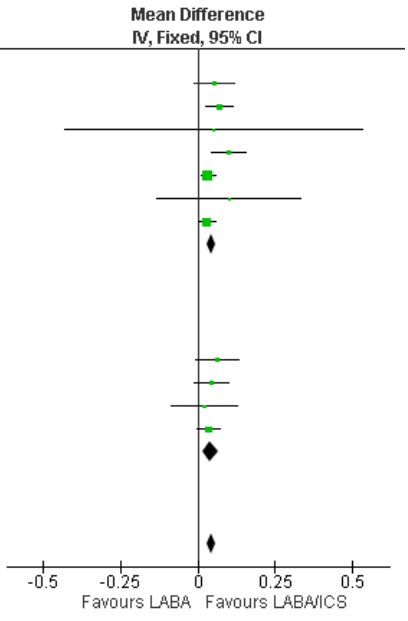


Publication bias assessment: funnel plot for trough FEV1 at 3 months

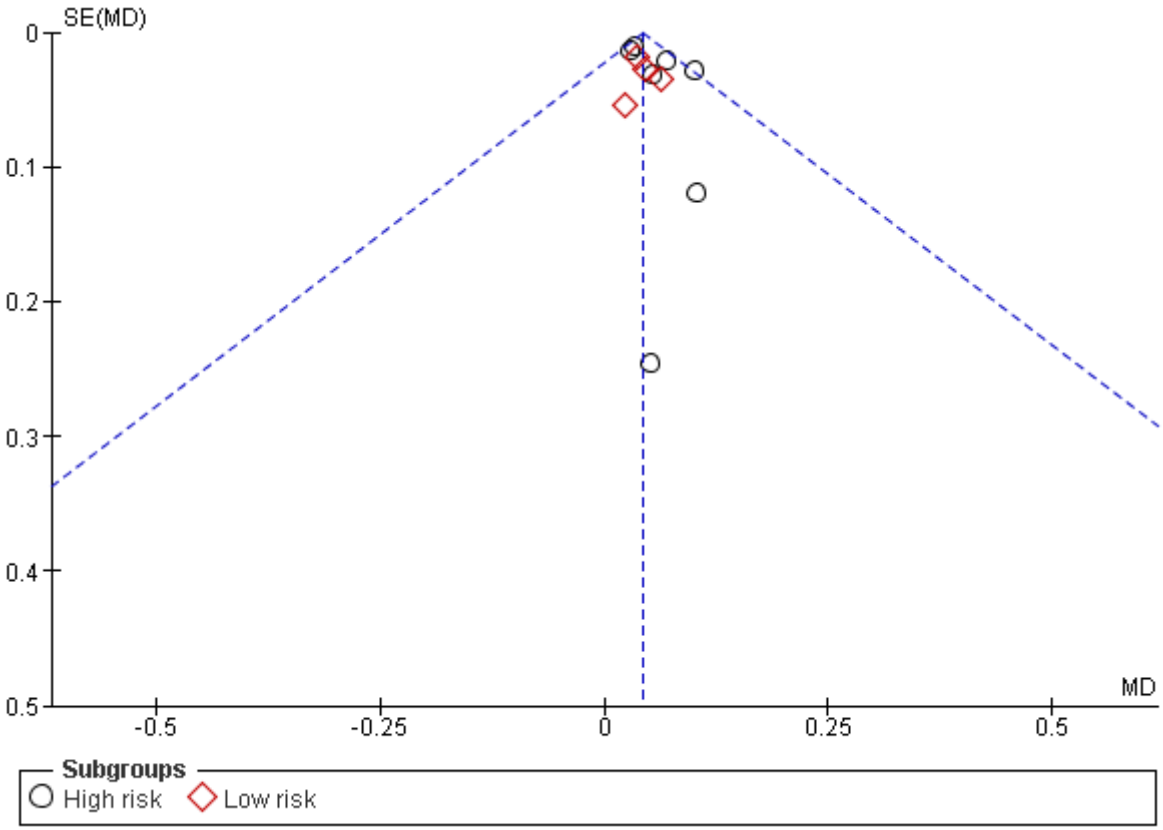


Change in Trough FEV1 (L) at 6 months

Study or Subgroup	LABA/ICS Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.15.1 High risk								
Anzueto 2009	0.001	0.427	306	-0.053	0.353	275	4.3%	0.05 [-0.01, 0.12]
Calverley 2003 TRISTAN	0.122	0.287	298	0.052	0.24	310	9.8%	0.07 [0.03, 0.11]
Ferguson 2008	-0.012	3.297	321	-0.064	2.713	277	0.1%	0.05 [-0.43, 0.53]
Ohar 2014	0.14	0.351	280	0.04	0.313	271	5.6%	0.10 [0.04, 0.16]
RISE 2017	0.008	0.21	606	-0.025	0.198	613	33.1%	0.03 [0.01, 0.06]
SCO40041 2008	0.148	0.769	80	0.046	0.738	81	0.3%	0.10 [-0.13, 0.33]
Tashkin 2008	0.08	0.206	558	0.05	0.19	284	22.3%	0.03 [0.00, 0.06]
Subtotal (95% CI)			**2449**			**2111**	**75.5%**	**0.04 [0.03, 0.06]**
Heterogeneity: Chi² = 7.55, df = 6 (P = 0.27); I² = 21%								
Test for overall effect: Z = 5.61 (P < 0.00001)								
5.15.2 Low risk								
Hanania 2003	0.165	0.289	124	0.102	0.259	119	3.7%	0.06 [-0.01, 0.13]
Mahler 2002	0.133	0.133	70	0.089	0.197	76	5.9%	0.04 [-0.01, 0.10]
Rossi 2014	0.039	0.662	288	0.017	0.65	293	1.5%	0.02 [-0.08, 0.13]
SCO100470 2006	0.06	0.293	508	0.024	0.296	517	13.4%	0.04 [-0.00, 0.07]
Subtotal (95% CI)			**990**			**1005**	**24.5%**	**0.04 [0.01, 0.07]**
Heterogeneity: Chi² = 0.60, df = 3 (P = 0.90); I² = 0%								
Test for overall effect: Z = 3.02 (P = 0.003)								
Total (95% CI)			**3439**			**3116**	**100.0%**	**0.04 [0.03, 0.06]**
Heterogeneity: Chi² = 8.18, df = 10 (P = 0.61); I² = 0%								
Test for overall effect: Z = 6.37 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								

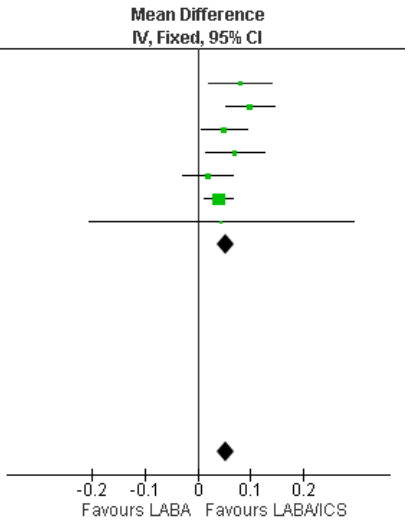


Publication bias assessment: funnel plot for trough FEV1 at 3 months

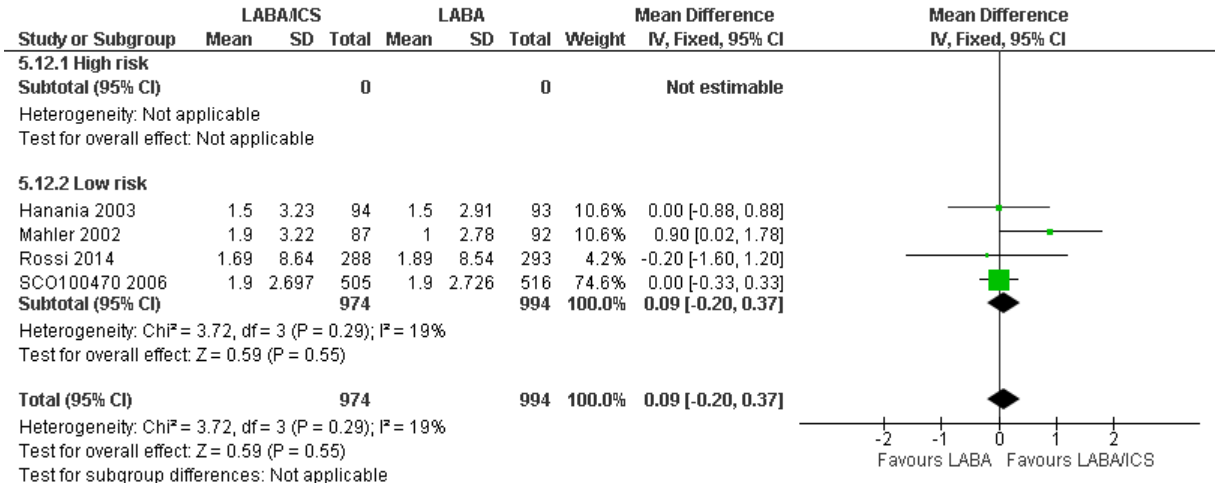


Change in Trough FEV1 (L) at 12 months

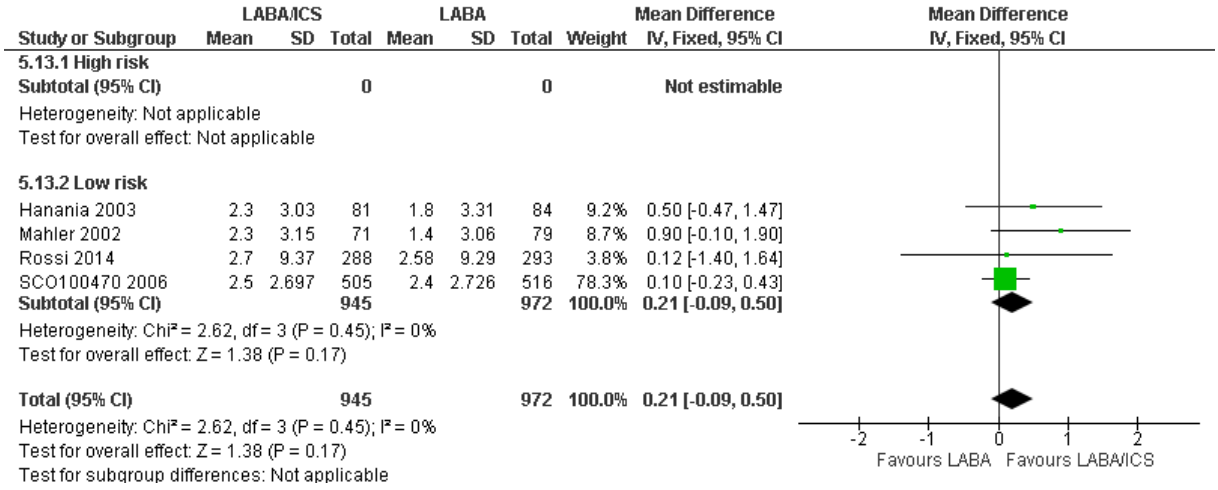
Study or Subgroup	LABA/ICS Mean	SD	Total	LABA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.16.1 High risk								
Anzueto 2009	-0.017	0.349	269	-0.097	0.334	246	8.5%	0.08 [0.02, 0.14]
Calverley 2003 TRISTAN	0.113	0.286	269	0.015	0.255	255	13.8%	0.10 [0.05, 0.14]
Calverley 2010	0.08	0.28	470	0.03	0.28	233	15.3%	0.05 [0.01, 0.09]
Ferguson 2008	-0.012	0.375	276	-0.082	0.261	235	9.6%	0.07 [0.01, 0.13]
Rennard 2009	0.07	0.343	408	0.05	0.333	384	13.3%	0.02 [-0.03, 0.07]
SCO40041 2008	0.1	0.11	121	0.06	0.11	124	39.0%	0.04 [0.01, 0.07]
Sharafkhaneh 2012	0.095	0.769	73	0.05	0.734	68	0.5%	0.04 [-0.20, 0.29]
Subtotal (95% CI)			**1886**			**1545**	**100.0%**	**0.05 [0.04, 0.07]**
Heterogeneity: Chi² = 7.55, df = 6 (P = 0.27); I² = 21%								
Test for overall effect: Z = 6.06 (P < 0.00001)								
5.16.2 Low risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**1886**			**1545**	**100.0%**	**0.05 [0.04, 0.07]**
Heterogeneity: Chi² = 7.55, df = 6 (P = 0.27); I² = 21%								
Test for overall effect: Z = 6.06 (P < 0.00001)								
Test for subgroup differences: Not applicable								



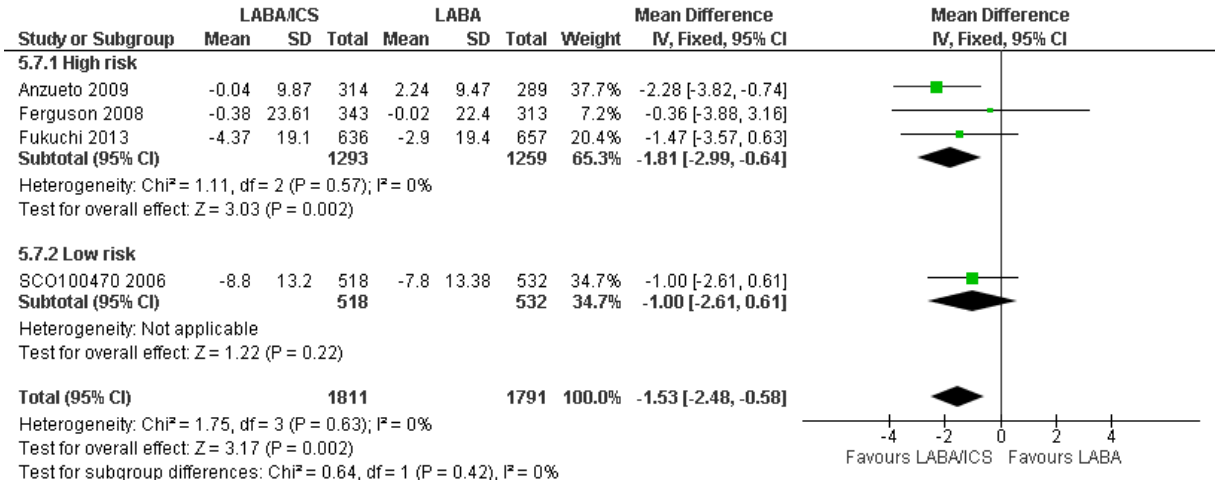
Transition Dyspnoea Index (TDI) focal score at 3 months



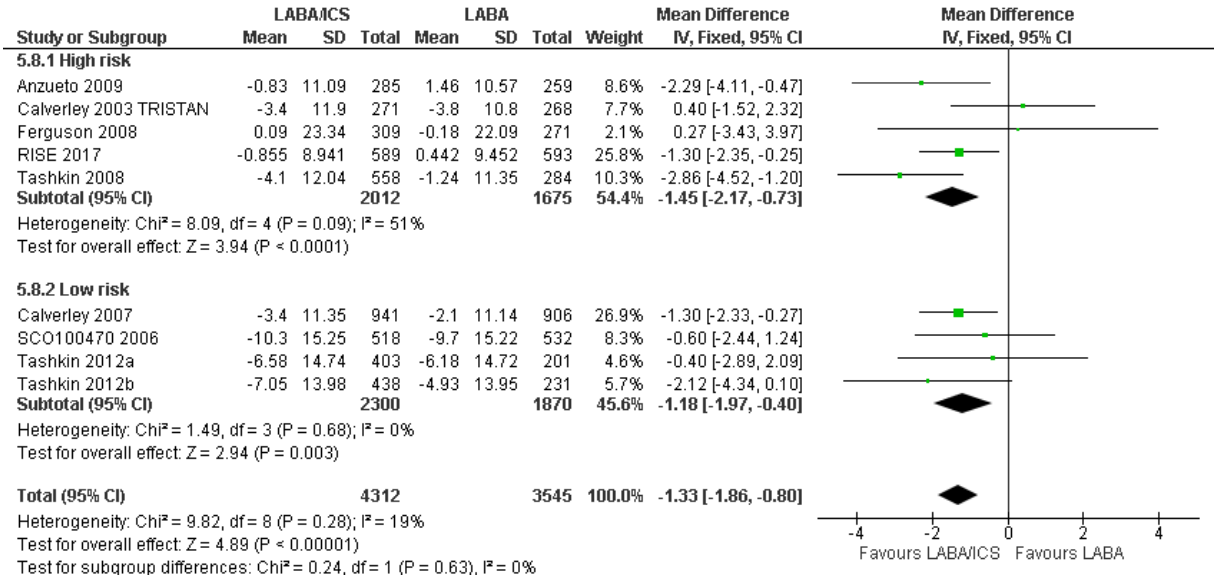
Transition Dyspnoea Index (TDI) focal score at 6 months



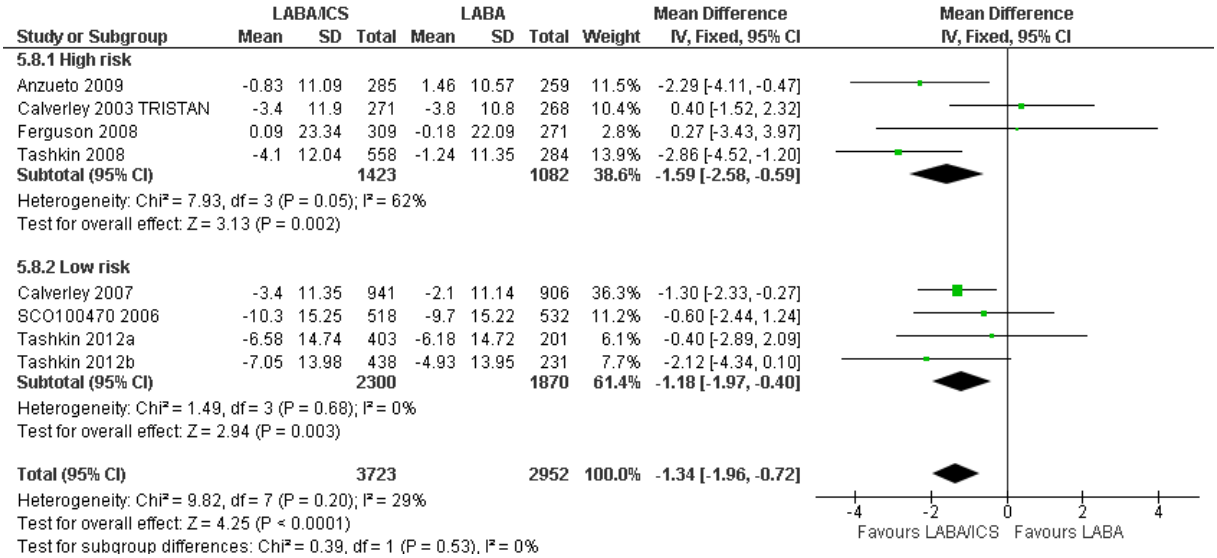
St. George's Respiratory Questionnaire (SGRQ), total score at 3 months



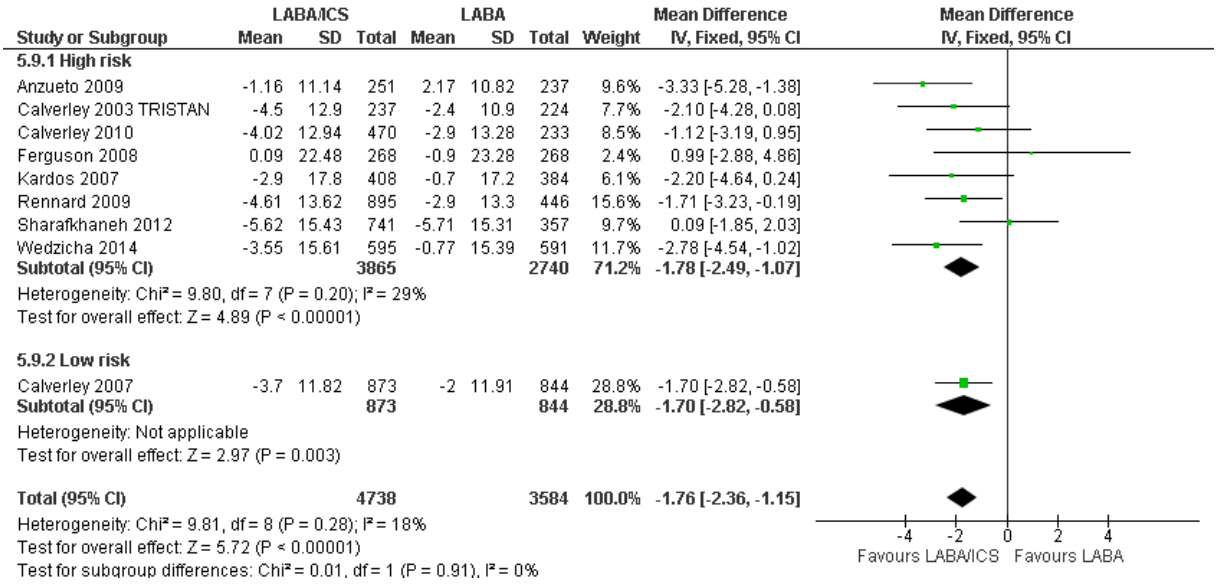
St. George's Respiratory Questionnaire (SGRQ), total score at 6 months



Sensitivity analysis: SGRQ at 6 months

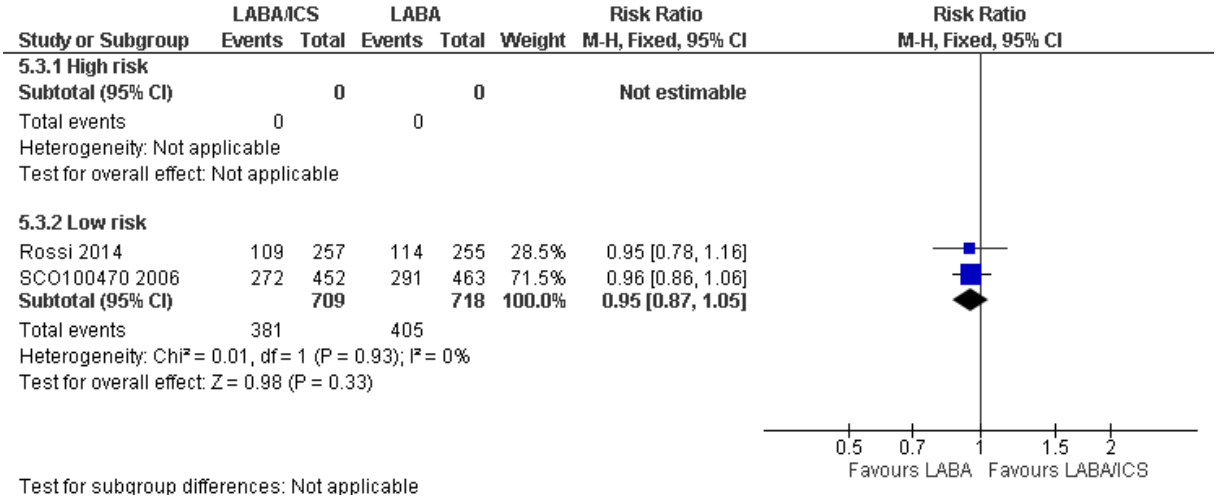


1 ***St. George's Respiratory Questionnaire (SGRQ), total score at 12 months***



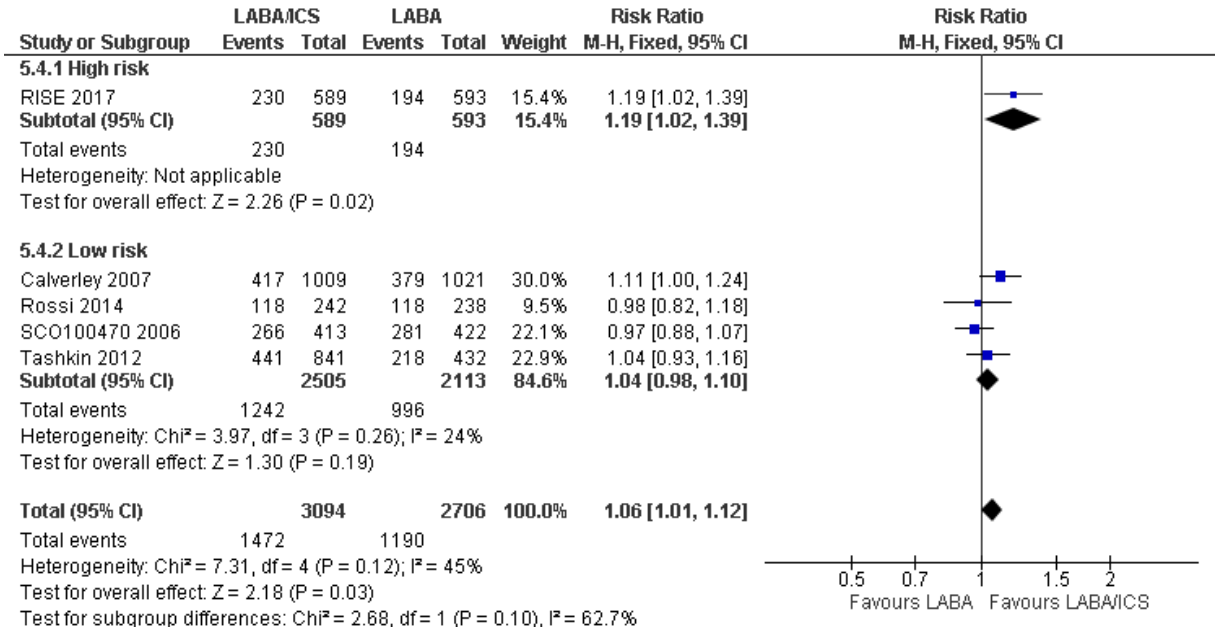
2

3 ***People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months***

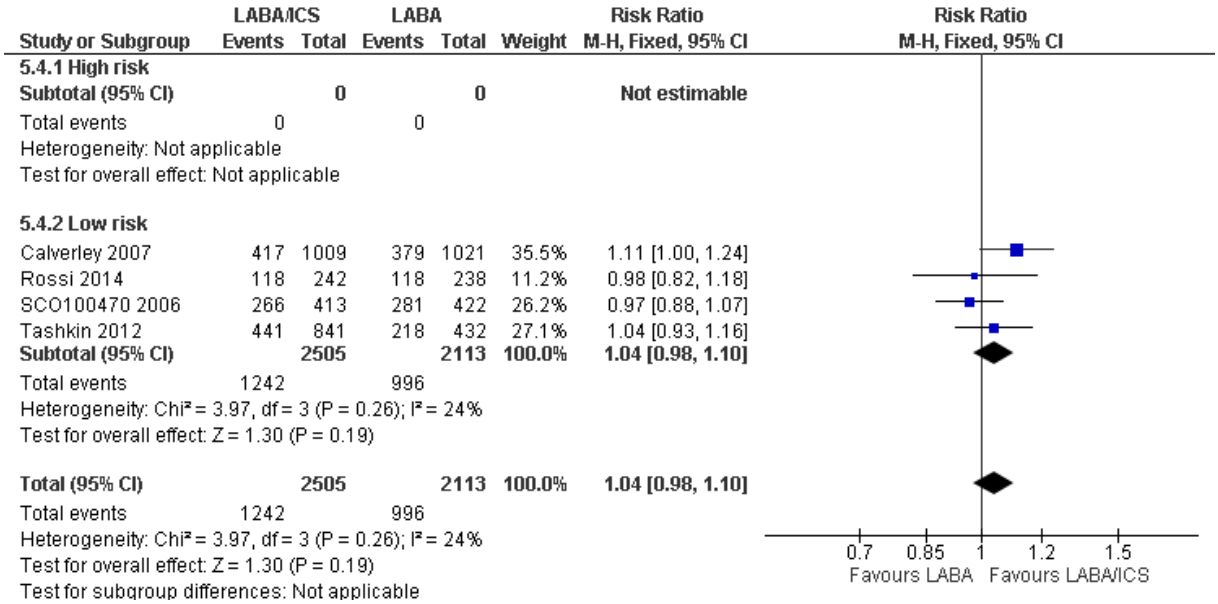


4 Test for subgroup differences: Not applicable

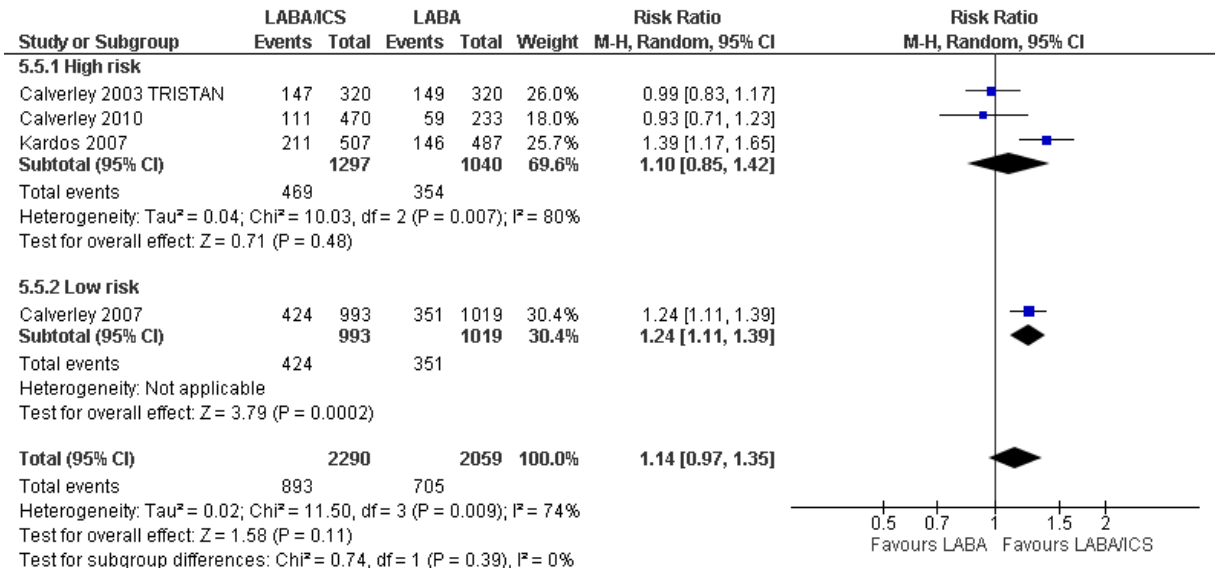
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months



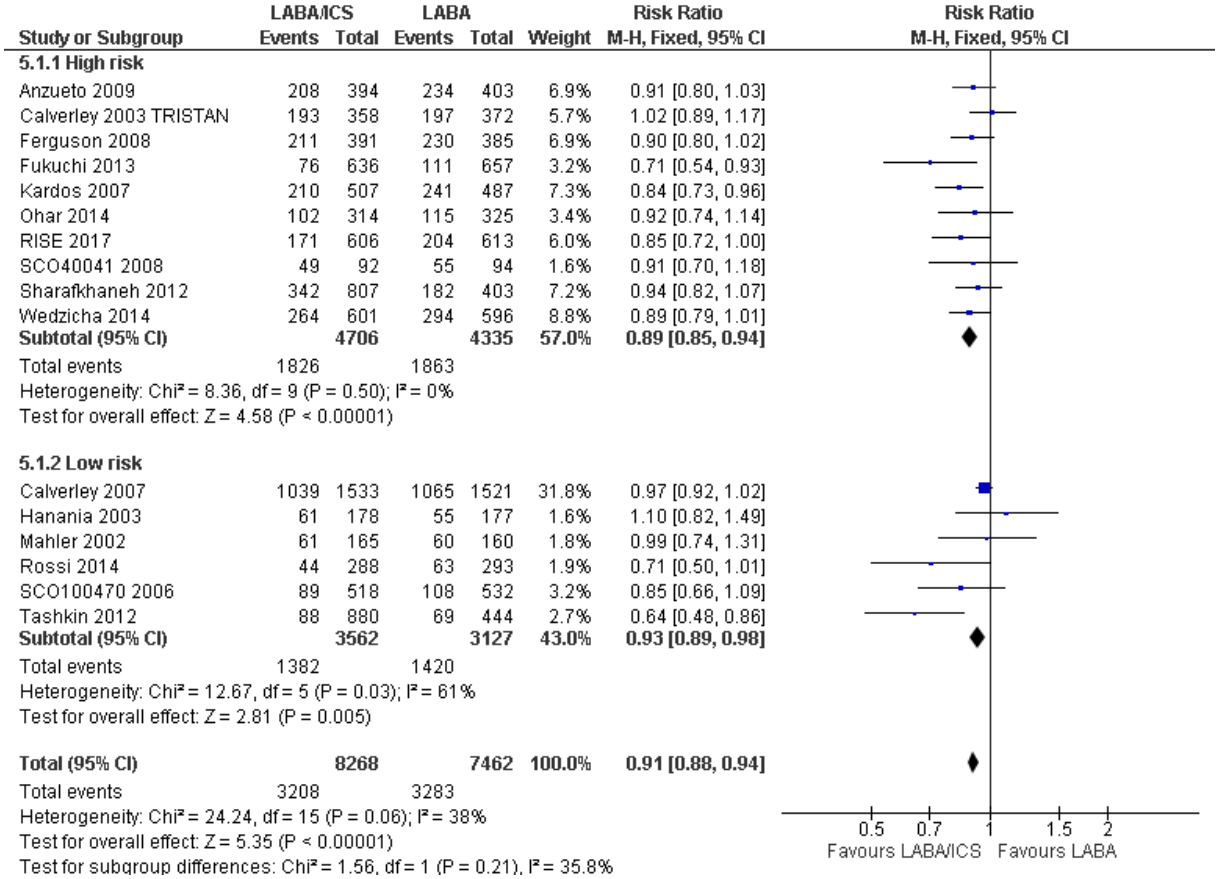
Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ) at 6 months



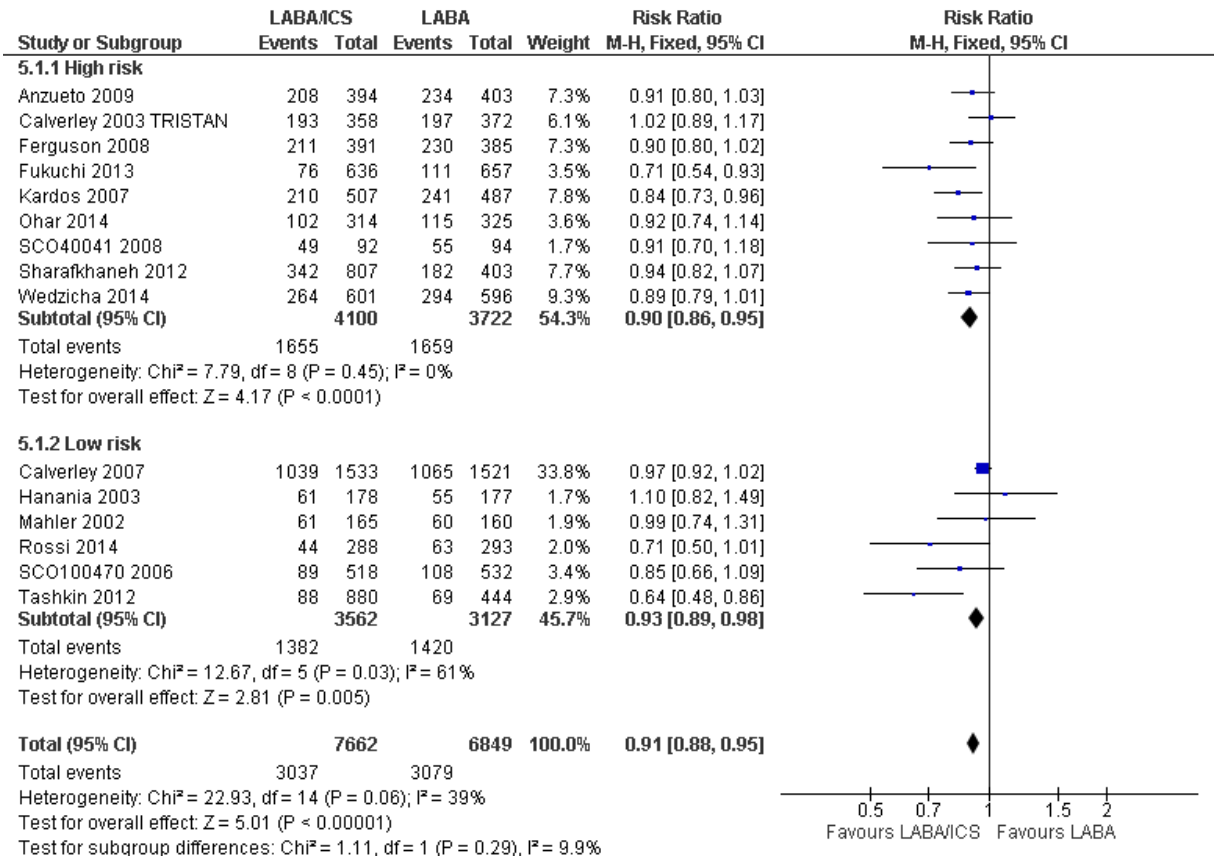
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months



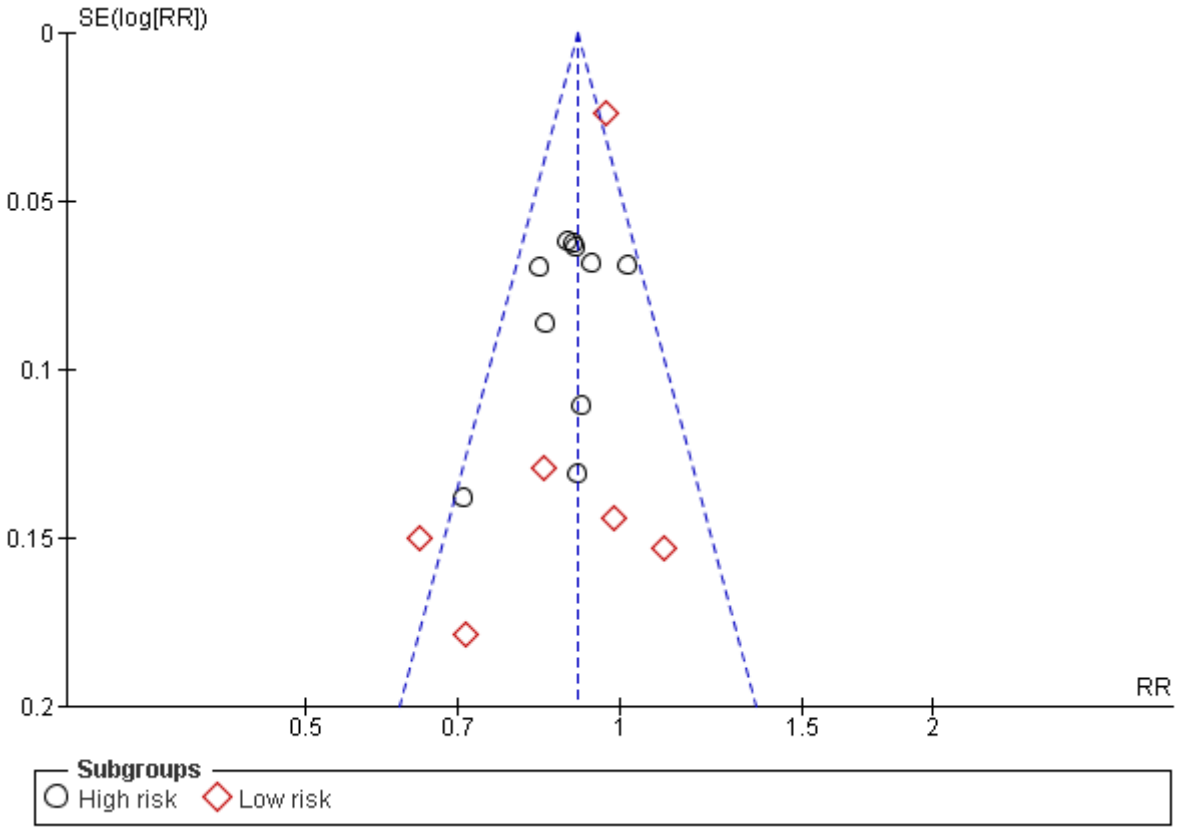
People with ≥ 1 moderate to severe exacerbation



Sensitivity analysis: people with ≥ 1 moderate to severe exacerbation

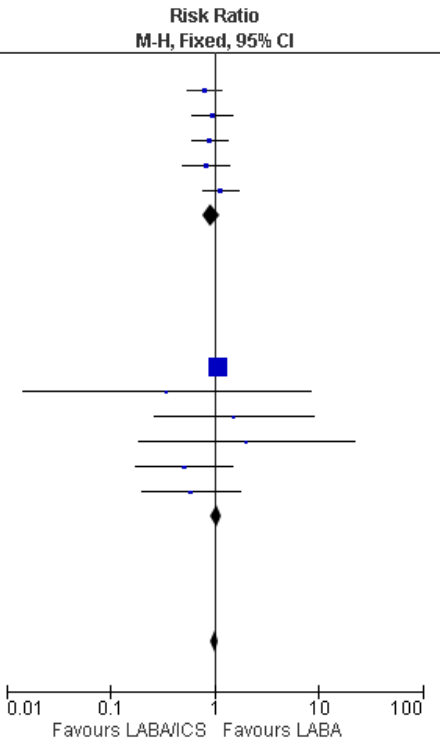


Publication bias assessment: funnel plot for moderate to severe exacerbations

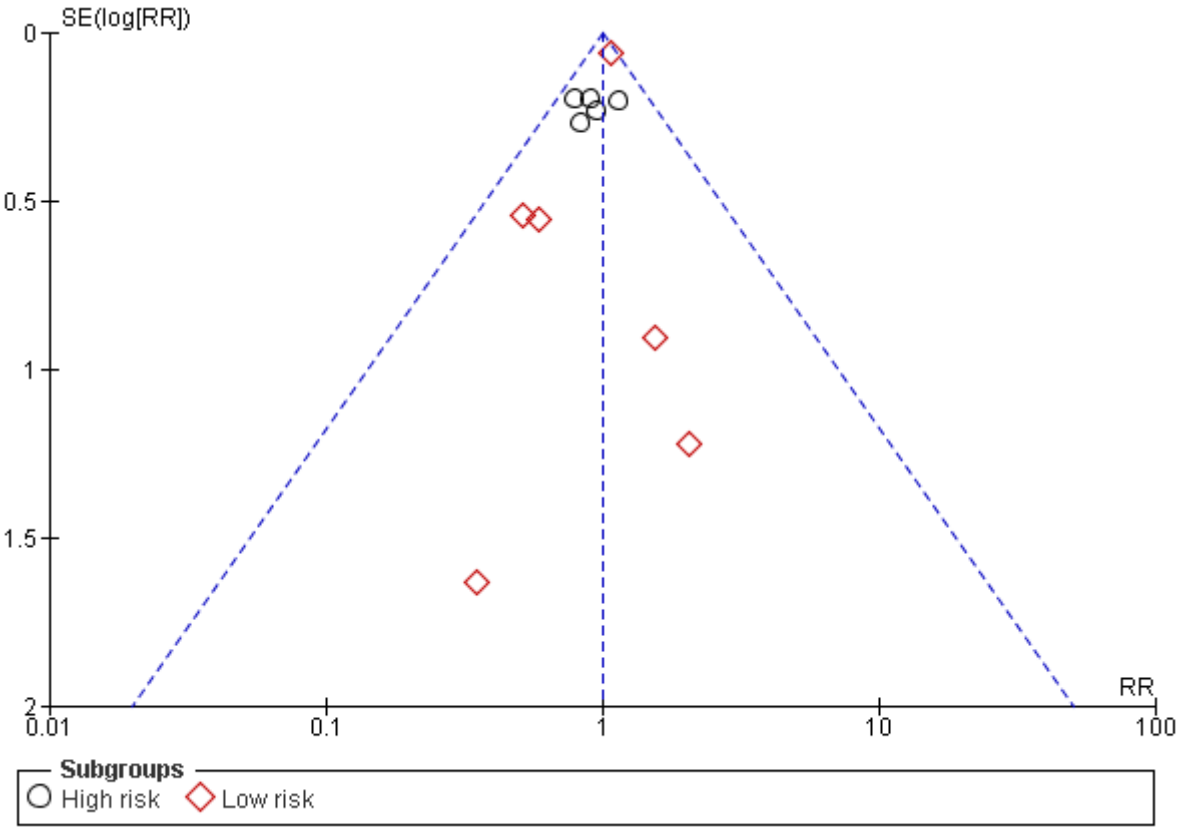


People with ≥ 1 severe exacerbation requiring hospitalisation

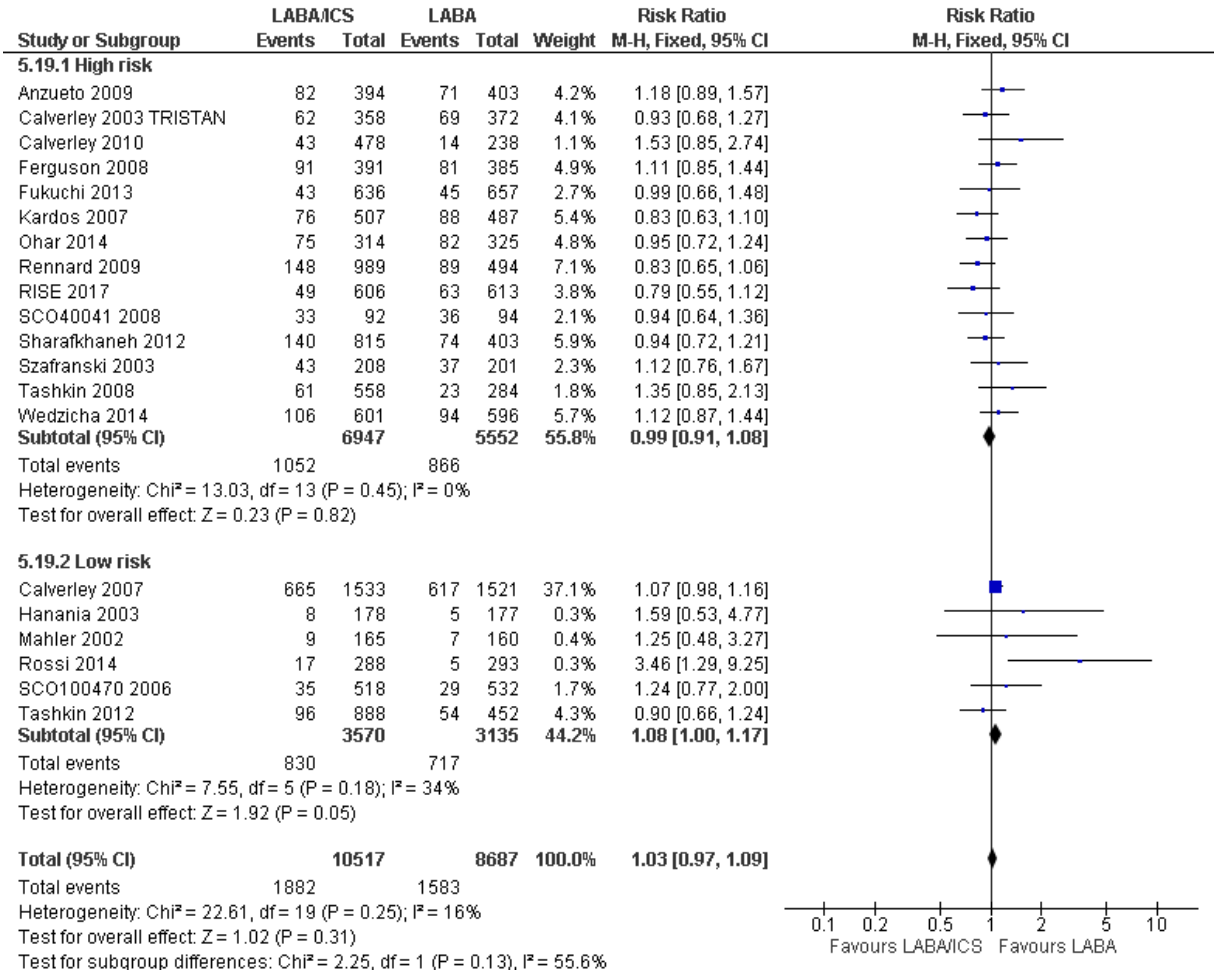
Study or Subgroup	LABA/ICS Events	LABA/ICS Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 High risk						
Anzueto 2009	39	385	50	393	8.3%	0.80 [0.54, 1.18]
Calverley 2003 TRISTAN	32	358	35	372	5.8%	0.95 [0.60, 1.50]
Ferguson 2008	42	391	46	385	7.8%	0.90 [0.61, 1.33]
Fukuchi 2013	24	636	30	657	5.0%	0.83 [0.49, 1.40]
Ohar 2014	43	314	39	325	6.4%	1.14 [0.76, 1.71]
Subtotal (95% CI)		**2084**		**2132**	**33.3%**	**0.92 [0.76, 1.11]**
Total events	180		200			
Heterogeneity: Chi² = 1.80, df = 4 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
5.2.2 Low risk						
Calverley 2007	400	1533	373	1521	63.0%	1.06 [0.94, 1.20]
Hanania 2003	0	118	1	124	0.2%	0.35 [0.01, 8.51]
Mahler 2002	3	114	2	117	0.3%	1.54 [0.26, 9.04]
Rossi 2014	2	288	1	293	0.2%	2.03 [0.19, 22.32]
SCO100470 2006	5	518	10	532	1.7%	0.51 [0.18, 1.49]
Tashkin 2012	7	880	6	444	1.3%	0.59 [0.20, 1.74]
Subtotal (95% CI)		**3451**		**3031**	**66.7%**	**1.04 [0.93, 1.18]**
Total events	417		393			
Heterogeneity: Chi² = 3.80, df = 5 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**5535**		**5163**	**100.0%**	**1.00 [0.90, 1.11]**
Total events	597		593			
Heterogeneity: Chi² = 6.91, df = 10 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.5%						



Publication bias assessment: funnel plot for severe exacerbations



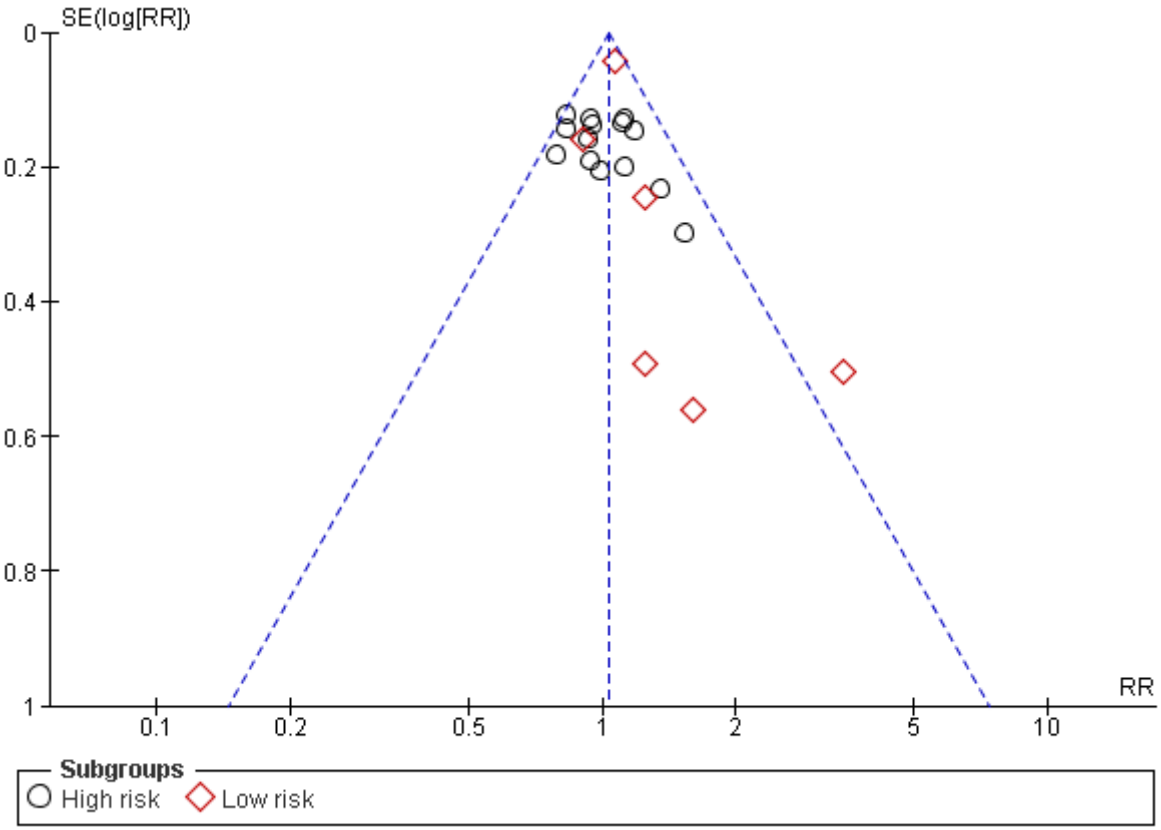
1 ***People with ≥ 1 Serious Adverse Event (SAE)***



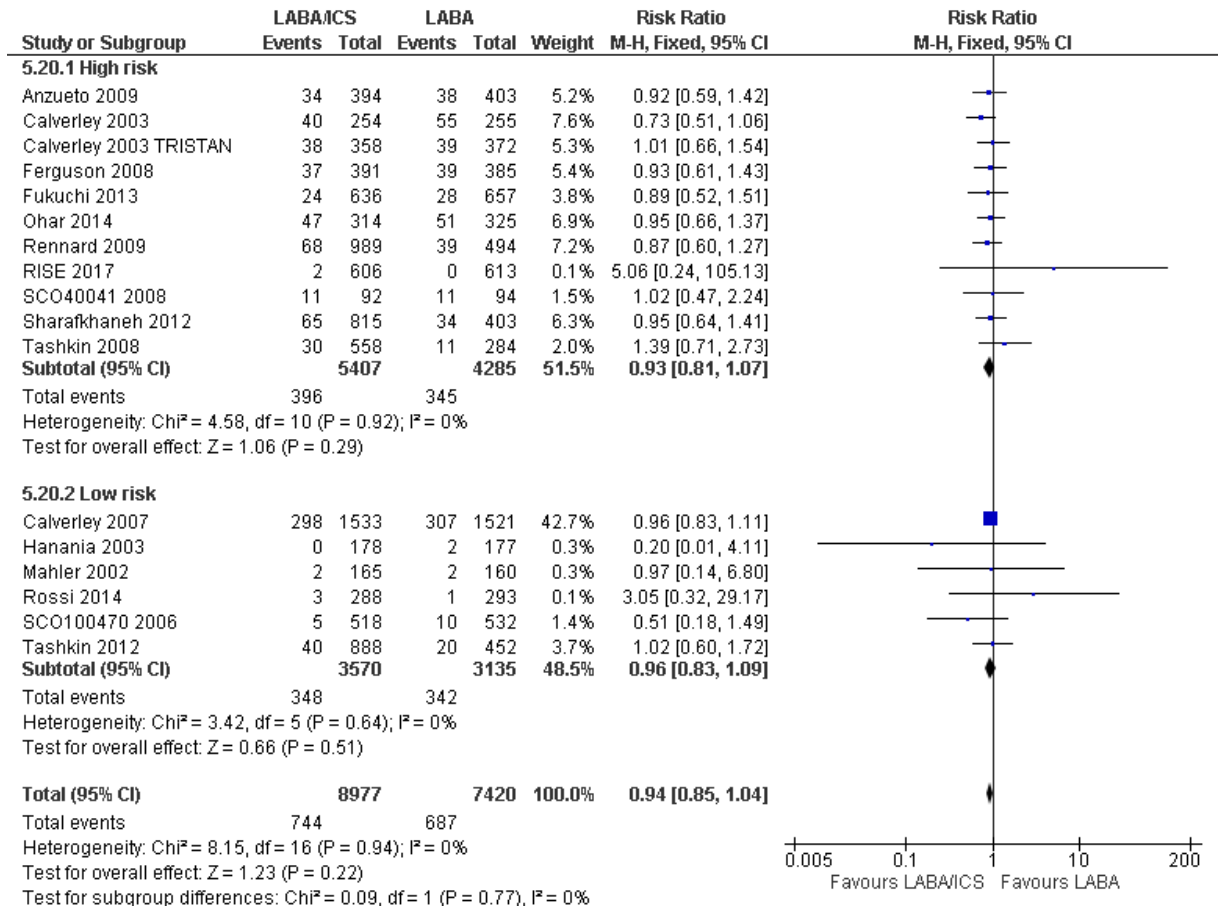
Study or Subgroup	LABA/ICS Events	LABA/ICS Total	LABA Events	LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.19.1 High risk						
Anzueto 2009	82	394	71	403	4.2%	1.18 [0.89, 1.57]
Calverley 2003 TRISTAN	62	358	69	372	4.1%	0.93 [0.68, 1.27]
Calverley 2010	43	478	14	238	1.1%	1.53 [0.85, 2.74]
Ferguson 2008	91	391	81	385	4.9%	1.11 [0.85, 1.44]
Fukuchi 2013	43	636	45	657	2.7%	0.99 [0.66, 1.48]
Kardos 2007	76	507	88	487	5.4%	0.83 [0.63, 1.10]
Ohar 2014	75	314	82	325	4.8%	0.95 [0.72, 1.24]
Rennard 2009	148	989	89	494	7.1%	0.83 [0.65, 1.06]
RISE 2017	49	606	63	613	3.8%	0.79 [0.55, 1.12]
SCO40041 2008	33	92	36	94	2.1%	0.94 [0.64, 1.36]
Sharafkhaneh 2012	140	815	74	403	5.9%	0.94 [0.72, 1.21]
Szafranski 2003	43	208	37	201	2.3%	1.12 [0.76, 1.67]
Tashkin 2008	61	558	23	284	1.8%	1.35 [0.85, 2.13]
Wedzicha 2014	106	601	94	596	5.7%	1.12 [0.87, 1.44]
Subtotal (95% CI)		**6947**		**5552**	**55.8%**	**0.99 [0.91, 1.08]**
Total events	1052		866			
Heterogeneity: Chi² = 13.03, df = 13 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
5.19.2 Low risk						
Calverley 2007	665	1533	617	1521	37.1%	1.07 [0.98, 1.16]
Hanania 2003	8	178	5	177	0.3%	1.59 [0.53, 4.77]
Mahler 2002	9	165	7	160	0.4%	1.25 [0.48, 3.27]
Rossi 2014	17	288	5	293	0.3%	3.46 [1.29, 9.25]
SCO100470 2006	35	518	29	532	1.7%	1.24 [0.77, 2.00]
Tashkin 2012	96	888	54	452	4.3%	0.90 [0.66, 1.24]
Subtotal (95% CI)		**3570**		**3135**	**44.2%**	**1.08 [1.00, 1.17]**
Total events	830		717			
Heterogeneity: Chi² = 7.55, df = 5 (P = 0.18); I² = 34%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Total (95% CI)		**10517**		**8687**	**100.0%**	**1.03 [0.97, 1.09]**
Total events	1882		1583			
Heterogeneity: Chi² = 22.61, df = 19 (P = 0.25); I² = 16%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 2.25, df = 1 (P = 0.13), I² = 55.6%						

2

Publication bias assessment: funnel plot for SAEs

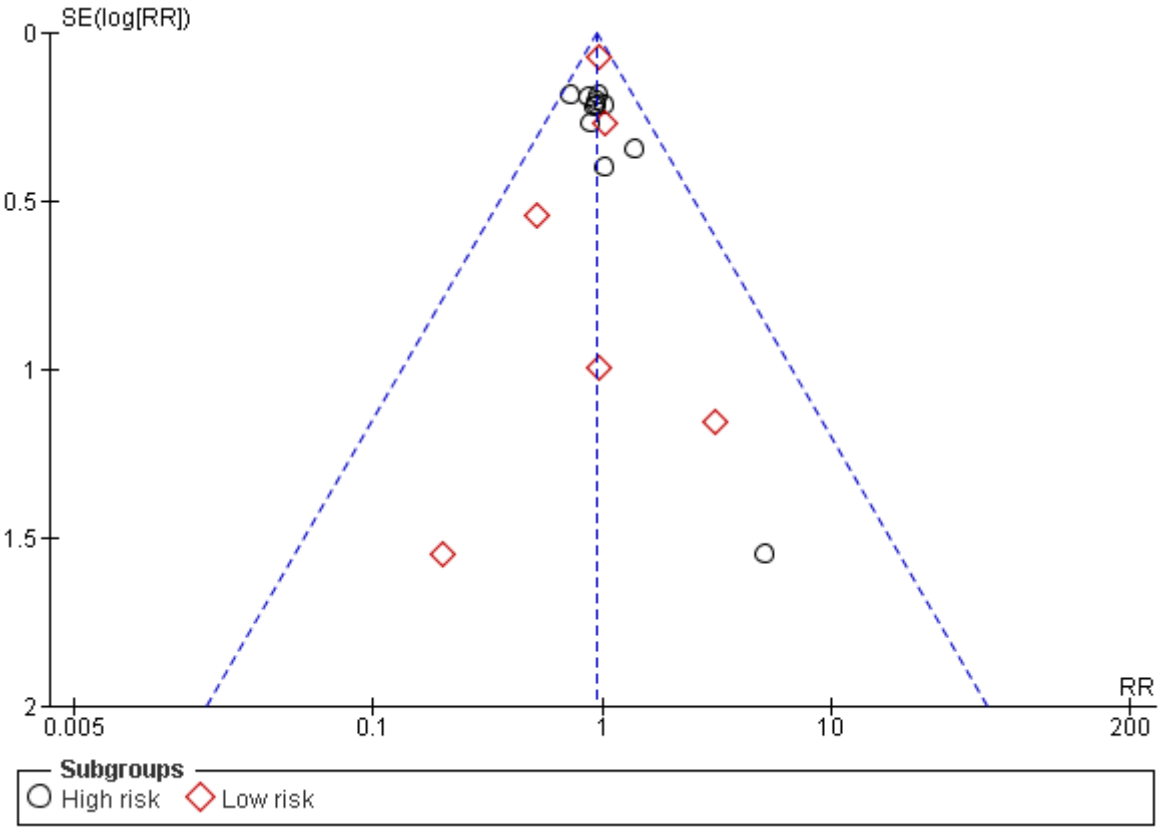


1 ***People with ≥ 1 COPD SAE***

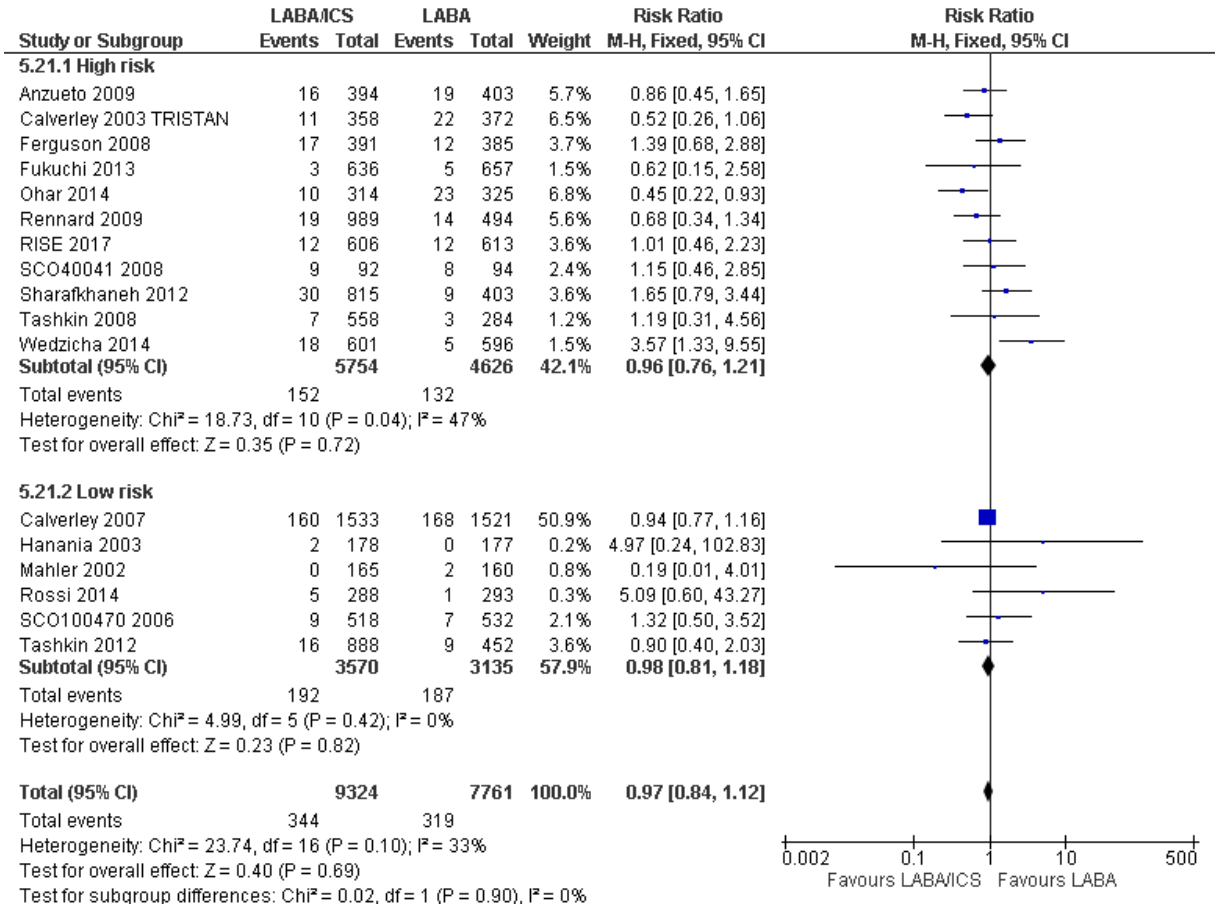


2

Publication bias assessment: funnel plot for COPD SAEs

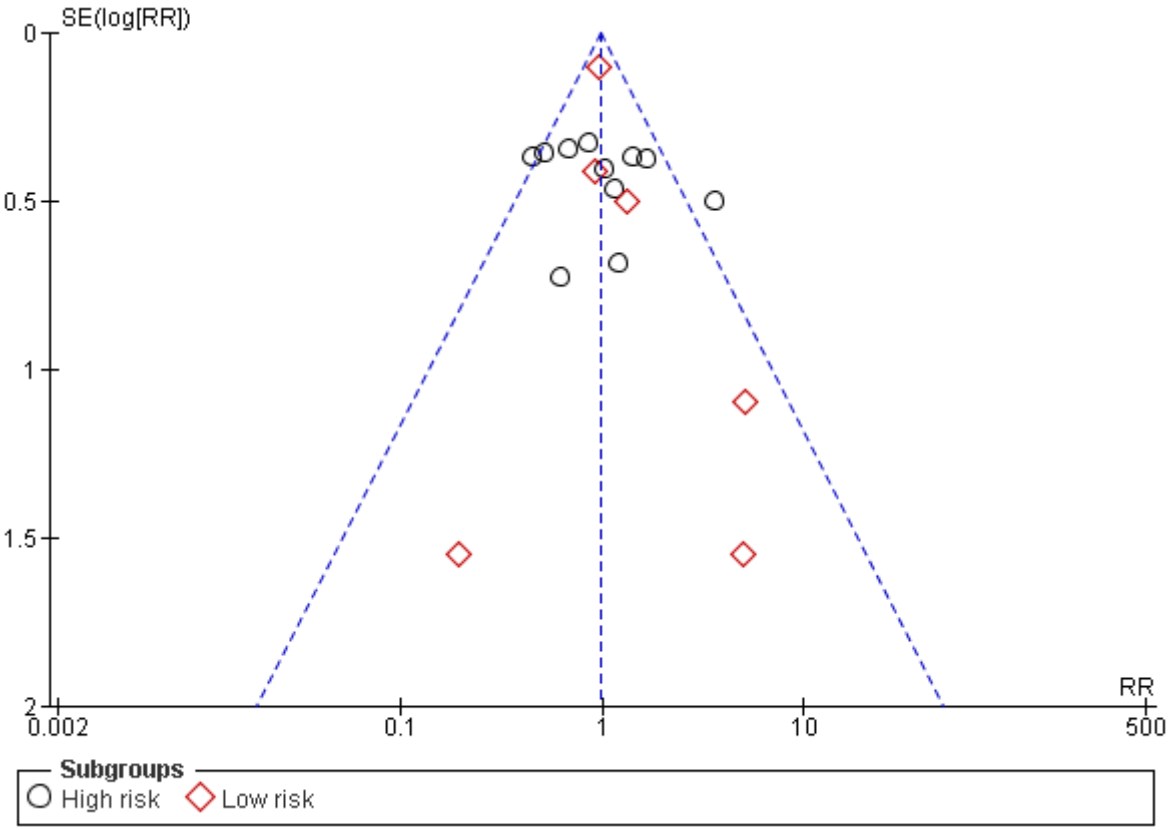


1 ***People with ≥ 1 cardiac SAE***

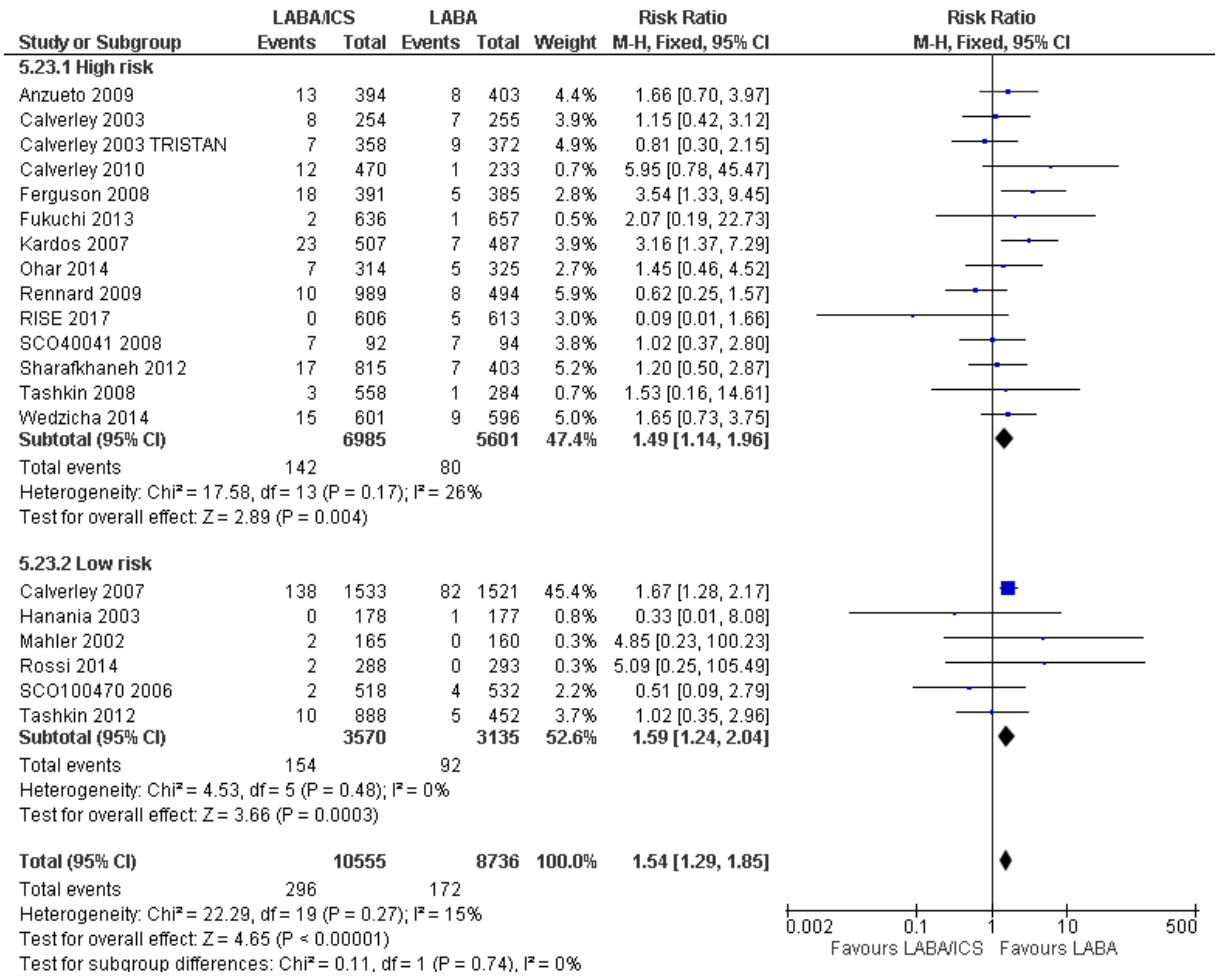


2

Publication bias assessment: funnel plot for cardiac SAEs

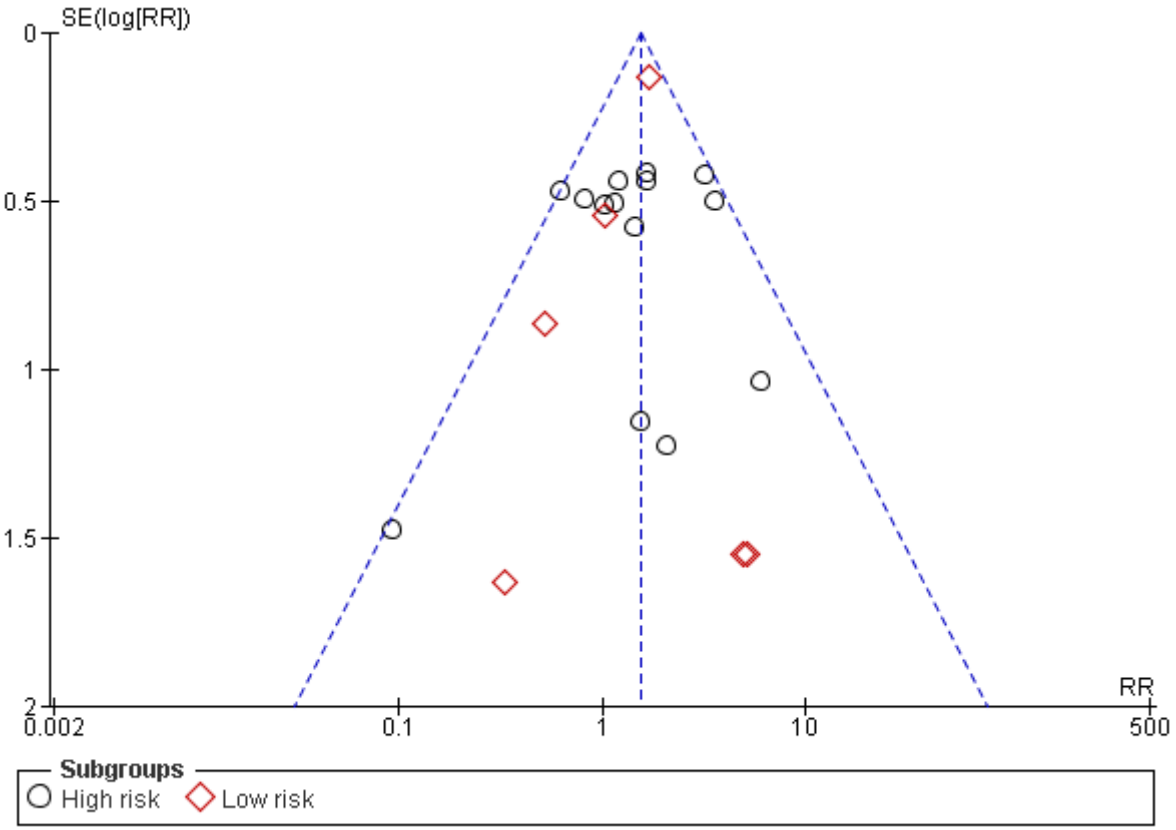


1 ***People with ≥ 1 session of pneumonia***

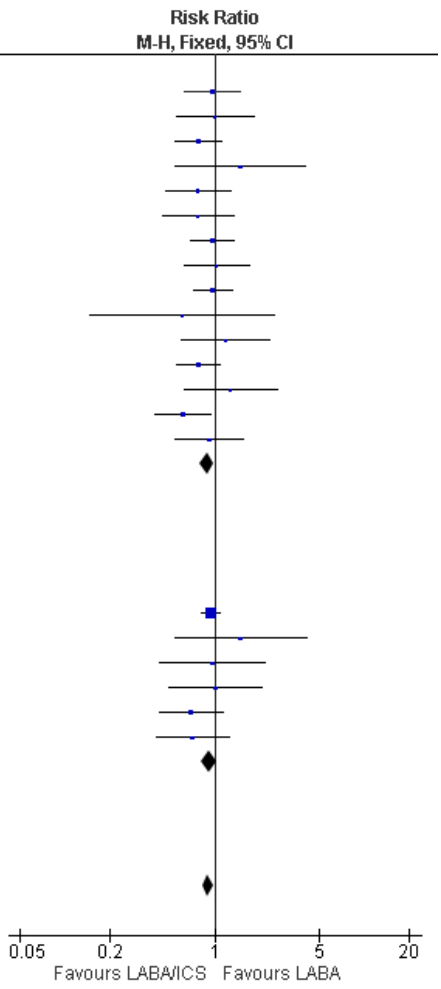


2

Publication bias assessment: funnel plot for pneumonia



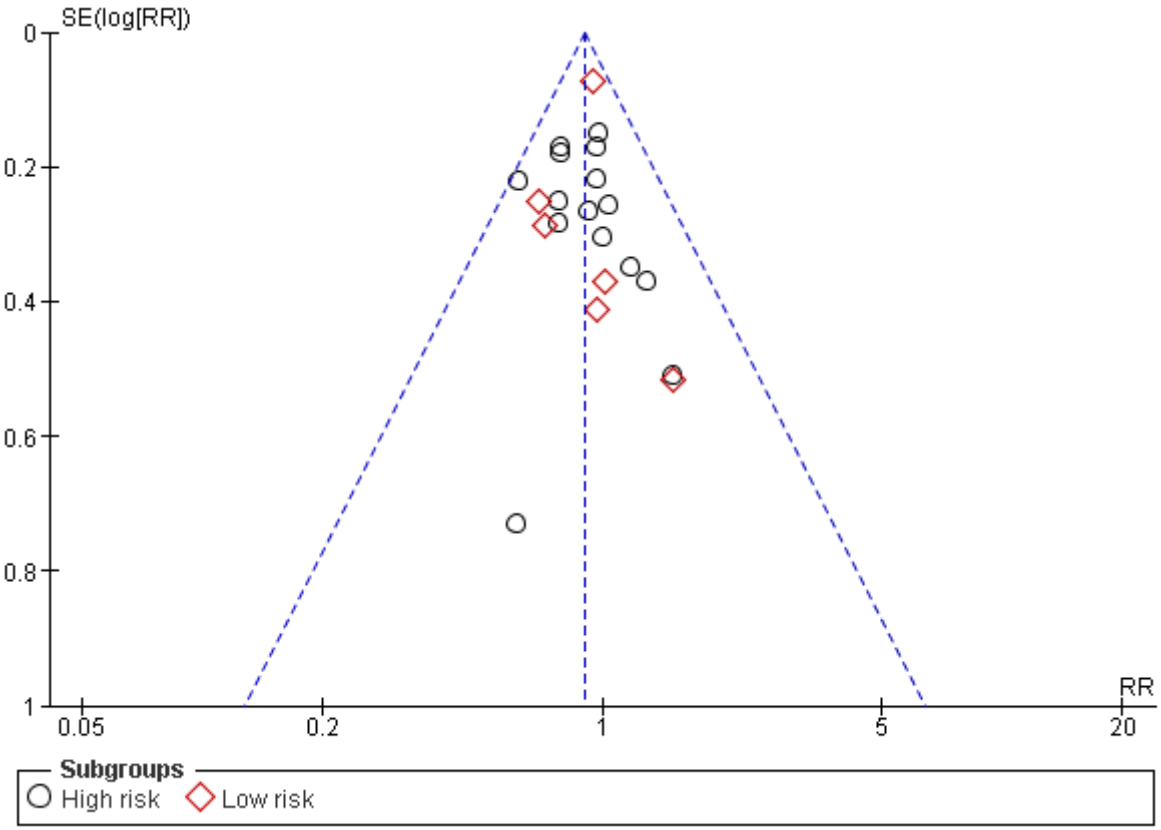
1 ***Drop-outs due to adverse events***



Study or Subgroup	LABA/ICS Events	Total	LABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.22.1 High risk						
Anzueto 2009	37	394	39	403	4.2%	0.97 [0.63, 1.49]
Calverley 2003	20	254	20	255	2.2%	1.00 [0.55, 1.82]
Calverley 2003 TRISTAN	46	358	61	372	6.5%	0.78 [0.55, 1.12]
Calverley 2010	15	478	5	238	0.7%	1.49 [0.55, 4.06]
Ferguson 2008	26	391	33	385	3.6%	0.78 [0.47, 1.27]
Fukuchi 2013	21	636	28	657	3.0%	0.77 [0.44, 1.35]
Kardos 2007	61	507	61	487	6.7%	0.96 [0.69, 1.34]
Ohar 2014	28	314	28	325	3.0%	1.04 [0.63, 1.71]
Rennard 2009	117	989	60	494	8.7%	0.97 [0.73, 1.30]
RISE 2017	3	606	5	613	0.5%	0.61 [0.15, 2.53]
SCO40041 2008	15	92	13	94	1.4%	1.18 [0.59, 2.34]
Sharafkhaneh 2012	79	815	50	403	7.2%	0.78 [0.56, 1.09]
Szafranski 2003	16	208	12	201	1.3%	1.29 [0.63, 2.65]
Tashkin 2008	41	558	34	284	4.9%	0.61 [0.40, 0.94]
Wedzicha 2014	26	601	28	596	3.0%	0.92 [0.55, 1.55]
Subtotal (95% CI)		**7201**		**5807**	**56.9%**	**0.89 [0.79, 1.00]**
Total events	551		477			
Heterogeneity: Chi² = 8.68, df = 14 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.96 (P = 0.05)						
5.22.2 Low risk						
Calverley 2007	289	1533	303	1521	32.9%	0.95 [0.82, 1.09]
Hanania 2003	9	178	6	177	0.7%	1.49 [0.54, 4.10]
Mahler 2002	11	165	11	160	1.2%	0.97 [0.43, 2.17]
Rossi 2014	14	288	14	293	1.5%	1.02 [0.49, 2.10]
SCO100470 2006	25	518	37	532	4.0%	0.69 [0.42, 1.14]
Tashkin 2012	28	888	20	452	2.9%	0.71 [0.41, 1.25]
Subtotal (95% CI)		**3570**		**3135**	**43.1%**	**0.92 [0.81, 1.05]**
Total events	376		391			
Heterogeneity: Chi² = 3.16, df = 5 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**10771**		**8942**	**100.0%**	**0.90 [0.83, 0.98]**
Total events	927		868			
Heterogeneity: Chi² = 12.03, df = 20 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						

