Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is a respiratory disease that causes progressive symptoms of breathlessness, cough and mucus build-up. It is the fourth or fifth most common cause of death worldwide and is associated with significant healthcare costs.

Inhaled long-acting beta$_2$-agonists (LABAs) are widely prescribed to manage the symptoms of COPD when short-acting agents alone are no longer sufficient. Twice-daily treatment with an inhaled LABA is aimed at relieving symptoms, improving exercise tolerance and quality of life, slowing decline and even improving lung function and preventing and treating exacerbations.

Objectives

To assess the effects of twice-daily long-acting beta$_2$-agonists compared with placebo for patients with COPD on the basis of clinically important endpoints, primarily quality of life and COPD exacerbations.

Search methods

We searched the Cochrane Airways Group trials register, ClinicalTrials.gov and manufacturers' websites in June 2013.

Selection criteria

Parallel, randomised controlled trials (RCTs) recruiting populations of patients with chronic obstructive pulmonary disease. Studies were required to be at least 12 weeks in duration and designed to assess the safety and efficacy of a long-acting beta$_2$-agonist against placebo.

Data collection and analysis

Data and characteristics were extracted independently by two review authors, and each study was assessed for potential sources of bias. Data for all outcomes were pooled and subgrouped by LABA agent (formoterol 12 μg, formoterol 24 μg and salmeterol 50 μg) and then were separately analysed by LABA agent and subgrouped by trial duration. Sensitivity analyses were conducted for the proportion of participants taking inhaled corticosteroids and for studies with high or uneven rates of attrition.

Main results

Twenty-six RCTs met the inclusion criteria, randomly assigning 14,939 people with COPD to receive twice-daily LABA or placebo. Study duration ranged from three months to three years; the median duration was six months. Participants were more often male with moderate to severe symptoms at randomisation; mean forced expiratory volume in 1 second (FEV_1) was between 33% and 55% predicted normal in the studies, and mean St George's Respiratory Questionnaire score (SGRQ) ranged from 44 to 55 when reported.

Moderate-quality evidence showed that LABA treatment improved quality of life on the SGRQ (mean difference (MD) -2.32, 95% confidence interval (CI) -3.09 to -1.54; I^2 = 50%; 17 trials including 11,397 people) and reduced the number of exacerbations requiring hospitalisation (odds ratio (OR) 0.73, 95% CI 0.56 to 0.95; I^2 = 10%; seven trials including 3804 people). In absolute terms, 18 fewer people per 1000 were hospitalised as the result of an exacerbation while receiving LABA therapy over a weighted mean of 7 months (95% CI 3 to 31 fewer). Scores were also improved on the Chronic Respiratory Disease Questionnaire (CRQ), and more people receiving LABA treatment showed clinically important improvement of at least four points on the SGRQ.

The number of people who had exacerbations requiring a course of oral steroids or antibiotics was also lower among those taking LABA (52 fewer per 1000 treated over 8 months; 95% CI 24 to 78 fewer, moderate quality evidence).

Mortality was low, and combined findings of all studies showed that LABA therapy did not significantly affect mortality (OR 0.90, 95% CI 0.75 to 1.08; I^2 = 21%; 23 trials including 14,079 people, moderate quality evidence). LABA therapy did not affect the rate of serious adverse events (OR 0.97, 95% CI 0.83 to 1.14; I^2 = 34%, moderate quality evidence), although there was significant unexplained heterogeneity, especially between the two formoterol doses.

LABA therapy improved predose FEV_1 by 73 mL more than placebo (95% CI 48 to 98; I^2 = 71%, low quality evidence), and people were more likely to withdraw from placebo than from LABA therapy (OR 0.74, 95% CI 0.69 to 0.80; I^2 = 0%). Higher rates of withdrawal in the placebo arm may reduce our confidence in some results, but the disparity is more likely to reduce the magnitude of difference between LABA and placebo than inflate the true effect; removing studies at highest risk of bias on the basis of high and unbalanced attrition did not change conclusions for the primary outcomes.

Authors' conclusions

Moderate-quality evidence from 26 studies showed that inhaled long-acting $beta_2$-agonists are effective over the medium and long term for patients with moderate to severe COPD. Their use is associated with improved quality of life and reduced exacerbations, including those requiring hospitalisation. Overall, findings showed that inhaled LABAs did not significantly reduce mortality or serious adverse events.

PLAIN LANGUAGE SUMMARY

Long-acting $beta_2$-agonists for people with COPD

We wanted to know whether twice-daily treatment with an inhaled long-acting $beta_2$-agonist was better than treatment with a dummy inhaler for people with chronic obstructive pulmonary disease (COPD).

Background to the review

COPD is a disease of the lungs that causes airways to narrow. As a result, people with COPD experience symptoms of breathlessness, cough and mucus buildup, which worsen over time. Cigarette smoking is the most common cause of COPD, and it is the fourth or fifth most common cause of death worldwide.

Inhaled salmeterol and formoterol, known as long-acting $beta_2$-agonists (LABAs), are widely used to manage the symptoms of COPD, so it is important to understand their benefits and side effects. They are often introduced when inhaled treatments for quick relief from symptoms (e.g. salbutamol) are no longer helpful. LABAs are designed to be taken twice a day to control symptoms and reduce the likelihood of flare-ups.

What did we find?

Twenty-six studies (including 14,939 people with moderate to severe symptoms of COPD) compared twice-daily salmeterol or formoterol with a dummy inhaler. The evidence gathered for this review is current up to June 2013. Results within studies were described most often after six months of treatment, but some were reported at three months and others after as long as three years. More men than women took part, and they had moderate to severe symptoms when they began treatment.

People who took LABA inhalers showed greater improvement on quality of life scales than those taking dummy inhalers, and they had fewer serious flare-ups that resulted in a hospital stay (18 fewer per 1000). They also had better lung function than people who had taken placebo. LABA inhalers did not reduce the number of people who died, and no significant difference was noted in the number who had serious adverse events while taking the medication.

These studies were most often sponsored by drug companies and were generally well designed. People in the studies did not know which treatment they were getting, and neither did the people doing the research. Several studies did not describe flare-ups, hospital stays or lung volume, so there is a chance that evidence obtained in future studies would change the strength of what has been concluded. Additionally, quite a lot of variation was noted between studies in the effects of LABA inhalers on quality of life, serious side effects and lung function. This may be explained in part by variation in study methods regarding what medications people could continue to take.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Long-acting beta$_2$-agonists compared with placebo for chronic obstructive pulmonary disease

Patient or population: people with chronic obstructive pulmonary disease
Intervention: long-acting beta$_2$-agonists
Comparison: placebo
Setting: community

Outcomes Follow-up: weighted means presented for each outcome	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Long-acting beta$_2$-agonists				
Quality of life[1] St George's Respiratory Questionnaire (SGRQ); lower scores are better 16 months	**45.3** (mean of reported placebo endpoints)	Mean score in the intervention groups was **2.32 units lower** (3.09 to 1.54 lower)	**MD -2.32** (-3.09 to -1.54)	11,397 (17 studies)	⊕⊕⊕◯ **moderate2**[1]	A difference of 4 points is generally accepted to be of clinical significance
Severe exacerbations (hospitalisations) 7 months	**71 per 1000**	**53 per 1000** (40 to 68)	**OR 0.73** (0.56 to 0.95)	2859 (7 studies)	⊕⊕⊕◯ **moderate**[3]	I^2 = 10%, P = 0.35
Moderate exacerbations (course of antibiotics or oral steroids) 8 months	**238 per 1000**	**186 per 1000** (160 to 214)	**OR 0.73** (0.61 to 0.87)	3375 (7 studies)	⊕⊕⊕◯ **moderate**[3]	I^2 = 8%, P = 0.37
Severe/moderate exacerbations (hospitalisation *or* course of medication *or* ER visit) 8 months	**336 per 1000**	**308 per 1000** (278 to 340)	**OR 0.88** (0.76 to 1.02)	3968 (7 studies)	⊕⊕⊕◯ **moderate**[3]	I^2 = 0%, P = 0.80

Mortality (all-cause) 14 months	**5 per 1000**	**5 per 1000** (4 to 5)	**OR 0.90** (0.75 to 1.08)	14,079 (23 studies)	⊕⊕⊕◯ **moderate**[4]	I^2 = 21%, P = 0.21
Participants with one or more serious adverse event (non-fatal)[1] 15 months	**86 per 1000**	**84 per 1000** (74 to 97)	**OR 0.97** (0.83 to 1.14)	12,446 (20 studies)	⊕⊕⊕◯ **moderate**[5]	
Predose FEV_1 (mL)[1] 7 months; higher is better	**1221 mL** (mean of reported placebo endpoint scores)	Mean predose FEV_1 in the intervention groups was **73 mL higher** (48 to 98 mL higher)	**MD 73 mL** (48 to 98 mL)	6125 (14 studies)	⊕⊕◯◯ **low**[6,7]	Subgroup differences (I^2 = 84%) discussed in high heterogeneity within subgroups, with potential baseline differences

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

n.b. Unless otherwise stated, significant subgroup differences were not found.
[1] Quality of life, serious adverse events and FEV_1 were analysed with random effects as the result of heterogeneity.
[2] I^2 = 50%, P <0.01 (-1 for inconsistency)
[3] Several studies did not report exacerbations in a form that could be included in any of the three outcomes included in this review (-1 for publication bias)
[4] Confidence intervals include important benefit and potential harm (-1 for imprecision)
[5] I^2 = 34%, P = 0.06; opposite direction of effect observed for the two formoterol doses (-1 for inconsistency)
[6] I^2 = 71%, P <0.01 (-1 for inconsistency)
[7] Several studies did not report the outcome in a way that could be included in the meta-analysis

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterised by chronic and progressive breathlessness, cough, sputum production and airflow obstruction, which leads to restricted activity and poor quality of life (GOLD 2013). The World Health Organization (WHO) has estimated that COPD, which includes emphysema, chronic bronchitis and small airways disease, is the fourth or fifth most common single cause of death worldwide, and that the treatment and management costs associated with COPD present a significant burden to public health. In the United Kingdom (UK), the annual cost of COPD for the National Health Service (NHS) is estimated to be £1.3 million per 100,000 people (NICE 2011). Furthermore, because of its slow onset and under-recognition of the disease, it is heavily underdiagnosed (GOLD 2013).

COPD comprises a combination of bronchitis and emphysema and involves chronic inflammation and structural changes in the lung. Cigarette smoking is the most important risk factor, but air pollution and occupational dust and chemicals are also recognised risk factors. COPD is a progressive disease that leads to decreased lung function over time, even with the best available care. No cure for COPD is known, although it is a preventable and treatable disease. As yet, apart from smoking cessation and non-pharmacological treatments such as long-term oxygen therapy in hypoxic patients, and pulmonary rehabilitation, no intervention has been shown to reduce mortality (GOLD 2013; Puhan 2011). Management of the disease is multifaceted and includes interventions for smoking cessation (van der Meer 2001), pharmacological treatments (GOLD 2013), education (Effing 2007), and pulmonary rehabilitation (Lacasse 2006; Puhan 2011). Pharmacological therapy is aimed at relieving symptoms, improving exercise tolerance and quality of life, slowing decline and even improving lung function, and preventing and treating exacerbations. COPD exacerbations impair patients' quality of life (GOLD 2013), and a large part of the economic burden of COPD is attributed to the cost of managing exacerbations, particularly those resulting in the use of acute care services, or hospitalisations (Hutchinson 2010). In the UK, one in eight emergency admissions to hospital is for COPD, which makes it the second largest cause of emergency admissions, and one of the most costly conditions treated by the NHS (NICE 2011). Appropriate pharmacological management of the disease is therefore important, particularly for reducing and preventing exacerbations.

Description of the intervention

Pharmacological management of COPD tends to begin with one treatment, and additional therapies are introduced as necessary to relieve symptoms and reduce the frequency and severity of exacerbations (ATS/ERS 2011; GOLD 2013). The first step often involves a short-acting bronchodilator for control of breathlessness when needed: either a short-acting beta$_2$-agonist (SABA), such as salbutamol, or the short-acting muscarinic antagonist (SAMA) ipratropium. For persistent or worsening breathlessness associated with lung function decline, long-acting bronchodilators may be introduced (ATS/ERS 2011; GOLD 2013). These comprise twice daily long-acting beta$_2$-agonists (LABAs; duration of action 12 hours); once-daily long-acting beta$_2$-agonists (sometimes referred to as ultra long-acting; duration of action 24 hours); and the once-daily long-acting anticholinergic agent tiotropium. Regular treatment with long-acting bronchodilators is preferred over treatment with regular short-acting bronchodilators on the basis of efficacy and side effects (Beeh 2010; GOLD 2013). Theophylline, an oral phosphodiesterase (PDE) inhibitor, is an alternative when bronchodilators are not available or affordable. However, theophylline is less effective and is less well tolerated than inhaled long-acting bronchodilators. For patients with severe or very severe COPD (i.e. with forced expiratory volume in 1 second (FEV_1) < 50% predicted) and with repeated exacerbations, GOLD 2013 recommends the addition of inhaled corticosteroids (ICS) to bronchodilator treatment. ICS are anti-inflammatory drugs that are licenced as combination inhalers with LABAs. This group of patients with severe COPD may also benefit from treatment with the PDE_4 inhibitor roflumilast, which may reduce the risk of exacerbations (GOLD 2013).

How the intervention might work

LABAs are widely used in the management of COPD, alone or in combination with other bronchodilators, ICS or both. Commonly used LABAs include twice-daily salmeterol and formoterol and the new once-daily preparation, indacaterol. All inhaled beta$_2$-agonists activate beta$_2$-receptors on different cells in the lung. Activation of the receptor on airway smooth muscle leads to a cascade of reactions that result in dilation of the airways. However, the exact mechanism of action differs between the various LABAs, and different efficacy and safety profiles can be expected between them. LABAs are commonly used to relieve symptoms and reduce exacerbations in stable COPD (Rodrigo 2008). Possible side effects of LABAs include cardiac effects such as arrhythmia and palpitations, muscle tremors, headache and metabolic imbalances such as hypokalaemia and increased glucose levels (Berger 2008).

Why it is important to do this review

LABAs are used widely and play a central role in the management of COPD (ATS/ERS 2011; GOLD 2013; NICE 2010). An earlier Cochrane systematic review has presented evidence on the effects of LABAs for patients with poorly reversible COPD (Appleton

2006). However, in this systematic review, we summarised the evidence regarding the efficacy and safety of twice-daily LABAs (i.e. those with a 12-hour duration of action) compared with placebo in all patients with COPD. The efficacy and safety of the once-daily LABA indacaterol in comparison with other LABAs and placebo will be assessed in another Cochrane systematic review (Geake 2012).

This review forms part of a suite of reviews on long-acting therapies for COPD, including long-acting anticholinergics, long-acting beta$_2$-agonists, ultra-long-acting beta$_2$-agonists, PDE$_4$ inhibitors, and ICS (Cheyne 2012; Chong 2011; Chong 2012; Geake 2012; Karner 2011; Karner 2011a; Karner 2012; Karner 2012a; Karner 2012b; Nannini 2010; Nannini 2010a; Nannini 2012; Spencer 2011; Welsh 2011; Yang 2012). These reviews, which look at long-term treatment for COPD, will ultimately be summarised in an overview.

OBJECTIVES

To assess the effects of twice-daily long-acting beta$_2$-agonists compared with placebo for patients with COPD on the basis of clinically important endpoints, primarily quality of life and COPD exacerbations.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a parallel-group design, of at least 12 weeks' duration. We did not exclude studies on the basis of blinding. We excluded cross-over trials, as we were looking at long-term effects including adverse events.

Types of participants

We included RCTs that recruited participants with a clinical diagnosis of COPD based on the following (GOLD 2013).

1. Forced expiratory volume after one second (FEV$_1$)/forced vital capacity (FVC) ratio < 0.7, which confirms the presence of persistent airflow limitation.
2. Several of the following key indicators:
   i) Progressive and/or persistent dyspnoea (breathlessness);
   ii) Chronic cough;
   iii) Chronic sputum production; and
   iv) History of exposure to risk factors (tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals).

We excluded RCTs in which participants had to have asthma as well as COPD to be included.

Types of interventions

We included studies in which participants were randomly assigned to receive the following.

1. Salmeterol 50 μg or placebo twice daily.
2. Formoterol 12 μg or placebo twice daily.
3. Formoterol 24 μg or placebo twice daily.

We included studies that allowed concomitant short-acting bronchodilators, provided they were not part of the trial treatment under study. We did not include studies in which most participants were receiving other COPD treatments.

Types of outcome measures

Primary outcomes

1. Quality of life; mean difference and responders analysis (number of participants with clinically significant improvement or worsening); measured with a scale validated for COPD, such as St George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRQ).
2. Severe COPD exacerbations (COPD exacerbations leading to hospitalisation).

Secondary outcomes

1. Moderate COPD exacerbations.[a]
2. Mortality; all-cause.
3. Non-fatal serious adverse events; all-cause.
4. Trough (predose) FEV$_1$.
5. Withdrawals from study treatment.

[a]A sample definition of COPD exacerbation is "an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" (GOLD 2013).

Search methods for identification of studies

Electronic searches

We identified trials 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 conference abstracts found through handsearching (see Appendix 1 for further

details). We searched all records in the CAGR coded 'COPD' using the following terms:
(*formoterol or salmeterol or Serevent or Foradil or Oxis or LABA or long-acting* or "long acting*")
We also searched ClinicalTrials.gov using search terms described in Appendix 2. We searched all databases up to June 2013, with no restriction on date or language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched the manufacturers' websites (GlaxoSmithKline and AstraZeneca) for additional information on studies identified through the electronic searches.

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts of citations retrieved through literature searches and obtained in full text those deemed to be potentially relevant. We assigned each reference to a study identifier and assessed each against the inclusion criteria of this protocol (see Criteria for considering studies for this review). Any disagreements were resolved by consensus.

Data extraction and management

Two review authors independently extracted information from each study to record the following characteristics.

- Design (design, total study duration, number of study centres and location).
- Participants (number randomly assigned to each treatment, mean age, gender, baseline lung function, smoking history, reversibility, inclusion criteria and exclusion criteria).
- Interventions (run-in, intervention and control treatments including concentration and formulation).
- Outcomes (definition of exacerbation and outcome data using end of study as time of analysis for all studies).

In the event that treatment arms of interest with different doses were included, these findings were combined when possible according to recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). If the data could not be combined, we used the trial arm with the dose offering greatest homogeneity with other trials regarding dose. We also subgrouped primary outcome data according to dose. Any discrepancies in the data were resolved by discussion, or by consultation with a third party when necessary.