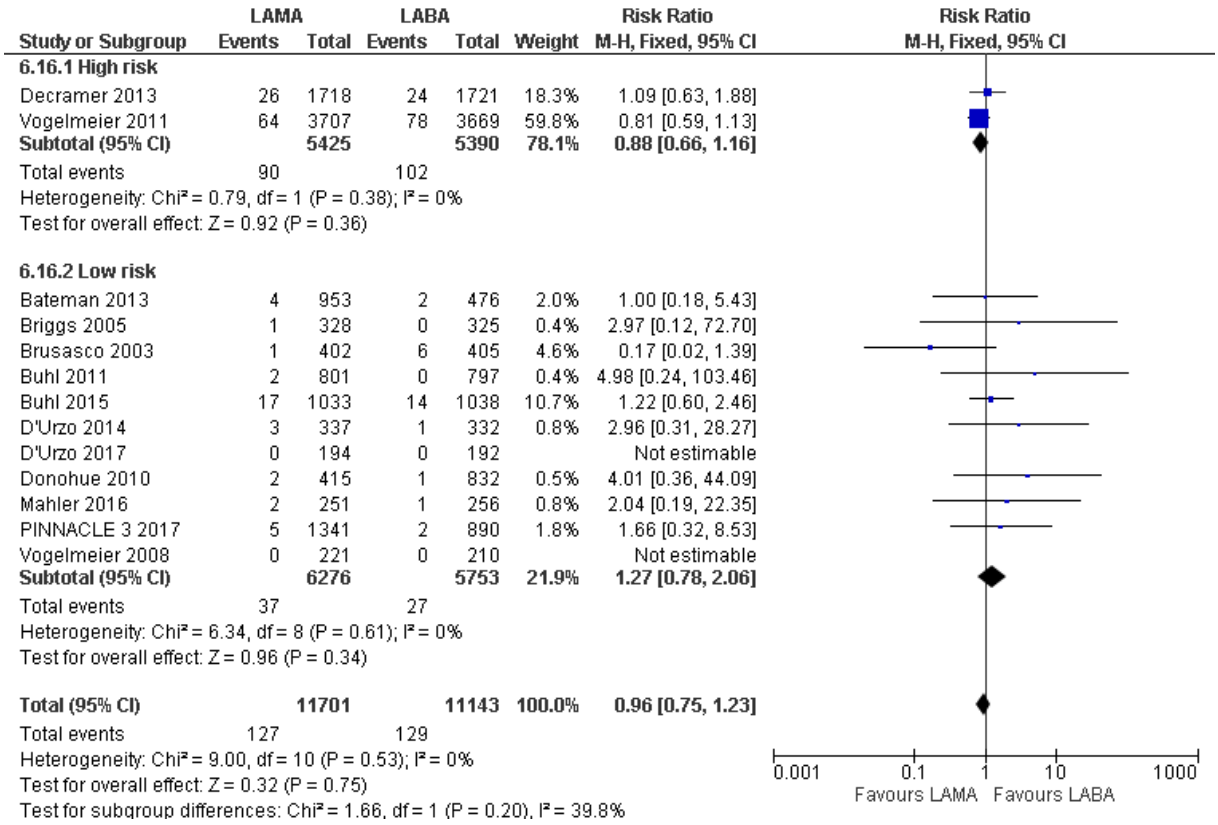
2

Publication bias assessment: funnel plot for drop-outs due to adverse events



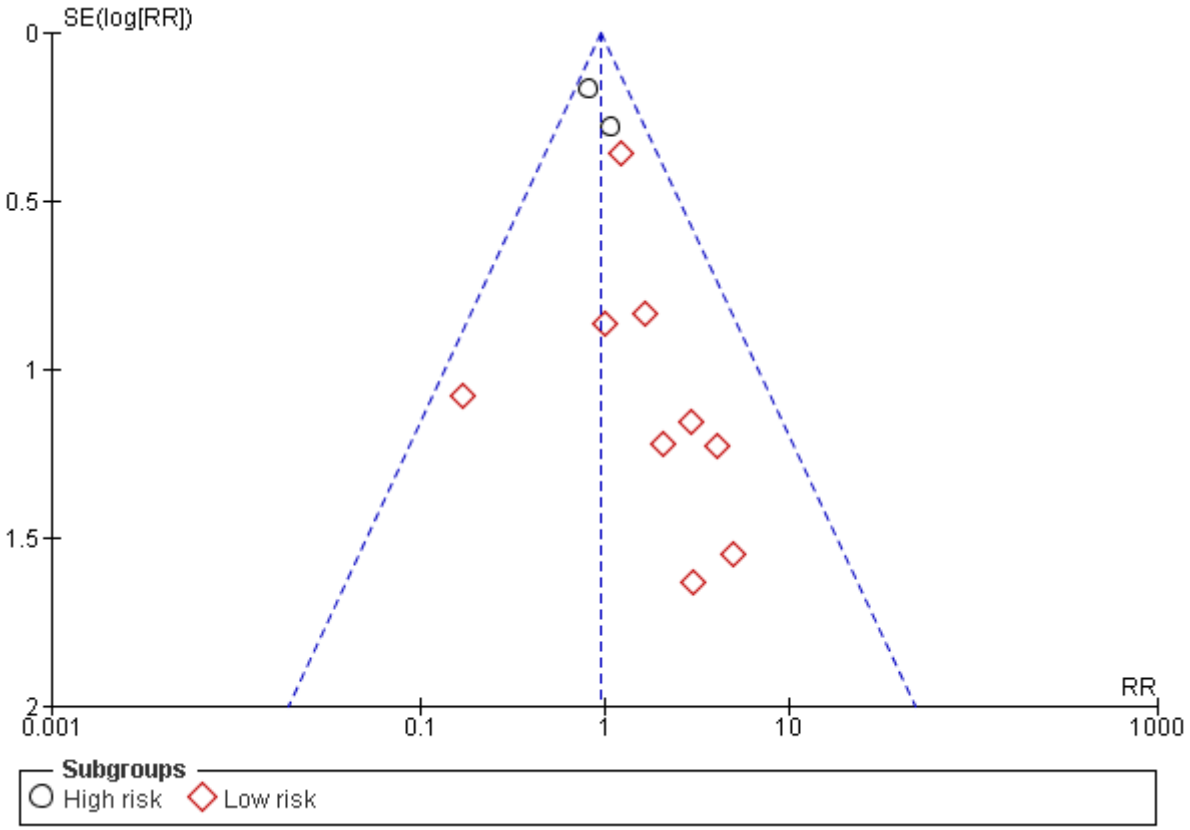
1 **LAMA versus LABA**

2 ***All-cause mortality***



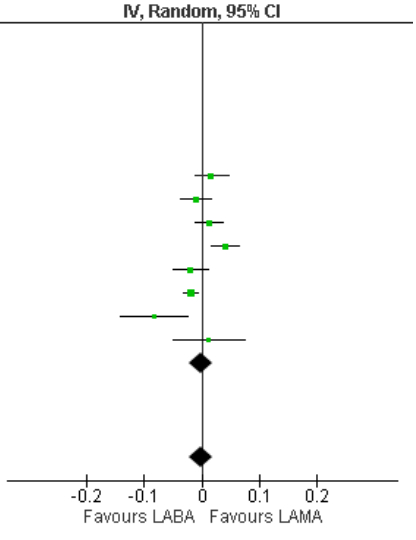
3

Publication bias assessment: funnel plot for all-cause mortality

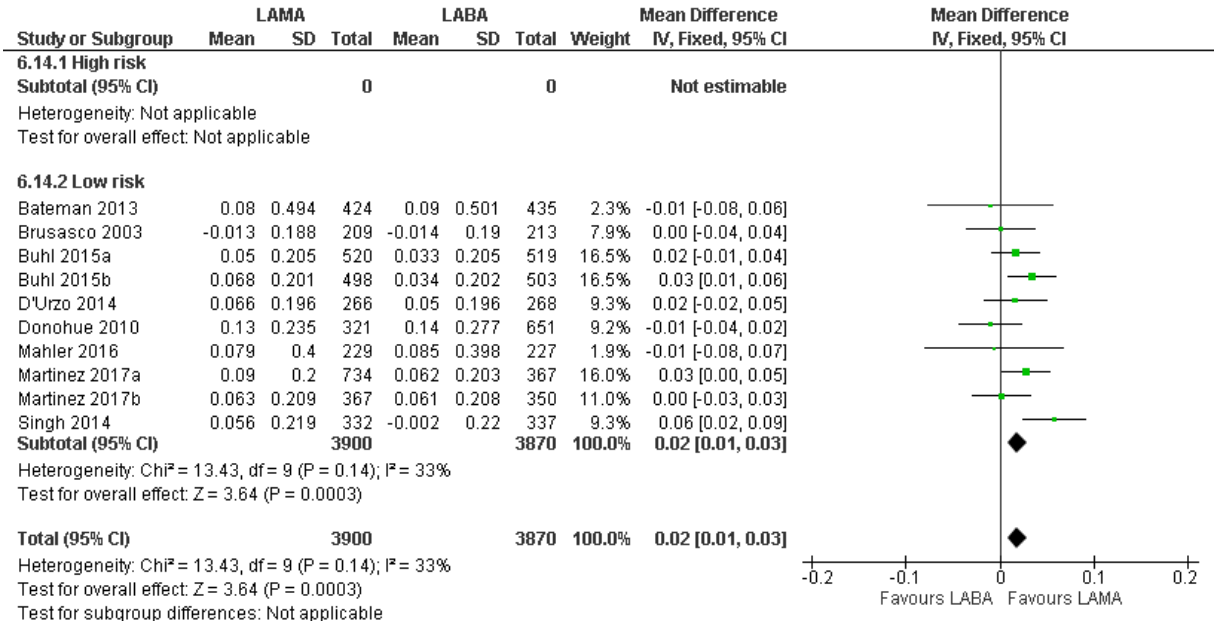


Change in Trough FEV1 (L) at 3 months

Study or Subgroup	LAMA Mean	LAMA SD	LAMA Total	LABA Mean	LABA SD	LABA Total	Weight	Mean Difference IV, Random, 95% CI
6.13.1 High risk								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
6.13.2 Low risk								
Briggs 2005	0.088	0.181	328	0.071	0.198	325	13.4%	0.02 [-0.01, 0.05]
Buhl 2011	0.12	0.244	595	0.13	0.237	562	13.7%	-0.01 [-0.04, 0.02]
Buhl 2015a	0.07	0.205	520	0.057	0.205	519	14.4%	0.01 [-0.01, 0.04]
Buhl 2015b	0.088	0.201	498	0.047	0.202	503	14.4%	0.04 [0.02, 0.07]
Donohue 2010	0.15	0.227	349	0.17	0.263	700	12.9%	-0.02 [-0.05, 0.01]
Hoshino 2013	0.044	0.012	15	0.062	0.021	14	17.2%	-0.02 [-0.03, -0.01]
Hoshino 2014	0.056	0.119	16	0.139	0.0149	20	7.3%	-0.08 [-0.14, -0.02]
Mahler 2016	0.104	0.34	229	0.091	0.339	227	6.7%	0.01 [-0.05, 0.08]
Subtotal (95% CI)			**2550**			**2870**	**100.0%**	**-0.00 [-0.02, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 29.49, df = 7 (P = 0.0001); I² = 76%								
Test for overall effect: Z = 0.21 (P = 0.84)								
Total (95% CI)			**2550**			**2870**	**100.0%**	**-0.00 [-0.02, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 29.49, df = 7 (P = 0.0001); I² = 76%								
Test for overall effect: Z = 0.21 (P = 0.84)								
Test for subgroup differences: Not applicable								

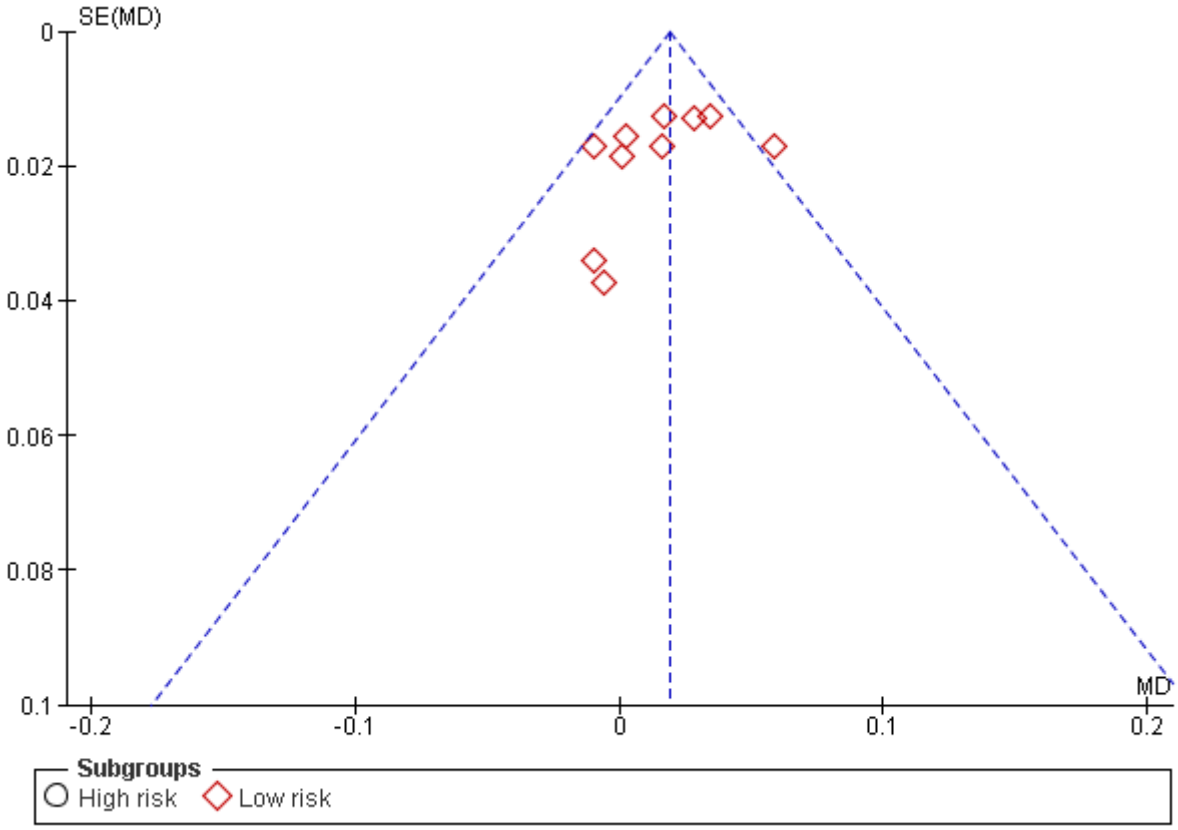


1 ***Change in Trough FEV1 (L) at 6 months***



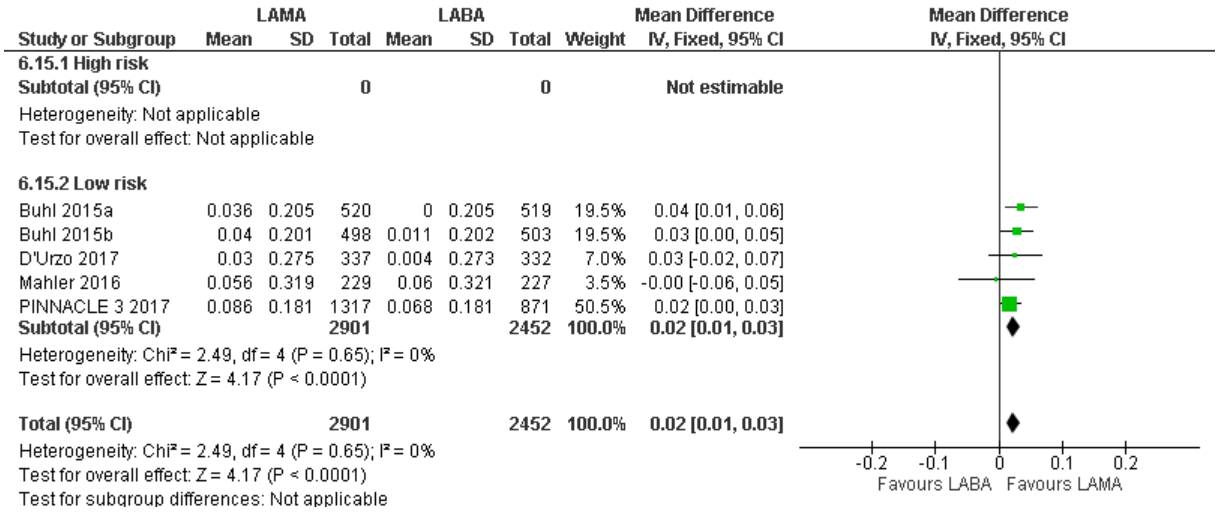
2

3 *Publication bias assessment: funnel plot for change in trough FEV1 at 6 months*

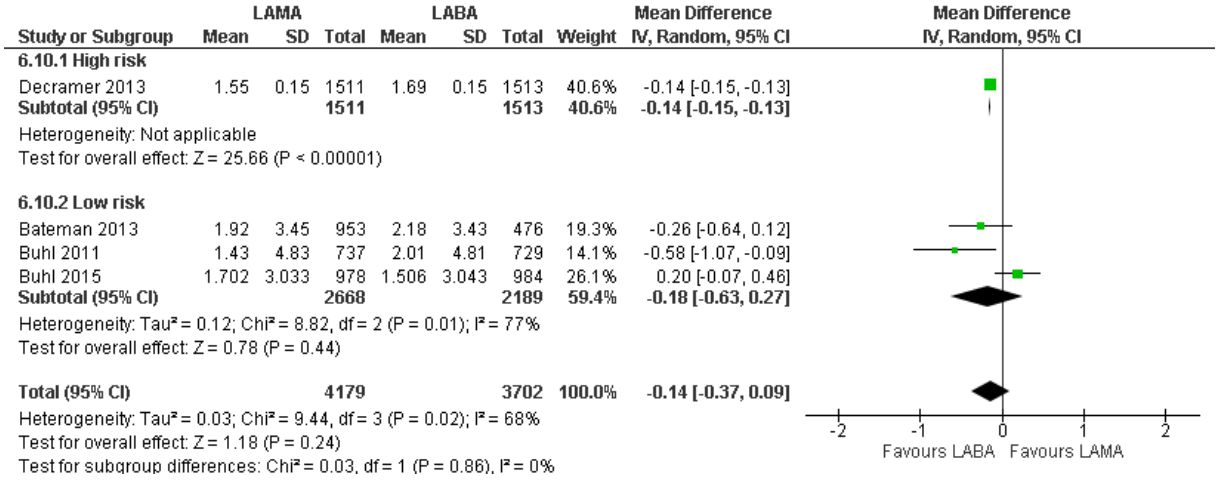


4

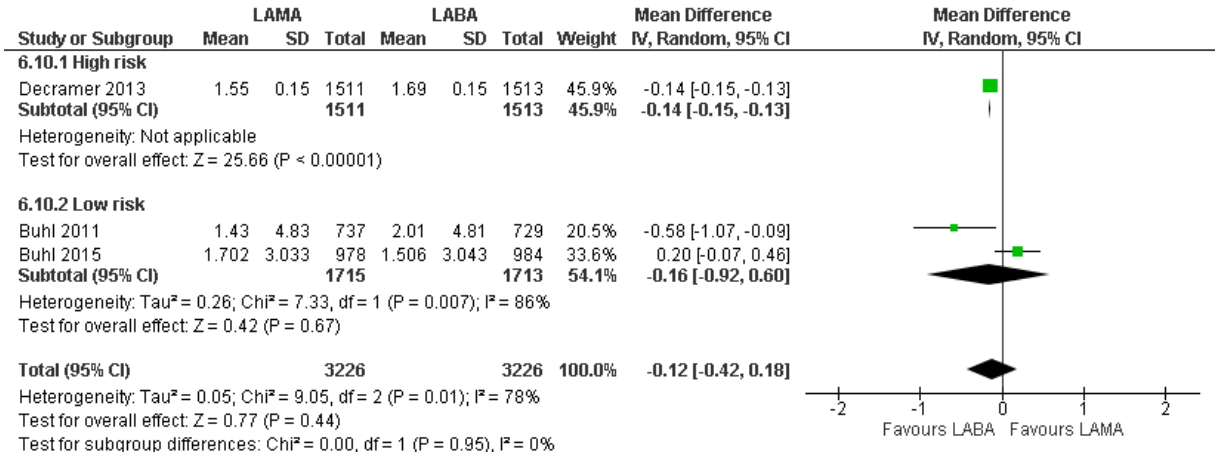
Change in Trough FEV1 (L) at 12 months



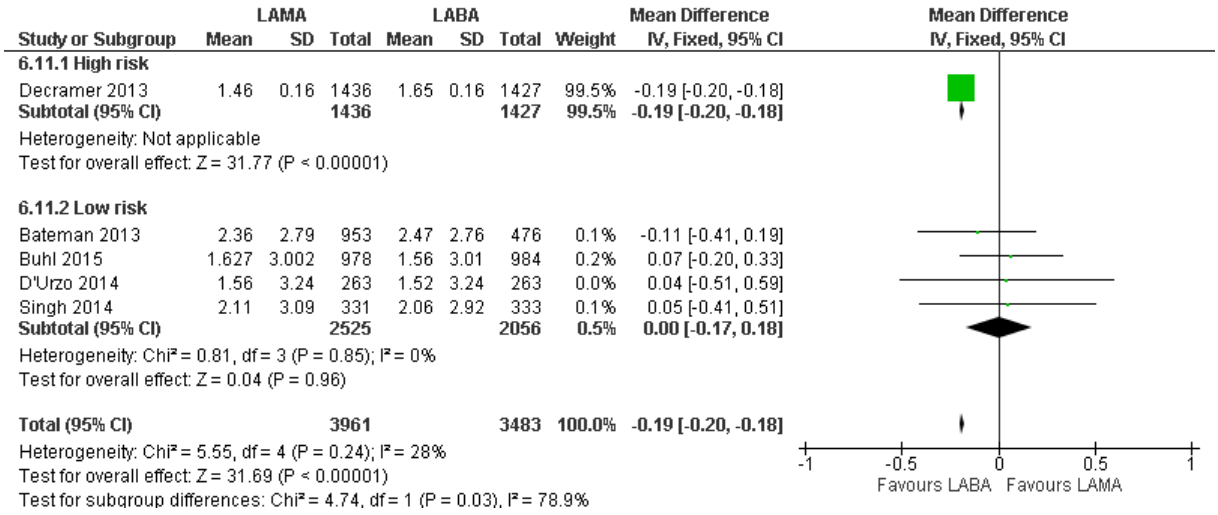
Transition Dyspnoea Index (TDI) focal score at 3 months



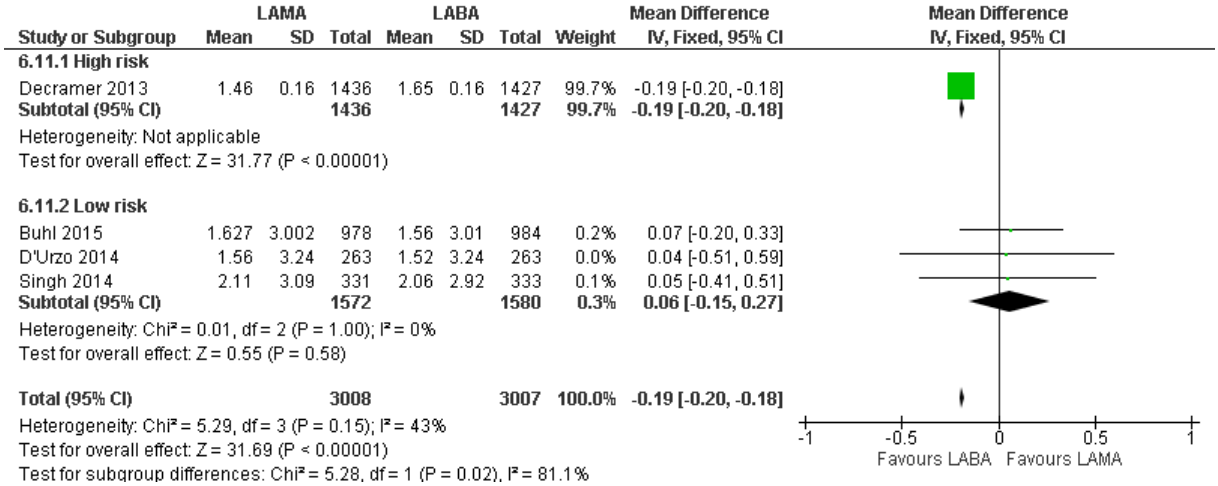
Sensitivity analysis: TDI at 3 months



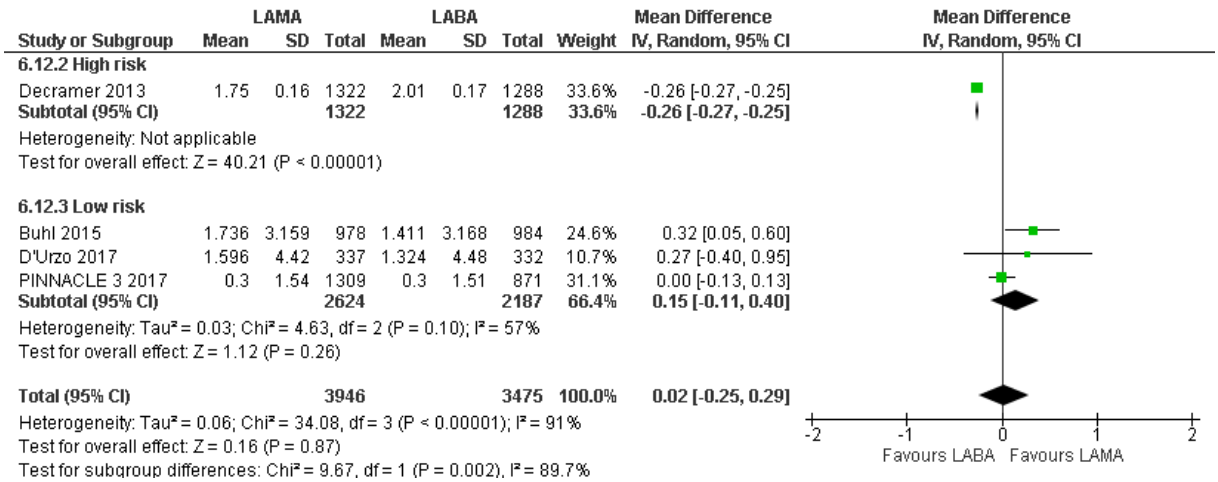
Transition Dyspnoea Index (TDI) focal score at 6 months



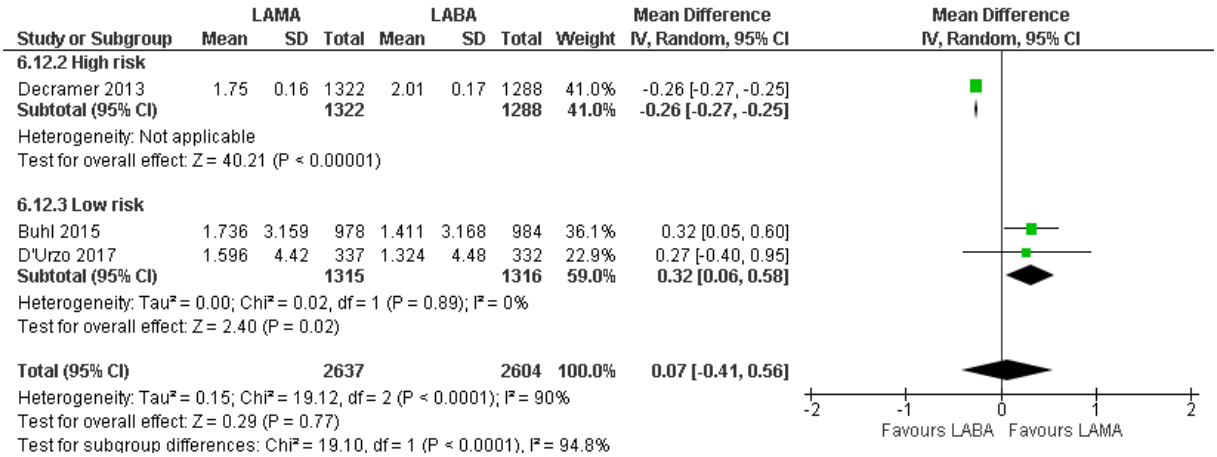
Sensitivity analysis: TDI at 6 months



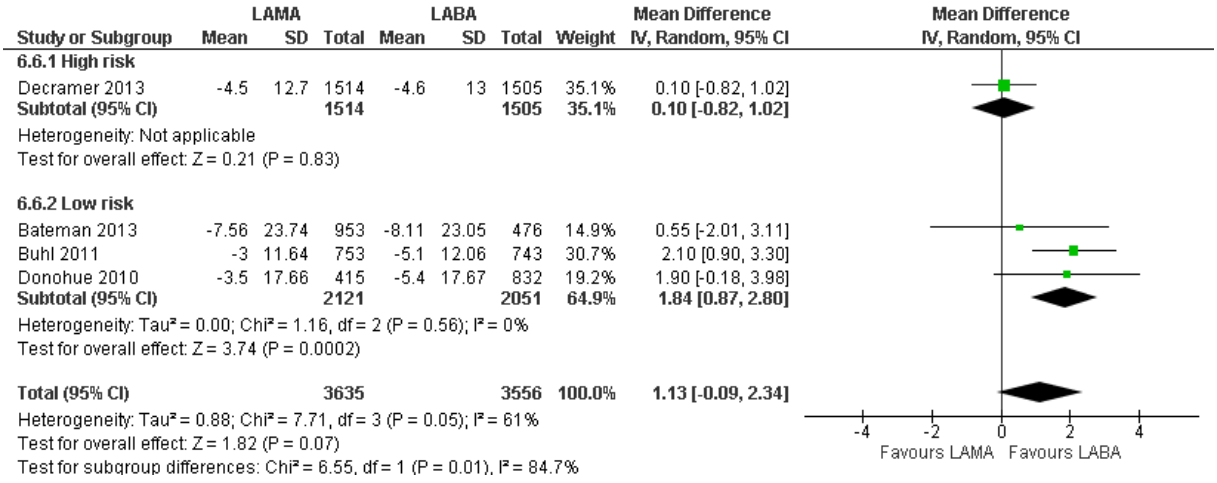
Transition Dyspnoea Index (TDI) focal score at 12 months



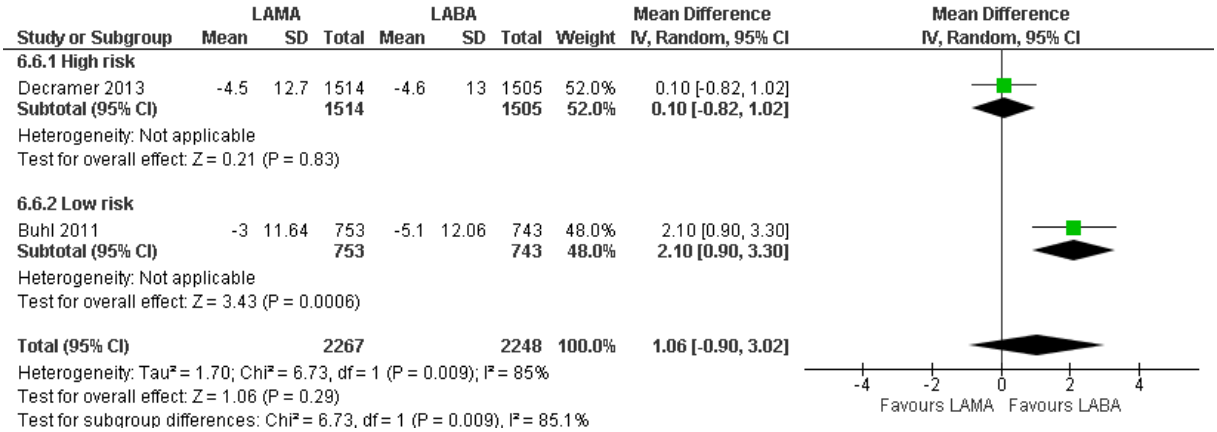
Sensitivity analysis: TDI at 12 months



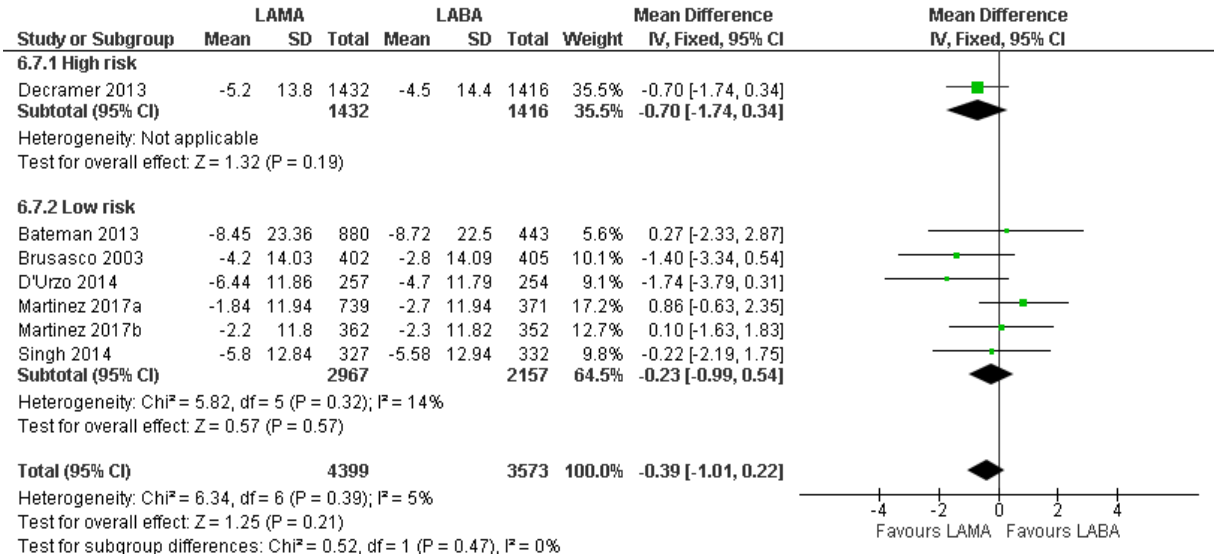
St. George's Respiratory Questionnaire (SGRQ), total score at 3 months



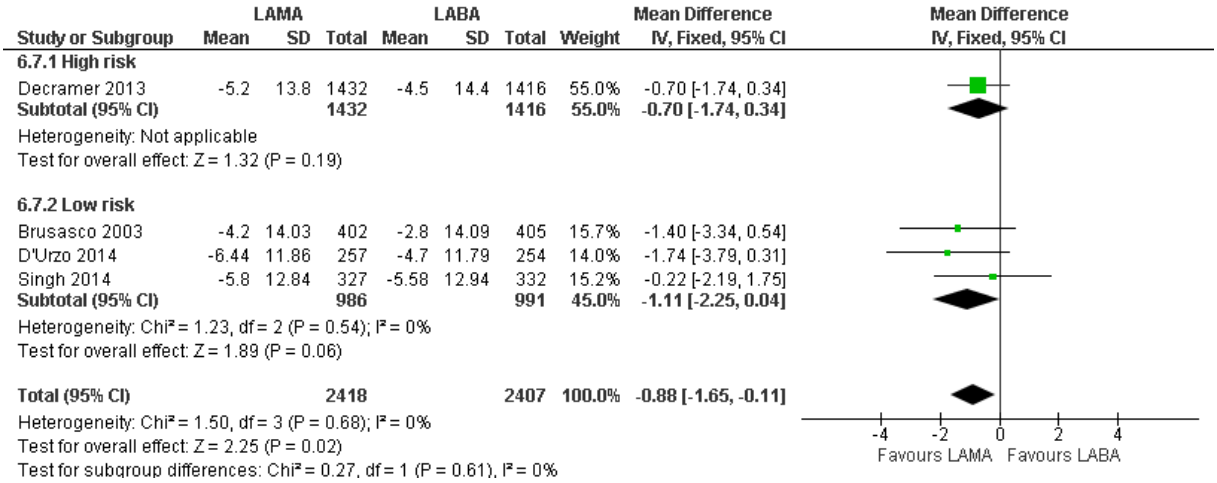
Sensitivity analysis: SGRQ at 3 months



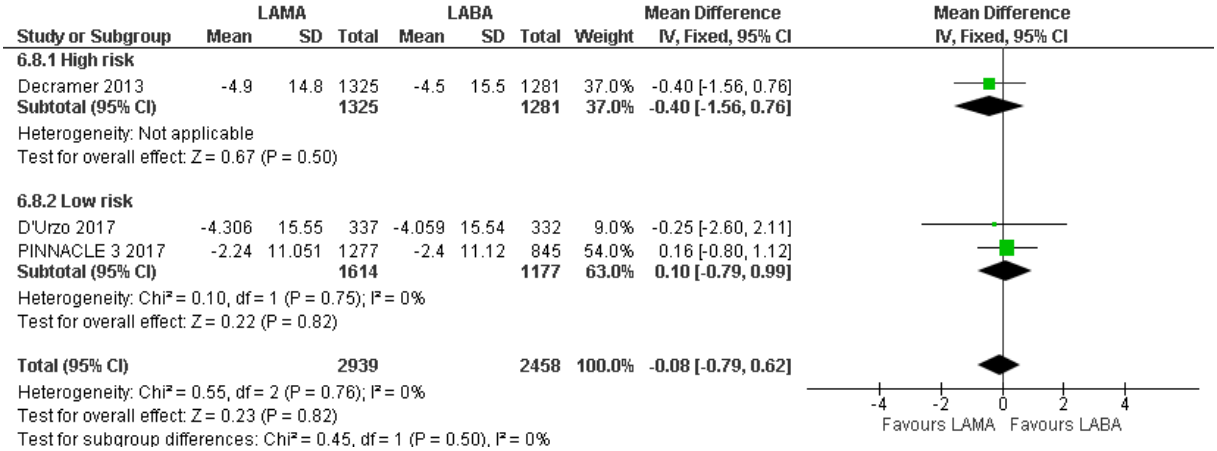
St. George's Respiratory Questionnaire (SGRQ), total score at 6 months



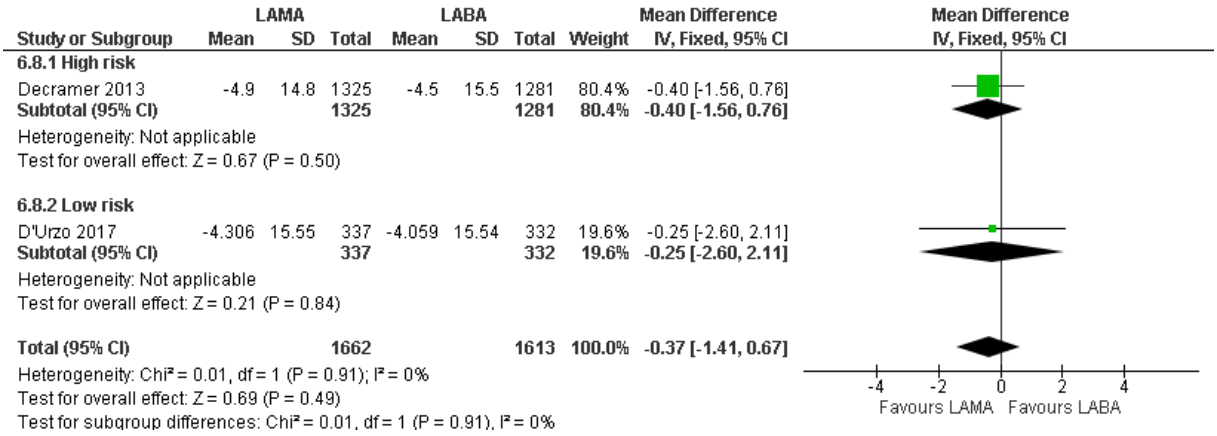
Sensitivity analysis: SGRQ at 6 months



St. George's Respiratory Questionnaire (SGRQ), total score at 12 months

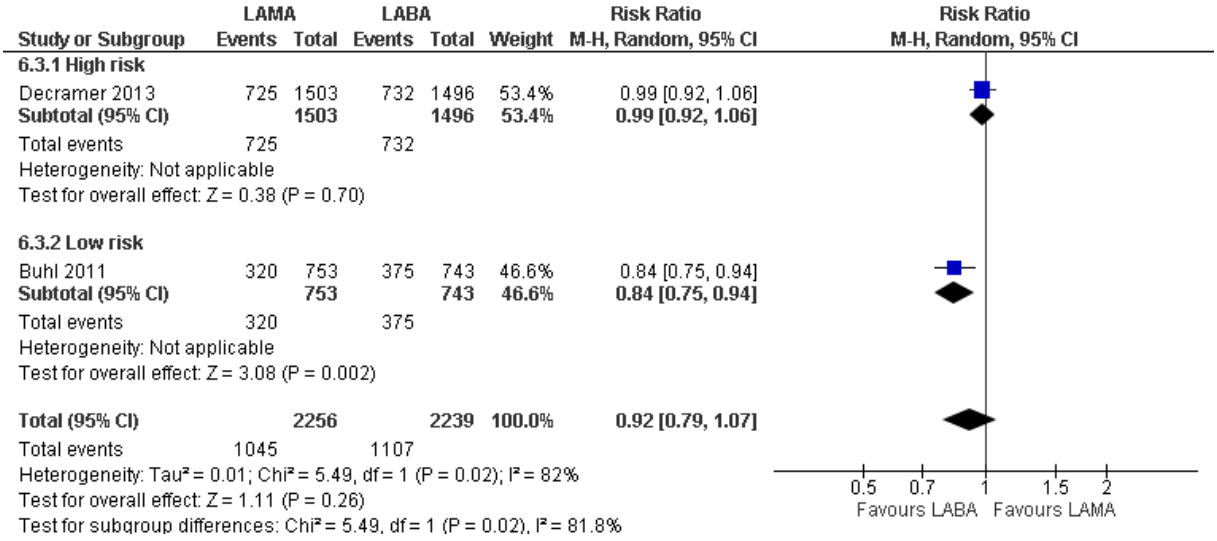


1 *Sensitivity analysis: SGRQ at 12 months*



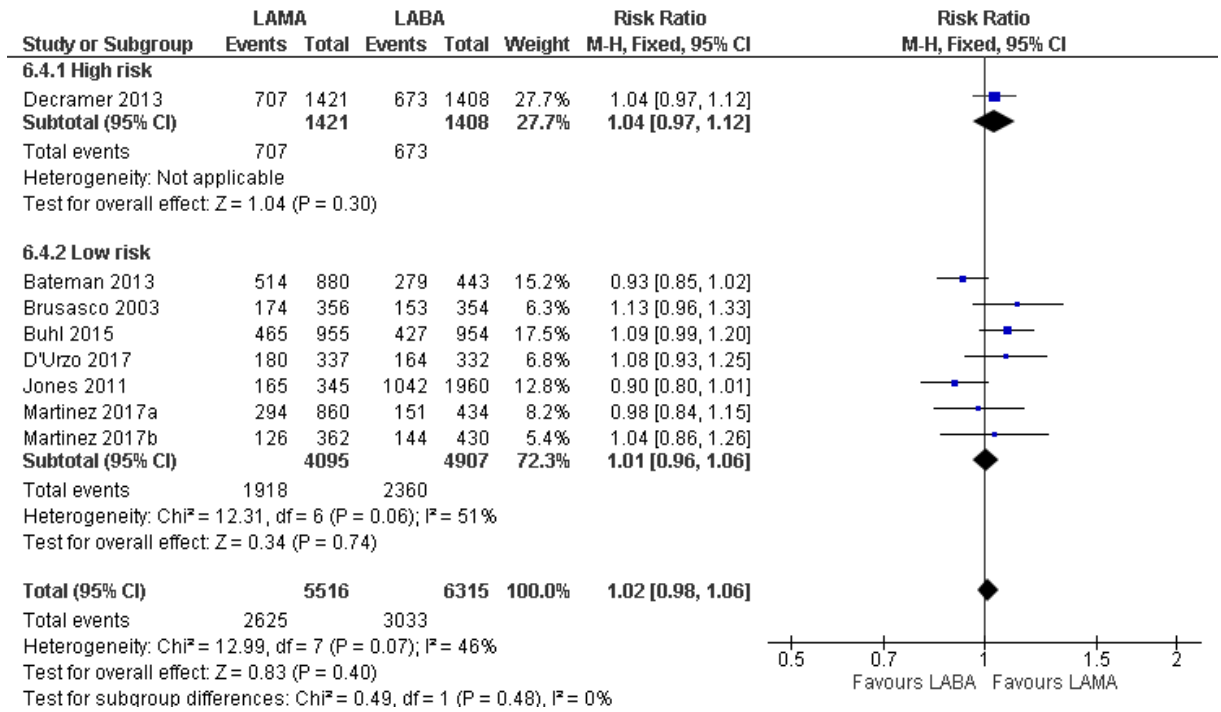
2

3 ***People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months***

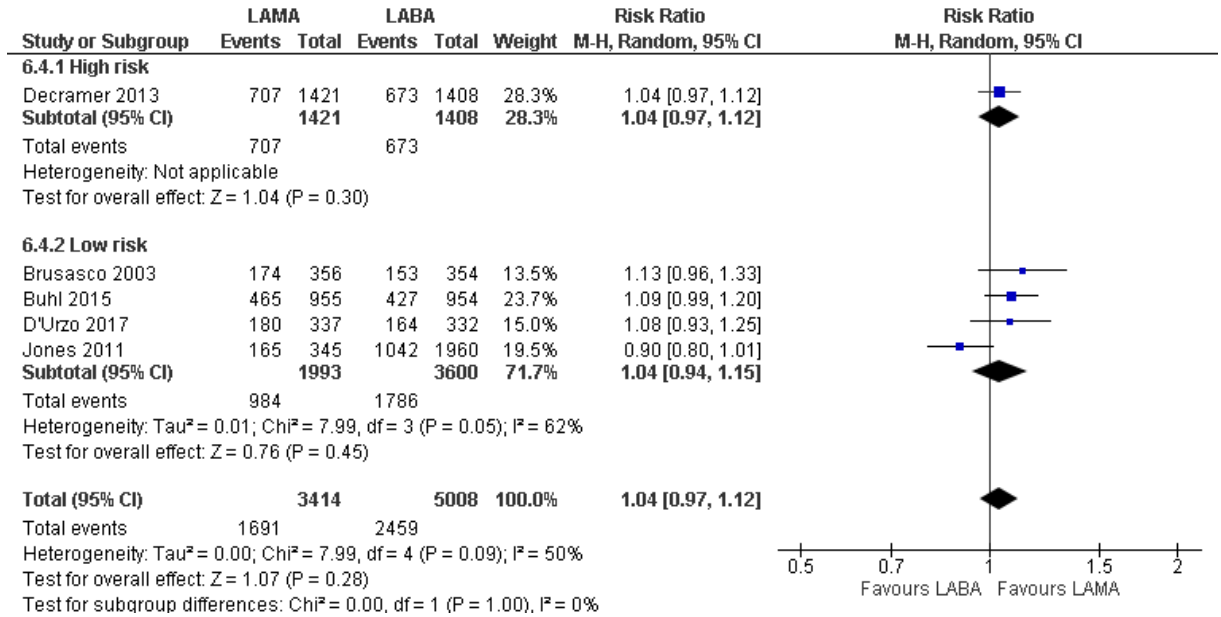


4

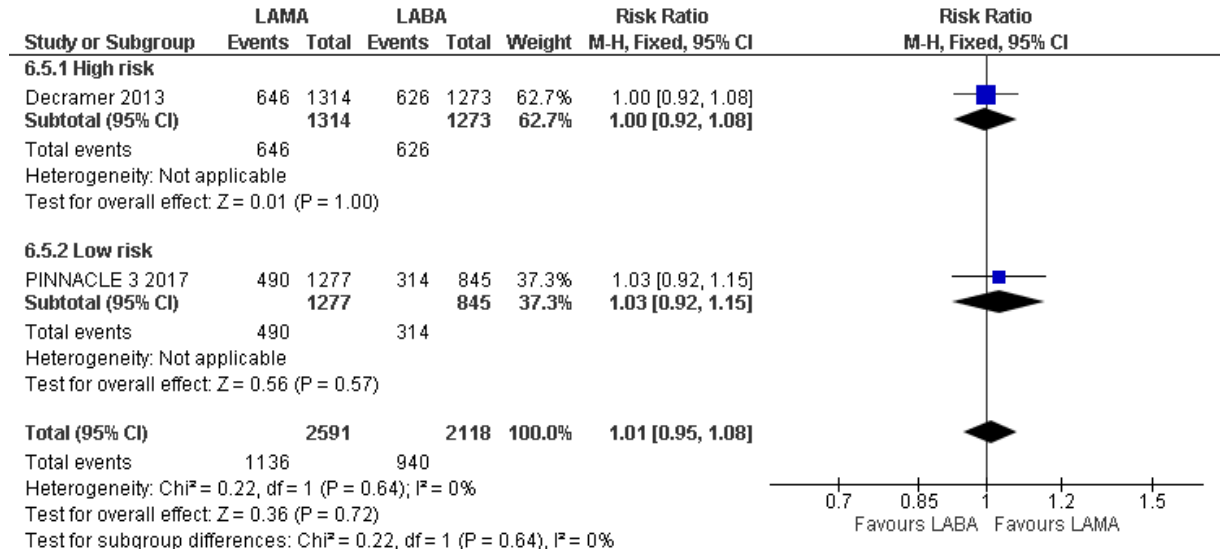
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months



Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ) at 6 months



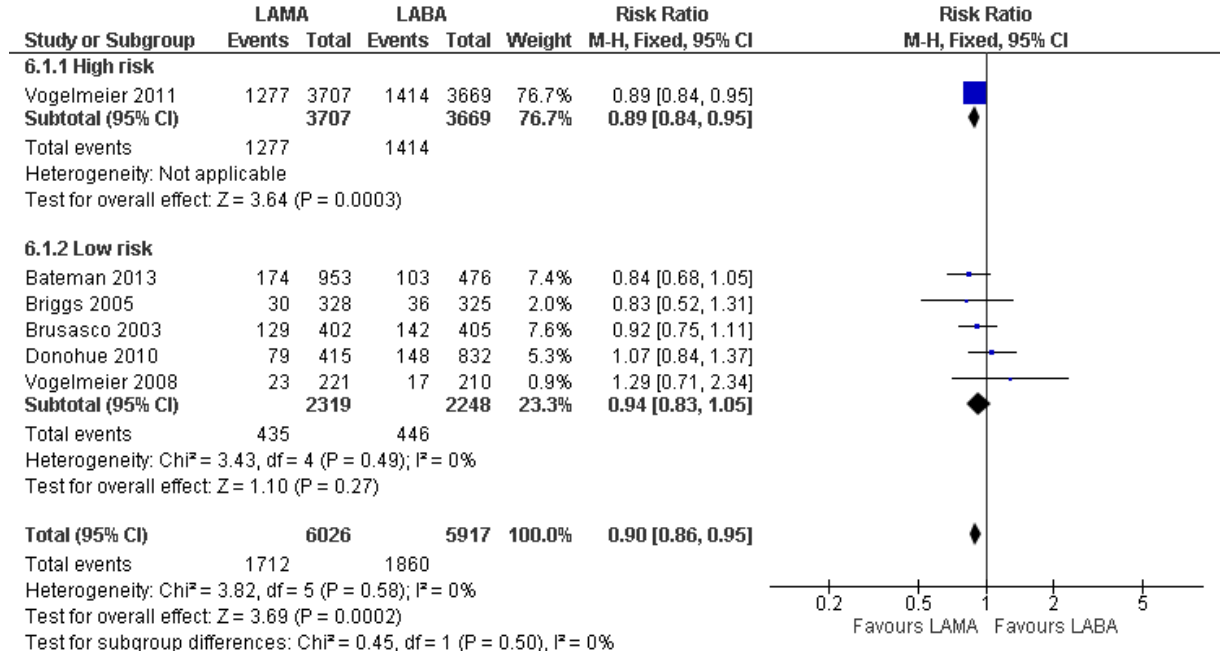
1 ***People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months***



2

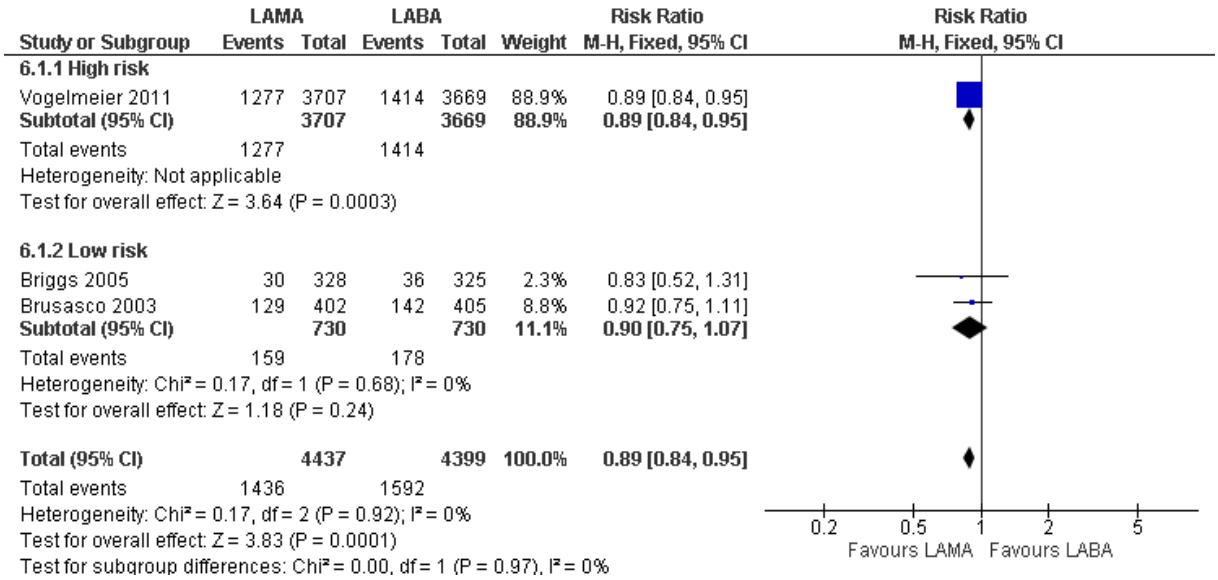
3

4 ***People with ≥ 1 moderate to severe exacerbation***

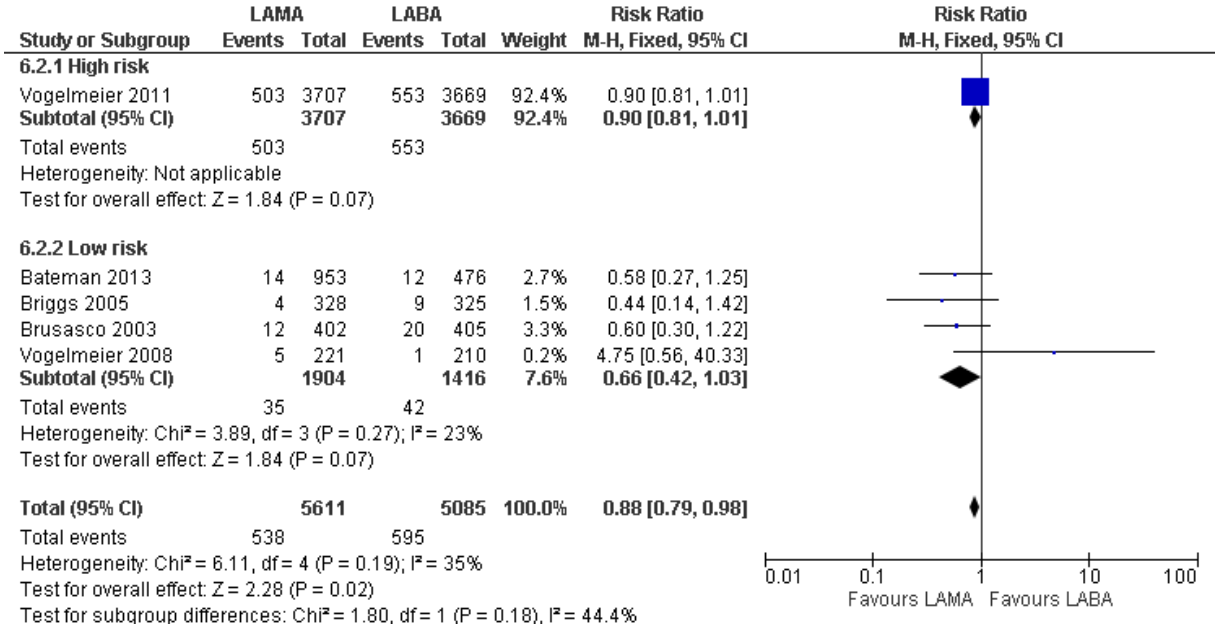


5

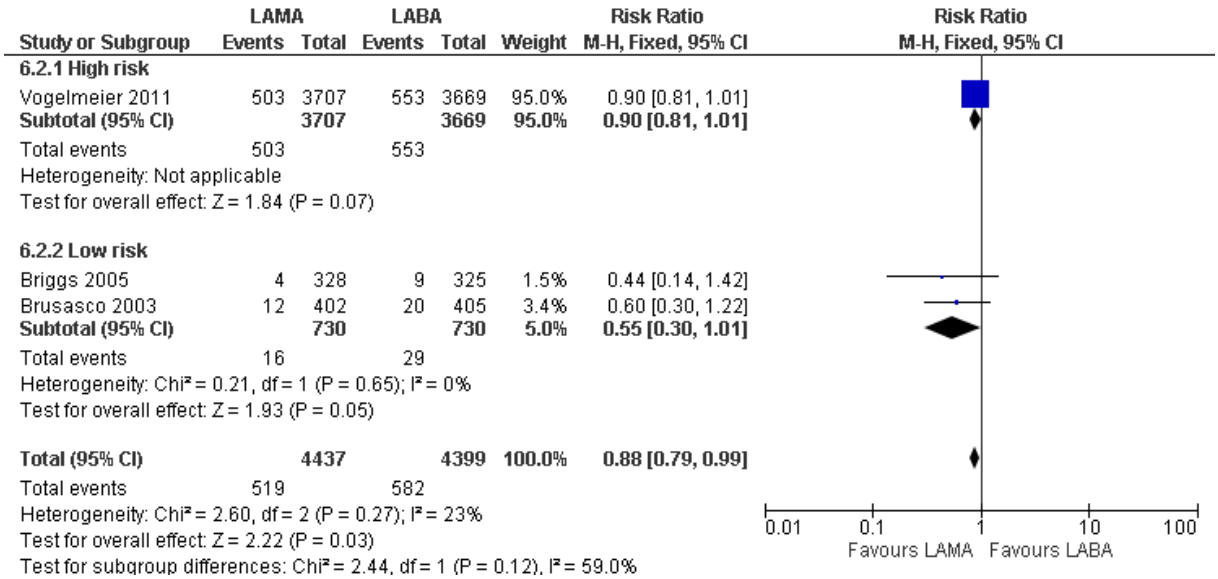
Sensitivity analysis: people with ≥ 1 moderate to severe exacerbation



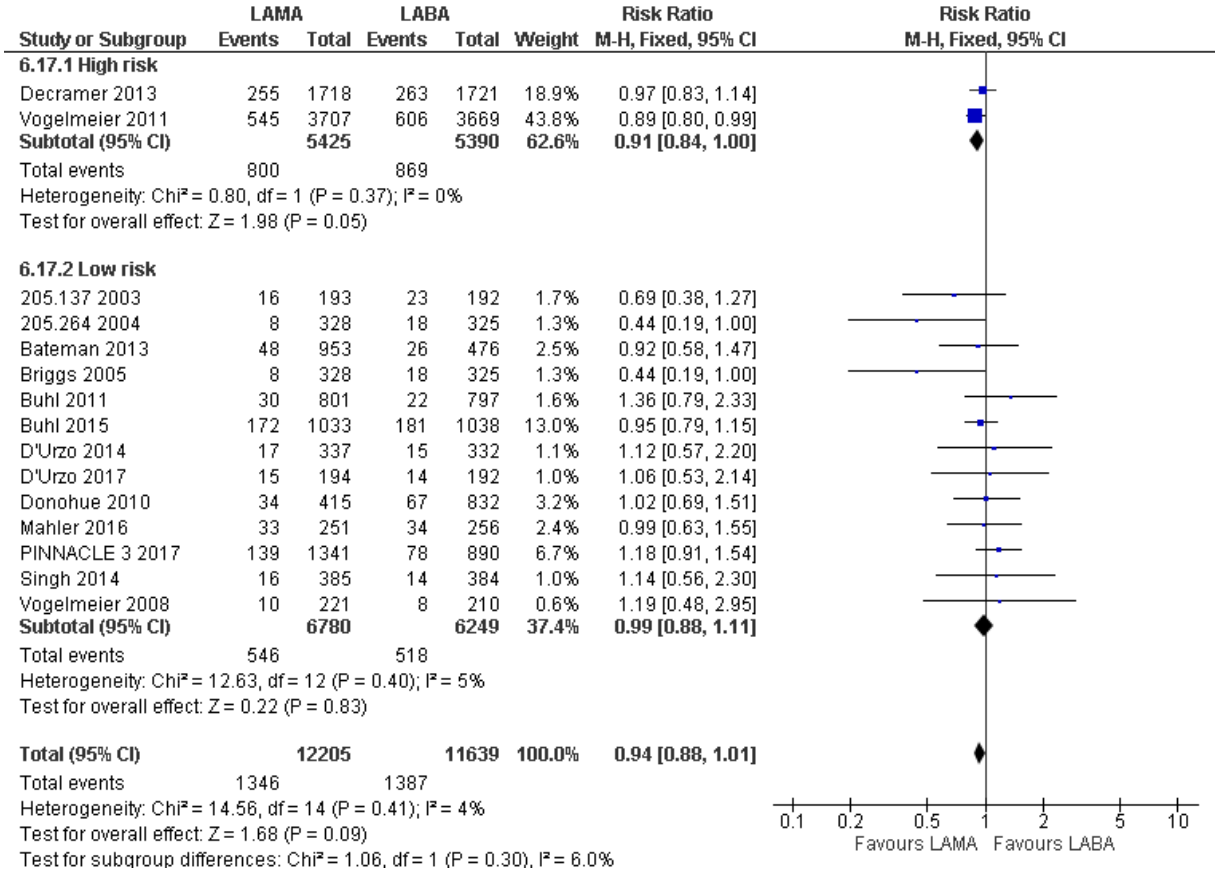
People with ≥ 1 severe exacerbation requiring hospitalisation



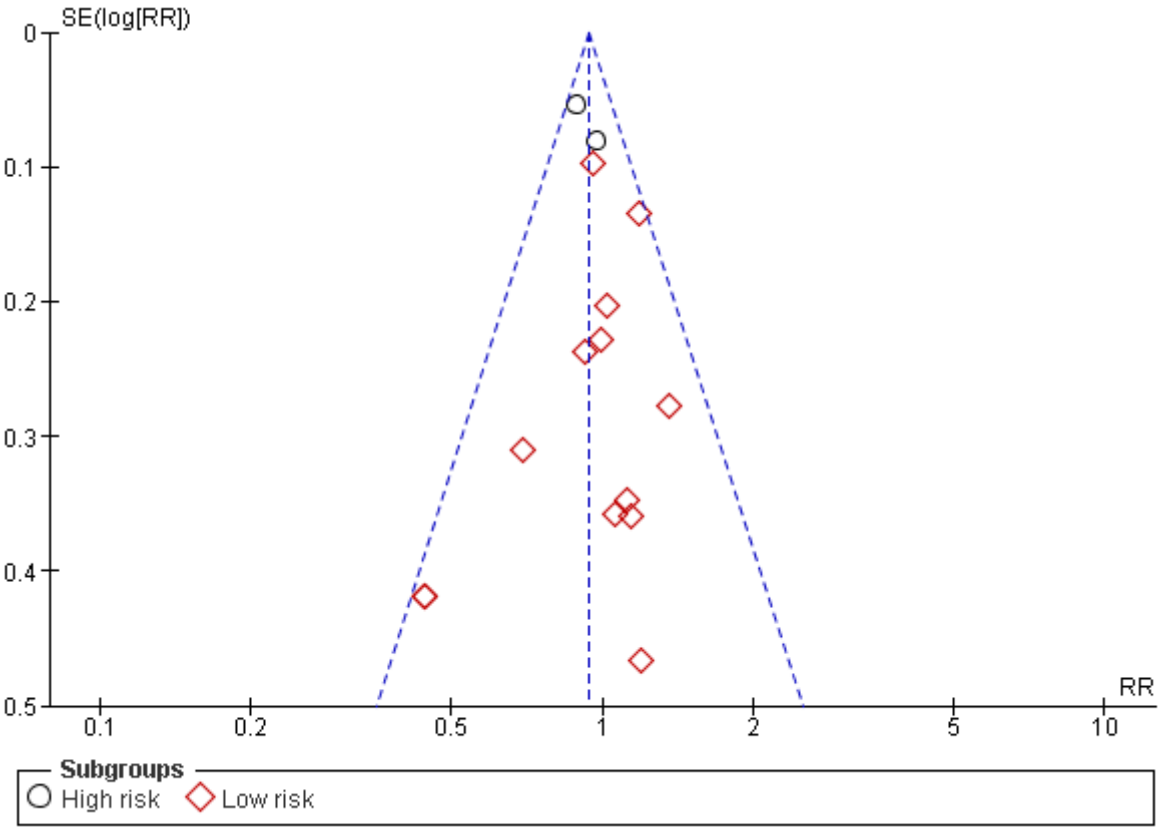
Sensitivity analysis: people with ≥ 1 severe exacerbation



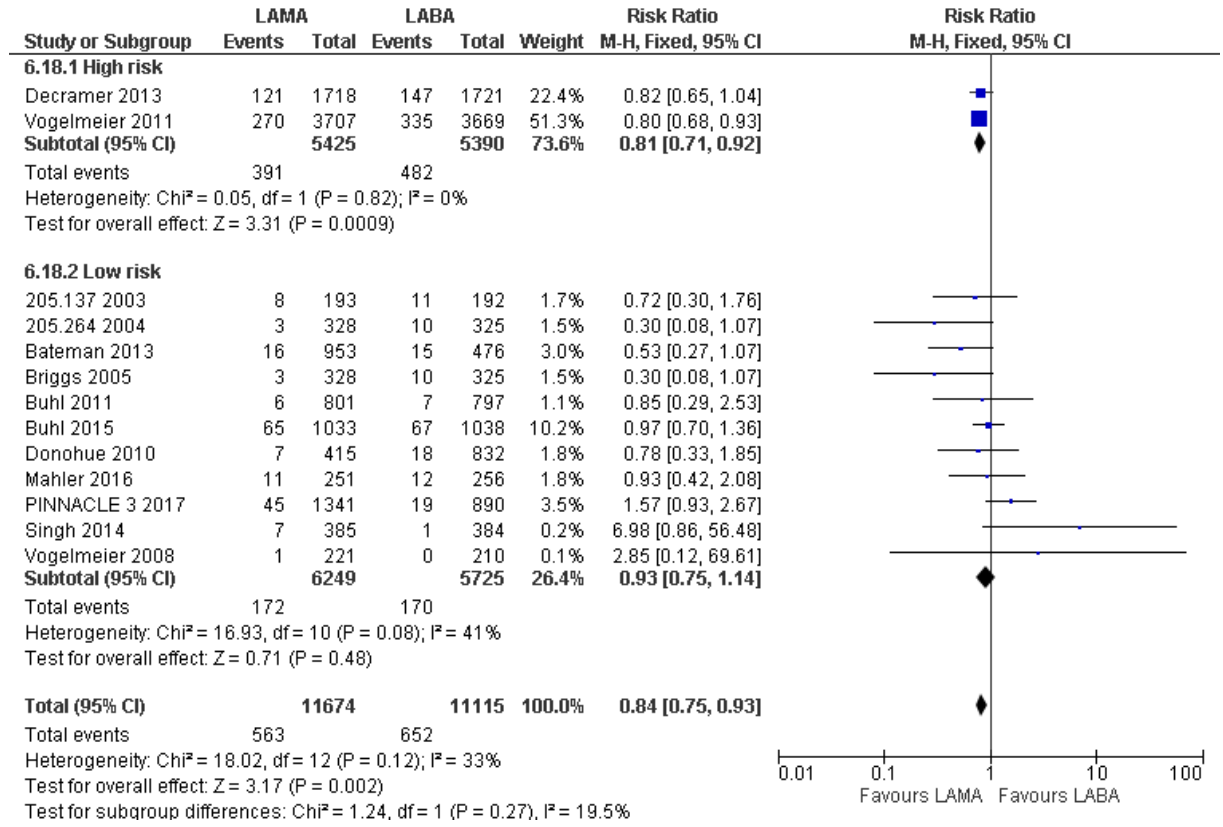
People with ≥ 1 Serious Adverse Event (SAE)