Assessment of risk of bias in included studies

For the following items, two review authors independently assessed the risk of bias and graded each potential source of bias as high risk, low risk or unclear risk and resolved disagreements by consensus, according to recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009).

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.

Measures of treatment effect

Dichotomous data: We analysed dichotomous data variables (such as mortality and withdrawals) using Mantel-Haenzsel odds ratios (ORs) with 95% confidence intervals (CIs). If events were rare, we employed the Peto odds ratio. If count data were not available as the number of participants experiencing an event but rather were reported as rate ratios, we transformed them into log rate ratios and analysed the data using generic inverse variance (GIV).
Continuous data: We analysed continuous outcome data as fixed-effect mean differences (MDs) with 95% CIs unless excessive heterogeneity was found.

Unit of analysis issues

We analysed dichotomous data using participants as the unit of analysis. For continuous data, the MD based on change from baseline was preferred over the MD based on absolute values.

Dealing with missing data

If outcome data or key study characteristics were not reported in the primary publication, we searched clinical trial reports and contacted study authors and sponsors for additional information. We used intention-to-treat (ITT) analysis on outcomes from all randomly assigned participants when possible. We also considered, as part of the sensitivity analysis, the impact of the unknown status of participants who withdraw from the trials.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by recording differences in study design and participant characteristics between individual studies. We assessed the extent of statistical variation among study results by using the I^2 measurement.

Assessment of reporting biases

We tried to minimise reporting bias from non-publication of studies or selective outcome reporting by using a broad search strategy,

checking references of included studies and relevant systematic reviews and contacting study authors to request additional outcome data. We visually inspected funnel plots when 10 or more studies were included.

Data synthesis

For all outcomes, we analysed each LABA and dose separately; however for our primary outcomes, we also pooled the three comparisons. We analysed data using a fixed-effect model, but when heterogeneity was noted (I^2 > 30%), we used a random-effects model and explored the heterogeneity (see Subgroup analysis and investigation of heterogeneity). We presented the findings of our primary outcomes in a 'Summary of findings' table generated with the use of GradePro software and according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009).

Subgroup analysis and investigation of heterogeneity

When substantial heterogeneity was identified among the studies (I^2 > 30%), we explored it by analysing the data by the following subgroups.

- Duration of LABA therapy (≤ 1 year; > 1 year).
- Disease severity at baseline (FEV_1 < 50% predicted; FEV_1 ≥ 50% predicted).

Sensitivity analysis

We assessed the robustness of our analyses by performing sensitivity analyses and systematically excluding the following studies from the overall analysis.

- Those at high risk of bias.
- Those with high and/or uneven withdrawal rates
- Concurrent use of inhaled steroids*

*Studies where more than fifty percent of patients continued taking ICS or other COPD medications were excluded. However, included studies in which a significant proportion (but not the majority) of patients continued taking ICS or other COPD medications were removed in a sensitivity analysis.

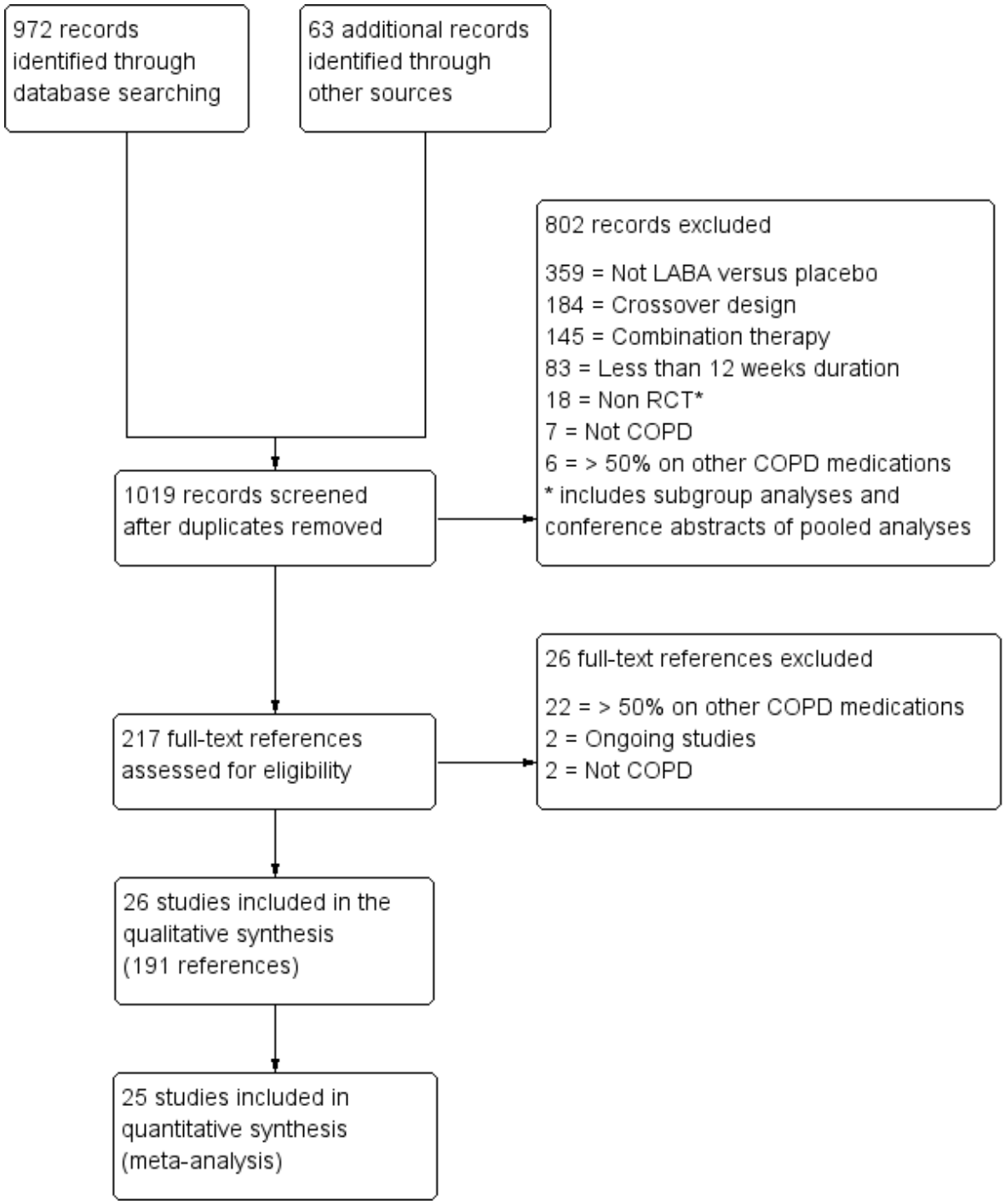
RESULTS

Description of studies

Results of the search

Nine hundred and seventy-two references were identified through searches of online databases, and 63 additional references were found by searching other resources (drug company websites, reference lists of systematic reviews, clinicaltrials.gov). After 16 duplicates were removed, 802 of the remaining 1019 references were excluded by sifting titles and abstracts. The most common reasons for exclusion were that no LABA versus placebo comparison was performed (n = 359) and that the study used a cross-over design (n = 184). Full reasons for exclusion are listed in Figure 1. Full texts were consulted for the remaining 217 references, and 191 were found to meet all of the inclusion criteria, representing 26 studies. The main reason for exclusion at this stage was that more than 50% of participants in the trials were taking concomitant COPD medications (n = 22). Full details of the search history can be found in Appendix 1 and Appendix 2.

Figure 1. Study flow diagram.



Included studies

Twenty-six studies met the inclusion criteria, randomly assigning 14,939 people with a diagnosis of COPD to LABA or placebo. All but one of the trials (Watkins 2002) contributed data to at least one analysis. Calverley 2007 [TORCH] contributed the greatest number of people to the analyses, with 3087 people randomly assigned to the two groups of interest. A small industry-funded trial, SLMF4010 2005 included the smallest number of people, with 17 people randomly assigned to each group.

Design and duration

All twenty-six studies were randomised, double-blind, parallel-group controlled trials. Nine trials lasted for three months, 10 for six months and six for a year.The remaining trial (Calverley 2007 [TORCH]) was a three-year study. In accordance with the protocol, separate analyses of the three included LABA doses were subgrouped according to length of trial (three, six, 12 and 36 months). Distribution of studies among the four duration categories and descriptive statistics of age and sex are given in Table 1.

Participant inclusion and exclusion criteria

Full details of the inclusion and exclusion criteria for each trial can be found in Characteristics of included studies. Inclusion and exclusion criteria were largely similar across trials. Participants were required to be over the age of 40 (35 in three studies) and to have a smoking history of at least 10 pack-years.

Baseline characteristics of participants

Full details of the baseline characteristics of participants in each study can be found in Characteristics of included studies. Participants' mean age was similar across trials, ranging from 58.8 to 67.2 years in individual trial arms. Trial participants were most often male (range 50% to 94%, median 75%) and Caucasian (range 46% to 100%, median 92%). Seventeen trials reported mean or median smoking pack-years; medians ranged from 40 to 60, and means ranged from 35.4 to 52.5, pack-years. Twenty studies reporting percentage predicted FEV_1 indicated that the populations were of moderate to high disease severity, with baseline means ranging from 32.6% to 54.7%. Distribution of mean percentage predicted FEV_1 at baseline within studies and mean baseline SGRQ (when reported) are presented in Table 2.

Descriptive statistics were analysed separately for the formoterol and salmeterol studies to check for systematic differences between trials of drugs made by different manufacturers. Percentage reversibility was reported in only 12 studies (46%), of which only two were studying salmeterol. Within the ten formoterol studies (both doses), reversibility reported for each arm ranged from 4.7% to 19.5%, with a mean value of 8.8. For the salmeterol studies, the mean was 7.9 and ranged from 4 to 13 in individual trial arms. Mean percentage predicted FEV_1 was better reported (77% of studies), and no differences in baseline severity were apparent between formoterol and salmeterol; the formoterol studies had a mean of 44.7, ranging from 32.6 to 54.7, and the salmeterol studies a mean of 43.0, ranging from 37.7 to 53. Given the relative homogeneity of these metrics between subgroups and between the individual trials, it was not deemed appropriate to subgroup results on the basis of severity.

Characteristics of the interventions

Fourteen studies included the comparison of formoterol 12 μg twice daily (or metered dose equivalent) and placebo. Three of these studies (Aalbers 2002; Dahl 2001; Rossi 2002) also included a formoterol 24 μg twice-daily arm. One additional study, Wadbo 2002, used only the comparison of formoterol 24 μg. Most formoterol studies used matching dry powder Turbuhaler devices to deliver blinded study medication. The remaining 11 studies compared salmeterol 50 μg twice daily (or equivalent) with placebo, primarily using blinded Diskus dry powder inhalers. Studies allowed the use of a short-acting $beta_2$-agonist as reliever medication during the study period (salbutamol or terbutaline).

Outcomes and analysis structure

Health-related quality of life measured on the St George's Respiratory Questionnaire (SGRQ) was reported in most of the studies. The SGRQ is a well-validated and widely used measure of health status in patients with chronic airflow limitation; the total score ranges from 0 (perfect health) to 100 (most severe status) and includes three components of symptoms, activity and impacts. Only three of these studies (Bogdan 2011; Brusasco 2003; Kornmann 2011) reported the number of people improving by four or more points on the SGRQ, which is generally accepted to be the minimal clinically important difference. In two studies (Doherty 2012 and Szafranski 2003), variance was not given for the comparison of interest. In these cases, standard deviations of 14.5 were imputed on the basis of population variance and on that of other arms within the studies to increase the number of studies in the analysis. Four additional studies reported quality of life data using the Chronic Respiratory Diseases Questionnaire (CRQ) (Hanania 2003; Mahler 1999; Mahler 2002; Rennard 2001), of which two reported mean change with no measure of variance. All four were analysed separately from the main SGRQ analysis to reduce possible sources of heterogeneity, with missing variances imputed from those reported in Mahler 1999 and Rennard 2001. Because these

four studies all compared salmeterol with placebo and were of three months' and six months' duration, results for the CRQ were not part of the subgroup analyses. Therefore, the quality of life data could be presented in a more clinically meaningful format by using mean differences on the SGRQ scale. For this outcome and predose FEV_1, mean change and endpoint data were analysed together, and footnotes were entered to clarify which data were available.

The second primary outcome, severe COPD exacerbations requiring hospitalisation, was quite poorly reported. Seven studies (nine comparisons) reported this as an outcome, of which five also reported the number of people with one or more moderate COPD exacerbations (those requiring a course of antibiotics or oral steroids). Rennard 2001 and Calverley 2003b [TRISTAN] reported data that could be included in the moderate exacerbations analyses but not hospitalisations. Two additional studies, Mahler 1999 and Nelson 2007, did not explicitly define exacerbations but were included in the moderate exacerbations analysis because rates were more consistent with these rates in other studies. Data for hospitalisations are collated in Analysis 1.4 and for moderate exacerbations in Analysis 1.6.

Seven additional studies reported the overall number of people who had *either* one or more moderate *or* severe exacerbations during the study, and these data are presented separately in Analysis 1.5. Overall, 18 studies reported exacerbation count data that could be included in at least one of these three analyses. Four studies presented no data related to exacerbations (Aalbers 2002; Kornmann 2011; Wadbo 2002; Watkins 2002), and four further studies reported data as rate ratios or yearly patient rates that could not be incorporated with data from the other studies (Calverley 2007 [TORCH]; SLMF4010 2005; Szafranski 2003; Tashkin 2008 [SHINE]).

Mortality was well reported and was missing only in Aalbers 2002, Wadbo 2002 and Watkins 2002. Watkins 2002 did not contribute data to any analysis. Calverley 2007 [TORCH], the largest and longest study, was unique in tracking the status of all participants at endpoint, regardless of how long they stayed in the study. For this reason, the nature and quality of mortality data from this study are likely to differ from those of other studies in the analysis. The number of participants experiencing one or more serious adverse events was reported in slightly fewer studies. Within the six studies that could not be included, one reported only the number of serious cardiac adverse events, and the others reported overall serious and non-serious events combined.

Lung function as measured by predose FEV_1 was not consistently reported. Half of the studies reported data that could be used in meta-analysis as mean change or endpoint scores with corresponding variance. Two studies reported absolute means at endpoint, and all other studies reported mean change from baseline. Two studies reporting change did not report a measure of variance (Calverley 2003a; Tashkin 2012), so standard deviations were imputed by calculating the mean of the change variances from the remaining nine studies.The remaining studies either reported other lung function measures that could not be analysed with predose FEV_1 (e.g. peak expiratory flow, postbronchodilator FEV_1) or did not present the data in a format that could be incorporated in the meta-analysis. Rennard 2001 aimed to detect differences of effect between participants with high or low reversibility, and so the merged results may represent a heterogeneous population that is different from that seen in other studies.

Three trials-Aalbers 2002, Dahl 2001 and Rossi 2002-included two LABA arms that met inclusion criteria for the review, and in these cases, all three arms were included and the placebo arm of each was split in comparison 1. In these cases, the power of the overall analysis is accurate, but the power to detect subgroup differences may be reduced. In comparisons 2, 3 and 4, where LABA doses are split into different analyses, no adjustments were made to the participant totals. When studies reported data at more than one time point of interest, we reported only the duration subgroup totals-not the pooled effect (i.e. data for the same participants were not double counted, but power to detect subgroup differences may be increased). For this reason, slight discrepancies may be evident between a subgroup result in comparison 1 and the corresponding effect in the following comparisons subgrouped by trial duration.

Sensitivity analyses

Use of inhaled corticosteroids (ICS) during the study period

As stated in the protocol, we intended to exclude trials in which more than 50% of participants were taking other COPD medications. Most available data in the study reports related to ICS use during the randomised period, and this was used as a proxy in cases where the preferred data were not available. Ten studies required that other medications, including ICS, were stopped during the run-in. Eight further studies did not explicitly report the proportion of participants taking other medications, and inferences based on pharmacological exclusion criteria could not be made. Hanrahan 2008 reported that 28.6% and 23.9% of participants in the salmeterol and placebo groups, respectively, were taking regular ICS during the study period, and so the study was included. Similarly, Nelson 2007 reported that 33% and 38% of participants in the formoterol and placebo groups were taking COPD medications during the study period that were not part of the randomised interventions. Because ICS use fell just above or just below the predefined 50% threshold in the remaining six studies (Campbell 2005; Dahl 2001; Dahl 2010; Kornmann 2011; Rossi 2002; Vogelmeier 2008), these studies were removed from the primary outcomes in a sensitivity analysis.

Studies at high risk of bias/those with high or uneven withdrawal rates

Because no studies were rated at high risk of bias for either of the selection bias parameters, or for detection or performance bias, a

sensitivity analysis was performed to remove the eight studies that were rated at high risk of bias due to attrition (Dahl 2010; Hanania 2003; Mahler 1999; Mahler 2002; Nelson 2007; Rennard 2009; SLMF4010 2005; Szafranski 2003). Given that high risk judgements in the reporting bias parameter usually were made because studies were already missing from analyses, it was not appropriate to perform a sensitivity analysis on selective outcome reporting. Reporting bias is reflected in the grade ratings of the affected outcomes.

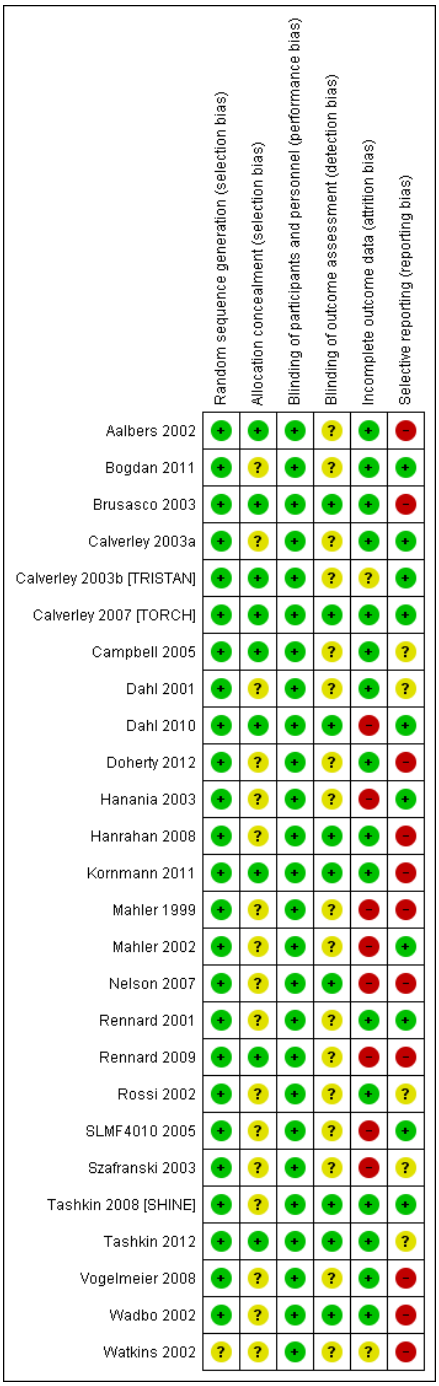
Excluded studies

Details of why studies were excluded from the review, including exact percentages of participants taking additional COPD medications, can be found in Characteristics of excluded studies. Six studies (22 citations) were excluded because a clear majority of the participants were taking other COPD medications (Boyd 1995; Celli 2003; Chapman 2002; Dal Negro 2003; Rutten-van Molken 1999; Stockley 2006). One additional trial (two publications) was excluded because the inclusion criteria allowed for participants with asthma or COPD, and data for diagnostic subgroups were not presented (Steffensen 1996).