Publication bias assessment: funnel plot for SAEs

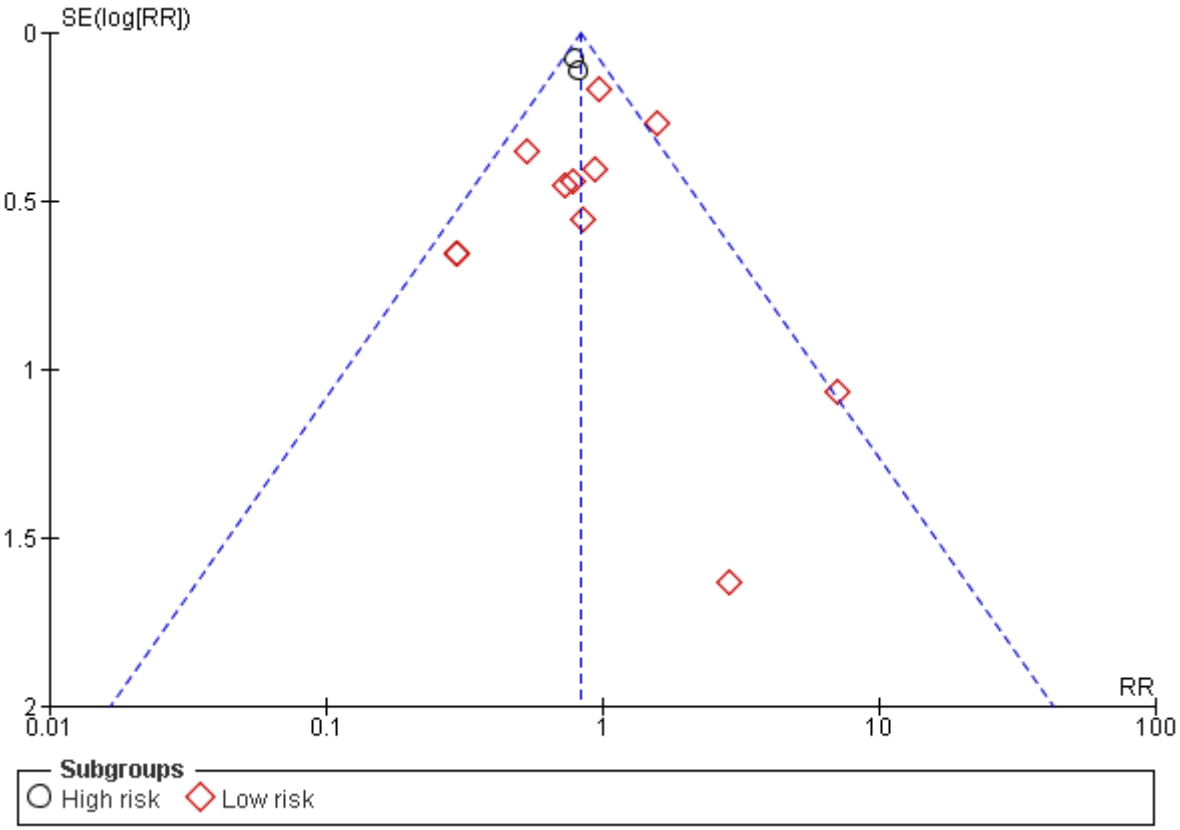


1 ***People with ≥ 1 COPD SAE***

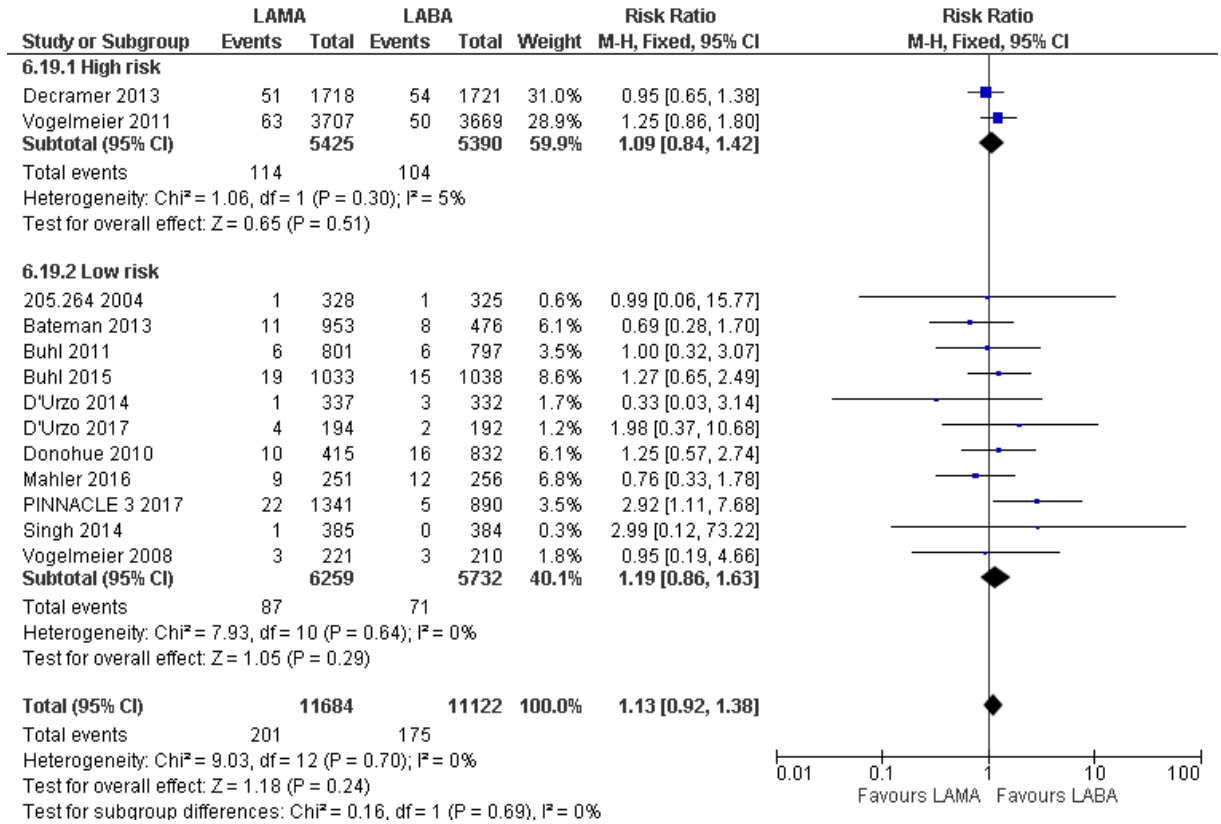


2

Publication bias assessment: funnel plot for COPD SAEs

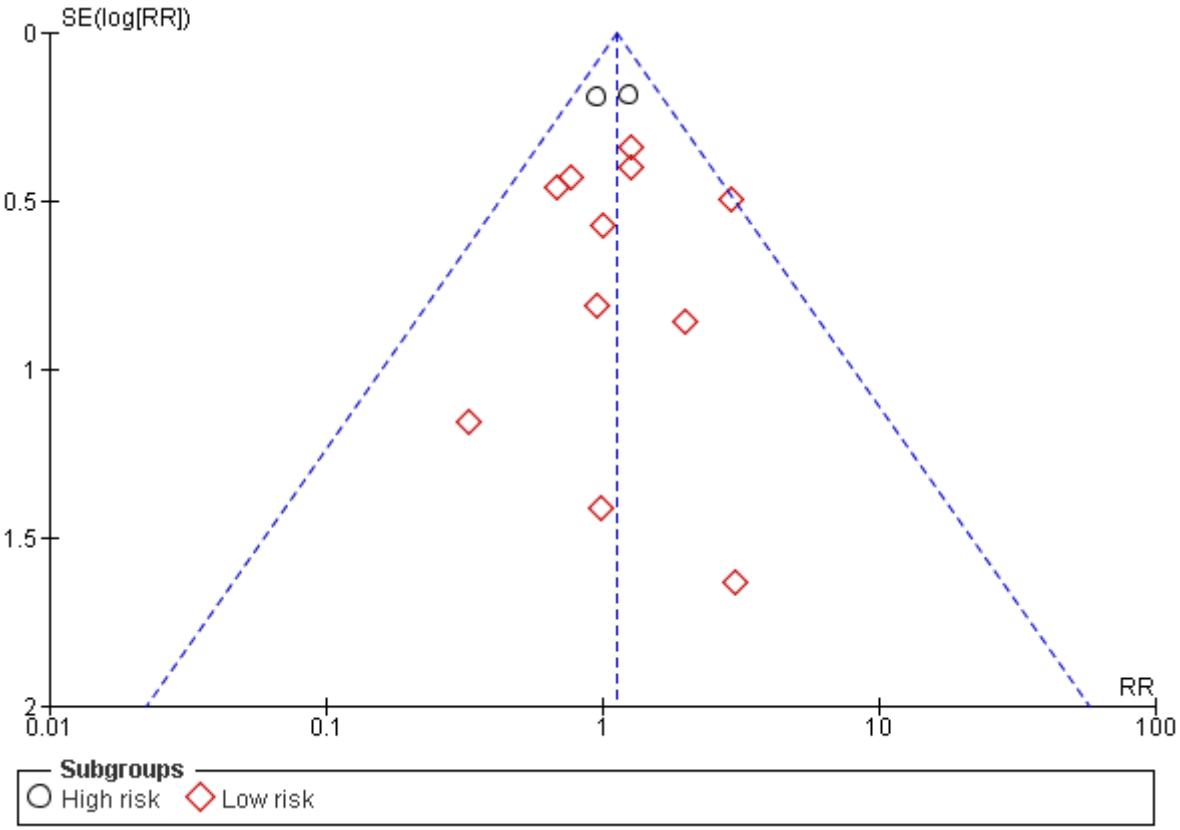


1 ***People with ≥ 1 cardiac SAE***

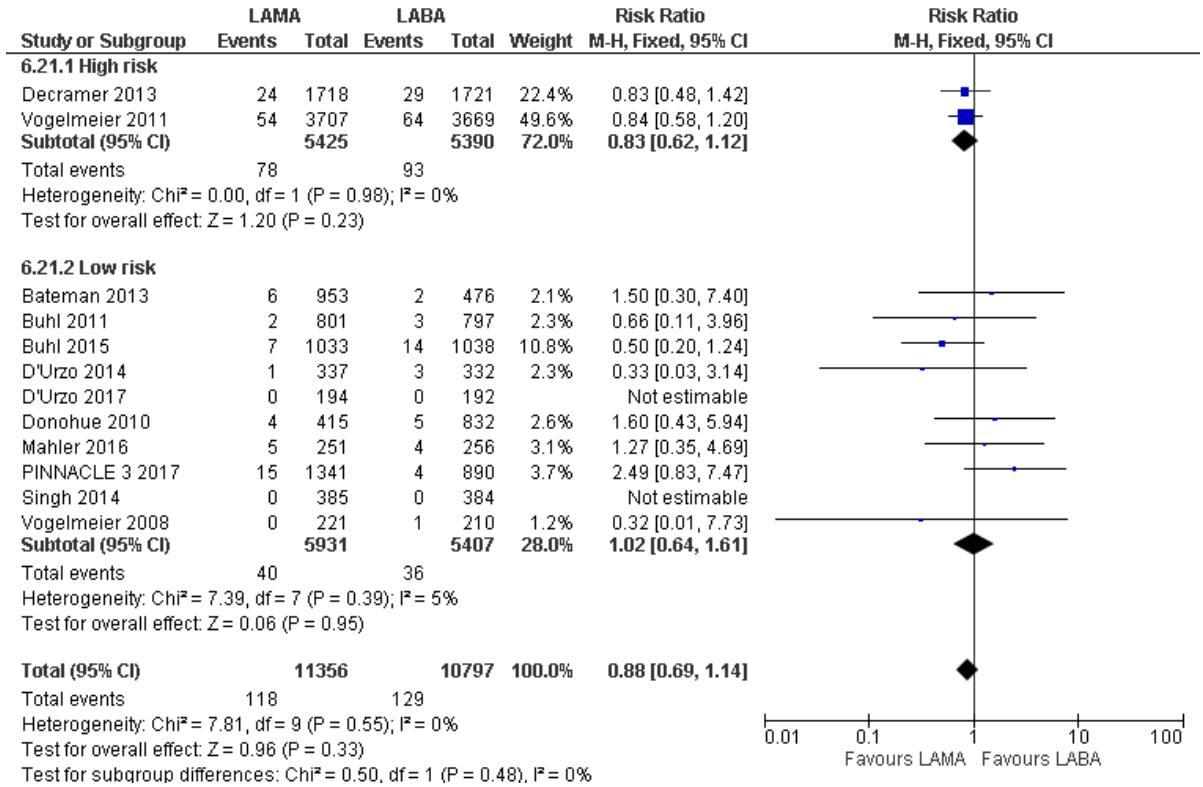


2

Publication bias assessment: funnel plot for cardiac SAEs

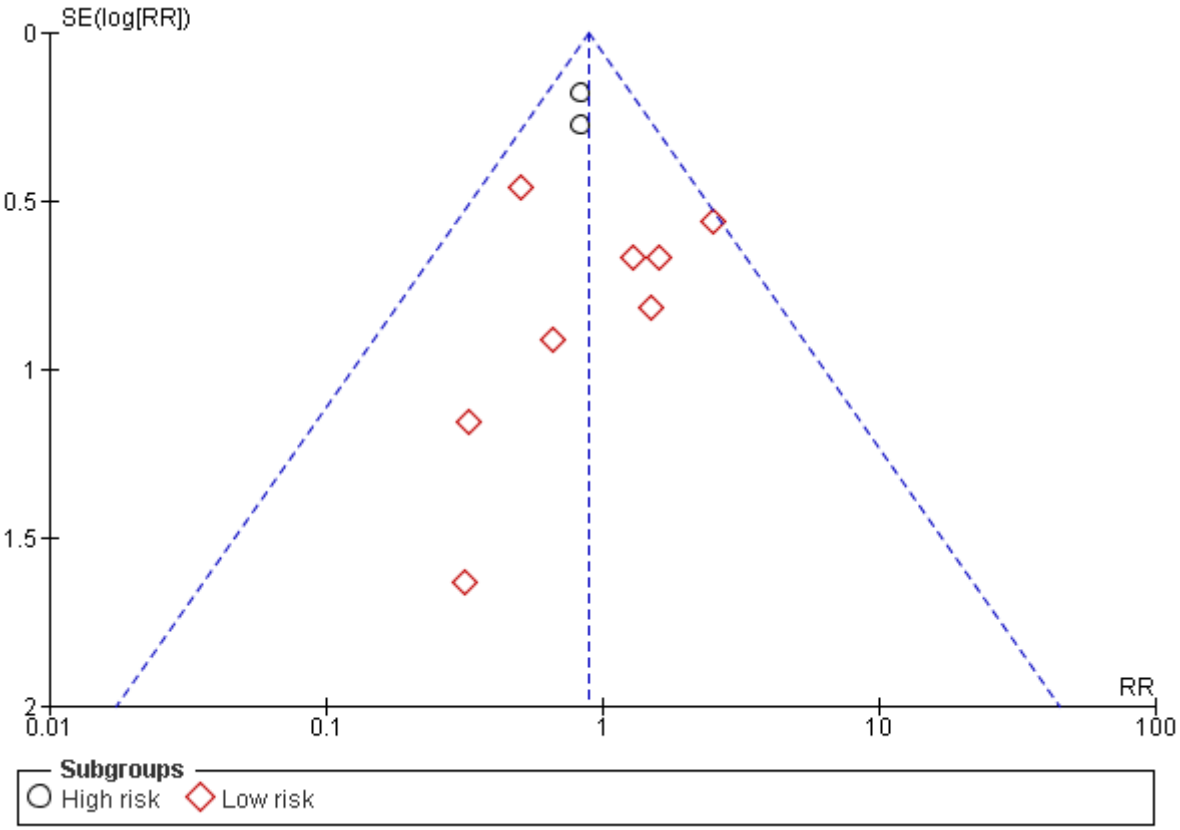


1 ***People with ≥ 1 session of pneumonia***

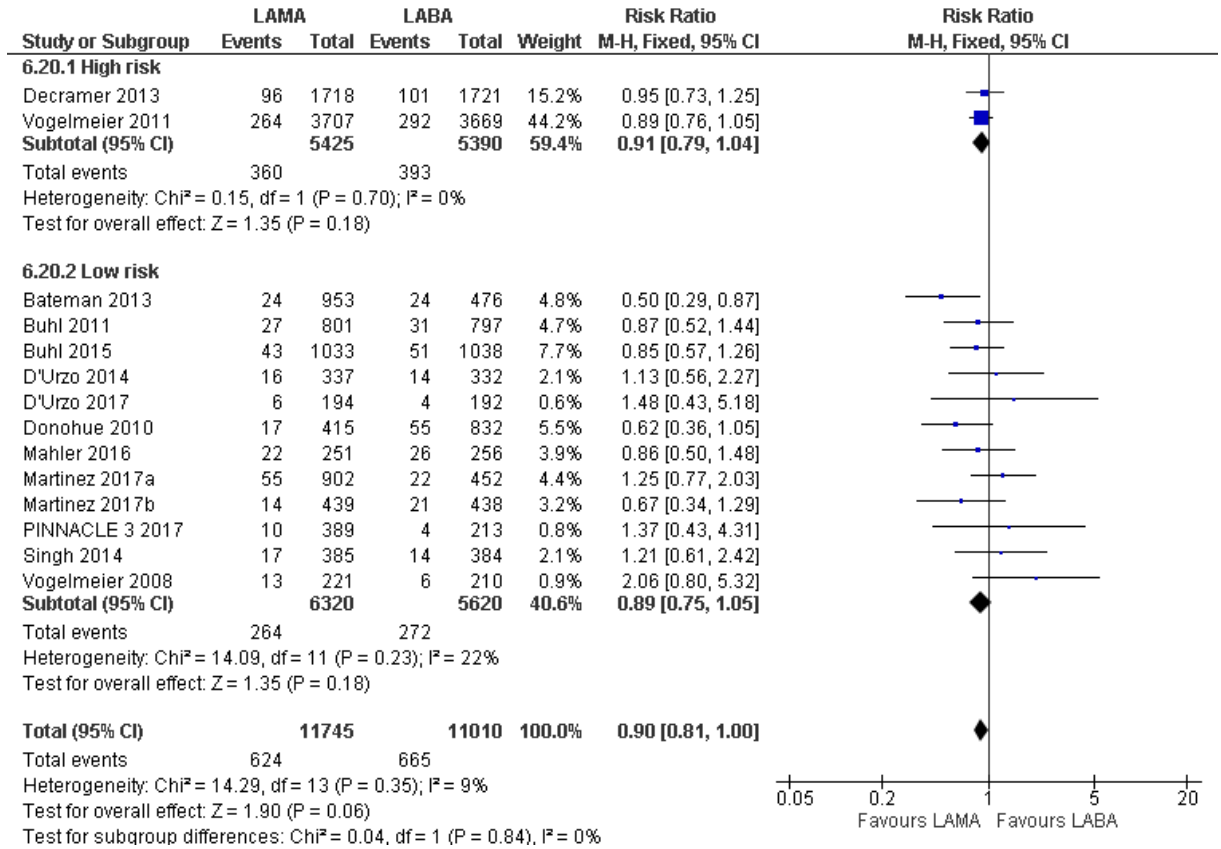


2

Publication bias assessment: funnel plot for pneumonia

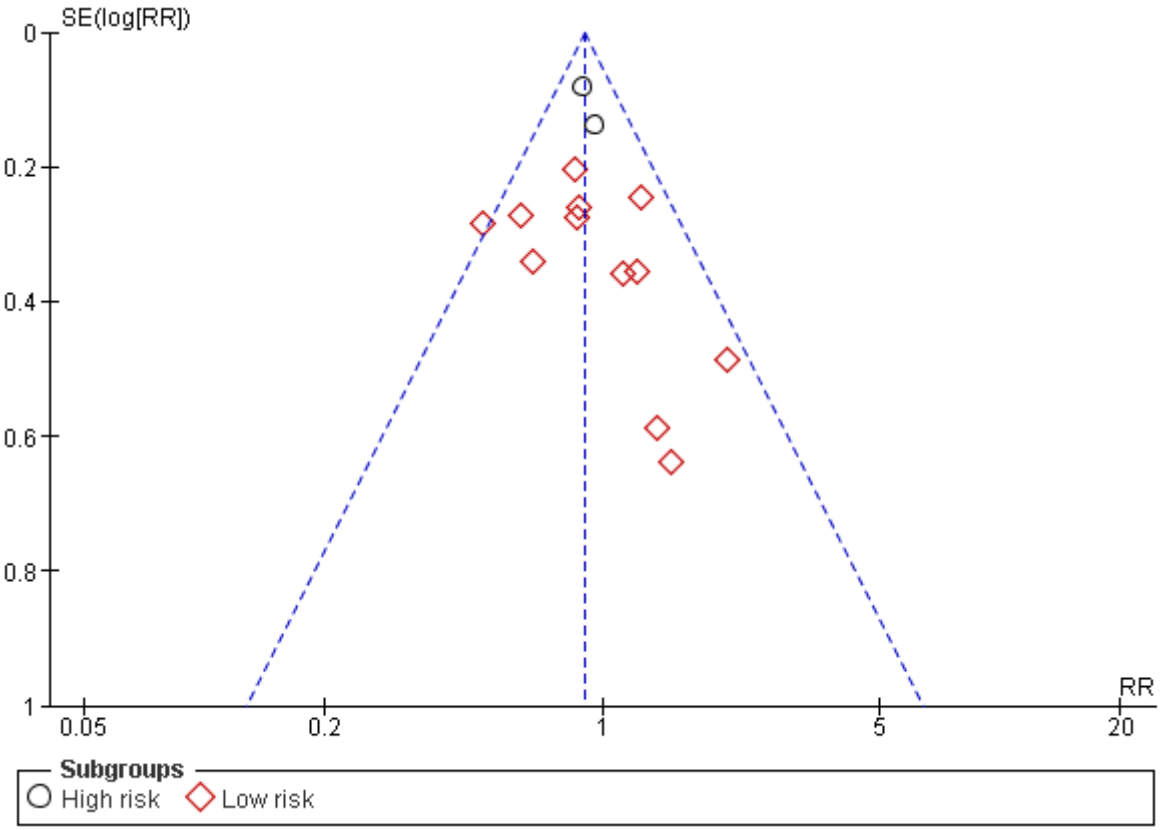


1 ***Drop-outs due to adverse events***



2

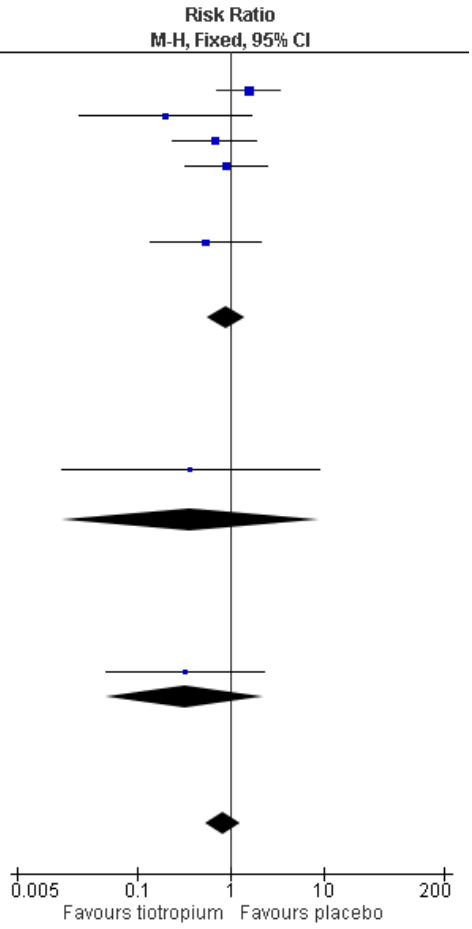
Publication bias assessment: funnel plot for drop-outs due to adverse events



1 LAMA monotherapy

2 Tiotropium (18 micrograms or 5 micrograms in total) versus placebo

3 *All-cause mortality (including ICS subgroup analysis)*



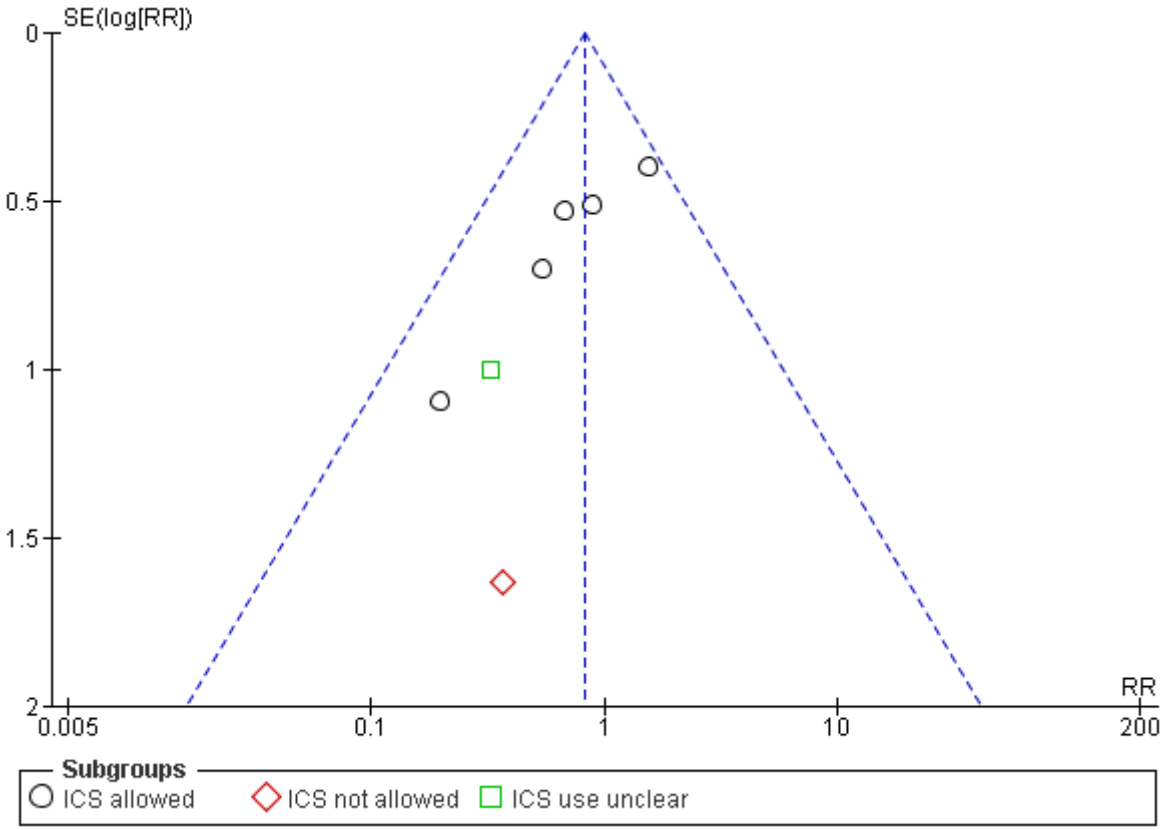
Study or Subgroup	Tiotropium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 ICS allowed						
Bateman 2010b (1)	16	670	10	653	24.3%	1.56 [0.71, 3.41]
Brusasco 2003	1	402	5	400	12.0%	0.20 [0.02, 1.70]
Casaburi 2002	7	550	7	371	20.1%	0.67 [0.24, 1.91]
Dusser 2006	7	500	8	510	19.0%	0.89 [0.33, 2.44]
Singh 2015a (2)	0	203	0	204		Not estimable
Singh 2015a (3)	0	203	0	202		Not estimable
Tonnel 2008	3	266	6	288	13.8%	0.54 [0.14, 2.14]
Verkindre 2006	0	46	0	54		Not estimable
Voshaar 2008 (4)	0	180	0	181		Not estimable
Subtotal (95% CI)		**3020**		**2863**	**89.3%**	**0.88 [0.55, 1.40]**
Total events	34		36			
Heterogeneity: Chi² = 4.64, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.1.2 ICS not allowed						
Johansson 2008 (5)	0	107	1	117	3.4%	0.36 [0.01, 8.85]
Troosters 2014 (6)	0	238	0	291		Not estimable
Subtotal (95% CI)		**345**		**408**	**3.4%**	**0.36 [0.01, 8.85]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
1.1.3 ICS use unclear						
Beeh 2006	2	1236	2	403	7.2%	0.33 [0.05, 2.31]
Subtotal (95% CI)		**1236**		**403**	**7.2%**	**0.33 [0.05, 2.31]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**4601**		**3674**	**100.0%**	**0.82 [0.53, 1.28]**
Total events	36		39			
Heterogeneity: Chi² = 5.88, df = 6 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Chi² = 1.18, df = 2 (P = 0.55), I² = 0%						

Footnotes

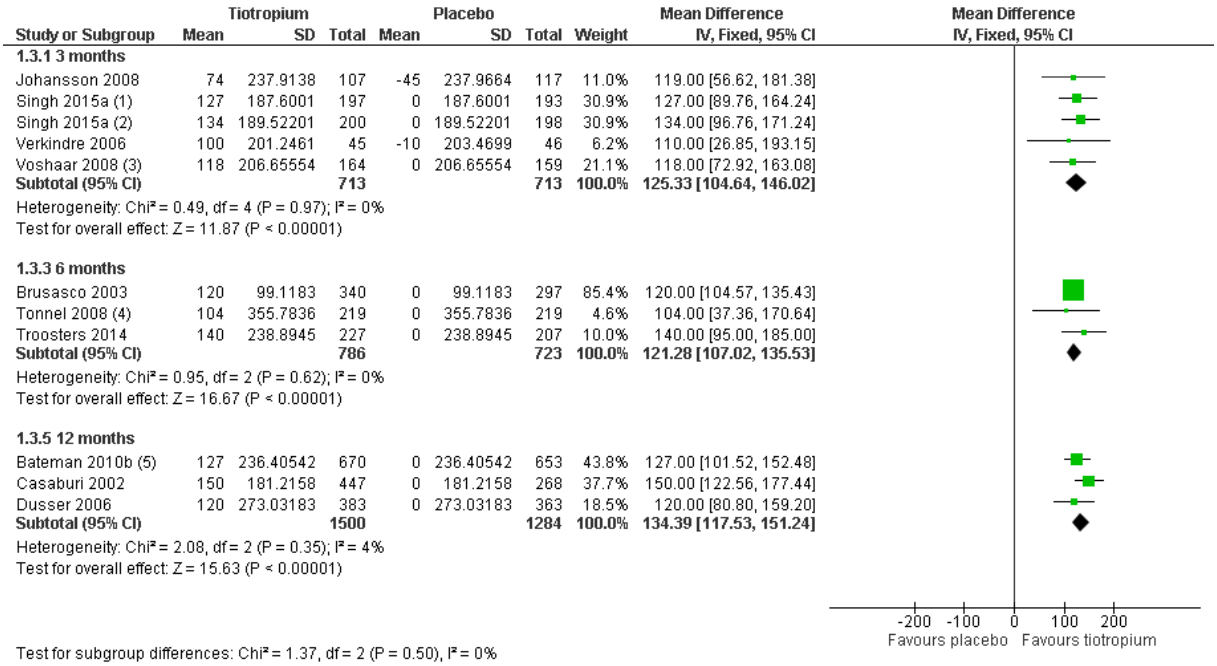
(1) Data used for 5mcg total dose only
(2) OTEMTO 1
(3) OTEMTO 2
(4) Data used for 5mcg total dose only
(5) <2% of participants were taking pulmonary medication at baseline
(6) Participants were maintenance medication naive at baseline.

4

Publication bias assessment: all-cause mortality

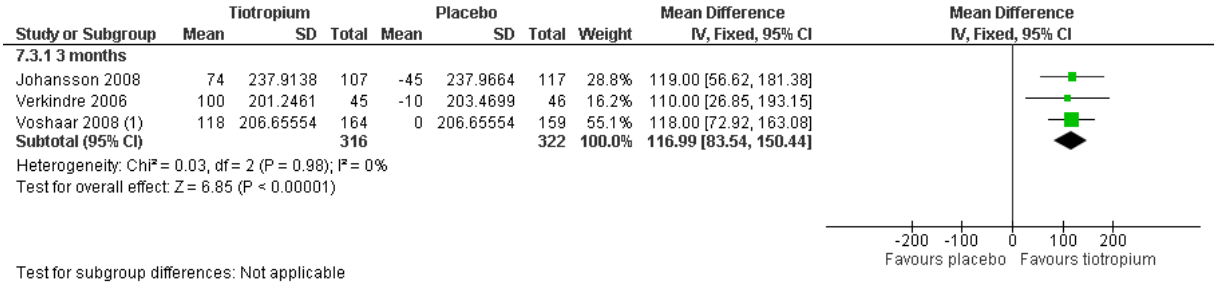


1 ***Change in Trough FEV1 (ml)***



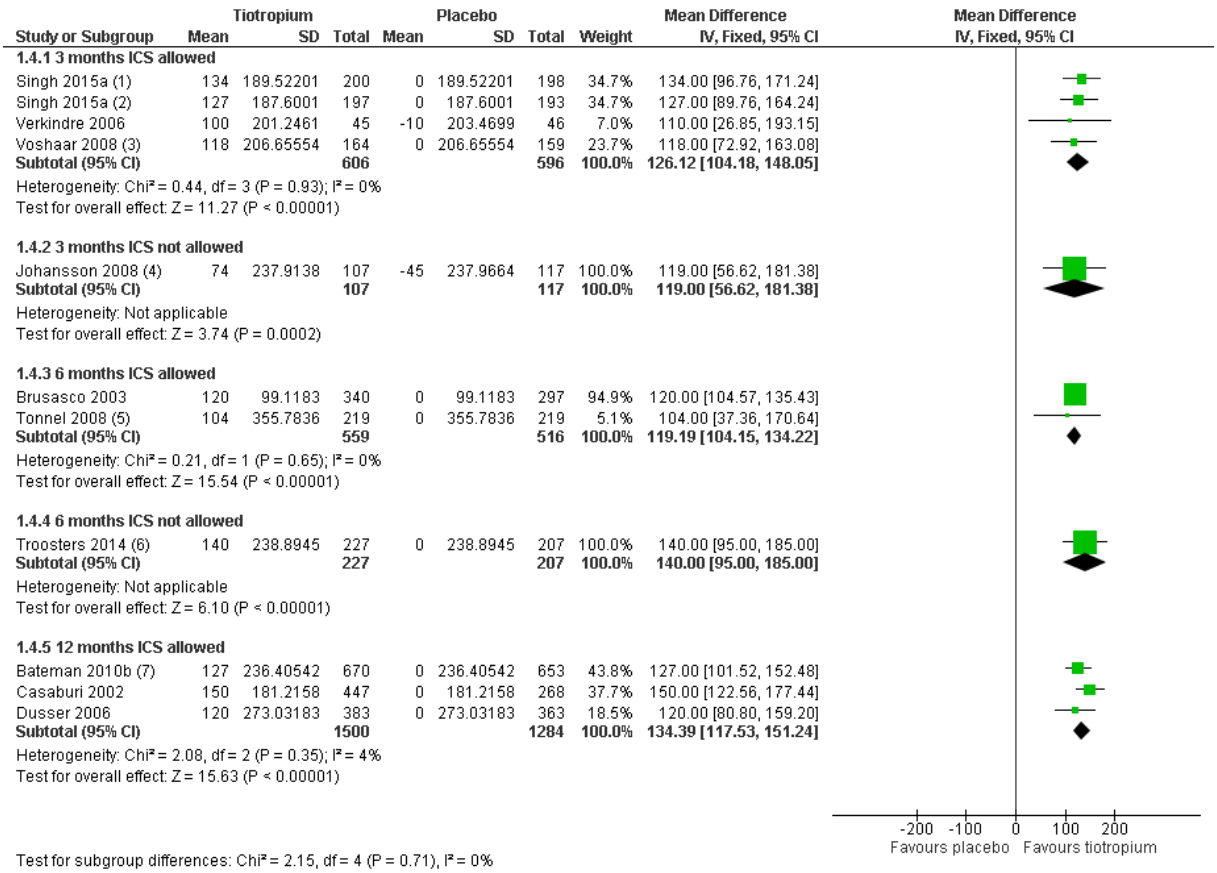
2

3 *Sensitivity analysis: trough FEV1 at 3 months*



4

ICS subgroup analysis: change in Trough FEV1 (ml)

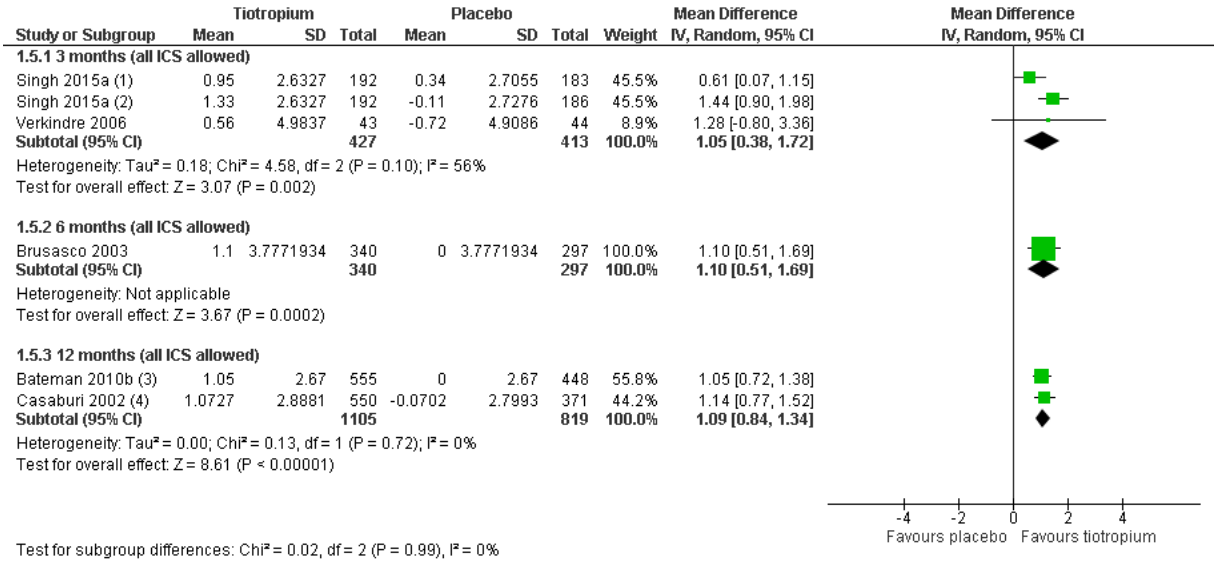


Test for subgroup differences: Chi² = 2.15, df = 4 (P = 0.71), I² = 0%

Footnotes

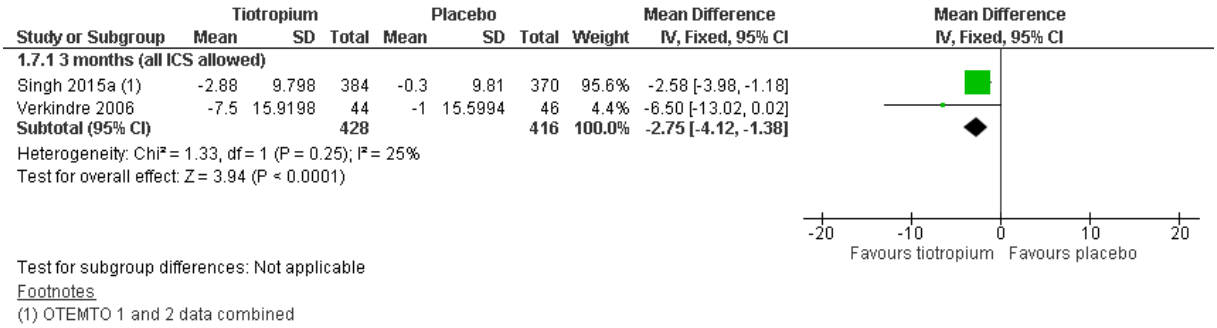
(1) OTEMTO 1
(2) OTEMTO 2
(3) Data used for 5mcg total dose only
(4) <2% of participants were taking pulmonary medication at baseline
(5) 9 months study duration
(6) Participants were maintenance medication naive at baseline.
(7) Data used for 5mcg total dose only

1 ***Transition Dyspnoea Index (TDI) focal score (all studies allowed ICS usage)***



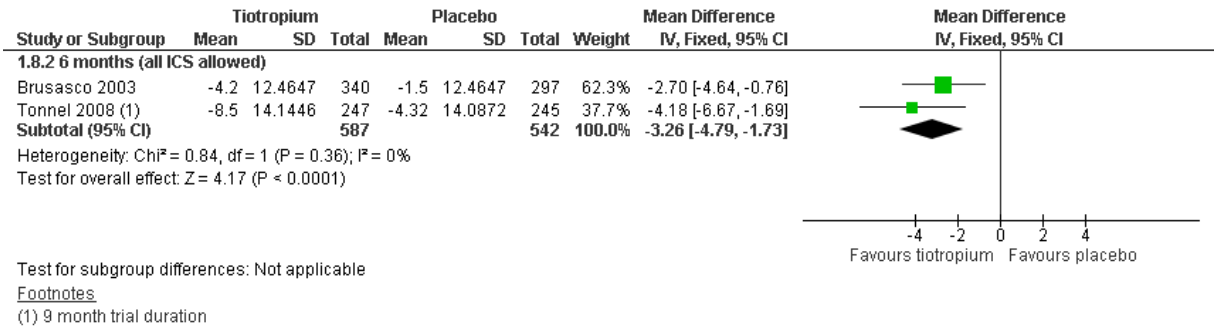
2

3 ***St. George's Respiratory Questionnaire (SGRQ), total score at 3 months (all studies***
4 ***allowed ICS usage)***



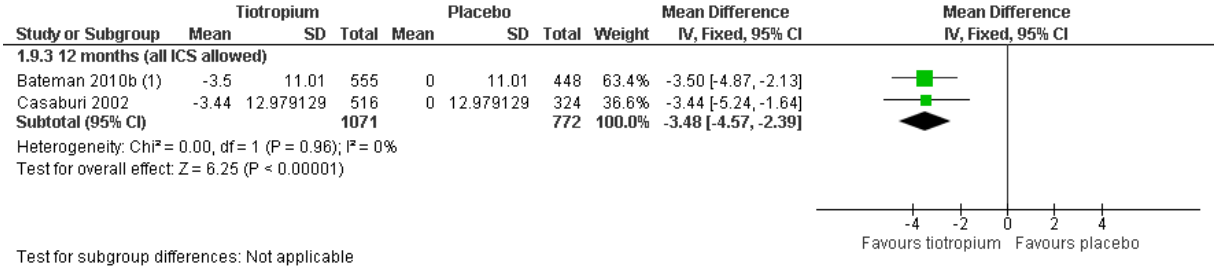
5

6 ***St. George's Respiratory Questionnaire (SGRQ), total score at 6 months (all studies***
7 ***allowed ICS usage)***

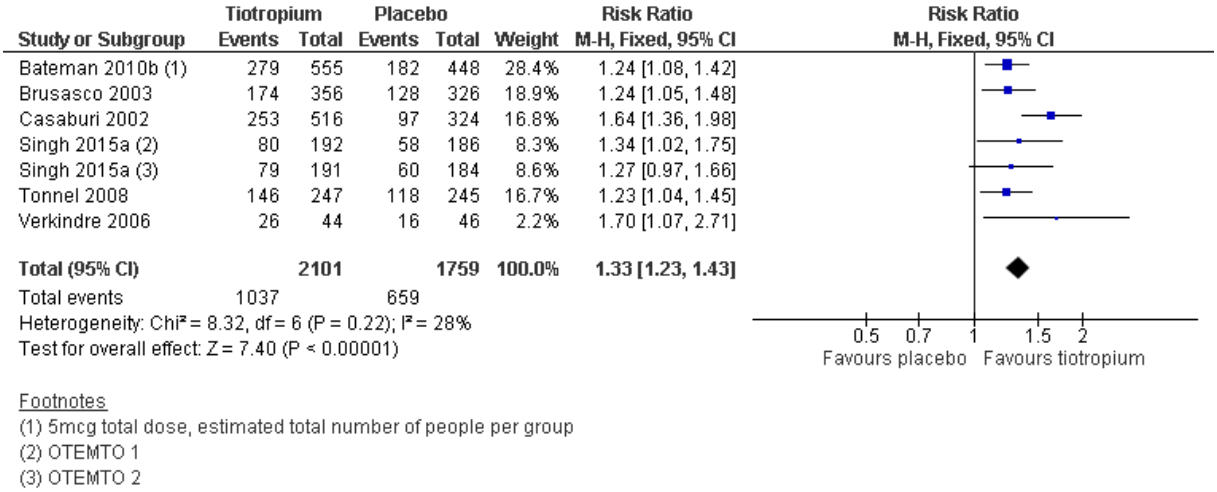


8

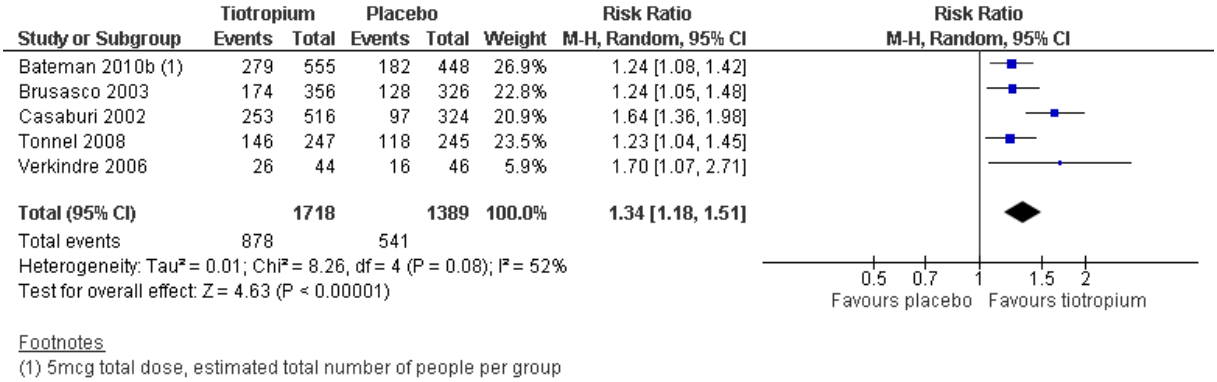
St. George's Respiratory Questionnaire (SGRQ), total score at 12 months (all studies allowed ICS usage)



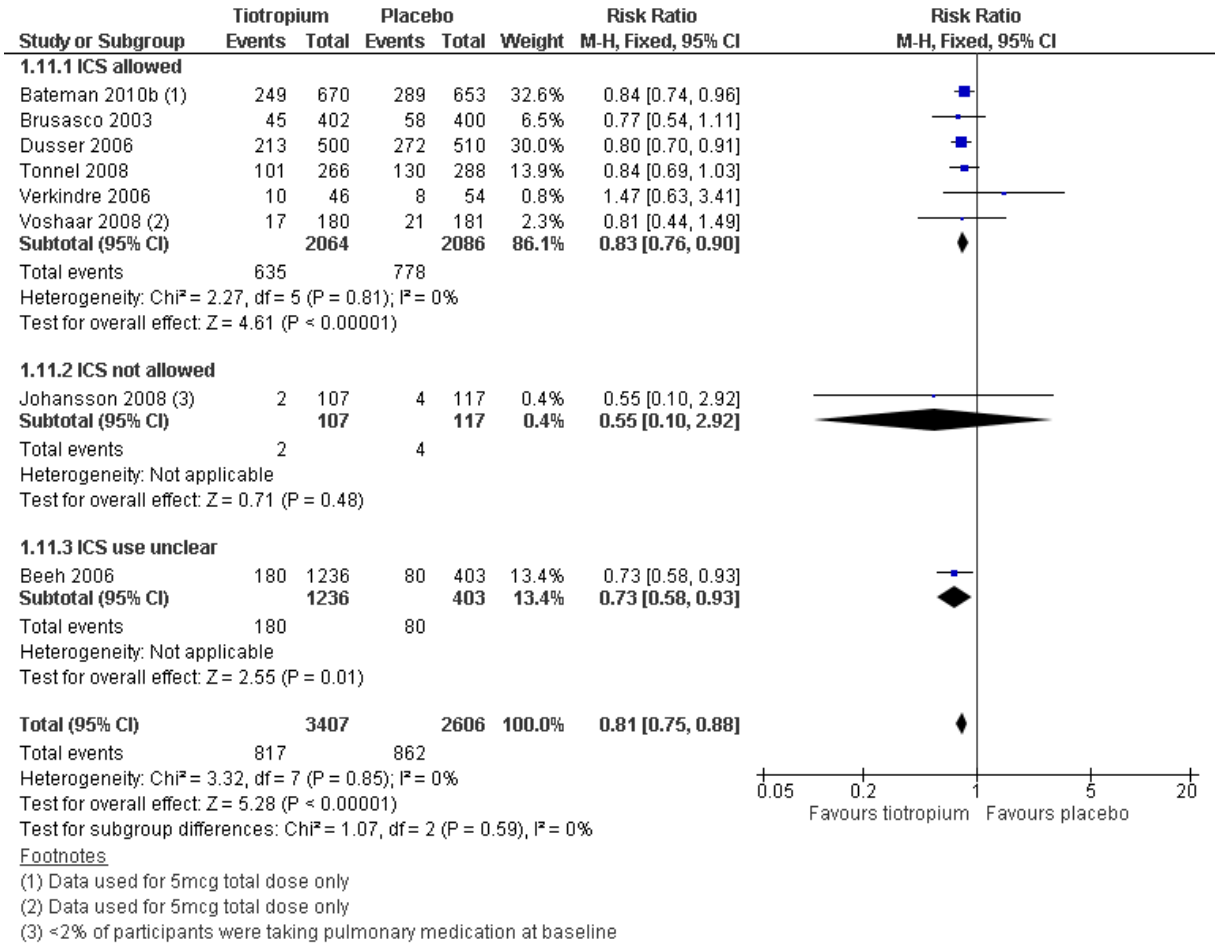
People with ≥ 4 units improvement in quality of life (SGRQ) (all studies allowed ICS usage)



Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ)

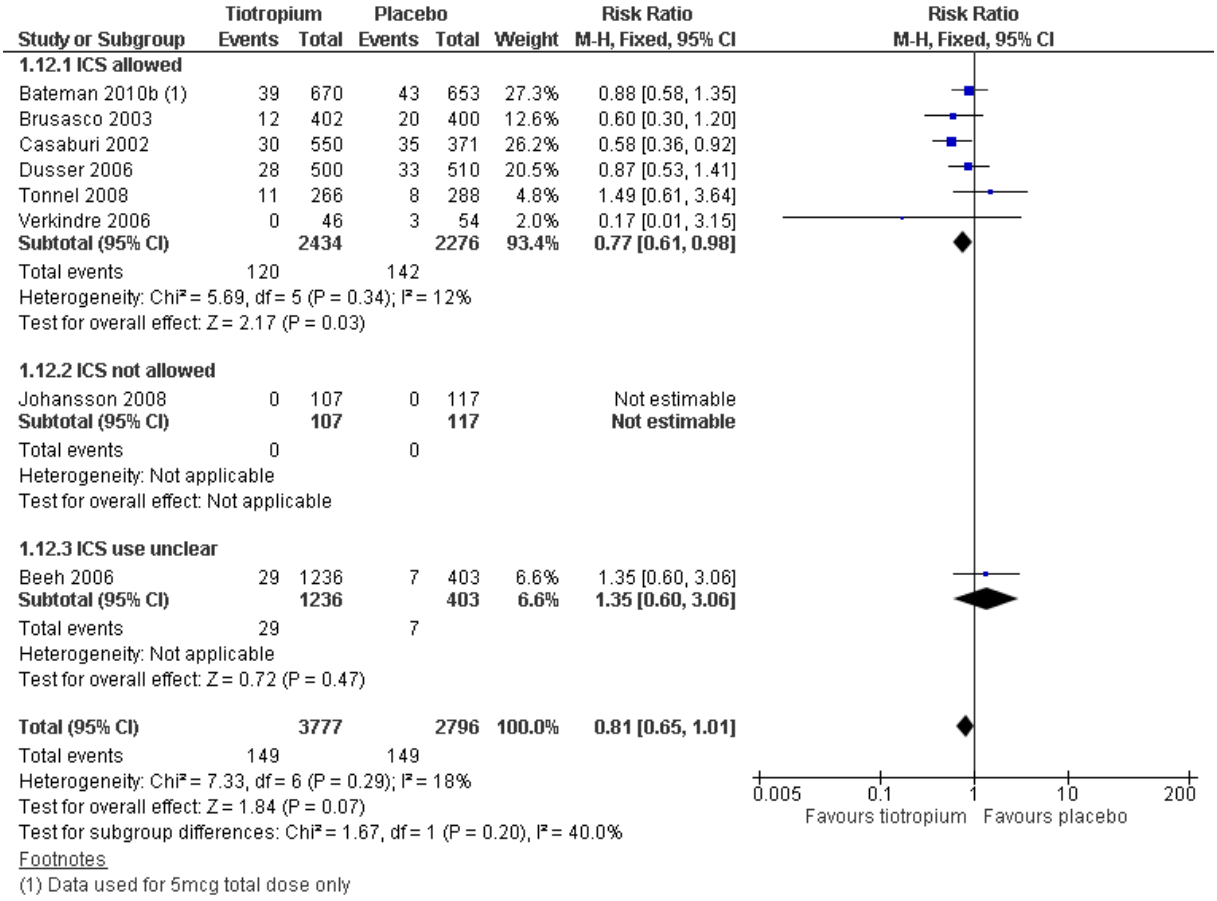


1 ***People with ≥ 1 moderate to severe exacerbation (including ICS subgroup analysis)***

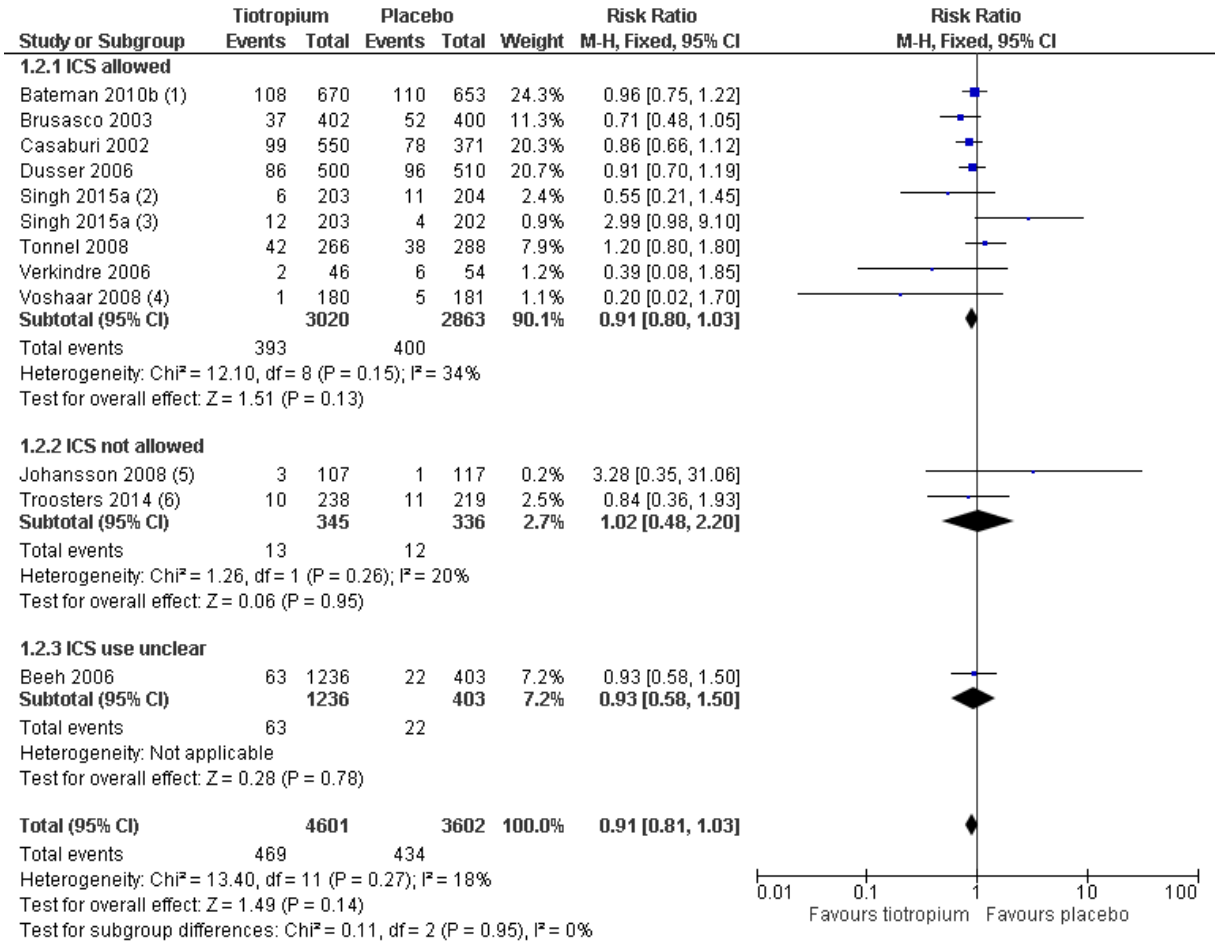


2

People with ≥ 1 severe exacerbation (requiring hospitalisation) (including ICS subgroup analysis)



1 ***People with ≥ 1 Serious Adverse Event (SAE) (including ICS subgroup analysis)***

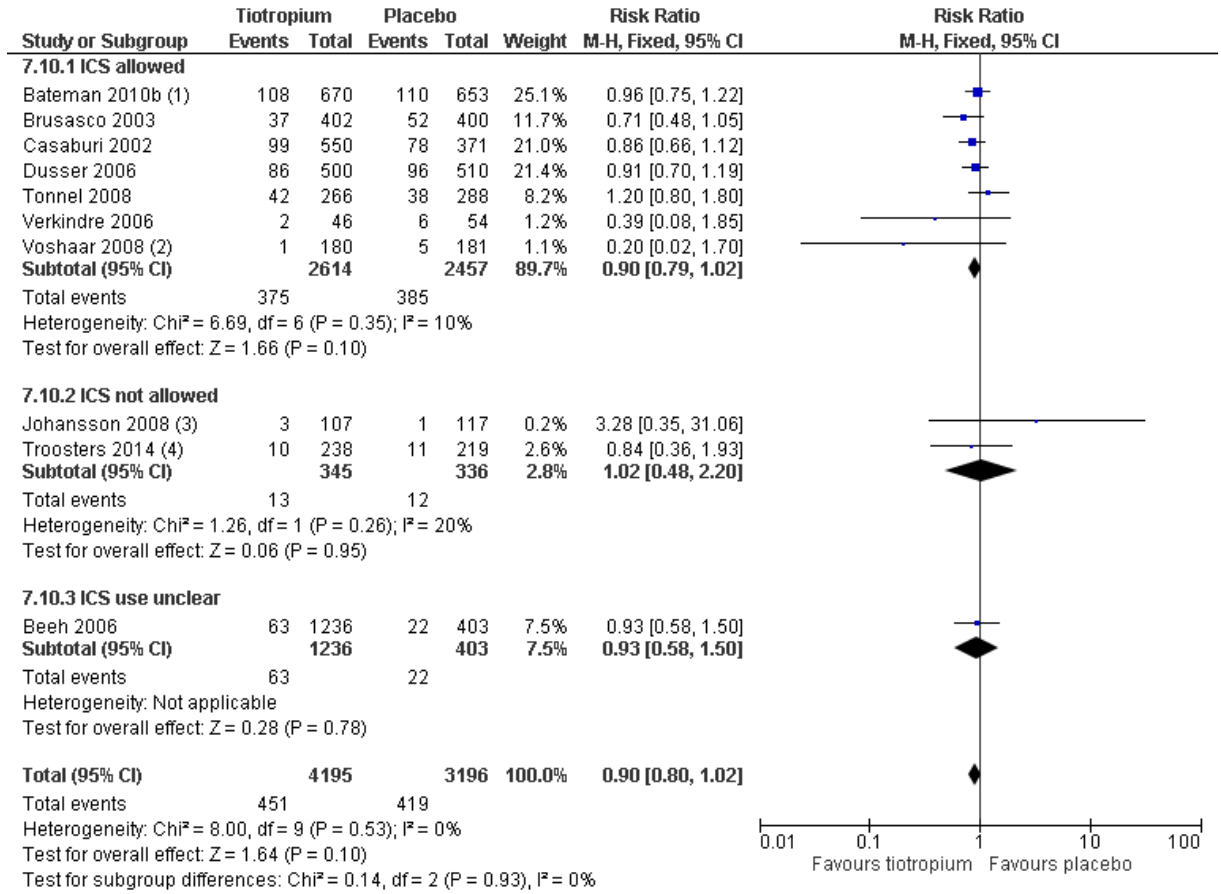


Footnotes

(1) Data used for 5mcg total dose only
(2) OTEMTO 1
(3) OTEMTO 2
(4) Data used for 5mcg total dose only
(5) <2% of participants were taking pulmonary medication at baseline
(6) Participants were maintenance medication naive at baseline.

2

Sensitivity analysis:SAEs



Footnotes

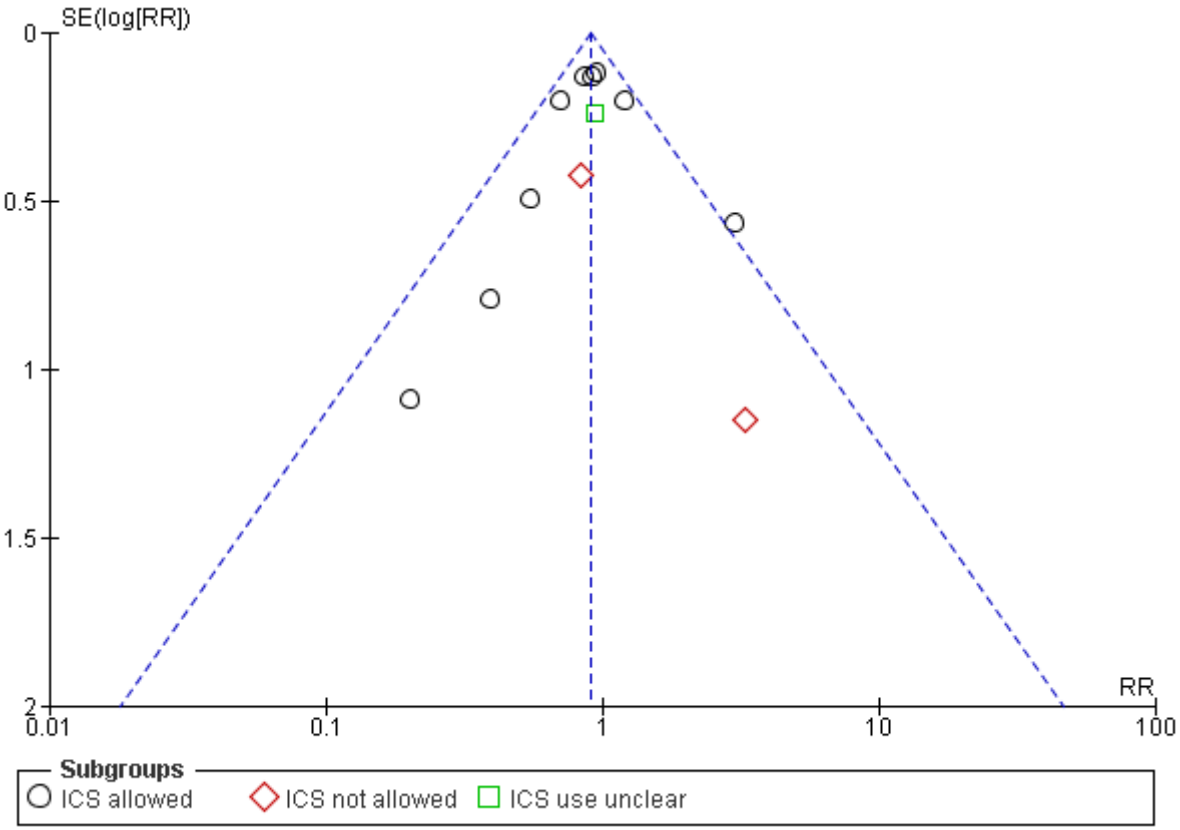
(1) Data used for 5mcg total dose only

(2) Data used for 5mcg total dose only

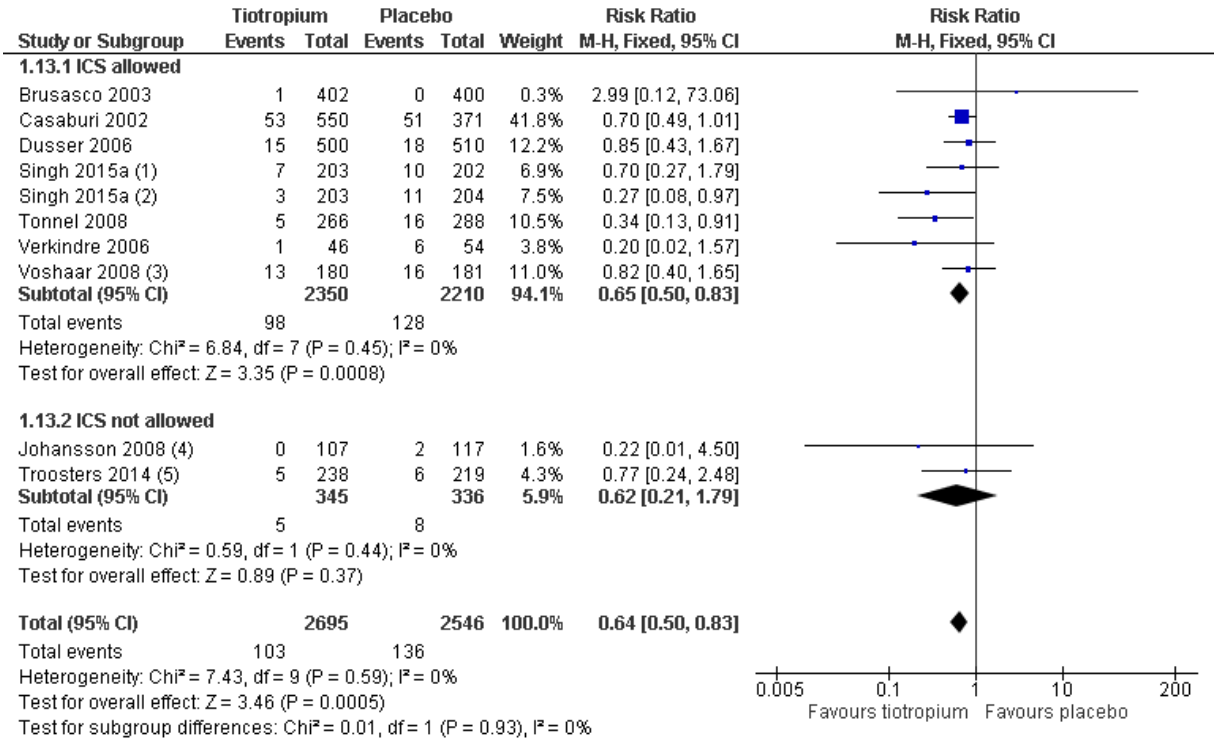
(3) <2% of participants were taking pulmonary medication at baseline

(4) Participants were maintenance medication naive at baseline.

Publication bias assessment: serious adverse events



1 ***Drop-outs due to adverse events (including ICS subgroup analysis)***



Footnotes

(1) OTEMTO 2

(2) OTEMTO 1

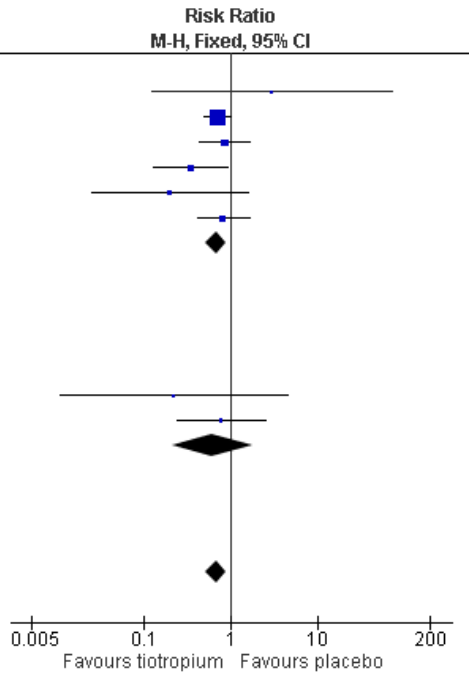
(3) Data used for 5mcg total dose only

(4) <2% of participants were taking pulmonary medication at baseline

(5) Participants were maintenance medication naive at baseline.

2

Sensitivity analysis: dropouts due to adverse events



Study or Subgroup	Tiotropium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.13.1 ICS allowed						
Brusasco 2003	1	402	0	400	0.4%	2.99 [0.12, 73.06]
Casaburi 2002	53	550	51	371	48.8%	0.70 [0.49, 1.01]
Dusser 2006	15	500	18	510	14.3%	0.85 [0.43, 1.67]
Tonnel 2008	5	266	16	288	12.3%	0.34 [0.13, 0.91]
Verkindre 2006	1	46	6	54	4.4%	0.20 [0.02, 1.57]
Voshaar 2008 (1)	13	180	16	181	12.8%	0.82 [0.40, 1.65]
Subtotal (95% CI)		**1944**		**1804**	**93.1%**	**0.68 [0.52, 0.89]**
Total events	88		107			
Heterogeneity: Chi² = 4.83, df = 5 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.80 (P = 0.005)						
7.13.2 ICS not allowed						
Johansson 2008 (2)	0	107	2	117	1.9%	0.22 [0.01, 4.50]
Troosters 2014 (3)	5	238	6	219	5.0%	0.77 [0.24, 2.48]
Subtotal (95% CI)		**345**		**336**	**6.9%**	**0.62 [0.21, 1.79]**
Total events	5		8			
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Total (95% CI)		**2289**		**2140**	**100.0%**	**0.67 [0.52, 0.88]**
Total events	93		115			
Heterogeneity: Chi² = 5.42, df = 7 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.94 (P = 0.003)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						

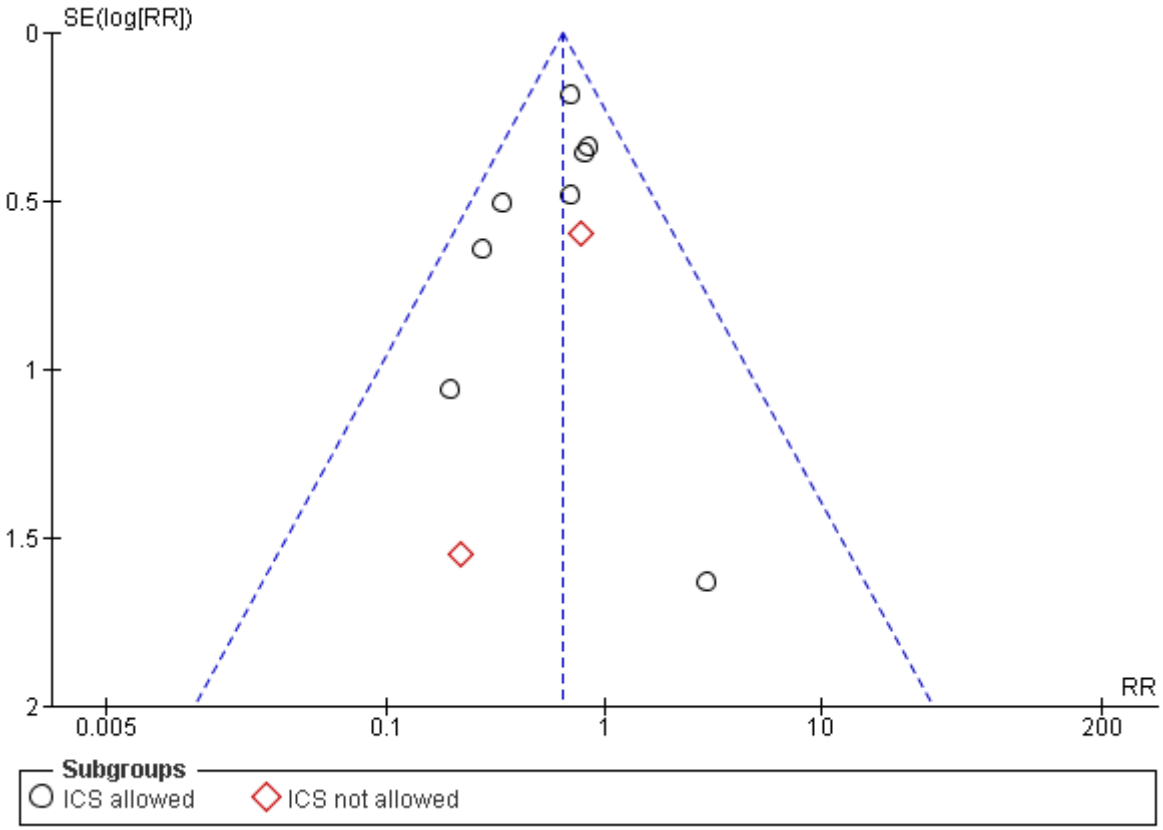
Footnotes

(1) Data used for 5mcg total dose only

(2) <2% of participants were taking pulmonary medication at baseline

(3) Participants were maintenance medication naive at baseline.

Publication bias assessment: drop-outs due to adverse events

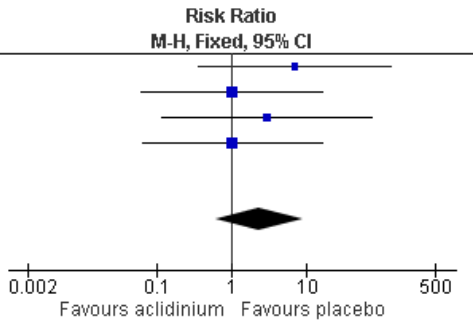


Aclidinium (400 micrograms twice daily) versus placebo

All-cause mortality

Study or Subgroup	Aclidinium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Urzo 2014b (1)	3	337	0	331	16.9%	6.88 [0.36, 132.60]
Jones 2012 (2)	1	269	1	273	33.2%	1.01 [0.06, 16.14]
Kerwin 2012b (3)	1	190	0	186	16.9%	2.94 [0.12, 71.64]
Rennard 2013 (4)	1	177	1	182	33.0%	1.03 [0.06, 16.31]
Singh 2014a (5)	0	385	0	194		Not estimable
Total (95% CI)		**1358**		**1166**	**100.0%**	**2.33 [0.60, 9.05]**
Total events	6		2			

Heterogeneity: Chi² = 1.22, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

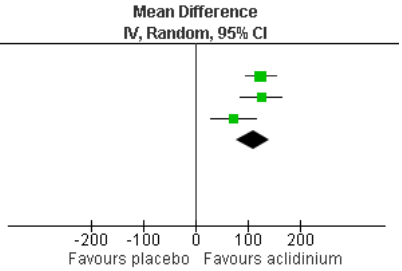


Footnotes
(1) AUGMENT
(2) ATTAIN
(3) ACCORD COPD I
(4) ACCORD COPD II
(5) ACLIFORM

1 ***Change in Trough FEV1 (ml) at 3 months***

Study or Subgroup	Aclidinium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 3 months								
Kerwin 2012b (1)	99.675	199.593	190	-23.87	54.8139	185	40.1%	123.55 [94.09, 153.00]
Lee 2015	57	161.5374	129	-68	161.5374	128	31.3%	125.00 [85.50, 164.50]
Rennard 2013 (2)	72	189.6689	148	0	189.6689	151	28.6%	72.00 [29.00, 115.00]
Subtotal (95% CI)			**467**			**464**	**100.0%**	**109.23 [77.84, 140.63]**

Heterogeneity: Tau² = 414.40; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 6.82 (P < 0.00001)



Test for subgroup differences: Not applicable

Footnotes

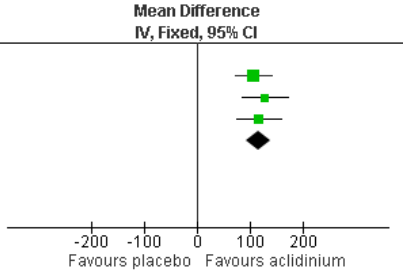
(1) ACCORD COPD I (mean and SE estimated from a graph)
(2) ACCORD COPD I

2

3 ***Change in Trough FEV1 (ml) at 6 months***

Study or Subgroup	Aclidinium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.4.2 6 months								
D'Urzo 2014b (1)	66	196	266	-40	198	232	43.2%	106.00 [71.30, 140.70]
Jones 2012 (2)	128	257.4965	272	0	257.4965	276	28.0%	128.00 [84.88, 171.12]
Singh 2014a (3)	56	219	332	-60	227	159	28.9%	116.00 [73.57, 158.43]
Subtotal (95% CI)			**870**			**667**	**100.0%**	**115.04 [92.24, 137.84]**

Heterogeneity: Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 9.89 (P < 0.00001)



Test for subgroup differences: Not applicable

Footnotes

(1) AUGMENT
(2) ATTAIN, ITT population sample sizes assumed
(3) ACLIFORM

4

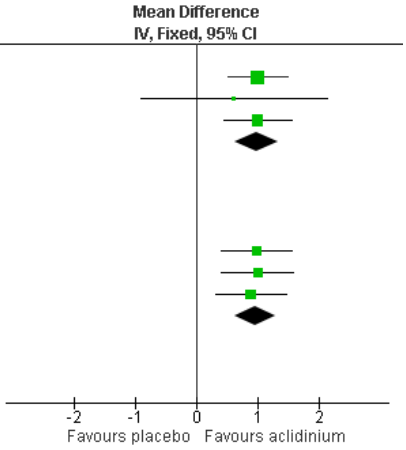
5 ***Transition Dyspnoea Index (TDI) focal score***

Study or Subgroup	Aclidinium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.10.1 3 months								
Kerwin 2012b (1)	1.5	2.7742	190	0.5	2.0534	185	52.8%	1.00 [0.51, 1.49]
Lee 2015 (2)	2.1021	5.866	129	1.4895	6.6592	128	5.4%	0.61 [-0.92, 2.15]
Rennard 2013 (3)	1.3	2.4331	148	0.3	2.4576	151	41.8%	1.00 [0.45, 1.55]
Subtotal (95% CI)			**467**			**464**	**100.0%**	**0.98 [0.62, 1.34]**

Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.36 (P < 0.00001)

2.10.2 6 months								
D'Urzo 2014b (4)	1.56	3.26	263	0.58	3.23	224	33.5%	0.98 [0.40, 1.56]
Jones 2012 (5)	1	3.5113164	272	0	3.5113164	276	32.4%	1.00 [0.41, 1.59]
Singh 2014a (6)	2.11	3	331	1.22	3.01	156	34.2%	0.89 [0.32, 1.46]
Subtotal (95% CI)			**866**			**656**	**100.0%**	**0.96 [0.62, 1.29]**

Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 5.60 (P < 0.00001)



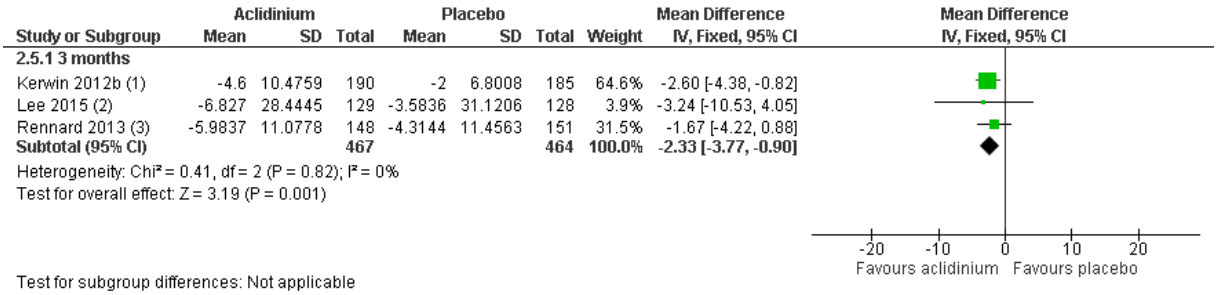
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Footnotes

(1) ACCORD COPD I (mean and SE estimated from a graph)
(2) Mean and SE estimated from a graph
(3) ACCORD COPD II (SE estimated from a graph)
(4) AUGMENT
(5) ATTAIN, ITT population sample sizes assumed
(6) ACLIFORM

6

1 ***St. George's Respiratory Questionnaire (SGRQ), total score, at 3 months***



Test for subgroup differences: Not applicable

Footnotes

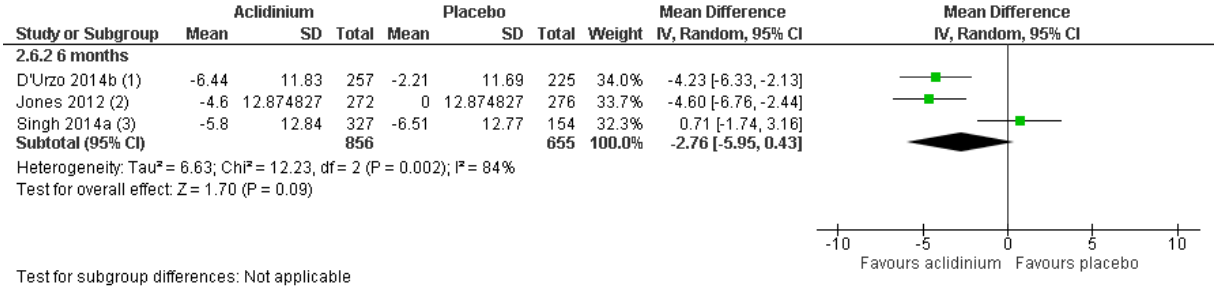
(1) ACCORD COPD I (mean and SE estimated from a graph)

(2) Mean and SE estimated from a graph

(3) ACCORD COPD II (mean and SE estimated from a graph)

2

3 ***St. George's Respiratory Questionnaire (SGRQ), total score, at 6 months***



Test for subgroup differences: Not applicable

Footnotes

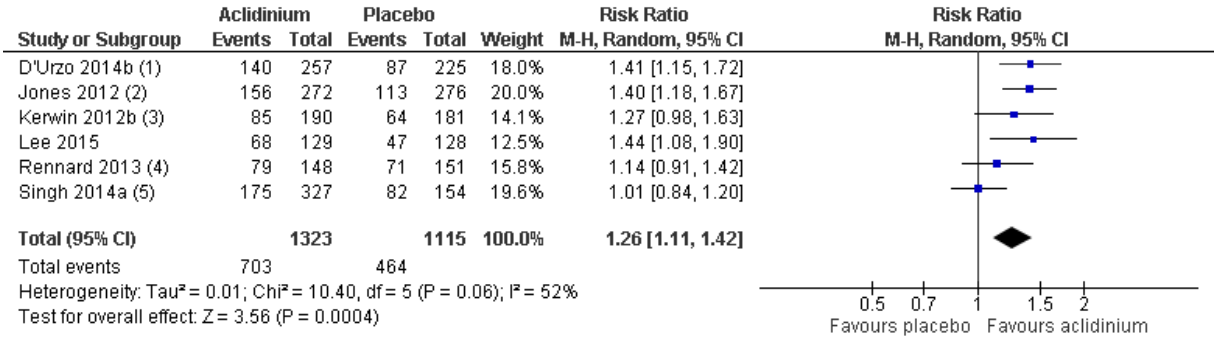
(1) AUGMENT

(2) ATTAIN, ITT population sample sizes assumed

(3) ACLIFORM

4

5 ***People with ≥ 4 units improvement in quality of life (SGRQ)***



Footnotes

(1) AUGMENT

(2) ATTAIN, ITT population sample sizes assumed

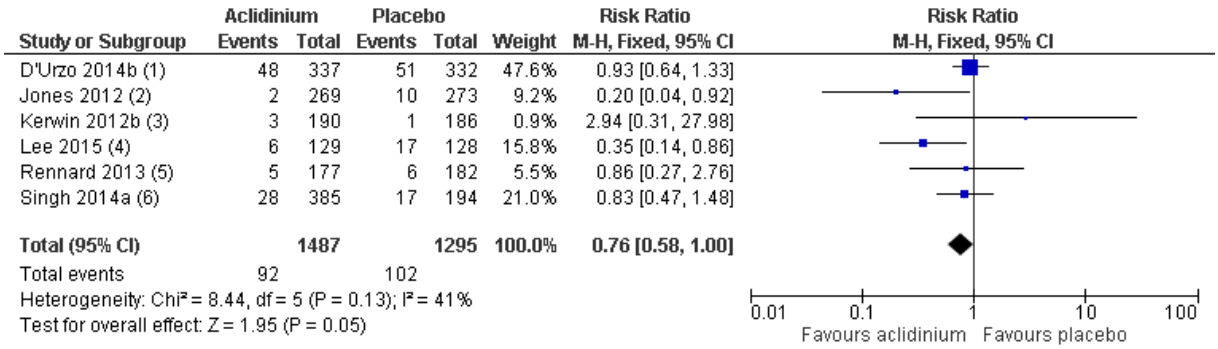
(3) ACCORD COPD I, data estimated from a graph

(4) ACCORD COPD II

(5) ACLIFORM

6

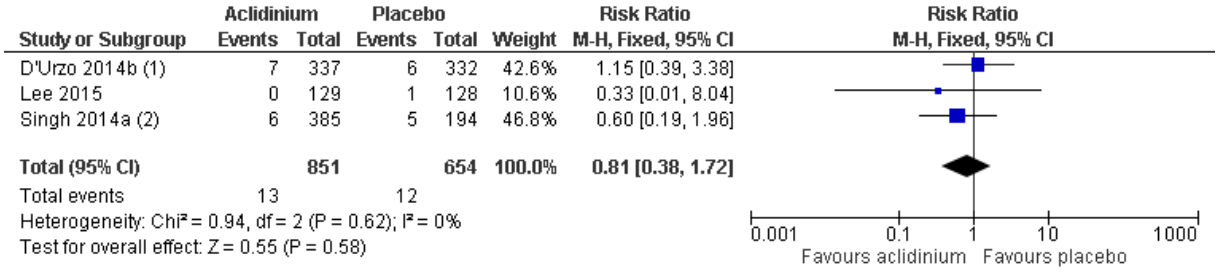
1 ***People with ≥ 1 moderate to severe exacerbation***



Footnotes
(1) AUGMENT
(2) ATTAIN, exacerbation SAE data
(3) ACCORD COPD I, exacerbation SAE data
(4) Includes moderate and severe exacerbations data combined
(5) ACCORD COPD II, exacerbation SAE data
(6) ACLIFORM

2

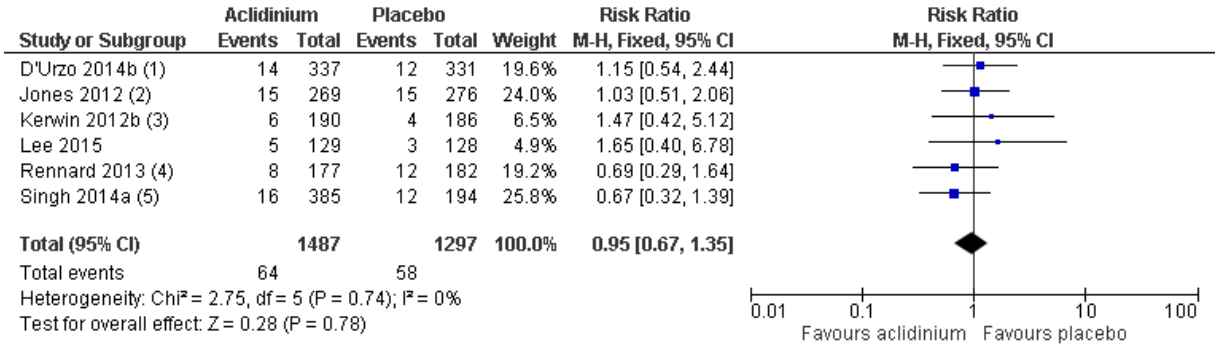
3 ***People with ≥ 1 severe exacerbation (requiring hospitalisation)***



Footnotes
(1) AUGMENT
(2) ACLIFORM

4

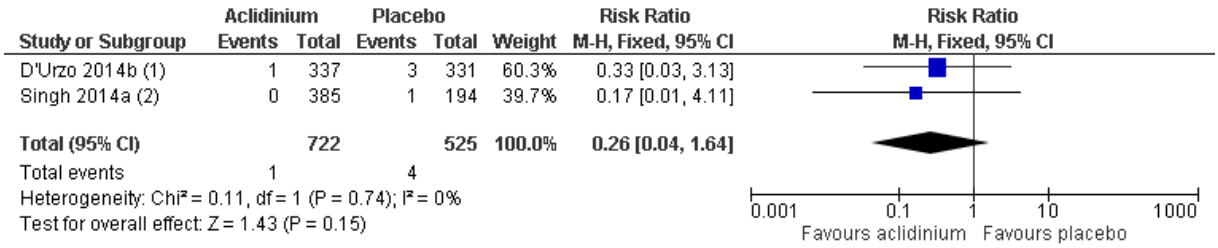
5 ***People with ≥ 1 Serious Adverse Event (SAE)***



Footnotes
(1) AUGMENT
(2) ATTAIN
(3) ACCORD COPD I
(4) ACCORD COPD II
(5) ACLIFORM

6

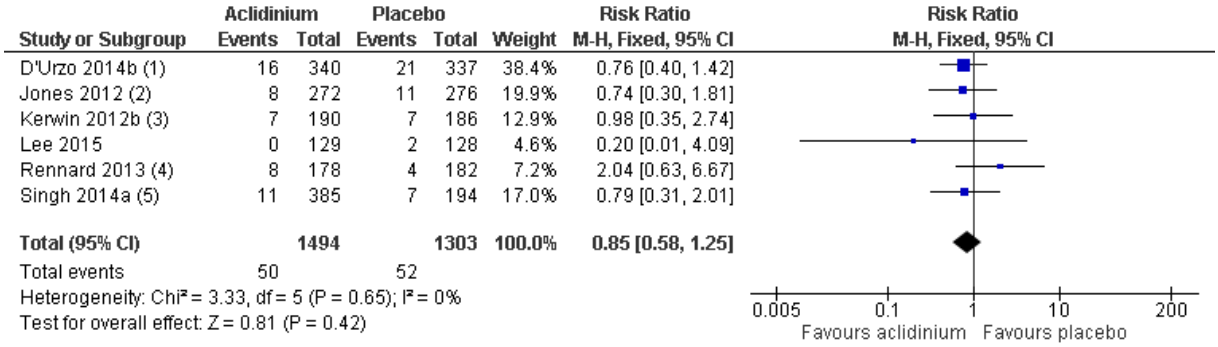
1 ***People with ≥ 1 session of pneumonia***



Footnotes
(1) AUGMENT
(2) ACLIFORM

2

3 ***Drop-outs due to adverse events***

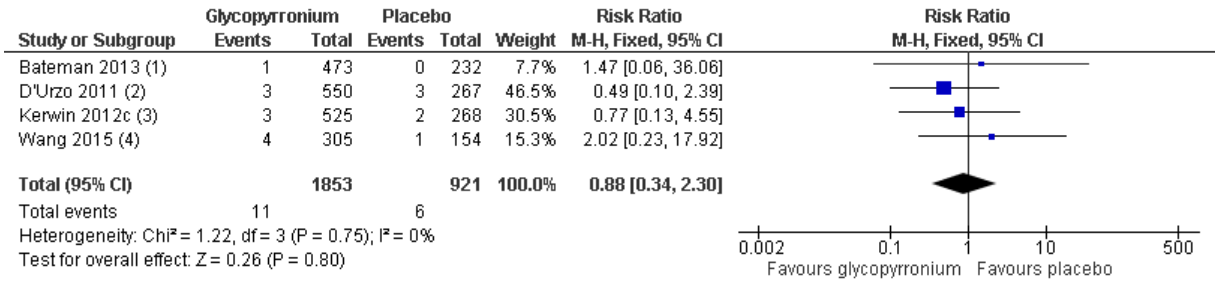


Footnotes
(1) AUGMENT
(2) ATTAIN
(3) ACCORD COPD I
(4) ACCORD COPD II
(5) ACLIFORM

4

5 **Glycopyrronium bromide (50 micrograms once daily) versus placebo**

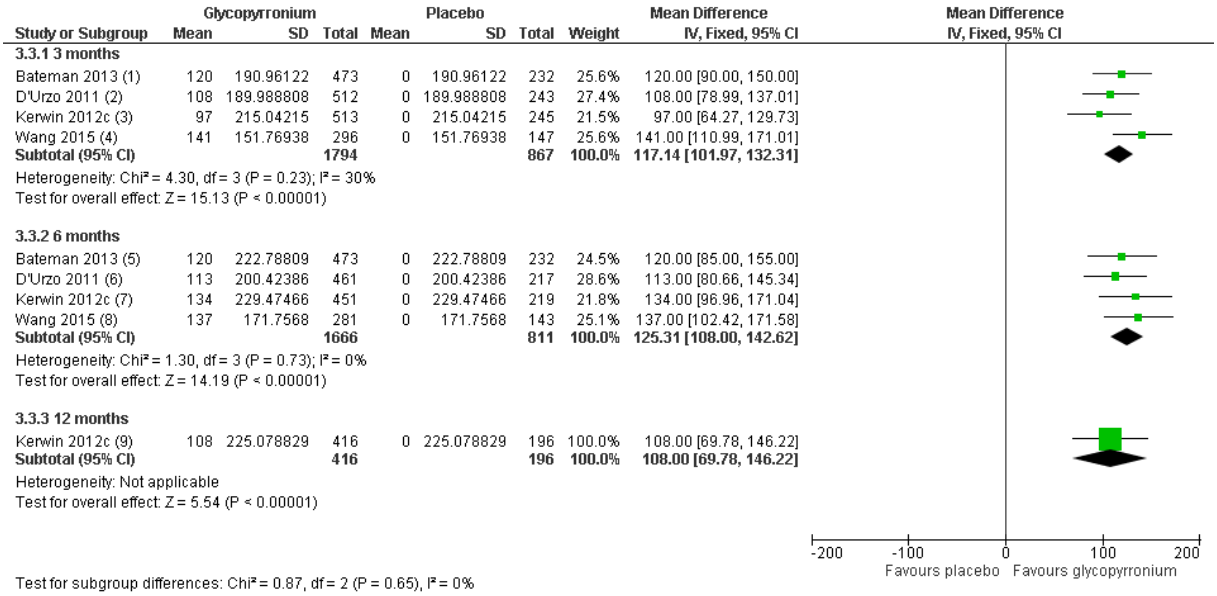
6 ***All-cause mortality***



Footnotes
(1) SHINE
(2) GLOW 1
(3) GLOW 2
(4) GLOW 7

7

Change in Trough FEV1 (ml)