Risk of bias in included studies

The methodological quality of the included trials was good. None of the studies were at high risk of selection, performance or detection bias, but there was high risk of bias for attrition in eight studies and selective reporting of outcomes in 11 studies. More detailed descriptions by domain (allocation generation, allocation concealment, blinding and incomplete data) are given below. Details of the risk of bias rating for each study and the reasons for each rating can be found in Characteristics of included studies and a summary of judgements by study and domain can be found in Figure 2. When studies funded by the same company were rated as unclear for one or more domain, we attempted to clarify study methods with the funder.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

None of the included studies were rated as having high risk of bias for either of the two allocation parameters (random sequence generation and allocation concealment).

With the exception of Watkins 2002 (which was not a full trial report and hence was rated as unclear), all of the trials were rated as having low risk of bias for random sequence generation. Although several of the trials did not adequately describe the methods of sequence generation used, the authors agreed that this was likely due to variations in reporting standards. All of the studies were industry sponsored; therefore the authors deemed it reasonable to assume that standardised drug company methods were used (i.e. computerised random list generators).

Nine studies (Aalbers 2002; Brusasco 2003; Calverley 2003b [TRISTAN]; Calverley 2007 [TORCH] Campbell 2005; Dahl 2010; Kornmann 2011; Rennard 2009; Tashkin 2012) fully described methods used for allocation concealment and were thus rated as having low risk of bias. Although some drug companies might have standard protocols for concealing allocation, the authors agreed that studies would be rated as unclear unless the methods used were properly described for this parameter. The remaining 17 studies were rated as unclear for this reason.

Blinding

None of the studies were rated as having high risk of bias for either of the two blinding parameters (participants and personnel, and outcome assessment).

When a study was described as double-blind and no specific details were reported in the original report, trial registrations most often confirmed that the blind applied to participants and investigators. As a result, all trials were rated as having low risk of bias for this parameter. Twelve studies specifically described double-dummy procedures and matched inhalers.

Studies were not rated as having low risk of bias for blinding of outcome assessors unless blinding was explicitly stated in the trial report or the protocol registration. This was the case for only nine of the studies; therefore most were rated as unclear.

Incomplete outcome data

More than half of the included studies were rated as having low risk of bias for this parameter (N = 16), either because dropout was deemed to be low and even between groups, or because dropout was considered acceptable given the methods of imputation described in the report. Two studies were rated as unclear: Calverley 2003b [TRISTAN] had high and even dropout in both arms but did not sufficiently describe the method of imputation to warrant a 'low' rating, and Watkins 2002 provided no information related to attrition. The remaining eight studies were considered to be at high risk of bias, either because dropout was very high in both groups, or because dropout was deemed excessive or uneven given the method of imputation or the analysis method used (i.e. per protocol or completers only).

Selective reporting

Twenty studies could be linked with their protocol registration on clinicaltrials.gov or with their industry report, allowing comparison of prespecified outcomes with published or unpublished results. Of these, ten reported all stated outcomes in a way that allowed them to be combined in meta-analysis (Bogdan 2011; Calverley 2003a; Calverley 2003b [TRISTAN]; Calverley 2007 [TORCH]; Dahl 2010; Hanania 2003; Mahler 2002; Rennard 2001; SLMF4010 2005; Tashkin 2008 [SHINE]). Five studies that could not be linked to their trial registration documents but did not show clear evidence of selective outcome reporting were rated as unclear (Campbell 2005; Dahl 2001; Rossi 2002; Szafranski 2003; Tashkin 2012). Eleven studies were rated as having high risk of bias either because outcomes that were stated in the protocol were not reported in sufficient detail in the results, or because key outcomes expected in COPD trials were not included, regardless of whether they were named in a protocol (e.g. mortality, adverse events, exacerbations).

Funnel plots were constructed for the primary outcomes. Figure 3 is not suggestive of any serious publication bias of the SGRQ. However, some evidence suggests a small study effect on severe exacerbations (those resulting in hospitalisation), which might be due to publication bias, as shown in Figure 4.

Figure 3. Funnel plot of comparison: 1 All LABA versus placebo [subgrouped by drug], outcome: 1.1 Quality of life (SGRQ total score).

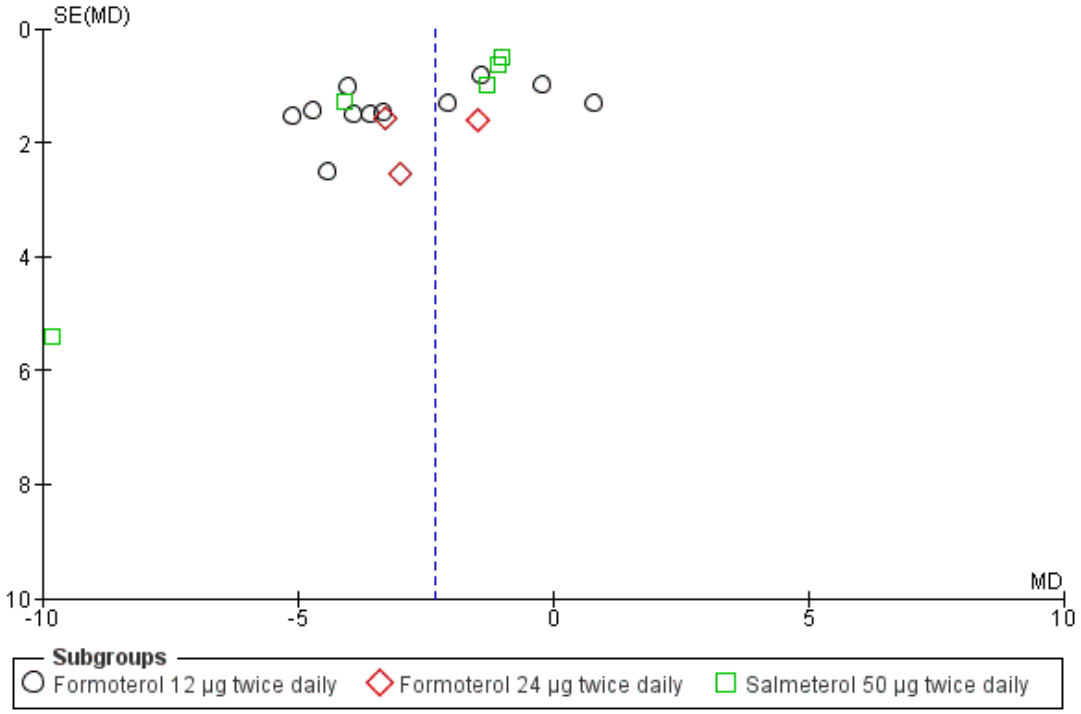
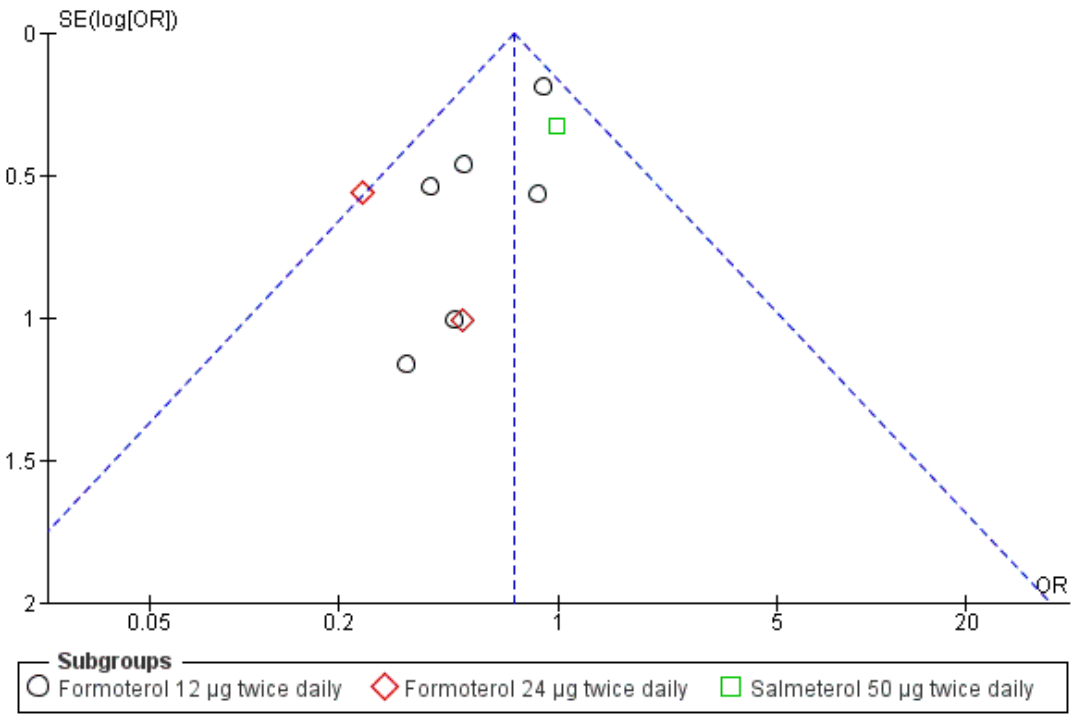


Figure 4. Funnel plot of comparison: 1 All LABA versus placebo [subgrouped by drug], outcome: 1.4 Severe exacerbations (hospitalisations).



Other potential sources of bias

No other sources of bias were identified in the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Long-acting beta$_2$-agonists compared with placebo for chronic obstructive pulmonary disease

Full details of the analyses and their GRADE ratings can be found in Data and analyses and Summary of findings for the main comparison. The first comparison presents results for all outcomes, with studies subgrouped according to the type and dose of LABA. Comparisons 2, 3 and 4 show results for formoterol 12 μg, formoterol 24 μg and salmeterol 50 μg, respectively (all twice daily), subgrouped according to study duration. The final comparison presents data for the two primary outcomes, excluding six studies in which relatively large proportions of the population were taking regular COPD therapies other than the study medication (see '*Use of inhaled corticosteroids (ICS) during the study period*' in Included studies).

Primary outcomes

Health-related quality of life

Improvement on the St George's Respiratory Questionnaire (SGRQ) was greater with LABA therapy than with placebo (MD -2.32, 95% CI -3.09 to -1.54; I^2 = 50%, P = 0.007; Analysis 1.1), based on data from 11,397 people in 17 studies. Results were analysed using a random-effects model because heterogeneity was high, and the outcome was downgraded from high to moderate quality for this reason. Heterogeneity could not be explained by differences between the effects of LABA drug and dose (test for subgroup difference, I^2 = 0%, P = 0.45). The difference between LABA and placebo was significant for all three LABA agents separately, but important heterogeneity was noted within the formoterol 12 μg and salmeterol 50 μg subgroups (I^2 = 57% and 48%, respectively).

More people taking a LABA showed clinically important improvement of at least four points on the SGRQ (OR 1.58, 95% CI 1.32 to 1.90; I^2 = 86%, P = 0.0007; Analysis 1.2) based on 1871 people in three studies. Data were insufficient to allow conclusions regarding the difference between formoterol and salmeterol.

Four salmeterol studies reporting the Chronic Respiratory Dis-

ease Questionnaire (CRQ) were analysed separately and showed a significant benefit of LABA therapy (MD 3.10, 95% CI 1.22 to 4.98; I^2 = 0%, P = 0.58; Analysis 1.3) with no heterogeneity. Because so few trials reported the CRQ and the number of people achieving a minimally clinically important difference (MCID) on the SGRQ of 4 units, we did subgroup and sensitivity analyses on the SGRQ continuous data only.

A test for subgroup differences suggested that some of the heterogeneity within the 12 trials which randomised people to either formoterol or placebo may be explained by differences in study duration (I^2 = 75%, P = 0.02; Analysis 2.1). The effect of twice-daily formoterol 24 μg was significant when analysed separately but lacked precision because only three studies compared the dose with placebo (MD -2.32, 95% CI -4.52 to -0.13; I^2 = 0%, P = 0.76; Analysis 3.1). No difference was detected between the two three-month trials (Dahl 2001; Wadbo 2002) and the year-long Rossi 2002 study. With so few studies, no heterogeneity was evident between or within subgroups. Unlike the formoterol 12 μg analysis, trial duration did not appear to be an important source of heterogeneity in the salmeterol included trials (I^2 = 0%, P = 0.41; Analysis 4.1).

The overall pooled effect and drug subgroup effects were largely consistent with the original analysis after removal of five studies identified as having a high proportion of ICS use during the trial (see Included studies-*Use of inhaled corticosteroids (ICS) during the study period).* The magnitude of improvement due to LABA therapy was reduced after the studies were removed, but somewhat tighter confidence intervals and less between-study heterogeneity were noted (MD -1.53, 95% CI -2.08 to -0.98; I^2 = 34%, P = 0.12; Analysis 5.1).

Four of the eight studies rated as having high risk of bias reported the SGRQ: three from the formoterol 12 subgroup and one from the salmeterol subgroup. After these studies were removed, the pooled difference between LABA and placebo remained significant but was again reduced (MD -1.60, 95% CI -2.15 to -1.05; I^2 = 42%, P = 0.04; Analysis 6.1).

Severe COPD exacerbations (requiring hospitalisation)

When data from seven studies were combined (nine comparisons), the number of people hospitalised for COPD exacerbations was lower among LABA-treated participants than in those receiving placebo (OR 0.73, 95% CI 0.56 to 0.95; Analysis 1.4). Although little evidence was found for explicit selective outcome reporting within trials, the outcome was downgraded for publication bias and was rated as having moderate quality; more than half of the studies did not report the outcome of high interest to patients and clinicians, and the estimate might have been different if all studies could have been included in the analysis (see Included studies-*Outcomes and analysis structure*). No heterogeneity was noted between trials, and the results of a test for subgroup differences between drugs/doses were not significant (I^2 = 57.5%, P = 0.10).

No evidence of a statistically significant effect of trial duration was observed in the formoterol 12 μg trials (six studies across three duration subgroups). Similarly, no significant difference was observed between the three-month Dahl 2001 study and the 12-month Rossi 2002 study comparing formoterol 24 μg with placebo. Only one six-month study comparing salmeterol and placebo reported hospitalisation rates, so no assumptions could be made regarding relative effects of trial duration.

The pooled effect of LABA *versus* placebo decreased in magnitude and was no longer significant after four studies with a high percentage of participants taking inhaled corticosteroids (six comparisons) were removed. This effect was based on only three remaining trials (OR 0.85, 95% CI 0.62 to 1.16; Analysis 5.2), and the change in effect could be explained by another variable. None of the eight studies rated as having high risk of bias reported the number of participants with exacerbations requiring hospitalisation, so the outcome does not appear in the sensitivity analysis.

Secondary outcomes

Moderate COPD exacerbations (requiring a course of antibiotics *and/or oral steroids)*

LABA treatment reduced the number of people who had one or more exacerbations requiring a course of antibiotics, oral steroids or both compared with placebo (OR 0.73, 95% CI 0.61 to 0.87; I^2 = 8%, P = 0.37; Analysis 1.6), with minimal heterogeneity. The quantity of data for the outcome was similar to that provided for severe COPD exacerbations, so the outcome was downgraded for publication bias for the same reasons and was rated as having moderate quality. No evidence suggested important subgroup differences on the basis of which LABA/dose was used (I^2 = 0%, P = 0.68). The three studies that compared formoterol 12 μg with placebo showed no significant benefit (OR 0.78, 95% CI 0.56 to 1.07; I^2 = 7%, P = 0.34; Analysis 2.3) with little heterogeneity, and no evidence was found of differential effectiveness related to study duration. The higher-dose formoterol 24 μg did show a significant reduction relative to placebo (OR 0.57, 95% CI 0.38 to 0.88; Analysis 3.3), although this was based on a total of 124 events in one study (Rossi 2002). Four studies that compared salmeterol with placebo showed an overall reduction in moderate exacerbations with the study drug (OR 0.75, 95% CI 0.60 to 0.94; I^2 = 40%, P = 0.17; Analysis 4.3), with some non-significant heterogeneity and no observed differences related to study duration.

Moderate/severe COPD exacerbations (requiring hospitalisation *or a course of antibiotics/oral steroids or ER visit)*

Around half of the studies did not report rates of moderate and severe COPD exacerbations as separate outcomes, as we had defined in the protocol, but rather reported a composite rate, which could not be combined with the other data; therefore we decided to present these data separately in the review. As with the other two exacerbation outcomes, the outcome was rated of moderate quality after it was downgraded for publication bias.

LABA treatment did not significantly reduce the number of people with moderate or severe exacerbations compared with placebo (OR

0.88, 95% CI 0.76 to 1.02; I^2 = 0%, P = 0.80; Analysis 1.5), as determined on the basis of seven studies with 1142 participants. No between-study or between-drug heterogeneity was observed. Since the outcome was added, post hoc and subgroup analyses have been reported for the other two exacerbation outcomes, and we did not perform separate subgroup analyses of trial duration for this outcome.