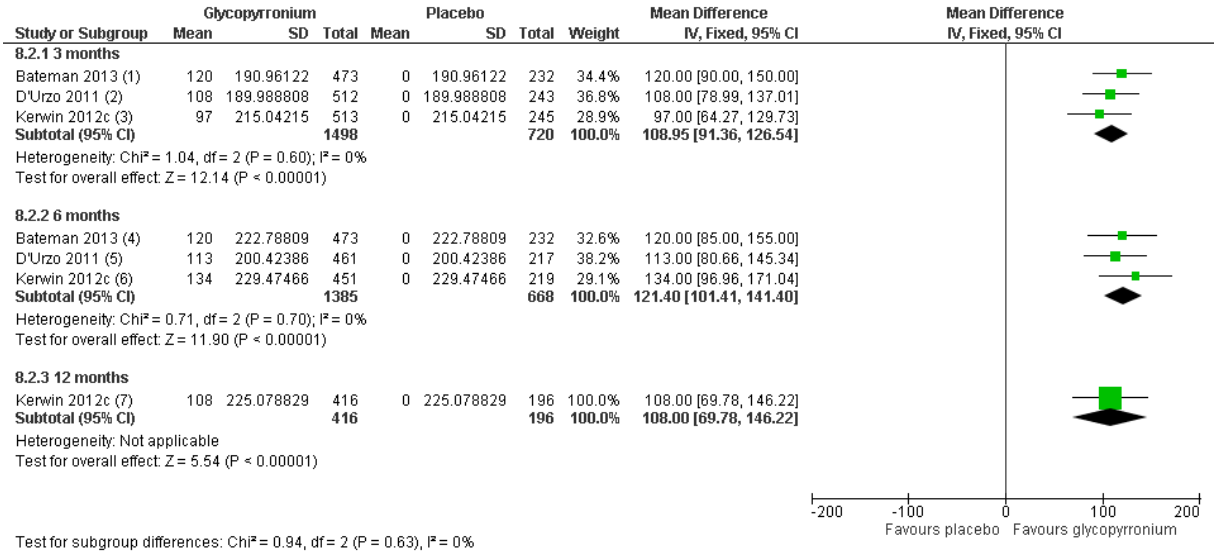


Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0%

Footnotes

(1) SHINE
(2) GLOW 1
(3) GLOW 2
(4) GLOW 7
(5) SHINE
(6) GLOW1
(7) GLOW 2
(8) GLOW 7
(9) GLOW 2

Sensitivity analysis: change in trough FEV1

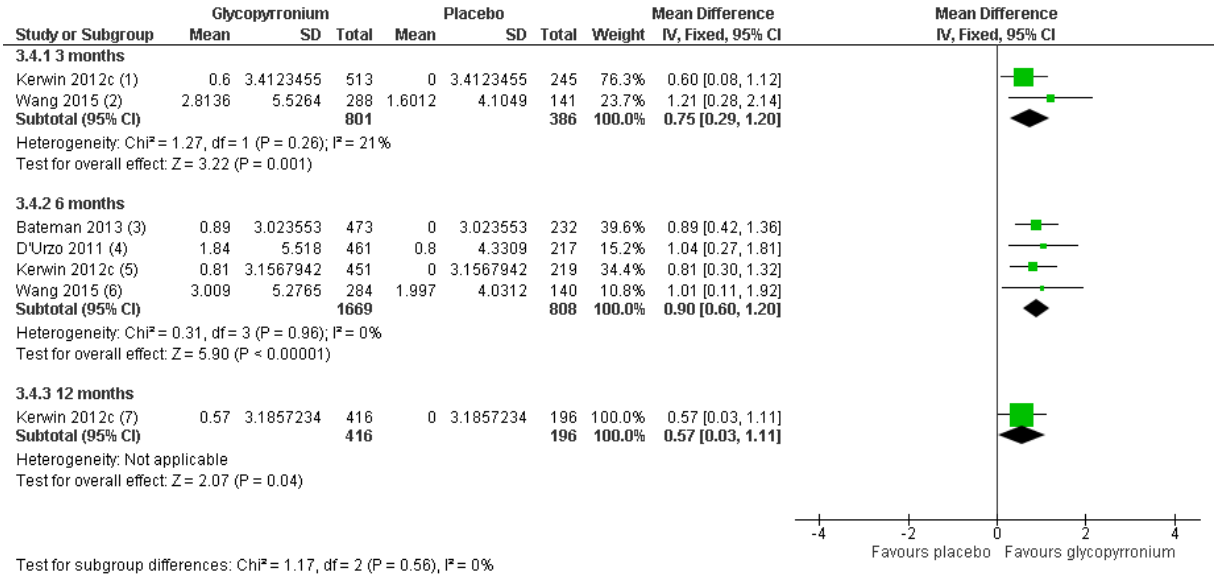


Test for subgroup differences: Chi² = 0.94, df = 2 (P = 0.63), I² = 0%

Footnotes

(1) SHINE
(2) GLOW 1
(3) GLOW 2
(4) SHINE
(5) GLOW1
(6) GLOW 2
(7) GLOW 2

1 ***Transition Dyspnoea Index (TDI) focal score***



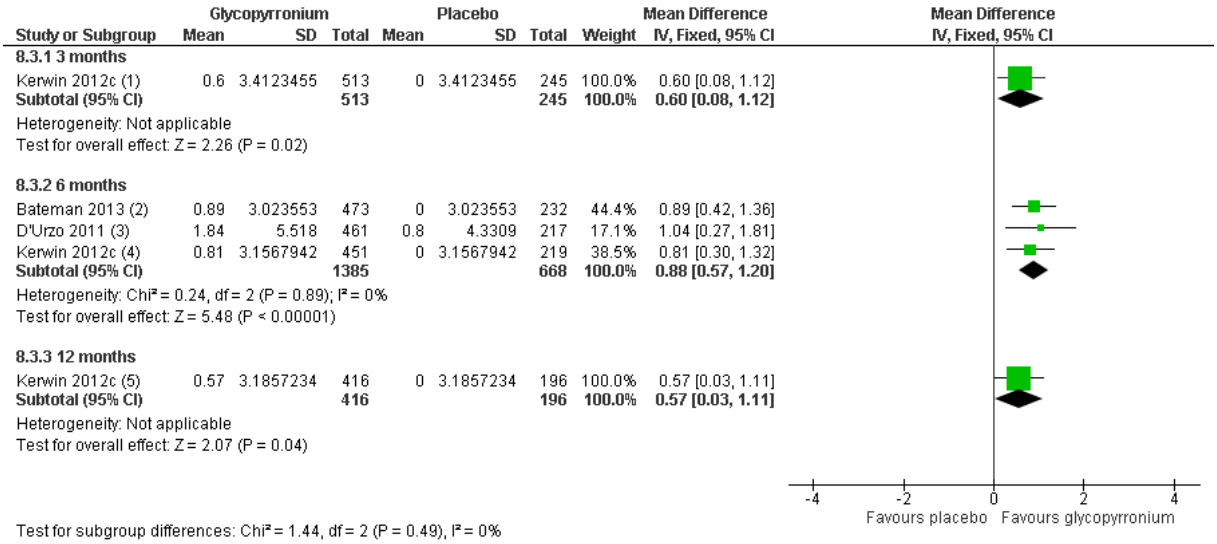
Test for subgroup differences: Chi² = 1.17, df = 2 (P = 0.56), I² = 0%

Footnotes

(1) GLOW 2
(2) GLOW 7 (mean and SE estimated from a graph)
(3) SHINE
(4) GLOW 1
(5) GLOW 2
(6) GLOW 7 (mean and SE estimated from a graph)
(7) GLOW 2

2

3 *Sensitivity analysis: TDI*



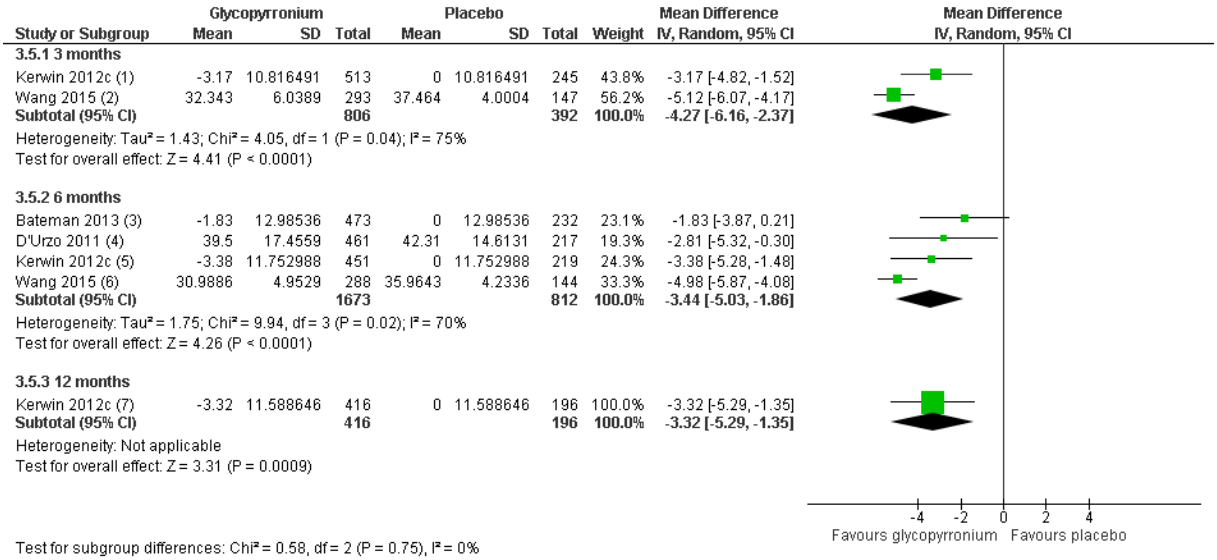
Test for subgroup differences: Chi² = 1.44, df = 2 (P = 0.49), I² = 0%

Footnotes

(1) GLOW 2
(2) SHINE
(3) GLOW 1
(4) GLOW 2
(5) GLOW 2

4

1 *St. George's Respiratory Questionnaire (SGRQ), total score*



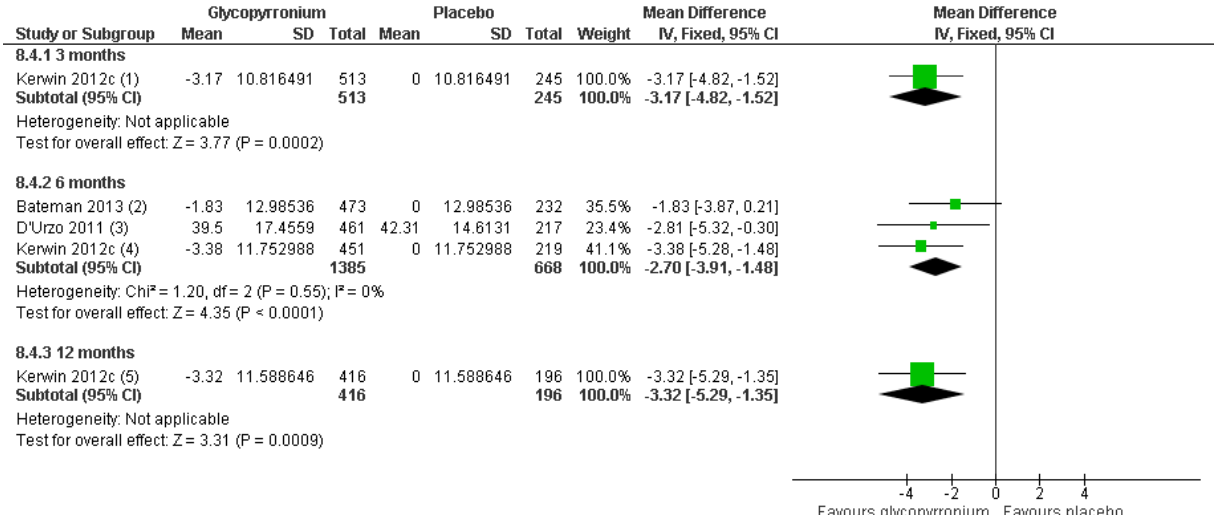
Test for subgroup differences: Chi² = 0.58, df = 2 (P = 0.75), I² = 0%

Footnotes

(1) GLOW 2
(2) GLOW 7 (mean and SE estimated from a graph)
(3) SHINE
(4) GLOW 1
(5) GLOW 2
(6) GLOW 7 (mean and SE estimated from a graph)
(7) GLOW 2

2

3 *Sensitivity analysis: SGRQ*



Test for subgroup differences: Chi² = 0.37, df = 2 (P = 0.83), I² = 0%

Footnotes

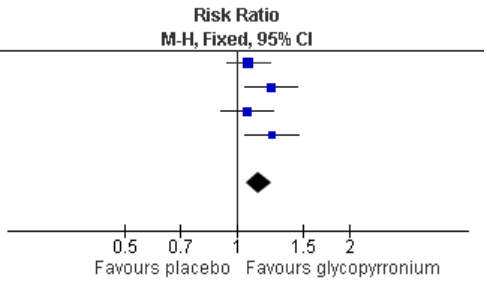
(1) GLOW 2
(2) SHINE
(3) GLOW 1
(4) GLOW 2
(5) GLOW 2

4

1 ***People with ≥ 4 units improvement in quality of life (SGRQ)***

Study or Subgroup	Glycopyrronium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2013 (1)	286	473	131	232	31.8%	1.07 [0.94, 1.22]
D'Urzo 2011 (2)	262	461	100	217	24.6%	1.23 [1.05, 1.45]
Kerwin 2012c (3)	226	416	100	196	24.6%	1.06 [0.90, 1.25]
Wang 2015 (4)	196	288	79	144	19.0%	1.24 [1.05, 1.47]
Total (95% CI)		**1638**		**789**	**100.0%**	**1.14 [1.06, 1.23]**
Total events	970		410			

Heterogeneity: Chi² = 3.36, df = 3 (P = 0.34); I² = 11%
Test for overall effect: Z = 3.33 (P = 0.0009)



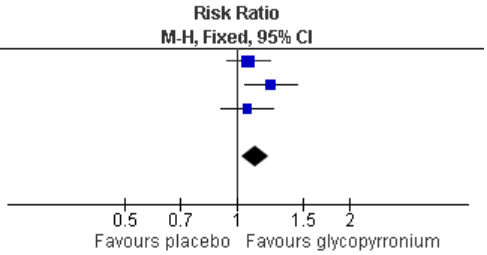
Footnotes
(1) SHINE
(2) GLOW 1
(3) GLOW 2
(4) GLOW 7

2

3 *Sensitivity analysis: people with ≥ 4 units improvement in quality of life (SGRQ)*

Study or Subgroup	Glycopyrronium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2013 (1)	286	473	131	232	39.3%	1.07 [0.94, 1.22]
D'Urzo 2011 (2)	262	461	100	217	30.4%	1.23 [1.05, 1.45]
Kerwin 2012c (3)	226	416	100	196	30.4%	1.06 [0.90, 1.25]
Total (95% CI)		**1350**		**645**	**100.0%**	**1.12 [1.02, 1.22]**
Total events	774		331			

Heterogeneity: Chi² = 2.11, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 2.49 (P = 0.01)



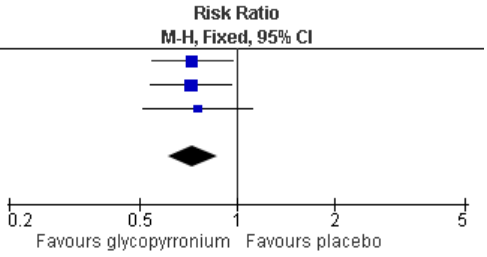
Footnotes
(1) SHINE
(2) GLOW 1
(3) GLOW 2

4

5 ***People with ≥ 1 moderate to severe exacerbation***

Study or Subgroup	Glycopyrronium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2013 (1)	89	473	60	232	38.3%	0.73 [0.55, 0.97]
D'Urzo 2011 (2)	93	532	63	260	40.2%	0.72 [0.54, 0.96]
Wang 2015 (3)	51	305	34	154	21.5%	0.76 [0.51, 1.12]
Total (95% CI)		**1310**		**646**	**100.0%**	**0.73 [0.61, 0.87]**
Total events	233		157			

Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)



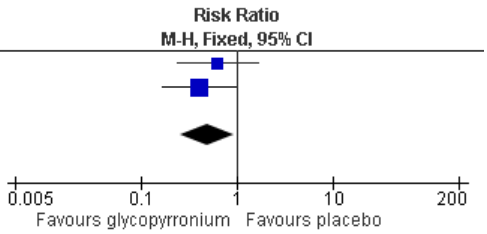
Footnotes
(1) SHINE. Data provided by author on request
(2) GLOW 1
(3) GLOW 7

6

1 ***People with ≥ 1 severe exacerbation (requiring hospitalisation)***

Study or Subgroup	Glycopyrronium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2013 (1)	9	473	7	232	38.9%	0.63 [0.24, 1.67]
D'Urzo 2011 (2)	9	532	11	260	61.1%	0.40 [0.17, 0.95]
Total (95% CI)		**1005**		**492**	**100.0%**	**0.49 [0.26, 0.93]**
Total events	18		18			

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)



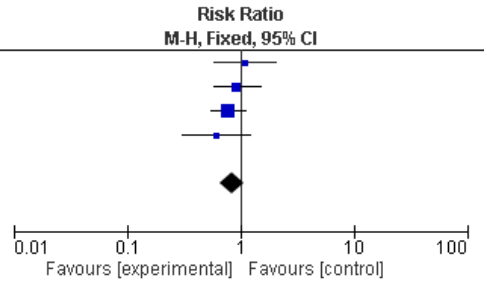
Footnotes
(1) SHINE. Data provided by author on request.
(2) GLOW1

2

3 ***People with ≥ 1 Serious Adverse Event (SAE)***

Study or Subgroup	Glycopyrronium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2013 (1)	29	473	13	232	13.9%	1.09 [0.58, 2.06]
D'Urzo 2011 (2)	46	550	24	267	25.8%	0.93 [0.58, 1.49]
Kerwin 2012c	66	525	43	268	45.4%	0.78 [0.55, 1.12]
Wang 2015 (3)	17	305	14	154	14.8%	0.61 [0.31, 1.21]
Total (95% CI)		**1853**		**921**	**100.0%**	**0.84 [0.66, 1.07]**
Total events	158		94			

Heterogeneity: Chi² = 1.82, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)



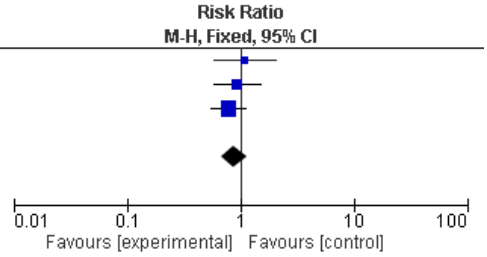
Footnotes
(1) SHINE
(2) GLOW 1
(3) GLOW 7

4

5 *Sensitivity analysis: people with ≥ 1 non-fatal Serious Adverse Event (SAE)*

Study or Subgroup	Glycopyrronium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bateman 2013 (1)	29	473	13	232	16.3%	1.09 [0.58, 2.06]
D'Urzo 2011 (2)	46	550	24	267	30.3%	0.93 [0.58, 1.49]
Kerwin 2012c	66	525	43	268	53.4%	0.78 [0.55, 1.12]
Total (95% CI)		**1548**		**767**	**100.0%**	**0.88 [0.68, 1.14]**
Total events	141		80			

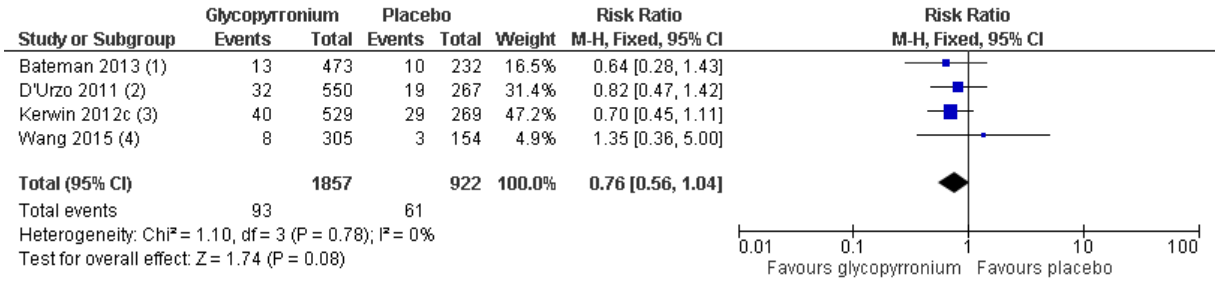
Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)



Footnotes
(1) SHINE
(2) GLOW 1

6

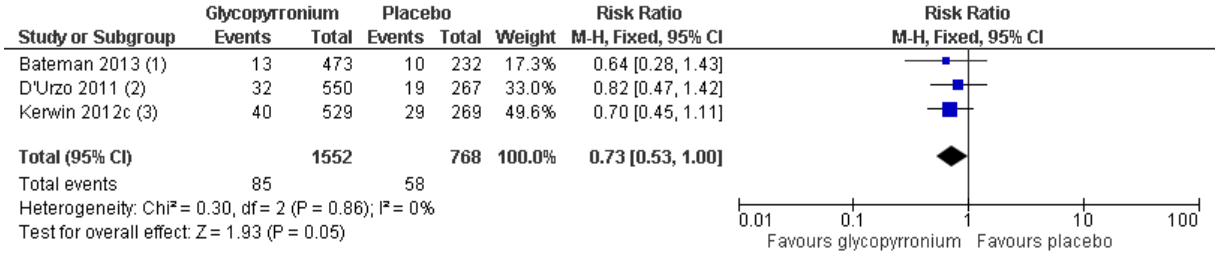
1 ***Drop-outs due to adverse events***



Footnotes
(1) SHINE
(2) GLOW 1
(3) GLOW 2
(4) GLOW 7

2

3 *Sensitivity analysis: dropouts due to adverse events*

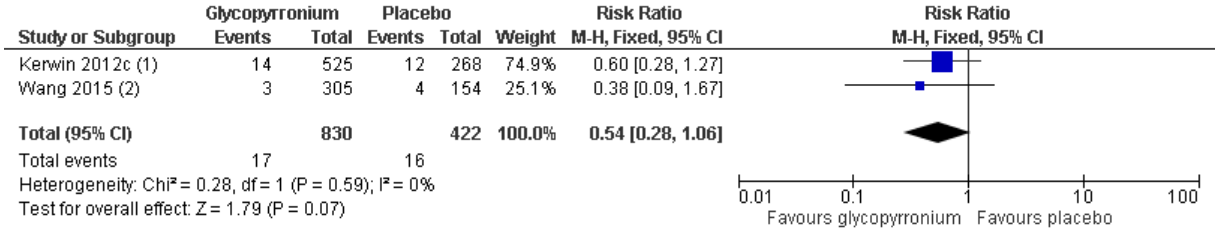


Footnotes
(1) SHINE
(2) GLOW 1
(3) GLOW 2

4

5

6 ***People with ≥ 1 session of pneumonia***



Footnotes
(1) GLOW 2, data extracted for adverse events rather than SAEs
(2) GLOW 7

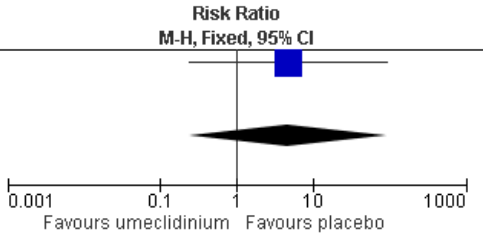
7

Umeclidinium bromide (62.5 micrograms once daily) versus placebo

All-cause mortality

Study or Subgroup	Umeclidinium Events	Umeclidinium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donahue 2013a	3	418	0	280	100.0%	4.69 [0.24, 90.53]
Trivedi 2014	0	69	0	68		Not estimable
Total (95% CI)		**487**		**348**	**100.0%**	**4.69 [0.24, 90.53]**
Total events	3		0			

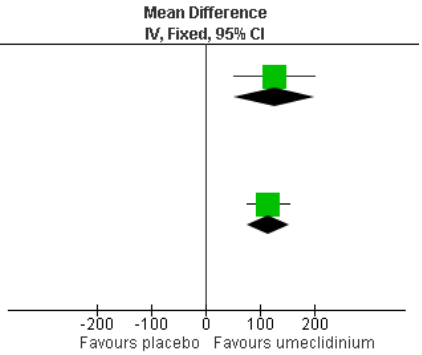
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)



Change in Trough FEV1 (ml)

Study or Subgroup	Umeclidinium Mean	Umeclidinium SD	Umeclidinium Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
4.2.1 3 months								
Trivedi 2014	127	223.8833	69	0	223.8833	68	100.0%	127.00 [52.02, 201.98]
Subtotal (95% CI)			**69**			**68**	**100.0%**	**127.00 [52.02, 201.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.32 (P = 0.0009)								
4.2.2 6 months								
Donahue 2013a	119	257.6076	418	4	264.3846	280	100.0%	115.00 [75.39, 154.61]
Subtotal (95% CI)			**418**			**280**	**100.0%**	**115.00 [75.39, 154.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.69 (P < 0.00001)								

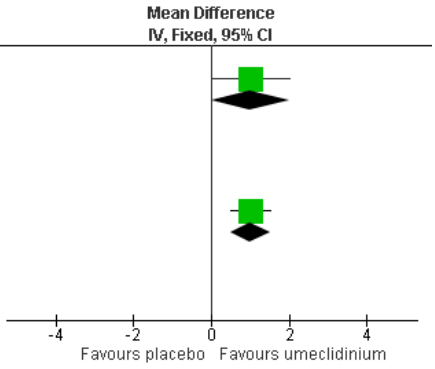
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%



Transition Dyspnoea Index (TDI) focal score

Study or Subgroup	Umeclidinium Mean	Umeclidinium SD	Umeclidinium Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 3 months								
Trivedi 2014	1	2.684206	62	0	2.684206	50	100.0%	1.00 [0.00, 2.00]
Subtotal (95% CI)			**62**			**50**	**100.0%**	**1.00 [0.00, 2.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.96 (P = 0.05)								
4.4.2 6 months								
Donahue 2013a	2.2	2.8889	326	1.2	2.8566	204	100.0%	1.00 [0.50, 1.50]
Subtotal (95% CI)			**326**			**204**	**100.0%**	**1.00 [0.50, 1.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.90 (P < 0.0001)								

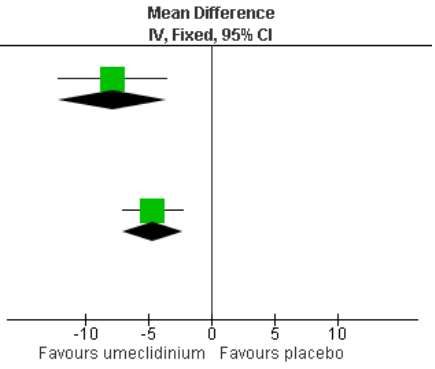
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%



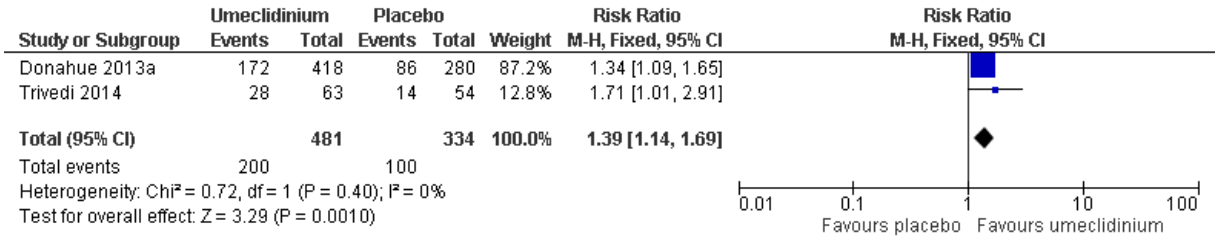
St. George's Respiratory Questionnaire (SGRQ), total score

Study or Subgroup	Umeclidinium Mean	Umeclidinium SD	Umeclidinium Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
4.5.1 3 months								
Trivedi 2014	-7.9	11.5421	62	0	11.5421	50	100.0%	-7.90 [-12.20, -3.60]
Subtotal (95% CI)			**62**			**50**	**100.0%**	**-7.90 [-12.20, -3.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.60 (P = 0.0003)								
4.5.2 6 months								
Donahue 2013a	-7.25	15.3951	418	-2.56	15.8965	280	100.0%	-4.69 [-7.07, -2.31]
Subtotal (95% CI)			**418**			**280**	**100.0%**	**-4.69 [-7.07, -2.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.87 (P = 0.0001)								

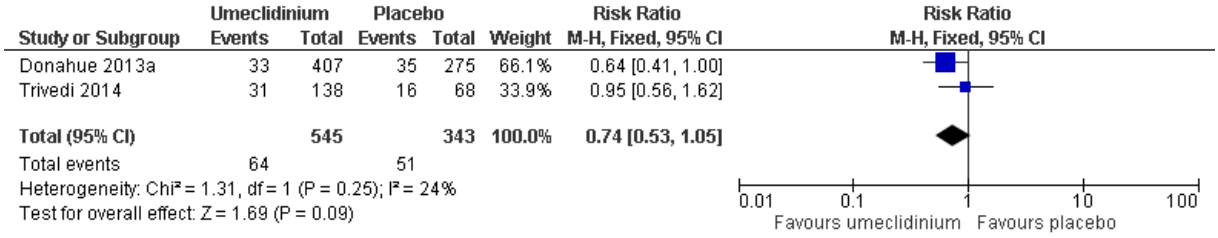
Test for subgroup differences: Chi² = 1.64, df = 1 (P = 0.20), I² = 39.0%



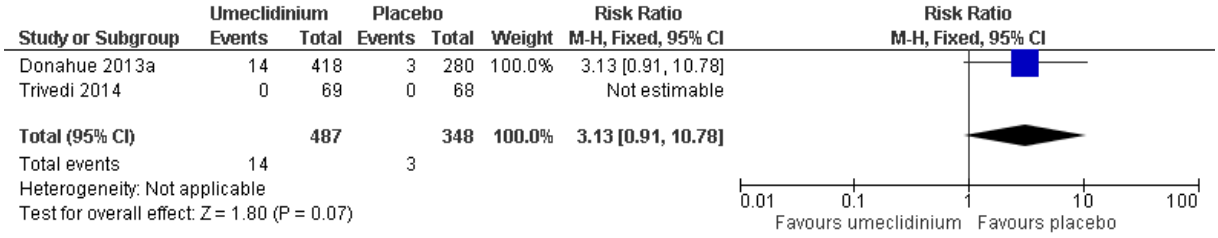
People with ≥ 4 units improvement in quality of life (SGRQ)



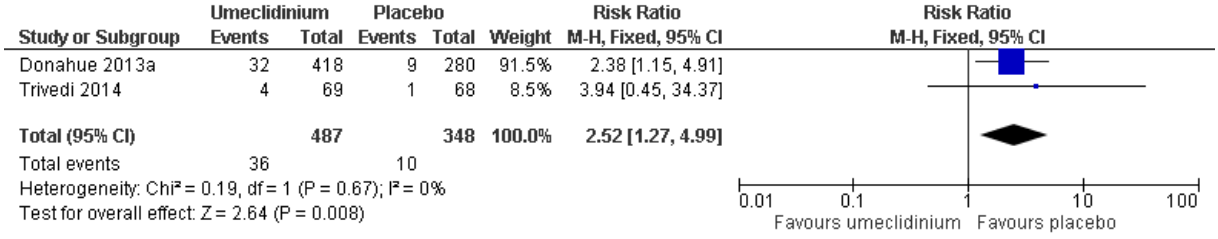
People with ≥ 1 moderate to severe exacerbation



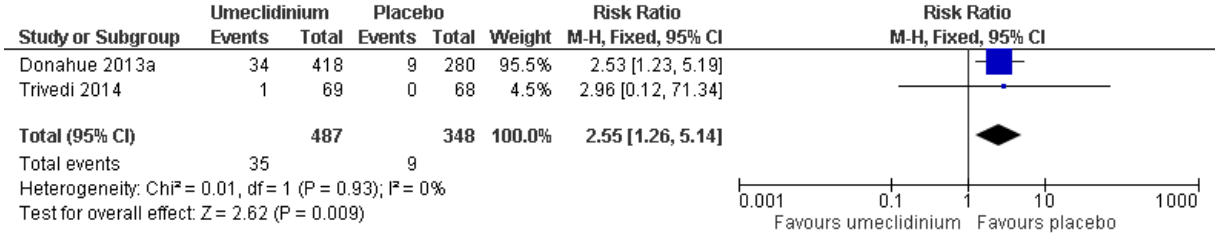
People with ≥ 1 severe exacerbation (requiring hospitalisation)



People with ≥ 1 Serious Adverse Event (SAE)



Dropouts due to adverse events



Appendix G – Network meta-analysis results

Inhaled therapy combinations

The following tables and figures are based on data from the Cochrane review and the models they have developed. However, the dichotomous data has been altered by the NICE Guidelines Updates Team to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B. The network diagrams were supplied by the Cochrane group.

Model fit statistics for all outcomes

Table 20: Model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
Change in FEV 1							
50	FEV1 at 3 months (low risk)	RE model- fixed class effect	-513.58	105.6	107	0.03 (0.02, 0.03)	RE model- fixed class effect
		RE model- random class effect	-516.52	102.3		0.02 (0.01 - 0.03)	
		FE model- fixed class effect	-421.49	229.0		-	
		FE model-random class effect	-481.10	155.2		-	
11	FEV1 at 3 months (high risk)	RE model- fixed class effect	-114.44	22.9	23	0.01 (0, - 0.04)	FE model- fixed class effect
		RE model- random class effect	-112.86	22.1		0.02 (0, - 0.03)	
		FE model- fixed class effect	-114.95	26.0		-	
		FE model-random class effect	-113.78	22.5		-	

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
30	FEV1 at 6 months (low risk)	RE model- fixed class effect	-324.38	68.3	69	0.02 (0.007 - 0.03)	FE model- fixed class effect[5]
		RE model- random class effect	-325.15	66.2		0.009 (0 - 0.02)	
		FE model- fixed class effect	-315.31	91.4		-	
		FE model-random class effect	-326.62	69.0		-	
11	FEV1 at 6 months (high risk)	RE model- fixed class effect	-103.62	22.7	24	0.02 (0 - 0.05)	FE model- fixed class effect
		RE model- random class effect	-104.58	20.4		0.01 (0 - 0.05)	
		FE model- fixed class effect	-103.97	25.9		-	
		FE model-random class effect	-106.00	20.1		-	
13	FEV1 at 12 months (low risk)	RE model- fixed class effect	-150.21	32.7	31	0.02 (0.01 - 0.03)	FE model- random class effect
		RE model- random class effect	-153.85	28.4		0.01 (0 - 0.03)	
		FE model- fixed class effect	-142.19	49.0		-	
		FE model-random class effect	-156.07	27.9		-	
13		RE model- fixed class effect	-128.137	26.2	29	0.01 (0.00, 0.03)	FE model- fixed class effect

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
	FEV1 at 12 months (high risk)	RE model- random class effect	-126.15	25.8		0.01 (0.00, 0.04)	
		FE model- fixed class effect	-129.39	28.2		-	
		FE model- random class effect	-127.55	26.5		-	
Moderate to severe exacerbations							
38	Low risk	RE model- fixed class effects	384.09	72.7	72	0.14 (0.008, 0.37)	FE model- fixed class effect
		FE model – fixed class effect	384.26	77.0		-	
		FE model- random class effect	389.95	75.3		-	
21	High risk	RE model- fixed class effects	42.65	24.5	27	0.07 (0.008, 0.14)	RE model- fixed class effects
		FE model – fixed class effect	48.22	36.5		-	
		FE model - random class effect: Class 2 shares variance with class 1, Class 4 has variance equal to class 3	49.36	33.33		-	
Severe exacerbations							
31	Low risk	RE model- fixed class effect	270.29	64.8	60	0.10 (0.006, 0.43)	FE model – fixed class effect

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
		FE model – fixed class effect	268.61	66.2		-	
13	High risk	RE model – fixed class effect	71.89	16.6	20	0.07 (0.003, 0.26)	FE model- fixed class effect
		FE model- fixed class effect	70.30	17.4		-	
Dropouts due to adverse events							
66	Low risk	RE model- fixed class effects	848.00	155.6	146	0.09 (0.004, 0.24)	FE model- random class effect[6]
		RE model- random class effects	847.10	145.5		0.07 (0.004, 0.21)	
		FE model- fixed class effect	846.70	160.5		-	
		FE model- random class effect	846.30	148.4		-	
25	High risk	RE model- fixed class effects	344.54	45.4	55	0.06 (0.002, 0.18)	FE model- fixed class effect
		RE model- random class effects	349.07	40.0		0.07 (0.003, 0.20)	
		FE model- fixed class effect	342.43	45.4		-	
		FE model- random class effect	347.33	46.1		-	
SGRQ total score at 3 months							
28	Low risk	RE model- fixed class effects	170.91	43.8	59	0.19 (0.006 - 0.67)	FE model- fixed class effect

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
		RE model- random class effects	178.56	46.5		0.23 (0.01 - 0.81)	
		FE model- fixed class effect	169.00	43.6		-	
		FE model- random class effect	176.09	46.11		-	
9	High risk	RE model- fixed class effects	60.89	20.4	19	0.66 (0.03 - 2.93)	FE model- fixed class effect
		RE model- random class effects	62.96	19.4		1.14 (0.05 - 4.77)	
		FE model- fixed class effect	59.353	21.3		-	
		FE model- random class effect	62.33	20.7		-	
SGRQ total score at 6 months							
20	Low risk	RE model- fixed class effects	149.50	45.8	47	0.36 (0.17, 1.08)	FE model- fixed class effect
		RE model- random class effects	155.28	46.5		0.41 (0.20, 1.21)	
		FE model- fixed class effect	148.02	48.2		-	
		FE model- random class effect	154.22	48.5		-	
10	High risk	RE model- fixed class effects	65.030	22.9	22	0.61 (0.31, 2.03)	FE model- fixed class effect

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
		RE model- random class effects	67.57	22.5		0.91 (0.50, 3.03)	
		FE model- fixed class effect	64.00	25.1		-	
		FE model- random class effect	67.61	25.4		-	
SGRQ total score at 12 months							
6	Low risk	RE model- fixed class effects	42.48	14.2	15	0.61 (0.29, 2.51)	FE model- fixed class effect
		FE model- fixed class effect	41.25	15.1		-	
14	High risk	RE model- fixed class effects	94.26	31.4	32	0.81 (0.12, 1.75)	FE model- fixed class effect
		RE model- random class effects	95.87	31.7		0.57 (0.03, 1.77)	
		FE model- fixed class effect	96.60	39.8		-	
SGRQ responders at 3 months							
22	Low risk	RE model- fixed class effects	337.64	39.8	44	0.04 (0.002, 0.15)	FE model- fixed class effect
		FE model- random class effects	341.54	40.3		-	
		FE model- fixed class effect	335.70	40.3		-	
SGRQ responders at 6 months							

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
19	Low risk	RE model- fixed class effects	380.57	46.4	47	0.14 (0.06, 0.23)	RE model- fixed class effects
		RE model- random class effects	382.78	46.3		0.11 (0.01, 0.22)	
		FE model- fixed class effect	391.67	70.6		-	
SGRQ responders at 12 months							
7	High risk	RE model- fixed class effects	137.86	16.9	16	0.16 (0.01, 0.48)	FE model- fixed class effect
		RE model- random class effects	139.16	16.4		0.26 (0.03, 1.12)	
		FE model- fixed class effect	139.08	22.0		-	
TDI at 3 months							
30	Low risk	RE model- fixed class effects	14.34	61.7	63	0.17 (0.02, 0.32)	RE model- fixed class effects
		FE model- fixed class effect	17.97	75.5		-	
TDI at 6 months							
18	Low risk	RE model- fixed class effects	2.31	36.6	41	0.09 (0.004, 0.24)	FE model- fixed class effect
		FE model- fixed class effect	0.59	37.7		-	
		FE model- random class effect	4.15	34.9		-	
TDI at 12 months							

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
6	Low risk	RE model- fixed class effects	-6.91	14.2	16	0.16 (0.01, 0.43)	FE model- fixed class effect
		RE model- random class effect	-4.72	14.5		0.16 (0.01, 0.61)	
		FE model- fixed class effect	-5.15	19.6		-	
Serious adverse events (SAEs)							
67	Low risk	RE model- fixed class effects	891.21	145.8	145	0.04 (0, 0.15)	FE model- fixed class effect
		RE model- random class effects	895.78	143.9		0.05 (0.002, 0.16)	
		FE model- fixed class effect	889.36	147.7		-	
		FE model- random class effect	894.81	145.6		-	
24	High risk	RE model- fixed class effects	378.46	49.1	53	0.06 (0.002, 0.17)	FE model- fixed class effect
		FE model- fixed class effect	376.70	50.9		-	
		FE model- random class effect	379.79	47.9		-	
COPD SAEs							
63	Low risk[2]	RE model- fixed class effects	662.62	144.2	135	0.16 (0.002, 0.38)	RE model- fixed class effects
		RE model- random class effects	665.07	140.1		0.13 (0.006, 0.37)	

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
		RE model- random class effects with continuity correction[1]	669.96	129.3		0.12 (0.006, 0.35)	
		FE model- random class effect	664.86	143.9		-	
20	High risk	RE model- fixed class effects	283.74	42.6	44	0.06 (0.002, 0.21)	FE model- fixed class effect
		FE model- fixed class effect	282.07	43.2		-	
		FE model- random class effect	283.74	41.0		-	
Cardiac SAEs							
58	Low risk	RE model- fixed class effects	578.42	151.2	127	0.17 (0.006, 0.48)	FE model- fixed class effect
		RE model- random class effects	581.40	147.0		0.16 (0.008, 0.49)	
		FE model- fixed class effect	577.25	155.8		-	
		FE model- fixed class effect with continuity correction[1]	585.10	135.6		-	
19	High risk	RE model- fixed class effects	256.42	51.5	42	0.28 (0.02, 0.67)	FE model- fixed class effect[4]
		RE model- random class effects	253.42	44.9		0.23 (0.01, 0.65)	
		FE model- fixed class effect	257.45	59.8		-	

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
		FE model- random class effect	253.13	48.2		-	
		FE model- random class effect, class 4 variance equal to class 3*	253.13	48.2		-	
		RE model- random class effect, class 4 variance equal to class 3*	253.33	44.7		0.23 (0.01, 0.66)	
Pneumonia							
61	Low risk	RE model- fixed class effects	531.76	167.3	133	0.23 (0.05, 0.61)	FE model- fixed class effect
		RE model- random class effects	531.13	158.4		0.22 (0.05, 0.78)	
		RE model with informative prior- fixed class effects[3]	531.76	167.3		0.23 (0.05, 0.65)	
		FE model- fixed class effect	532.14	174.3		-	
24	High risk	RE model- fixed class effects	280.12	60.0	53	0.22 (0.01, 0.61)	FE model- fixed class effect
		FE model- fixed class effect	278.71	63.2		-	
		FE model- random class effect	281.64	60.1		-	
Mortality							
51	Low risk[2]	RE model- fixed class effects	432.44	129.4	110	0.20 (0.006, 0.69)	RE model- fixed class effects

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
		RE model- fixed class effects with continuity correction[1]	450.78	104.8		0.14 (0.003, 0.51)	
		RE model- random class effects	436.03	125.8		0.28 (0.01, 0.82)	
		FE model- random class effect	436.07	129.6		-	
24	High risk	RE model- fixed class effects	271.00	51.45	53	0.17 (0.009, 0.49)	FE model- fixed class effect
		FE model- fixed class effect	269.87	53.87		-	
		FE model- random class effect	273.52	51.96		-	

* The variance of class 4 was made equal to class 3 to try to improve model fit in the absence of sufficient information about the variance of class 4.

1. For continuity corrected models, the zero event data was changed to read 0.5 and 0.5 events were also added to the comparator arm. This was done to try to improve model fit.
2. The FE model with fixed class effect was not included as the model failed to converge due to the number of zero events in the data.
3. The Turner informative prior for the SD was used to try to improve model fit.
4. The FE model with fixed class effects was used here as models with random effect terms did not converge due to the lack of data to estimate the random effect terms.
5. The FE model with fixed class effects was used here as the models with random effect terms resulted in large 95% CrI due to a lack of data to estimate the random effect terms.
6. The FE model with random class effect was chosen here as a better fitting model because the total residual deviance for the FE model with fixed class effect was very large compared to the number of data points and the means of the posterior distributions were not close to the medians.

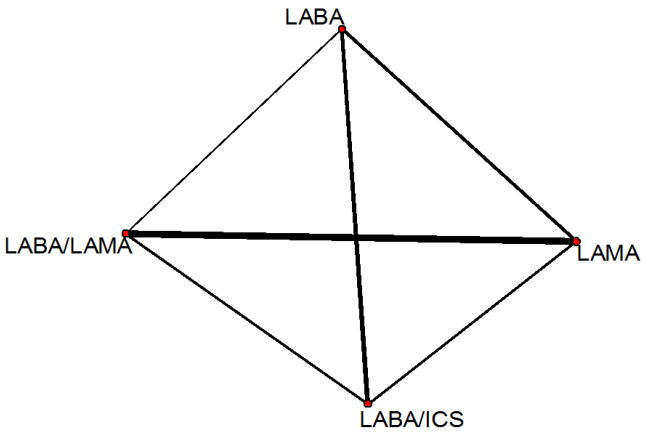
1

1 **Change in FEV1 at 3 months**

2 ***Low risk***

3 *Network diagram*

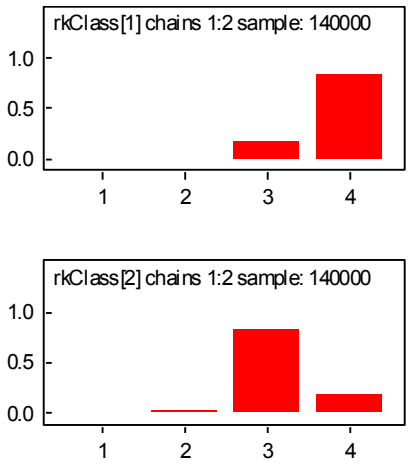
4 **Figure 3 Diagram of the network of studies (by drug class) underlying the NMA.**



5

6 *Rank probability histograms*

7 **Figure 4 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**



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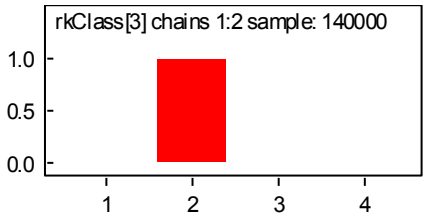
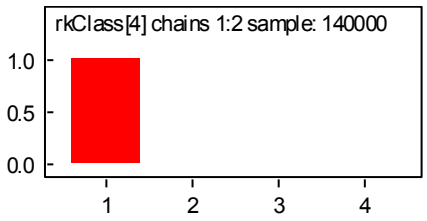
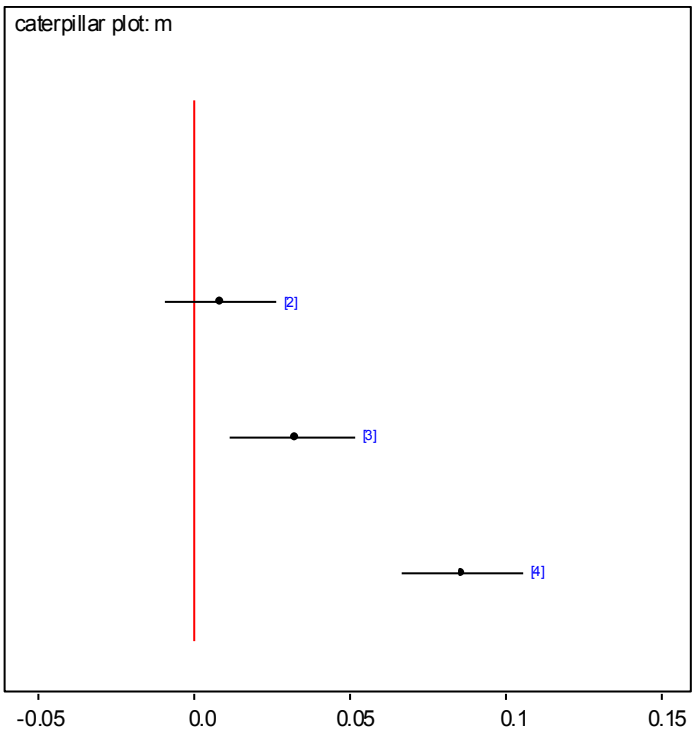




Caterpillar plot

Figure 5 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA)



Mileage chart

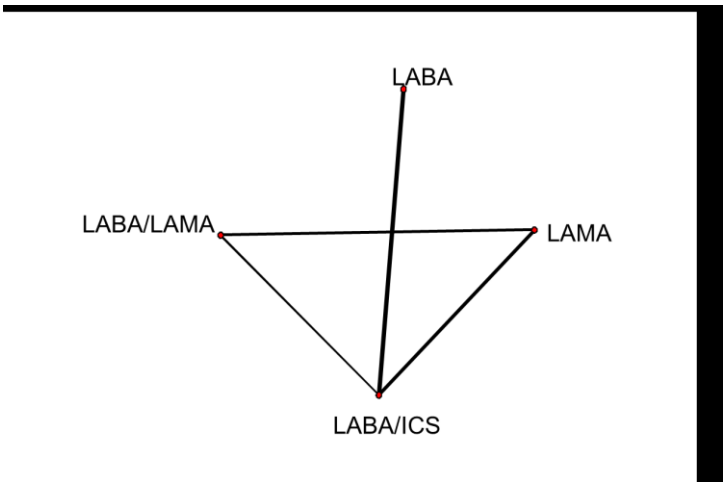
Table 21 Relative effectiveness of all pairwise combinations. (Mean difference with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-0.00 (-0.02, 0.02)	0.05 (0.04, 0.06)	0.07 (0.03, 0.12)
LAMA	0.01 (-0.01, 0.03)		0.02 (-0.02, 0.07)	0.07 (0.06, 0.08)
LABA/ICS	0.03 (0.01, 0.05)	0.02 (0.00, 0.04)		0.08 (0.03, 0.12)
LABA/LAMA	0.09 (0.07, 0.11)	0.08 (0.06, 0.09)	0.05 (0.03, 0.07)	

High risk

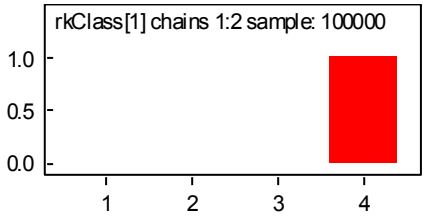
Network diagram

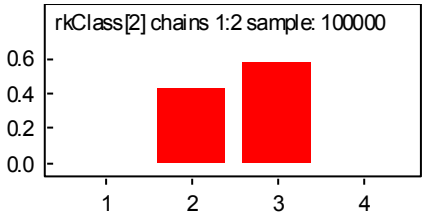
Figure 6 Diagram of the network of studies (by drug class) underlying the NMA.

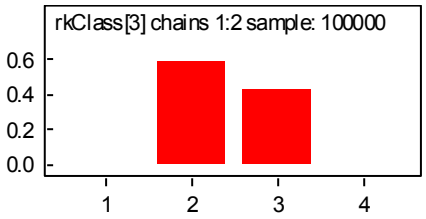


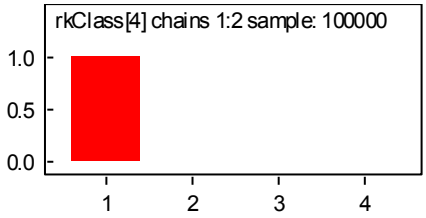
Rank probability histograms

Figure 7 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



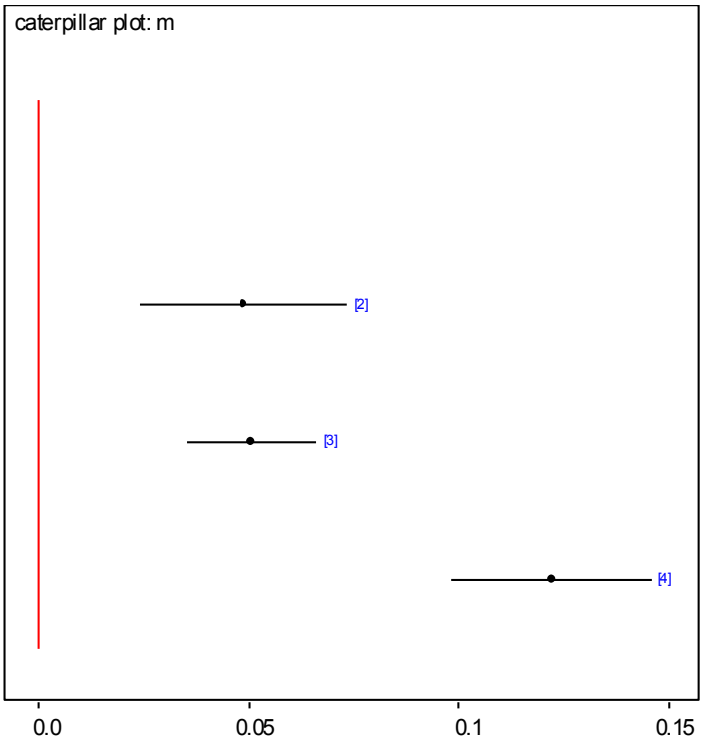






Caterpillar plot

Figure 8 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 22 Relative effectiveness of all pairwise combinations. (Mean difference with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

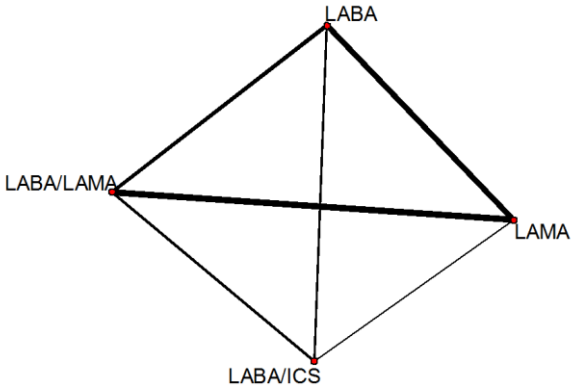
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	0.05 (0.04, 0.07)	-
LAMA	0.05 (0.02, 0.07)		0.01 (-0.02, 0.04)	0.06 (0.02, 0.09)
LABA/ICS	0.05 (0.04, 0.07)	0.00 (-0.02, 0.02)		0.08 (0.06, 0.10)
LABA/LAMA	0.12 (0.10, 0.15)	0.07 (0.05, 0.10)	0.07 (0.05, 0.09)	

Change in FEV1 at 6 months

Low risk

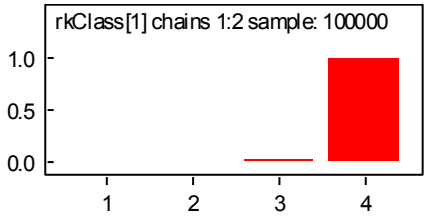
Network diagram

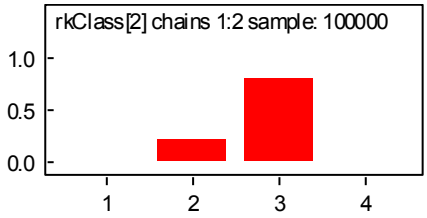
Figure 9 Diagram of the network of studies (by drug class) underlying the NMA.

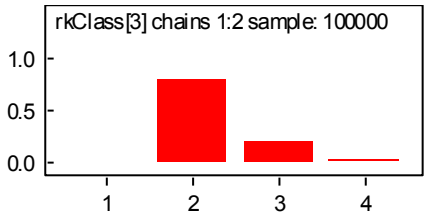


Rank probability histograms

Figure 10 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)







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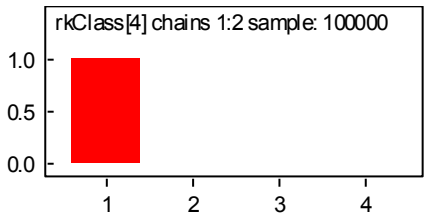
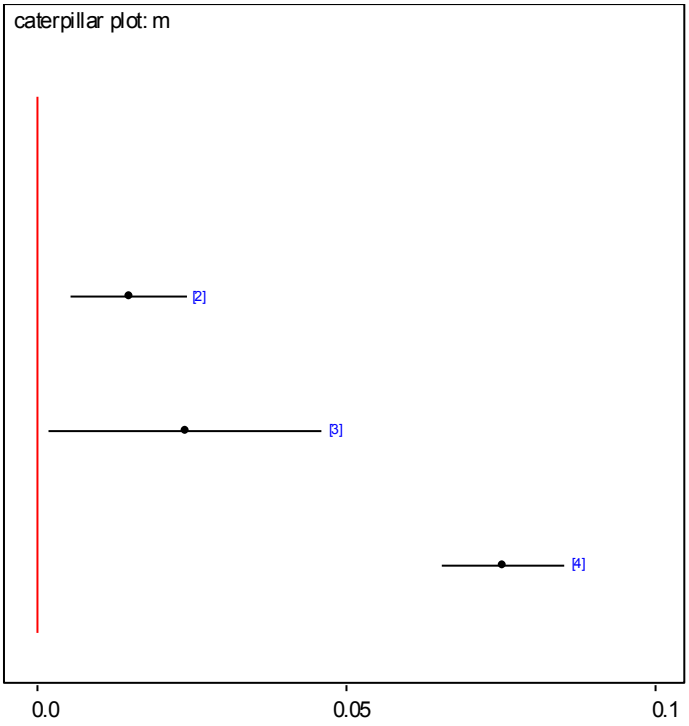


2

3 *Caterpillar plot*

4 **Figure 11 Relative effectiveness of all options versus LABA. (Mean differences with**
5 **95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3=**
6 **LABA/ICS, class 4 = LABA/LAMA.)**



7

Mileage chart

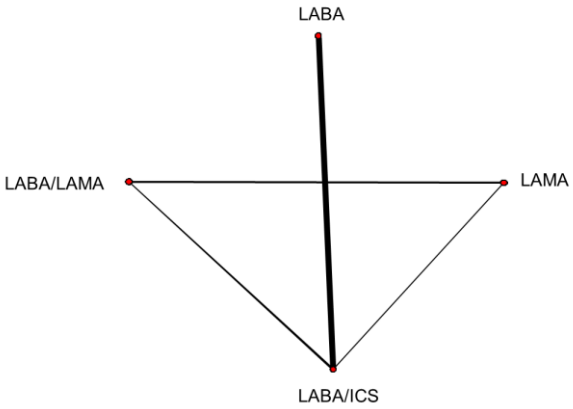
Table 23 Relative effectiveness of all pairwise combinations. (Mean difference with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/LA MA
LABA		0.02 (0.01, 0.03)	0.04 (0.01, 0.07)	0.07 (0.06, 0.08)
LAMA	0.01 (0.01, 0.02)		-0.00 (-0.06, 0.06)	0.06 (0.05, 0.07)
LABA/ICS	0.02 (0.00, 0.05)	0.01 (-0.01, 0.03)		0.10 (0.05, 0.15)
LABA/LAMA	0.08 (0.07, 0.09)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)	

High risk

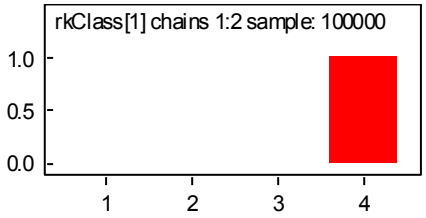
Network diagram

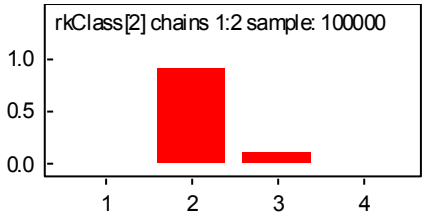
Figure 12 Diagram of the network of studies (by drug class) underlying the NMA.

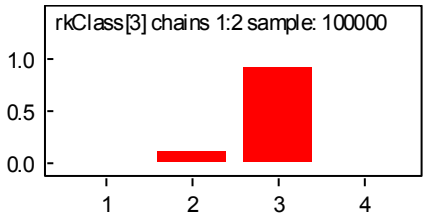


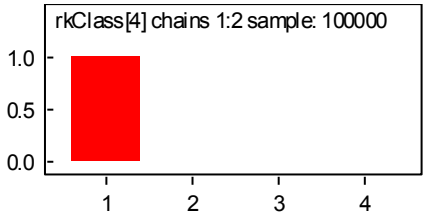
Rank probability histograms

Figure 13 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



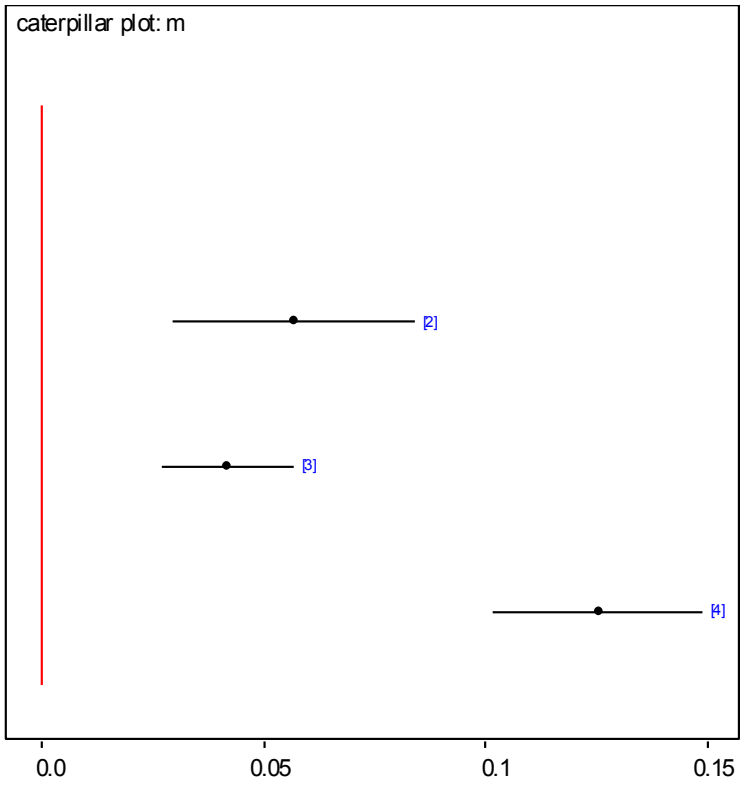






Caterpillar plot

Figure 14 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 24 Relative effectiveness of all pairwise combinations. (Mean difference with 95% confidence interval for pair wise data across the top of the chart and 95% credible interval for NMA derived data along the side.)

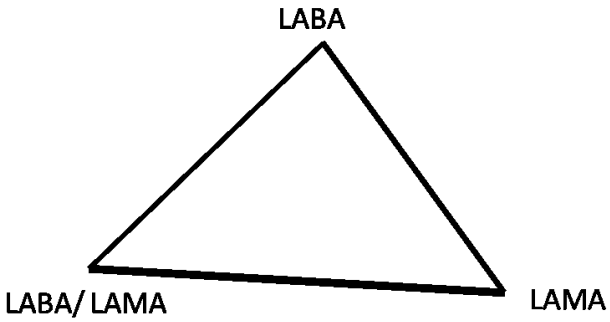
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	0.04 (0.03, 0.06)	-
LAMA	0.06 (0.03, 0.08)		-0.01 (-0.04, 0.02)	0.06 (0.02, 0.10)
LABA/ICS	0.04 (0.03, 0.06)	-0.01 (-0.04, 0.01)		0.09 (0.07, 0.11)
LABA/LAMA	0.13 (0.10, 0.15)	0.07 (0.04, 0.09)	0.08 (0.06, 0.10)	

Change in FEV1 at 12 months

Low risk

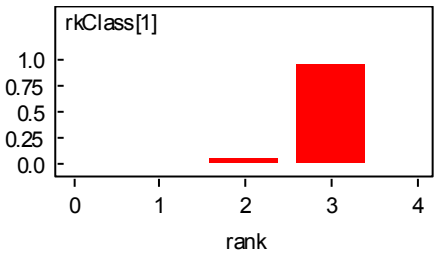
Network diagram

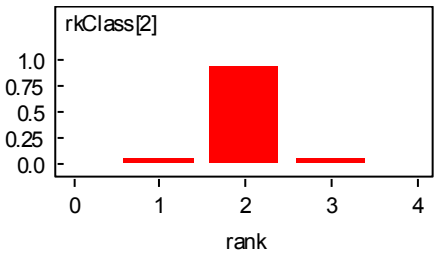
Figure 15 Diagram of the network of studies (by drug class) underlying the NMA.

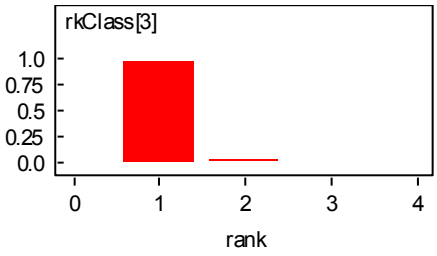


Rank probability histograms

Figure 16 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/LAMA. Rank 1 is best.)

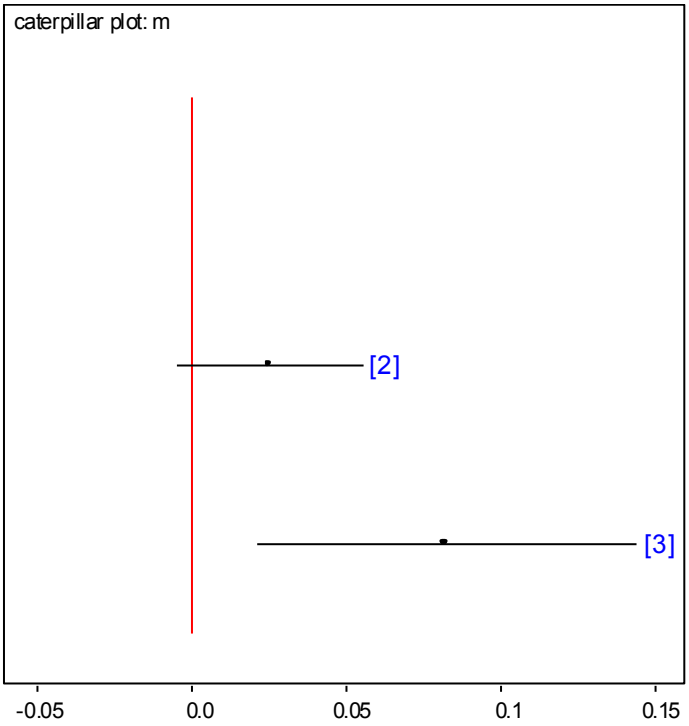






Caterpillar plot

Figure 17 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/LAMA.)



Mileage chart

Table 25 Relative effectiveness of all pairwise combinations. (Mean difference with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ LAMA
LABA		0.02	0.07

	LABA	LAMA	LABA/ LAMA
		(0.01, 0.03)	(0.06, 0.08)
LAMA	0.03 (0.00, 0.06)		0.06 (0.04, 0.08)
LABA/LAMA	0.08 (0.02, 0.14)	0.06 (-0.01, 0.13)	

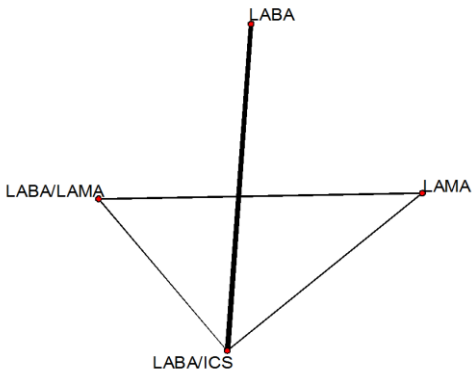
1

2

3 ***High risk***

4 *Network diagram*

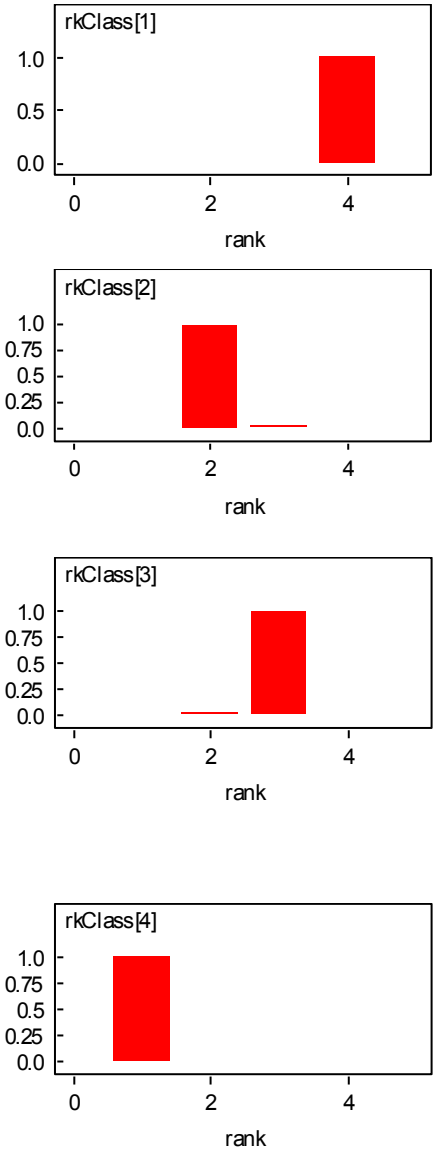
5 **Figure 18 Diagram of the network of studies (by drug class) underlying the NMA.**



6

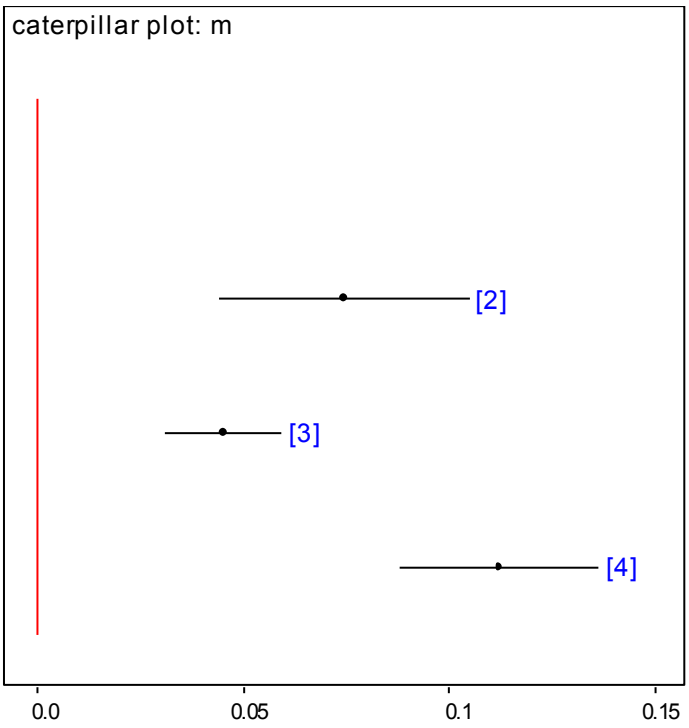
Rank probability histograms

Figure 19 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 20 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 26 Relative effectiveness of all pairwise combinations. (Mean difference with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

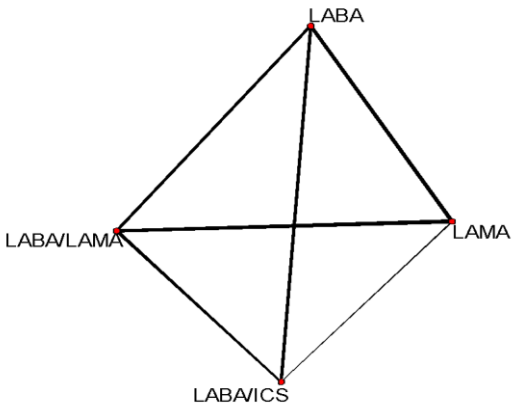
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	0.05 (0.04, 0.07)	-
LAMA	0.07 (0.04, 0.11)		-0.01 (-0.08, 0.05)	0.05 (0.01, 0.09)
LABA/ICS	0.05 (0.03, 0.06)	-0.03 (-0.06, -0.00)		0.06 (0.04, 0.08)
LABA/LAMA	0.11 (0.09, 0.14)	0.04 (0.01, 0.07)	0.07 (0.05, 0.09)	

1 **Moderate to severe exacerbations**

2 ***Low risk***

3 *Network diagram*

4 **Figure 21 Diagram of the network of studies (by drug class) underlying the NMA.**

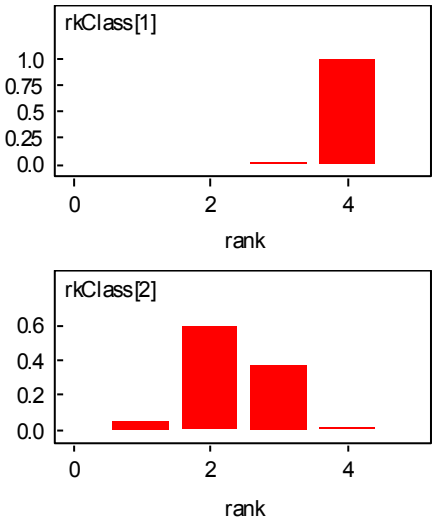


5

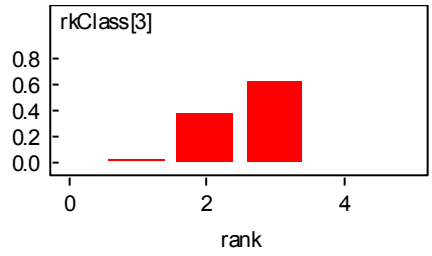
6 *Rank probability histograms*

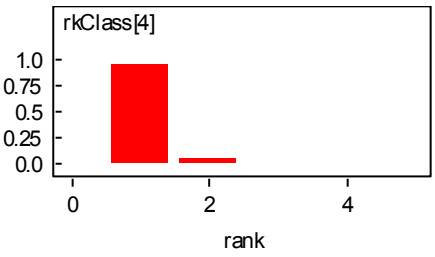
7 **Figure 22 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**

9



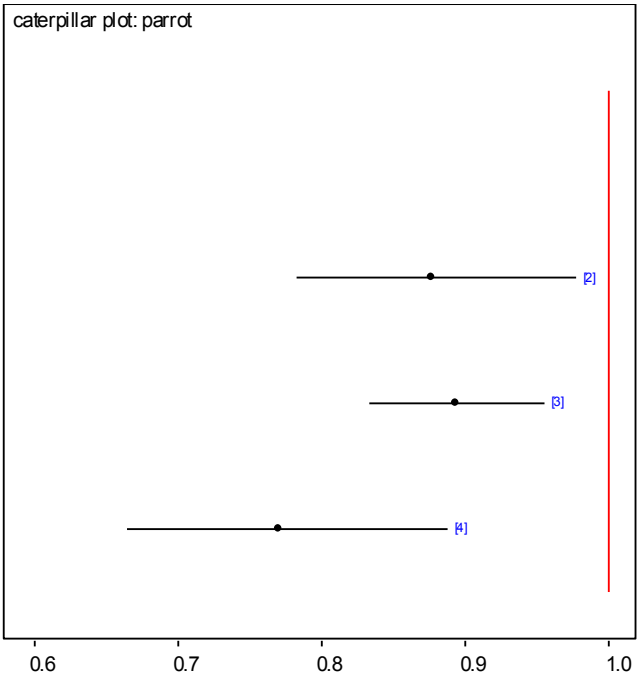
10





Caterpillar plot

Figure 23 Relative effectiveness of all options versus LABA. (Hazard ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

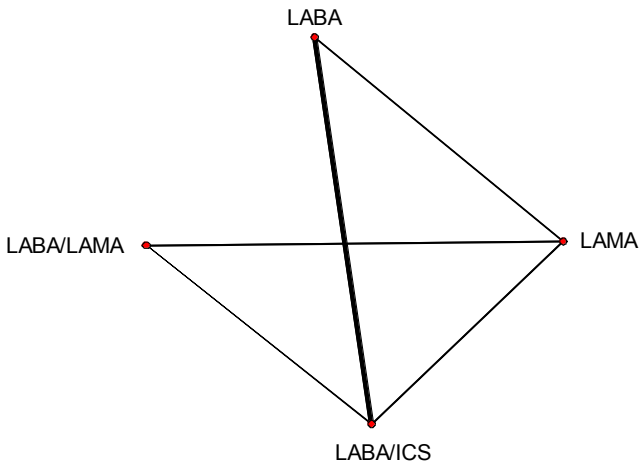
Table 27 Relative effectiveness of all pairwise combinations. (Hazard ratios with 95% credible intervals for NMA derived data along the side. Pair wise data is not shown here as it was calculated as RR.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	-	-
LAMA	0.88 (0.78, 0.98)		-	-
LABA/ICS	0.89 (0.83, 0.96)	1.02 (0.90, 1.16)		-
LABA/LAMA	0.77 (0.67, 0.89)	0.88 (0.75, 1.03)	0.86 (0.74, 1.00)	

High risk

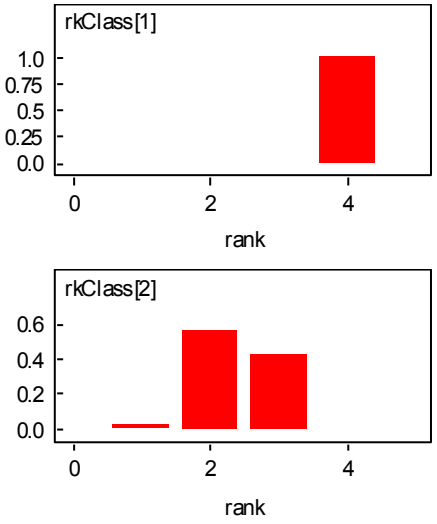
Network diagram

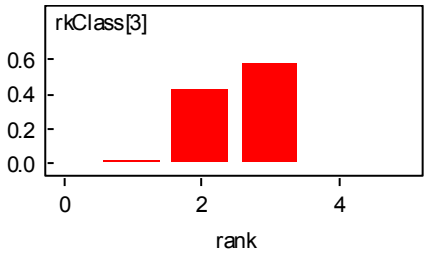
Figure 24 Diagram of the network of studies (by drug class) underlying the NMA.

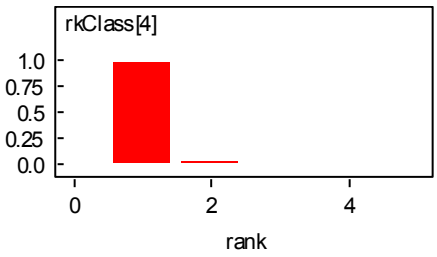


Rank probability histograms

Figure 25 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)

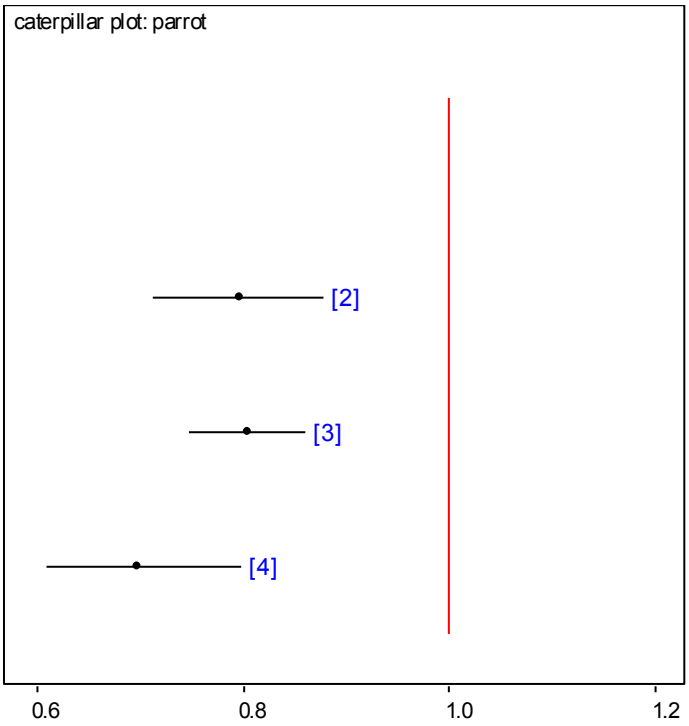






Caterpillar plot

Figure 26 Relative effectiveness of all options versus LABA. (Hazard ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 28 Relative effectiveness of all pairwise combinations. (Hazard ratios with 95% credible intervals for NMA derived data along the side. Pair wise data is not shown here as it was calculated as RR.)

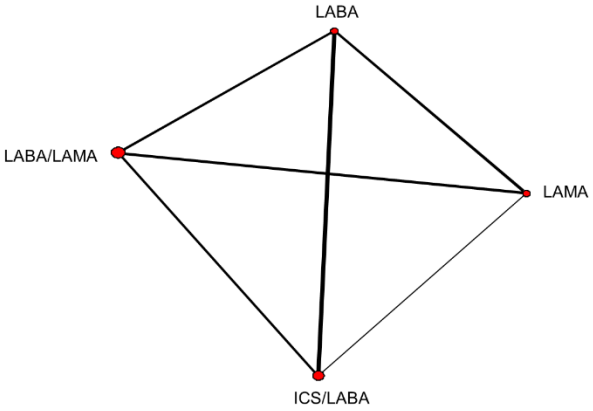
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	-	-
LAMA	0.80 (0.71, 0.88)		-	-
LABA/ICS	0.80 (0.75, 0.86)	1.10 (0.91, 1.13)		-
LABA/LAMA	0.70 (0.61, 0.80)	0.88 (0.78, 0.99)	0.87 (0.76, 0.99)	

1 **Severe exacerbations**

2 ***Low risk***

3 *Network diagram*

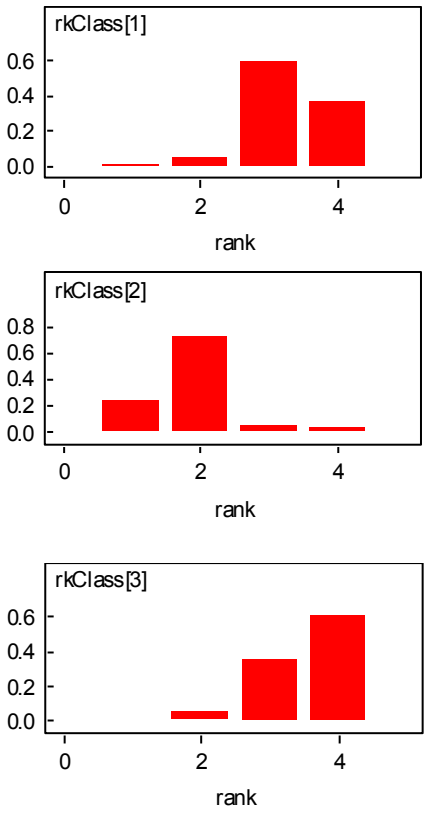
4 **Figure 27 Diagram of the network of studies (by drug class) underlying the NMA.**



5

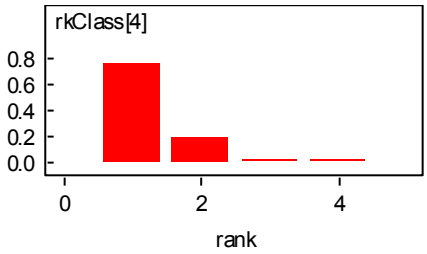
6 *Rank probability histograms*

7 **Figure 28 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**



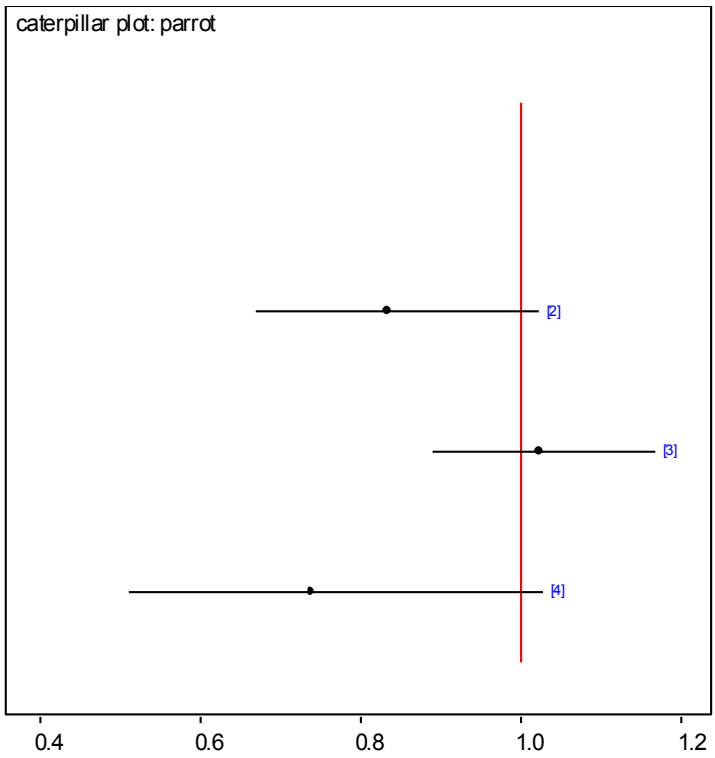
9

10



Caterpillar plot

Figure 29 Relative effectiveness of all options versus LABA. (Hazard ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 29 Relative effectiveness of all pairwise combinations. (Hazard ratios with 95% credible intervals for NMA derived data along the side. Pair wise data is not shown here as it was calculated as RR.)

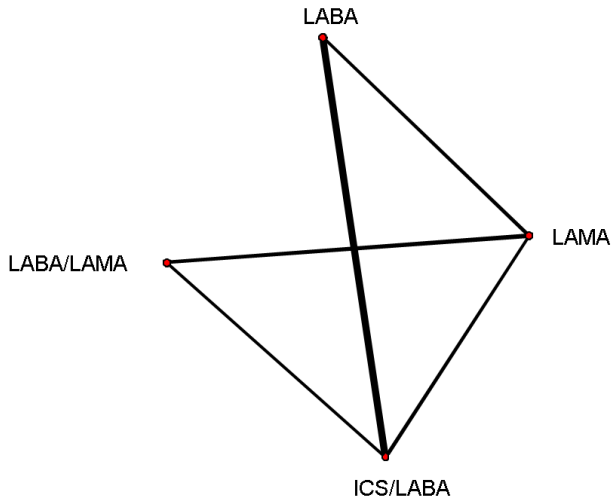
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	-	-
LAMA	0.83 (0.67, 1.02)		-	-

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA/ICS	1.02 (0.89, 1.17)	1.24 (0.96, 1.58)		-
LABA/LAMA	0.74 (0.51, 1.03)	0.89 (0.62, 1.24)	0.72 (0.50, 1.02)	

High risk

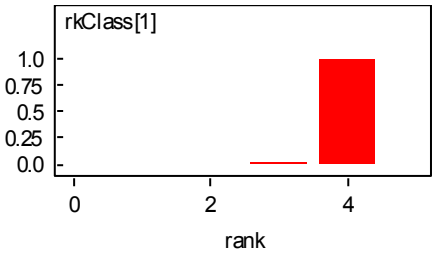
Network diagram

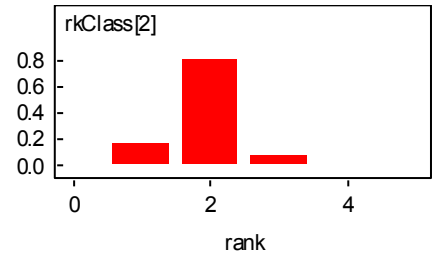
Figure 30 Diagram of the network of studies (by drug class) underlying the NMA.



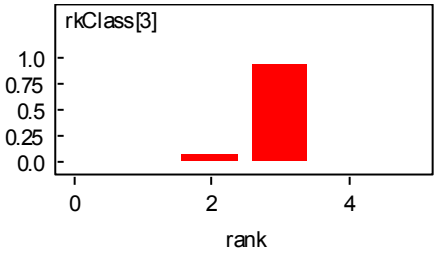
Rank probability histograms

Figure 31 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)

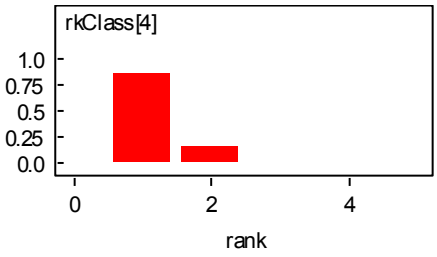

rkClass[1]
1.0
0.75
0.5
0.25
0.0
0
2
4
rank


rkClass[2]
0.8
0.6
0.4
0.2
0.0
0
2
4
rank

1


rkClass[3]
1.0
0.75
0.5
0.25
0.0
0
2
4
rank

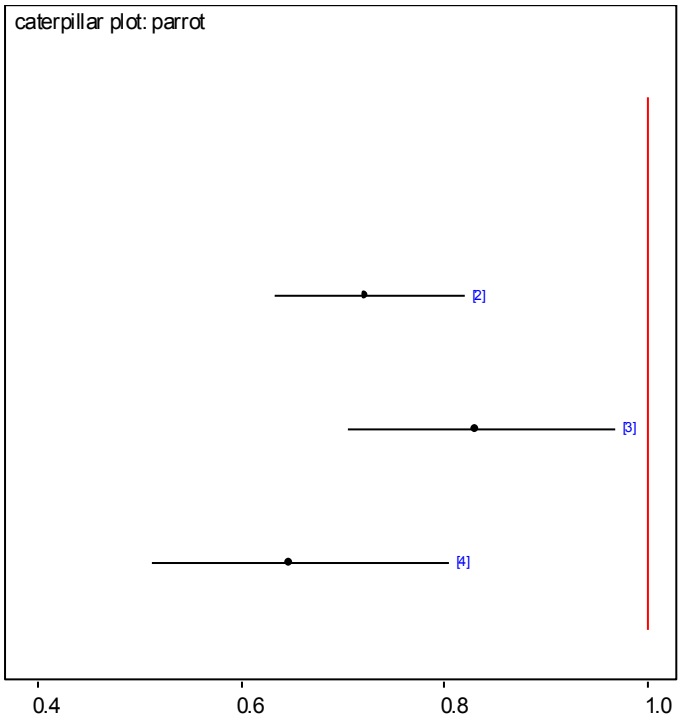
2


rkClass[4]
1.0
0.75
0.5
0.25
0.0
0
2
4
rank

3

Caterpillar plot

Figure 32 Relative effectiveness of all options versus LABA. (Hazard ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 30 Relative effectiveness of all pairwise combinations. (Hazard ratios with 95% credible intervals for NMA derived data along the side. Pair wise data is not shown here as it was calculated as RR.)

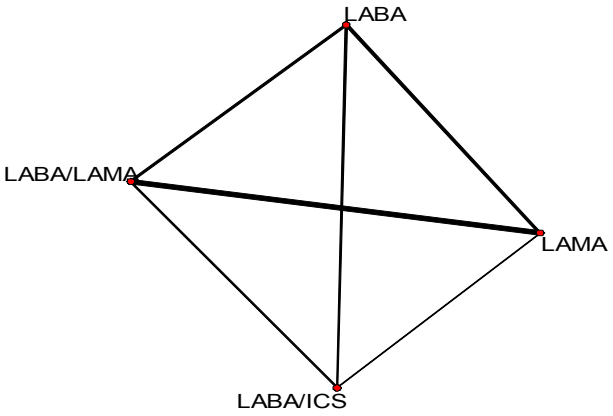
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-	-	-
LAMA	0.72 (0.63, 0.82)		-	-
LABA/ICS	0.83 (0.71, 0.97)	1.15 (0.97, 1.14)		-
LABA/LAMA	0.65 (0.51, 0.81)	0.90 (0.71, 1.11)	0.78 (0.64, 0.93)	

Dropouts due to adverse events

Low risk

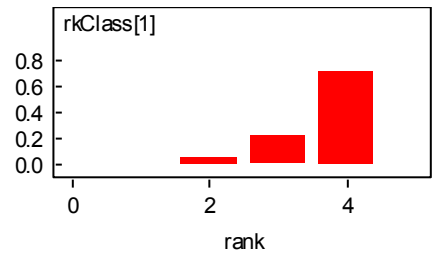
Network diagram

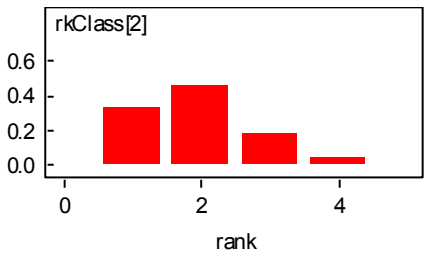
Figure 33 Diagram of the network of studies (by drug class) underlying the NMA.

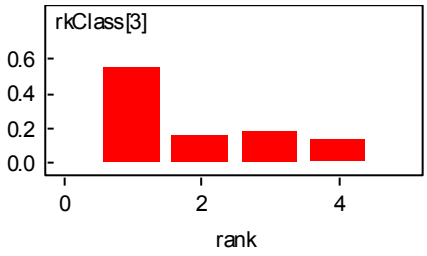


Rank probability histograms

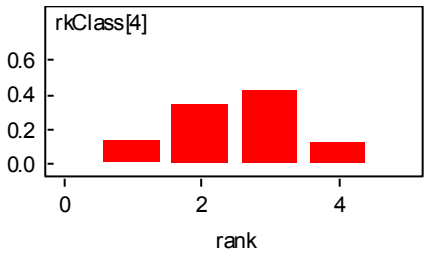
Figure 34 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)







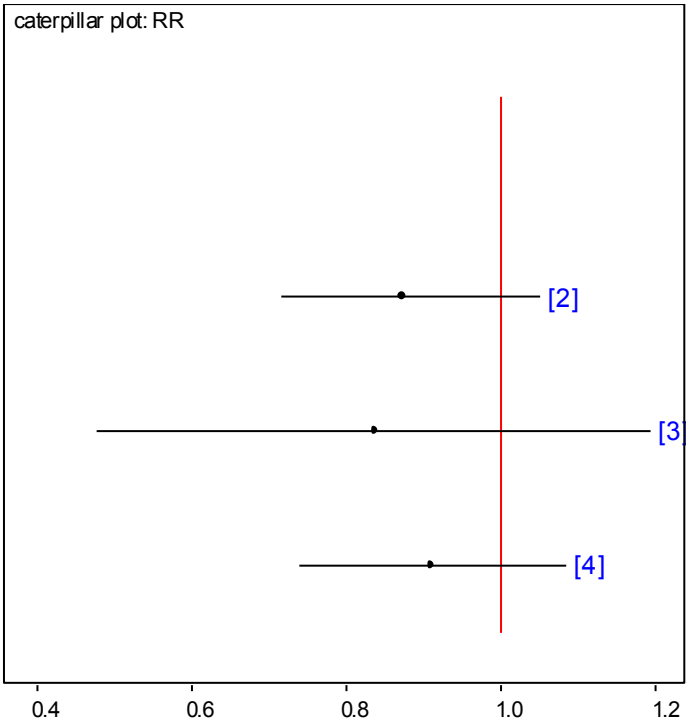
1



2

3 *Caterpillar plot*

4 **Figure 35 Relative effectiveness of all options versus LABA. (Risk ratios with 95%**
5 **credible intervals and line of no effect in red. Class 2 = LAMA, class 3=**
6 **LABA/ICS, class 4 = LABA/LAMA.)**



7

Mileage chart

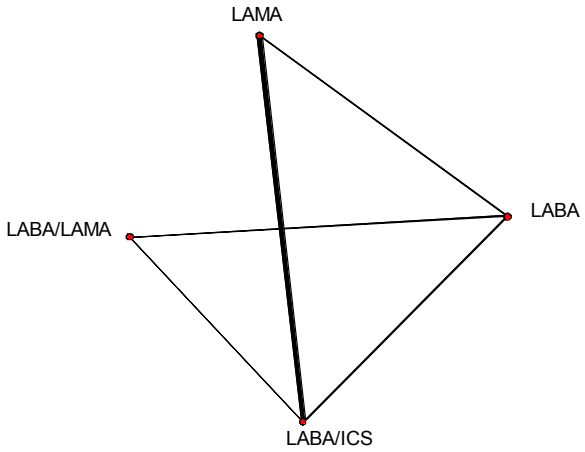
Table 31 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.90 (0.81, 1.00)	0.92 (0.81, 1.05)	0.93 (0.77, 1.13)
LAMA	0.87 (0.72, 1.05)		0.81 (0.46, 1.45)	1.08 (0.82, 1.42)
LABA/ICS	0.84 (0.48, 1.20)	0.96 (0.55, 1.40)		0.91 (0.70, 1.18)
LABA/LAMA	0.91 (0.74, 1.09)	1.05 (0.86, 1.24)	1.15 (0.75, 1.88)	

High risk

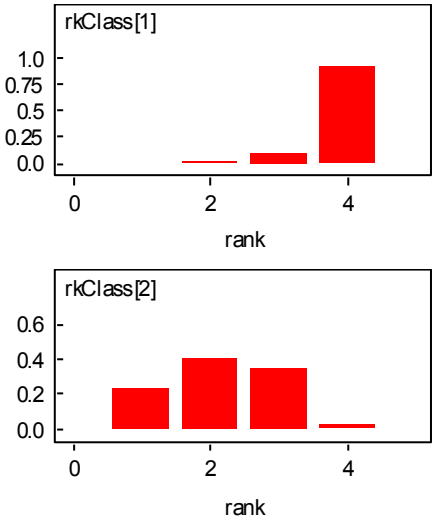
Network diagram

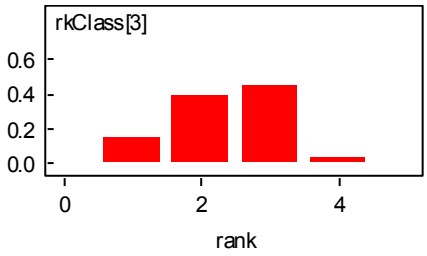
Figure 36 Diagram of the network of studies (by drug class) underlying the NMA.

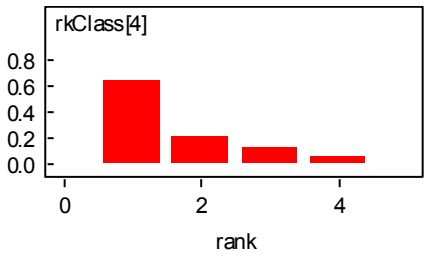


Rank probability histograms

Figure 37 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)

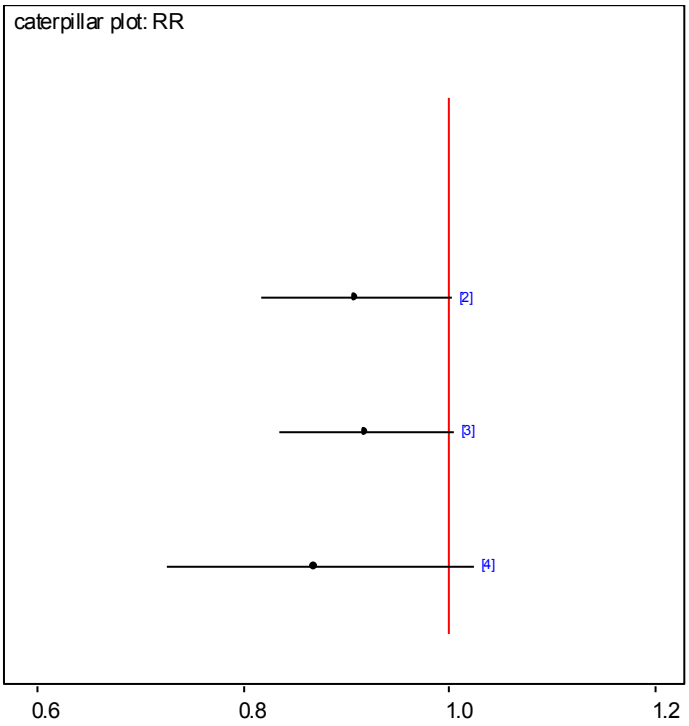






Caterpillar plot

Figure 38 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 32 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

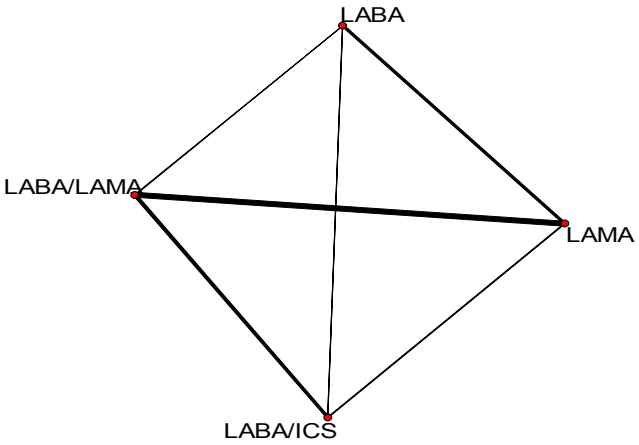
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.91 (0.79, 1.04)	0.89 (0.79. 1.00)	-
LAMA	0.91 (0.82, 1.00)		1.04 (0.76, 1.42)	0.81 (0.54, 1.19)
LABA/ICS	0.92 (0.84, 1.01)	1.01 (0.90, 1.14)		0.89 (0.71, 1.12)
LABA/LAMA	0.87 (0.73, 1.03)	0.96 (0.80, 1.13)	0.95 (0.80, 1.11)	

1 **SGRQ at 3 months**

2 ***Low risk***

3 *Network diagram*

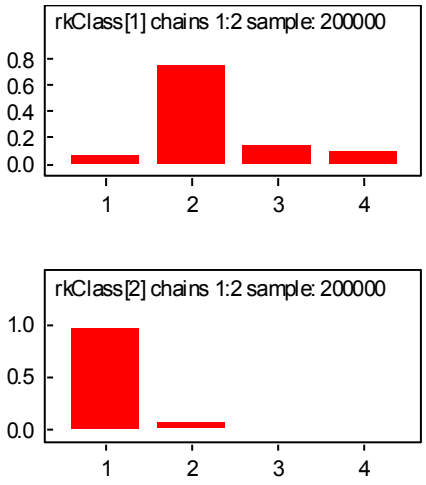
4 **Figure 39 Diagram of the network of studies (by drug class) underlying the NMA.**



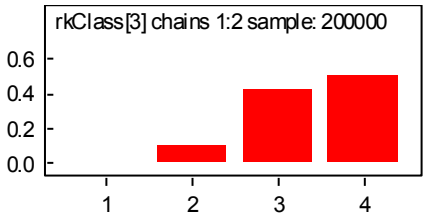
5

6 *Rank probability histograms*

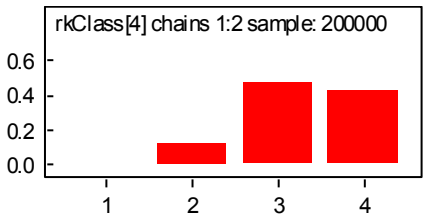
7 **Figure 40 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)**



9



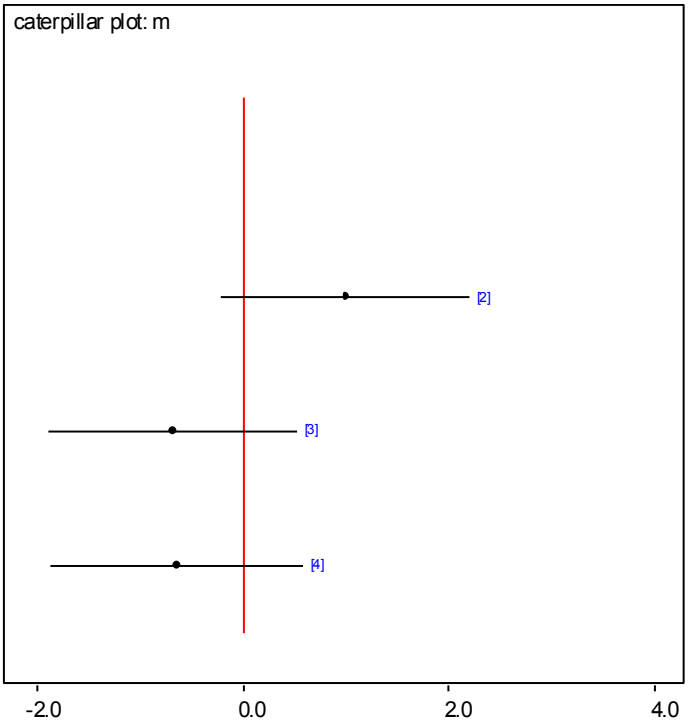
1



2

3 *Caterpillar plot*

4 **Figure 41 Relative effectiveness of all options versus LABA. (Mean differences with**
5 **95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3=**
6 **LABA/ICS, class 4 = LABA/LAMA.)**



7

Mileage chart

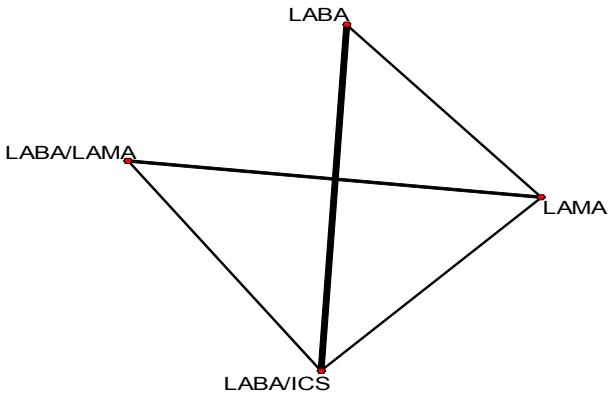
Table 33 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.84 (0.87, 2.80)	-1.00 (-2.61, 0.61)	-1.29 (-4.29, 1.17)
LAMA	1.01 (-0.20, 2.22)		-1.48 (-3.41, 0.45)	-1.60 (-2.19, -1.01)
LABA/ICS	-0.67 (-1.88, 0.54)	-1.68 (-2.59, -0.78)		-0.03 (-1.02, 0.96)
LABA/LAMA	-0.63 (-1.86, 0.60)	-1.64 (-2.20,-1.08)	0.04 (-0.79, 0.88)	

High risk

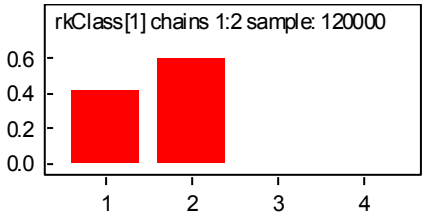
Network diagram

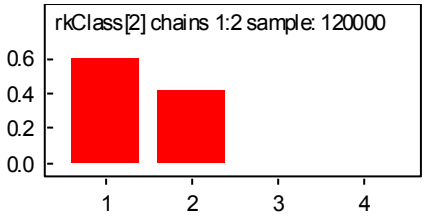
Figure 42 Diagram of the network of studies (by drug class) underlying the NMA.

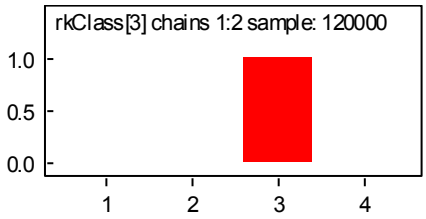


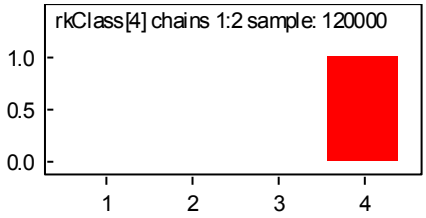
Rank probability histograms

Figure 43 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)



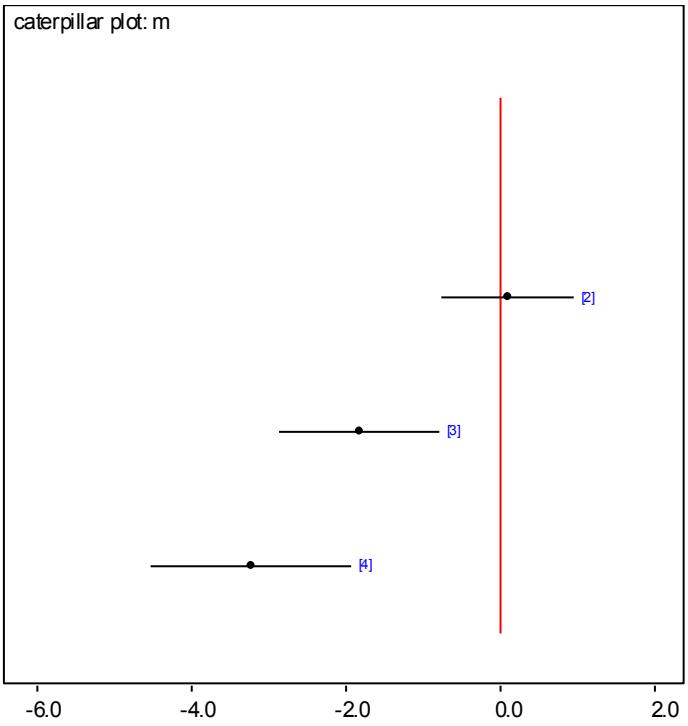






Caterpillar plot

Figure 44 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 34 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

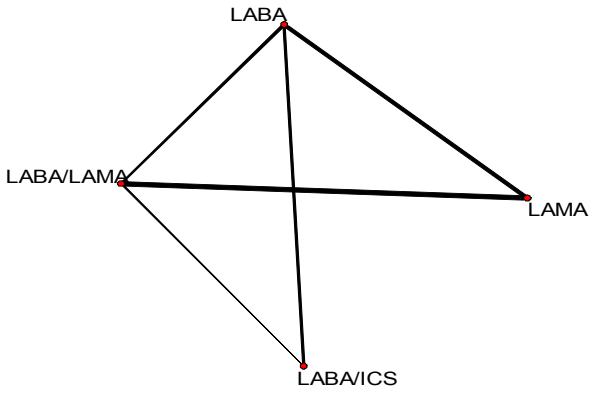
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.10 (-0.82, 1.02)	-1.81 (-2.99, -0.64)	-
LAMA	0.10 (-0.76, 0.96)		-1.06 (-4.39, 2.27)	-3.68 (-5.84, -1.52)
LABA/ICS	-1.82 (-2.86, 0.78)	-1.92 (-3.10, -0.74)		-1.30 (-2.35, -0.25)
LABA/LAMA	-3.21 (-2.86, -0.78)	-3.31 (-4.67, -1.97)	-1.39 (-2.37,-0.42)	

SQRQ at 6 months

Low risk

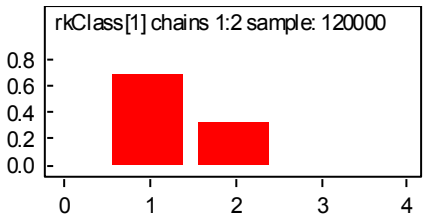
Network diagram

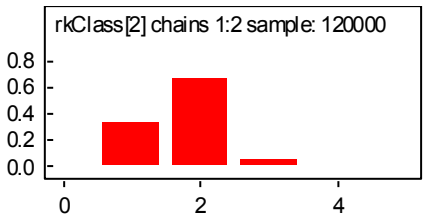
Figure 45 Diagram of the network of studies (by drug class) underlying the NMA.

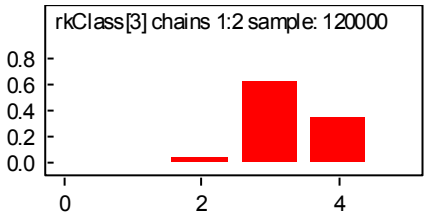


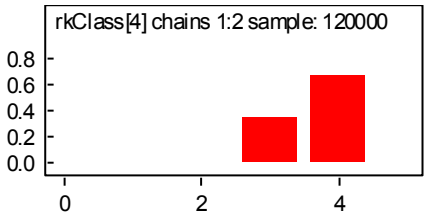
Rank probability histograms

Figure 46 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)



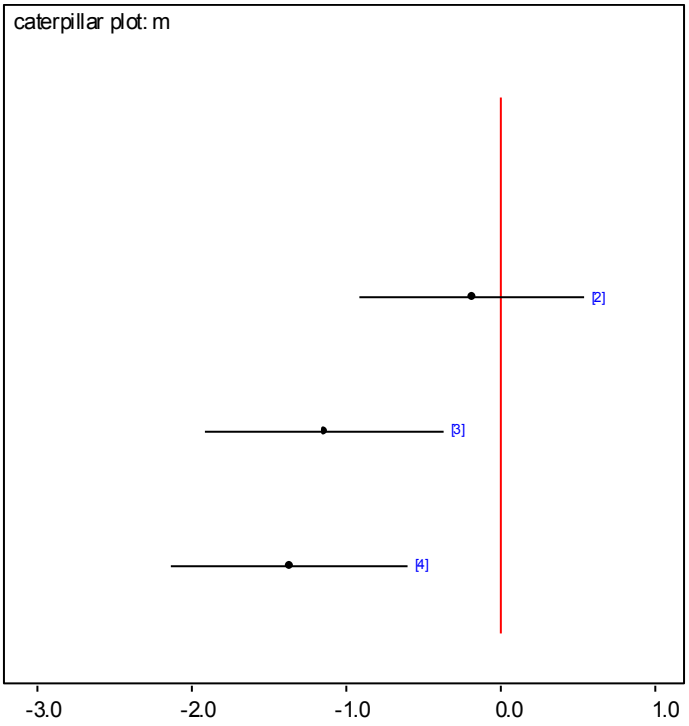






Caterpillar plot

Figure 47 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 35 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

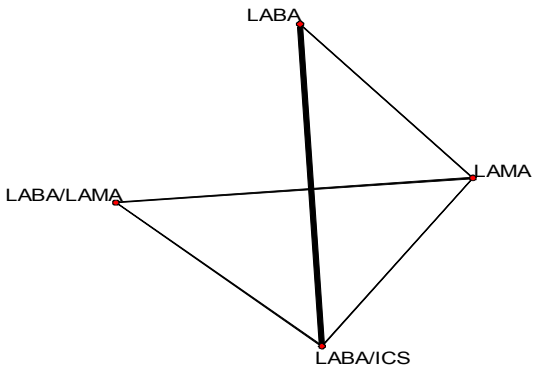
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-0.23 (-0.99, 0.54)	-1.18 (-1.97, -0.40)	-1.09 (-1.96, -0.22)
LAMA	-0.18		-	-1.20

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
	(-0.43, 0.55)			(-1.83, -0.57)
LABA/ICS	-1.14 (-1.40, -0.37)	-0.95 (-1.31, 0.09)		-0.99 (-4.12, 2.14)
LABA/LAMA	-1.36 (-1.63, -0.60)	-1.18 (-1.40, -0.56)	-0.23 (-0.59, 0.82)	

1 ***High risk***

2 *Network diagram*

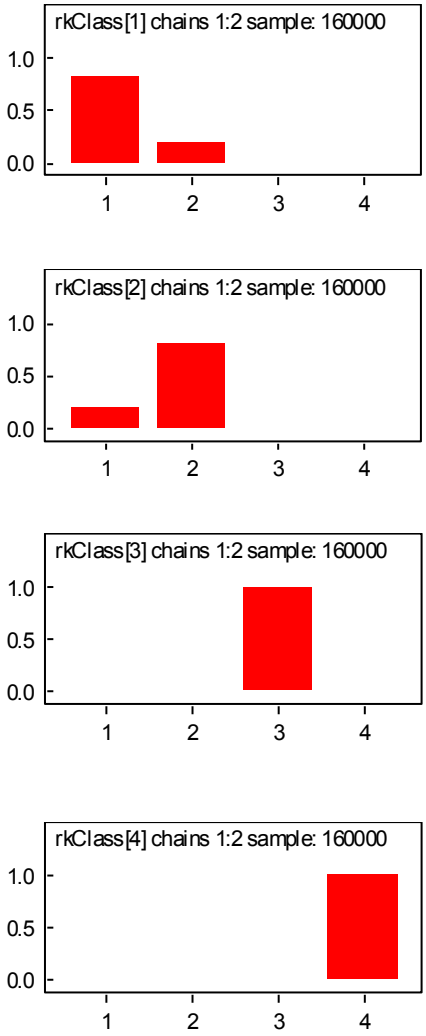
3 **Figure 48 Diagram of the network of studies (by drug class) underlying the NMA.**



4

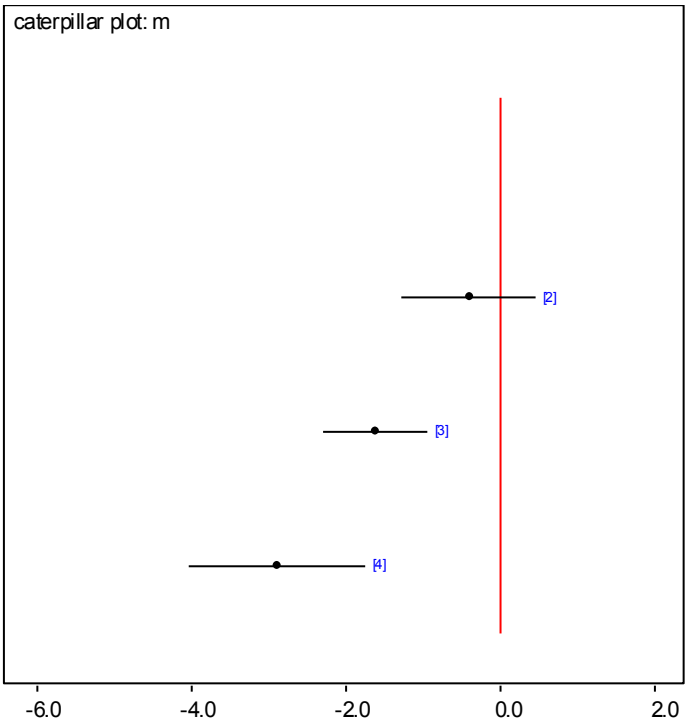
Rank probability histograms

Figure 49 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)



Caterpillar plot

Figure 50 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 36 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

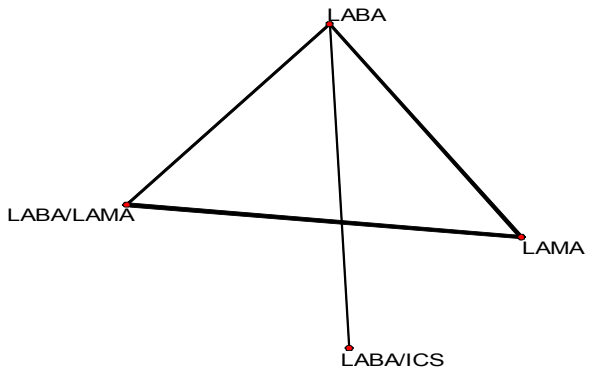
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-0.70 (-1.74, 0.34)	-1.45 (-2.17, -0.73)	-
LAMA	-0.39 (-0.69, 0.47)		-1.97 (-3.79, -0.15)	-2.79 (-5.02, -0.56)
LABA/ICS	-1.60 (-1.83, -0.93)	-1.21 (-1.53, -0.25)		-1.20 (-2.28, -01.2)
LABA/LAMA	-2.88 (-3.27, -1.73)	-2.48 (-2.91, -1.23)	-1.27 (-1.61, -0.29)	

1 **SGRQ at 12 months**

2 ***Low risk***

3 *Network diagram*

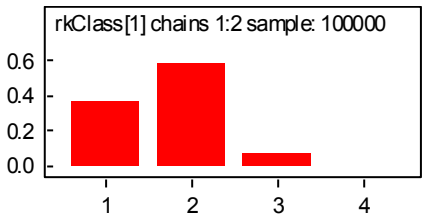
4 **Figure 51 Diagram of the network of studies (by drug class) underlying the NMA.**

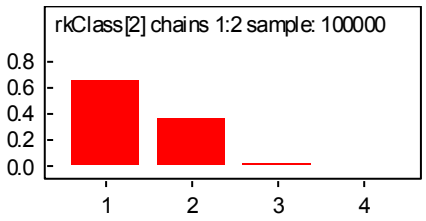


5

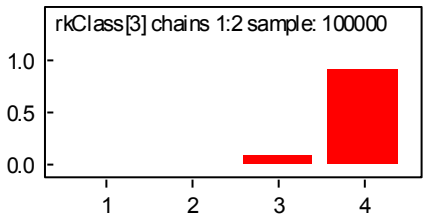
6 *Rank probability histograms*

7 **Figure 52 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)**

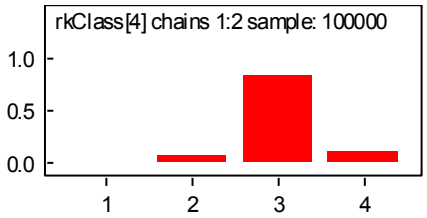




9

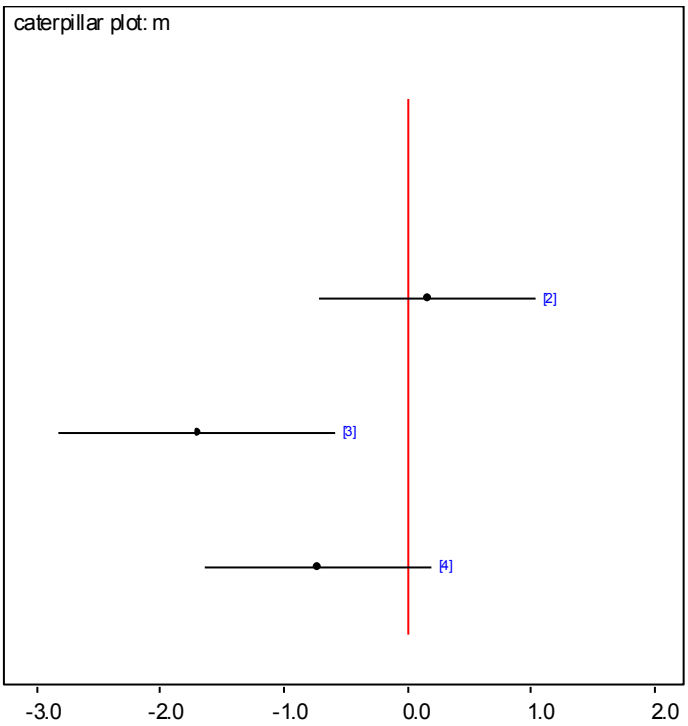


10



Caterpillar plot

Figure 53 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 37 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

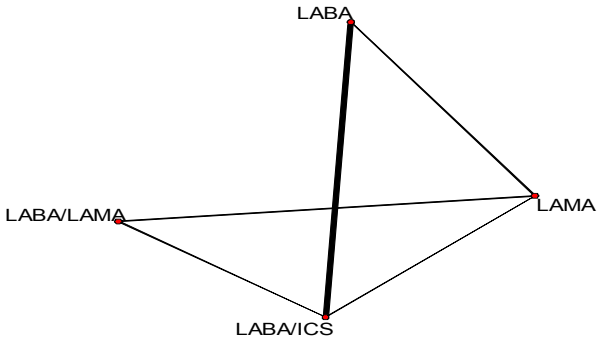
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.10 (-0.79, 0.99)	-1.70 (-2.82, -0.58)	-0.69 (-1.64, 0.25)
LAMA	0.16 (-0.14,1.04)		-	-0.87 (-1.64, -0.10)
LABA/ICS	-1.69	-1.85		-

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
	(-2.08, -0.57)	(-2.34, -0.43)		
LABA/LAMA	-0.72 (-1.04, 0.20)	-0.89 (-1.15, -0.11)	0.97 (0.47, 2.42)	

1 ***High risk***

2 *Network diagram*

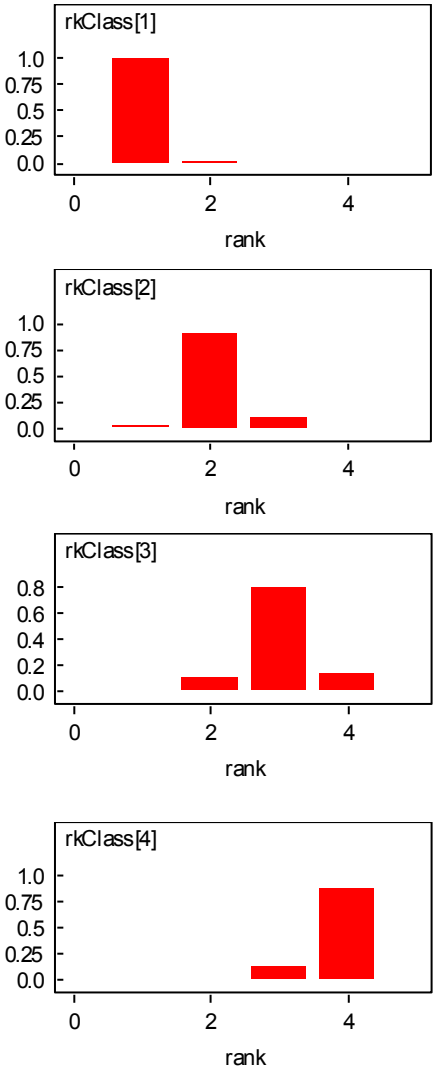
3 **Figure 54 Diagram of the network of studies (by drug class) underlying the NMA.**



4

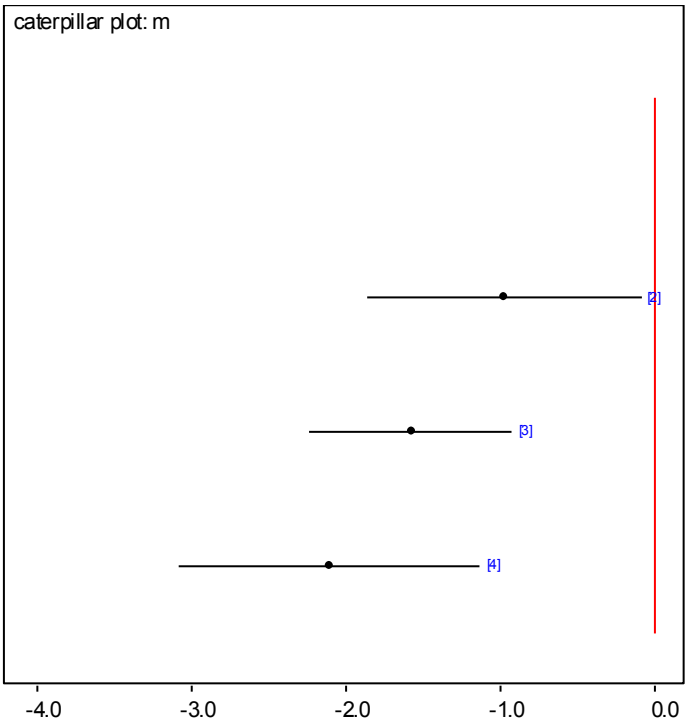
Rank probability histograms

Figure 55 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)



Caterpillar plot

Figure 56 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 38 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

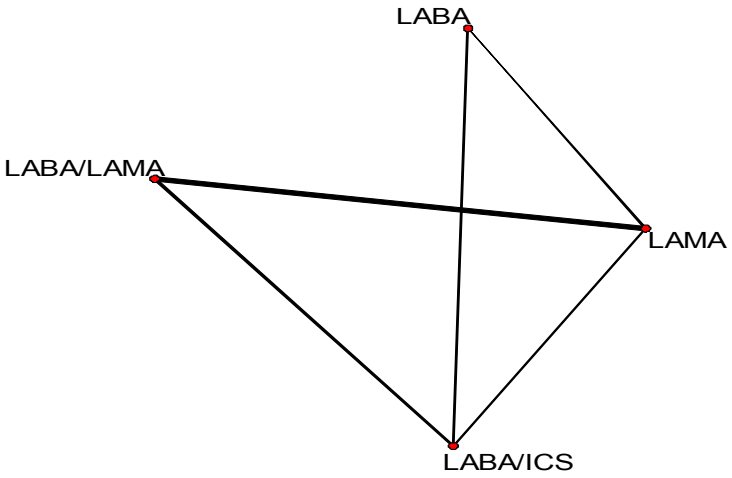
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-0.40 (-1.56, 0.76)	-1.78 (-2.49, -1.07)	-
LAMA	-0.98 (-1.86, 0.08)		-0.99 (-2.98, 1.00)	-3.38 (-5.83, -0.93)
LABA/ICS	-1.57 (-2.23, -0.92)	-0.60 (-1.48, 0.29)		-1.20 (-2.34,-0.06)
LABA/LAMA	-2.10 (-3.08, -1.13)	-1.12 (-1.88, -0.37)	-0.53 (-1.42, 0.36)	

1 **SGRQ responders at 3 months**

2 ***Low risk***

3 *Network diagram*

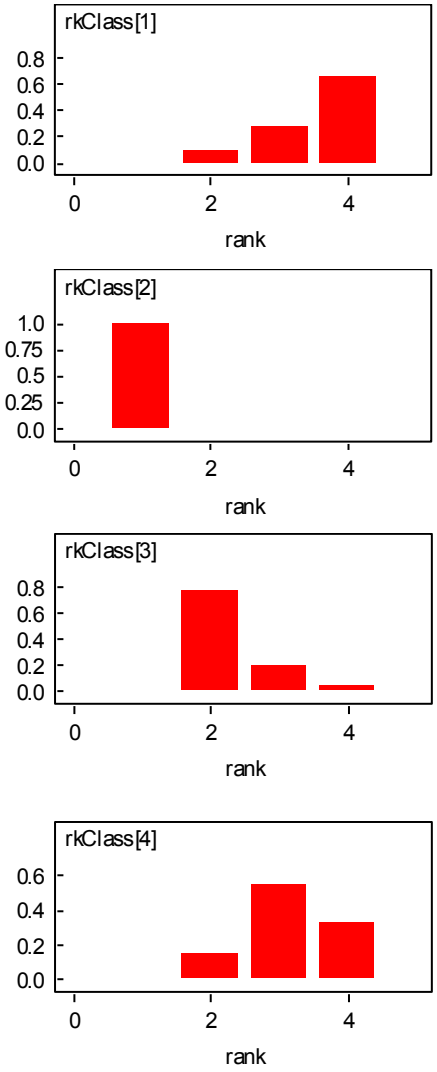
4 **Figure 57 Diagram of the network of studies (by drug class) underlying the NMA.**



5

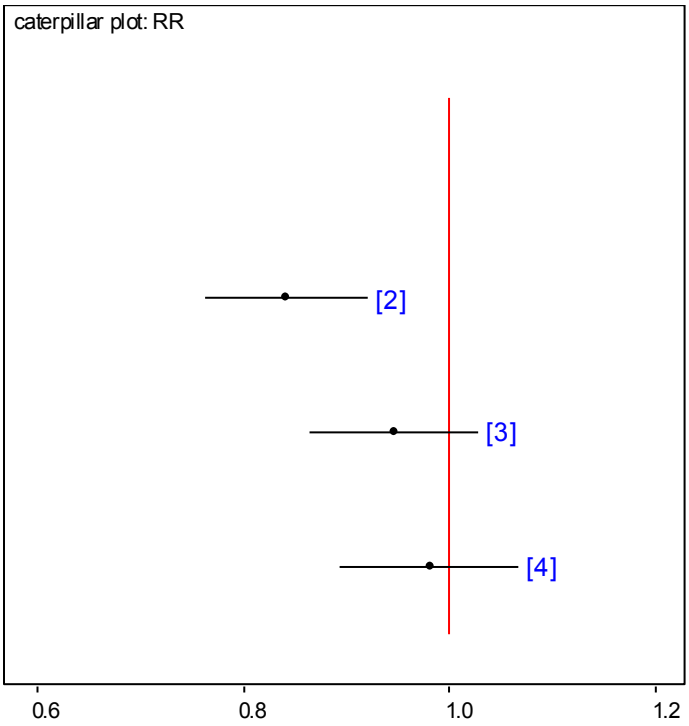
Rank probability histograms

Figure 58 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)



Caterpillar plot

Figure 59 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3 = LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 39 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

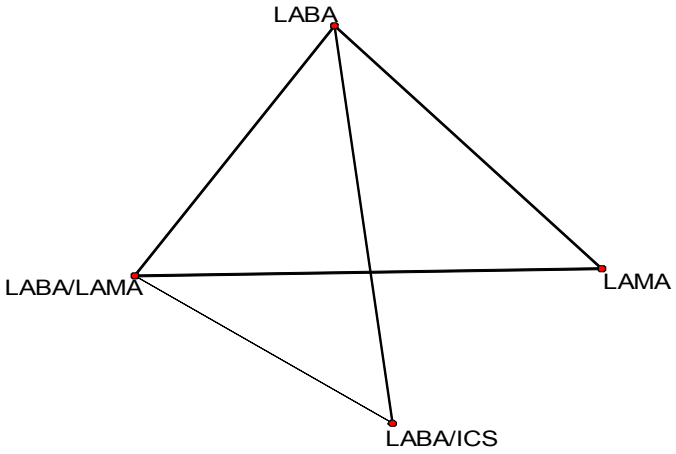
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.84 (0.75, 0.94)	0.95 (0.87, 1.05)	-
LAMA	0.84 (0.76, 0.92)		1.14 (0.95, 1.36)	1.14 (1.08, 1.21)
LABA/ICS	0.95 (0.86, 1.03)	1.13 (1.04, 1.22)		1.04 (0.96, 1.12)
LABA/LAMA	0.98 (0.89, 1.07)	1.17 (1.10, 1.24)	1.04 (0.97, 1.11)	

SGRQ responders at 6 months

Low risk

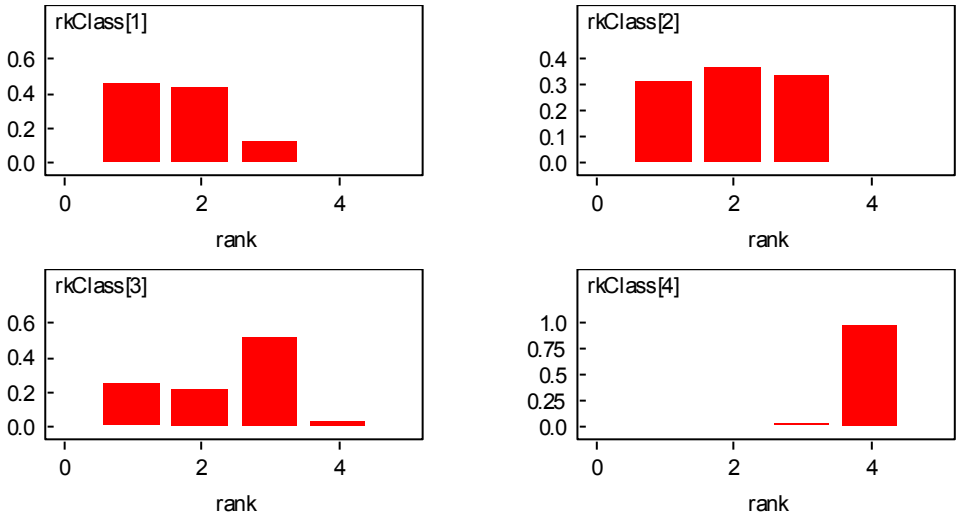
Network diagram

Figure 60 Diagram of the network of studies (by drug class) underlying the NMA.



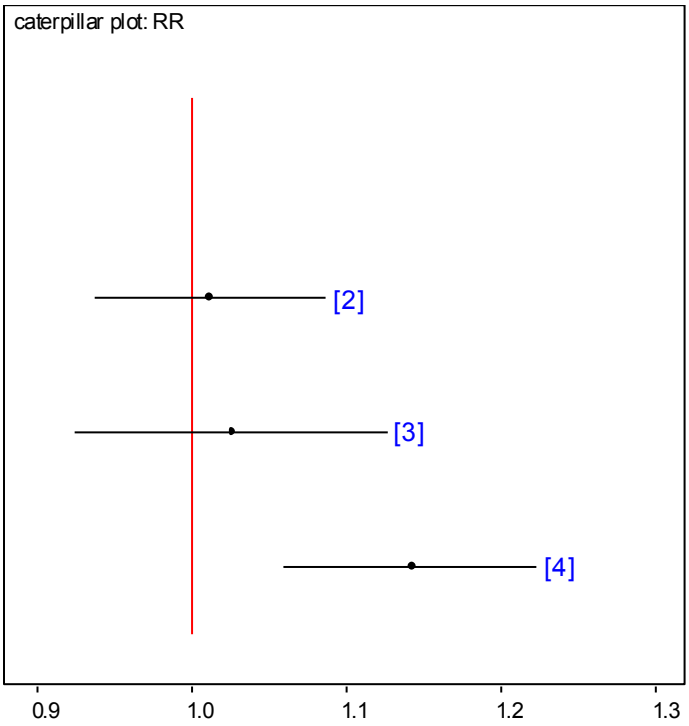
Rank probability histograms

Figure 61 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)



Caterpillar plot

Figure 62 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 40 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

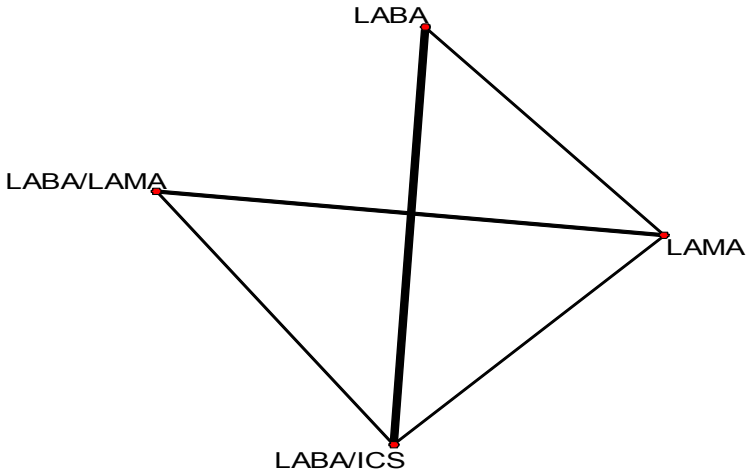
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.01 (0.96, 1.06)	1.04 (0.98, 1.10)	1.14 (1.04, 1.24)
LAMA	1.01 (0.94, 1.09)		-	1.11 (1.07, 1.16)
LABA/ICS	1.03 (0.93, 1.13)	1.02 (0.90, 1.14)		1.13 (0.94, 1.36)
LABA/LAMA	1.14 (1.06, 1.22)	1.13 (1.05, 1.21)	1.12 (0.99, 1.25)	

1 **SGRQ responders at 12 months**

2 ***High risk***

3 *Network diagram*

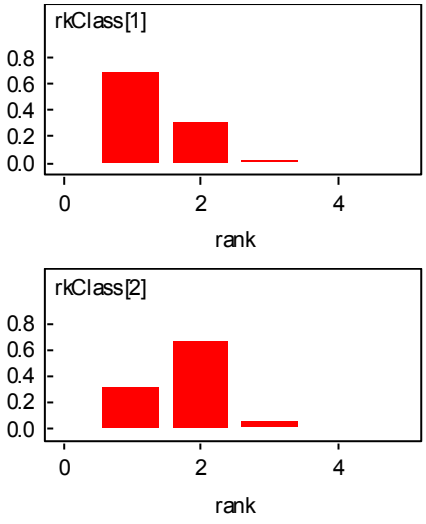
4 **Figure 63 Diagram of the network of studies (by drug class) underlying the NMA.**



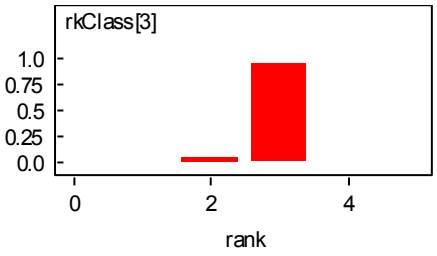
5

6 *Rank probability histograms*

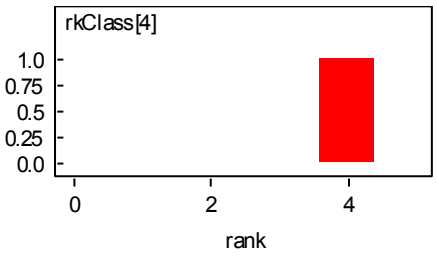
7 **Figure 64 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 4 is best.)**



9



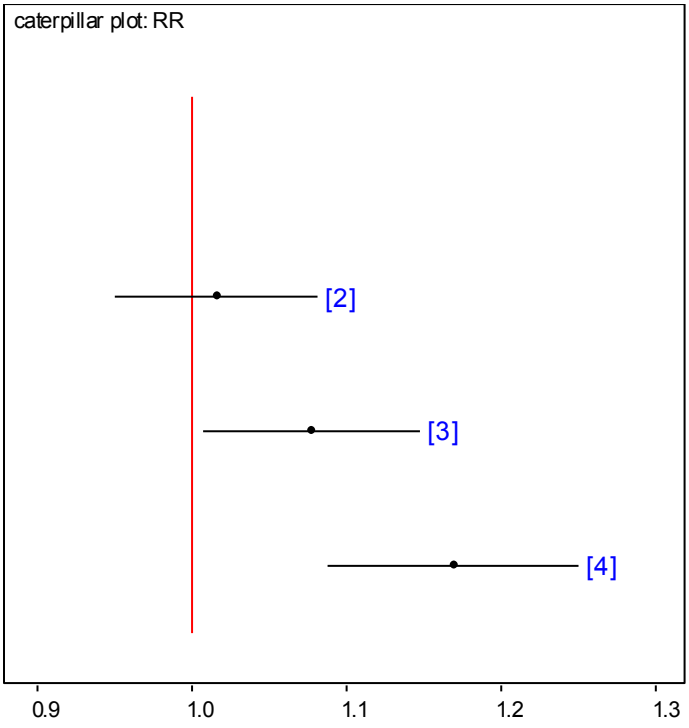
1



2

3 *Caterpillar plot*

4 **Figure 65 Relative effectiveness of all options versus LABA. (Risk ratios with 95%**
5 **credible intervals and line of no effect in red. Class 2 = LAMA, class 3=**
6 **LABA/ICS, class 4 = LABA/LAMA.)**



7

Mileage chart

Table 41 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

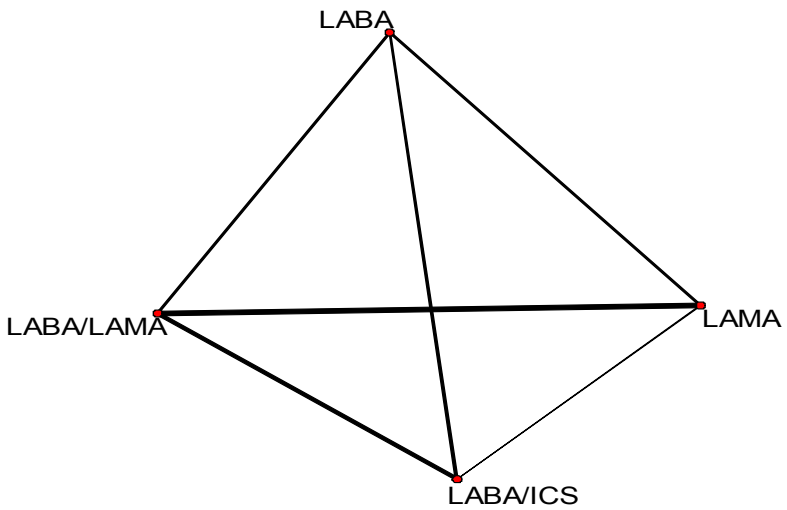
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.00 (0.92, 1.08)	1.10 (0.85, 1.42)	-
LAMA	1.02 (0.95, 1.08)		1.10 (0.93, 1.31)	1.12 (1.02, 1.22)
LABA/ICS	1.08 (1.01, 1.15)	1.06 (0.99, 1.13)		1.13 (1.04, 1.21)
LABA/LAMA	1.17 (1.09, 1.25)	1.15 (1.08, 1.23)	1.09 (1.03, 1.14)	

TDI at 3 months

Low risk

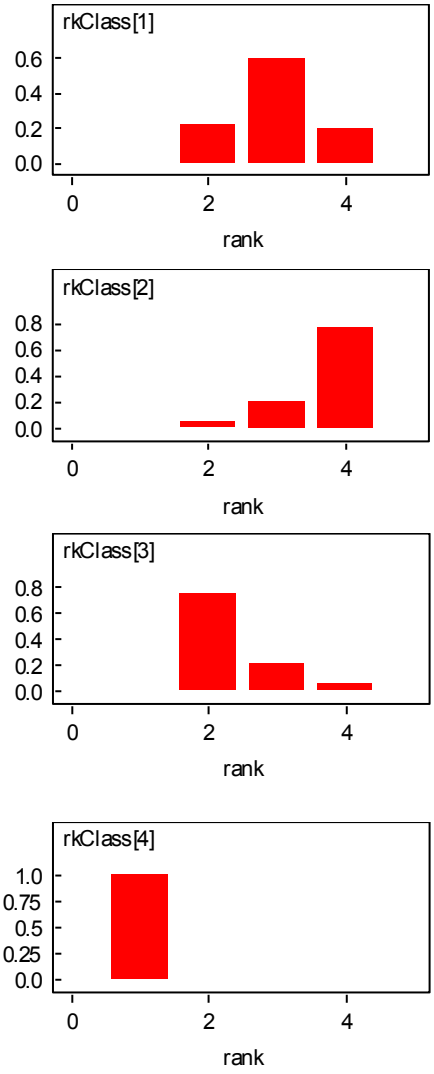
Network diagram

Figure 66 Diagram of the network of studies (by drug class) underlying the NMA.



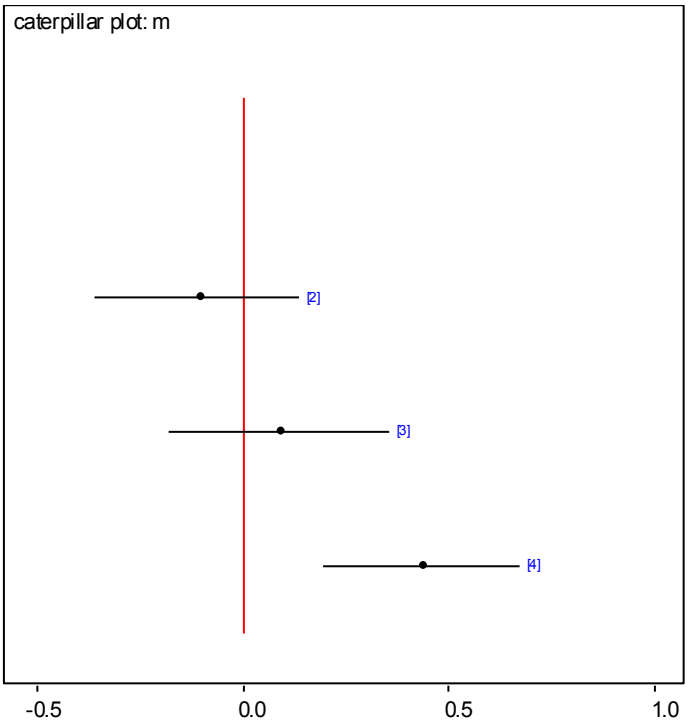
Rank probability histograms

Figure 67 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 68 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 42 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

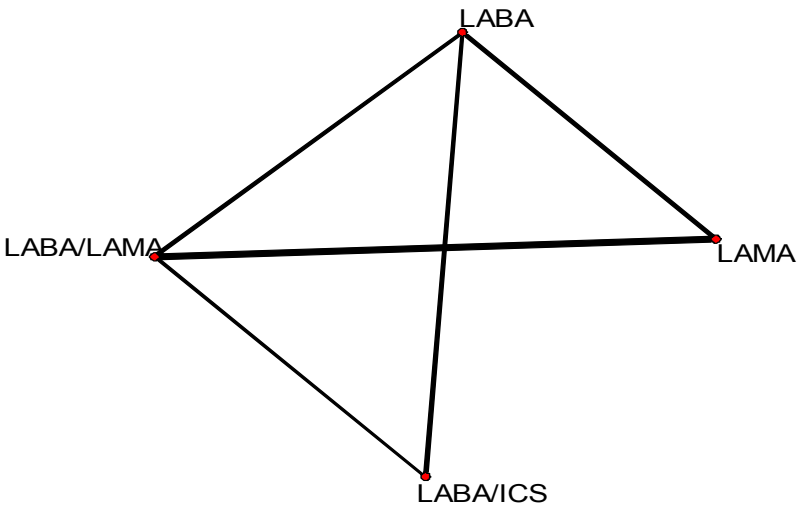
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-0.18 (-0.63, 0.27)	0.09 (-0.20, 0.37)	0.52 (0.31, 0.74)
LAMA	-0.10 (-0.36, 0.14)		0.50 (0.20, 0.81)	0.48 (0.34, 0.62)
LABA/ICS	0.09 (-0.18, 0.36)	0.19 (-0.07, 0.47)		0.40 (0.02, 0.78)
LABA/LAMA	0.44 (0.20, 0.67)	0.54 (0.36, 0.73)	0.35 (0.12, 0.56)	

1 **TDI at 6 months**

2 ***Low risk***

3 *Network diagram*

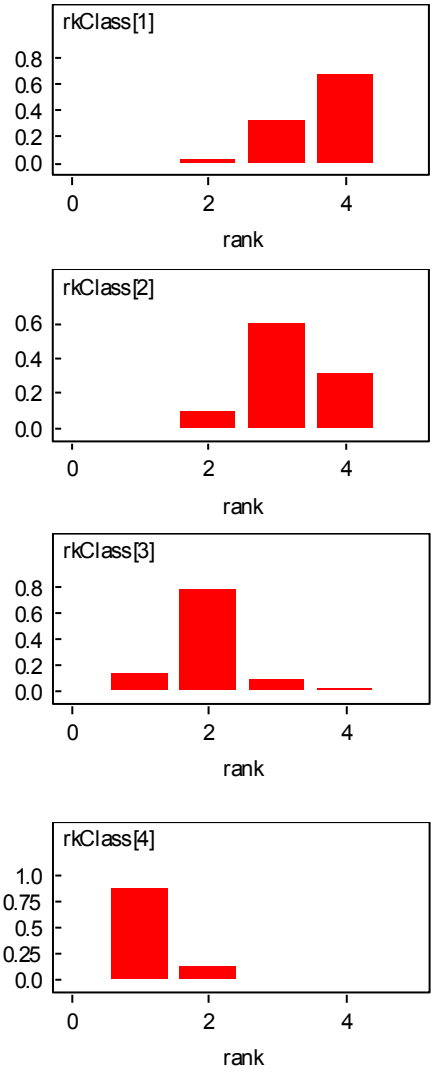
4 **Figure 69 Diagram of the network of studies (by drug class) underlying the NMA.**



5

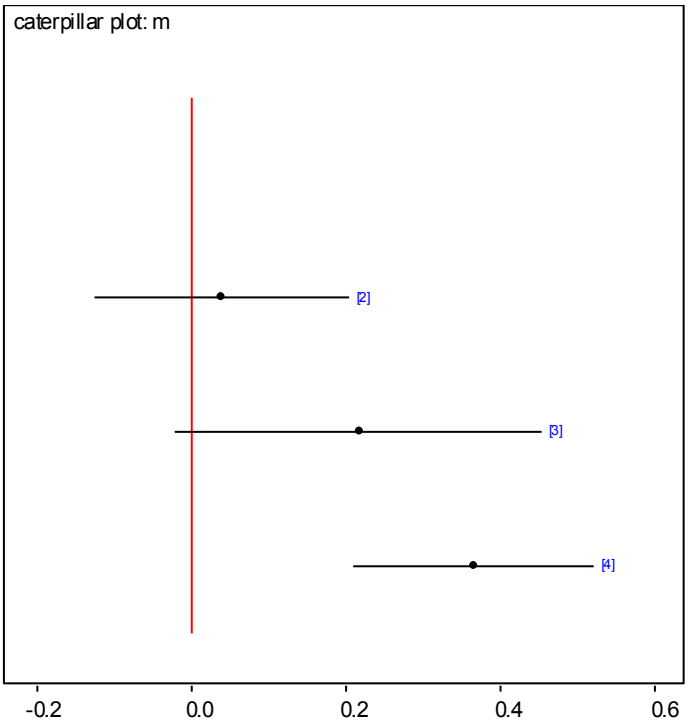
Rank probability histograms

Figure 70 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 71 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 43 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

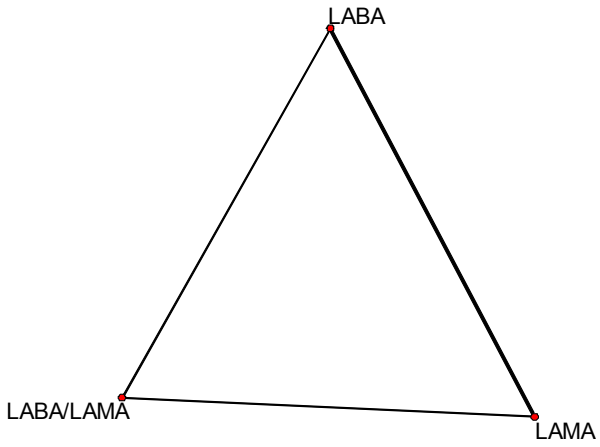
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		-0.19 (-0.20, -0.18)	0.21 (-0.09, 0.50)	0.40 (0.23, 0.57)
LAMA	0.04 (-0.12, 0.21)		-	0.32 (0.17, 0.46)
LABA/ICS	0.22 (-0.02, 0.46)	0.18 (-0.09, 0.45)		0.13 (-0.24, 0.51)
LABA/LAMA	0.37 (0.21, 0.52)	0.33 (0.18, 0.47)	0.15 (-0.10, 0.40)	

TDI at 12 months

Low risk

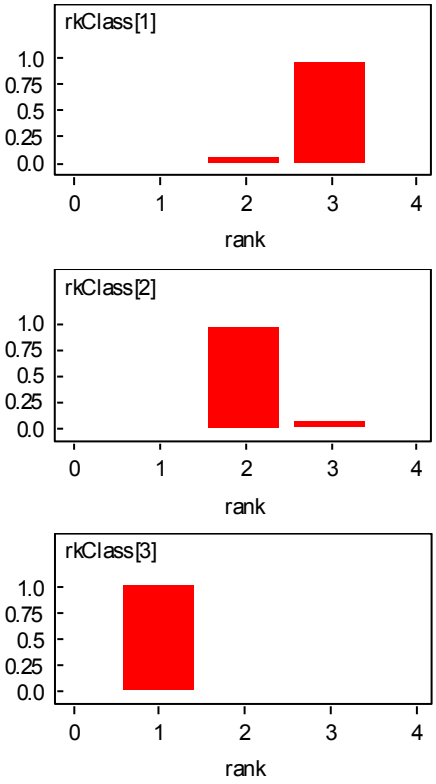
Network diagram

Figure 72 Diagram of the network of studies (by drug class) underlying the NMA.



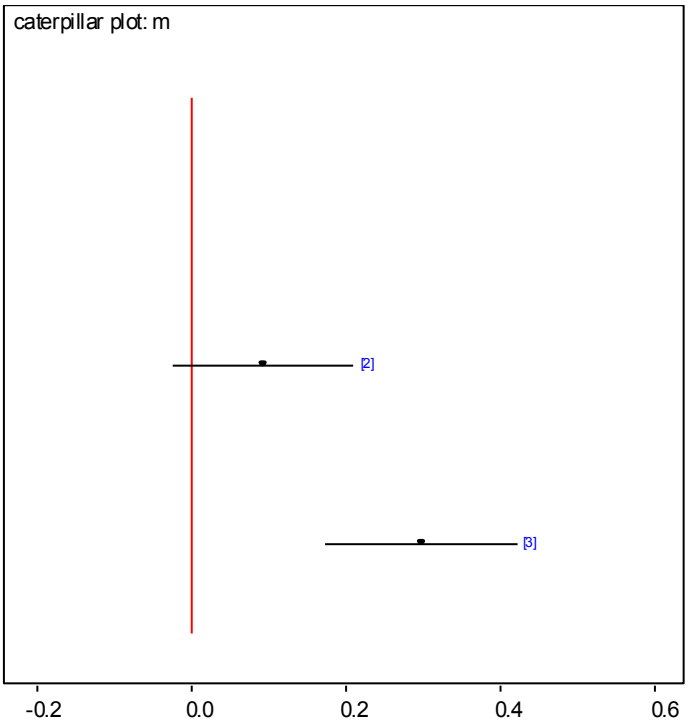
Rank probability histograms

Figure 73 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 74 Relative effectiveness of all options versus LABA. (Mean differences with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/LAMA.)



Mileage chart

Table 44 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

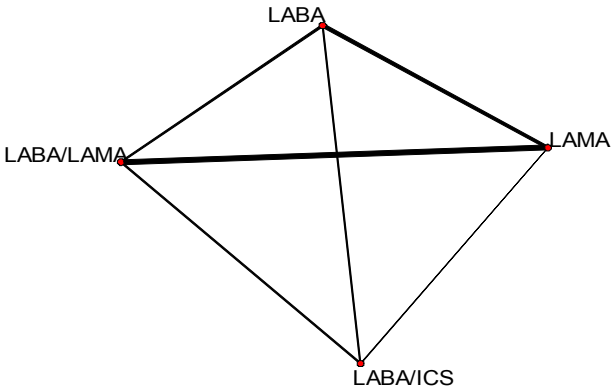
	LABA	LAMA	LABA/ LAMA
LABA		0.15 (-0.11, 0.40)	0.42 (0.06, 0.77)
LAMA	0.09 (-0.02, 0.21)		0.22 (0.11, 0.34)
LABA/LAMA	0.30 (0.17, 0.42)	0.20 (0.09. 0.32)	

1 **Total SAEs**

2 ***Low risk***

3 *Network diagram*

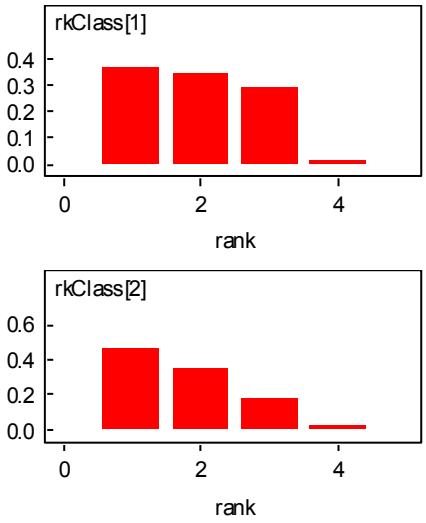
4 **Figure 75 Diagram of the network of studies (by drug class) underlying the NMA.**



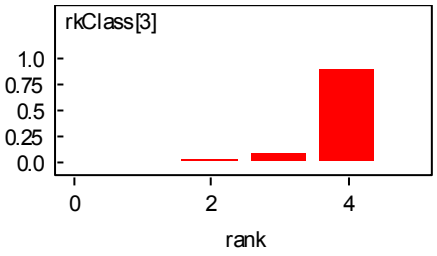
5

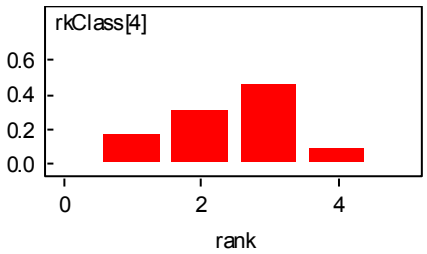
6 *Rank probability histograms*

7 **Figure 76 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**



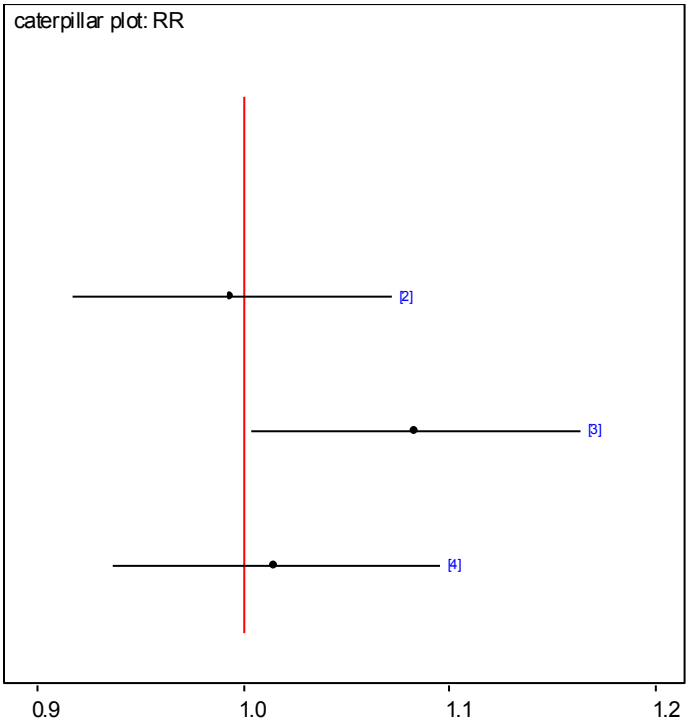
9





Caterpillar plot

Figure 77 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

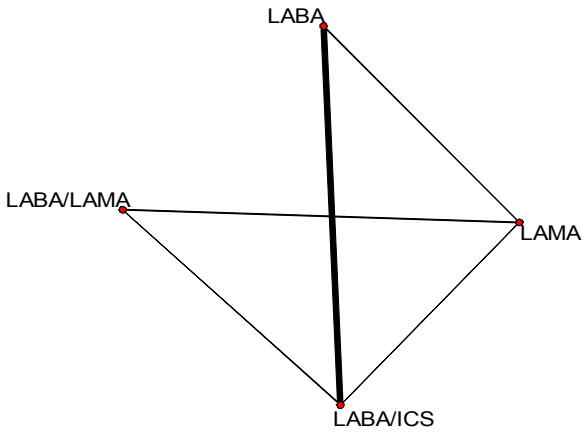
Table 45 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.99 (0.88, 1.11)	1.08 (1.00, 1.17)	1.05 (0.92, 1.19)
LAMA	0.99 (0.92, 1.07)		0.93 (0.50, 1.72)	1.02 (0.92, 1.13)
LABA/ICS	1.08 (1.01, 1.16)	1.09 (0.99, 1.20)		0.89 (0.69, 1.15)
LABA/LAMA	1.02 (0.94, 1.10)	1.02 (0.95, 1.10)	0.94 (0.85, 1.03)	

High risk

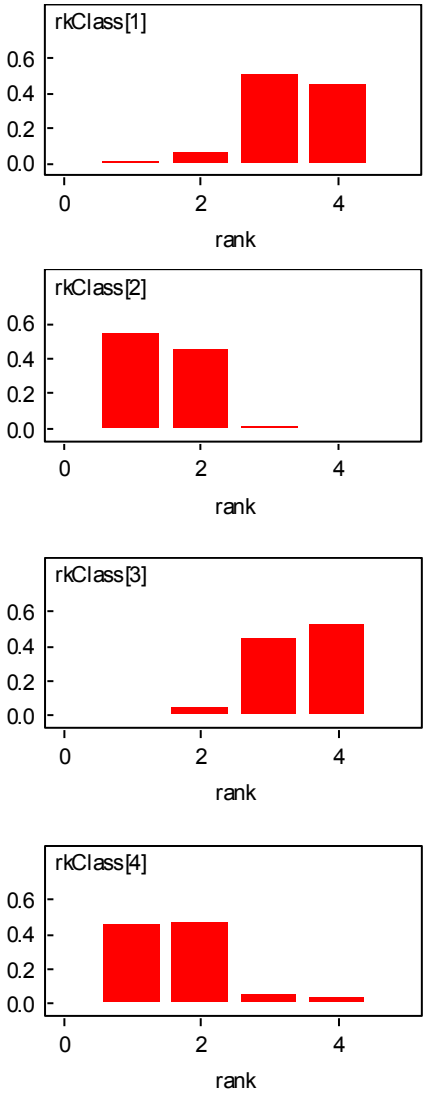
Network diagram

Figure 78 Diagram of the network of studies (by drug class) underlying the NMA.