Mortality; all-cause

Study deaths were relatively uncommon; therefore the analyses were conducted using Peto odds ratio, as this method does not require adjustment for zero cells. LABA treatment did not significantly reduce mortality compared with placebo (OR 0.90, 95% 0.75 to 1.08; I^2 = 21%, P = 0.21; Analysis 1.7), and a degree of between-study heterogeneity was noted. The outcome was downgraded for imprecision and was rated as having moderate quality because the confidence intervals for the pooled effect included important benefit and potential harm. A test for subgroup differences between drugs was not statistically significant (I^2 = 55%, P = 0.11). Results of a test for subgroup differences related to the duration of the formoterol trials were not significant (Analysis 2.4). In the two formoterol 24 μg trials that reported all-cause mortality, only one death occurred in the LABA group of Rossi 2002; the confidence intervals were too wide to allow interpretation of direction or magnitude of effects (Analysis 3.4) or assumptions based on trial length. Four studies with no events did not contribute to the salmeterol analysis (Analysis 4.4), and the effect was largely influenced by the large Calverley 2007 [TORCH] study (93% of total weight). This large study was unique because it was much longer than the other trials (at three years), and investigators logged mortality for all participants, regardless of how long they stayed in the study. Between-trial heterogeneity was not significant in the salmeterol analysis (I^2 = 29%, P = 0.22); a test for subgroup differences regarding trial duration also was not significant (I^2 = 0%).

Non-fatal serious adverse events; all-cause

All studies included in the analysis reported this outcome with participants as the level of analysis (i.e. number of people who had serious adverse events as opposed to the number of adverse events in total). When findings of all studies were pooled, no difference was observed between LABA and placebo (OR 0.97, 95% CI 0.83 to 1.14; I^2 = 34%, P = 0.06; Analysis 1.8). Heterogeneity was significant at P = 0.1, and unexplained differences between the two formoterol doses showed opposite directions of effect. A test for subgroup differences indicated that some of the heterogeneity may be explained by these differences in individual drugs/doses, which were significant (I^2 = 83%, P = 0.002). It is unclear whether formoterol 12 μg significantly increases rates of serious adverse events, as the confidence interval touched the line of no effect (OR 1.20, 95% CI 1.00 to 1.43; I^2 = 14%, P = 0.32; Analysis 2.5), and differences in trial duration were not statistically significant. Three formoterol 24 μg studies showed that serious adverse events were lowered by LABA use (OR 0.53, 95% CI 0.36 to 0.79; I^2 = 0%, P = 0.67; Analysis 3.5) with no significant heterogeneity, although confidence intervals were quite wide. Studies that compared salmeterol 50 μg with placebo showed no significant differences between groups (OR 0.94; 95% CI 0.83 to 1.06; I^2 = 13%, P = 0.33; Analysis 4.5) based on nine studies with 1608 events. Some statistically insignificant heterogeneity between trial results was noted and could not be explained by reliable differences in trial duration.

Predose forced expiratory volume in one second (trough FEV_1)

The predose FEV_1 of participants taking LABA was 73 mL higher at the end of the trials than that of participants taking placebo inhalers (95% CI 48 to 98; I^2 = 71%, P < 0.0001; Analysis 1.9); this finding was based on data from 6125 participants in thirteen studies that reported the outcome. A large degree of heterogeneity was noted, so the analysis was downgraded for inconsistency. Half of the studies did not report the outcome or reported the outcome in a way that could not be entered in meta-analysis; therefore it was downgraded for publication bias and was rated as having low quality. A test for subgroup differences suggested that the heterogeneity may be accounted for by differences between formoterol 12 μg and salmeterol 50 μg (no formoterol 24 studies reported trough FEV_1) (I^2 = 84%, P = 0.01). Individually, formoterol 12 μg (MD 45 mL, 95% CI 29 to 60) and salmeterol 50 μg (MD 101 mL, 95% CI 60 to 142) were associated with improved predose FEV_1 relative to placebo.

No heterogeneity was observed between the formoterol 12 μg studies (I^2 = 0%, P = 0.57), and no observable differences related to trial duration were reported. In the salmeterol 50 μg studies, heterogeneity was substantial (I^2 = 69%, P = 0.003), and a test for subgroup differences of study duration suggested that the benefits of LABA treatment over placebo become less distinct over time (I^2 = 87%, P = 0.0005; Analysis 4.6). Some of the heterogeneity may have been introduced by within-subgroup variation in the recruited populations. For example, Rennard 2001 split the population by high and low reversibility to compare the effects of salmeterol on different participant groups, and the data entered into the analysis represent the population as a whole.

Withdrawal from study treatment

Withdrawal rates were higher for placebo than for LABA treatment (OR 0.74, 95% CI 0.69 to 0.80; I^2 = 0%, P = 0.75; Analysis 1.10), as determined on the basis of data from all studies except Watkins 2002. The formoterol 24 μg studies contributed the least data to the analysis and showed no difference between LABA and placebo, although subgroup differences between drugs and doses were not significant (I^2 = 0%, P = 0.66). No heterogeneity between trials was noted, and no evidence showed significant subgroup differences between dose categories. No clear effects of trial duration were evident.

DISCUSSION

Summary of main results

Twenty-six studies including nearly 15,000 people with moderate to severe COPD were included in the review. Participants in the studies were more often male with mean baseline FEV_1 between 33% and 55% predicted normal and mean SGRQ ranging from 44 to 55.

LABA treatment significantly improved quality of life and reduced hospitalisations relative to placebo, although unexplained variation was noted within the quality of life data. Exacerbations were not consistently defined in trials, but across three definitions (those leading to hospitalisation, requiring a course of antibiotics or steroids or either), good evidence suggested that LABA therapy was effective. In terms of adverse events, no significant difference was observed in rates of mortality or serious adverse events between LABA and placebo.

Most subgroup differences between drugs and between dose groups were not significant. Significant differences in serious adverse events data were complicated by the unexplained disparity of effect direction for the two formoterol doses, and the difference in FEV_1 between formoterol and salmeterol is complicated by substantial heterogeneity within the salmeterol studies for that outcome. Systematic differences between drug company methodology and recruitment procedures may preclude comparisons between salmeterol and formoterol.

Participants were more likely to withdraw from placebo than from LABA therapy (OR 0.74, 95% CI 0.69 to 0.80; I^2 = 0%), although sensitivity analyses removing studies at highest risk of bias for this reason did not change conclusions for the primary outcomes.

Overall completeness and applicability of evidence

The current review expanded and updated a previous Cochrane review that looked only at patients with poorly reversible COPD (Appleton 2006). Because the inclusion criteria were widened to include all patients with a diagnosis of COPD, findings are likely to apply to a larger group of patients for whom LABA therapy is indicated. Trials were largely consistent in their inclusion of moderately to severely affected participants, as confirmed through smoking and medication history and spirometric indices.

Because of variation in study protocols regarding the use of other COPD medications, it is difficult to accurately judge to which groups of patients the evidence accurately applies. However, the sensitivity analysis removing studies in which a large proportion of participants were taking other COPD medications goes some way to dispel this uncertainty, given that results were very similar to those of the original pooled analysis. Similarly, systematic differences may be noted between trials of salmeterol and those of formoterol because different manufacturers conducted most of the trials for these two drugs. However, analysis of descriptive statistics for the baseline measurements showed that the populations recruited to trials of salmeterol were similar to those enrolled in the formoterol trials (percentage reversibility and percentage predicted FEV_1). Outlier studies (those recruiting unusually severe or mild participants) may still have introduced heterogeneity within analyses, and differences may have been masked by inconsistent reporting of severity metrics across the data set and the lack of individual participant data. Additionally, significantly higher withdrawal in the placebo groups is likely to be due primarily to lack of efficacy leading to protocol violations (Calverley 2003). This may have reduced the effectiveness of randomisation and decreased the magnitude of difference between groups by removing from the analysis participants with the most severe conditions who had been assigned to placebo.

Only three trials tested the higher dose of formoterol (24 μg twice daily) against placebo, of which two also included an arm that received the more commonly prescribed 12 μg dose. The higher dose is the maximum indicated by the British National Formulary (BNF) for additional symptom relief (BNF 2009), and, in this sense, the tendency for trials to use the lower dose is consistent with licensing and practice. Similarly, the use of 12 μg twice daily is consistent and hence comparable with the dose received through combination preparations of budesonide and formoterol. In addition, little variation in inhaler devices was seen within the formoterol or salmeterol studies, with most formoterol studies using masked Turbuhaler devices, and most salmeterol trials using the Diskus. However, fact that inhaler devices differed fairly systematically between the two drugs may have contributed to subgroup differences.

It is unclear whether unpublished trials are missing from the review or, in some cases, whether all data are reported in the available papers and unpublished industry summaries. Attempts to ascertain with GlaxoSmithKline, AstraZeneca and Novartis whether all conducted studies and measures within them were included were not fruitful in time for publication.

Quality of the evidence

The methodological quality of the included trials was good, and the single conference abstract of unknown quality did not contribute any data to the analysis. All studies were double-blind, and so results are unlikely to be compromised by detection or performance biases. Similarly, most studies controlled adequately for selection bias or were presumed to do so, in accordance with industry protocol. Although evidence suggested bias from high and unbalanced attrition in some trials and significantly higher withdrawal in the placebo arm when analysed, sensitivity analyses showed that conclusions did not change when studies at highest risk of bias were removed from the primary outcomes. It is possible that higher attrition in the placebo group across many of the trials could have diluted the true difference between LABA and placebo for some outcomes; if we accept that people who drop out of studies have a less positive outcome than those who do not, the

placebo estimate could appear more favourable than if everyone had contributed endpoint data, depending on the method used to impute values for missing data points (i.e. last observation carried forward or other imputation models).

As described above, some evidence of selective reporting bias was found, both within trials that failed to report key outcomes or those stated in the prospectively registered protocols, and in terms of the possibility that trials (industry funded or independent) may remain unpublished (Song 2010). Several studies did not report exacerbations or trough FEV_1 in a way that could be included in the review, so additional evidence obtained in future studies might change our confidence in these results.

Most studies were sponsored by drug companies, and they generally were of good quality. A lot of variation between studies was noted in the effect of LABA inhalers on quality of life, serious side effects and lung function. Although studies with around half of people taking additional medications were removed in a sensitivity analysis, the variation in allowed co-medications and the numbers taking them may explain some of the variation in reported findings.

Potential biases in the review process

Review authors made every effort to identify all relevant published and unpublished studies by using additional methods to catch anything that might not have been found in the main electronic search (e.g. searching drug company databases and clinical trial registration sites, checking reference lists). However, attempts to obtain data directly from drug companies were not successful, and we did not routinely contact individual trial authors for additional data unless outcomes were clearly selectively reported. Unpublished studies (industry funded or otherwise) may exist that might change our confidence in the conclusions. All authors adhered to the most recent best practice guidelines in terms of study selection, resolution of disagreements, data extraction and analysis to reduce bias and errors.

Agreements and disagreements with other studies or reviews

Five previous reviews were identified that specifically analysed LABA versus placebo. Results of this review were consistent with results for salmeterol 50 μg as reported in the previous Cochrane review specifically looking at patients with poorly reversible COPD (Appleton 2006). Specifically, benefit was associated with twice-daily salmeterol 50 μg in terms of FEV_1, quality of life and exacerbations. This review found that formoterol 12 μg also improves these outcomes-a fact that was previously unclear. The benefits of formoterol 24 μg remain unclear, and salmeterol 100 μg was not included in the current review, as this dose is not recommended in current clinical practice.

Kliber 2010 concluded that mortality was not significantly reduced by LABA therapy, and this conclusion was consistent with this review, despite some differences in trial inclusion criteria. Similarly, Rodrigo 2008 found comparable benefits of LABA on exacerbation frequency, spirometry and quality of life, and again, no significant effect on mortality.

Upon looking solely at salmeterol, Stockley 2006a found that study participants were less likely to withdraw when taking the study drug than when taking placebo, and that key efficacy measures were improved at three, six and 12 months.

Wang 2012 concluded that formoterol did not improve exacerbations unless used in conjunction with inhaled corticosteroids. However, Wang 2012 did not include trials of less than six months, excluded small trials and included trials of indacaterol, which may explain why the results differ.

AUTHORS' CONCLUSIONS

Implications for practice

This review and meta-analysis provide moderate-quality evidence that inhaled long-acting $beta_2$-agonists are effective over medium and long term for use in patients with moderate or severe COPD. Excluding trials in which about half of people were receiving ongoing treatment with inhaled corticosteroids or other medications for COPD gave similar effect estimates and reduced variation in the results. LABA therapy is associated with improved patient quality of life and reduced exacerbations, including those requiring hospitalisation. Overall, it was found that inhaled LABAs did not significantly reduce mortality or serious adverse events.

Implications for research

More consistent reporting of exacerbations in clinically and financially meaningful categories is needed (i.e. those requiring hospitalisation as distinct from those requiring changes to medication). We have found plenty of evidence for the comparison between the LABAs salmeterol and formoterol and placebo in relation to quality of life, and we would not suggest that any further research is needed. However, for new and emerging LABAs (such as indacaterol), trials will be needed to determine whether they are safe, effective and cost-effective. Future clinical trials on LABAs in COPD should focus on head-to-head comparisons with other long-acting agents.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aalbers 2002

Methods	**Design**: randomised, multi-centre, double-blind, parallel-group study **Duration**: 3 months (+ 2 weeks run-in period) **Location**: The study took place in 86 centres in nine countries (Australia, Belgium, Denmark, Germany, Hungary, The Netherlands, Norway, Poland and UK)
Participants	**Population**: 516 participants were randomly assigned to formoterol 12 μg twice daily (166), formoterol 24 μg twice daily (177) and placebo (173) **Baseline characteristics**: Mean age (years): formoterol 12 μg, 63.3; formoterol 24 μg, 61.9; placebo, 61.8 % Male: formoterol 12 μg, 71.7; formoterol 24 μg, 69.5; placebo, 65.3 % Reversibility: formoterol 12 μg, 5.8; formoterol 24 μg, 6.5; placebo, 6.7 % FEV_1 predicted: formoterol 12 μg, 54.5; formoterol 24 μg, 54.7; placebo, 53.8 **Inclusion criteria**: male or female current or former smokers with a history of at least 10 pack-years and a clinical diagnosis of COPD Prebronchodilator FEV_1 had to be > 0.7 L and 40% to 70% of predicted, FEV_1/forced vital capacity (FVC) ratio < 89% pred normal for females and < 88% for males and the total symptom score had to be 2 or greater on at least 7 days of the run-in period **Exclusion criteria**: history of asthma or seasonal rhinitis before age 40; current respiratory tract disorder other than COPD; significant or unstable heart disease; other significant gastro, hepatic, renal or endocrine disease
Interventions	• Formoterol 12 μg twice daily • Formoterol 24 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: terbutaline (0.5 mg), prednisolone (10 mg), methylprednisolone (8 mg) and betamethasone (1 mg) were allowed during the study period. Excluded medications included inhaled and oral $beta_2$-agonists, inhaled anticholinergics, xanthine derivatives, leukotriene antagonists, ephedrine and parenteral glucocorticosteroids
Outcomes	**Lung function**: FEV_1, FVC and dyspnoea (TDI) **Adverse events**: non-fatal serious adverse events **Other**: withdrawal, symptom scores and % of symptom-free days, shuttle walking test, use of relief medication
Notes	**Funding**: AstraZeneca **Study number**: unknown **Definitions**: none (exacerbations not reported)

Risk of bias

Bias	Authors' judgement	Support for judgement

Aalbers 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to the four treatments in balanced blocks using a computer-generated schedule after completing the run-in period
Allocation concealment (selection bias)	Low risk	Individually sealed treatment codes indicating the allocated treatment for each participant were available at each clinic for emergency situations
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study-all inhalers used in the study were of identical appearance, and active and placebo inhalers were indistinguishable in taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment were found
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were similar and below 20% in each group (formoterol 12 μg 18.1%, formoterol 24 μg 15.3%, placebo 15.6%)
Selective reporting (reporting bias)	High risk	Results for all specified outcomes were reported, but key outcomes expected for COPD were omitted (HRQoL, exacerbations, mortality)

Bogdan 2011

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group, multinational phase III study **Duration**: 3 months (+ 2 weeks run-in period) **Location**: 65 centres in Japan, Romania, Russia and Ukraine
Participants	**Population**: 407 participants were randomly assigned to formoterol 12 μg twice daily (199) and placebo (208) **Baseline characteristics**: Mean age (years): formoterol 12 μg, 66.7; formoterol 24 μg, 67.2; placebo, 66.3 % Male: formoterol 12 μg, 85.4; placebo, 89.4 % White: formoterol 12 μg, 45.7; placebo, 47.1 % Reversibility: formoterol 12 μg, 10.7; placebo, 11.3 Pack-years: formoterol 12 μg, 46.5; placebo, 47.4 % FEV_1 predicted: 50.4; formoterol 12 μg, 51.5; placebo, 52.5 **Inclusion criteria**: > 40 years old; clinical diagnosis of COPD (postbronchodilator FEV_1 < 80% predicted, and postbronchodilator FEV_1/FVC < 70%); history of at least 10 pack-years; symptom score of at least 2 points on at least 6 of the last 10 days of the run-

	in period **Exclusion criteria**: history of asthma; history of clinical diagnosis of atopic disease such as allergic rhinitis; significant or unstable ischaemic heart disease or other cardiovascular conditions, other respiratory tract disorders or significant disease
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: salbutamol (100 μg pMDI) and short-acting anticholinergics were allowed as rescue medication. Excluded medication included long-acting anticholinergics and glucocorticoid treatment (including inhaled corticosteroids)
Outcomes	**HRQoL**: St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: number requiring hospitalisation and/or a course of antibiotics and/or systemic steroid therapy **Lung function**: change (ratio) from baseline to end of treatment period in FEV_1 60 minutes postdose, FVC 60 minutes postdose, FEV_1 and FVC predose and 5 minutes postdose **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, use of salbutamol as reliever medication (measured as inhalations/day), COPD symptom scores (night-time awakenings due to symptoms, breathlessness and cough)
Notes	**Funding**: AstraZeneca **Study number**: AstraZeneca ID D5122C00001; registration NCT00628862 **Definitions**: Exacerbations were defined as requiring hospitalisation and/or a course of antibiotics and/or systemic steroid therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment. No details of sequence generation methods but assumed to adhere to usual AstraZeneca methods
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial registration states masking was double-blind for subject, caregiver and investigator
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was uneven but relatively low in all groups (formoterol 12, 8.5%; placebo, 10.6%)
Selective reporting (reporting bias)	Low risk	Checked paper against protocol. Results for all specified outcomes were reported and could be included