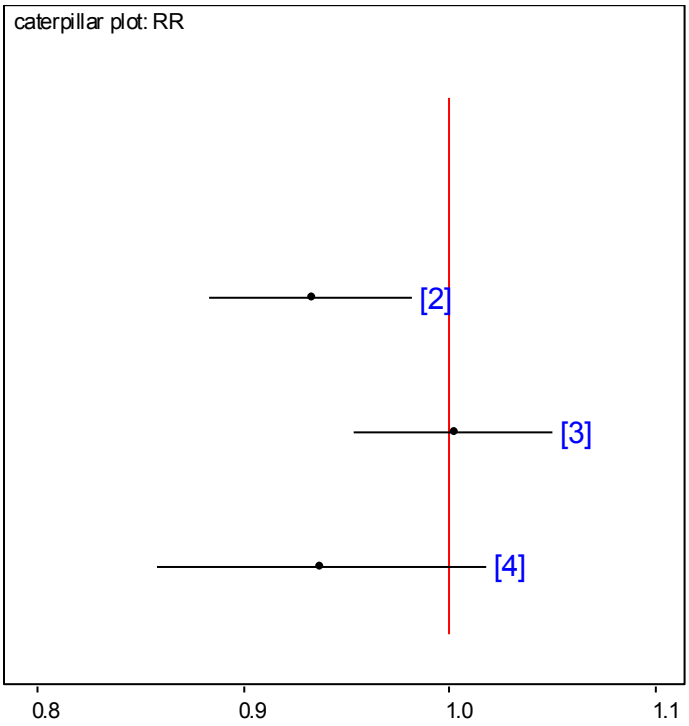
Rank probability histograms

Figure 79 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 80 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 46 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

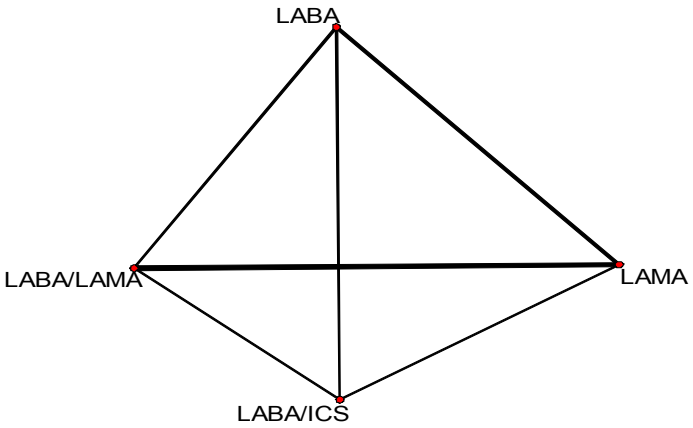
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.91 (0.84, 1.00)	0.99 (0.91, 1.08)	-
LAMA	0.93 (0.88, 0.98)		1.20 (1.02, 1.41)	0.98 (0.84, 1.15)
LABA/ICS	1.00 (0.95, 1.05)	1.08 (1.01, 1.14)		0.92 (0.80, 1.06)
LABA/LAMA	0.94 (0.86, 1.02)	1.01 (0.92, 1.09)	0.94 (0.86, 1.01)	

1 **COPD SAEs**

2 ***Low risk***

3 *Network diagram*

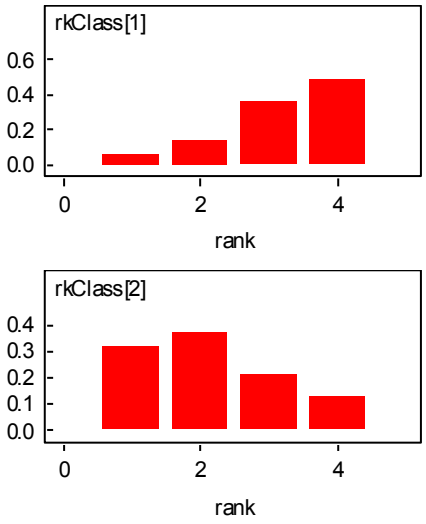
4 **Figure 81 Diagram of the network of studies (by drug class) underlying the NMA.**



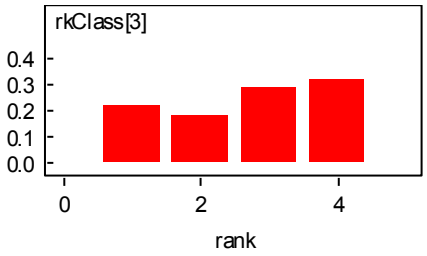
5

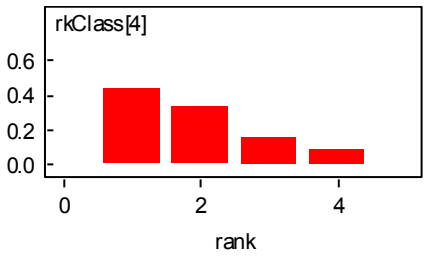
6 *Rank probability histograms*

7 **Figure 82 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**



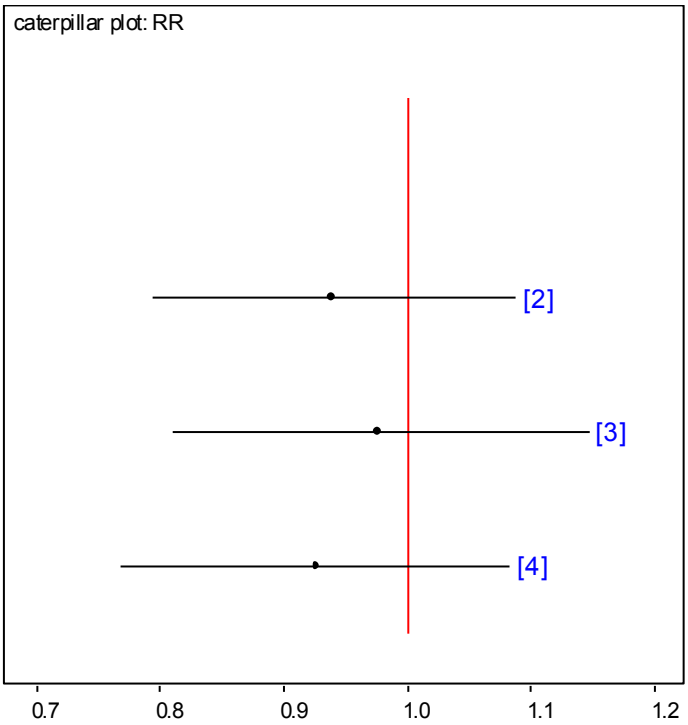
9





Caterpillar plot

Figure 83 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

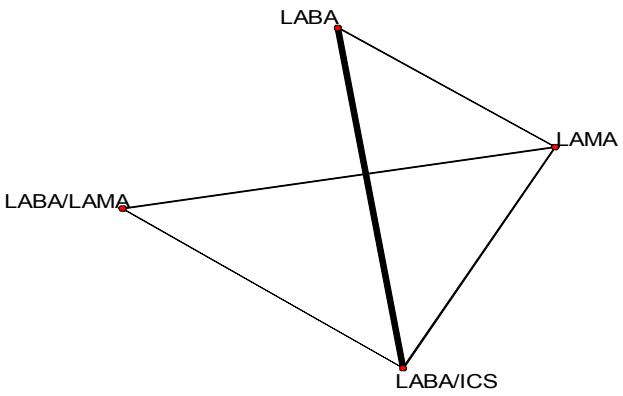
Table 47 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.93 (0.75, 1.14)	0.96 (0.83, 1.09)	1.08 (0.85, 1.38)
LAMA	0.93 (0.79, 1.09)		1.00 (0.23, 4.37)	0.96 (0.80, 1.16)
LABA/ICS	0.98 (0.81, 1.15)	1.04 (0.84, 1.29)		0.81 (0.50, 1.30)
LABA/LAMA	0.93 (0.77, 1.08)	0.99 (0.85, 1.14)	0.96 (0.77, 1.16)	

High risk

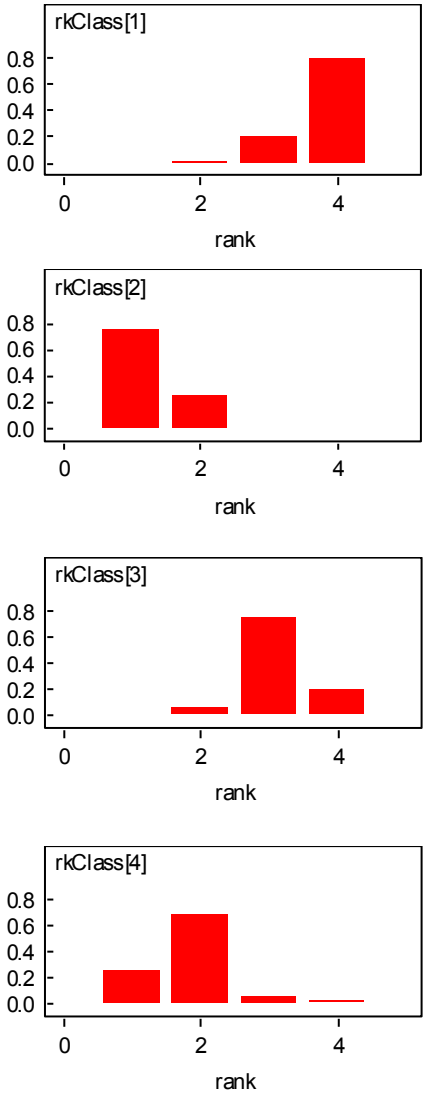
Network diagram

Figure 84 Diagram of the network of studies (by drug class) underlying the NMA.



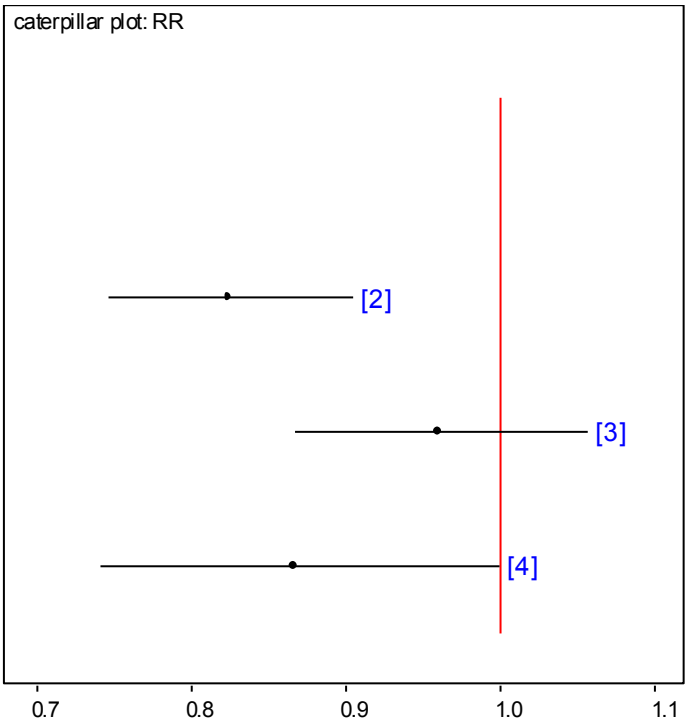
Rank probability histograms

Figure 85 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 86 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 48 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

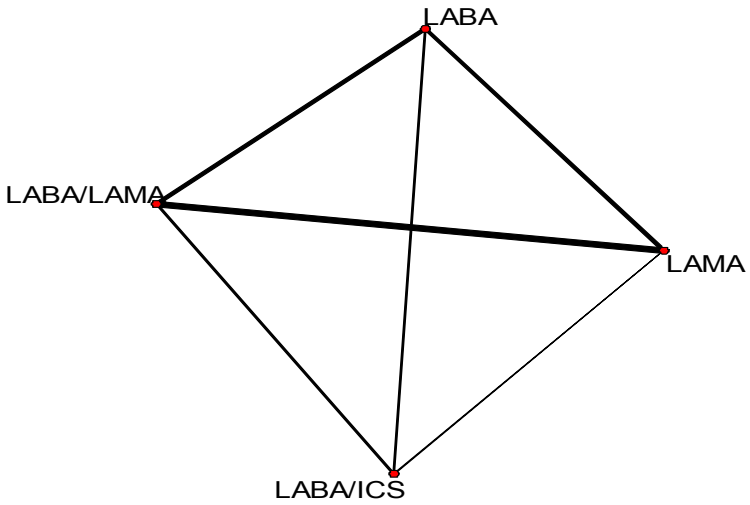
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.81 (0.71, 0.92)	0.93 (0.81, 1.07)	-
LAMA	0.82 (0.75, 0.91)		1.28 (0.99, 1.65)	1.07 (0.86, 1.33)
LABA/ICS	0.96 (0.87, 1.06)	1.17 (1.04, 1.31)		0.88 (0.73, 1.06)
LABA/LAMA	0.87 (0.74, 1.00)	1.05 (0.91, 1.21)	0.90 (0.79, 1.03)	

1 **Cardiac SAEs**

2 ***Low risk***

3 *Network diagram*

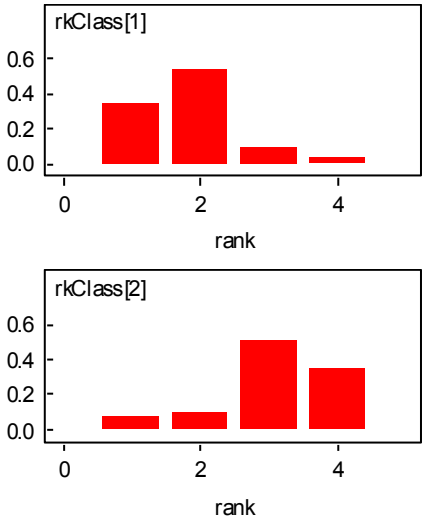
4 **Figure 87 Diagram of the network of studies (by drug class) underlying the NMA.**



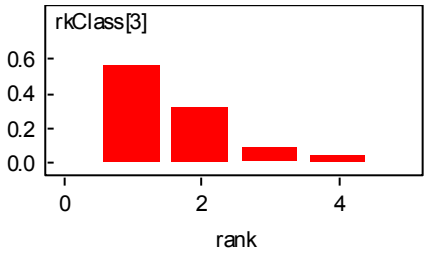
5

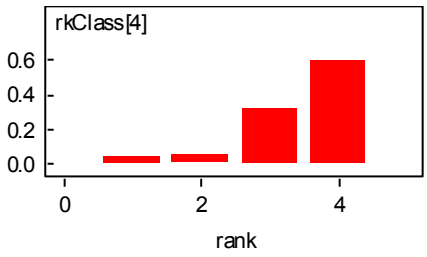
6 *Rank probability histograms*

7 **Figure 88 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**



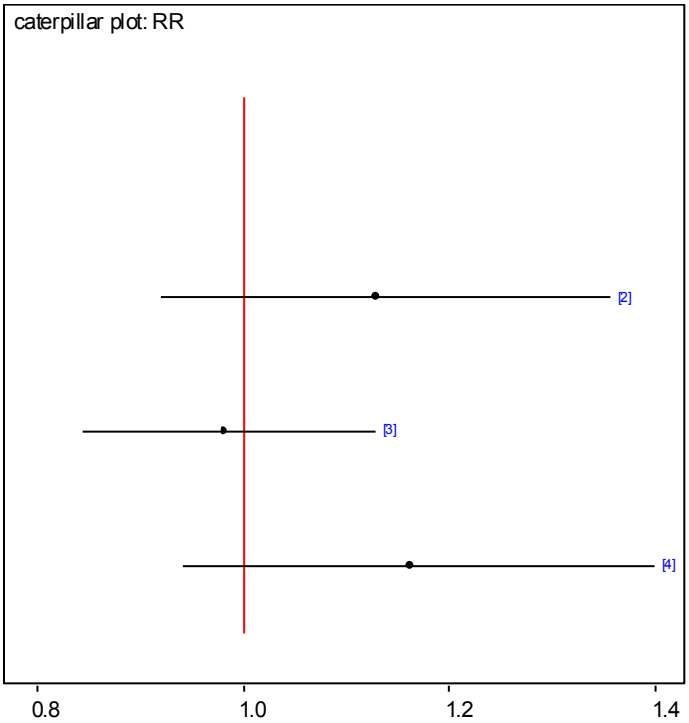
9





Caterpillar plot

Figure 89 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

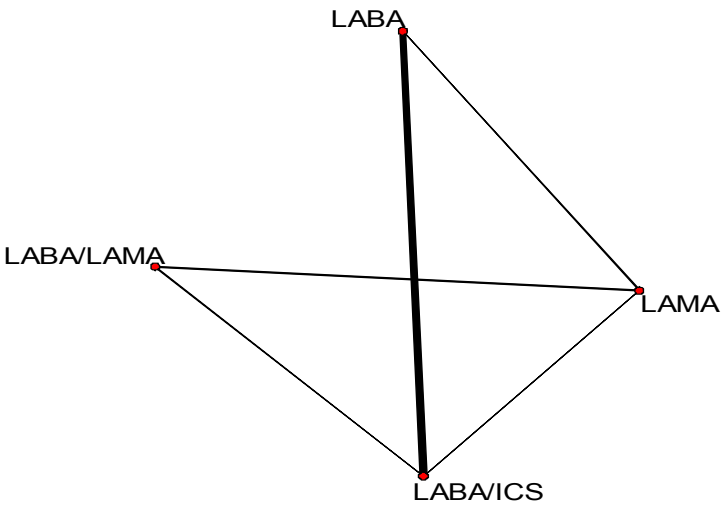
Table 49 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.19 (0.86, 1.63)	0.98 (0.81, 1.18)	1.28 (0.88, 1.86)
LAMA	1.13 (0.92, 1.36)		0.14 (0.02, 1.15)	1.08 (0.82, 1.42)
LABA/ICS	0.98 (0.85, 1.13)	0.88 (0.70, 1.10)		0.91 (0.45, 1.81)
LABA/LAMA	1.16 (0.94, 1.40)	1.03 (0.87, 1.23)	1.19 (0.94, 1.48)	

High risk

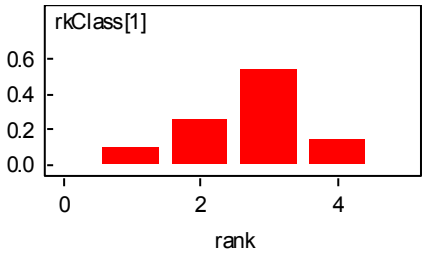
Network diagram

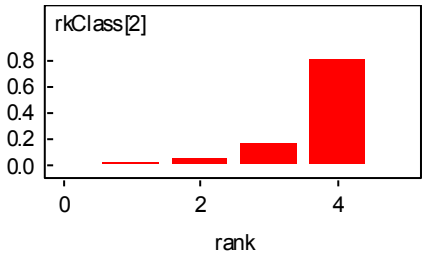
Figure 90 Diagram of the network of studies (by drug class) underlying the NMA.



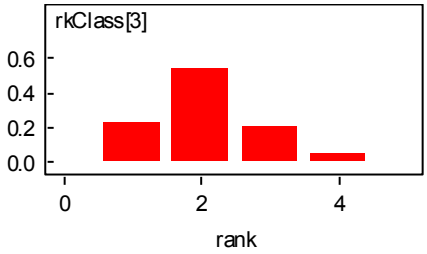
Rank probability histograms

Figure 91 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)

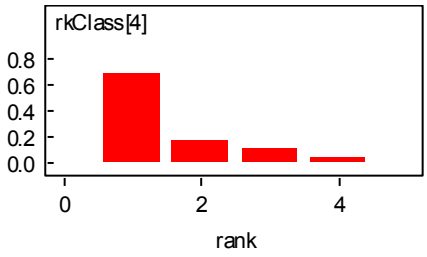

rkClass[1]
0.6
0.4
0.2
0.0
0
2
4
rank


rkClass[2]
0.8
0.6
0.4
0.2
0.0
0
2
4
rank

1


rkClass[3]
0.6
0.4
0.2
0.0
0
2
4
rank

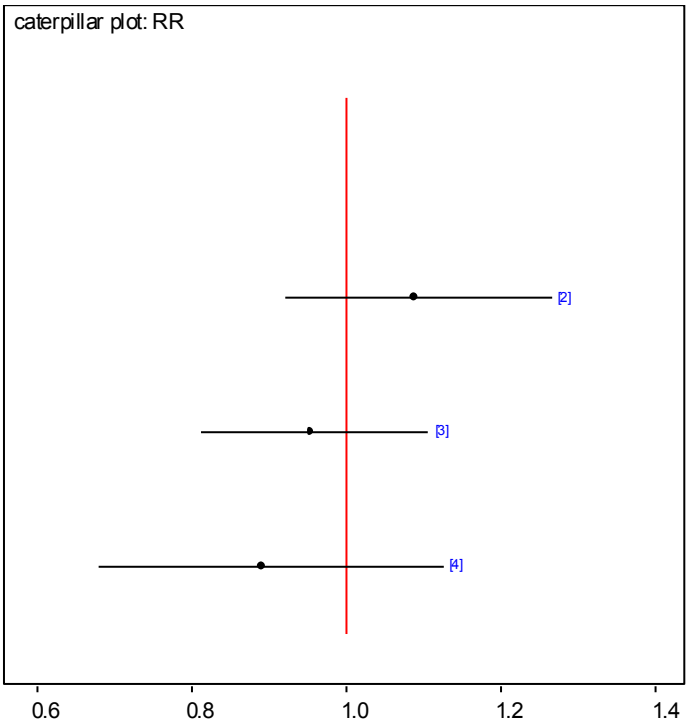
2


rkClass[4]
0.8
0.6
0.4
0.2
0.0
0
2
4
rank

3

Caterpillar plot

Figure 92 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 50 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

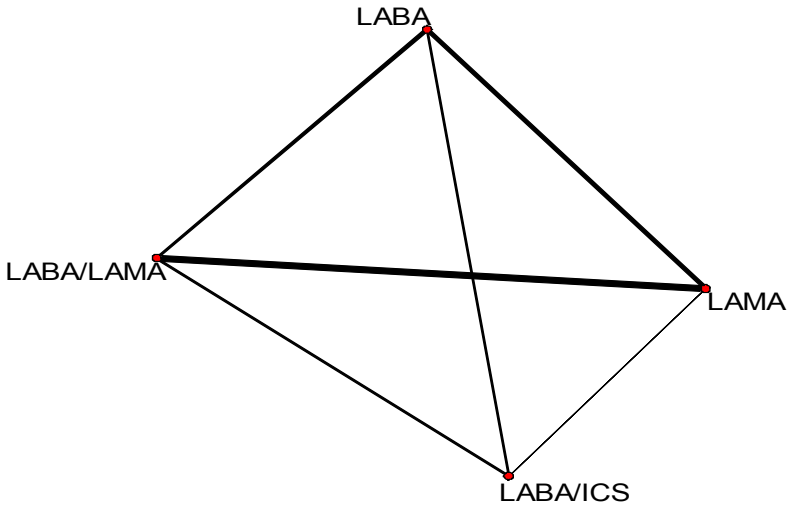
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.09 (0.84, 1.42)	0.96 (0.76, 1.21)	-
LAMA	1.09 (0.92, 1.27)		0.68 (0.41, 1.15)	0.81 (0.54, 1.19)
LABA/ICS	0.96 (0.81, 1.11)	0.88 (0.73, 1.06)		0.87 (0.50, 1.28)
LABA/LAMA	0.89 (0.68, 1.13)	0.82 (0.64, 1.02)	0.94 (0.73, 1.17)	

1 **Pneumonia**

2 ***Low risk***

3 *Network diagram*

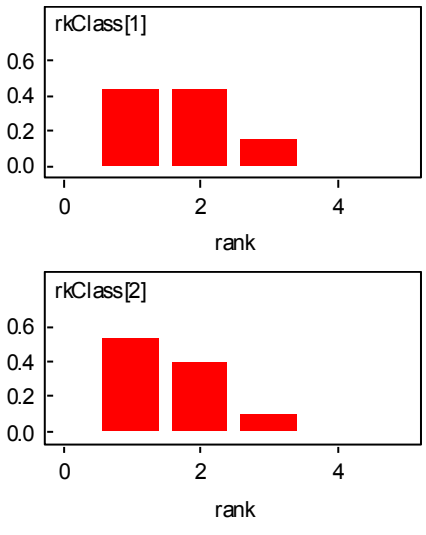
4 **Figure 93 Diagram of the network of studies (by drug class) underlying the NMA.**



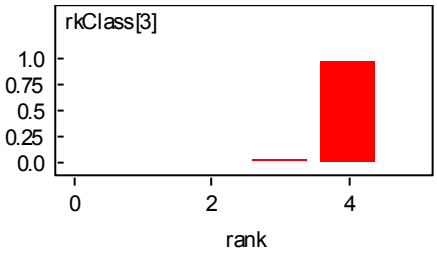
5

6 *Rank probability histograms*

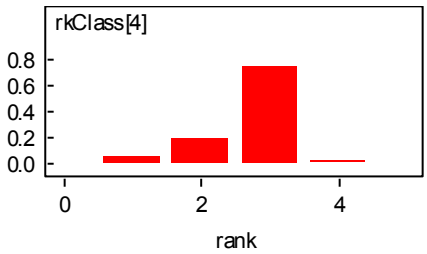
7 **Figure 94 Probability of the treatment assuming each treatment rank. (Class 1= LABA,**
8 **class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)**



9



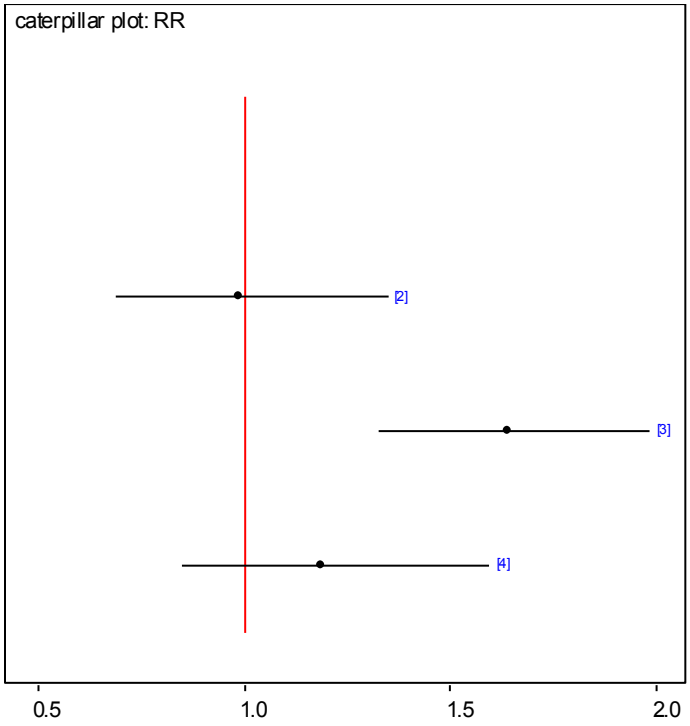
1



2

3 *Caterpillar plot*

4 **Figure 95 Relative effectiveness of all options versus LABA. (Risk ratios with 95%**
5 **credible intervals and line of no effect in red. Class 2 = LAMA, class 3=**
6 **LABA/ICS, class 4 = LABA/LAMA.)**



7

Mileage chart

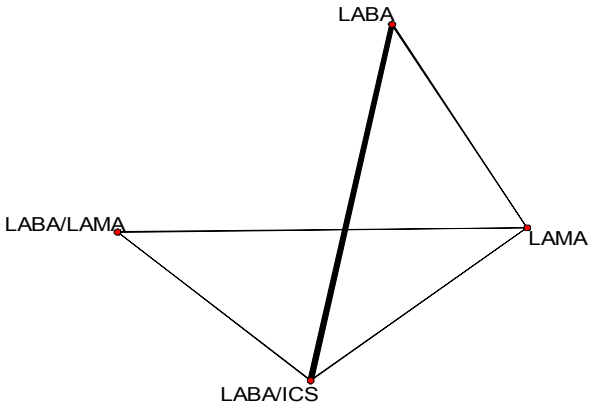
Table 51 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.02 (0.64, 1.61)	1.59 (1.24, 2.04)	1.59 (1.01, 2.51)
LAMA	0.99 (0.69, 1.35)		5.83 (0.71, 47.97)	1.26 (0.88, 1.79)
LABA/ICS	1.64 (1.33, 1.99)	1.70 (1.16, 2.44)		0.42 (0.19, 0.93)
LABA/LAMA	1.19 (0.85, 1.60)	1.22 (0.89, 1.63)	0.73 (0.51, 1.01)	

High risk

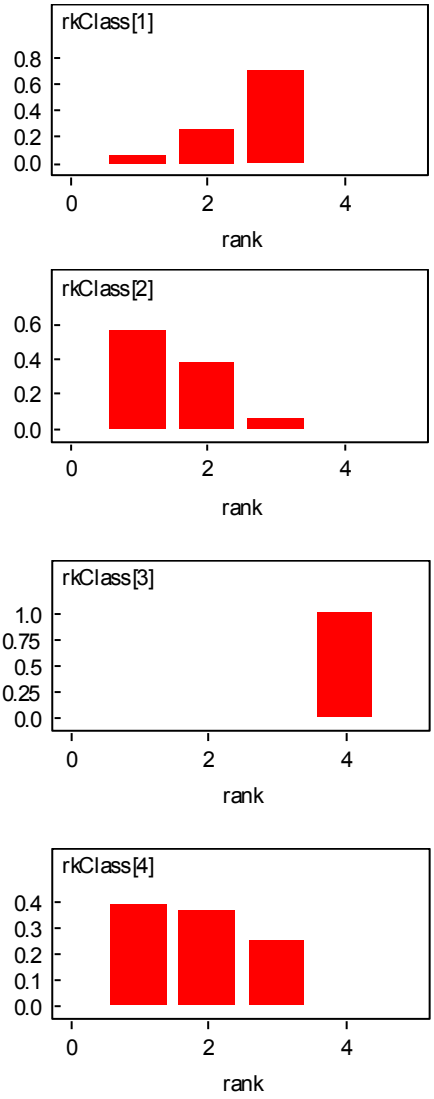
Network diagram

Figure 96 Diagram of the network of studies (by drug class) underlying the NMA.



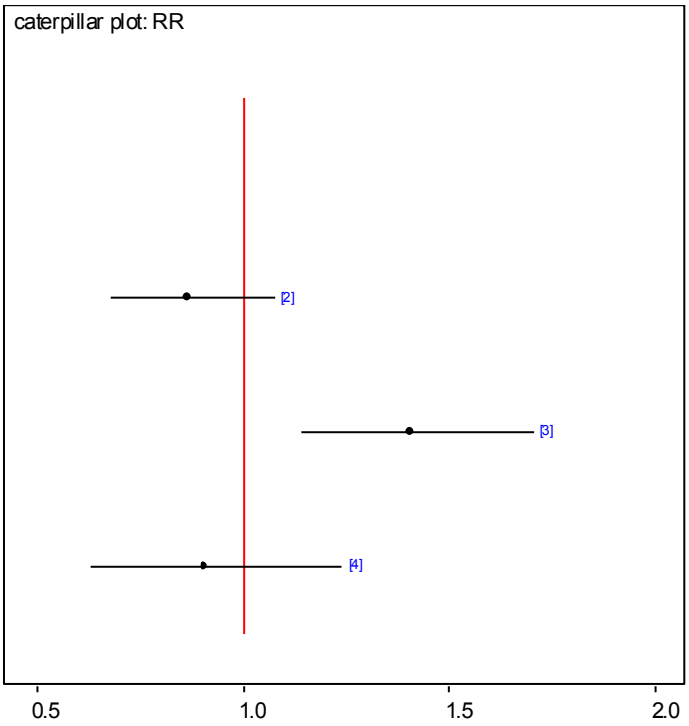
Rank probability histograms

Figure 97 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 98 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 52 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

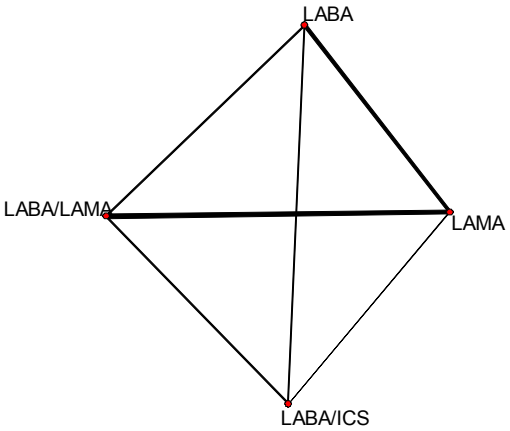
	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.83 (0.62, 1.12)	1.49 (1.14, 1.96)	-
LAMA	0.87 (0.68, 1.08)		1.78 (1.07, 2.95)	0.98 (0.61, 1.59)
LABA/ICS	1.41 (1.15, 1.71)	1.64 (1.27, 2.09)		0.63 (0.41, 0.96)
LABA/LAMA	0.91 (0.63, 1.24)	1.05 (0.75, 1.42)	0.65 (0.47, 0.86)	

Mortality

Low risk

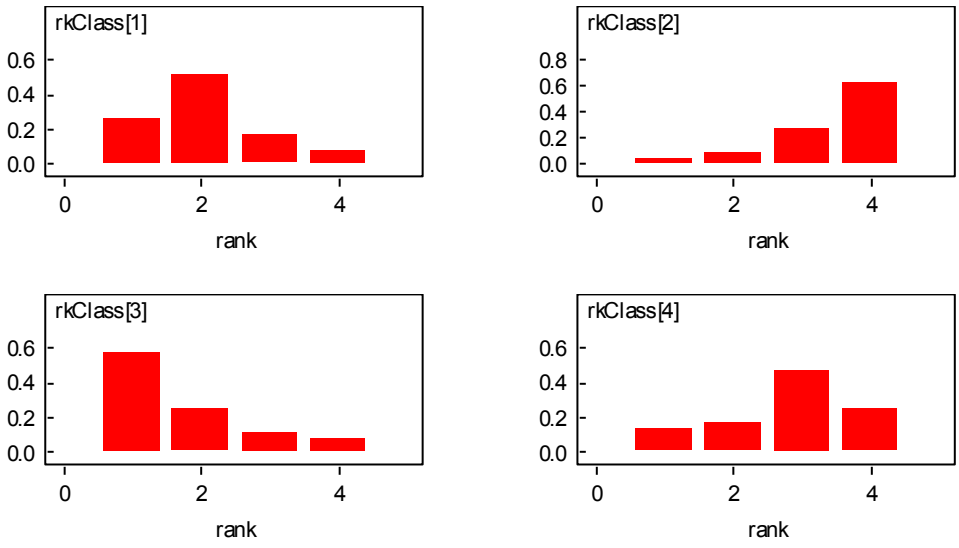
Network diagram

Figure 99 Diagram of the network of studies (by drug class) underlying the NMA.



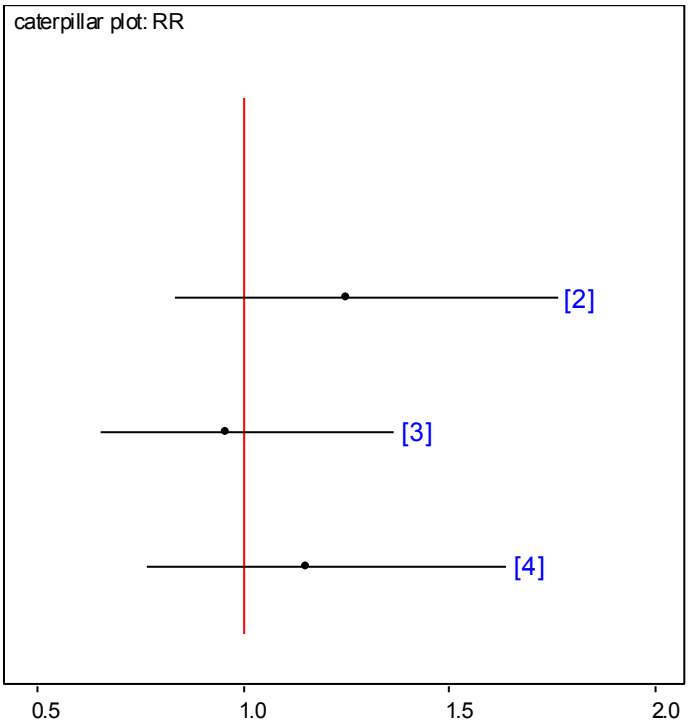
Rank probability histograms

Figure 100 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)



Caterpillar plot

Figure 101 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

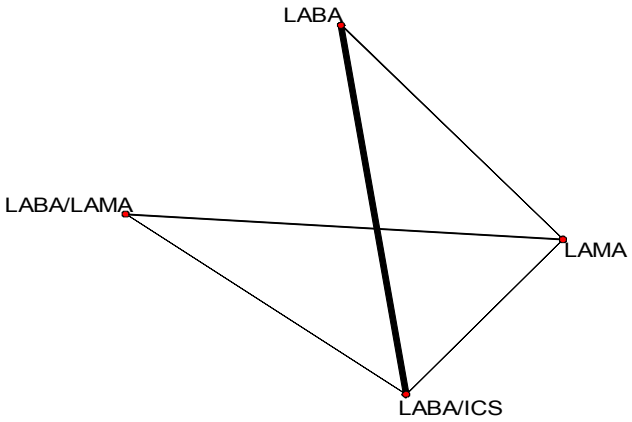
Table 53 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		1.34 (0.82, 2.20)	0.94 (0.79, 1.13)	1.15 (0.68, 1.94)
LAMA	1.25 (0.84, 1.76)		0.44 (0.07, 2.91)	0.99 (0.69, 1.42)
LABA/ICS	0.96 (0.65, 1.37)	0.79 (0.48, 1.24)		1.13 (0.42, 3.02)
LABA/LAMA	1.15 (0.77, 1.64)	0.93 (0.68, 1.25)	1.23 (0.75, 1.93)	

High risk

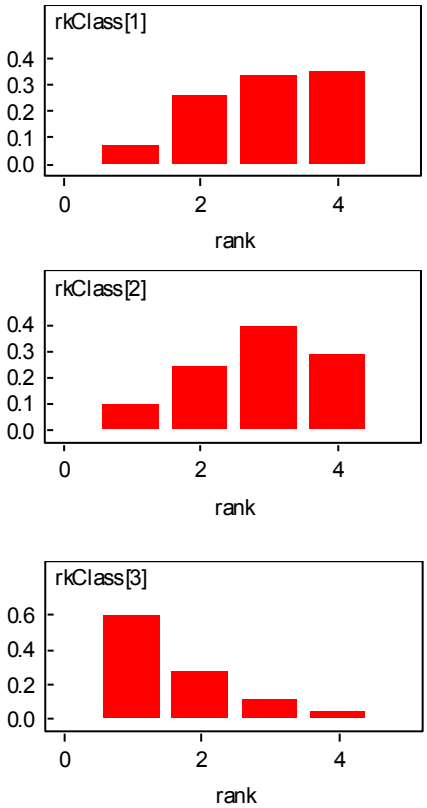
Network diagram

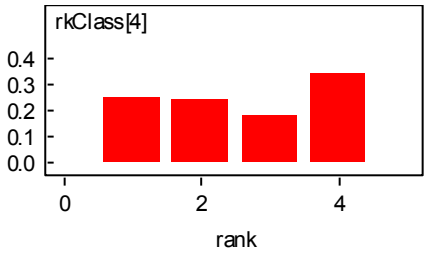
Figure 102 Diagram of the network of studies (by drug class) underlying the NMA.



Rank probability histograms

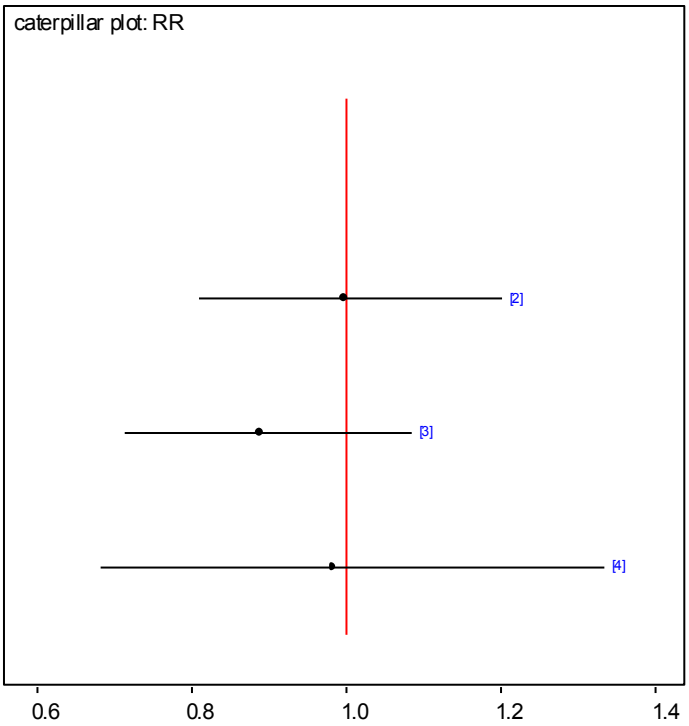
Figure 103 Probability of the treatment assuming each treatment rank. (Class 1= LABA, class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA. Rank 1 is best.)





Caterpillar plot

Figure 104 Relative effectiveness of all options versus LABA. (Risk ratios with 95% credible intervals and line of no effect in red. Class 2 = LAMA, class 3= LABA/ICS, class 4 = LABA/LAMA.)



Mileage chart

Table 54 Relative effectiveness of all pairwise combinations. (Risk ratios with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
LABA		0.88 (0.66, 1.16)	0.98 (0.73, 1.33)	-
LAMA	1.00 (0.81, 1.20)		0.54 (0.32, 0.90)	1.06 (0.67, 1.67)
LABA/ICS	0.89	0.90		1.00

	LABA	LAMA	LABA/ ICS	LABA/ LAMA
	(0.71, 1.09)	(0.70, 1.13)		(0.57, 1.76)
LABA/LAMA	0.98 (0.68, 1.34)	0.99 (0.71, 1.31)	1.11 (0.79, 1.50)	

LAMA monotherapy

Model fit statistics for all outcomes

Table 55: Model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
10	SGRQ total score at 3 months	FE	70.889	26.52	20	-	RE
		RE	66.878	19.11		1.557 (0.323, 3.785)	
10	SGRQ total score at 6 months	FE	74.527	37.01	20	-	RE
		RE	62.949	20.45		2.091 (0.751, 4.277)	
11	TDI score at 3 months	FE	15.583	21.16	22	-	FE
		RE	16.722	19.89		0.260 (0.013, 0.750)	
21	SGRQ responders	FE	317.487	47.56	42	-	FE
		RE	317.958	42.4		0.116 (0.005, 0.270)	
21	Moderate to severe exacerbations	FE	275.874	41.3	42	-	FE
		RE	278.027	41.4		0.074 (0.004, 0.231)	
14	Severe exacerbations	FE	154.545	30.37	28	-	
		RE	155.738	29.06		0.234 (0.007, 0.733)	FE

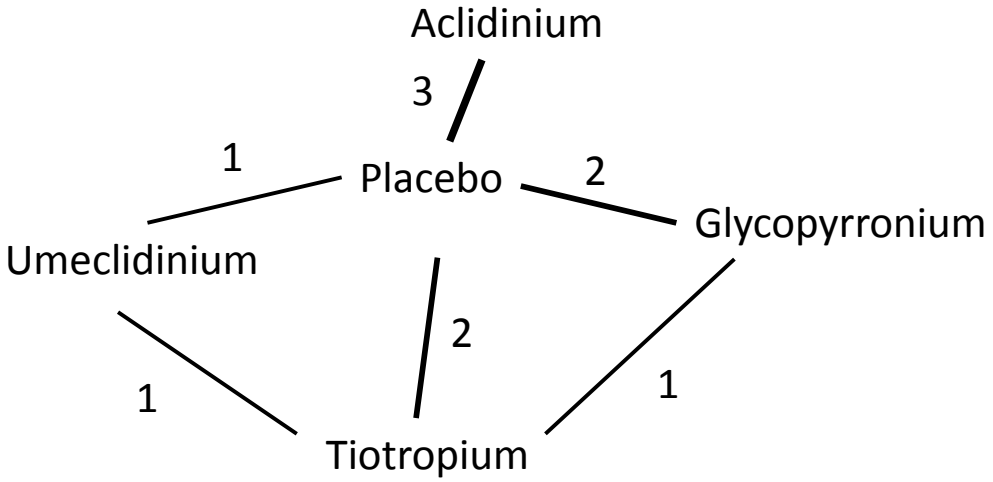
Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
24	Dropouts due to adverse events	FE	254.034	51.37	48	-	FE
		RE	255.543	50.19		0.178 (0.011, 0.504)	
17	Mortality	FE	141.667	41.24	34	-	FE
		RE	142.548	37.91		0.696 (0.033, 2.144)	
26	Serious adverse events	FE	313.441	53.21	52	-	FE
		RE	315.215	52.39		0.105 (0.003, 0.315)	

1

SGRQ total score at 3 months

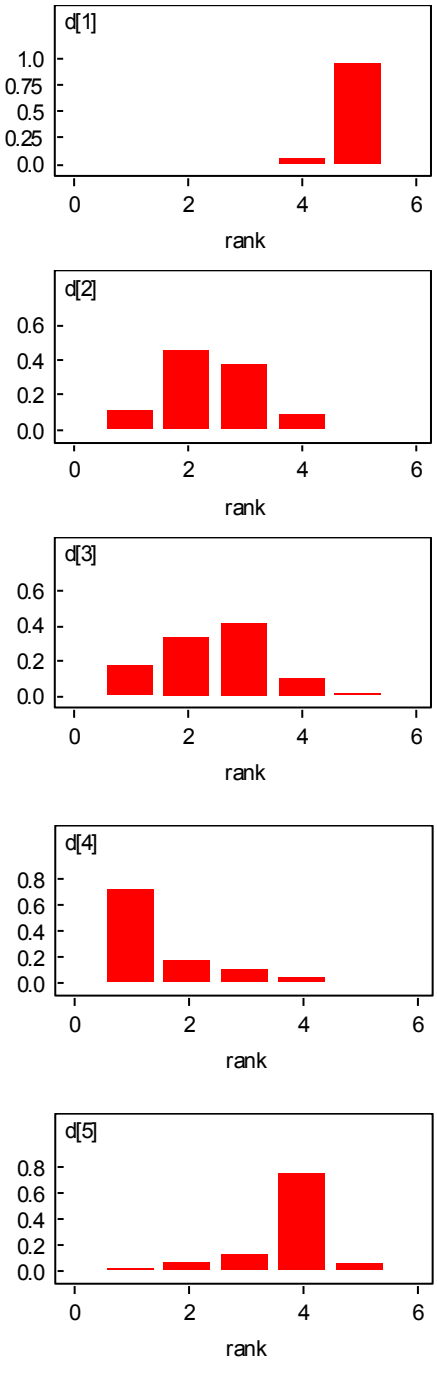
Network diagram

Figure 105 Diagram of the network of studies underlying the NMA with the number of trials for each comparison.



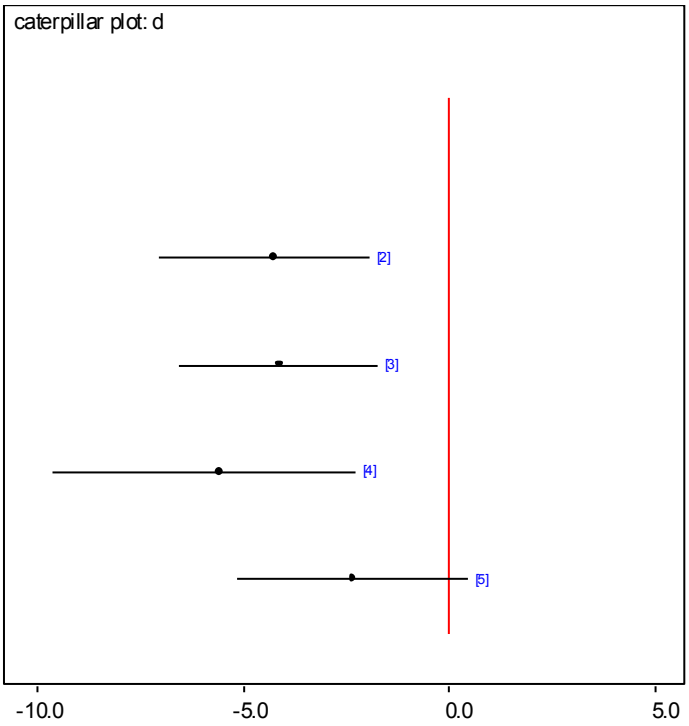
Rank probability histograms

Figure 106 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 1 is best.)



Caterpillar plot

Figure 107 Relative effectiveness of all options versus placebo. (Mean differences with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.).



Mileage chart

Table 56 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

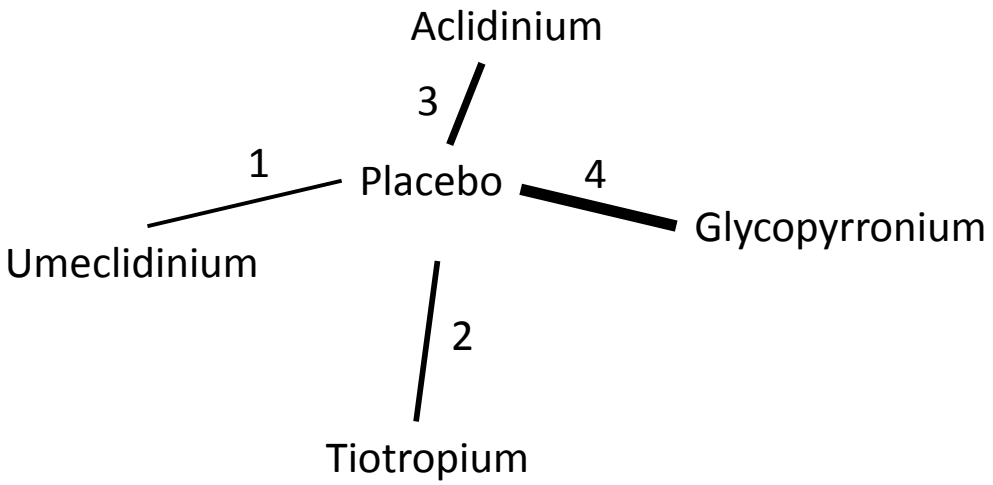
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		-2.75 (-4.12, -1.38)	-4.27 (-6.16, -2.37)	-7.90 (-12.20, 3.60)	-2.33 (-3.77, -0.90)
Tiotropium	-4.24 (-7.03, -1.91)		0.65 (-1.19, 2.49)	-0.46 (-2.04, 1.12)	-
Glycopyrronium	-4.10 (-6.55, -1.70)	0.14 (-2.55, 3.24)		-	-
Umeclidinium	-5.56 (-9.58, -2.25)	-1.32 (-4.83, 1.86)	-1.46 (-5.88, 2.23)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	-2.33 (-5.11, 0.47)	1.91 (-1.63, 5.92)	1.78 (-1.93, 5.47)	3.23 (-1.02, 8.17)	

1 **SGRQ total score at 6 months**

2 ***Network diagram***

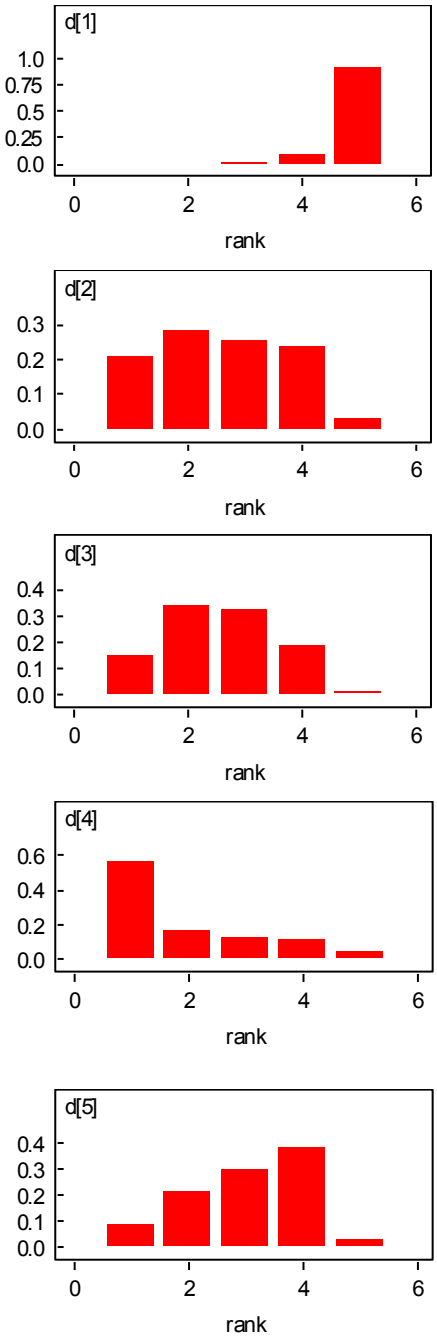
3 **Figure 108 Diagram of the network of studies underlying the NMA with the number of**
4 **trials for each comparison.**



5

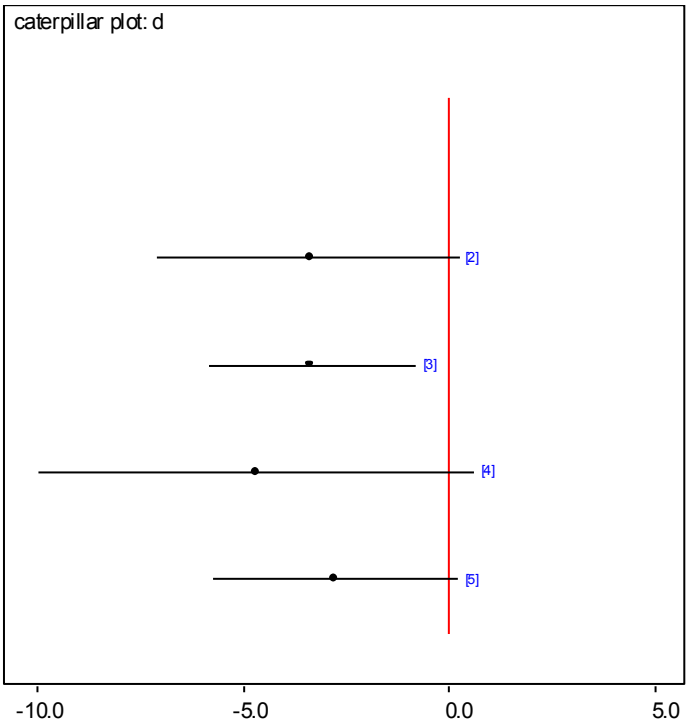
Rank probability histograms

Figure 109 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 1 is best.)



Caterpillar plot

Figure 110 Relative effectiveness of all options versus placebo. (Mean differences with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 57 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

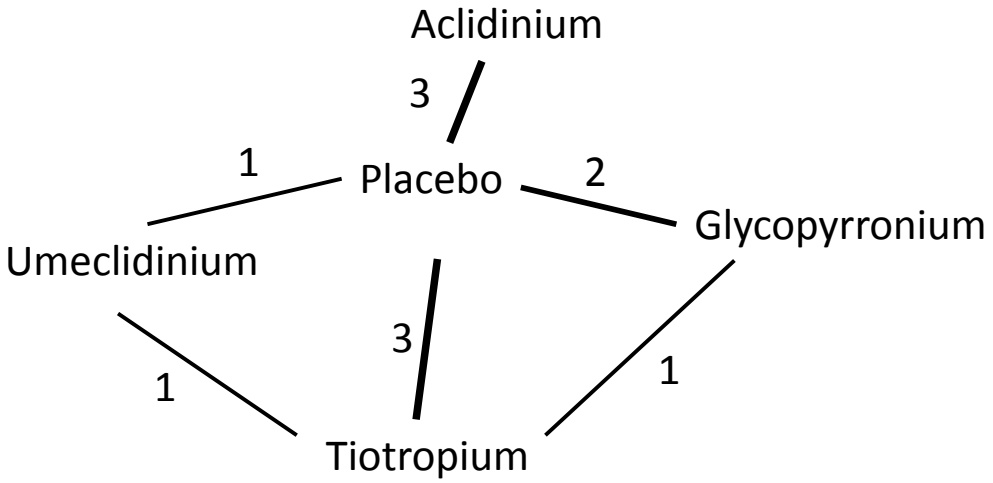
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		-3.58 (-5.02, -2.15)	-3.44 (-5.03, -1.86)	-4.69 (-7.07, -2.31)	-2.76 (-5.95, 0.43)
Tiotropium	-3.38 (-7.05, 0.26)		-	-	-
Glycopyrronium	-3.38 (-5.82, -0.80)	0.00 (-4.34, 4.46)		-	-
Umeclidinium	-4.68 (-9.94, 0.61)	-1.30 (-7.65, 5.24)	-1.30 (-7.15, 4.44)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	-2.79 (-5.69, 0.23)	0.59 (-4.01, 5.35)	0.59 (-3.35, 4.42)	1.90 (-4.04, 7.91)	

1 **TDI score at 3 months**

2 ***Network diagram***

3 **Figure 111 Diagram of the network of studies underlying the NMA with the number of**
4 **trials for each comparison.**

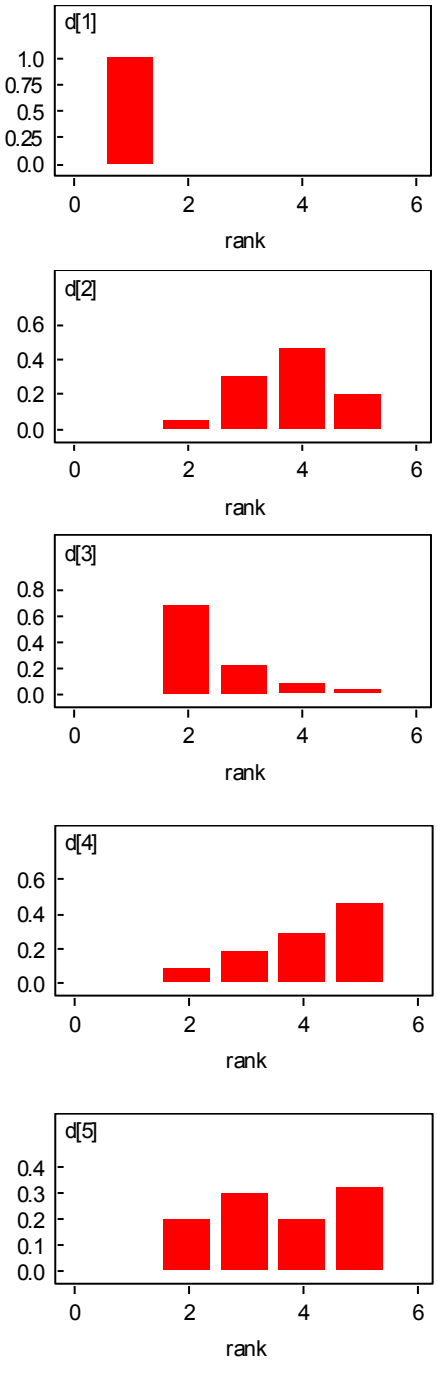


5

6

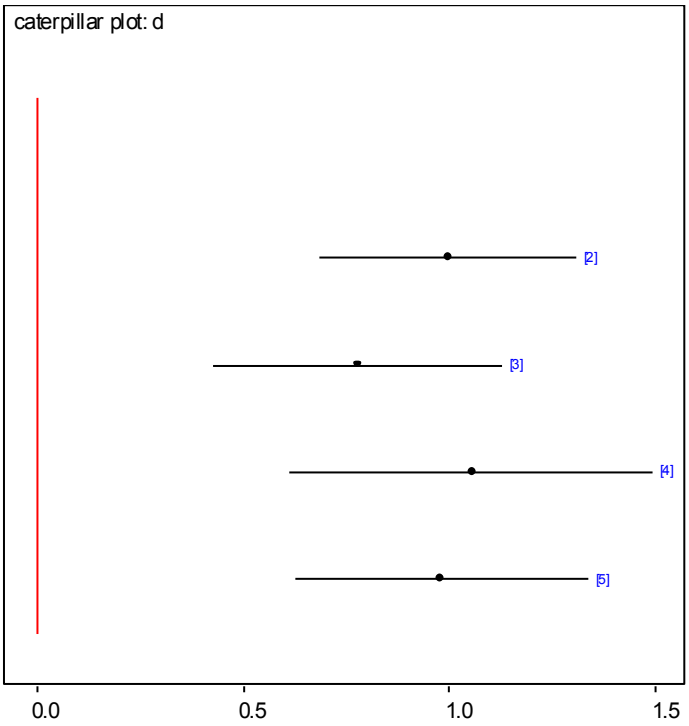
Rank probability histograms

Figure 112 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 5 is best.)



Caterpillar plot

Figure 113 Relative effectiveness of all options versus placebo. (Mean differences with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 58 Relative effectiveness of all pairwise combinations. (Mean differences with 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

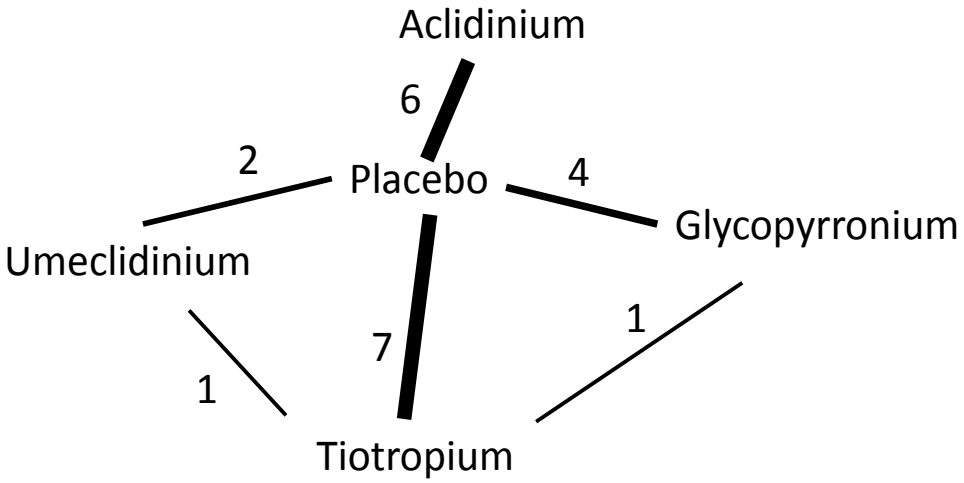
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		1.05 (0.38, 1.72)	0.75 (0.29, 1.20)	1.00 (0.00, 2.00)	0.98 (0.61, 1.36)
Tiotropium	1.00 (0.69, 1.31)		-0.19 (-0.61, 0.24)	0.06 (-0.30, 0.42)	-
Glycopyrronium	0.78 (0.44, 1.14)	-0.22 (-0.46, 0.13)		-	-
Umeclidinium	1.06 (0.62, 1.49)	0.06 (-0.28, 0.39)	0.27 (-0.20, 0.75)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	0.98 (0.63, 1.34)	-0.02 (-0.50, 0.46)	0.20 (-0.30, 0.70)	-0.08 (-0.64, 0.49)	

SGRQ responders

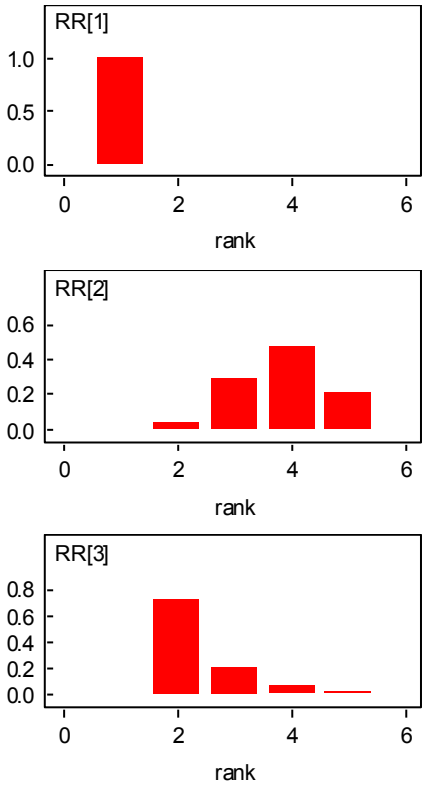
Network diagram

Figure 114 Diagram of the network of studies underlying the NMA with the number of trials for each comparison.

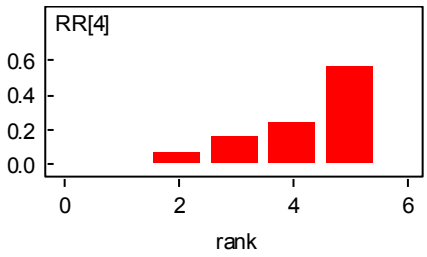


Rank probability histograms

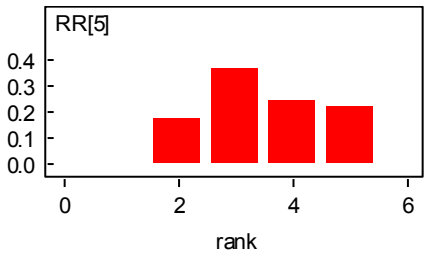
Figure 115 Probability of the treatment assuming each treatment rank**. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 5 is best.)**


RR[1]
1.0
0.5
0.0
0
2
4
6
rank
RR[2]
0.6
0.4
0.2
0.0
0
2
4
6
rank
RR[3]
0.8
0.6
0.4
0.2
0.0
0
2
4
6
rank

1


RR[4]
0.6
0.4
0.2
0.0
0
2
4
6
rank

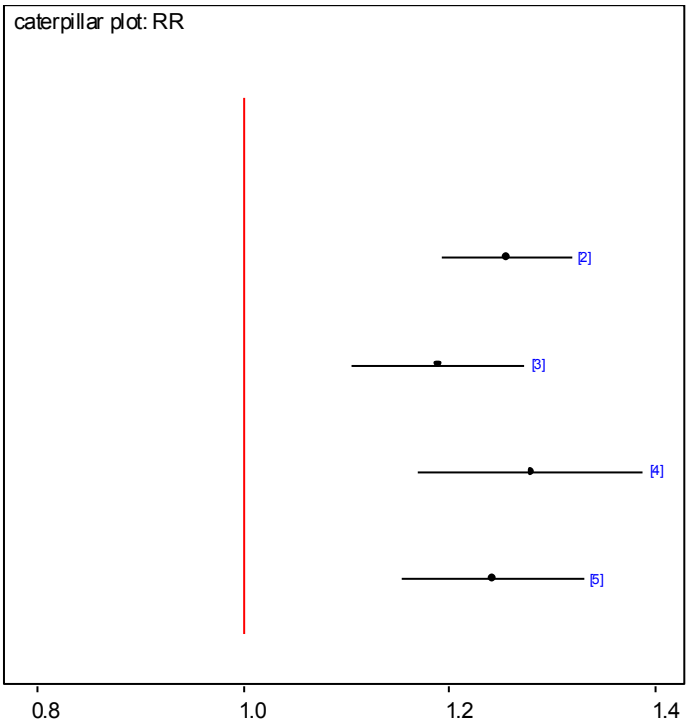
2


RR[5]
0.4
0.3
0.2
0.1
0.0
0
2
4
6
rank

3

Caterpillar plot

Figure 116 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 59 Relative effectiveness of all pairwise combinations. (Risk ratios 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

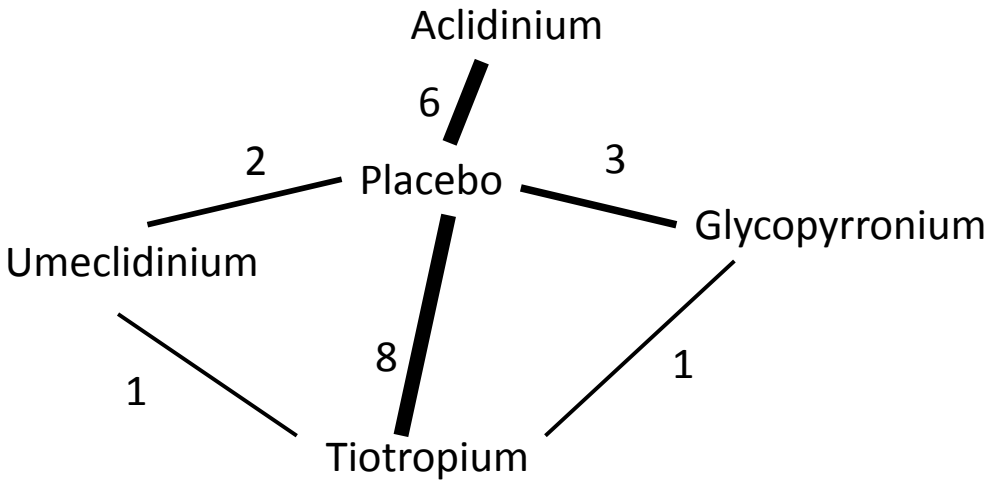
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		1.33 (1.24, 1.43)	1.14 (1.06, 1.23)	1.36 (1.12, 1.65)	1.24 (1.09, 1.41)
Tiotropium	1.26 (1.19,1.32)		1.02 (0.88, 1.17)	1.03 (0.90, 1.17)	-
Glycopyrronium	1.19 (1.12, 1.27)	0.95 (0.87, 1.02)		-	-
Umeclidinium	1.28 (1.17, 1.39)	1.02 (0.94, 1.10)	1.08 (0.97, 1.20)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	1.24 (1.16, 1.33)	0.99 (0.91, 1.08)	1.05 (0.95, 1.15)	0.97 (0.87, 1.09)	

Moderate to severe exacerbations

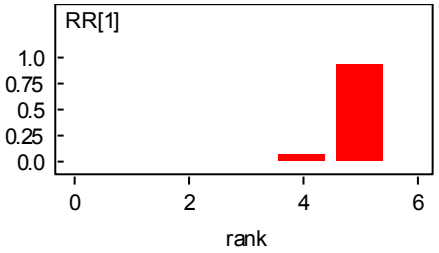
Network diagram

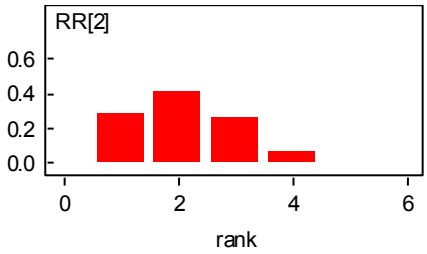
Figure 117 Diagram of the network of studies underlying the NMA with the number of trials for each comparison.



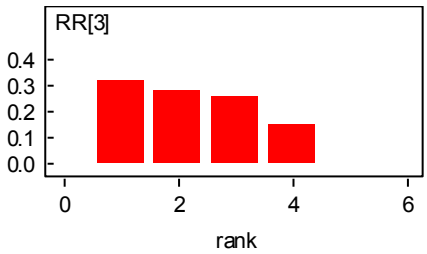
Rank probability histograms

Figure 118 Probability of the treatment assuming each treatment rank**. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 1 is best.)**

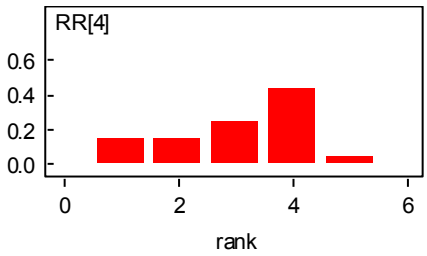



RR[2]
0.6
0.4
0.2
0.0
0
2
4
6
rank

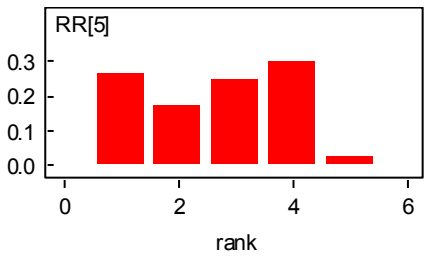
1


RR[3]
0.4
0.3
0.2
0.1
0.0
0
2
4
6
rank

2


RR[4]
0.6
0.4
0.2
0.0
0
2
4
6
rank

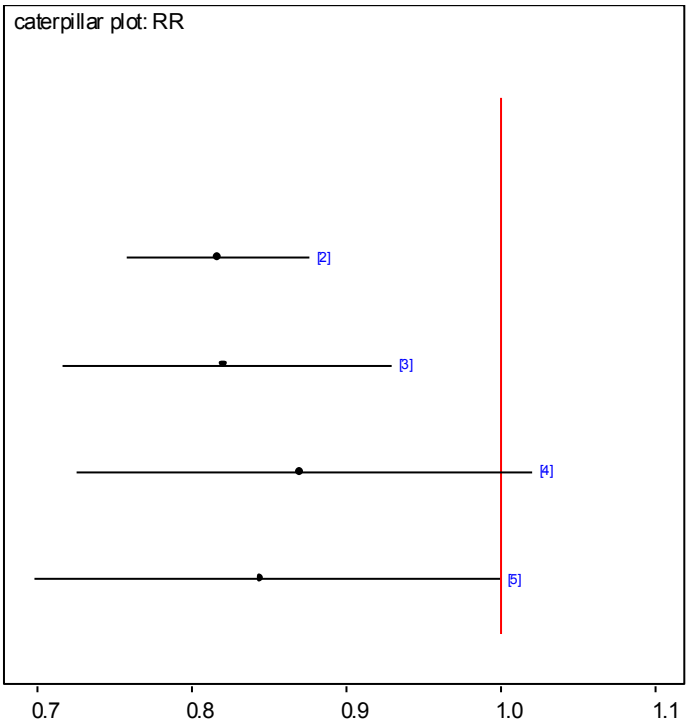
3


RR[5]
0.3
0.2
0.1
0.0
0
2
4
6
rank

4

Caterpillar plot

Figure 119 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 60 Relative effectiveness of all pairwise combinations. (Risk ratios 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

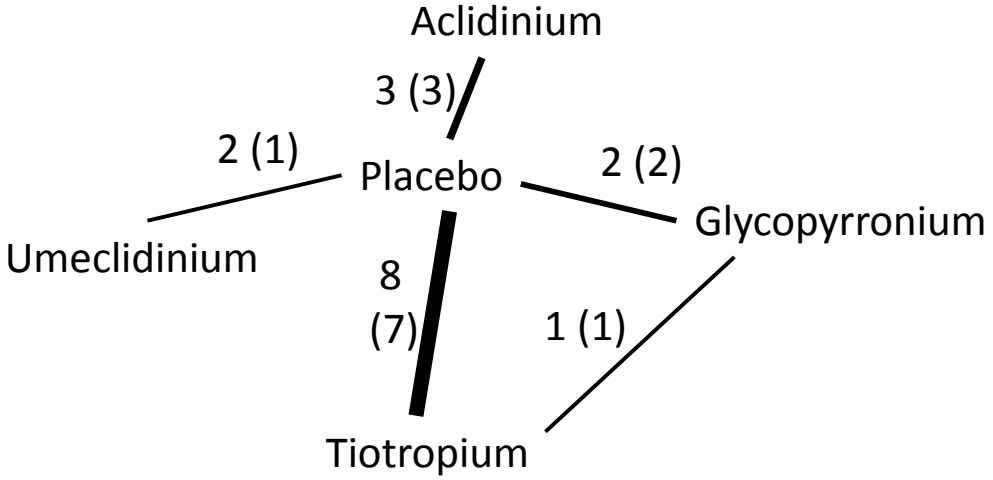
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		0.81 (0.75, 0.88)	0.73 (0.58, 0.92)	0.74 (0.53, 1.05)	0.78 (0.64, 0.95)
Tiotropium	0.87 (0.76, 0.88)		1.33 (0.78, 2.26)	1.21 (0.84, 1.73)	-
Glycopyrronium	0.82 (0.72, 0.93)	1.01 (0.87, 1.16)		-	-
Umeclidinium	0.87 (0.73, 1.02)	1.07 (0.89,1.25)	1.06 (0.85, 1.30)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	0.85 (0.70, 1.00)	1.04 (0.84,1.24)	1.03 (0.82, 1.28)	0.98 (0.76, 1.25)	

Severe exacerbations

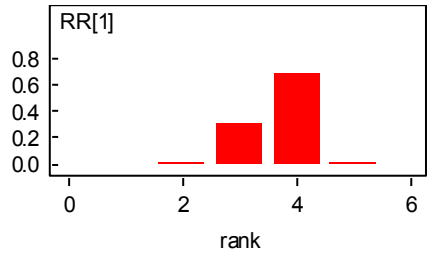
Network diagram

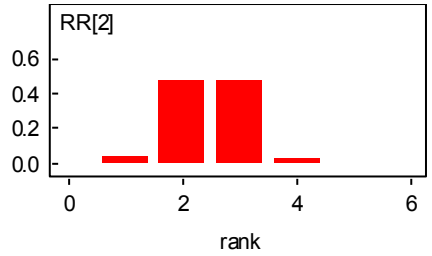
Figure 120 Diagram of the network of studies underlying the NMA with the number of trials for each comparison. (The numbers in brackets represent the numbers of included trials after trials with zero events in both arms are removed.)

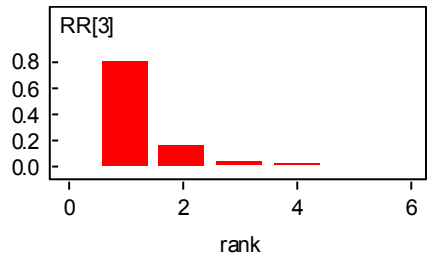


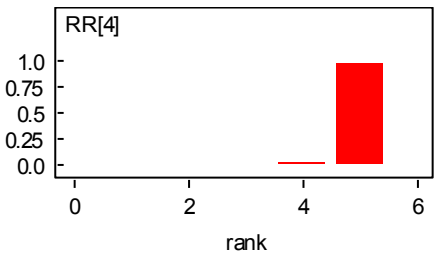
Rank probability histograms

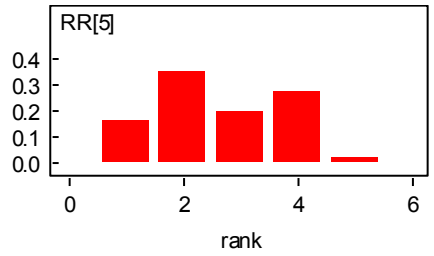
Figure 121 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 1 is best.)





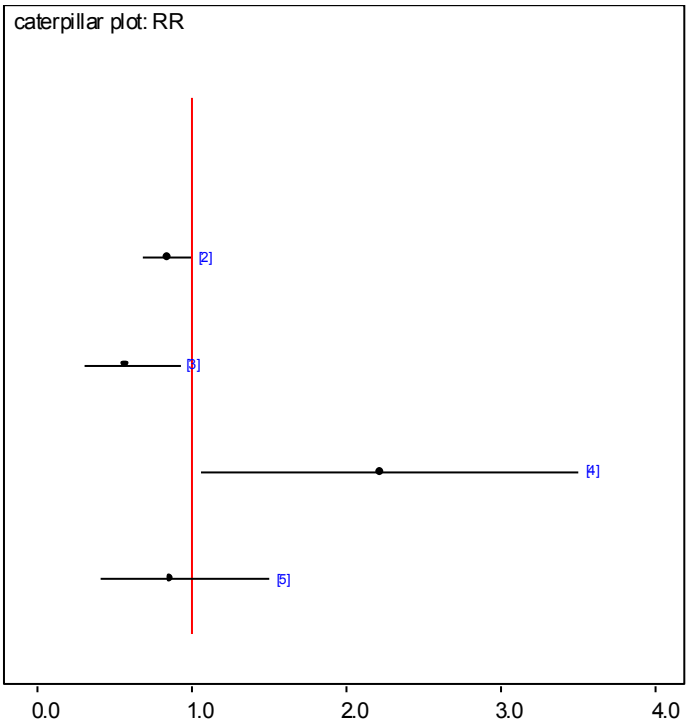






Caterpillar plot

Figure 122 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 61 Relative effectiveness of all pairwise combinations. (Risk ratios 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

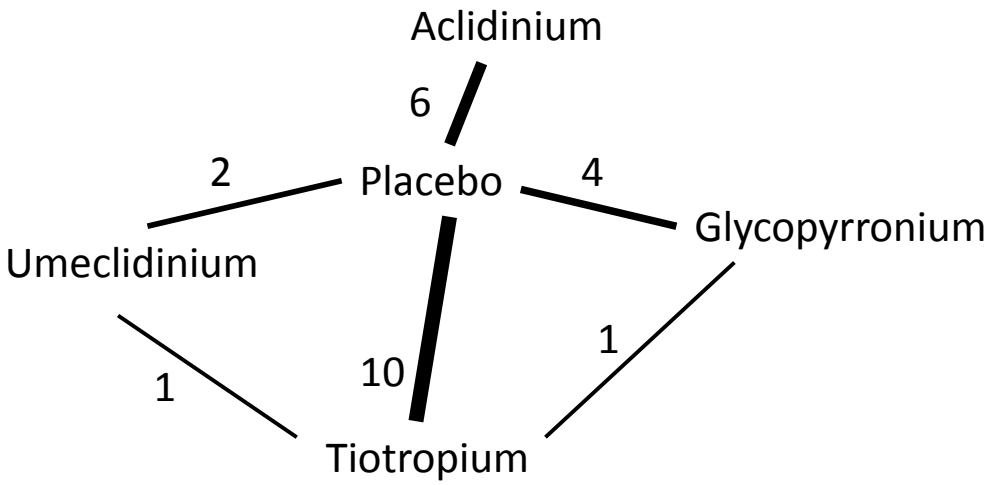
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		0.81 (0.65, 1.01)	0.40 (0.17, 0.95)	3.13 (0.91, 10.78)	0.95 (0.47, 1.92)
Tiotropium	0.84 (0.70, 1.01)		0.67 (0.11, 3.99)	-	-
Glycopyrronium	0.57 (0.31, 0.93)	0.68 (0.36, 1.13)		-	-
Umeclidinium	2.22 (1.07, 3.51)	2.66 (1.24, 4.34)	4.20 (1.64, 8.38)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	0.87 (0.41, 1.51)	1.04 (0.48, 1.85)	1.64 (0.63, 3.46)	0.43 (0.16, 0.96)	

Dropouts due to adverse events

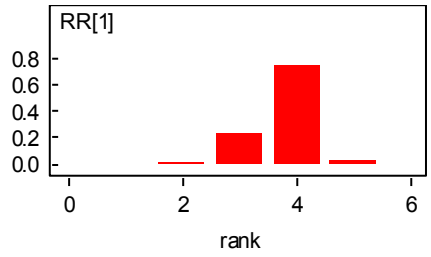
Network diagram

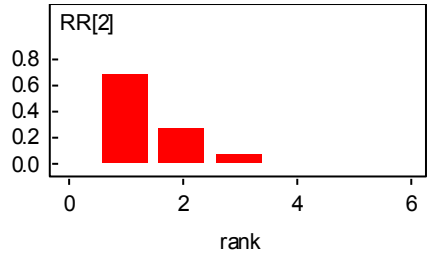
Figure 123 Diagram of the network of studies underlying the NMA with the number of trials for each comparison.

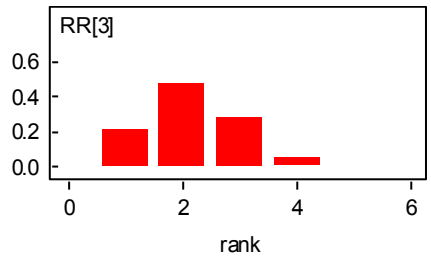


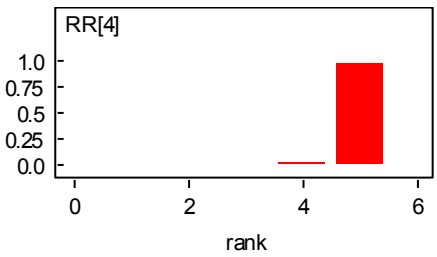
Rank probability histograms

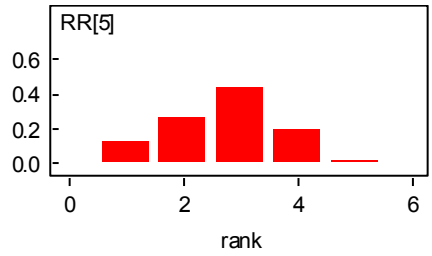
Figure 124 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 1 is best.)





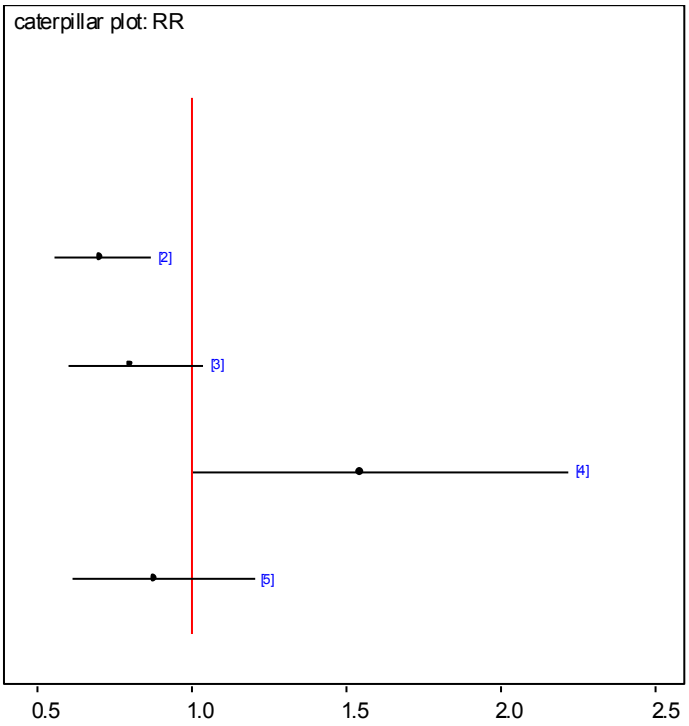






Caterpillar plot

Figure 125 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 62 Relative effectiveness of all pairwise combinations. (Risk ratios 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

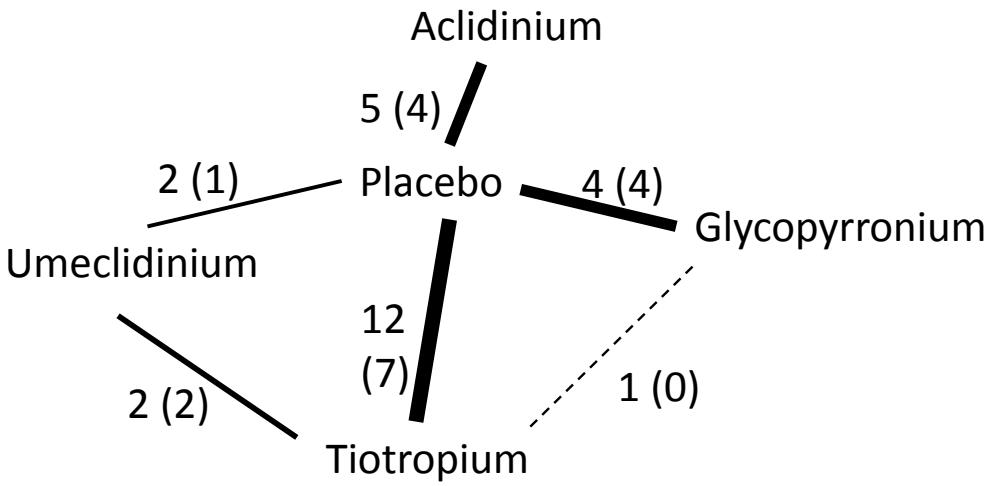
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		0.64 (0.50, 0.83)	0.76 (0.56, 1.03)	2.53 (1.23. 5.19)	0.89 (0.62, 1.30)
Tiotropium	0.71 (0.56, 0.87)		1.41 (0.45,4.41)	1.11 (0.45, 2.71)	-
Glycopyrronium	0.80 (0.60,1.04)	1.15 (0.80, 1.60)		-	-
Umeclidinium	1.55 (1.01, 2.22)	2.21 (1.39, 3.29)	1.96 (1.17, 3.06)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	0.88 (0.62, 1.21)	1.26 (0.83, 1.83)	1.12 (0.71, 1.68)	0.59 (0.34, 0.97)	

Mortality

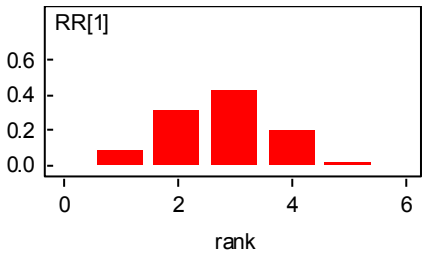
Network diagram

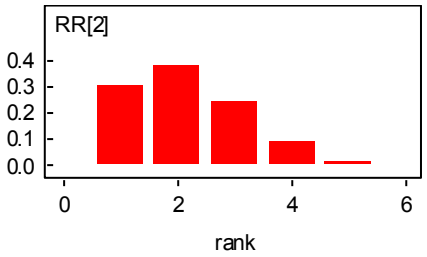
Figure 126 Diagram of the network of studies underlying the NMA with the number of trials for each comparison. (The numbers in brackets represent the numbers of included trials after trials with zero events in both arms are removed. The dashed line represents a connection that is lost once the zero event trials are removed.)

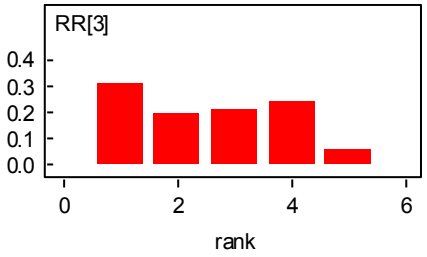


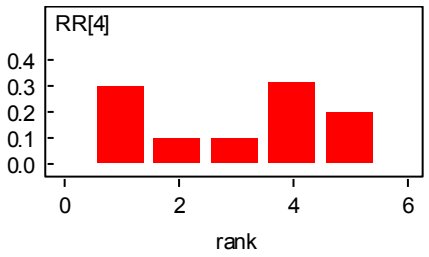
Rank probability histograms

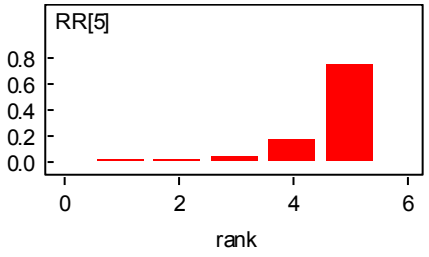
Figure 127 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium. Rank 1 is best.)





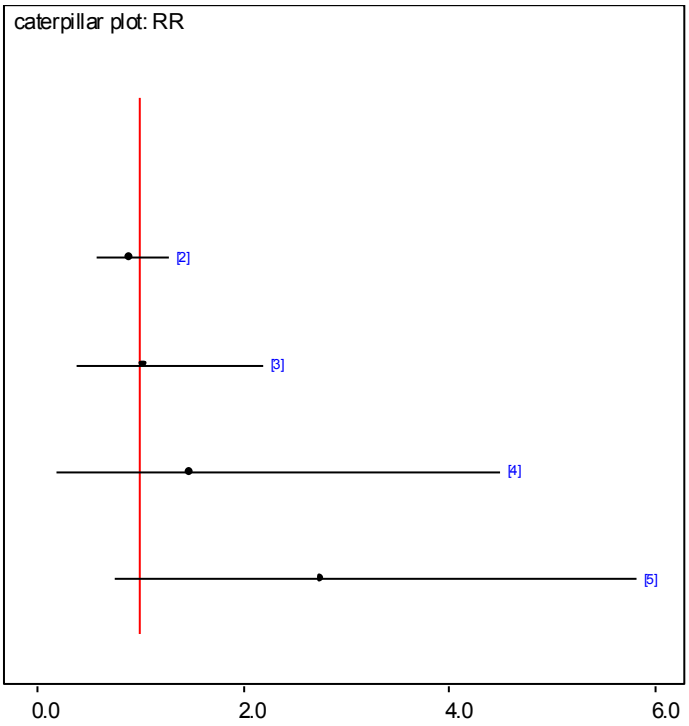






Caterpillar plot

Figure 128 Relative effect of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. Group 2 = tiotropium, group 3 = glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)



Mileage chart

Table 63 Relative effectiveness of all pairwise combinations. (Risk ratios 95% confidence intervals for pair wise data across the top of the chart and 95% credible intervals for NMA derived data along the side.)

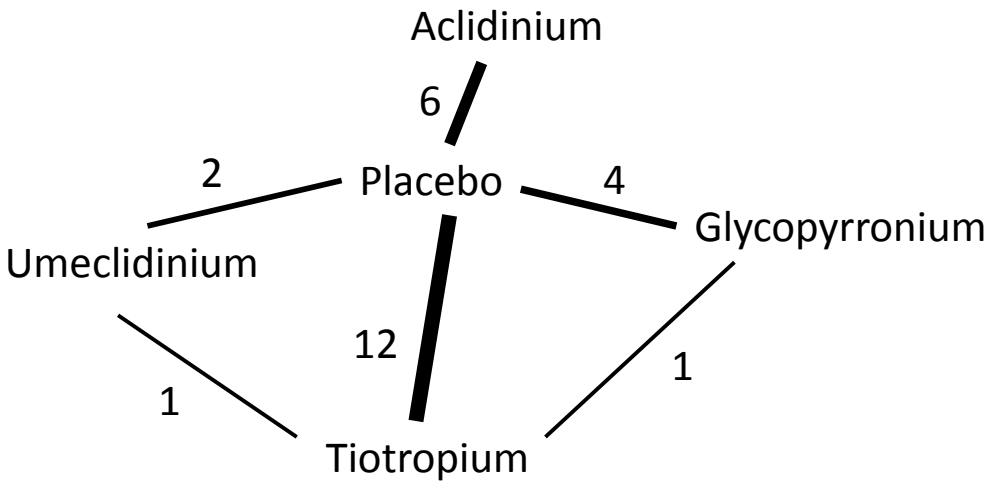
	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		0.82 (0.53, 1.28)	0.88 (0.34, 2.30)	4.69 (0.24, 90.53)	2.33 (0.60, 9.05)
Tiotropium	0.90 (0.58,1.30)		-	0.20 (0.01, 4.15)	-
Glycopyrronium	1.04 (0.39, 2.20)	1.21 (0.41, 2.78)		-	-
Umeclidinium	1.48 (0.20,4.50)	1.70 (0.23, 5.27)	1.73 (0.18, 6.30)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	2.76 (0.77, 5.83)	3.21 (0.82, 7.43)	3.23 (0.61, 9.33)	3.60 (0.36, 15.62)	

Serious adverse events

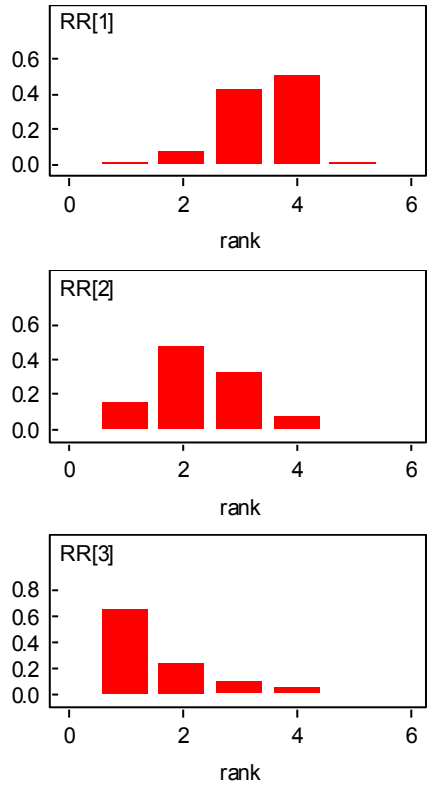
Network diagram

Figure 129 Diagram of the network of studies underlying the NMA with the number of trials for each comparison.

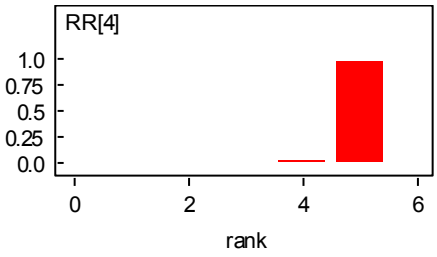


1 ***Rank probability histograms***

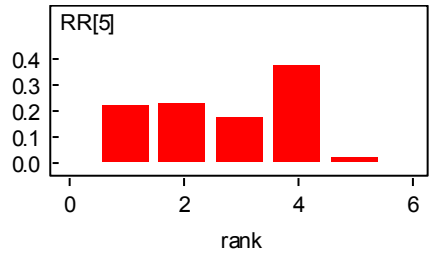
2 **Figure 130 Probability of the treatment assuming each treatment rank. (Group 1=**
3 **placebo, group 2 = tiotropium, group 3 = glycopyrronium, group 4 =**
4 **umeclidinium, group 5 = aclidinium. Rank 1 is best.)**



5



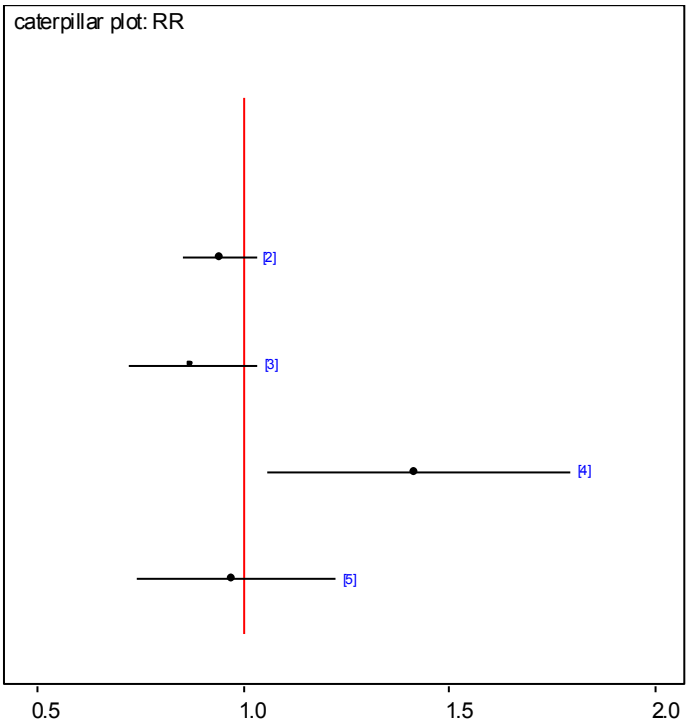
6



7

1 ***Caterpillar plot***

2 **Figure 131 Relative effect of all options versus placebo. (Risk ratios with 95% credible**
3 **intervals and line of no effect in red. Group 2 = tiotropium, group 3 =**
4 **glycopyrronium, group 4 = umeclidinium, group 5 = aclidinium.)**



5

6 ***Mileage chart***

7 **Table 64 Relative effectiveness of all pairwise combinations. (Risk ratios 95%**
8 **confidence intervals for pair wise data across the top of the chart and 95%**
9 **credible intervals for NMA derived data along the side.)**

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Placebo		0.91 (0.78, 1.07)	0.84 (0.66, 1.07)	2.52 (1.27, 4.99)	0.95 (0.67, 1.35)
Tiotropium	0.94 (0.85, 1.04)		1.01 (0.14, 7.12)	1.21 (0.60, 2.43)	-
Glycopyrronium	0.87 (0.72,1.04)	0.93 (0.75, 1.13)		-	-
Umeclidinium	1.42 (1.06, 1.80)	1.51 (1.12, 1.93)	1.64 (1.16, 2.19)		-

	Placebo	Tiotropium	Glycopyrronium	Umeclidinium	Aclidinium
Aclidinium	0.97 (0.75, 1.23)	1.04 (0.78, 1.33)	1.12 (0.81, 1.51)	0.70 (0.48, 0.99)	

1

Appendix H – GRADE tables

Inhaled therapy combinations

The following tables are based on evidence of effect sizes from the Cochrane review. However, the dichotomous data has been altered by the NICE Guideline Updates Team to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B. The completion of the GRADE tables was carried out by the NICE Guideline Updates Team.

LABA/LAMA versus LABA/ICS

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower favours LABA/LAMA)								
9	RCT	8,796	RR 1.03 (0.63, 1.68)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Change in trough FEV1 (L) at 3 months (higher favours LABA/LAMA)								
7	RCT	6,446	MD 0.08 (0.04, 0.11)	Serious[5]	Very serious[2]	Not serious	Serious[3]	Very low
Change in trough FEV1 (L) at 6 months (higher favours LABA/LAMA)								
4	RCT	5,292	MD 0.09 (0.07, 0.11)	Not serious	Not serious	Not serious	Serious[3]	Moderate
Change in trough FEV1 (L) at 12 months (higher favours LABA/LAMA)								
1 (Wedzicha 2016)	RCT	3,192	MD 0.06 (0.04, 0.08)	Not serious	N/A	Not serious	Not serious	High
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/LAMA)								
6	RCT	4,129	MD 0.40 (0.02, 0.78)	Serious[5]	Very serious[2]	Not serious	Not serious	Very low
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/LAMA)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
3	RCT	1,780	MD 0.13 (-0.24, 0.51)	Serious[5]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/LAMA)								
6	RCT	6,342	MD -0.62 (-1.34, 0.10)	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/LAMA)								
3	RCT	4,360	MD -1.18 (-2.20, -0.16)	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour LABA/LAMA)								
1 (Wedzicha 2016)	RCT	3,195	MD -1.20 (-2.34,-0.06)	Not serious	N/A	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months (higher favours LABA/LAMA)								
4	RCT	1,227	RR 1.04 (0.96, 1.12)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/LAMA)								
1 (Vogelmeier 2013)	RCT	427	RR 1.13 (0.94, 1.36)	Not serious	N/A	Not serious	Serious[3]	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LABA/LAMA)								
1 (Wedzzicha 2016)	RCT	3,195	RR 1.13 (1.04, 1.21)	Not serious	N/A	Not serious	Not serious	High
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/LAMA)								
7	RCT	7,687	RR 0.91 (0.85, 0.98)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 severe exacerbation (lower values favour LABA/LAMA)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
5	RCT	6,214	RR 0.88 (0.76, 1.02)	Not serious	Serious[4]	Not serious	Serious[3]	Low
People with ≥ 1 SAE (lower values favour LABA/LAMA)								
9	RCT	8,796	RR 0.91 (0.81, 1.03)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 COPD SAE (lower values favour LABA/LAMA)								
9	RCT	8,796	RR 0.87 (0.73, 1.04)	Not serious	Not serious	Not serious	Serious[3]	Moderate
People with ≥ 1 cardiac SAE (lower values favour LABA/LAMA								
9	RCT	8,796	RR 0.88 (0.62, 1.23)	Not serious	Not serious	Not serious	Serious[3]	Moderate
People with ≥ 1 session of pneumonia (lower values favour LABA/LAMA)								
8	RCT	8,753	RR 0.57 (0.39, 0.83)	Not serious	Not serious	Not serious	Serious[3]	Moderate
Drop-outs due to adverse events (lower values favour LABA/LAMA								
9	RCT	8,796	RR 0.90 (0.76, 1.07)	Not serious	Not serious	Not serious	Serious[3]	Moderate

1. Non-significant result.
2. $I^2 > 66.7\%$
3. 95% confidence interval crosses one end of a defined MID interval.
4. I^2 between 33.3% and 66.7%
5. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.

1 **LABA/LAMA versus LAMA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower favours LABA/LAMA)								
24	RCT	20,683	RR 1.00 (0.75, 1.33)	Very serious[4]	Not serious	Not serious	Serious[1]	Very low
Change in trough FEV1 (L) at 3 months (higher favours LABA/LAMA)								
18	RCT	13,891	MD 0.07 (0.06, 0.08)	Serious[5]	Serious[2]	Not serious	Not serious	Low
Change in trough FEV1 (L) at 6 months (higher favours LABA/LAMA)								
14	RCT	11,002	MD 0.06 (0.05, 0.07)	Serious[5]	Serious[2]	Not serious	Not serious	Low
Change in trough FEV1 (L) at 12 months (higher favours LABA/LAMA)								
7	RCT	8,072	MD 0.06 (0.04, 0.08)	Very serious[4]	Serious[2]	Not serious	Not serious	Very low
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/LAMA)								
10	RCT	7,027	MD 0.48 (0.34, 0.62)	Serious[5]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/LAMA)								
7	RCT	6,099	MD 0.32 (0.17, 0.46)	Serious[5]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LABA/LAMA)								
3	RCT	4,953	MD 0.22 (0.11, 0.34)	Very serious[4]	Not serious	Not serious	Not serious	Low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/LAMA)								
12	RCT	10,259	MD -1.74 (-2.31,-1.18)	Serious[5]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/LAMA)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
11	RCT	9,217	MD -1.32 (-1.92, -0.71)	Very serious[4]	Not serious	Not serious	Not serious	Low
St. George's Respiratory Questionnaire (SGRQ at 12 months (lower values favour LABA/LAMA)								
5	RCT	6,000	MD -1.10 (-1.83, -0.36)	Very serious[4]	Not serious	Not serious	Not serious	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months (higher favours LABA/LAMA)								
9	RCT	4,490	RR 1.14 (1.08, 1.21)	Serious[5]	Not serious	Not serious	Not serious	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/LAMA)								
10	RCT	10,177	RR 1.12 (1.07, 1.16)	Very serious[4]	Not serious	Not serious	Not serious	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LABA/LAMA)								
2	RCT	4,015	RR 1.10 (1.02, 1.17)	Very serious[4]	Not serious	Not serious	Not serious	Low
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/LAMA)								
9	RCT	7,398	RR 0.97 (0.79, 1.19)	Very serious[4]	Serious[2]	Not serious	Serious[3]	Very low
People with ≥ 1 severe exacerbation (lower values favour LABA/LAMA)								
8	RCT	5,241	RR 0.89 (0.70, 1.15)	Not serious	Not serious	Not serious	Serious[3]	Moderate
People with ≥ 1 SAE (lower values favour LABA/LAMA)								
25	RCT	21,453	RR 1.01 (0.93, 1.10)	Very serious[4]	Not serious	Not serious	Not serious	Low
People with ≥ 1 COPD SAE (lower values favour LABA/LAMA)								
22	RCT	20,101	RR 1.00 (0.87, 1.16)	Very serious[4]	Not serious	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People with ≥ 1 cardiac SAE (lower values favour LABA/LAMA)								
22	RCT	20,736	RR 0.98 (0.79, 1.23)	Very serious[4]	Not serious	Not serious	Serious[3]	Very low
People with ≥ 1 session of pneumonia (lower values favour LABA/LAMA)								
24	RCT	21,048	RR 1.15 (0.87, 1.53)	Very serious[4]	Not serious	Not serious	Serious[3]	Very low
Drop-outs due to adverse events (lower values favour LABA/LAMA)								
26	RCT	21,877	RR 1.10 (0.97, 1.25)	Very serious[4]	Not serious	Not serious	Not serious	Low

1. Non-significant result.
2. I^2 between 33.3% and 66.7%
3. 95% confidence interval crosses one end of a defined MID interval.
4. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.
5. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.

1 **LABA/LAMA versus LABA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower favours LABA/LAMA)								
10	RCT	7,930	RR 1.15 (0.68, 1.94)	Serious[5]	Not serious	Not serious	Serious[1]	Low
Change in trough FEV1 (L) at 3 months (higher favours LABA/LAMA)								
4	RCT	2,469	MD 0.07 (0.03, 0.12)	Serious[5]	Very serious[2]	Not serious	Serious[3]	Very low
Change in trough FEV1 (L) at 6 months (higher favours LABA/LAMA)								
8	RCT	6,144	MD 0.07	Serious[5]	Not serious	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(0.06, 0.08)					
Change in trough FEV1 (L) at 12 months (higher favours LABA/LAMA)								
6	RCT	5,063	MD 0.07 (0.06, 0.08)	Very serious[6]	Not serious	Not serious	Not serious	Low
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/LAMA)								
3	RCT	3,342	MD 0.52 (0.31, 0.74)	Serious[5]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/LAMA)								
4	RCT	4,126	MD 0.40 (0.23, 0.57)	Serious[5]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LABA/LAMA)								
3	RCT	4,516	MD 0.42 (0.06, 0.77)	Very serious[6]	Very serious[2]	Not serious	Not serious	Very low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/LAMA)								
1 (Bateman 2013)	RCT	950	MD -1.29 (-4.29, 1.17)	Very serious[6]	N/A	Not serious	Serious[3]	Very low
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/LAMA)								
5	RCT	3,649	MD -1.09 (-1.96, -0.22)	Very serious[6]	Not serious	Not serious	Not serious	Low
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour LABA/LAMA)								
2	RCT	2,507	MD -0.69 (-1.64, 0.25)	Very serious[6]	Not serious	Not serious	Not serious	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/LAMA)								
6	RCT	5,870	RR 1.14 (1.04, 1.24)	Very serious[6]	Serious[4]	Not serious	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LABA/LAMA)								
1 (PINNACLE 3 2017)	RCT	1,820	RR 1.11 (0.99, 1.25)	Very serious[6]	N/A	Not serious	Not serious	Low
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/LAMA)								
5	RCT	2,488	RR 0.81 (0.67, 0.97)	Very serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 severe exacerbation (lower values favour LABA/LAMA)								
6	RCT	2,898	RR 0.82 (0.62, 1.09)	Serious[5]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 SAE (lower values favour LABA/LAMA)								
11	RCT	8,699	RR 1.05 (0.92, 1.19)	Very serious[6]	Not serious	Not serious	Not serious	Low
People with ≥ 1 COPD SAE (lower values favour LABA/LAMA)								
8	RCT	7,068	RR 1.08 (0.85, 1.38)	Serious[5]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 cardiac SAE (lower values favour LABA/LAMA)								
11	RCT	8,699	RR 1.28 (0.88, 1.86)	Very serious[6]	Not serious	Not serious	Serious[3]	Very low
People with ≥ 1 session of pneumonia (lower values favour LABA/LAMA)								
10	RCT	8,252	RR 1.59 (1.10, 2.51)	Serious[5]	Not serious	Not serious	Serious[3]	Low
Drop-outs due to adverse events (lower values favour LABA/LAMA)								
13	RCT	9,202	RR 0.93 (0.77, 1.13)	Very serious[6]	Serious[4]	Not serious	Serious[3]	Very low

1. Non-significant result.

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2. I^2> 66.7%.								
3. 95% confidence interval crosses one end of a defined MID interval.								
4. I^2 between 33.3% and 66.7%.								
5. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.								
6. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.								

1 **LABA/ICS versus LAMA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower favours LABA/ICS)								
5	RCT	2,395	RR 0.53 (0.32, 0.87)	Serious[6]	Not serious	Not serious	Not serious	Moderate
Change in trough FEV1 (L) at 3 months (higher favours LABA/ICS)								
7	RCT	2,327	MD 0.02 (-0.02, 0.06)	Very serious[7]	Very serious[1]	Not serious	Not serious	Very low
Change in trough FEV1 (L) at 6 months (higher favours LABA/ICS)								
2	RCT	1,301	MD -0.01 (-0.03, 0.02)	Serious[6]	Not serious	Not serious	Not serious	Moderate
Change in trough FEV1 (L) at 12 months (higher favours LABA/ICS)								
2	RCT	933	MD -0.01 (-0.08, 0.05)	Very serious[7]	Serious[2]	Not serious	Not serious	Very low
Change in trough FEV1 (L) at 2 years (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	786	MD -0.01 (-0.05, 0.03)	Serious[6]	N/A	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/ICS)								
2	RCT	1,323	MD 0.50	Serious[6]	Not serious	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(0.20, 0.81)					
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	1,103	MD 0.30 (-0.06, 0.66)	Serious[6]	N/A	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	942	MD 0.00 (-0.40, 0.40)	Serious[6]	N/A	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 2 years (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	814	MD 0.20 (-0.25, 0.65)	Serious[6]	N/A	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/ICS)								
3	RCT	814	MD -1.37 (-3.04, 0.30)	Serious[6]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/ICS)								
1 (Wedzicha 2008)	RCT	999	MD -1.97 (-3.79, -0.15)	Serious[6]	N/A	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour LABA/ICS)								
1 (Wedzicha 2008)	RCT	847	MD -0.99 (-2.98, 1.00)	Serious[6]	N/A	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 2 years (lower values favour LABA/ICS)								
1 (Wedzicha 2008)	RCT	730	MD -1.04 (-3.29, 1.21)	Serious[6]	N/A	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months (higher favours LABA/ICS)								
2	RCT	823	RR 1.09 (0.94, 1.26)	Serious[6]	Not serious	Serious[5]	Serious[3]	Very low
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	1,236	RR 1.17 (0.99, 1.37)	Serious[6]	N/A	Not serious	Serious[3]	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	1,227	RR 1.10 (0.93, 1.31)	Serious[6]	N/A	Not serious	Serious[3]	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 2 years (higher favours LABA/ICS)								
1 (Wedzicha 2008)	RCT	1,229	RR 1.19 (1.00, 1.41)	Serious[6]	N/A	Not serious	Serious[3]	Low
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/ICS)								
3	RCT	2,203	RR 1.04 (0.95, 1.13)	Serious[6]	Not serious	Not serious	Not serious	Moderate
People with ≥ 1 severe exacerbation (lower values favour LABA/ICS)								
3	RCT	2,203	RR 1.26 (0.97, 1.63)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 SAE (lower values favour LABA/ICS)								
5	RCT	2,590	RR 1.17 (1.00, 1.38)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 COPD SAE (lower values favour LABA/ICS)								
5	RCT	2,590	RR 1.27 (0.99, 1.63)	Serious[6]	Not serious	Not serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People with ≥ 1 cardiac SAE (lower values favour LABA/ICS)								
3	RCT	2,208	RR 0.59 (0.36, 0.97)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 session of pneumonia (lower values favour LABA/ICS)								
4	RCT	2,465	RR 1.95 (1.20, 3.18)	Serious[6]	Not serious	Not serious	Serious[3]	Low
Drop-outs due to adverse events (lower values favour LABA/ICS)								
6	RCT	2,657	RR 0.98 (0.75, 1.29)	Serious[6]	Not serious	Not serious	Very serious[4]	Very low

1. I^2>66.7%
2. I^2 between 33.3% and 66.7%.
3. 95% confidence interval crosses one end of a defined MID interval.
4. 95% confidence interval crosses both ends of a defined MID interval.
5. > 33.3% of the weight in a meta-analysis came from a partially indirect study.
6. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.
7. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.

1 **LABA/ICS versus LABA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower favours LABA/ICS)								
21	RCT	19,681	RR 0.95 (0.82, 1.11)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Change in trough FEV1 (L) at 3 months (higher favours LABA/ICS)								
12	RCT	7,829	MD 0.05 (0.04, 0.06)	Very serious[6]	Not serious	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in trough FEV1 (L) at 6 months (higher favours LABA/ICS)								
11	RCT	6,555	MD 0.04 (0.03, 0.06)	Very serious[6]	Not serious	Not serious	Not serious	Low
Change in trough FEV1 (L) at 12 months (higher favours LABA/ICS)								
7	RCT	3,431	MD 0.05 (0.04, 0.07)	Very serious[6]	Not serious	Not serious	Not serious	Low
Change in trough FEV1 (L) at 3 years (higher favours LABA/ICS)								
1 (SCO40041 2008)	RCT	111	MD 0.04 (-0.24, 0.31)	Not serious	N/A	Not serious	Very serious[2]	Low
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/ICS)								
4	RCT	1,9868	MD 0.09 -0.21, 0.37)	Not serious	Not serious	Not serious	Not serious	High
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/ICS								
4	RCT	1,917	MD 0.21 (-0.09, 0.50)	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/ICS)								
4	RCT	3,602	MD -1.53 (-2.48, -0.58)	Serious[7]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/ICS)								
9	RCT	7,857	MD -1.33 (-1.86, -0.80)	Serious[7]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour LABA/ICS)								
9	RCT	8,322	MD -1.76 (-2.36, -1.15)	Serious[7]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 3 years (lower values favour LABA/ICS)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Calverley 2007)	RCT	1,315	MD -2.20 (-3.63, -0.77)	Not serious	N/A	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months (higher favours LABA/ICS)								
2	RCT	786	RR 0.95 (0.87, 1.05)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/ICS)								
5	RCT	5,800	RR 1.06 (1.01, 1.12)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LABA/ICS)								
4	RCT	4,349	RR 1.14 (0.97, 1.35)	Not serious	Very serious[3]	Not serious	Serious[4]	Very low
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 years (higher favours LABA/ICS)								
1 (Calverley 2007)	RCT	1,916	RR 1.15 (1.00, 1.33)	Not serious	N/A	Not serious	Serious[4]	Moderate
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/ICS)								
16	RCT	15,730	RR 0.91 (0.88, 0.94)	Serious[7]	Serious[5]	Not serious	Not serious	Low
People with ≥ 1 severe exacerbation (lower values favour LABA/ICS)								
11	RCT	10,698	RR 1.00 (0.90, 1.11)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 SAE (lower values favour LABA/ICS)								
20	RCT	19,204	RR 1.03 (0.97, 1.09)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 COPD SAE (lower values favour LABA/ICS)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
17	RCT	16,397	RR 0.94 (0.85, 1.04)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 cardiac SAE (lower values favour LABA/ICS)								
17	RCT	17,085	RR 0.97 (0.84, 1.12)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 session of pneumonia (lower values favour LABA/ICS)								
20	RCT	19,291	RR 1.54 (1.29, 1.85)	Not serious	Not serious	Not serious	Not serious	High
Drop-outs due to adverse events (lower values favour LABA/ICS)								
21	RCT	19,713	RR 0.90 (0.83, 0.98)	Not serious	Not serious	Not serious	Not serious	High

1. 95% CI crosses the line of no effect.
2. Non-significant result.
3. I^2>66.7%.
4. 95% confidence interval crosses one end of a defined MID interval.
5. I^2 between 33.3% and 66.7%.
6. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.
7. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.

1 **LAMA versus LABA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower favours LAMA)								
13	RCT	22,844	RR 0.96 (0.75, 1.23)	Not serious	Not serious	Not serious	Serious[1]	Moderate
Change in trough FEV1 (L) at 3 months (higher favours LAMA)								
8	RCT	5,420	MD -0.00	Very serious[6]	Very serious[2]	Not serious	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(-0.02, 0.02)					
Change in trough FEV1 (L) at 6 months (higher favours LAMA)								
10	RCT	7,770	MD 0.02 (0.01, 0.03)	Very serious[6]	Not serious	Not serious	Not serious	Low
Change in trough FEV1 (L) at 12 months (higher favours LAMA)								
5	RCT	5,353	MD 0.02 (0.01, 0.03)	Very serious[6]	Not serious	Not serious	Not serious	Low
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LAMA)								
4	RCT	7,881	MD -0.14 (-0.37, 0.09)	Serious[7]	Very serious[2]	Not serious	Not serious	Very low
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LAMA)								
5	RCT	7,444	MD -0.19 (-0.20, -0.18)	Not serious	Not serious	Not serious	Not serious	High
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LAMA)								
4	RCT	7,421	MD 0.02 (-0.25, 0.29)	Serious[7]	Very serious[2]	Not serious	Not serious	Very low
St. George's Respiratory Questionnaire (SGRQ), 3 months (lower values favours LAMA)								
4	RCT	7,191	MD 1.13 (-0.09, 2.34)	Very serious[6]	Serious[3]	Not serious	Not serious	Very low
St. George's Respiratory Questionnaire (SGRQ), 6 months (lower values favour LAMA)								
7	RCT	7,972	MD -0.39 (-1.01, 0.22)	Very serious[6]	Not serious	Not serious	Not serious	Low
St. George's Respiratory Questionnaire (SGRQ), 12 months (lower values favour LAMA)								
3	RCT	5,397	MD -0.08 (-0.79, 0.62)	Very serious[6]	Not serious	Not serious	Not serious	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months (higher favours LAMA)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2	RCT	4,495	MD 0.92 (0.79, 1.07)	Serious[7]	Very serious[2]	Not serious	Serious[4]	Very low
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LAMA)								
8	RCT	11,831	MD 1.02 (0.98, 1.06)	Serious[7]	Serious[3]	Not serious	Not serious	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LAMA)								
2	RCT	4,709	MD 1.10 (0.95, 1.08)	Very serious[6]	Not serious	Not serious	Not serious	Low
People with ≥ 1 moderate to severe exacerbation (lower values favour LAMA)								
6	RCT	11,943	RR 0.90 (0.86, 0.95)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 severe exacerbation (lower values favour LAMA)								
5	RCT	10,696	RR 0.88 (0.79, 0.98)	Not serious	Serious[2]	Not serious	Serious[4]	Low
People with ≥ 1 SAE (lower values favour LAMA)								
15	RCT	23,844	RR 0.94 (0.88, 1.01)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 COPD SAE (lower values favour LAMA)								
13	RCT	22,789	RR 0.84 (0.75, 0.93)	Not serious	Not serious	Not serious	Serious[4]	Moderate
People with ≥ 1 cardiac SAE (lower values favour LAMA)								
13	RCT	22,806	RR 1.13 (0.92, 1.38)	Not serious	Not serious	Not serious	Serious[4]	Moderate
People with ≥ 1 session of pneumonia (lower values favour LAMA)								
12	RCT	22,153	RR 0.88 (0.69, 1.14)	Not serious	Not serious	Not serious	Serious[4]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Drop-outs due to adverse events (lower values favour LAMA)								
14	RCT	22,755	RR 0.90 (0.81, 1.00)	Not serious	Not serious	Not serious	Not serious	High

1. Non-significant result.
2. I^2>66.7%.
3. I^2 between 33.3% and 66.7%.
4. 95% confidence interval crosses one end of a defined MID interval.
5. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.
6. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.

1

1 **Sensitivity analyses**

2 ***LABA/LAMA versus LABA/ICS***

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/LAMA)								
5	RCT	3,072	MD 0.19 (-0.04, 0.41)	Serious[1]	Not serious	Not serious	Not serious	Moderate
1. > 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.								

3 ***LABA/LAMA versus LAMA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/LAMA)								
8	RCT	5,132	MD 0.48 (0.32, 0.65)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/LAMA)								
6	RCT	4,672	MD 0.30 (0.14, 0.47)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LABA/LAMA)								
2	RCT		MD 0.31 (0.05, 0.56)	Serious[1]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/LAMA)								
8	RCT	6,116	MD -1.77 (-2.42, -1.12)	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/LAMA)								
6	RCT	3,756	MD -1.00 (-1.84, -0.17)	Not serious	Not serious	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
St. George's Respiratory Questionnaire (SGRQ at 12 months (lower values favour LABA/LAMA)								
2	RCT	1,364	MD -0.13 (-1.64, 1.38)	Serious[1]	Not serious	Not serious	Not serious	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) at 3 months (higher favours LABA/LAMA)								
8	RCT	4,003	RR 1.17 (1.10, 1.24)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/LAMA)								
6	RCT	4,760	RR 1.12 (1.07, 1.18)	Serious[1]	Not serious	Not serious	Not serious	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LABA/LAMA)								
1	RCT	2,272	RR 1.08 (0.97, 1.19)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/LAMA)								
4	RCT	2,588	RR 0.99 (0.59, 1.65)	Not serious	Serious[2]	Not serious	Very serious[3]	Very low
People with ≥ 1 severe exacerbation (lower values favour LABA/LAMA)								
4	RCT	2,892	RR 0.87 (0.66, 1.14)	Not serious	Not serious	Not serious	Serious[4]	Moderate

1. > 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.
2. I^2 between 33.3% and 66.7%
3. 95% confidence interval crosses both ends of a defined MID interval.
4. 95% confidence interval crosses one end of a defined MID interval.

1 ***LABA/LAMA versus LABA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/LAMA)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2	RCT	2,392	MD 0.61 (0.36, 0.86)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LABA/LAMA)								
3	RCT	3,176	MD 0.44 (0.25, 0.63)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LABA/LAMA)								
2	RCT	2,643	MD 0.62 (0.37, 0.88)	Serious[1]	Not serious	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/LAMA)								
2	RCT	1,180	MD -1.72 (-3.13, -0.30)	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour LABA/LAMA)								
1	RCT	667	MD 0.41 (-1.96, 2.79)	Serious[1]	N/A	Not serious	Not serious	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/LAMA)								
3	RCT	3,267	RR 1.22 (1.14, 1.30)	Serious[1]	Serious[2]	Not serious	Serious[3]	Very low
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/LAMA)								
2	RCT	786	RR 0.75 (0.38, 1.47)	Not serious	Serious[2]	Not serious	Very serious[4]	Very low
People with ≥ 1 severe exacerbation (lower values favour LABA/LAMA)								
3	RCT	1,196	RR 0.84 (0.61, 1.17)	Serious[1]	Not serious	Not serious	Serious[3]	Low

1. > 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.
2. I^2 between 33.3% and 66.7%.
3. 95% confidence interval crosses one end of a defined MID interval.

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
4. 95% CI confidence interval crosses both ends of a defined MID interval.								

1 ***LABA/ICS versus LAMA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LABA/ICS)								
1	RCT	1,198	MD 0.50 (0.18, 0.82)	Serious[1]	N/A	Not serious	Not serious	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour LABA/ICS)								
2	RCT	747	MD -1.30 (-3.00, 0.41)	Serious[1]	Not serious	Serious[2]	Not serious	Low
1. > 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias. 2. > 33.3% of the weight in a meta-analysis came from a partially indirect study.								

2 ***LABA/ICS versus LABA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour LABA/ICS)								
8	RCT	6,675	MD -1.34 (-1.96, -0.72)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LABA/ICS)								
4	RCT	4,618	RR 1.04 (0.98, 1.10)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 moderate to severe exacerbation (lower values favour LABA/ICS)								
15	RCT	14,511	RR 0.91 (0.88, 0.95)	Not serious	Serious[1]	Not serious	Not serious	Moderate
1. I^2 between 33.3% and 66.7%.								

1

2 ***LABA versus LAMA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in Transition Dyspnoea Index (TDI) at 3 months (higher favours LAMA)								
3	RCT	6,452	MD -0.12 (-0.42, 0.18)	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
Change in Transition Dyspnoea Index (TDI) at 6 months (higher favours LAMA)								
4	RCT	6,015	MD -0.19 (-0.20, -0.18)	Not serious	Serious[3]	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) at 12 months (higher favours LAMA)								
3	RCT	5,241	MD 0.07 (-0.41, 0.56)	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
St. George's Respiratory Questionnaire (SGRQ), 3 months (lower values favours LAMA)								
2	RCT	4,515	MD 1.06 (-0.90, 3.30)	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
St. George's Respiratory Questionnaire (SGRQ), 6 months (lower values favour LAMA)								
4	RCT	4,825	MD -0.88 (-1.65, -0.11)	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ), 12 months (lower values favour LAMA)								
2	RCT	3,275	MD -0.37 (-1.41, 0.67)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) at 6 months (higher favours LAMA)								
5	RCT	8,422	RR 1.04 (0.97, 1.12)	Serious[1]	Serious[3]	Not serious	Not serious	Low
People with ≥ 4 units improvement in quality of life (SGRQ) at 12 months (higher favours LAMA)								
1	RCT	2,587	RR 1.00	Not serious	N/A	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(0.92, 1.08)					
People with ≥ 1 moderate to severe exacerbation (lower values favour LAMA)								
3	RCT	8,836	RR 0.89 (0.84, 0.95)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 1 severe exacerbation (lower values favour LAMA)								
3	RCT	8,836	RR 0.88 (0.79, 0.99)	Not serious	Not serious	Not serious	Serious[4]	Moderate

1. > 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.
2. I^2>66.7%.
3. I^2 between 33.3% and 66.7%.
4. 95% confidence interval crosses one end of a defined MID interval.

1

1 **Network meta-analyses**

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
FEV1 3 months low risk								
50	RCT	22,359	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
FEV1 3 months high risk								
11	RCT	10,962	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
FEV1 6 months low risk								
30	RCT	27,461	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Very low
FEV1 6 months high risk								
11	RCT	10,603	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
FEV1 12 months low risk								
13	RCT	16,282	See appendix G	Serious[1]	Not serious	Serious[3]	Serious[5]	Very low
FEV1 12 months high risk								
13	RCT	9,762	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
Moderate to severe exacerbations low risk								
38	RCT	23,874	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Moderate to severe exacerbations high risk								
21	RCT	23,575	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Moderate
Severe exacerbations low risk								
31	RCT	21,120	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Severe exacerbations high risk								
13	RCT	16,830	See appendix G	Not serious	Not serious	Not serious	Not serious	High
Dropouts due to adverse events low risk								
66	RCT	61, 541	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
Dropouts due to adverse events high risk								

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
25	RCT	30,322	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
SGRQ at 3 months low risk								
28	RCT	18,114	See appendix G	Serious[1]	Not serious	Serious[7]	Not serious	Low
SGRQ at 3 months high risk								
9	RCT	11,044	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
SGRQ at 6 months low risk								
20	RCT	21,306	See appendix G	Serious[1]	Not serious	Serious[7]	Not serious	Low
SGRQ at 6 months high risk								
10	RCT	12,748	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
SGRQ at 12 months low risk								
6	RCT	9,749	See appendix G	Very serious[2]	Not serious	Not serious	Not serious	Low
SGRQ at 12 months high risk								
14	RCT	15,459	See appendix G	Serious[1]	Not serious	Very serious[4]	Not serious	Very low
SGRQ responders at 3 months low risk								
22	RCT	14,351	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
SGRQ responders at 6 months low risk								
19	RCT	20,385	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
SGRQ responders at 12 months high risk								
7	RCT	11,089	See appendix G	Not serious	Not serious	Serious[3]	Not serious	Moderate
TDI at 3 months low risk								
30	RCT	21,471	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
TDI at 6 months low risk								
18	RCT	18,503	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
TDI at 12 months low risk								

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
6	RCT	14,280	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
SAEs low risk								
67	RCT	64,855	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
SAEs high risk								
24	RCT	31,721	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
COPD SAEs low risk								
63	RCT	61,759	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
COPD SAEs high risk								
20	RCT	29,744	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Cardiac SAEs low risk								
58	RCT	62,663	See appendix G	Serious[1]	Not serious	Not serious[8]	Not serious	Moderate
Cardiac SAEs high risk								
19	RCT	28,316	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
Pneumonia low risk								
61	RCT	61, 157	See appendix G	Serious[1]	Not serious	Serious[3,8]	Not serious	Low
Pneumonia high risk								
24	RCT	33,952	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Mortality low risk								
51	RCT	57,880	See appendix G	Serious[1]	Not serious	Serious[3]	Serious[6]	Very low
Mortality high risk								
24	RCT	31,674	See appendix G	Serious[1]	Not serious	Not serious	Serious[6]	Low

1. >33.3% of studies in the NMA at moderate or high risk of bias.
2. >33.3% of studies in the NMA at high risk of bias.
3. DIC for a random-effects model lower than the DIC for a fixed-effects model.

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4. DIC for a random-effects model lower than the DIC for a fixed-effects model and meaningful differences between point estimates from direct and indirect evidence. 5. All comparisons in NMA rated as being of at least serious risk of imprecision. 6. Not possible to distinguish any meaningfully distinct treatment options in the network. 7. Meaningful differences between point estimates from direct and indirect evidence. 8. Not downgraded (or downgraded again) despite meaningful differences between point estimates from direct and indirect evidence due to the NMA data resolving an inconsistency in the pair-wise data.								

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2

1 LAMA monotherapy

2 Tiotropium (18 micrograms or 5 micrograms in total) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower values favour tiotropium bromide)										
12	RCT	8, 275	RR: 0.82 (0.53, 1.28)	1.06 per 100	0.87 per 100 (0.56, 1.36)	Serious[6]	Not serious	Not serious	Serious[2]	Low
Change in trough FEV1 (ml) at 3 months (higher values favour tiotropium bromide)										
5	RCT	1,426	MD: 125.33 (104.64, 146.02)	N/A	N/A	Serious[6]	Not serious	Not serious	Not serious	Moderate
Change in trough FEV1 (ml) at 6 months (higher values favour tiotropium bromide)										
3	RCT	1, 509	MD: 121.68 (107.2, 135.53)	N/A	N/A	Serious[6]	Not serious	Not serious	Not serious	Moderate
Change in trough FEV1 (ml) at 12 months (higher values favour tiotropium bromide)										
2	RCT	2, 784	MD: 134.39 (117.53, 151.24)	N/A	N/A	Serious[6]	Not serious	Not serious	Not serious	Moderate
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour tiotropium bromide)										
3	RCT	840	MD: 1.05 (0.38, 1.72)	N/A	N/A	Very serious[7]	Serious[1]	Not serious	Serious[3]	Very low
Change in Transition Dyspnoea Index (TDI) focal score at 6 months (higher values favour tiotropium bromide)										
1 (Brusasco 2003)	RCT	637	MD: 1.10 (0.51, 1.69)	N/A	N/A	Serious[8]	N/A	Not serious	Serious[3]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 12 months (higher values favour tiotropium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2	RCT	1, 924	MD: 1.09 (0.84, 1.34)	N/A	N/A	Serious[6]	Not serious	Not serious	Serious[3]	Low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour tiotropium bromide)										
2	RCT	844	MD: -2.75 (-4.12, -1.38)	N/A	N/A	Very serious[7]	Not serious	Not serious	Serious[3]	Very low
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour tiotropium bromide)										
2	RCT	1,129	MD: -3.26 (-4.79, -1.73)	N/A	N/A	Serious[6]	Not serious	Not serious	Serious[3]	Low
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour tiotropium bromide)										
2	RCT	1,843	MD: -3.48 (-4.57, -2.39)	N/A	N/A	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour tiotropium bromide)										
7	RCT	3,860	RR: 1.33 (1.24, 1.43)	37.46 per 100	49.83 per 100 (46.46, 53.57)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 moderate to severe exacerbation (lower values favour tiotropium bromide)										
8	RCT	6,013	RR: 0.81 (0.75, 0.88)	33.08 per 100	26.79 per 100 (24.81, 29.11)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 severe exacerbation (requiring hospitalisation) (lower values favour tiotropium bromide)										
8	RCT	6,573	RR: 0.81 (0.65, 1.01)	5.33 per 100	4.32 per 100 (3.46, 5.38)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour tiotropium bromide)										
12	RCT	8,203	RR: 0.91 (0.81, 1.03)	12.05 per 100	10.96 per 100 (9,76, 12.41)	Serious[6]	Not serious	Not serious	Not serious	Moderate
Drop-outs due to adverse events (lower values favour tiotropium bromide)										
10	RCT	5,421	RR: 0.64 (0.50, 0.83)	5.34 per 100	3.42 per 100	Serious[6]	Not serious	Not serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					(2.67, 4.43)					
People with ≥ 1 session of pneumonia (lower values favour tiotropium bromide)										
1 (Johansson 2008)	RCT	244	RR: 7.65 (0.40, 146.37)	Not calculable[4]	-	Not serious	N/A	Not serious	Very serious[5]	Low

1. I^2 between 33.3% and 66.7%.
2. Non-significant result.
3. 95% confidence interval crosses one end of an MID interval.
4. Not calculable as zero events in control arm.
5. 95% confidence interval crosses both ends of an MID interval.
6. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.
7. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.

1 **Aclidinium (400 micrograms twice daily) versus placebo**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower values favour aclidinium bromide)										
5	RCT	2,524	RR: 2.33 (0.60, 9.05)	0.17 per 100	0.4 per 100 (0.1, 1.55)	Serious[6]	Not serious	Not serious	Serious[3]	Low
Change in trough FEV1 (ml) at 3 months (higher values favour aclidinium bromide)										
3	RCT	931	MD: 109.23 (77.84, 140.63)	N/A	N/A	Not serious	Serious[1]	Not serious	Serious[4]	Low
Change in trough FEV1 (ml) at 6 months (higher values favour aclidinium bromide)										
3	RCT	1,537	MD: 115.04	N/A	N/A	Serious[6]	Not serious	Not serious	Serious[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(92.24, 137.84)							
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour aclidinium bromide)										
3	RCT	931	MD: 0.98 (0.61, 1.34)	N/A	N/A	Serious[6]	Not serious	Not serious	Serious[4]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 6 months (higher values favour aclidinium bromide)										
3	RCT	1,522	MD: 0.96 (0.62, 1.29)	N/A	N/A	Serious[6]	Not serious	Not serious	Serious[4]	Low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour aclidinium bromide)										
3	RCT	931	MD: -2.33 (-3.77, -0.90)	N/A	N/A	Not serious	Not serious	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour aclidinium bromide)										
3	RCT	1,511	MD: -2.76 (-5.95, 0.43)	N/A	N/A	Serious[6]	Very serious[2]	Not serious	Serious[4]	Very low
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour aclidinium bromide)										
6	RCT	2,438	RR: 1.26 (1.11, 1.42)	41.61 per 100	52.43 per 100 (46.19, 58.68)	Serious[6]	Serious[1]	Not serious	Serious[4]	Very low
People with ≥ 1 moderate to severe exacerbation (lower values favour aclidinium bromide)										
6	RCT	2,782	RR: 0.76 (0.58, 1.00)	7.88 per 100	5.99 per 100 (4.57, 7.88)	Serious[6]	Serious[1]	Not serious	Serious[4]	Very low
People with ≥ 1 severe exacerbation (requiring hospitalisation) (lower values favour aclidinium bromide)										
4	RCT	1,505	RR: 0.81 (0.38, 1.72)	1.83 per 100	1.49 per 100 (0.70, 3.16)	Serious[6]	Not serious	Not serious	Very serious[5]	Very low
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour aclidinium bromide)										
6	RCT	2,784	RR: 0.95 (0.67, 1.35)	4.47 per 100	4.25 per 100 (3.00, 6.04)	Serious[6]	Not serious	Not serious	Very serious[5]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Drop-outs due to adverse events (lower values favour aclidinium bromide)										
6	RCT	2,797	RR: 0.85 (0.58, 1.25)	4.07 per 100	3.46 per 100 (2.36, 5.08)	Serious[6]	Not serious	Not serious	Serious[4]	Low
People with ≥ 1 session of pneumonia (lower values favour aclidinium bromide)										
2	RCT	1,247	RR: 0.26 (0.04, 1.64)	0.76 per 100	0.20 (0.03, 1.25)	Serious[6]	Not serious	Not serious	Very serious[5]	Very low

1. I^2 between 33.3% and 66.7%.
2. I^2 > 66.7%
3. Non-significant result.
4. 95% confidence interval crosses one end of a defined MID interval.
5. 95% confidence interval crosses both ends of a defined MID interval.
6. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.

1 **Glycopyrronium (50 micrograms once daily) versus placebo**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower values favour glycopyrronium bromide)										
4	RCT	2,774	RR: 0.88 (0.34, 2.30)	0.65 per 100	0.57 per 100 (0.22, 1.50)	Serious[3]	Not serious	Not serious	Serious[1]	Low
Change in trough FEV1 (ml) at 3 months (higher values favour glycopyrronium bromide)										
4	RCT	2,670	MD: 117.14 (101.97, 132.31)	N/A	N/A	Serious[3]	Not serious	Not serious	Not serious	Moderate
Change in trough FEV1 (ml) at 6 months (higher values favour glycopyrronium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
4	RCT	2,477	MD: 125.31 (108.00, 142.62)	N/A	N/A	Serious[3]	Not serious	Not serious	Not serious	Moderate
Change in trough FEV1 (ml) at 12 months (higher values favour glycopyrronium bromide)										
1 (Kerwin 2012c)	RCT	612	MD: 108.00 (69.78, 146.22)	N/A	N/A	Serious[4]	N/A	Not serious	Serious[2]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour glycopyrronium bromide)										
2	RCT	1,187	MD: 0.75 (0.29, 1.20)	N/A	N/A	Serious[3]	Not serious	Not serious	Serious[2]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 6 months (higher values favour glycopyrronium bromide)										
4	RCT	2,477	MD: 0.90 (0.60, 1.20)	N/A	N/A	Serious[3]	Not serious	Not serious	Serious[2]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 12 months (higher values favour glycopyrronium bromide)										
1 (Kerwin 2012c)	RCT	612	MD: 0.57 (0.03, 1.11)	N/A	N/A	Serious[4]	N/A	Not serious	Serious[2]	Low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour glycopyrronium bromide)										
2	RCT	1,198	MD: -4.27 (-6.16, -2.37)	N/A	N/A	Very serious[6]	Not serious	Not serious	Serious[2]	Very low
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour glycopyrronium bromide)										
4	RCT	2,485	MD: -3.44 (-5.03, -1.86)	N/A	N/A	Very serious[6]	Not serious	Not serious	Serious[2]	Very low
St. George's Respiratory Questionnaire (SGRQ) at 12 months (lower values favour glycopyrronium bromide)										
1 (Kerwin 2012c)	RCT	612	MD: -3.32 (-5.29, -1.35)	N/A	N/A	Serious[4]	N/A	Not serious	Serious[2]	Low
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour glycopyrronium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
4	RCT	2,427	RR: 1.14 (1.06, 1.23)	51.96 per 100	59.24 per 100 (55.08, 63.92)	Serious[3]	Not serious	Not serious	Not serious	Moderate
People with ≥ 1 moderate to severe exacerbation (lower values favour glycopyrronium bromide)										
3	RCT	1,956	RR: 0.73 (0.61, 0.87)	24.30 per 100	17.74 per 100 (14.83, 21.14)	Serious[3]	Not serious	Not serious	Serious[2]	Low
People with ≥ 1 severe exacerbation (requiring hospitalisation) (lower values favour glycopyrronium bromide)										
2	RCT	1,497	RR: 0.49 (0.26, 0.93)	3.66 per 100	1.79 per 100 (0.95, 3.40)	Serious[3]	Not serious	Not serious	Serious[2]	Low
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour glycopyrronium bromide)										
4	RCT	2,774	RR: 0.84 (0.66, 1.07)	10.21 per 100	8.57 per 100 (6.74, 10.92)	Serious[3]	Not serious	Not serious	Serious[2]	Low
Drop-outs due to adverse events (lower values favour glycopyrronium bromide)										
4	RCT	2,779	RR: 0.76 (0.56, 1.04)	6.62 per 100	5.03 per 100 (3.70, 6.88)	Serious[3]	Not serious	Not serious	Serious[2]	Low
People with ≥ 1 session of pneumonia (lower values favour glycopyrronium bromide)										
2	RCT	2,069	RR: 0.54 (0.28, 1.06)	3.79 per 100	2.05 per 100 (1.06, 4.02)	Serious[3]	Not serious	Not serious	Serious[2]	Low

1. Non-significant result.
2. 95% confidence interval crosses one end of a defined MID interval.
3. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.
4. Study at moderate risk of bias.
5. 95% confidence interval crosses both ends of a defined MID interval.
6. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias.

1 **Umeclidinium (62.5 micrograms once daily) versus placebo**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower values favour umeclidinium bromide)										
2	RCT	835	RR: 4.69 (0.24, 90.53)	Not calculable[6]	-	Not serious	N/A[1]	Not serious	Serious[2]	Moderate
Change in trough FEV1 (ml) at 3 months (higher values favour umeclidinium bromide)										
1 (Trivedi 2014)	RCT	112	MD: 127.00 (52.00, 202.00)	N/A	N/A	Serious[5]	N/A	Not serious	Serious[3]	Low
Change in trough FEV1 (ml) at 6 months (higher values favour umeclidinium bromide)										
1 (Donahue 2013a)	RCT	698	MD: 115.00 (75.39, 154.61)	N/A	N/A	Not serious	N/A	Not serious	Serious[3]	Moderate
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour umeclidinium bromide)										
1 (Trivedi 2014)	RCT	112	MD: 1.00 (0.00, 2.00)	N/A	N/A	Serious[5]	N/A	Not serious	Serious[3]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 6 months (higher values favour umeclidinium bromide)										
1 (Donahue 2013a)	RCT	530	MD: 1.00 (0.50, 1.50)	N/A	N/A	Not serious	N/A	Not serious	Serious[3]	Moderate
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour umeclidinium bromide)										
1 (Trivedi 2014)	RCT	112	MD: -7.90 (-12.20, -3.60)	N/A	N/A	Serious[5]	N/A	Not serious	Serious[3]	Low
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour umeclidinium bromide)										
1 (Donahue 2013a)	RCT	698	MD: -4.69 (-7.07, -2.31)	N/A	N/A	Not serious	N/A	Not serious	Serious[3]	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour umeclidinium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2	RCT	815	RR: 1.39 (1.14, 1.69)	29.94 per 100	41.62 per 100 (34.13, 50.60)	Not serious	Not serious	Not serious	Serious[3]	Moderate
People with ≥ 1 moderate to severe exacerbation (lower values favour umeclidinium bromide)										
2	RCT	904	RR: 0.74 (0.53, 1.04)	14.66 per 100	10.84 per 100 (7.77, 15.24)	Serious[6]	Not serious	Not serious	Serious[3]	Low
People with ≥ 1 severe exacerbation (requiring hospitalisation) (lower values favour umeclidinium bromide)										
2	RCT	835	RR: 3.13 (0.91, 10.78)	0.86 per 100	2.70 per 100 (0.78, 9.29)	Not serious	N/A[1]	Not serious	Serious[3]	Moderate
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour umeclidinium bromide)										
2	RCT	835	RR: 2.52 (1.27, 4.99)	2.87 per 100	7.24 per 100 (3.65, 14.34)	Not serious	Not serious	Not serious	Not serious	High
Drop-outs due to adverse events (lower values favour umeclidinium bromide)										
2	RCT	698	RR: 2.55 (1.26. 5.14)	2.59 per 100	6.59 per 100 (3.26, 13.29)	Not serious	Not serious	Not serious	Not serious	High

1. One study has no events in either arm and, as a result, the RR could not be calculated.
2. Non-significant result.
3. 95% confidence interval crosses one end of a defined MID interval.
4. > 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.
5. Study at moderate risk of bias.
6. Not calculable as there are zero events in the placebo arm.

1 **Glycopyrronium (50 micrograms once daily) versus Tiotropium bromide (18 micrograms in total)**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in trough FEV1 (ml) at 3 months (higher values favour glycopyrronium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Chapman 2014)	RCT	630	MD: 4.00 (-25.50, 33.50)	N/A	N/A	Not serious	N/A	Not serious	Not serious	High
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	630	MD: -0.19 (-0.61, 0.24)	N/A	N/A	Not serious	N/A	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	630	MD: 0.65 (-1.19, 2.49)	N/A	N/A	Not serious	N/A	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	630	RR: 1.02 (0.88, 1.17)	54.11 per 100	55.20 per 100 (47.62, 63.31)	Not serious	N/A	Not serious	Not serious	High
People with ≥ 1 moderate to severe exacerbation (lower values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	630	RR: 1.33 (0.78, 2.26)	6.96 per 100	9.26 per 100 (5.43, 15.73)	Not serious	N/A	Not serious	Very serious[1]	Low
People with ≥ 1 severe exacerbation (requiring hospitalisation) (lower values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	630	RR: 0.67 (0.11, 3.99)	0.95 per 100	0.64 per 100 (0.1, 3.79)	Not serious	N/A	Not serious	Very serious[1]	Low
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	657	RR: 0.85 (0.39, 1.88)	3.94 per 100	3.35 per 100 (1.54, 7.84)	Not serious	N/A	Not serious	Very serious[1]	Low
Drop-outs due to adverse events (lower values favour glycopyrronium bromide)										
1 (Chapman 2014)	RCT	657	RR: 1.41 (0.45, 4.41)	1.52 per 100	2.14 per 100 (0.68, 6.68)	Not serious	N/A	Not serious	Very serious[1]	Low
People with ≥ 1 session of pneumonia (lower values favour glycopyrronium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Chapman 2014)	RCT	657	RR: 0.67 (0.11, 4.00)	0.91 per 100	0.61 per 100 (0.10, 3.64)	Not serious	N/A	Not serious	Very serious[1]	Low

1. 95% confidence interval crosses both ends of a defined MID interval.

1 **Umeclidinium (62.5 micrograms once daily) versus Tiotropium bromide (18 micrograms in total)**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
All-cause mortality (lower values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	1,017	RR: 0.20 (0.01, 4.15)	0.39 per 100	0.08 per 100 (0.01, 1.63)	Not serious	N/A	Not serious	Serious[1]	Moderate
Change in trough FEV1 (ml) at 3 months (higher values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	1, 012	MD: 53.00 (25.28, 80.72)	N/A	N/A	Not serious	N/A	Not serious	Not serious	High
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	982	MD: 0.06 (-0.30, 0.42)	N/A	N/A	Not serious	N/A	Not serious	Not serious	High
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	967	MD: -0.46 (-2.04, 1.12)	N/A	N/A	Not serious	N/A	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	967	RR: 1.03 (0.90, 1.17)	48.77 per 100	50.23 per 100	Not serious	N/A	Not serious	Not serious	High
People with ≥ 1 moderate to severe exacerbation (lower values favour umeclidinium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Feldman 2016)	RCT	1,017	RR: 1.21 (0.84, 1.73)	9.45 per 100	11.43 per 100	Not serious	N/A	Not serious	Serious[2]	Moderate
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	1,017	RR: 1.21 (0.60, 2.43)	2.76 per 100	3.33 per 100 (1.65, 6.70)	Not serious	N/A	Not serious	Very serious[3]	Low
Drop-outs due to adverse events (lower values favour umeclidinium bromide)										
1 (Feldman 2016)	RCT	1,017	RR: 1.11 (0.45, 2.71)	1.77 per 100	1.97 per 100 (0.80, 4.80)	Not serious	N/A	Not serious	Very serious[3]	Low

1. Non-significant result.
2. 95% confidence interval crosses one end of a defined MID interval.
3. 95% confidence interval crosses both ends of a defined MID interval.

1 Sensitivity analysis

2 *Tiotropium (18 micrograms or 5 micrograms in total) versus placebo*

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in trough FEV1 (ml) at 3 months (higher values favour tiotropium bromide)										
3	RCT	638	MD 116.99 (83.54, 150.44)	N/A	N/A	Not serious	Not serious	Not serious	Serious[1]	Moderate
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour tiotropium bromide)										
1 (Verkindre 2006)	RCT	87	MD: 1.28 (-0.80, 3.36)	N/A	N/A	Serious[8]	N/A	Not serious	Serious[1]	Low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour tiotropium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Verkindre 2006)	RCT	90	MD: -6.50 (-13.02, 0.02)	N/A	N/A	Serious[4]	N/A	Not serious	Serious[1]	Low
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour tiotropium bromide)										
5	RCT	3,107	RR: 1.34 (1.18, 1.51)	32.47 per 100	43.51 per 100 (38.31, 49.03)	Serious[3]	Serious[1]	Not serious	Serious[1]	Very low
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour tiotropium bromide)										
10	RCT	7,391	RR: 0.90 (0.80, 1.02)	13.11 per 100	11.80 per 100 (10.49, 13.37)	Serious[3]	Not serious	Not serious	Not serious	Moderate
Drop-outs due to adverse events (lower values favour tiotropium bromide)										
8	RCT	4,429	RR: 0.67 (0.52, 0.88)	5.37 per 100	3.60 per 100 (2.79, 4.73)	Serious[3]	Not serious	Not serious	Serious[1]	Low

1. 95% confidence interval crosses one end of a defined MID interval.
2. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.
3. Study at moderate risk of bias.

1 ***Glycopyrronium (50 micrograms once daily) versus placebo***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in trough FEV1 (ml) at 3 months (higher values favour glycopyrronium bromide)										
3	RCT	2,218	MD: 108.95 (91.36, 126.54)	N/A	N/A	Serious[2]	Not serious	Not serious	Serious[1]	Low
Change in trough FEV1 (ml) at 6 months (higher values favour glycopyrronium bromide)										
3	RCT	2,053	MD: 121.40	N/A	N/A	Serious[2]	Not serious	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(101.41, 141.40)							
Change in Transition Dyspnoea Index (TDI) focal score at 3 months (higher values favour glycopyrronium bromide)										
1 (Kerwin 2012c)	RCT	758	MD: 0.60 (0.08, 1.12)	N/A	N/A	Serious[2]	N/A	Not serious	Serious[1]	Low
Change in Transition Dyspnoea Index (TDI) focal score at 6 months (higher values favour glycopyrronium bromide)										
3	RCT	2,053	MD: 0.88 (0.57, 1.20)	N/A	N/A	Serious[2]	Not serious	Not serious	Serious[1]	Low
St. George's Respiratory Questionnaire (SGRQ) at 3 months (lower values favour glycopyrronium bromide)										
1 (Kerwin 2012c)	RCT	758	MD: -3.17 (-4.82, -1.52)	N/A	N/A	Serious[2]	N/A	Not serious	Serious[1]	Low
St. George's Respiratory Questionnaire (SGRQ) at 6 months (lower values favour glycopyrronium bromide)										
3	RCT	2,053	MD -2.70 (-3.91, -1.48)	N/A	N/A	Serious[2]	Not serious	Not serious	Not serious	Moderate
People with ≥ 4 units improvement in quality of life (SGRQ) (higher values favour glycopyrronium bromide)										
3	RCT	1,995	RR: 1.12 (1.02, 1.22)	51.32 per 100	57.48 per 100 (52.34, 62.61)	Serious[2]	Not serious	Not serious	Not serious	Moderate
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour glycopyrronium bromide)										
3	RCT		RR: 0.88 (0.68, 1.41)	10.43 per 100	9.18 per 100 (7.09,14.71)	Serious[2]	Not serious	Not serious	Very serious[4]	Very low
Drop-outs due to adverse events (lower values favour glycopyrronium bromide)										
3	RCT	2,320	RR: 0.73 (0.53, 1.00)	7.55 per 100	5.51 per 100 (4.00, 7.55)	Serious[2]	Not serious	Not serious	Serious[1]	Low
People with ≥ 1 session of pneumonia (lower values favour glycopyrronium bromide)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Kerwin 2012c)	RCT	793	RR: 0.60 (0.28, 1.27)	4.48 per 100	2.69 per 100 (1.25, 5.69)	Serious[3]	N/A	Not serious	Very serious[4]	Very low

1. 95% confidence interval crosses one end of a defined MID interval.
2. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias.
3. Study at moderate risk of bias.
4. 95% confidence interval crosses both ends of a defined MID interval.

1 **Network meta-analyses**

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SGRQ total score at 3 months								
10	RCT	4,682	See appendix G	Serious[1]	Not serious	Serious[3]	Not serious	Low
SGRQ total score at 6 months								
10	RCT	5, 823	See appendix G	Serious[1]	Not serious	Serious[3]	Serious[4]	Very low
TDI score at 3 months								
11	RCT	4,682	See appendix G	Very serious[2]	Not serious	Not serious	Not serious	Low
SQRQ responders								
21	RCT	11,137	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Moderate to severe exacerbations								
21	RCT	6,961	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Severe exacerbations								
14*	RCT	10,579	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Dropouts due to adverse events								
24	RCT	13,326	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate
Mortality								

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
17*	RCT	12,907	See appendix G	Serious[1]	Not serious	Serious[5]	Serious[4]	Very low
Serious adverse events								
26	RCT	23,477	See appendix G	Serious[1]	Not serious	Not serious	Not serious	Moderate

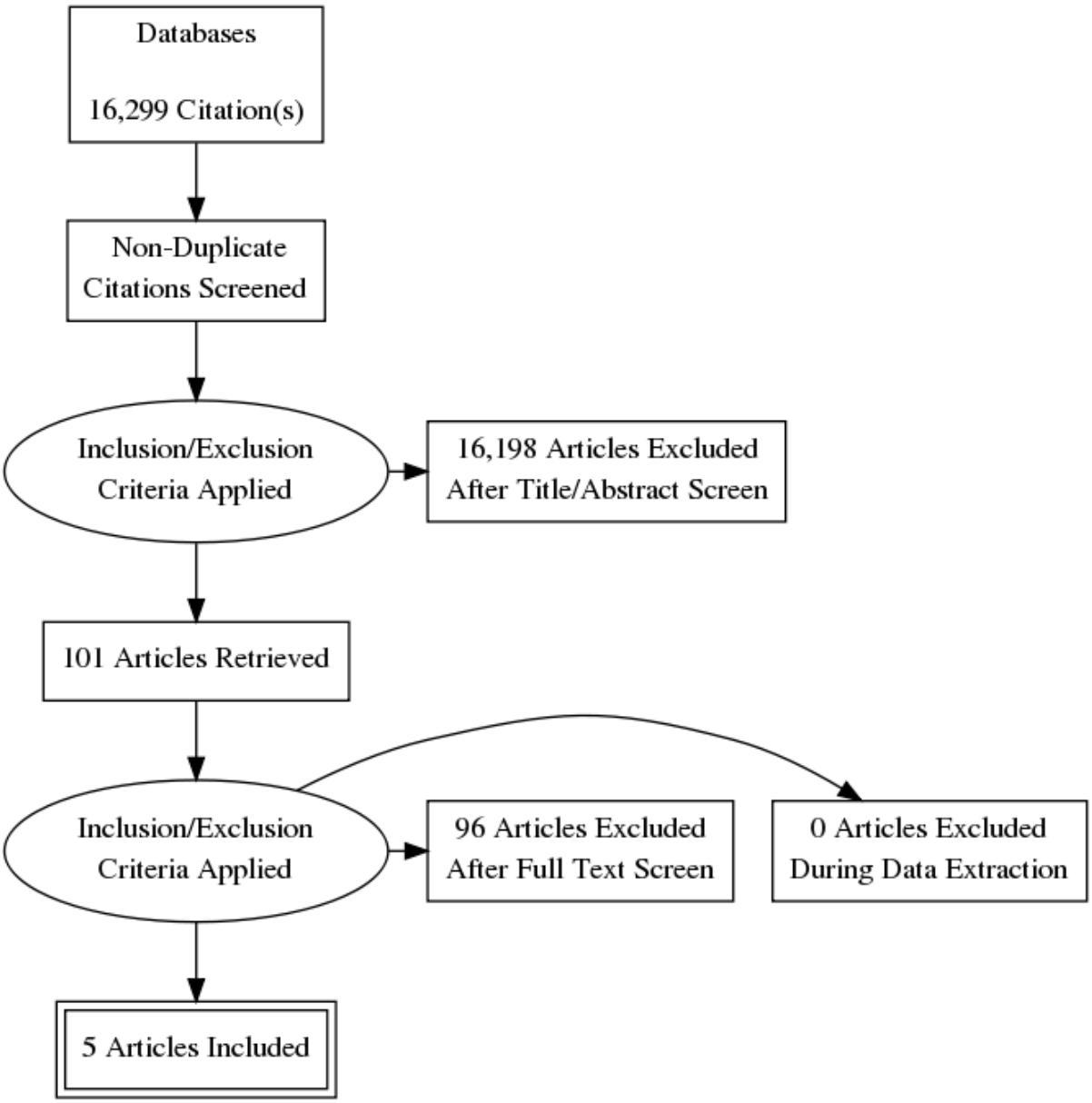
* Studies with zero events in both arms removed from analysis.

1. >33.3% of studies in the NMA at moderate or high risk of bias.
2. >33.3% of studies in the NMA at high risk of bias.
3. DIC for a random-effects model lower than the DIC for a fixed-effects model.
4. All comparisons in NMA rated as being of at least serious risk of imprecision.
5. Meaningful differences between point estimates from direct and indirect evidence.

1

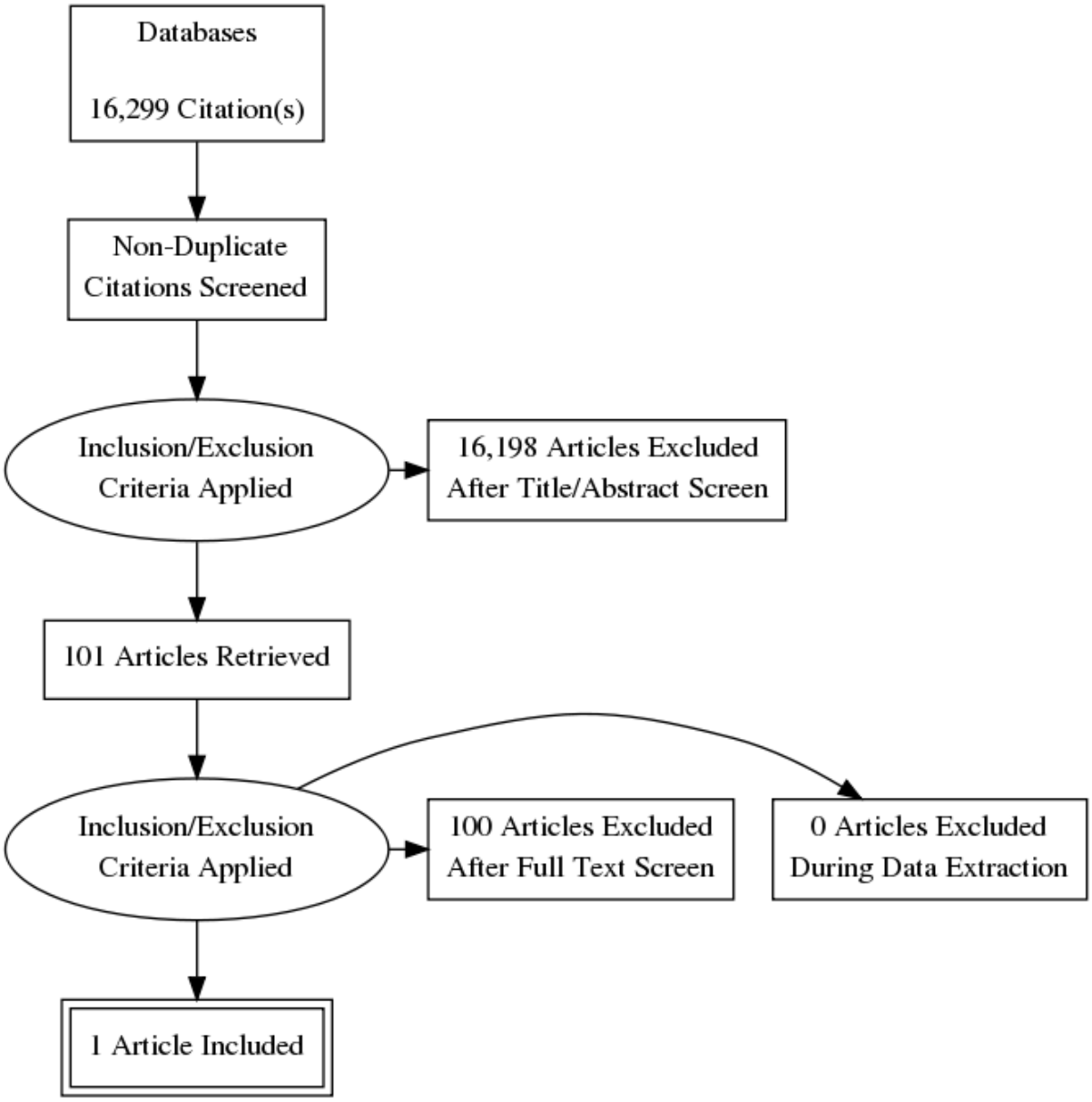
1 Appendix H – Economic evidence study selection

2 Inhaled therapy combinations



3

1 **LAMA monotherapy**



2

1 Appendix I – Health economic evidence profiles

2 Inhaled therapy combinations

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Gani (2010)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Tiotropium (LAMA) versus salmeterol (LABA)	UK	1 year N/A (time horizon only 1 year)	Tiotropium dominates salmeterol	Probabilistic sensitivity analysis indicates that tiotropium has a 97% probability of being cost-effective at a £20,000/QALY threshold. Subgroup analyses by disease severity show that tiotropium dominates salmeterol for patients with moderate, severe, and very severe COPD.