Brusasco 2003

Methods	**Design**: pooled results from two randomised, double-blind, double-dummy, parallel-group design 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 randomly assigned to salmeterol 50 μg twice daily (405) and placebo (400) **Baseline characteristics**: Mean age (years): salmeterol, 64.1; placebo, 64.6 % Male: salmeterol, 75.1; placebo, 76.3 Pack-years: salmeterol, 44.8; placebo, 42.4 % FEV_1 predicted: salmeterol, 37.7; placebo, 38.7 **Inclusion criteria**: Participants were required to have relatively stable airway obstruction with FEV_1 < 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	• Salmeterol 50 μg twice daily • Combination of salmeterol and tiotropium placebos **Inhaler device**: dry powder inhaler **Co-medication**: 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
Outcomes	**HRQoL**: mean change from baseline on the SGRQ and number whose score decreased by at least 4 units **COPD exacerbations**: number of exacerbations, number of exacerbation days, percentage of participants with at least one COPD exacerbation, time to first COPD exacerbation, hospital admissions for any reason and for an exacerbation, days hospitalised,

	percentage of participants with at least one hospital admission for a COPD exacerbation, time to first hospital admission due to a COPD exacerbation **Lung function**: FEV_1, FVC, dyspnoea (evaluated using the Baseline Dyspnoea Index (BDI) and the TDI) **Adverse events**: all-cause mortality **Other**: withdrawal, non-scheduled contacts with physicians and other healthcare providers (use of the intensive care unit), disability days (days unable to perform daily activities) and employment status
Notes	**Funding**: Boehringer Ingelheim **Study number**: Boehringer Ingelheim 205.130/205.137 **Definitions**: Exacerbations were defined as a complex of respiratory symptoms (new onset or an increase in at least one of cough, sputum, dyspnoea, wheeze or chest discomfort) lasting at least 3 days and usually associated with a therapeutic intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated by Boehringer Ingelheim with the use of 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 participant was identified by a unique medication number. Each eligible participant was assigned the lowest medication number available to the investigator at the time of randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Boehringer Ingelheim was responsible for preparing and coding study medication in a blinded fashion (Boehringer Ingelheim study drug and control were indistinguishable). Participants, investigators and study personnel remained blinded with regard to treatment assignments up to database lock. Double-dummy technique was used to blind different application devices
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In all studies, a selection of standard respiratory endpoints, such as pulmonary function, SGRQ, TDI, treadmill, exacerbations, etc., were used. Outcome assessors remained blinded with regard to treatment assignments up to database lock

Brusasco 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were relatively even between groups (salmeterol, 18.8%, placebo, 25.8%)
Selective reporting (reporting bias)	High risk	FEV_1 [secondary outcome] was not reported in a way that could be included in the qualitative synthesis, and no data were reported for serious adverse events

Calverley 2003a

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group study **Duration**: 12 months (+ 2 weeks run-in period) **Location**: 109 centres in 15 countries or regions
Participants	**Population**: 511 participants were randomly assigned to formoterol 12 μg twice daily (255) and placebo (256) **Baseline characteristics**: Mean age (years): formoterol 12 μg, 63; placebo, 65 % Male: formoterol 12 μg, 75; placebo, 75 % Reversibilty: formoterol 12 μg, 6.0; placebo, 6.0 Pack-years: formoterol 12 μg, 38; placebo, 39 % FEV_1 predicted: formoterol 12 μg, 36; placebo, 36 % taking ICS: formoterol 12 μg, 0; placebo, 0 **Inclusion criteria**: Males and females > 40 years old; history of at least 10 pack-years; COPD for at least 2 years; < 70% FEV_1/FVC, FEV_1 < 50% predicted; 1+ COPD exacerbations requiring medication in previous 2 to 12 months **Exclusion criteria**: history of asthma or seasonal allergic rhinitis before age 40; any relevant cardiovascular disorders or other disease
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: 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	**HRQoL**: St Georges Respiratory Questionnaire (SGRQ) **COPD exacerbations**: number of 'severe' exacerbations, time to first severe exacerbation and mild exacerbations **Lung function**: FEV_1, FVC, morning and evening PEF **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, diary cards, rescue medication use, use of antitussives and other COPD medication, symptom scores, night-time awakenings due to COPD, healthcare contacts and sick leave related to COPD

Calverley 2003a (*Continued*)

Notes	**Funding**: AstraZeneca **Study number**: AZ study ID SD-039-0670 **Definitions**: 'Severe' exacerbations were defined as intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms (coded as severe and moderate in the review); 'mild' exacerbations were described as the number of days with intake of 4 or more puffs of rescue medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment. No details of sequence generation methods but assumed to adhere to usual AstraZeneca methods
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study reported as double-blind (participants and investigators)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal even but high in both groups (formoterol, 43.5%; placebo, 41.4%). An intention-to-treat analysis was used for all hypothesis testing
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported and could be included. Only an inexact P-value was given for quality of life [primary outcome], which was included as an approximation in the analysis

Calverley 2003b [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 (Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Lithuania, The Netherlands, New Zealand, Norway, Poland, Russia, South Africa, Spain, Sweden, Switzerland and United Kingdom)

Calverley 2003b [TRISTAN] (*Continued*)

Participants	**Population**: 733 participants were randomly assigned to salmeterol 50 μg twice daily (372) and placebo (361) **Baseline characteristics**: Mean age (years): salmeterol, 63.2; placebo 63.4 % Male: salmeterol, 70; placebo, 75 % Reversibilty: salmeterol, 3.7; placebo, 4.0 % White: salmeterol, 99; placebo, 98 Pack-years: salmeterol, 43.7; placebo, 43.4 % FEV_1 predicted: salmeterol, 44.3; placebo, 44.2 **Inclusion criteria**: $\geq$ 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) $FEV_1 \geq 25\%$ to $\leq 70\%$ of predicted normal; poor reversibility of airflow obstruction (defined as an increase < 10% of predicted normal FEV_1 value 30 minutes after inhalation of 400 μg salbutamol) and FEV_1/forced vital capacity (FVC) ratio $\leq 70\%$ **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	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: 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	**HRQoL**: Health status was assessed with St George's Respiratory Questionnaire **COPD exacerbations**: acute exacerbations (see notes) **Lung function**: FEV_1 (at least 6 hours after medication), pretreatment FVC and post-bronchodilator FEV_1 and FVC, morning PEF **Adverse events**: any adverse event, non-fatal serious adverse event and all-cause mortality **Other**: withdrawal, diary cards recording use of relief medication, symptom scores and night-time awakenings
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SFCB3024 **Definitions**: Exacerbations were defined as worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids or both (coded as moderate for this review). Episodes that required corticosteroid treatment or hospital admission were noted separately

Risk of bias

Bias	Authors' judgement	Support for judgement

Calverley 2003b [TRISTAN] (*Continued*)

Random sequence generation (selection bias)	Low risk	We used a randomisation schedule generated by the Patient Allocation for Clinical Trials (PACT) programme to assign participants to study treatment groups
Allocation concealment (selection bias)	Low risk	Every participating centre was supplied with a list of participant numbers (assigned to participants at their first visit) and a list of treatment numbers. Participants who satisfied eligibility criteria were assigned the next sequential treatment number from the list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs were labelled to ensure that both the participant and the investigator were unaware of the allocated treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal relatively even but high in both groups (salmeterol, 32.0%, placebo, 38. 8%); the intent-to-treat (ITT) population, consisting of all participants who were randomly assigned 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 and could be included in the meta-analysis

Calverley 2007 [TORCH]

Methods	**Design**: a multi-centre, randomised, double-blind, parallel-group, placebo-controlled study **Duration**: 36 months (+ 3 weeks run-in period) **Location**: 466 centres in 42 countries comprising 190 centres in USA, 134 centres in Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom), 46 centres in Eastern Europe (Bulgaria, Croatia, Czech Republic, Hungary, Estonia, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine), 37 centres in Asia Pacific (China, Hong Kong, Malaysia, Philippines, Singapore, Taiwan, Thailand) and 59 centres in other regions (Australia, New Zealand, South Africa, Canada, Argentina, Brazil, Chile, Mexico)
Participants	**Population**: 3087 participants were randomly assigned to salmeterol 50 μg twice daily (1542) and placebo (1545) **Baseline characteristics**: Mean age (years): salmeterol, 65.1; placebo, 65.0 % Male: salmeterol, 76.3; placebo, 76.3 % White: salmeterol, 82; placebo, 82 Pack-years: salmeterol, 49.3; placebo, 48.6 % FEV_1 predicted: salmeterol, 43.6; placebo, 44.1 **Inclusion criteria**: male or female current or former smokers; history of at least 10 pack-years; clinical diagnosis of COPD; aged 40 to 80 years inclusive, with pre-bronchodilator FEV_1 < 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 $alpha_1$-antitrypsin; exacerbation during run-in period
Interventions	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Ventolin as relief, inhaled long-acting bronchodilators and long-term oral corticosteroids (theophyllines long- and short-acting, SABAs and short-acting 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	**HRQoL**: assessed by St. George's Respiratory Questionnaire **COPD exacerbations**: rates of moderate and severe COPD exacerbations **Lung function**: adjusted mean change FEV_1 **Adverse events**: all-cause mortality, non-fatal serious adverse events **Other**: withdrawal
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SCO30003; trial registration NCT00268216 **Definitions**: Exacerbations were defined as symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalisation or a combination of these
Risk of bias	

Calverley 2007 [TORCH] (*Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	[From protocol] "Subjects will be assigned to study treatment in accordance with the randomisation schedule, which will be generated using the GW computer 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" ['central' interpreted as being masked from individual study centres]
Blinding of participants and personnel (performance bias) All outcomes	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) All outcomes	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. Unclear for other outcomes
Incomplete outcome data (attrition bias) All outcomes	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 participant who withdraws prematurely from the study, all available data up to the time of discontinuation were included in the analyses. Mortality data were collected for participants who withdrew early
Selective reporting (reporting bias)	Low risk	All relevant outcomes stated in the protocol were reported in detail. Exacerbation data could not be included with the rest of the data, as they were given only as rate per patient-year

Campbell 2005

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group study **Duration**: 6 months (+ 3 weeks run-in period) **Location**: 73 centres in eight countries (Bulgaria, Hungary, Israel, The Netherlands, Romania, Spain, Sweden and the UK)
Participants	**Population**: 432 participants were randomly assigned to formoterol 12 μg twice daily (215) and placebo (217) **Baseline characteristics**: Mean age (years): formoterol, 60; placebo, 60 % Male: formoterol, 61; placebo, 73 % Reversibilty: formoterol, 5.1; placebo, 4.7 Pack-years: formoterol, 37; placebo, 37 % FEV_1 predicted: formoterol, 53.0; placebo, 54.1 % taking ICS: formoterol, 47; placebo, 44 **Inclusion criteria**: older than 40 years of age; clinical diagnosis of COPD with at least 2 years of symptoms, FEV_1 40% to 70% predicted, FEV_1/slow VC < 70%; history of at least 10 pack-years **Exclusion criteria**: history of asthma or seasonal allergic rhinitis; onset before age 40; inhaled corticosteroid dose change; oral steroid use or significant COPD exacerbation in the past month
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Allowed medications were terbutaline (0.5 mg) used as reliever [in the two arms used in the review]; inhaled and nasal corticosteroids without modification of dosage or frequency of administration. Disallowed medications included domiciliary oxygen; disodium cromoglycate; ephedrine; antihistamines; beta-blockers and bronchodilators other than the study medication
Outcomes	**HRQoL**: assessed using St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: time to first severe exacerbation; number of participants with at least one exacerbation **Lung function**: FEV_1 % change, morning PEF, slow VC **Adverse events**: non-fatal serious adverse events and all-cause mortality **Other**: combined symptom score (CSS), reliever medication use
Notes	**Funding**: AstraZeneca **Study number**: unknown **Definitions**: Exacerbations were defined as the need for oral steroids, change in dose of inhaled corticosteroids or the need for antibiotics or hospitalisation [coded as moderate and severe in the present review]

Risk of bias

Bias	Authors' judgement	Support for judgement

Campbell 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Treatment was randomly assigned in balanced blocks using a computer-generated scheme
Allocation concealment (selection bias)	Low risk	Randomisation scheme was provided in coded envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment period (participants and investigators)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intention-to-treat approach was used throughout. Unclear how data were imputed, but withdrawal rates were similar and below 20% in both groups (formoterol, 14.0%, placebo, 18.0%)
Selective reporting (reporting bias)	Unclear risk	No trial protocol could be located against which to check all preregistered outcomes as reported

Dahl 2001

Methods	**Design**: multicenter, double-blind, randomised, parallel-group, placebo-controlled study **Duration**: 6 months (+ 2 weeks run-in period) **Location**: Denmark, Netherlands, Poland, Russia, UK
Participants	**Population**: 586 participants were randomly assigned to formoterol 12 μg twice daily (194), formoterol 24 μg twice daily (192) and placebo (200) **Baseline characteristics**: Mean age (years): formoterol 12, 64.3; formoterol 24, 63.5; placebo, 63.4 % Male: formoterol 12, 74.2; formoterol 24, 75.6; placebo, 78.5 Pack-years: formoterol 12, 46.0; formoterol 24, 42.2; placebo, 42.5 % FEV_1 predicted: formoterol 12, 46.0; formoterol 24, 45.0; placebo, 43.9 % taking ICS: formoterol 12, 47; formoterol 24, 53; placebo, 54 **Inclusion criteria**: males and females aged 40 and older; history of at least 10 pack-years; clinical diagnosis of COPD **Exclusion criteria**: history of asthma; respiratory tract infection in the past month; need for long-term oxygen therapy
Interventions	• Formoterol 12 μg twice daily • Formoterol 24 μg twice daily • Placebo

	Inhaler device: dry powder inhaler **Co-medication**: Salbutamol was provided as rescue; inhaled corticosteroids (ICS) were allowed if stable; short courses of antibiotics, oral corticosteroids and/or oxygen could be used in case of exacerbation or infection. Initiation or discontinuation of ICS or recent change in dose was not allowed; neither were parenteral or oral corticosteroids, theophylline, anticholinergics or other LABAs
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: frequency of level 1, 2 and 3 exacerbations (definitions below) **Lung function**: FEV_1 area under the curve over 12 hours and at individual time points, morning PEF **Adverse events**: non-fatal serious adverse events and all-cause mortality **Other**: withdrawal, vital signs, electrocardiograms and clinical laboratory evaluations, number of puffs of rescue medication, daily total symptom scores
Notes	**Funding**: Novartis **Study number**: unknown **Definitions**: First level of exacerbation was defined as days with at least two individual symptom scores of 2 or greater and/or a reduction in PEF from baseline of greater than 20%; second level of exacerbation: course of additional therapy (corticosteroids, antibiotics or oxygen) [coded as moderate for this review]; third level: COPD-related hospitalisations [coded as severe for this review]

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned to receive one of the following four regimens [no other details given but industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was obtained by double-dummy dosing [assumed participants and investigators]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Statistical analysis was carried out according to the intent-to-treat principle. [Unclear how data were imputed across outcomes. Dropout higher in placebo group but considered low overall in all three groups (formoterol 12, 6.7%; formoterol 24, 6.8%, placebo, 14.5%)]

Dahl 2001 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Moderate exacerbation rates not reported for each group, but all other outcomes could be included in the meta-analysis. Trial protocol could not be located against which to check all preregistered outcomes as 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)
Participants	**Population**: 867 participants were randomly assigned to formoterol 12 μg twice daily (435) and placebo (432) **Baseline characteristics**: Mean age (years): formoterol, 64; placebo, 63 % Male: formoterol, 80.2; placebo, 81.5 % Reversibility: formoterol, 10.1; placebo, 10.8 Pack-years: formoterol, 40; placebo, 43 % FEV_1 predicted: formoterol, 52.5; placebo, 52.0 % taking ICS: formoterol, 50.9; placebo, 51.9 **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 hospitalisation for COPD exacerbation within the previous 6 weeks
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: 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	**HRQoL**: assessed by St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: frequency of exacerbations (definition below) **Lung function**: trough (predose) FEV_1 and PEF, dyspnoea (baseline and transition scores) **Adverse events**: any adverse events and all-cause mortality **Other**: withdrawal, use of rescue medication, change in concomitant medications, 6-minute walk test, ECG, vital signs and haematology
Notes	**Funding**: Novartis **Study number**: NCT00393458 **Definitions**: Exacerbations were defined as onset or worsening of more than one respiratory symptom for > 3 consecutive days (based on diary cards or participants' reports

Dahl 2010 (*Continued*)

	of their health since the previous visit) plus documented proof of intensified treatment (e.g. systemic steroids, antibiotics or oxygen) and/or hospitalisation or emergency room visit [coded as moderate and severe]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned 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) All outcomes	Low risk	Double-blind double-dummy trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Protocol states double-blind for participant, caregiver, investigator and outcomes assessor (http://www.clinicaltrials.gov/ct2/show/NCT00393458)
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy results are presented for the modified intention-to-treat (ITT) population, including all randomly assigned participants who received at least one dose of study drug, but excluding patients from six sites owing to non-conformance with good clinical practice. Withdrawal relatively high in both groups (formoterol, 25.7; placebo, 31.7)
Selective reporting (reporting bias)	Low risk	Checked paper against protocol. All outcomes stated in the protocol were reported

Doherty 2012

Methods	**Design**: randomised, double-blind, placebo-controlled trial **Duration**: 6 months (+ 2 weeks run-in period) **Location**: 164 centres in North, Central and South America, Europe, Africa and Asia
Participants	**Population**: 479 participants were randomly assigned to formoterol 10 μg twice daily (243) and placebo (236) **Baseline characteristics**: Mean age (years): formoterol, 59.7; placebo, 58.8

	% Male: formoterol, 74.9; placebo, 75.4 % White: formoterol, 68.7; placebo, 65.7 % Reversibility: formoterol, 10.4; placebo, 9.5 Pack-years: formoterol, 45.9; placebo, 43.5 % FEV_1 predicted: formoterol, 38.2; placebo, 38.0 **Inclusion criteria**: males and females aged 40 and older; FEV_1/FVC < 70%; PFEV 25% to 60%; COPD symptoms for at least 24 months; history of at least 10 pack-years **Exclusion criteria**: current diagnosis of asthma; marked bronchodilator reversibility; recent COPD exacerbation; history of lung cancer/surgery; other significant medical illness
Interventions	• Formoterol 10 μg twice daily • Placebo **Inhaler device**: metered dose inhaler **Co-medication**: open-label, short-acting beta$_2$-agonist (SABA)/short-acting anticholinergic combination was allowed. All long-acting COPD treatments (LABA, inhaled corticosteroids, LABA/ICS FDC or long-acting anticholinergics) were disallowed
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (including number reaching a minimally clinically important difference) **COPD exacerbations**: time to first mild, moderate or severe exacerbation. Number of people with exacerbations **Lung function**: FEV_1 area under the curve from 0 to 12 hours postdose (at weeks 13 and 26 LOCF); trough FEV_1 (not for LABA placebo comparison) **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, COPD symptom-free nights
Notes	**Funding**: Merck & Co **Study number**: NCT00383721 **Definitions**: A mild exacerbation was defined as a clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: 12+ inhalations/day of SABA/short-acting anticholinergic, or 2+ nebulised treatments/day of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days. A moderate exacerbation was defined as a clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease. A severe exacerbation was defined as a deterioration of COPD that resulted in emergency treatment or hospitalisation because of COPD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in a 1:1:1:1:1 ratio [industry sponsored]
Allocation concealment (selection bias)	Unclear risk	Participants who discontinued early were not replaced [no other details given]

Doherty 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy. Protocol states participants and investigators were blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Protocol and paper do not provide details about blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were quite different (formoterol, 20.6%; placebo, 28.4%), but efficacy analyses and safety summaries were based on the intent-to-treat principle for all randomly assigned participants
Selective reporting (reporting bias)	High risk	Quality of life [primary outcome] was not reported in a way that could be analysed for the comparison in question. All other stated and expected outcomes were reported and analysed

Hanania 2003

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group, 24-week clinical trial **Duration**: 6 months (+ 2 weeks run-in period) **Location**: 75 centres in the USA, one in Puerto Rico
Participants	**Population**: 362 participants were randomly assigned to salmeterol 50 μg twice daily (177) and placebo (185) **Baseline characteristics**: Mean age (years): salmeterol, 64.2; placebo, 64.8 % Male: salmeterol, 57.6; placebo, 68.1 % White: salmeterol, 93.2; placebo, 93.5 Pack-years (median): salmeterol, 57; placebo, 56 % FEV_1 predicted: salmeterol, 42; placebo, 42 **Inclusion criteria**: males and females aged 40 and older; clinical diagnosis of COPD; history of at least 20 pack-years and cough productive of sputum on most days for at least 3 months of the year for at least 2 years; FEV_1/FVC ratio < 70% and baseline FEV_1 < 65% predicted but > 0.70 L **Exclusion criteria**: current diagnosis of asthma; abnormal clinically significant ECG; moderate or severe exacerbation during the run-in period; any significant medical disorder
Interventions	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Stable regimens of theophylline were allowed (no change in dose for 1 month before screening) [only 11% were taking these medications]. Disallowed medica-

	tions included oral corticosteroids within the past 6 weeks and long-term oxygen therapy, and participants discontinued the use of corticosteroids and bronchodilators
Outcomes	**HRQoL**: assessed with the Chronic Respiratory Disease Questionnaire (CRQ). Clinically meaningful difference of 10 points **COPD exacerbations**: See 'definitions' **Lung function**: morning predose and 2-hour postdose FEV_1, morning peak expiratory flow (PEF), dyspnoea (as assessed by the transition dyspnoea index [TDI]) **Adverse events**: **Other**: withdrawal, supplemental albuterol use, symptoms of chronic bronchitis (as assessed by the Chronic Bronchitis Symptom Questionnaire [CBSQ])
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SFCA3007 **Definitions**: Exacerbations were defined by treatment, with moderate exacerbations requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations requiring hospitalisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by reversibility (defined as a 12% and 200-mL increase in FEV_1 from baseline after administration of 400 g albuterol) and investigative site [sequence generation not described but study was industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind [presumed participant and investigator]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal high and even between groups (formoterol, 31.7%, placebo, 31.9%). To account for participant withdrawals, end point 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

Hanania 2003 (*Continued*)

Selective reporting (reporting bias)	Low risk	All expected and stated outcomes were reported. Quality of life data were not included, as QOL was measured on the CRQ rather than the SGRQ

Hanrahan 2008

Methods	**Design**: Pooled results from two identically designed phase III multicentre double-blind, double-dummy, placebo- and active-controlled, parallel-group, multiple-dose randomised trials [Baumgartner 2007 and NCT00064402] **Duration**: 3 months (+ 2 weeks run-in period) **Location**: 60 sites in the first study and 64 sites in the second study (all in the United States)
Participants	**Population**: 583 participants were randomly assigned to salmeterol 50 μg twice daily (290) and placebo (293) **Baseline characteristics**: Mean age (years): salmeterol, 62.8; placebo, 63.2 % Male: salmeterol, 58.6; placebo, 60.4 % White: salmeterol, 93.4; placebo, 96.6 % FEV_1 predicted: salmeterol, 40.9; placebo, 41.3 % taking ICS: salmeterol, 28.6; placebo, 23.9 **Inclusion criteria**: males and females aged 35 and older; primary clinical COPD diagnosis; FEV_1 < 65% predicted and > 0.70 L; FEV_1/FVC < 70%; > 15 pack-years; breathlessness severity on dyspnoea scale > 2 **Exclusion criteria**: life-threatening/unstable respiratory status within 30 days; asthma or any chronic respiratory disease other than COPD; lung resection > 1 full lobe; clinically significant abnormal electrocardiograms at screening
Interventions	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: metered dose inhaler **Co-medication**: Albuterol and ipratropium metered dose inhaler were provided as rescue and supplemental medications; corticosteroid or xanthines were allowed if the dose had been stable for 14 days. Use of non-protocol-specified beta-agonists, continuous supplemental oxygen and beta-blockers was not permitted during the study period
Outcomes	**HRQoL**: not reported **COPD exacerbations**: proportion of participants experiencing protocol-defined COPD exacerbations **Lung function**: % change in trough FEV_1 from baseline and average area under the curve **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, ECG and Holter monitoring
Notes	**Funding**: Sepracor **Study number**: NCT00064402 and NCT00064415 **Definitions**: Exacerbation was defined as an increase in symptoms leading to any change

	in baseline medication or additional medical attention (e.g. hospitalisation, emergency room visit)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to LABA treatment or placebo [industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Protocols state participant, investigator and outcomes assessor were blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Among 1465 randomly assigned participants, 1456 took at least 1 dose of double-blind study medication (ITT participants) . Withdrawal higher in placebo group (salmeterol, 14.5%, placebo, 21.8%)
Selective reporting (reporting bias)	High risk	SGRQ [primary outcome] named in protocol but not reported. All other outcome data provided

Kornmann 2011

Methods	**Design**: randomised, double-blind, placebo-controlled trial **Duration**: 6 months (+ 2 weeks run-in period) **Location**: 142 centres in 15 countries (Brazil, Canada, Colombia, Czech Republic, Denmark, Germany, Hungary, Iceland, India, Italy, Norway, Peru, Russia, Slovakia, Taiwan and Finland)
Participants	**Population**: 669 participants were randomly assigned to salmeterol 50 μg twice daily (334) and placebo (335) **Baseline characteristics**: Mean age (years): salmeterol, 63; placebo, 64 % Male: salmeterol, 75; placebo, 77 % Reversibility: salmeterol, 11; placebo, 13 Pack-years: salmeterol, 40; placebo, 41 % FEV_1 predicted: salmeterol, 53; placebo, 53 % taking ICS: salmeterol, 46; placebo, 40

	Inclusion criteria: Males and females aged 40 and older; diagnosis of moderate to severe COPD; history of at least 20 pack-years; < 80% and > 30% predicted FEV_1; FEV_1/FVC < 0.70 **Exclusion criteria**: history of asthma; hospitalisation for COPD exacerbation in the 6 weeks before Visit 1 or during run-in; requiring oxygen therapy; respiratory tract infection within 6 weeks before Visit 1 and during the run-in period; concomitant pulmonary disease; history of long QTc syndrome or QTc interval > 450 ms for males and > 470 ms for females; clinically significant condition
Interventions	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Concomitant medication with inhaled corticosteroids was allowed if stable for 1 month before screening and remained stable throughout the study; salbutamol was provided for relief. Participants previously taking fixed combinations of ICS and LABA were switched to equivalent ICS monotherapy
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (including proportion meeting minimal clinically important difference) **COPD exacerbations**: not reported **Lung function**: trough FEV_1, transition dyspnoea index, morning and evening PEF **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, use of relief medication, days of poor COPD control, vital signs and ECGs
Notes	**Funding**: Novartis **Study number**: NCT00567996 **Definitions**: Trough FEV_1 was defined as average of the 23 hour 10 minute and 23 hour 45 minute postdose FEV_1 readings

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated to treatment in a 1:1:1 ratio (with stratification for smoking status) using an automated system
Allocation concealment (selection bias)	Low risk	Using an automated system [concealment assumed by automatisation]
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant, investigator, outcomes assessor all blind [from protocol]. Blinding was maintained from randomisation until database lock unless any participant emergencies arose

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant, investigator, outcomes assessor all blind [from protocol]. Blinding was maintained from randomisation until database lock unless any participant emergencies arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal somewhat higher in placebo group (salmeterol, 15%; placebo, 20.1%). Efficacy data were analysed for the intention-to-treat (ITT) population, comprising all randomly assigned participants who received at least one dose of the study drug. The population for the safety analysis comprised all participants who received at least one dose of the study drug
Selective reporting (reporting bias)	High risk	FEV_1 data given only in graphical form. No exacerbation data provided. SGRQ reported only as a dichotomous outcome

Mahler 1999

Methods	**Design**: Stratified, randomised, double-blind, double-dummy, placebo-controlled, parallel-group clinical trial **Duration**: 3 months (+ 2 to 3 weeks run-in period) **Location**: multiple sites at clinics and university medical centres throughout the United States
Participants	**Population**: 278 participants were randomly assigned to salmeterol 42 μg twice daily (135) and placebo (143) **Baseline characteristics**: Mean age (years): salmeterol, 63.2; placebo, 63.2 % Male: salmeterol, 71.9; placebo, 76.2 % White: salmeterol, 91.9; placebo, 90.9 Pack-years: salmeterol, 60.2; placebo, 60.2 % FEV_1 predicted: salmeterol, 42.1; placebo, 40.8 **Inclusion criteria**: males and females aged 35 and older; history of at least 10 pack-years; diagnosis of COPD; FEV_1 > 0.7 L and < 65% predicted normal; FEV_1/FVC < 70% **Exclusion criteria**: unstable respiratory status within the previous 4 weeks; history of asthma or chronic respiratory disease other than COPD; clinically significant concurrent disease
Interventions	• Salmeterol 42 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Albuterol was allowed for acute symptomatic relief; participants receiving a stable regimen of oral (< 10 mg prednisone per day) or inhaled corticosteroids

	continued these treatments. Oxygen therapy other than nocturnal use was disallowed, as were changes in medications for COPD within 4 weeks before the screening visit and inability to discontinue treatment with theophylline, ipratropium or oral B-agoing therapy
Outcomes	**HRQoL**: assessed by the Chronic Respiratory Disease Questionnaire (CDRQ), including the proportion of participants meeting minimal clinically important difference from baseline **COPD exacerbations**: time to first COPD exacerbation; percentage of participants experiencing one or more exacerbations **Lung function**: spirometric measures over 12 hours (FEV_1, FVC), area under the 12-hour curve for FEV_1, dyspnoea severity on the transition dyspnoea index **Adverse events**: adverse events, vital signs and all-cause mortality **Other**: six-minute walk test (6MW) within 4 hours of the morning dose of study medication, participant-rated intensity of breathlessness on the Borg dyspnoea scale before and after the 6MW, participant self-rating of symptoms, night-time awakenings, supplemental albuterol use, ECG
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SLGA4005 **Definitions**: Exacerbations were not defined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified, randomised trial [GSK sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy [assumed participant and investigator]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal more than twice as high in the placebo group (salmeterol, 6.7%, placebo, 16.1%). Analyses were performed on three groups of participants: all participants, responsive and non-responsive strata [no mention of intention-to-treat principle or imputation]

Mahler 1999 (*Continued*)

Selective reporting (reporting bias)	High risk	Different FEV_1 outcome from other studies, cannot be included. No serious adverse event data

Mahler 2002

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial **Duration**: 6 months (+ 2 weeks run-in period) **Location**: 65 centres in the United States
Participants	**Population**: 341 participants were randomly assigned to salmeterol 50 μg twice daily (160) and placebo (181) **Baseline characteristics**: Mean age (years): salmeterol, 63.5; placebo, 64.0 % Male: salmeterol, 64.4; placebo, 75.1 % White: salmeterol, 95.0; placebo, 91.7 Pack-years (median): salmeterol, 52.5; placebo, 60 % FEV_1 predicted: salmeterol, 40; placebo, 41 **Inclusion criteria**: males and females aged 40 and older; history of at least 20 pack-years; diagnosis of COPD; FEV_1 < 65% of predicted but > 0.70 L, FEV_1/FVC ratio < 70%; daily cough productive of sputum for 3 months of the year for 2 consecutive years and dyspnoea **Exclusion criteria**: current diagnosis of asthma; abnormal clinically significant ECG; moderate or severe exacerbation during the run-in period; any significant medical disorder
Interventions	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Albuterol was allowed as needed, as were stable regimens of theophylline. Disallowed medications included oral corticosteroid use in the past 6 weeks, long-term oxygen therapy, corticosteroids and all bronchodilators
Outcomes	**HRQoL**: assessed on the CRQ **COPD exacerbations**: time to exacerbation and proportions of participants experiencing at least one moderate/severe COPD exacerbation **Lung function**: AM predose and 2-hour postdose FEV_1, serial FEV_1 over 12 hours, morning (AM) peak expiratory flow rate (PEFR) **Adverse events**: non-fatal serious adverse events and all-cause mortality **Other**: Chronic Bronchitis Symptoms Questionnaire (CBSQ), supplemental albuterol (MDI or nebules), night-time awakenings requiring the use of albuterol
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SFCA3006 **Definitions**: Moderate exacerbations were defined as those requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations were those requiring hospitalisation

Mahler 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by reversibility and investigative site to ensure a balance between treatment groups at each site and in terms of the numbers of reversible participants [no other details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind [participant and investigator]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal high and uneven between groups (salmeterol, 28%, placebo, 38%). Analyses based on the intent-to-treat (ITT) population consisted of all randomly assigned participants who had taken at least one dose of double-blind study drug
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes were reported in detail and were included, except quality of life, because the study used a different measure than was used in the other studies

Nelson 2007

Methods	**Design**: randomised, double-blind, double-dummy, placebo- and active-controlled trial **Duration**: 3 months (+ 4 to 14 days run-in period) **Location**: 38 centres across the United States
Participants	**Population**: 228 participants were randomly assigned to formoterol 12 μg twice daily (114) and placebo (114) **Baseline characteristics**: Mean age (years): formoterol, 63.0; placebo, 63.5 % Male: formoterol, 53.5; placebo, 57.0 % White: formoterol, 83.3; placebo, 86.0 % taking other COPD med: formoterol, 33.3; placebo, 37.7 **Inclusion criteria**: males and females aged 40 and older; diagnosis of COPD; history

	of at least 10 pack-years; FEV_1 30% to < 70% predicted; FEV_1/FVC ration < 70% **Exclusion criteria**: current or past diagnosis of asthma; respiratory tract infection or acute exacerbation of COPD within the previous month; other significant disease
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Albuterol was allowed as rescue medication and the use of inhaled or oral steroids was permitted if the corticosteroid dose was stable for 1 month. Disallowed medications included oxygen therapy, non-selective beta-blockers, MAOIs and other bronchodilators
Outcomes	**HRQoL**: not reported **COPD exacerbations**: number of participants experiencing at least one exacerbation during the study **Lung function**: not reported **Adverse events**: cardiac adverse events, all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, Holter monitoring, ECG
Notes	**Funding**: Dey Pharma **Study number**: NCT00215436 **Definitions**: Exacerbations were not defined in the paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned in a 1:1:1 ratio [no other details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded electronic ECG and Holter monitor data were assessed by a central laboratory (Quintiles Transnational Corporation, Mumbai, India) to look for clinically significant abnormalities according to predetermined criteria. Blinded investigators rated the intensity of each AE and categorised each for potential relationship to study medication

Nelson 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal twice as high in placebo group as in drug group [formoterol, 10.5%, placebo, 20.2%]. The safety population consisted of all participants who received ≥ 1 dose of study medication [not given for efficacy population]
Selective reporting (reporting bias)	High risk	HRQoL, severe exacerbations [primary outcomes] and FEV_1 [secondary] were not reported

Rennard 2001

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group study **Duration**: 3 months (+ run-in period of unknown length) **Location**: 27 clinical centres in the United States
Participants	**Population**: 267 participants were randomly assigned to salmeterol 42 μg twice daily (132) and placebo (135) **Baseline characteristics**: Mean age (years): salmeterol, 63.9; placebo, 63.7 % Male: salmeterol, 61.4; placebo, 64.4 % White: salmeterol, 93.2; placebo, 97.0 **Inclusion criteria**: males and females aged 35 and older; diagnosis of COPD; FEV_1 > 0.7 L and < 65% predicted normal; FEV_1/FVC < 70% **Exclusion criteria**: pulmonary infection within 4 weeks before the study; significant cardiovascular disease; history of malignancy within the previous two years; significantly abnormal ECG or lab results; history of hypersensitivity to any beta-agonist or anticholinergic compound
Interventions	• Salmeterol 42 μg twice daily • Placebo **Inhaler device**: metered-dose inhaler **Co-medication**: up to 14-day courses of oral corticosteroids for exacerbations; participants using ICS at entry must have maintained a stable regimen for the duration of the study. Participants were required to discontinue the use of theophylline, ipratropium and oral beta-agonists for the duration of the study; participants requiring oral corticosteroid therapy > 10 mg prednisone or continuous oxygen therapy were excluded
Outcomes	**HRQoL**: Quality of life (QOL) was measured using the Chronic Respiratory Disease Questionnaire (CRQ) and the Pittsburgh Sleep Quality Index (PSQI) **COPD exacerbations**: COPD exacerbations **Lung function**: FEV_1, forced vital capacity (FVC), forced expiratory flow in the middle half of FVC (FEF25% to 75%) assessments, peak expiratory flow, Transitional Dyspnea Index (TDI) score, FEV_1 area under the curve (AUC) calculated from 12-hour serial pulmonary function tests (PFTs) **Adverse events**: **Other**: 6-Minute walk, Borg dyspnoea score, participant self-rating of symptoms, night-