(a) Only includes two of the interventions of interest (LAMA monotherapy and LABA monotherapy)
(b) Short time horizon, does not include treatment-related adverse events, no empirical data on costs, potential conflict of interest

3

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion[(c)]	Uncertainty
Hertel (2012)	1. Partially applicable [a] 2. Potentially serious limitations [b]	LABA LAMA LAMA+LABA LABA+ICS	UK	Lifetime 3.5% discount rate	Results for ICS-tolerant patients: Strategy / Δ Costs / Δ QALYs / ICER LABA - - - LAMA £28 0.03 £933 LABA/ICS £98 0.01 £9,800 LAMA + LABA £219 0.02 £10,950	The authors only report sensitivity analysis results for the comparison of LAMA + LABA/ICS + roflumilast versus LAMA + LABA/ICS, which was not relevant to the review question.

Results for ICS-intolerant patients:

Strategy	Δ Costs	Δ QALYs	ICER
LABA	-	-	-
LAMA	£28	0.03	£575
LAMA + LABA	£219	0.02	£15,700

(a) Only includes patients with severe/very severe COPD. Contains the interventions of interest, but also includes treatments in combination with roflumilast, and only reports sensitivity analysis results for LAMA + LABA/ICS + roflumilast
(b) Does not include treatment-related adverse events. Does not report sensitivity analysis results for comparisons of interest. Relies on assumed exacerbation rates. Potential conflict of interest
(c) ICERs calculated manually for the comparisons of interest relevant to the review question as authors only provided costs and QALYs for each strategy

1

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Price (2013)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Indacaterol 150 µg and 300 µg daily (LABA) versus tiotropium 18 µg daily (LAMA)	UK	3 years 3.5% discount rate	Both dosages of indacaterol dominate tiotropium	Probabilistic sensitivity analysis showed that indacaterol is associated with an 84% probability of being cost-effective compared to tiotropium (unclear which dosage of indacaterol this refers to). Scenarios with a 5 year and lifetime time horizon showed that indacaterol remains dominant over tiotropium.

(a) Only includes two of the interventions of interest (LAMA monotherapy and LABA monotherapy)
(b) Short time time horizon, does not include treatment-related adverse events, potential conflict of interest

2

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Punekar (2015)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Umeclidinium/vilanterol combination (LAMA + LABA) versus tiotropium monotherapy (LAMA)	UK	Lifetime 3.5% discount rate	Umeclidinium/vilanterol produces an ICER of £2,088/QALY compared to tiotropium	Probabilistic sensitivity analysis showed that umeclidinium/vilanterol has an 84.9% probability of being cost-effective at a threshold of £20,000/QALY. One-way sensitivity analyses in which the time horizon of the model was reduced to one and five years, and in which the benefit of treatment was assumed to only last for 12 months improved the ICER of umeclidinium/vilanterol.

(a) Only includes two of the interventions of interest (LAMA + LABA and LAMA monotherapy)
(b) Does not include treatment effects on exacerbations in the analysis. Does not include treatment-related adverse events. Potential conflict of interest.

1

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Ramos (2016)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Aclidinium bromide/formoterol (LAMA + LABA) versus aclidinium bromide alone (LAMA)	UK	5 years 3.5% discount rate	Aclidinium bromide/formoterol produces an ICER of £2,976/QALY compared to aclidinium bromide alone	Probabilistic sensitivity analysis showed that aclidinium bromide/formoterol is associated with a 79% probability of being cost-effective at a threshold of £20,000/QALY. One-way sensitivity analyses in which the time horizon of the

						model was set to 1 and 15 years showed that aclidinium bromide/formoterol dominates aclidinium bromide alone.

(a) Only includes two of the interventions of interest (LAMA + LABA and LAMA monotherapy)
(b) Does not include treatment effects on exacerbations in the analysis. Does not include treatment-related adverse events. Potential conflict of interest.

LAMA monotherapy

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Eklund (2016)	1. Partially applicable [a] 2. Very serious limitations [b]	Tiotropium versus glycopyrronium	UK	Lifetime time horizon 3.5% discount rate	Tiotropium produces a cost saving of €169 (£147) and generates an additional 0.23 QALYs, and therefore dominates glycopyrronium	One-way sensitivity analyses showed that tiotropium remained the cost-effective option when key parameters were set to high and low plausible values. Tiotropium also dominated glycopyrronium in subgroup analyses by starting GOLD stage.

(a) Does not include all the comparators of interest (only compares two LAMAs)
(b) Effectiveness data taken from a study with no blinding for tiotropium. Does not include treatment-related adverse events. Does not include a probabilistic sensitivity analysis. Potential conflict of interest.

Appendix K – Excluded studies

Clinical studies

Inhaled therapy combinations

The following excluded studies list with reasons for exclusion was taken directly from the updated Cochrane review.

Study	Reason for exclusion
1237.20	2 week study
1237.4	4 week study
1237.7	Crossover
Barnes 2010	2 week study. 26 week results in Donohue 2010
Bateman 2010	No qualified comparison (formulation and/or dose not approved)
Beeh 2014	Crossover
Beeh 2016	Crossover
Berton 2016	3 week crossover study
Cazzola 2007	Insufficient data
Celli 2014	No qualified comparison (formulation and/or dose not approved)
CQAB149BIL01	No qualified comparison (Indacaterol vs LABA)
CQMF149F2202	No qualified comparison (formulation and/or dose not approved)
D'Urzo 2013	No qualified comparison (formulation and/or dose not approved)
Dahl 2013	4 week study
DB2116132	Crossover
DB2116133	Crossover
Donohue 2002	Duplicate of Brusasco 2003
Donohue 2003	Duplicate of Brusasco 2003
Donohue 2014	No qualified comparison (formulation and/or dose not approved)
Dransfield 2013	No qualified comparison (formulation and/or dose not approved)
Fang 2018	Poor quality study (dropout rate too high)
Ferguson 2014	No qualified comparison (formulation and/or dose not approved)
Geld 2013	No qualified comparison (formulation and/or dose not approved)
Hodder 2007	Duplicate of Brusasco 2003
HZC113108	No qualified comparison (formulation and/or dose not approved)
Jones 1997	No qualified comparison (formulation and/or dose not approved)
Jones 2012	No qualified comparison (formulation and/or dose not approved)
Kerwin 2012x	No qualified comparison (formulation and/or dose not approved)
Kerwin 2013	No qualified comparison (formulation and/or dose not approved)
Kurashima 2009	Crossover
Magnussen 2012	8 week study
Mahler 2014	6 week study

Study	Reason for exclusion
Mahmud 2007	COPD not defined. Insufficient data
Make 2014	Abstract only. Insufficient information
Maltais 2014	No qualified comparison (formulation and/or dose not approved)
Maltais 2014a	Crossover
Maltais 2014b	Crossover
Martinez 2013	No qualified comparison (formulation and/or dose not approved)
MORACTO1	6 week study
MORACTO2	6 week study
PT003016-00	No comparator, 4 week study
Rabe 2008	6 week study
Rennard 2013	No qualified comparison (formulation and/or dose not approved)
Rossi 2012	6 week study
SCO100646	Crossover
Siler 2016	No qualified comparison (formulation and/or dose not approved)
Singh 2016	Crossover
Tashkin 2016	7 day crossover study
To 2011	Insufficient data. Abstract only
Van Noord 2010	6 week study
Vestbo 2016	Did not meet inclusion criteria (FF/VI compared with existing maintenance tx)
Vogelmeier 2010	No qualified comparison (dose not approved)
Vogelmeier 2010.2	14 day study
Vogelmeier 2013x	Spin-off of Vogelmeier 2011
Watz 2016	Crossover
Wouters 2005	Did not meet inclusion criteria
Zheng 2015	No qualified comparison (formulation and/or dose not approved)

1 ***Studies excluded from the additional Cochane group search***

Short Title	Title	Reason for exclusion
Crim (2017)	Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: the SUMMIT trial	Comparator in study does not match that specified in protocol *Vilanterol has not been approved as standalone agent.*
Kerwin (2017a)	Dual bronchodilation with indacaterol maleate/glycopyrronium bromide compared with umeclidinium bromide/vilanterol in patients with moderate-to-severe COPD: results from two randomized, controlled, cross-over studies	Not a relevant study design (RCT) *Crossover study*
Kerwin (2017b)	Efficacy and safety of glycopyrrolate/eFlow((R)) CS (nebulized glycopyrrolate) in moderate-to-very-severe COPD: results from the glycopyrrolate for	Study does not contain any relevant interventions *Nebulized medication not included in*

	obstructive lung disease via electronic nebulizer (GOLDEN) 3 and 4 randomized controlled trials	*protocol.*
Lipson (2017)	FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease	Comparator in study does not match that specified in protocol *Triple therapy is not considered.*
Molino (2017)	Effects of combination therapy indacaterol/glycopyrronium versus tiotropium on moderate to severe COPD: evaluation of impulse oscillometry and exacerbation rate	Study does not contain any of the outcomes of interest
Papi (2017)	Fluticasone propionate/formoterol for COPD management: a randomized controlled trial	Study does not contain any relevant interventions *Fluticasone propionate/formoterol is not approved/licensed for COPD.*
Siler (2016)	A randomized, parallel-group study to evaluate the efficacy of umeclidinium/vilanterol 62.5/25 µg on health-related quality of life in patients with COPD	Comparator in study does not match that specified in protocol *Vilanterol has not been approved as standalone agent.*
Vestbo (2017)	Single inhaler extra fine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial	Comparator in study does not match that specified in protocol *Comparator is triple therapy.*

1

2

3

1 **LAMA monotherapy**

Short Title	Title	Reason for exclusion
Abrahams (2012)	Comparison of BEA2180 to tiotropium and placebo via respimat in patients with chronic obstructive pulmonary disease (COPD)	• Conference abstract
Abrahams (2013)	Safety and efficacy of the once-daily anticholinergic BEA2180 compared with tiotropium in patients with COPD	• Trial involving a drug that is not licenced in the UK *Comparator is BAE2180.*
Abrahams (2015)	Effect of tiotropium + olodaterol on the use of nighttime rescue medication in patients with COPD: Results from four randomized, double-blind studies	• Conference abstract
Abrahams (2016)	Tiotropium/olodaterol therapy provides symptomatic benefits irrespective of prior maintenance treatment: Post hoc analyses of the OTEMTO studies	• Conference abstract
Adams (2006)	Tiotropium in COPD patients not previously receiving maintenance respiratory medications	• Additional publication of an included or excluded study that does not provide any extra relevant information
Almazar (2013)	The utility of tiotropium among patients with COPD: An update of a meta-analysis of randomized controlled trials (UTAC Update)	• Conference abstract
Ambrosino (2008)	Tiotropium and exercise training in COPD patients: effects on dyspnoea and exercise tolerance	• Part of a more complex intervention *Part of a more complex intervention with 8 weeks pulmonary rehabilitation during 25 weeks of tiotropium versus placebo treatment.*
Anzueto (2005)	One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium	• Additional publication of an included or excluded study that does not provide any extra relevant information
Anzueto (2009)	Impact of frequency of COPD exacerbations on pulmonary function, health status and clinical outcomes	• Additional publication of an included or excluded study that does not provide any extra relevant information
Anzueto (2013)	A post hoc pooled analysis of exacerbations among US participants in randomized controlled trials of tiotropium	• Pooled analysis of included and/or excluded trials
Ayers (2015)	QVA149, twice daily, is well tolerated in patients with moderate-to-severe COPD and has a safety profile similar to placebo: FLIGHT1 and FLIGHT2 pooled analysis in the subgroup of patients from the USA	• Conference abstract

Short Title	Title	Reason for exclusion
Banerji (2013)	Dual bronchodilation with QVA149 reduces COPD exacerbations: Results from the ignite program	• Conference abstract
Banerji (2014)	Once-daily dual bronchodilation with QVA149 reduces COPD exacerbations: Results from the ignite program	• Conference abstract
Barr (2005)	Inhaled tiotropium for stable chronic obstructive pulmonary disease	• More recent systematic review included that covers the same topic
Barr (2006)	Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis	• More recent systematic review included that covers the same topic
Bateman (2010a)	A one-year trial of tiotropium Respimat plus usual therapy in COPD patients	• Concomitant drug use issues
Bateman (2015)	Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT)	• Pooled analysis of included and/or excluded trials
Bruel (2010)	Does tiotropium lower exacerbation and hospitalization frequency in COPD patients? Results of a meta-analysis (Structured abstract)	• More recent systematic review included that covers the same topic
Buckley (2013)	Evaluating whether inconsistencies are present in a mixed treatment comparison of trough forced expiratory volume in 1 second at 12 weeks	• Conference abstract
Burgel (2014)	Tiotropium might improve survival in subjects with COPD at high risk of mortality	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues
Calverley (2016)	Effect of tiotropium on night-time awakening and daily rescue medication use in patients with COPD	• Additional publication of an included or excluded study that does not provide any extra relevant information
Casaburi (2000)	The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group	• Additional publication of an included or excluded study that does not provide any extra relevant information
Casaburi (2005)	Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD	• Part of a more complex intervention *Participants also took part in pulmonary rehabilitation during the trial.*

Short Title	Title	Reason for exclusion
Casaburi (2014)	Effects of tiotropium on hyperinflation and treadmill exercise tolerance in mild to moderate chronic obstructive pulmonary disease	• Study duration is <12 weeks or treatment of interest lasts < 12 weeks *Cross-over trial with 6 weeks treatment with drug.*
Celli (2009)	Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease.	• Concomitant drug use issues
Celli (2010)	Cardiovascular safety of tiotropium in patients with COPD	• Pooled analysis of included and/or excluded trials
Celli (2014)	Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study	• Drug dose in trial is >20% above or below the licenced for UK dose *Umeclidinium bromide is used at a non-UK licenced dose (125mcg).*
Celli (2015)	Effects of Tiotropium on Exacerbations in Patients with COPD with Low or High Risk of Exacerbations: A Post-Hoc Analysis from the 4-Year UPLIFT Trial	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Chan (2007)	A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease	• Concomitant drug use issues *During the treatment period, patients were permitted to take LABAs.*
Chapman (2013a)	Once-daily QVA149 improves lung function, dyspnoea and health status regardless of disease severity and prior medications: The shine study	• Conference abstract
Chapman (2013b)	Comparison of the efficacy and safety of once-daily glycopyrronium with blinded tiotropium in patients with COPD: The GLOW5 study	• Conference abstract
Chapman (2014a)	Once-daily QVA149 improves lung function, dyspnoea, and health status independent of disease severity and prior medications: The shine study	• Conference abstract
Chapman (2015a)	QVA149 Improves Lung Function, Dyspnoea, and Health Status Independent of Previously Prescribed Medications and COPD Severity: A Subgroup Analysis from the SHINE and ILLUMINATE Studies	• Pooled analysis of included and/or excluded trials

Short Title	Title	Reason for exclusion
Chapman (2015b)	Overall and Cardiovascular Safety of Aclidinium Bromide in Patients With COPD: A Pooled Analysis of Six Phase III, Placebo-Controlled, Randomized Studies	• Pooled analysis of included and/or excluded trials
Cheyne (2015)	Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *Ipratropium is not a LAMA or placebo.*
Cole (2012)	Concomitant use of ipratropium and tiotropium in chronic obstructive pulmonary disease	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *Review of trials of concomitant use of ipratropium and tiotropium.*
Cooper (2011)	Tiotropium reduces risk of exacerbations irrespective of previous use of inhaled anticholinergics in placebo-controlled clinical trials	• Pooled analysis of included and/or excluded trials
Cooper (2013)	Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial	• Concomitant drug use issues *Patients continued all respiratory medications other than inhaled anticholinergics.*
Cope (2012)	Efficacy of once-daily indacaterol 75 mug relative to alternative bronchodilators in COPD: a study level and a patient level network meta-analysis	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *Systematic review and network meta-analysis focusing on indacaterol versus other bronchodilators.*
Cope (2013)	Comparative efficacy of long-acting bronchodilators for COPD: a network meta-analysis	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *NMA comparing LAMAs and LABAs.*
Covelli (2005)	Absence of electrocardiographic findings and improved function with once-daily tiotropium in patients with chronic obstructive pulmonary disease	• Concomitant drug use issues *Concomitant treatment with short- and long-acting Beta-agonists was allowed.*
Decramer (2009)	Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *All respiratory medications, except other inhaled anticholinergic drugs,*

Short Title	Title	Reason for exclusion
		were permitted during the trial.
Decramer (2011)	Premature discontinuation during the UPLIFT study	• Additional publication of an included or excluded study that does not provide any extra relevant information *Study is examining outcomes for completers versus non-completers.* • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Decramer (2014)	Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials	• Drug dose in trial is >20% above or below the licenced for UK dose *Umeclidinium monotherapy dose is 125mcg.*
Dong (2012)	Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: Systematic review and mixed treatment comparison meta-analysis of randomized controlled trials	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *NMA comparing LAMA, LABA and ICS combinations.*
Donohue (2002)	A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol.	• Additional publication of an included or excluded study that does not provide any extra relevant information
Donohue (2003)	Tolerance to bronchodilating effects of salmeterol in COPD	• Additional publication of an included or excluded study that does not provide any extra relevant information
Donohue (2010)	Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium	• Multi-drug RCT that lacks blinding for the LAMA arm *Trial was examining indacaterol versus placebo or tiotropium, but the tiotropium was administered open-label.*
Donohue (2013b)	Long-term cardiovascular safety of aclidinium bromide in patients with COPD	• Conference abstract
Donohue (2014)	Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease:	• Drug dose in trial is >20% above or below the licenced for UK dose *Umeclidinium bromide is used at a*

Short Title	Title	Reason for exclusion
	results from a 52-week, randomized, double-blind, placebo-controlled study	*non-UK licenced dose (125mcg).*
D'Urzo (2013)	Aclidinium bromide improves lung function in a wide range of patients with moderate to severe COPD: Pooled subgroup analysis of the ACCORD COPD i and II and ATTAIN trials	• Conference abstract
D'Urzo (2013b)	Efficacy and safety of fixed-dose combination aclidinium bromide/formoterol fumarate in patients with COPD: Results from the AUGMENT COPD trial	• Conference abstract
D'Urzo (2014a)	Once daily glycopyrronium for the treatment of COPD: pooled analysis of the GLOW1 and GLOW2 studies	• Additional publication of an included or excluded study that does not provide any extra relevant information *Paper presents the pooled analysis of GLOW1 and GLOW2 trials. This data is available in the original trial reports.*
D'Urzo (2015)	Safety of inhaled glycopyrronium in patients with COPD: a comprehensive analysis of clinical studies and post-marketing data	• Pooled analysis of included and/or excluded trials
D'Urzo (2017)	A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease	• Not a relevant study design (RCT) *Study is an extension of an RCT where consenting participants were re-enrolled in the same groups, but there were large numbers of people who did not choose to re-enrol.*
Ferguson (2013)	Cardiovascular safety of aclidinium bromide in COPD: Pooled results from 3 placebo-controlled studies	• Conference abstract
Ferguson (2015a)	Lung function response with tiotropium + olodaterol maintenance treatment in patients with COPD in the TONADO and OTEMTO studies: A subgroup analysis by age	• Conference abstract
Ferguson (2015b)	Tiotropium + olodaterol provides improvements in SGRQ and dyspnoea compared with monotherapy Components in Patients with COPD: Results from four randomized, double-blind studies	• Conference abstract
Ferguson (2016)	Benefits of tiotropium/olodaterol on symptoms and health-related quality of life in patients with moderate to severe COPD with chronic bronchitis and/or emphysema	• Conference abstract
Ferguson (2017)	Effect of tiotropium and olodaterol on symptoms and patient-reported outcomes in	• Pooled analysis of included and/or excluded trials

Short Title	Title	Reason for exclusion
	patients with COPD: results from four randomised, double-blind studies	
Fernandez (2010)	Efficacy of tiotropium in COPD patients from Asia: A subgroup analysis from the uplift trial	• Conference abstract
Fogel (2015)	Cardiovascular safety of QVA149 in patients with moderate-to-severe COPD: Pooled analysis of FLIGHT1 and FLIGHT2 clinical studies	• Conference abstract
Freeman (2007)	Efficacy and safety of tiotropium in COPD patients in primary care--the SPiRiva Usual CarE (SPRUCE) study	• Concomitant drug use issues *Participants were allowed to continue with their usual treatments during the trial, including LABAs.*
Frenzel (2014)	Once daily QVA149 provides superior improvements in lung function compared with glycopyrronium and tiotropium in severe COPD patients: A 52 week pooled analysis	• Conference abstract
Frith (2013)	Benefits of dual bronchodilation with QVA149 once daily versus placebo, indacaterol, NVA237 and tiotropium in patients with COPD: The shine study	• Conference abstract
Frith (2016)	Glycopyrronium (GLY) and tiotropium (TIO) comparison: Lung function, dyspnoea and health status in COPD patients in all gold groups	• Conference abstract
Frith (2017)	Effect of tiotropium and olodaterol, alone and with exercise training, on exercise endurance in COPD	• Conference abstract
Fukuchi (2011)	Efficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial	• Additional publication of an included or excluded study that does not provide any extra relevant information *Study is looking at a subgroup analysis of Asian participants.* • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Gelb (2011)	Lack of protective effect of tiotropium vs induced dynamic hyperinflation in moderate COPD	• Study duration is <12 weeks or treatment of interest lasts < 12 weeks
Gelb (2013)	Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD	• Comparator in study does not match that specified in protocol *The trial lacks a placebo control or*

Short Title	Title	Reason for exclusion
		second, different LAMA comparator arm.
Goyal (2015)	Effect of glycopyrronium on lung function, dyspnoea and health status in COPD patients in all gold groups	• Conference abstract
Goyal (2015b)	Comparison of glycopyrronium (GLY) and tiotropium (TIO) on lung function, dyspnoea and health status in COPD patients in all gold groups	• Conference abstract
GSK (2012)	A12-week, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of GSK573719 delivered once-daily via a novel dry powder inhaler in subjects with chronic obstructive pulmonary disease	• Not a peer-reviewed publication
Halpin (2009)	Patient-level pooled analysis of the effect of tiotropium on COPD exacerbations and related hospitalisations	• Pooled analysis of included and/or excluded trials
Halpin (2012)	Exacerbation frequency and course of COPD	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Halpin (2015)	Tiotropium HandiHaler and Respimat in COPD: a pooled safety analysis	• Pooled analysis of included and/or excluded trials
Hashimoto (2016)	Efficacy and safety of indacaterol/glycopyrronium in Japanese patients with COPD: a subgroup analysis from the SHINE study	• Additional publication of an included or excluded study that does not provide any extra relevant information *Subgroup analysis of Japanese participants.*
Hilleman (2009)	A systematic review of the cardiovascular risk of inhaled anticholinergics in patients with COPD	• More recent systematic review included that covers the same topic
Hodder (2011)	Lack of paradoxical bronchoconstriction after administration of tiotropium via Respimat Soft Mist Inhaler in COPD	• Additional publication of an included or excluded study that does not provide any extra relevant information
Ismaila (2014)	Comparative efficacy of umeclidinium bromide versus other long-acting anticholinergic monotherapies as treatments for COPD patients	• Conference abstract

Short Title	Title	Reason for exclusion
Jones (2011a)	Profiling the effects of indacaterol on dyspnoea and health status in patients with COPD	• Study does not contain any relevant interventions *Tiotropium is administered open-label.*
Jones (2011b)	Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease.	• Drug dose in trial is >20% above or below the licenced for UK dose *Drug used at 200mcg once a day.*
Jones (2014)	Characterisation and impact of reported and unreported exacerbations: results from ATTAIN	• Additional publication of an included or excluded study that does not provide any extra relevant information *Study focuses on the use of an exacerbation diary and presents data in categories that are not useful for this review. Data is for the ATTAIN study.*
Jones (2015)	Analysis of improvement in SGRQ component scores with QVA149: Pooled data from the FLIGHT1 and FLIGHT2 studies	• Conference abstract
Jones (2015a)	QVA149 demonstrates superior improvements in health status, as measured by SGRQ total score in patients with moderate-to-severe COPD: Pooled analysis from the FLIGHT1 and FLIGHT2 studies	• Conference abstract
Jones (2016)	The effect of aclidinium bromide on daily respiratory symptoms of COPD, measured using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) diary: pooled analysis of two 6-month Phase III studies	• Pooled analysis of included and/or excluded trials
Kaplan (2010)	Effect of tiotropium on quality of life in COPD: a systematic review	• More recent systematic review included that covers the same topic
Karabis (2012)	Comparative efficacy of aclidinium bromide 400 MCG bid versus tiotropium 18 MCG and 5 MCG QD as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD): A network meta-analysis	• Conference abstract
Karabis (2013)	Network meta-analysis with fractional polynomials for repeated trough FEV1 measures in COPD: Aclidinium bromide 400 mug bid versus tiotropium 18 mug QD	• Conference abstract
Karabis (2013a)	Assessing non-inferiority of aclidinium bromide 400 mg bid versus tiotropium 18 mg and 5 mg qd in patients with chronic	• Conference abstract

Short Title	Title	Reason for exclusion
	obstructive pulmonary disease (COPD) by means of a network meta-analysis	
Kato (2011)	NVA237 once daily improves symptoms and reduces exacerbations of COPD and associated hospitalizations: The glow1 trial	• Conference abstract
Kato (2011)	Sustained 24-hour bronchodilation with NVA237 once-daily in patients with COPD: The glow1 trial	• Conference abstract
Kerstjens (2015)	The impact of treatment with indacaterol in patients with COPD: A post-hoc analysis according to GOLD 2011 categories A to D	• Pooled analysis of included and/or excluded trials
Kerwin (2012a)	Safety and tolerability of aclidinium bromide in patients with COPD: Pooled results from placebo-controlled phase III studies	• Conference abstract
Kerwin (2014)	Twice-daily aclidinium bromide 400 mcg in elderly patients with chronic obstructive pulmonary disease (COPD): Pooled efficacy and safety results	• Conference abstract
Kerwin (2015)	QVA149 significantly improves lung function and reduces rescue medication use compared with its monocomponents in COPD patients with moderate-to-severe airflow limitation: Pooled analysis from the FLIGHT1 and FLIGHT2 studies	• Conference abstract
Kerwin (2015a)	Cardiovascular safety of glycopyrronium in patients with moderate-to-severe COPD: Pooled analysis from the GEM1, GEM2, FLIGHT1, and FLIGHT2 studies	• Conference abstract
Kerwin (2015b)	Safety profile of inhaled glycopyrronium twice daily in patients with moderate-to-severe COPD: Pooled analysis from four clinical trials	• Conference abstract
Kerwin (2015c)	Glycopyrronium demonstrates significant improvements in lung function in patients with moderate-to-severe COPD: Pooled analysis from the GEM1 and GEM2 studies	• Conference abstract
Kerwin (2015e)	QVA149 demonstrated significant improvement in lung function compared with placebo and its monocomponents: Pooled analysis from the FLIGHT1 and FLIGHT2 studies	• Conference abstract
Kerwin (2016)	Efficacy and Safety of Twice-Daily Glycopyrrolate Versus Placebo in Patients With COPD: The GEM2 Study	• Drug dose in trial is >20% above or below the licenced for UK dose *Glycopyrronium used at 15.6mcg twice daily.*

Short Title	Title	Reason for exclusion
Kerwin (2017)	Efficacy and safety of glycopyrrolate/eFlow CS (nebulized glycopyrrolate) in moderate-to-very-severe COPD: Results from the glycopyrrolate for obstructive lung disease via electronic nebulizer (GOLDEN) 3 and 4 randomized controlled trials	• Concomitant drug use issues *Background LABA use allowed.*
Kesten (2006)	Pooled clinical trial analysis of tiotropium safety	• Pooled analysis of included and/or excluded trials
Kesten (2007)	Premature discontinuation of patients: a potential bias in COPD clinical trials	• Additional publication of an included or excluded study that does not provide any extra relevant information
Kesten (2008)	Improvement in self-reported exercise participation with the combination of tiotropium and rehabilitative exercise training in COPD patients	• Part of a more complex intervention *Pulmonary rehabilitation is carried out while the participants are taking tiotropium or placebo.*
Kesten (2009)	Tiotropium HandiHaler in the treatment of COPD: a safety review	• Pooled analysis of included and/or excluded trials
Kliber (2010)	The effects of long-acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease	• More recent systematic review included that covers the same topic
Korenblat (2012)	NVA237 once daily improves dyspnoea and health-related quality of life in patients with COPD: The GLOW2 trial	• Conference abstract
Kostikas (2016)	Effect of indacaterol/glycopyrronium (IND/GLY) on patient-reported outcomes in men and women with COPD: A pooled analysis from the IGNITE programme	• Conference abstract
Kraemer (2012)	Dual bronchodilation with indacaterol and tiotropium in combination versus triple therapy, fixed-dose combinations, and monotherapy in COPD - A network meta-analysis of FEV1	• Conference abstract
Laforce (2015a)	Glycopyrronium improved health status, dyspnoea, and reduced rescue medication use in patients with moderate-to-severe COPD: Pooled analysis from GEM1 and GEM2 studies	• Conference abstract
LaForce (2015b)	Efficacy and safety of glycopyrronium in COPD patients with moderate-to-severe airflow limitation: The GEM1 study	• Conference abstract
LaForce (2016)	Efficacy and safety of twice-daily glycopyrrolate in patients with stable, symptomatic COPD with moderate-to-severe airflow limitation: the GEM1 study	• Drug dose in trial is >20% above or below the licenced for UK dose *Glycopyrronium used at 15.6mcg*

Short Title	Title	Reason for exclusion
		twice a day.
Larbig (2015)	Efficacy and safety of IND/GLY versus placebo and tiotropium in symptomatic patients with moderate-to-severe COPD: The 52-week radiate study	• Conference abstract
Lee (2014)	Indirect comparison of exacerbation frequency between aclidinium and tiotropium in patients with chronic obstructive pulmonary disease	• Conference abstract
Magnussen (2008)	Improvements with tiotropium in COPD patients with concomitant asthma	• Concomitant drug use issues *Participants were allowed to continue treatment with inhaled LABAs as concomitant medication.*
Mahler (2015)	FLIGHT: efficacy and safety of QVA149 (Indacaterol/Glycopyrrolate) versus its monocomponents and placebo in patients with COPD	• Duplicate reference
Mahler (2015a)	Dual bronchodilation with QVA149 improves dyspnoea in patients with moderate-to-severe COPD: Pooled analysis from the FLIGHT1 and FLIGHT2 studies	• Conference abstract
Mahler (2015b)	FLIGHT1 and FLIGHT2: Efficacy and Safety of QVA149 (Indacaterol/Glycopyrrolate) versus Its Monocomponents and Placebo in Patients with Chronic Obstructive Pulmonary Disease	• Drug dose in trial is >20% above or below the licenced for UK dose *Gylcopyrrolate is used at 15.6mcg twice daily.*
Maltais (2005)	Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD	• Study duration is <12 weeks or treatment of interest lasts < 12 weeks *Study lasts for 42 days.*
Maltais (2014)	Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials	• Cross- over trial *Data is not provided for the first 12 week period of treatment alone.*
Maltais (2016)	Effect of once-daily tiotropium and olodaterol, alone and combined with exercise training, on two measures of walking capacity in patients with COPD	• Conference abstract
Martinez (2016)	Effects of symptom severity at baseline on lung-function and SGRQ responses in the OTEMTO studies	• Conference abstract
Mathioudakis (2014)	Tiotropium HandiHaler improves the survival of patients with COPD: a systematic review and meta-analysis	• More recent systematic review included that covers the same topic

Short Title	Title	Reason for exclusion
Mathioudakis (2014)	Comparative mortality risk of tiotropium administered via handihaler or respimat in COPD patients: are they equivalent?	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *Paper focuses on differences between inhalers used to deliver tiotropium.*
McCrory (2003)	Anticholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease	• Study does not contain any relevant interventions *Systematic review focusing on Ipratropium*
McGarvey (2016)	Effect of aclidinium bromide on cough and sputum symptoms in moderate-to-severe COPD in three phase III trials	• Pooled analysis of included and/or excluded trials
Medic (2016)	Efficacy and Safety of Aclidinium/Formoterol versus Tiotropium in COPD: Results of an Indirect Treatment Comparison	• Systematic review or network meta-analysis focusing on an irrelevant intervention or comparator *Mixed treatment comparison looking at Aclidinium/Formoterol versus Tiotropium.*
Miravitlles (2016)	The efficacy of aclidinium/formoterol on lung function and symptoms in patients with COPD categorized by symptom status: a pooled analysis	• Pooled analysis of included and/or excluded trials
Moita (2008)	Tiotropium improves FEV1 in patients with COPD irrespective of smoking status	• Concomitant drug use issues *Concomitant use of LABAs was allowed.*
Morice (2010)	COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT)	• Additional publication of an included or excluded study that does not provide any extra relevant information *Subgroup analysis examining patients with COPD who are ≤ 50 years old.* • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Nct (2010)	To assess the long-term safety, efficacy and tolerability of inhaled aclidinium bromide in the treatment of moderate-to-severe chronic obstructive pulmonary disease (COPD) (LAS-MD-38)	• Not a peer-reviewed publication *Clinical trials.gov record.*
Nct (2011)	A 24-week evaluation of gsk573719/vilanterol (62.5/25mcg) and components in COPD	• Not a peer-reviewed publication *Clinical trials.gov record.*

Short Title	Title	Reason for exclusion
Nct (2012)	Efficacy, safety and tolerability of two fixed dose combinations of aclidinium bromide/formoterol fumarate, aclidinium bromide, formoterol fumarate and placebo for 28-weeks treatment in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD)	• Not a peer-reviewed publication *Clinical trials.gov record.*
Nct (2014)	Evaluate the effect of aclidinium bromide on long-term cardiovascular safety and COPD exacerbations in patients with moderate to very severe COPD (ASCENT COPD)	• Not a peer-reviewed publication *Clinical trials.gov record.*
Nct (2014)	A 24 week efficacy study of inhaled umeclidinium (UMEC) in patients of chronic obstructive pulmonary disease (COPD) using a novel dry powder inhaler (NDPI)	• Not a peer-reviewed publication *Clinical trials.gov record.*
Nct (2014)	Efficacy and safety of aclidinium bromide 400mcg compared to placebo and to tiotropium bromide in patients with stable moderate to severe chronic obstructive pulmonary disease (COPD)	• Not a peer-reviewed publication *Clinical trials.gov record.*
Neyt (2009)	Tiotropium in the treatment of chronic obstructive pulmonary disease health technology assessment (Structured abstract)	• More recent systematic review included that covers the same topic
Niewoehner (2005)	Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial	• Concomitant drug use issues *Patients continued all respiratory medications other than inhaled anticholinergics, including LABAs.*
O'Donnell (2004)	Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD	• Study duration is <12 weeks or treatment of interest lasts < 12 weeks *Study runs for 42 days.*
Parkes (2014)	Efficacy and safety of once-daily glycopyrronium compared with blinded tiotropium in patients with COPD: The GLOW5 study	• Conference abstract
Pleasants (2016)	Inhaled Umeclidinium in COPD Patients: A Review and Meta-Analysis	• More recent systematic review included that covers the same topic
Powrie (2007)	Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD	• Concomitant drug use issues *There is no information on concomitant drug use in the paper, but the Cochrane review states that anticholinergics other than the study drug were not permitted during the course of the study. However, there is no information provided about the*

Short Title	Title	Reason for exclusion
		continued use of LABAs.
Rennard (2014)	Long-term safety, tolerability, and efficacy of aclidinium bromide in patients with moderate to severe chronic obstructive pulmonary disease (COPD)	• Conference abstract
Rheault (2016)	A randomised, open-label study of umeclidinium versus glycopyrronium in patients with COPD	• Multi-drug RCT that lacks blinding for the LAMA arm
Rodrigo (2007)	Tiotropium for the treatment of stable chronic obstructive pulmonary disease: a systematic review with meta-analysis	• More recent systematic review included that covers the same topic
Rodrigo (2009)	Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis.	• More recent systematic review included that covers the same topic
Rodrigo (2009)	Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis	• Duplicate reference
Rosselli (2015)	Systematic review and meta-analysis of the effectiveness and safety of combination therapy with glycopyrronium-indacaterol compared with other first line therapies in patients with chronic obstructive pulmonary disease	• Conference abstract
Rottenkolber (2013)	Association between bronchodilator treatment and myocardial infarction in COPD patients: A structured assessment of systematic reviews and meta-analyses	• Conference abstract
Rottenkolber (2014)	Inhaled beta-2-agonists/muscarinic antagonists and acute myocardial infarction in COPD patients.	• More recent systematic review included that covers the same topic *Cochrane systematic reviews with same publication year are included instead.*
Salpeter (2006)	Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD (Structured abstract)	• More recent systematic review included that covers the same topic
Sekiya (2012)	Safety and efficacy of NVA237 once daily in Japanese patients: The GLOW4 trial	• Conference abstract
Singh (2008)	Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis	• More recent systematic review included that covers the same topic

Short Title	Title	Reason for exclusion
Singh (2011)	Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials.	• More recent systematic review included that covers the same topic
Singh (2011)	Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials	• Duplicate reference
Singh (2014b)	Effect of aclidinium bromide/formoterol fumarate fixed-dose combination (FDC) on night-time and early morning symptoms in COPD	• Conference abstract
Singh (2014c)	Evaluation of the efficacy and safety of two doses of aclidinium and formoterol in fixed-dose combination in patients with COPD: The acliform study	• Conference abstract
Singh (2015b)	A comparison of shuttle walking test endpoints in exercise studies in patients with COPD	• Conference abstract
Singh (2016a)	Effects of tiotropium+olodaterol versus tiotropium or placebo by COPD disease severity and previous treatment history in the OTEMTO studies	• Additional publication of an included or excluded study that does not provide any extra relevant information *Data analysed based on disease severity and previous treatment history.*
Singh (2016b)	Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol	• Additional publication of an included or excluded study that does not provide any extra relevant information
Somand (2005)	Tiotropium: a bronchodilator for chronic obstructive pulmonary disease	• More recent systematic review included that covers the same topic
Stanbrook (2009)	Tiotropium reduced exacerbations but not rate of FEV 1 decline in patients with COPD using other respiratory medications	• Review article, but not a systematic review
Sun (2007)	Evaluation of clinical effect and safety of tiotropium bromide in treating stable chronic obstructive pulmonary disease	• Concomitant drug use issues *It is unclear whether concomitant use of LABAs was permitted as this was not stated in the Cochrane review and the original paper is in Chinese.*
Suppli (2012)	Aclidinium Bromide: Clinical Benefit in Patients with Moderate to Severe COPD	• More recent systematic review included that covers the same topic

Short Title	Title	Reason for exclusion
Tang (2013)	Evaluation of the efficacy and safety of tiotropium bromide (5 micro g) inhaled via Respimat in Chinese patients with chronic obstructive pulmonary disease	• Concomitant drug use issues *All respiratory medications were allowed during the trial, apart from inhaled anti-cholinergics.*
Tashkin (2003)	Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses	• Additional publication of an included or excluded study that does not provide any extra relevant information
Tashkin (2008)	A 4-year trial of tiotropium in chronic obstructive pulmonary disease.	• Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Tashkin (2010a)	Long-term efficacy of tiotropium in relation to smoking status in the UPLIFT trial	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Tashkin (2010b)	Effect of tiotropium in men and women with COPD: results of the 4-year UPLIFT trial	• Additional publication of an included or excluded study that does not provide any extra relevant information *Subgroup analysis of data based on sex of participants.* • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Tashkin (2011)	Cardiovascular adverse events according to gold stage in the uplift trial	• Conference abstract
Tashkin (2012)	Efficacy of tiotropium in COPD patients with FEV1 >= 60% participating in the UPLIFT trial	• Additional publication of an included or excluded study that does not provide any extra relevant information *Data is presented for a subgroup of participants with FEV1 ≥ 60%.* • Concomitant drug use issues *The UPLIFT trial allowed participants*

Short Title	Title	Reason for exclusion
		to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.
Tashkin (2014)	Rate of comorbidities during the 4-year uplift trial in COPD: A post HOC analysis	• Conference abstract
Tashkin (2014a)	Acute bronchodilator responses decline progressively over 4 years in patients with moderate to very severe COPD	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Tashkin (2014b)	Tiotropium delivered via handi haler or respimat: Improvement in health related quality of life in patients with chronic obstructive pulmonary disease	• Conference abstract
Tashkin (2015)	Cardiac safety of tiotropium in patients with cardiac events: a retrospective analysis of the UPLIFT® trial	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled anticholinergic medications, and subgroup data for LABA usage is not presented here.*
Tashkin (2016)	Consistent improvement in health-related quality of life with tiotropium in patients with chronic obstructive pulmonary disease: Novel and conventional responder analyses	• Pooled analysis of included and/or excluded trials
Thompson (2014)	Dual bronchodilation with once-daily qva149 improves lung function, dyspnoea and health status and reduces symptoms, rescue medication use and exacerbations in patients with COPD: the ignite trials	• Conference abstract
Troosters (2010)	Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial	• Additional publication of an included or excluded study that does not provide any extra relevant information • Concomitant drug use issues *The UPLIFT trial allowed participants to continue their usual COPD medications, except for other inhaled*

Short Title	Title	Reason for exclusion
		anticholinergic medications, and subgroup data for LABA usage is not presented here.
Troosters (2016)	Effect of 8 and 12 weeks' once-daily tiotropium and olodaterol, alone and combined with exercise training, on exercise endurance during walking in patients with COPD	• Conference abstract
Tsiligianni (2017)	Response to Indacaterol/Glycopyrronium (IND/GLY) by Sex in Patients with COPD: A Pooled Analysis from the IGNITE Program	• Pooled analysis of included and/or excluded trials
Van den Bruel (2010)	Does tiotropium lower exacerbation and hospitalization frequency in COPD patients: results of a meta-analysis	• More recent systematic review included that covers the same topic
Van Noord (2000)	Tiotropium improved lung function more than ipratropium in chronic obstructive pulmonary disease	• Review article, but not a systematic review
van Noord (2009)	The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients	• Study duration is <12 weeks or treatment of interest lasts < 12 weeks *Cross-over trial with treatment duration of <12 weeks.*
Vincken (2002)	Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium.	• Comparator in study does not match that specified in protocol *Comparator is a short-acting anticholinergic agent*
Vogelmeier (2008)	Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study	• Multi-drug RCT that lacks blinding for the LAMA arm *Trial was examining formoterol alone or in combination with tiotropium versus placebo or tiotropium, but the tiotropium was administered open-label.*
Wang (2016a)	Evaluation of glycopyrronium therapy in Chinese patients versus predominantly caucasian populations in patients with moderate-to-severe COPD: Comparison of clinical data	• Conference abstract
Wark (2016)	QVA149 is more efficacious than tiotropium and salmeterol/fluticasone combination (SFC) in improving patient-reported outcomes and lung function in COPD patients with moderate to severe baseline dyspnoea: The ignite trials	• Conference abstract
Wedzicha (2013)	Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a	• Multi-drug RCT that lacks blinding for the LAMA arm *Tiotropium is used open-label.*

Short Title	Title	Reason for exclusion
	randomised, double-blind, parallel-group study	
Wedzicha (2013)	Glycopyrronium and tiotropium demonstrate similar improvements in lung function and reductions in exacerbations in severe-to-very severe COPD: The spark study	• Conference abstract
Wedzicha (2014a)	Once-daily QVA149 reduces exacerbations and improves health status in comparison with glycopyrronium and tiotropium in patients with severe-to-very severe COPD: The spark study	• Conference abstract
Wedzicha (2014b)	Dual bronchodilation with once-daily QVA149 reduces exacerbations, improves lung function and health status versus glycopyrronium and tiotropium in severe-to-very severe COPD patients: The spark study	• Conference abstract
Wedzicha (2014c)	Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients	• Pooled analysis of included and/or excluded trials
Wedzicha (2016)	Effect of Aclidinium Bromide on Exacerbations in Patients with Moderate-to-Severe COPD: A Pooled Analysis of Five Phase III, Randomized, Placebo-Controlled Studies	• Pooled analysis of included and/or excluded trials
Witek (2003a)	Minimal important difference of the transition dyspnoea index in a multinational clinical trial	• Additional publication of an included or excluded study that does not provide any extra relevant information
Witek (2003b)	Meaningful effect size and patterns of response of the transition dyspnoea index	• Additional publication of an included or excluded study that does not provide any extra relevant information
Woods (2013)	Aclidinium bromide: an alternative long-acting inhaled anticholinergic in the management of chronic obstructive pulmonary disease	• More recent systematic review included that covers the same topic
Worth (2011)	Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD	• Pooled analysis of included and/or excluded trials
Wu (2009)	The efficacy and safety of tiotropium in Chinese patients with stable chronic obstructive pulmonary disease: a meta-analysis	• More recent systematic review included that covers the same topic
Yadao (2016)	Efficacy and safety of qva149, a fixed-dose combination of indacaterol and	• Conference abstract

Short Title	Title	Reason for exclusion
	glycopyrrolate in symptomatic patients with moderate to severe COPD: Effect of gender	
Yan (2010)	Effect of domestic tiotropium bromide inhalation in patients with COPD at stable stage. [Chinese]	• Study not reported in English
Yohannes (2011)	Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes	• More recent systematic review included that covers the same topic
Yoshimura (2012)	Effects of tiotropium on sympathetic activation during exercise in stable chronic obstructive pulmonary disease patients.	• Comparator in study does not match that specified in protocol *Study does not contain a placebo arm for comparison with Tiotropium.*
Zhou (2017)	Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease	• Concomitant drug use issues *The use of other bronchodilators was allowed if the medication was initiated before recruitment to the trial.*

1 Economic studies

Short title	Title	Reason for exclusion
Agthe (2012)	Budget impact analysis of indacaterol in the treatment of COPD in a Finnish hospital district	Conference abstract
Altaf (2015)	Cost-effectiveness analysis of three different combinations of inhalers for severe and very severe chronic obstructive pulmonary disease patients at a tertiary care teaching hospital of South India	Does not use QALYs to measure health benefits
Antoniu (2012)	Roflumilast as add-on therapy to conventional inhalers in COPD: A cost-effectiveness analysis	Does not assess the comparators of interest
Anwar (2016)	Direct cost analysis and cost effectiveness analysis of chronic obstruction pulmonary disease in fatmawati public hospital	Conference abstract
Asukai (2012)	A UK based cost-utility analysis of indacaterol - A once-daily maintenance bronchodilator for patients with COPD	Conference abstract
Atsou (2011)	Effectiveness and cost-utility estimates of tiotropium treatment and pulmonary rehabilitation programs in French patients with chronic obstructive pulmonary disease	Conference abstract
Bolisega (2011)	Cost-utility of fluticasone compared with beclomethasone and budesonid in chronic obstructive pulmonary disease (COPD) in Poland	Conference abstract
Braceras (2015)	Cost minimization and budget impact analyses in the Basque Country for the treatment of moderate-to-severe chronic obstructive pulmonary disease using	Does not use QALYs to measure health benefits

Short title	Title	Reason for exclusion
	aclidinium bromide instead of tiotropium bromide	
Briggs (2010)	Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study (Provisional abstract)	Not conducted in a UK setting
Briones (2011)	A cost-effectiveness analysis on the use of indacaterol for the treatment of chronic obstructive pulmonary disease in Mexico	Conference abstract
Brosa (2009)	Cost-effectiveness analysis of tiotropium in the treatment of chronic obstructive pulmonary disease (COPD) Patients in Spain	Conference abstract
Bueno (2009)	Cost-effectiveness of Fluticasone Propionate/Salmeterol (500/50 MG) in the treatment of COPD in Brazilian public sector	Conference abstract
Chuck (2008)	Cost-effectiveness of combination therapy for chronic obstructive pulmonary disease	Not conducted in a UK setting
Costa-Scharplatz (2013)	Cost-effectiveness of glycopyrronium compared to tiotropium in COPD patients from a Swedish societal perspective	Conference abstract
Costa-Scharplatz (2015)	Cost-Effectiveness of Glycopyrronium Bromide Compared with Tiotropium in Patients with Chronic Obstructive Pulmonary Disease in Sweden	Not conducted in a UK setting
Dalal (2010)	Cost-effectiveness of combination fluticasone propionate/salmeterol 250/50 mcg versus salmeterol in chronic obstructive pulmonary disease (COPD): Data from two well controlled exacerbation trials	Conference abstract
Dalal (2010)	Cost-effectiveness of combination fluticasone propionate-salmeterol 250/50 microg versus salmeterol in severe COPD patients (Provisional abstract)	Conference abstract
Dalal (2010)	Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease	Does not use QALYs to measure health benefits
Dalal (2010)	Cost-effectiveness of combination fluticasone propionate-salmeterol 250/50 microg versus salmeterol in severe COPD patients	Does not use QALYs to measure health benefits
Dalal (2011)	COPD-related healthcare utilization and costs after discharge from a hospitalization or emergency department visit on a regimen of fluticasone propionate-salmeterol combination versus other maintenance therapies	Does not include a measure of health benefits

Short title	Title	Reason for exclusion
Earnshaw (2009)	Cost-effectiveness of fluticasone propionate/salmeterol (500/50 microg) in the treatment of COPD	Not conducted in a UK setting
Eklund (2015)	Cost-effectiveness of tiotropium versus usual care and glycopyrronium in the treatment of chronic obstructive pulmonary disease in Sweden	Not conducted in a UK setting
Eklund (2015)	Cost-effectiveness of tiotropium vs glycopyrronium in moderate to very severe COPD in Canada, Sweden and the UK	Conference abstract
Eklund (2015)	Cost-Effectiveness Of Tiotropium Vs Glycopyrronium In Moderate To Very Severe Copd In Spain	Conference abstract
Eklund (2016)	Cost-effectiveness of tiotropium versus glycopyrronium in moderate to very severe COPD in France	Conference abstract
Engstrom (2011)	The cost-effectiveness of roflumilast for COPD in Sweden	Conference abstract
Engstrom (2016)	Cost-effectiveness of roflumilast as add-on to triple inhaled therapy vs triple inhaled therapy in patients with severe and very severe COPD associated with chronic bronchitis in Sweden	Conference abstract
Erstad (2013)	Cost savings with interventions to reduce aerosolized bronchodilator use in ventilated patients	Does not use QALYs to measure health benefits
Fan (2014)	The cost effectiveness analysis of indacaterol versus tiotropium in a Chinese medical cost setting	Conference abstract
Fritscher (2008)	Seretide: a pharmacoeconomic analysis	Systematic review of economic evaluations
Garcia-Contreras (2011)	A cost-utility analysis on the use of indacaterol for the treatment of chronic obstructive pulmonary disease in Mexico	Conference abstract
Geitona (2011)	Economic evaluation of indacaterol versus tiotropium or formoterol for patients with moderate to severe COPD in Greece	Conference abstract
Geitona (2015)	Cost-Effectiveness Analysis Of The Fixed Combination Indacaterol/Glycopyrronium Vs	Conference abstract
Giraldo (2014)	Cost-effectiveness analysis of glycopyrronium versus tiotropium and fixed-dose combinations (formoterol/budesonide and salmeterol/fluticasone) for COPD in the Colombian health care system	Conference abstract
Gonzalez-Rojas (2015)	Development of a deterministic patient-level markov model of bronchodilator maintenance treatment in chronic obstructive pulmonary disease	Conference abstract

Short title	Title	Reason for exclusion
Gonzalez-Rojas (2015)	Validation of a patient-level markov model of bronchodilator maintenance treatment in chronic obstructive pulmonary disease	Conference abstract
Granell (2014)	Cost-Effectiveness Analysis of Indacaterol/Glycopyrronium (QVA149) as a Maintenance Bronchodilator Treatment in Adult Patients With Chronic Obstructive Pulmonary Disease in Spain	Conference abstract
Hedegaard (2012)	Cost-effectiveness of budesonide/formoterol versus fluticasone/salmeterol based on real-world effectiveness in patients with COPD	Conference abstract
Hedegaard (2013)	Cost effectiveness of budesonide/formoterol versus fluticasone/salmeterol from a swedish health care perspective based on real-world effectiveness and safety in patients with COPD	Conference abstract
Hedegaard (2013)	Cost effectiveness of budesonide/formoterol vs fluticasone/salmeterol: Real-world effectiveness and safety in COPD	Conference abstract
Herran (2016)	Cost-effectiveness analysis of tiotropium bromide for patients with severe obstructive pulmonary disease in Mexico	Conference abstract
Hettle (2012)	Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium	Compares LAMA against 'usual care' rather than one of the other comparators of interest
Hoogendoorn (2011)	Cost-effectiveness of tiotropium versus salmeterol: A trial-based analysis followed by a model-based extrapolation	Conference abstract
Hoogendoorn (2011)	Comparing the cost-effectiveness of a wide range of COPD interventions using a stochastic population model for COPD	Conference abstract
Hoogendoorn (2012)	Which long-acting bronchodilator is most cost-effective for the treatment of COPD?	Not conducted in a UK setting
Igarashi (2010)	Cost-utility analysis of tiotropium, medicine for chronic obstructive pulmonary diseases (COPD), in Japan	Conference abstract
Karabis (2014)	Economic evaluation of aclidinium bromide in the management of moderate to severe COPD: an analysis over 5 years	Not conducted in a UK setting
Kotchie (2011)	Fully incremental cost-effectiveness analysis of available treatment options in the management of severe COPD in the UK setting	Conference abstract
Kotchie (2011)	The cost-effectiveness of roflumilast in the management of severe COPD in the UK setting	Conference abstract

Short title	Title	Reason for exclusion
Lindner (2011)	Cost-effectiveness of roflumilast (daxas) in the treatment of chronic obstructive pulmonary disease (COPD) in Spain	Conference abstract
Lindner (2016)	Health technology assessments of LAMA/LABA combination products	Conference abstract
Malcolm (2013)	A UK based cost-effectiveness analysis of glycopyrronium bromide a new anti-muscarinic agent for the maintenance treatment of patients with COPD	Conference abstract
Margieva (2012)	Pharmacoeconomic analysis of roflumilast for treatment of adult patients with severe-to-very severe chronic obstructive pulmonary disease (COPD)	Conference abstract
Mauskopf (2010)	Cost effectiveness of tiotropium for chronic obstructive pulmonary disease: a systematic review of the evidence	Systematic review of economic evaluations
Miravitlles (2009)	An economic analysis of pharmacological treatment of COPD in Spain	Does not include a measure of health benefits
Miravitlles (2015)	Cost-Effectiveness Of Umeclidinium/Vilanterol In Symptomatic COPD Spanish Patients	Conference abstract
Miravitlles (2016)	Cost-effectiveness of combination therapy umeclidinium/vilanterol versus tiotropium in symptomatic COPD Spanish patients	Not conducted in a UK setting
Mittmann (2011)	Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives	Does not assess the comparators of interest
Neyt (2010)	Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions	Not conducted in a UK setting
Neyt (2012)	The Cost-Effectiveness of Tiotropium for the Treatment of Chronic Obstructive Pulmonary Disease (COPD): The Importance of the Comparator	Opinion piece
Nielsen (2012)	Cost-effectiveness of adding budesonide/formoterol to tiotropium in severe COPD patients in four Nordic countries	Conference abstract
Nielsen (2013)	Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries	Does not assess the comparators of interest
Oba (2009)	Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD	Not conducted in a UK setting
Onukwugha (2008)	Using cost-effectiveness analysis to sharpen formulary decision-making: the example of tiotropium at the Veterans Affairs health care system	Conference abstract

Short title	Title	Reason for exclusion
Pawlik (2016)	Economic evaluation of tiotropium/olodaterol administrated through the respimat inhaler as maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) in Poland	Conference abstract
Povero (2013)	Cost and cost-effectiveness analyses for moderate and severe COPD patients treated uniquely with tiotropium 18 mcg od for twenty-four months	Conference abstract
Price (2013)	Cost-effectiveness of the LABA/LAMA dual bronchodilator QVA149 in a Swedish setting	Conference abstract
Price (2014)	Cost-effectiveness of the LABA/LAMA dual bronchodilator indacaterol/glycopyrronium in a Swedish healthcare setting	Not conducted in a UK setting
Punekar (2015)	Health care utilisation and costs among COPD patients newly prescribed maintenance therapy in the United Kingdom (UK)	Conference abstract
Reyes-lopez (2012)	Cost-effectiveness of indacaterol on patients with Chronic Obstructive Pulmonary Disease (COPD) at the public Mexican health care system	Conference abstract
Reza (2016)	Cost Effectiveness of the Long-Acting beta2-Adrenergic Agonist (LABA)/Long-Acting Muscarinic Antagonist Dual Bronchodilator Indacaterol/Glycopyrronium Versus the LABA/Inhaled Corticosteroid Combination Salmeterol/Fluticasone in Patients with Chronic Obstructive Pulmonary Disease: Analyses Conducted for Canada, France, Italy, and Portugal	Not conducted in a UK setting
Roberts (2016)	Economic evaluations of fluticasone-propionate/salmeterol combination therapy for chronic obstructive pulmonary disease: a review of published studies	Systematic review of economic evaluations
Roggeri (2013)	Comparing costs and consequences of treating chronic obstructive pulmonary disease with budesonide/formoterol and fluticasone/salmeterol	Conference abstract
Ruiz (2015)	Cost-minimization analysis and budget impact of glycopyrronium bromide versus tiotropium bromide as a maintenance bronchodilator treatment in patients with moderate to severe chronic obstructive pulmonary disease (COPD)	Conference abstract
Rutten-van (2012)	Cost effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues	Systematic review of economic evaluations

Short title	Title	Reason for exclusion
Samyshkin (2011)	Cost-effectiveness of roflumilast in combination with bronchodilator therapies in patients with severe and very severe COPD in Switzerland	Conference abstract
Samyshkin (2013)	Cost-effectiveness of roflumilast in combination with bronchodilator therapies in patients with severe and very severe COPD in Switzerland	Does not assess the comparators of interest
Samyshkin (2014)	Cost-Effectiveness of Roflumilast as an Add-On Treatment to Long-Acting Bronchodilators in the Treatment of COPD Associated with Chronic Bronchitis in the United Kingdom	Does not assess the comparators of interest
Samyshkin (2014)	Cost-effectiveness of roflumilast as an add-on treatment to long-acting bronchodilators in the treatment of COPD associated with chronic bronchitis in the United Kingdom (Provisional abstract)	Conference abstract
Selya-Hammer (2016)	Development of an enhanced health-economic model and cost-effectiveness analysis of tiotropium + olodaterol Respimat fixed-dose combination for chronic obstructive pulmonary disease patients in Italy	Not conducted in a UK setting
Slejko (2014)	Incorporating a pharmacometric model-based meta-analysis into a health economic microsimulation model of COPD	Conference abstract
Slejko (2015)	Calibrating an integrated pharmacoeconomic-pharmacometric model of COPD treatment: What a difference the variance makes	Conference abstract
Slejko (2016)	Translating Pharmacometrics to a Pharmacoeconomic Model of COPD	Not conducted in a UK setting
Tebboth (2016)	UK-specific cost-effectiveness of tiotropium + olodaterol fixed-dose combination versus other LAMA + LABA combinations in patients with COPD	Compares different LAMA+LABA combinations with one another rather than with LAMA or LABA monotherapy or LABA+ICS
Thompson (2013)	Modeled heath economic benefits of a "real life" computer guided review in COPD	Does not use QALYs to measure health benefits
Torres (2013)	Cost-effectiveness analysis of glycopyrronium bromide in the treatment of chronic obstructive pulmonary disease in Spain	Conference abstract
Tran (2010)	A cost-effectiveness analysis of combination bronchodilator therapies in maintenance of moderate to severe chronic obstructive pulmonary disease (COPD)	Not conducted in a UK setting
van (2015)	Predictors of cost-effectiveness of selected COPD treatments in primary care: UNLOCK study protocol	Costs and health effects not reported

Short title	Title	Reason for exclusion
Van (2016)	Cost-effectiveness analyses of pharmacologic maintenance treatment for chronic obstructive pulmonary disease: A systematic review	Conference abstract
van (2017)	Systematic Review and Quality Appraisal of Cost-Effectiveness Analyses of Pharmacologic Maintenance Treatment for Chronic Obstructive Pulmonary Disease: Methodological Considerations and Recommendations	Systematic review of economic evaluations
Wilson (2017)	Cost-effectiveness analysis of umeclidinium/vilanterol for the management of patients with moderate to very severe COPD using an economic model	Not conducted in a UK setting
Yu (2011)	Cost-effectiveness analysis of roflumilast/tiotropium combination therapy vs	Conference abstract
Yu (2011)	Cost-effectiveness analysis of roflumilast/tiotropium combination therapy versus tiotropium monotherapy in patients with severe to very severe COPD	Does not assess the comparators of interest
Zalis'ka (2012)	Cost-benefit analysis of tiotropium and salmeterol treatment compare to usual practice on sample of employed economically active COPD patients in Ukraine	Conference abstract
Zaniolo (2010)	A cost-utility analysis for tiotropium bromide in the long term treatment of specific subgroups of Italian COPD patients	Conference abstract

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1 Appendix L – Research recommendations

2 Research question 1

Question	What features predict inhaled corticosteroid responsiveness most accurately in people with COPD?
Population	People diagnosed with COPD
Interventions	• LABA+ICS • LABA+LAMA+ICS
Comparator	• LABA • LABA+LAMA
Outcomes	• COPD exacerbations (moderate to severe and severe) • Respiratory health-related quality of life • Transition Dyspnoea Index (TDI) • Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropout due to adverse event • Trough FEV1 • Pneumonia • Exercise tolerance/ capacity (6MWD)
Study design	Randomised controlled trial
Subgroups	Smoking status and history (for example current smokers and ex-smokers)

3

Potential criterion	Explanation
Importance to patients, service users or the population	Brochodilators and /or steroids are the main pharmacological treatments used to manage COPD symptoms. There are a number of possible drug combinations available at the class level (and within each drug class). If the wrong class level combinations are prescribed then the person with COPD may experience breathlessness and a reduced quality of life. This may also have a negative impact on their families and society at large (for example, their employers and colleagues). It is therefore important to prescribe the most effective treatment for each person with COPD, including those with comorbidities such as asthma or asthmatic features that may make them steroid responsive. Randomised trials that include subgroup analysis of participants based on factors such as diagnosis of asthma, atopy, higher blood eosinophil count, substantial variation in FEV1 over time or substantial diurnal variation PEFR could provide useful information on this topic.
Relevance to NICE guidance	High-priority: it was possible to make recommendations for people with COPD and asthma based on the available evidence and the clinical expertise of the committee, but the recommendations could be substantially changed if additional studies were carried out that provided information about the characteristics of people with COPD who are responsive to steroids but do not have a diagnosis of asthma.
Current evidence base	There are a large number of trials that look at the effectiveness of brochodilators and /or steroids in people with COPD, but the majority of them specifically excluded people with comorbid asthma. As a result, there

Potential criterion	Explanation
	is a lack of evidence concerning the most effective treatments for people with COPD and asthmatic features.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with COPD who have comorbid asthma that intervention studies in this area should be feasible.

1 **Research question 2**

Question	What is the clinical and cost effectiveness of inhaled therapies (brochodilators and/or inhaled corticosteroids) in people with both stable COPD and asthma?
Population	People diagnosed with COPD and asthma
Interventions	• LAMA • LABA • LAMA+LABA • LABA+ICS • LABA+LAMA+ICS
Comparator	Each other
Outcomes	• COPD exacerbations (moderate to severe and severe) • Respiratory health-related quality of life • Transition Dyspnoea Index (TDI) • Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropout due to adverse event • Trough FEV1 • Pneumonia • Exercise tolerance/ capacity (6MWD)
Study design	Randomised controlled trial
Subgroups	Smoking status and history (for example current smokers and ex-smokers)

2

Potential criterion	Explanation
Importance to patients, service users or the population	Brochodilators and /or steroids are the main pharmacological treatments used to manage COPD symptoms. There are a number of possible drug combinations available at the class level (and within each drug class). If the wrong class level combinations are prescribed then the person with COPD may experience breathlessness and a reduced quality of life. This may also have a negative impact on their families and society at large (for example, their employers and colleagues). It is therefore important to prescribe the most effective treatment for each person with COPD, including those with comorbidities such as asthma.
Relevance to NICE guidance	High-priority: it was possible to make recommendations for this subgroup of people with COPD based on the available evidence and the clinical expertise of the committee, but the recommendations could be substantially changed if additional studies were carried out that specifically recruited people with COPD and cormorbid asthma.

Potential criterion	Explanation
Current evidence base	There are a large number of trials that look at the effectiveness of brochodilators and /or steroids in people with COPD, but the majority of them specifically excluded people with comorbid asthma. As a result, there is a lack of evidence concerning the most effective treatments for this subgroup of people with COPD.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with COPD who have comorbid asthma that intervention studies in this area should be feasible.

1

Appendix M – References

Included clinical studies

Inhaled therapy combinations

This list was taken from the Cochrane review directly and contains papers that relate to the included RCTs, including conference abstracts. This is in contrast to the usual process employed by the Guideline Updates Team where papers are only included if data has been extracted from them. Without duplicating the data extraction process, it is unclear which papers were used by the Cochrane group as a source of included data and so all of the related papers are included in the list below. The studies are grouped according to the main study reference first author and year or trial registration number, shown in bold.

205.137 2003

Unpublished data only [ClinicalTrials.gov: NCT02173691]

* Boehringer Ingelheim. A Multiple Dose Comparison of Tiotropium Inhalation Capsules, Salmeterol Inhalation Aerosol and Placebo in a Six-Month, Double-Blind, Double-Dummy, Safety and Efficacy Study in Patients with Chronic Obstructive Pulmonary Disease (COPD). https://trials.boehringer-ingelheim.com/public/trial_results_documents/205/205.137_U01-1231-02.pdf February 21st 2001.

205.264 2004

Unpublished data only [ClinicalTrials.gov: NCT00274560]

* Boehringer Ingelheim International. A Multiple Dose Comparison of Tiotropium Inhalation Capsules and Salmeterol Inhalation Aerosol in a 12 Week, Randomized, Double-Blind, Double-Dummy, Parallel Group Study in Patients with Chronic Obstructive Pulmonary Disease(COPD).. https://trials.boehringer-ingelheim.com/public/trial_results_documents/205/205.264_CO.pdf 03 FEB 2004.

A3401 2016

Published and unpublished data [ClinicalTrials.gov: NCT01985334]

* Novartis Pharmaceuticals. A prospective, multicenter, 12-week, randomized open-label study to evaluate the efficacy and safety of glycopyrronium(50 micrograms o.d.) or indacaterol maleate and glycopyrronium bromide fixed-dose combination (110/50 micrograms o.d.) regarding symptoms and health status in patients with moderate chronic obstructive pulmonary disease (COPD)switching from treatment with any standard COPD regimen. https://www.novctrd.com/CtrdWeb/displaypdf.nov?trialresultid=14229 29 Nov 2016.

Vogelmeier CF, Gaga M, Aalamian-Mattheis M, Greulich T, Marin JM, Castellani W, Ninane V, Lane S, Nunez X, Patalano F, Clemens A, and Kostikas K (2017) Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial. Respiratory research 18(1), 140

Aaron 2007

Published and unpublished data [ISRCTN: 29870041]

* Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease. Ann Intern Med 2007 Apr 17;146(8):545-55. [PubMed: 17310045]

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Published and unpublished data [ClinicalTrials.gov: NCT01342913; Other: 113107]

* Agustí A, de Teresa L, De Backer W, Zvarich MT, Locantore N, Barnes N, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J 2014 Mar;43(3):763-72. [PubMed: 24114969]

GlaxoSmithKline. A 12-week study to evaluate the 24 hour pulmonary function of Fluticasone Furoate (FF)/Vilanterol Inhalation Powder (FF/VI Inhalation Powder) once daily compared with Salmeterol/Fluticasone Propionate (FP) Inhalation Powder twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD). https://www.gsk-clinicalstudyregister.com/files2/gsk-113107-clinical-study-report-redact-v02.pdf Mar 30, 2015.

Anzueto 2009

Published and unpublished data [ClinicalTrials.gov: NCT00115492; Other: PMID: 19863361; Other: SCO100250]

* Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes.. COPD 2009 Oct;6(5):320-9. [PubMed: 19863361]

GlaxoSmithKline. A Randomized, Double-Blind, Parallel Group, 52-Week Study to Compare the Effect of Fluticasone Propionate/Salmeterol Diskus Combination Product 250/50mcg BID with Salmeterol Diskus 50mcg BID on the Annual Rate of Moderate/Severe Exacerbations in Subjects with Chronic Obstructive Pulmonary Disease. https://www.gsk-clinicalstudyregister.com/files2/gsk-sco100250-clinical-study-report-redact.pdf Sep 08, 2016.

Asai 2013

Published and unpublished data [ClinicalTrials.gov: NCT01285492; Other: ARISE; Other: CQVA149A1301]

* Asai K, Minakata Y, Hirata K, Fukuchi Y, Kitawaki T, Ikeda K, et al. QVA149 once-daily is safe and well tolerated and improves lung function and health status in Japanese patients with COPD: The ARISE study. European Respiratory Society Annual Congress 2013 2013; A2223.

B1303 2011

Published and unpublished data [ClinicalTrials.gov: NCT00876694; Other: CQAB149B1303]

* Novartis Pharmaceuticals. A 52-week Treatment, Multi-center, Randomized, Open Label, Parallel Group Study to Assess the Long Term Safety and Efficacy of Indacaterol (300 µg o.d.) Using Salmeterol (50 µg b.i.d.) as an Active Control in Japanese Patients With Chronic Obstructive Pulmonary Disease (COPD). https://clinicaltrials.gov/ct2/show/NCT00876694 November 8, 2011.

Bateman 2013

Published and unpublished data [ClinicalTrials.gov: NCT01202188; Other: CQVA149A2303 ; Other: SHINE]

* Bateman ED1, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013 Dec;42(6):1484-94. [PubMed: 23722616]

BI1237.22 2014

Published and unpublished data [ClinicalTrials.gov: NCT01536262; Other: 1237.22]

* Boehringer Ingelheim. A Randomised, Double-blind, Parallel-group Study to Assess the Safety and Efficacy of 52 Weeks of Once Daily Treatment of Orally Inhaled Tiotropium + Olodaterol Fixed-dose Combination (2.5µg / 5µg, 5µg / 5µg) and Olodaterol (5 µg) Delivered by the RESPIMAT Inhaler in Japanese Patients With Chronic Obstructive Pulmonary Disease (COPD). https://clinicaltrials.gov/ct2/show/NCT01536262 July 15, 2015.

Ichinose M, Kato M, Takizawa A, Sakamoto W, Gronke L, Tetzlaff K, and Fukuchi Y (2017) Long-term safety and efficacy of combined tiotropium and olodaterol in Japanese patients with chronic obstructive pulmonary disease. Respiratory investigation 55(2), 121-129

Bogdan 2011

Published and unpublished data [ClinicalTrials.gov: NCT00628862; Other: D5122C00001 ; Other: OCEAN]

* Bogdan MA, Aizawa H, Fukuchi Y, Mishima M, Nishimura M, Ichinose M.. Efficacy and safety of inhaled formoterol 4.5 and 9 µg twice daily in Japanese and European COPD patients: phase III study results. BMC Pulm Med 2011 Nov 15;11:51. [PubMed: 22085439]

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Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease (Review). Cochrane Database of Systematic Reviews 2012 Sep 12, Issue 9. Art. No.: CD009157. DOI: 10.1002/14651858.CD009157.pub2. [PubMed: 22972134]

Brusasco 2003

Published and unpublished data [ClinicalTrials.gov: NCT02172287; ClinicalTrials.gov: NCT02173691; Other: 205.130; Other: 205.137]

* Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S.. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003; 58(5): 399- 404. [PubMed: 12728159]

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2012 Sep 12. Art. No.: CD009157. DOI: 10.1002/14651858.CD009157.pub2. [PubMed: 22972134]

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* Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J 2011 Oct;38(4):797-803. [PubMed: 21622587]

Buhl 2015

Published and unpublished data [ClinicalTrials.gov: NCT01431274; ClinicalTrials.gov: NCT01431287; Other: 1237.5 ; Other: 1237.6; Other: TONADO 1&2]

* Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J 2015 Apr; 45 (4): 969-79. [PubMed: 25573406]

Buhl R, Magder S, Bothner U, Tetzlaff K, Voss F, Loaiza L, Vogelmeier CF, and McGarvey L (2017) Long-term general and cardiovascular safety of tiotropium/olodaterol in patients with moderate to very severe chronic obstructive pulmonary disease. Respiratory medicine 122, 58-66

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See Buhl 2015 for reference.

Buhl 2015b

Published and unpublished data [ClinicalTrials.gov: NCT01431287 ; Other: 1237.6 ; Other: TONADO 2]

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Buhl 2015c

Published and unpublished data [ClinicalTrials.gov: NCT01574651; Other: CQVA149ADE01]

* Buhl R, Gessner C, Schuermann W, Foerster K, Sieder C, Hiltl S, et al. Efficacy and safety of once-daily QVA149 compared with the free combination of once-daily tiotropium plus twice-daily formoterol in patients with moderate-to-severe COPD (QUANTIFY): a randomised, non-inferiority study.. Thorax 2015; 70 (4): 311- 9. [PubMed: 25677679]

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* Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003 Feb 8; 361 (9356): 449-56. [PubMed: 12583942]

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* Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007 Feb 22; 356 (8):775- 89. [PubMed: 17314337]

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* Calverley PM, Kuna P, Monsó E, Costantini M, Petruzzelli S, Sergio F, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. Respir Med 2010 Dec; 104 (12): 1858- 68. [PubMed: 20965712]

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Published and unpublished data [ClinicalTrials.gov: NCT01613326 ; Other: CNVA237A2314 ; Other: GLOW5]

* Chapman KR, Beeh KM, Beier J, Bateman ED, D'Urzo A, Nutbrown R. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. BMC Pulm Med 2014 Jan; 17 (14): 4. [PubMed: 24438744]

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* Novartis Pharmaceuticals. 24-week Study to Evaluate Efficacy and Safety of the Combination Budesonide / Indacaterol vs Fluticasone / Salmeterol in Patients With COPD. https://clinicaltrials.gov/ct2/show/NCT02055352 April 18, 2017.

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* GlaxoSmithKline. Evaluating the Control of COPD Symptoms in Patients Treated With Tiotropium Bromide 18mcg Once Daily Alone, ADOAIR 50/250mcg Twice Daily Alone or ADOAIR 50/250mcg Plus Tiotropium Bromide 18mcg. https://clinicaltrials.gov/ct2/show/NCT01762800 November 10, 2016.

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D'Urzo 2017

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Excluded clinical studies

Inhaled therapy combinations

This list was taken directly from the Cochrane review. The first author and year or trial registration number is used to reference the study.

1237.20

Unpublished data only [ClinicalTrials.gov: NCT01559116]

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Appendix N – Network meta-analysis summary tables

Inhaled therapy combinations

Low risk group

Table 65 Summary of NMA results for the low risk group.

The columns list the drug combinations and the rows list the outcomes. Within each box, the drug combinations in black represent results where there was an improvement in that outcome, but the point estimate was less than the defined minimal clinically important difference (MID). The treatments in green represent results where the effect was greater than the MID. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the drug was not better than any of the other drug combinations or, more rarely, where there was no data for that particular drug and outcome.

Outcome	LAMA+LABA	LABA+ICS	LAMA	LABA
FEV1 (3 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LABA	-	-
FEV1 (6 months)	Improvements compared to: • LAMA • LABA • LABA+ICS	Improvements compared to: • LABA	Improvements compared to: • LABA	-
FEV1 (12 months)	Improvements compared to: • LABA	-	Improvements compared to: • LABA	-
Moderate to severe exacerbations	Improvements compared to: • LABA	Improvements compared to: • LABA	Improvements compared to: • LABA	-
Severe exacerbations	-	-	-	-

Outcome	LAMA+LABA	LABA+ICS	LAMA	LABA
Dropouts due to adverse events	-	-	-	-
SGRQ (3 months)	Improvements compared to: • LAMA	Improvements compared to: • LAMA	-	-
SGRQ (6 months)	Improvements compared to: • LAMA • LABA	Improvements compared to: • LABA	-	-
SGRQ (12 months)	Improvements compared to: • LAMA	Improvements compared to: • LAMA+LABA • LAMA • LABA	-	-
SGRQ responders (3 months)	Improvements compared to: • LAMA	Improvements compared to: • LAMA	-	Improvements compared to: • LAMA
SGRQ responders (6 months)	Improvements compared to: • LAMA • LABA	-	-	-
TDI (3 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	-	-	-
TDI (6 months)	Improvements compared to: • LAMA • LABA	-	-	-
TDI (12 months)	Improvements compared to: • LAMA • LABA	-	-	-
Serious adverse events	-	-	-	Improvements compared to:

Outcome	LAMA+LABA	LABA+ICS	LAMA	LABA
				• LABA+ICS
COPD serious adverse events	-	-	-	-
Cardiac serious adverse events	-	-	-	-
Pneumonia	-	-	Improvements compared to: • LABA+ICS	Improvements compared to: • LABA+ICS
Mortality	-	-	-	-

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1 **High risk group**

2 **Table 66 Summary of NMA results for the high risk group.**

3 The columns list the drug combinations and the rows list the outcomes. Within each box, the drug combinations in black represent results where
4 there was an improvement in that outcome, but the point estimate was less than the defined minimal clinically important difference (MID). The
5 treatments in green represent results where the effect was greater than the MID. Results have been reversed where necessary to ensure that they
6 are presented as improvements. Boxes with dashes represent cases where the drug was not better than any of the other drug combinations or,
7 more rarely, where there was no data for that particular drug and outcome.

Outcome	LAMA+LABA	LABA+ICS	LAMA	LABA
FEV1 (3 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LABA	Improvements compared to: • LABA	-
FEV1 (6 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LABA	Improvements compared to: • LABA	-
FEV1 (12 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LABA	Improvements compared to: • LABA	-
Moderate to severe exacerbations	Improvements compared to: LABA+ICS LAMA LABA	Improvements compared to: • LABA	Improvements compared to: • LABA	-
Severe exacerbations	Improvements compared to: • LABA+ICS	Improvements compared to: • LABA	Improvements compared to: • LABA	-

Outcome	LAMA+LABA	LABA+ICS	LAMA	LABA
	• LABA			
Dropouts due to adverse events	-	-	-	-
SGRQ (3 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LAMA	-	-
SGRQ (6 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LAMA • LABA	-	-
SGRQ (12 months)	Improvements compared to: • LAMA • LABA	Improvements compared to: • LABA	-	-
SGRQ responders (12 months)	Improvements compared to: • LABA+ICS • LAMA • LABA	Improvements compared to: • LABA	-	-
Serious adverse events	-	-	Improvements compared to: • LABA+ICS • LABA	-
COPD serious adverse events	-	-	Improvements compared to: • LABA	-
Cardiac serious adverse events	-	-	-	-
Pneumonia	Improvements compared to: • LABA+ICS	-	Improvements compared to: • LABA+ICS	Improvements compared to: • LABA+ICS

Outcome	LAMA+LABA	LABA+ICS	LAMA	LABA
Mortality	-	-	-	-

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LAMA monotherapy

Table 67 Summary of the NMA results.

The columns list the drugs and the rows list the outcomes. Within each box, the drugs in black represent results where there was an improvement in that outcome, but the point estimate was less than the defined minimal clinically important difference (MID). The treatments in green represent results where the effect was greater than the MID. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the drug was not better than any of the other drugs or, more rarely, where there was no data for that particular drug and outcome.

Outcome	Aclidinium	Glycopyrronium	Tiotropium	Umeclidinium
Moderate to severe exacerbations	-	-	-	-
Severe exacerbations	Improvements compared to: • Umeclidium	Improvements compared to: • Umeclidinium	Improvements compared to: • Umeclidium	-
Dropouts due to adverse events	Improvements compared to: • Umeclidium	Improvements compared to: • Umeclidinium	Improvements compared to: • Umeclidium	-
SGRQ (3 months)	-	-	-	-
SGRQ (6 months)	-	-	-	-
SGRQ responders	-	-	-	-
TDI (3 months)	-	-	-	-
TDI (12 months)	-	-	-	-
Serious adverse events	Improvements compared to: • Umeclidium	Improvements compared to: • Umeclidium	Improvements compared to: • Umeclidium	-
Mortality	-	-	-	-