Rennard 2001 (*Continued*)

	time awakenings, supplemental albuterol use
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SLGA4004 **Definitions**: Exacerbations were defined as worsening symptoms of COPD requiring a change in drug therapy [coded as moderate for this review]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned to receive 1 of the 3 treatments [no other details provided, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided, included outcomes might be subject to detection bias [self-rated quality of life, exacerbations, all-cause mortality, serious adverse events and withdrawal]
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal quite similar between groups (salmeterol, 16.7%, placebo, 21.2). Last observation carried forward (LOCF) analyses were performed on all efficacy measurements to investigate the impact of drop-outs, and LOCF analyses (data not shown) were entirely consistent with those presented here
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes were reported in a way that could be included in the meta-analysis

Rennard 2009

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group, active- and placebo-controlled, multi-centre study **Duration**: 12 months (+ 2 weeks run-in period) **Location**: 237 sites in the USA, Europe and Mexico

Rennard 2009 (*Continued*)

Participants	**Population**: 976 participants were randomly assigned to formoterol 12 μg twice daily (495) and placebo (481) **Baseline characteristics**: Mean age (years): formoterol, 62.9; placebo, 62.9 % Male: formoterol, 65.3; placebo, 65.3 % White: formoterol, 92.3; placebo, 91.7 % Reversibility: formoterol, 16.9; placebo, 19.5 Pack-years (median): formoterol, 40; placebo, 40 % FEV_1 predicted: formoterol, 39.3; placebo, 40.8 **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 $alpha_1$-antitrypsin deficiency or other clinically significant co-morbidities precluding participation
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Salbutamol was allowed as relief medication. 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 short-term use
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: time to first exacerbation and number per participant-treatment year **Lung function**: predose FEV_1, one hour postdose FEV_1, morning and evening REF **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, participant-rated symptom scores
Notes	**Funding**: AstraZeneca **Study number**: NCT00206167 **Definitions**: Exacerbations were defined as worsening of COPD requiring an oral corticosteroid or hospitalisation [coded as moderate and severe for this review]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Designed to conform with the Declaration of Helsinki, and consistent with the International Conference on Harmonisation and Good Clinical Practice and applicable regulatory requirements

Rennard 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	Designed to conform with the Declaration of Helsinki, and consistent with the International Conference on Harmonisation and Good Clinical Practice and applicable regulatory requirements
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain blinding, participants received both a pressurised metered dose inhaler (pMDI) and a dry powder inhaler (DPI) containing active treatment or double-dummy placebo (PL), as appropriate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided. Outcomes could be affected by detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal even but high in both groups [formoterol 31.7%, placebo, 36.4%]. The efficacy analysis set (i.e. intent-to-treat population) included all randomly assigned participants who received at least one dose of randomly assigned study medication and contributed sufficient data for at least one co-primary or secondary efficacy end point to be calculated during the randomly assigned treatment period. The safety analysis population included all randomly assigned participants who received at least one dose of randomly assigned study medication and from whom any post--random assignment data were available
Selective reporting (reporting bias)	High risk	Serial spirometry was reported only for a subset. Exacerbations not reported in a way that could be included in the meta-analysis

Rossi 2002

Methods	**Design**: multi-centre, randomised, parallel-group, placebo-controlled study **Duration**: 12 months (+ 10 to 21 days run-in period) **Location**: 81 centres worldwide
Participants	**Population**: 645 participants were randomly assigned to formoterol 12 μg twice daily (211), 24 μg twice daily (214) and placebo (220) **Baseline characteristics**: Mean age (years): formoterol 12 μg, 63; formoterol 24 μg, 62; placebo, 63 % Male: formoterol 12 μg, 87.2; formoterol 24 μg, 83.2; placebo, 79.5 % on ICS: formoterol 12 μg, 47; formoterol 24 μg, 47; placebo, 49

	Inclusion criteria: males and females aged 40 and older; diagnosis of COPD; history of at least 10 pack-years; FEV_1 < 70% predicted; FEV_1/FVC ration < 0.89 **Exclusion criteria**: history of asthma; respiratory tract infection in the past month; need for long-term oxygen therapy
Interventions	• Formoterol 12 μg twice daily • Formoterol 24 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Stable participants receiving inhaled corticosteroid treatment were instructed to remain on that treatment throughout the study; Salbutamol (up to 8 puffs/d) was allowed as the rescue medication. Short courses of antibiotics, oral corticosteroids and/or oxygen were permitted in case of exacerbation or respiratory infection up to two times during the study. All other bronchodilating medications were discontinued
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: frequency of exacerbations, see definitions below **Lung function**: standardised AUC for FVC, absolute FEV_1 values at all time points, predose FEV_1, morning PEF **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, daily total symptom score, vital signs, ECG
Notes	**Funding**: Novartis **Study number**: unknown **Definitions**: Mild exacerbation = "bad days," defined as days with at least two individual symptom scores of 2 and/or a reduction in PEF from baseline of 20%; moderate exacerbation = undergo a course of additional therapy (i.e. corticosteroids, antibiotics or oxygen); severe exacerbation = COPD-related hospitalisations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised, parallel-group study [no specific details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	F12, F24 and PL were administered in a double-blind manner
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided, unclear whether outcomes included in the meta-analysis were subject to detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were relatively similar across the three groups (formoterol 12, 24. 6%, formoterol 24, 18.7%, placebo, 26.

		8%). The statistical analysis was carried out according to the intent-to-treat principle
Selective reporting (reporting bias)	Unclear risk	Key expected outcomes were reported (except FEV_1 [secondary] as AUC outcome) . No preregistered protocol was available against which to check all outcomes as reported

SLMF4010 2005

Methods	**Design**: multicentre, randomised, parallel-group, placebo-controlled, double-blind study **Duration**: 6 months (run-in not defined) **Location**: 9 centres in France
Participants	**Population**: 34 participants were randomly assigned to salmeterol 50 μg twice daily (17) and placebo (17) **Baseline characteristics**: Mean age (years): salmeterol, 62.9; placebo, 64.6 % Male: salmeterol, 94.1; placebo, 82.4 % White: salmeterol, 100; placebo, 100 **Inclusion criteria**: males and females aged 40 and older; history of at least 20 pack-years; diagnosis of COPD; FEV_1 > 60% of theoretical value, FEV_1/TLC ratio > 75% in absolute value and > 85% of theoretical value, FEV_1 reversibility > 12% and > 200 mL 20 minutes after 400 μg of salbutamol **Exclusion criteria**: history of asthma or allergy including non-respiratory signs (bronchial cancer, thoracic surgery, etc.); severe cardiovascular disease; exacerbation and/or other acute respiratory disease within 4 weeks before enrolment
Interventions	• Salmeterol 50 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: Disallowed medications included long-term oxygen therapy; inhaled or systemic corticosteroids and LABAs or theophyllines within 4 weeks of enrolment
Outcomes	**HRQoL**: change in St George's Respiratory Questionnaire (SGRQ) from visit 1 to 4 and from visit 4 to 6 **COPD exacerbations**: number experiencing exacerbations during the study period, and length of hospital stay **Lung function**: variations in IC, FRC, FEV_1, FIV_1 and total lung capacity (post-salbutamol - pre-salbutamol) **Adverse events**: non-fatal serious adverse events and all-cause mortality **Other**: withdrawal, exercise capacity, use of rescue medication, tobacco status
Notes	**Funding**: GlaxoSmithKline **Study number**: GSK identifier SLMF 4010 **Definitions**: Exacerbations were not well defined but included those leading to hospi-

	talisation [coded as moderate and severe for this review]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned and stratified on tobacco status [no other details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind [participant and investigator]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal very high in both groups [41.2% each]. ITT population included all randomly assigned participants who had received at least one dose of study medication and for whom the assessment data for at least one assessment criterion were available and were analysed on the basis of treatment allocated. Safety population consisted of all randomly assigned participants who had received at least one dose of study medication and were analysed on the basis of treatment really received
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes could be included in the analyses

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 (Argentina, Brazil, Denmark, Finland, UK, Italy, Mexico, Poland, Portugal, South Africa and Spain)
Participants	**Population**: 406 participants were randomly assigned to formoterol 12 μg twice daily (201) and placebo (205) **Baseline characteristics**: Mean age (years): formoterol, 63; placebo, 65

	% Male: formoterol, 76; placebo, 83 % Reversibility: formoterol, 6; placebo, 5 Pack-years: formoterol, 45; placebo, 45 % FEV_1 predicted: formoterol, 36; placebo, 36 **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	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: 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 $beta_2$-agonists from 48 hours before; inhaled short-acting $beta_2$-agonists from 6 hours before; other bronchodilators from 6 to 48 hours before
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: number of severe exacerbations **Lung function**: FEV_1, vital capacity, morning and evening PEF **Adverse events**: all-cause mortality and non-fatal serious adverse events **Other**: withdrawal, diary card data, short-acting $beta_2$-agonist use (rescue medication) , use of antitussives and other COPD medication, COPD symptom scores, night-time awakenings due to COPD symptoms, health care contacts and sick leave related to COPD symptoms
Notes	**Funding**: AstraZeneca **Study number**: AZ identifier SD-039-CR-0629 **Definitions**: Exacerbations were defined as intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms [coded as moderate and severe in this review]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A total of 812 participants were randomly assigned [no other details, industry sponsored]
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind [presumed participant and investigator]

Szafranski 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal high and uneven between groups (formoterol, 31.8%, placebo, 43.9%). An intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Quality of life [primary] stated as outcome but not reported in enough detail to be include in the meta-analysis. Other outcomes included

Tashkin 2008 [SHINE]

Methods	**Design**: randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre 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**: 584 participants were randomly assigned to formoterol 12 μg twice daily (284) and placebo (300) **Baseline characteristics**: Mean age (years): formoterol, 63.5; placebo, 63.2 % Male: formoterol, 65.5; placebo, 69.0 % White: formoterol, 92.3; placebo, 94.7 Pack-years (median): formoterol, 40; placebo, 40 % FEV_1 predicted: formoterol, 39.6; placebo,41.3 **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 alpha$_1$-antitrypsin deficiency or other clinically significant co-morbidities precluding participation
Interventions	• Formoterol 12 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: 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	**HRQoL**: assessed with St George's Respiratory Questionnaire (SGRQ) including number of people reaching threshold for minimal clinically important difference from baseline (4 units) **COPD exacerbations**: number per participant-treatment year **Lung function**: predose forced expiratory volume in 1 second (FEV_1) and 1-hour postdose FEV_1, dyspnoea, morning and evening PEF **Adverse events**: non-fatal serious adverse events and all-cause mortality **Other**: withdrawal, breathlessness diary
Notes	**Funding**: AstraZeneca **Study number**: AZ identifier D5899C00002; trial registration NCT00206154 **Definitions**: Exacerbations were defined as requiring treatment with oral corticosteroids and/or hospitalisation [coded as moderate and severe in this review]

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eligable participants were randomly assigned in balanced blocks according to a computer-generated randomisation scheme at each site
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain blinding, participants received both a pressurised metered dose inhaler (pMDI) and a dry powder inhaler (DPI) containing active treatment or placebo (PL) , or combinations of active treatment and placebo, as appropriate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ECG results were evaluated by a cardiologist in a blinded fashion through an independent ECG service provider
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were similar (21.5% formoterol, 25.7% placebo), and '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 and expected outcomes were reported in full and were included in the quantitative synthesis

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 and North America
Participants	**Population**: 421 participants were randomly assigned to formoterol 10 μg twice daily (209) and placebo (212) **Baseline characteristics**: Mean age (years): formoterol, 59.6; placebo, 58.8 % Male: formoterol, 72.7; placebo, 80.2 % White: formoterol, 77.0; placebo, 73.1 Pack-years: formoterol, 40.3; placebo, 40.29 **Inclusion criteria**: males and females aged 40 and older; history of at least 10 pack-years; moderate to severe COPD for at least 2 years; predicted FEV_1 between 25% and 60% normal **Exclusion criteria**: exacerbation in the four weeks before randomisation; significant medical illness; diagnosis of asthma, lung cancer or alpha$_1$-antitrypsin deficiency, lobectomy, pneumonectomy, lung volume reduction surgery or ocular problems
Interventions	• Formoterol 10 μg twice daily • Placebo **Inhaler device**: metered dose inhaler **Co-medication**: Participants were given open-label, short-acting beta$_2$-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	**HRQoL**: assessed with St George's Respiratory Questionnaire (SQRQ), reported as both final scores and the number of people experiencing a MCID (improvement or worsening by 4 units) **COPD exacerbations**: rates of moderate or severe exacerbations **Lung function**: serial FEV_1 postdose, standardised FEV_1 area under the curve **Adverse events**: non-fatal serious adverse events and all-cause mortality **Other**: withdrawal, systemic and ocular effects
Notes	**Funding**: Merck & Co/Schering-Plough **Study number**: NCT00383435 **Definitions**: If COPD exacerbation met criteria for a severe AE (e.g. was life-threatening, required hospitalisation or required prolonged hospitalisation), it was recorded as an adverse event (therefore, exacerbation data were coded as moderate in this review)

Risk of bias

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.

Tashkin 2012 (*Continued*)

		Randomisation was stratified according to the participant's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomly assigned treatment was provided to the investigative site by means of an interactive voice response system at the time participants were randomly assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Protocol describes the study masking
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Protocol describes the study masking
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates 17.7% in formoterol group and 25% in placebo group. ITT used
Selective reporting (reporting bias)	Unclear risk	Moderate exacerbations were not reported for the comparison of interest in this review [stated in protocol]

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 Germany (30), Italy (19), Netherlands (9), Russian Federation (9), Poland (7), Czech Republic (4), Spain (4) and Hungary (4)
Participants	**Population**: 419 participants were randomly assigned to formoterol 10 μg twice daily (210) and placebo (209) **Baseline characteristics**: Mean age (years): formoterol, 61.8; placebo, 62.5 % Male: formoterol, 75.7; placebo, 77.5 % Reversibility: formoterol, 11.4; placebo, 11.4 Pack-years: formoterol, 35.4; placebo, 40.1 % FEV_1 predicted: formoterol, 51.6; placebo, 51.1 % taking ICS: 40.6 to 43.9 across groups **Inclusion criteria**: males and females aged 40 and older; history of at least 10 pack-years; FEV_1 < 70% predicted normal; FEV_1/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

Interventions	• Formoterol 10 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: 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 beta$_2$-agonists were switched to receive the same dose of ICS and on-demand salbutamol
Outcomes	**HRQoL**: assessed with St Geoge's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: rates of moderate and severe exacerbations **Lung function**: FEV_1 and FEV measured at 5 minutes, 2 hours and 3 hours postdose, PEF **Adverse events**: all-cause mortality **Other**: withdrawal, 6-minute walk test, haematology, blood chemistry, ECG, daily diary card recoding symptoms, rescue salbutamol use
Notes	**Funding**: Novartis **Study number**: NCT00134979 **Definitions**: Moderate exacerbation was defined as requiring additional treatment; severe exacerbations were those leading to hospitalisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random assignment was not stratified [no other information given but assumed to follow conventional Novartis sequence generation methods]
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind for the treatment comparison used in this review
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific details regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low and even between groups (formoterol, 11.9%, placebo, 14.4%). Intent-to-treat (ITT) population consisted of all randomly assigned participants who received at least one dose of study medication. This population was used for efficacy and safety analyses

Selective reporting (reporting bias)	High risk	FEV_1 and SGRQ outcomes provided only in graphical form with inexact P-values

Wadbo 2002

Methods	**Design**: randomised, double-blind, parallel-group study **Duration**: 3 months (+ 2 weeks run-in period) **Location**: 14 centres in Sweden
Participants	**Population**: 121 participants were randomly assigned to formoterol 24 μg twice daily (61) and placebo (60) **Baseline characteristics**: Mean age (years): formoterol, 63.6; placebo, 63.6 % Male: formoterol, 54.1; placebo, 50.0 % Reversibility: formoterol, 5.8; placebo, 6.0 % FEV_1 predicted: formoterol, 33.3; placebo, 32.6 **Inclusion criteria**: males and females aged 40 to 75 years; history of at least 10 pack-years; diagnosis of COPD; history of reduced exercise capacity due to dyspnoea on exertion; FEV_1 < 60% predicted normal and FEV_1/FVC < 70% **Exclusion criteria**: adult asthma
Interventions	• Formoterol 24 μg twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: inhaled short-acting beta$_2$-agonists allowed as relief medication, and inhaled glucocorticoids and mucolytics allowed at a constant dose. No other bronchodilator medication permitted during the study, and participants requiring long-term oxygen therapy excluded
Outcomes	**HRQoL**: assessed with St George's Respiratory Questionnaire (SGRQ) **COPD exacerbations**: not reported **Lung function**: FEV_1 and FVC, walking and evening PEF, dyspnoea **Adverse events**: non-fatal serious adverse events **Other**: withdrawal, 6-minute walk test, blood gas tensions, diary card symptom scores, use of relief medication
Notes	**Funding**: Lund **Study number**: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants with a walking distance < 300 m were sequentially assigned the lowest randomisation number, and participants with a walking distance > 300 m were sequentially assigned the highest available

Wadbo 2002 (*Continued*)

		randomisation number
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study design [participants and investigators]
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator- and participant-rated outcomes [both blind]
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even between groups (formoterol, 27.9%; placebo, 26.7%). All analyses were performed according to the intention-to-treat approach
Selective reporting (reporting bias)	High risk	Key expected outcomes not reported (mortality and exacerbation rates), and no variance given for FEV_1 outcome

Watkins 2002

Methods	**Design**: randomised, double-blind trial **Duration**: 3 months
Participants	**Population**: 182 participants were randomly assigned to salmeterol 50 g twice daily (87) and placebo (95) **Baseline characteristics**: no baseline data reported **Inclusion criteria**: no information **Exclusion criteria**: no information
Interventions	• Salmeterol 50 g twice daily • Placebo **Inhaler device**: dry powder inhaler **Co-medication**: no information
Outcomes	**HRQoL**: no information **COPD exacerbations**: no information **Lung function**: FEV_1 area under the curve **Adverse events**: no information **Other**: no information
Notes	**Funding**: GlaxoSmithKline **Study number**: unknown **Only a conference abstract was available for this report, so no data could be included in the meta-analysis**
Risk of bias	

Watkins 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind [assumed investigator and participant]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided, but no outcomes could be included
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided regarding withdrawal rates or method of imputation
Selective reporting (reporting bias)	High risk	No full-text paper-only information from conference abstract. No outcomes could be included

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Boyd 1995	More than 50% taking other COPD medications [84% in total-including ICS, oral CS, methylxanthines, anticholinergics and beta$_2$-agonists]
Celli 2003	More than 50% taking other COPD medications [55% SABA, 54% ICS/oral CS, 33% anticholinergics, 25% LABAs, 22% xanthines]
Chapman 2002	More than 50% taking other COPD medications [placebo 55% and LABA 68% taking ICS; placebo 17% and LABA 24% taking theophylline]
Dal Negro 2003	More than 50% taking other COPD medications [all treated with theophylline]
Rutten-van Molken 1999	More than 50% taking other COPD medications [81% of salmeterol group and 76% of placebo group taking ICS, and all maintenance drugs other than the study medication continued at constant dosage]
Steffensen 1996	Entry criteria specified reversible obstructive airways disease, including asthma. Subgroups not reported
Stockley 2006	More than 50% taking other COPD medications [LABA 86% and placebo 89% in total-including ICS, anticholinergics and xanthines]

Characteristics of studies awaiting assessment *[ordered by study ID]*

Fattore 2005

Methods	**Design**: cost-analysis data were collected alongside a 12-month, multinational, randomised, double-blind, placebo-controlled trial **Location**: Italian National Health Service
Participants	272 participants (mean age = 65.27 years) equally distributed in four treatment groups [two of which received formoterol and placebo]
Interventions	• Formoterol (? dose) • Placebo
Outcomes	Average total cost per participant per year
Notes	Unclear which 12-month trial this ran alongside

Characteristics of ongoing studies *[ordered by study ID]*

NCT01437397

Trial name or title	Efficacy, Safety and Tolerability of Aclidinium Bromide/Formoterol Fumarate Compared With Formoterol Fumarate in Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) (LAC)
Methods	**Design**: randomised, double-blind, parallel-group, efficacy study Conducted at 208 study centres in four countries (Australia, Canada, New Zealand and the United States)
Participants	**Inclusion criteria**: current or former cigarette smokers at least 40 years of age 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 **Exclusion criteria**: patients who had been hospitalised for an acute COPD exacerbation within three months before visit 1; also, patients with any respiratory tract infection or COPD exacerbation in the 6 weeks before visit 1; any clinically significant respiratory conditions other than COPD; clinical history that suggests that the patient has asthma as opposed to COPD; long-term use of oxygen therapy > 15 hours/d; clinically significant cardiovascular condition; history of hypersensitivity reaction to inhaled anticholinergics
Interventions	• Formoterol 12 μg twice daily • Placebo twice daily The study also randomly assigned people to three aclidinium groups that were not relevant to the review
Outcomes	**Primary**: morning predose (trough) forced expiratory volume in one second (FEV_1) at week 24; time frame: change from baseline (week 0) to 24 weeks. Morning one-hour postdose FEV_1 at week 24; time frame: change from baseline (Week 0) to 24 weeks **Secondary**: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score, improvement in Transition Dyspnea Index (TDI) score
Starting date	First received on clinicaltrials.gov September 19, 2011

NCT01437397 (*Continued*)

Contact information	Funded by Forest Laboratories, no contact information listed
Notes	**Completed but no results posted. Final data collection for primary outcome in February 2013**

NCT01572792

Trial name or title	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)
Methods	**Design**: randomised, double-blind, parallel-group, safety/efficacy study Conducted at 208 study centres in four countries (Australia, Canada, New Zealand and the United States)
Participants	To be included in the extension phase, participants had to complete the treatment phase of the lead-in study (LAC-MD-31/NCT01437397) and provide written informed consent
Interventions	All participants remained in the same treatment group as for the lead-in study (NCT01437397) and continued on one of the four treatment arms or placebo • Formoterol 12 μg twice daily • Placebo twice daily The study also randomly assigned people to three aclidinium groups that were not relevant to the review
Outcomes	**Primary**: adverse events, clinical laboratory parameters, vital sign measurement, and electrocardiogram parameters
Starting date	First received on clinicaltrials.gov April 4, 2012
Contact information	Funded by Forest Laboratories, no contact information listed
Notes	**Completed but no results posted. Final data collection for primary outcome in June 2013**

DATA AND ANALYSES

Comparison 1. All LABA versus placebo [subgrouped by drug]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (SGRQ total score)	17	11397	Mean Difference (IV, Random, 95% CI)	-2.32 [-3.09, -1.54]
1.1 Formoterol 12 μg twice daily	11	5587	Mean Difference (IV, Random, 95% CI)	-2.66 [-3.84, -1.48]
1.2 Formoterol 24 μg twice daily	3	627	Mean Difference (IV, Random, 95% CI)	-2.51 [-4.51, -0.51]
1.3 Salmeterol 50 μg twice daily	5	5183	Mean Difference (IV, Random, 95% CI)	-1.64 [-2.78, -0.50]
2 Quality of life (number of people achieving the MCID on the SGRQ)	3	1871	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.32, 1.90]
2.1 Formoterol 12 μg twice daily	1	397	Odds Ratio (M-H, Fixed, 95% CI)	3.11 [2.06, 4.70]
2.2 Salmeterol 50 μg twice daily	2	1474	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [1.08, 1.64]
3 Quality of life (CRQ)	4	1193	Mean Difference (IV, Fixed, 95% CI)	3.10 [1.22, 4.98]
3.1 Salmeterol 50 μg twice daily	4	1193	Mean Difference (IV, Fixed, 95% CI)	3.10 [1.22, 4.98]
4 Severe exacerbations (hospitalisations)	7	3804	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
4.1 Formoterol 12 μg twice daily	6	2418	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.02]
4.2 Formoterol 24 μg twice daily	2	581	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.11, 0.73]
4.3 Salmeterol 50 μg twice daily	1	805	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.52, 1.86]
5 Severe/moderate exacerbations (hospitalisation *or* course of meds *or* ER visit	7	3968	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.76, 1.02]
5.1 Formoterol 12 μg twice daily	4	2682	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.04]
5.2 Salmeterol 50 μg twice daily	3	1286	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.16]
6 Moderate exacerbations (course of antibiotics and/or steroids)	7	3375	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
6.1 Formoterol 12 μg twice daily	3	968	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.51, 1.05]
6.2 Formoterol 24 μg twice daily	1	324	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 0.97]
6.3 Salmeterol 50 μg twice daily	4	2083	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.94]
7 Mortality (all-cause)	23	14079	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.75, 1.08]

7.1 Formoterol 12 μg twice daily	13	6343	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [0.87, 2.30]
7.2 Formoterol 24 μg twice daily	2	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.54 [0.07, 285.14]
7.3 Salmeterol 50 μg twice daily	10	7121	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.69, 1.01]
8 People with one or more non-fatal serious adverse event	20	12446	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.14]
8.1 Formoterol 12 μg twice daily	10	4829	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.99, 1.45]
8.2 Formoterol 24 μg twice daily	3	737	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.23, 0.77]
8.3 Salmeterol 50 μg twice daily	9	6880	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.10]
9 Predose FEV_1 (mL)	13	6125	Mean Difference (IV, Random, 95% CI)	72.92 [48.02, 97.82]
9.1 Formoterol 12 μg twice daily	6	3222	Mean Difference (IV, Random, 95% CI)	44.68 [29.39, 59.97]
9.2 Salmeterol 50 μg twice daily	7	2903	Mean Difference (IV, Random, 95% CI)	101.01 [59.84, 142.18]
10 Withdrawal	25	14763	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.69, 0.80]
10.1 Formoterol 12 μg twice daily	14	6597	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.68, 0.86]
10.2 Formoterol 24 μg twice daily	4	1001	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.14]
10.3 Salmeterol 50 μg twice daily	10	7165	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.65, 0.80]

Comparison 2. Formoterol 12 μg versus placebo [subgrouped by trial duration]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (SGRQ)	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 3 months	3	1627	Mean Difference (IV, Random, 95% CI)	-3.86 [-5.25, -2.46]
1.2 6 months	5	2427	Mean Difference (IV, Random, 95% CI)	-1.14 [-2.51, 0.23]
1.3 12 months	5	3079	Mean Difference (IV, Random, 95% CI)	-3.24 [-4.77, -1.71]
2 Severe exacerbations (hospitalisations)	6	2614	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.54, 0.98]
2.1 3 months	1	353	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.08, 2.60]
2.2 6 months	3	1319	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.26, 1.08]
2.3 12 months	2	942	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.57, 1.12]
3 Moderate exacerbations (course of antibiotics and/or steroids)	3	1078	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.07]
3.1 3 months	1	228	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.27, 2.12]
3.2 6 months	1	419	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
3.3 12 months	1	431	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.37]
4 Mortality (all-cause)	13	6553	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.89, 2.37]
4.1 3 months	5	1927	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.22 [0.64, 7.70]
4.2 6 months	4	1946	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.25 [0.98, 5.16]

4.3 12 months	4	2680	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.47, 1.88]
5 Patients with one or more serious adverse event	10	5039	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [1.00, 1.43]
5.1 3 months	2	799	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.57, 2.58]
5.2 6 months	4	1916	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.78, 1.55]
5.3 12 months	4	2324	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [1.00, 1.52]
6 Predose FEV_1 (mL)	6	3222	Mean Difference (IV, Fixed, 95% CI)	44.68 [29.39, 59.97]
6.1 3 months	1	407	Mean Difference (IV, Fixed, 95% CI)	40.0 [16.29, 63.71]
6.2 6 months	3	1437	Mean Difference (IV, Fixed, 95% CI)	44.41 [18.63, 70.18]
6.3 12 months	2	1378	Mean Difference (IV, Fixed, 95% CI)	53.46 [21.74, 85.17]
7 Withdrawal	14	6894	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.69, 0.86]
7.1 3 months	4	1368	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.94]
7.2 6 months	5	2335	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.89]
7.3 12 months	5	3191	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.94]

Comparison 3. Formoterol 24 μg versus placebo [subgrouped by trial duration]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (SGRQ)	3	707	Mean Difference (IV, Fixed, 95% CI)	-2.32 [-4.52, -0.13]
1.1 3 months	2	376	Mean Difference (IV, Fixed, 95% CI)	-2.04 [-4.65, 0.56]
1.2 12 months	1	331	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-7.06, 1.06]
2 Severe exacerbations (hospitalisations)	2	777	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.12, 0.67]
2.1 3 months	1	343	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.09, 2.75]
2.2 12 months	1	434	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.09, 0.65]
3 Moderate exacerbations (course of antibiotics and/or steroids)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mortality (all-cause)	2	825	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.60 [0.15, 383.12]
4.1 3 months	1	391	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 12 months	1	434	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.60 [0.15, 383.12]
5 People with one or more non-fatal serious adverse events	3	947	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.36, 0.79]
5.1 3 months	2	513	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.14, 0.94]
5.2 12 months	1	434	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.38, 0.89]
6 Withdrawal	4	1297	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.59, 1.05]
6.1 3 months	3	863	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.33]
6.2 12 months	1	434	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 0.99]

Comparison 4. Salmeterol 50 μg versus placebo [subgrouped by trial duration]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (SGRQ)	5	5183	Mean Difference (IV, Random, 95% CI)	-1.64 [-2.78, -0.50]
1.1 6 months	3	1405	Mean Difference (IV, Random, 95% CI)	-3.10 [-6.03, -0.17]
1.2 12 months	1	733	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.35, 0.15]
1.3 36 months	1	3045	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.00, 2.14]
2 Severe exacerbations (hospitalisations)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Moderate exacerbations (course of antibiotics and/or steroids)	4	2083	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.94]
3.1 3 months	2	545	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.03]
3.2 6 months	1	805	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.12]
3.3 12 months	1	733	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.17, 0.92]
4 Mortality (all-cause)	10	7121	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.69, 1.01]
4.1 3 months	3	1132	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.98]
4.2 6 months	5	2211	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.22, 1.46]
4.3 12 months	1	733	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.12, 1.50]
4.4 36 months	1	3045	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.71, 1.06]
5 People with one or more non-fatal serious adverse events	9	6880	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
5.1 3 months	2	850	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.45, 1.46]
5.2 6 months	5	2211	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.01]
5.3 12 months	1	733	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.88, 1.91]
5.4 36 months	1	3086	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.83, 1.11]
6 Predose FEV_1 (mL)	7	2903	Mean Difference (IV, Random, 95% CI)	101.01 [59.84, 142.18]
6.1 3 months	2	765	Mean Difference (IV, Random, 95% CI)	146.86 [114.38, 179.34]
6.2 6 months	4	1405	Mean Difference (IV, Random, 95% CI)	87.93 [39.05, 136.80]
6.3 12 months	1	733	Mean Difference (IV, Random, 95% CI)	59.0 [28.52, 89.48]
7 Withdrawal	10	7165	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.65, 0.80]
7.1 3 months	3	1132	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.44, 0.83]
7.2 6 months	5	2211	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.88]
7.3 12 months	1	733	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.01]
7.4 36 months	1	3089	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.64, 0.86]

Comparison 5. [Sensitivity analysis-ICS use] All LABA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (SGRQ)	12	8520	Mean Difference (IV, Fixed, 95% CI)	-1.53 [-2.08, -0.98]
1.1 Formoterol 12 μg twice daily	7	3782	Mean Difference (IV, Fixed, 95% CI)	-2.16 [-3.04, -1.27]
1.2 Formoterol 24 μg twice daily	1	121	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-4.62, 1.62]
1.3 Salmeterol 50 μg twice daily	4	4617	Mean Difference (IV, Fixed, 95% CI)	-1.12 [-1.84, -0.39]
2 Severe exacerbations (hospitalisations)	3	1795	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.16]
2.1 Formoterol 12 μg twice daily	2	990	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.15]
2.2 Salmeterol 50 μg twice daily	1	805	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.52, 1.86]

Comparison 6. [Sensitivity analysis-attrition] All LABA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (SGRQ)	13	9114	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.15, -1.05]
1.1 Formoterol 12 μg twice daily	8	3338	Mean Difference (IV, Fixed, 95% CI)	-2.07 [-3.06, -1.08]
1.2 Formoterol 24 μg twice daily	3	627	Mean Difference (IV, Fixed, 95% CI)	-2.25 [-4.56, 0.06]
1.3 Salmeterol 50 μg twice daily	4	5149	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-2.01, -0.61]

Analysis 1.1. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 1 Quality of life (SGRQ total score).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 1 Quality of life (SGRQ total score)

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Formoterol 12 µg twice daily							
Bogdan 2011 (1)	199	38.2 (14.5)	206	42.9 (14.5)		4.7 %	-4.70 [-7.52, -1.88]
Calverley 2003a	255	0.8 (17)	256	4.7 (17)		4.5 %	-3.90 [-6.85, -0.95]
Campbell 2005	215	-3.81 (13.5737)	217	-4.61 (13.5737)		5.3 %	0.80 [-1.76, 3.36]
Dahl 2001 (2)	181	41.7 (11.8)	86	46.8 (11.8)		4.3 %	-5.10 [-8.13, -2.07]
Dahl 2010	435	-5.7 (15.0231)	432	-1.7 (15.0231)		6.8 %	-4.00 [-6.00, -2.00]
Doherty 2012 (3)	243	-4.93 (14.5)	236	-2.88 (14.5)		5.2 %	-2.05 [-4.65, 0.55]
Rennard 2009	495	-2.9 (13.3)	481	-1.5 (12.7)		8.0 %	-1.40 [-3.03, 0.23]
Rossi 2002	159	40.9 (17.8)	80	45.3 (18.7)		2.1 %	-4.40 [-9.34, 0.54]
Szafranski 2003	201	-3.6 (15)	205	-0.03 (15)		4.5 %	-3.57 [-6.49, -0.65]
Tashkin 2008 [SHINE]	284	-1.24 (11.35)	300	-1.02 (12.41)		7.0 %	-0.22 [-2.15, 1.71]
Tashkin 2012	209	-6.19 (15.2)	212	-2.88 (15.2)		4.5 %	-3.31 [-6.21, -0.41]
Subtotal (95% CI)	**2876**		**2711**			**57.0 %**	**-2.66 [-3.84, -1.48]**
Heterogeneity: Tau^2 = 2.12; Chi^2 = 23.11, df = 10 (P = 0.01); I^2 =57%							
Test for overall effect: Z = 4.44 (P < 0.00001)							
2 Formoterol 24 µg twice daily							
Dahl 2001	169	43.5 (11.8)	86	46.8 (11.8)		4.2 %	-3.30 [-6.36, -0.24]
Rossi 2002	171	42.3 (19)	80	45.3 (18.7)		2.0 %	-3.00 [-7.99, 1.99]
Wadbo 2002	61	0 (8.59)	60	1.5 (8.9034)		4.1 %	-1.50 [-4.62, 1.62]
Subtotal (95% CI)	**401**		**226**			**10.4 %**	**-2.51 [-4.51, -0.51]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.70, df = 2 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 2.46 (P = 0.014)							
3 Salmeterol 50 µg twice daily							
Brusasco 2003	405	-2.8 (14.087)	400	-1.5 (14)		7.0 %	-1.30 [-3.24, 0.64]
Calverley 2003b [TRISTAN] (4)	372	45.2 (7.7149)	361	46.3 (9.5)		9.4 %	-1.10 [-2.35, 0.15]
Calverley 2007 [TORCH]	1521	-0.8 (14.0772)	1524	0.2 (14.0772)		10.3 %	-1.00 [-2.00, 0.00]

data for Bogdan 2011, Dahl 2001, Rossi 2002, and Calverley 2003b [TRISTAN] are entered as endpoint scores.

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Study or subgroup	LABA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kornmann 2011	292	-5.6 (15.4)	274	-1.5 (14.9)		5.4 %	-4.10 [-6.60, -1.60]
SLMF4010 2005	17	-7.1 (15.2555)	17	2.7 (16.0801)		0.5 %	-9.80 [-20.34, 0.74]
Subtotal (95% CI)	**2607**		**2576**			**32.6 %**	**-1.64 [-2.78, -0.50]**
Heterogeneity: Tau^2 = 0.73; Chi^2 = 7.76, df = 4 (P = 0.10); I^2 =48%							
Test for overall effect: Z = 2.81 (P = 0.0049)							
Total (95% CI)	**5884**		**5513**			**100.0 %**	**-2.32 [-3.09, -1.54]**
Heterogeneity: Tau^2 = 1.27; Chi^2 = 36.00, df = 18 (P = 0.01); I^2 =50%							
Test for overall effect: Z = 5.83 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.60, df = 2 (P = 0.45), I^2 =0.0%							

data for Bogdan 2011, Dahl 2001, Rossi 2002, and Calverley 2003b [TRISTAN] are entered as endpoint scores.

(1) Last available score with imputed SD (based on other studies). Change from baseline data and endpoint data were pooled in the analysis. Most studies reported change from baseline but

(2) SDs calculated from ANCOVA confidence intervals

(3) SDs for Doherty 2012 and Szafranski 2003 were imputed based on population variance and that of other arms within the studies

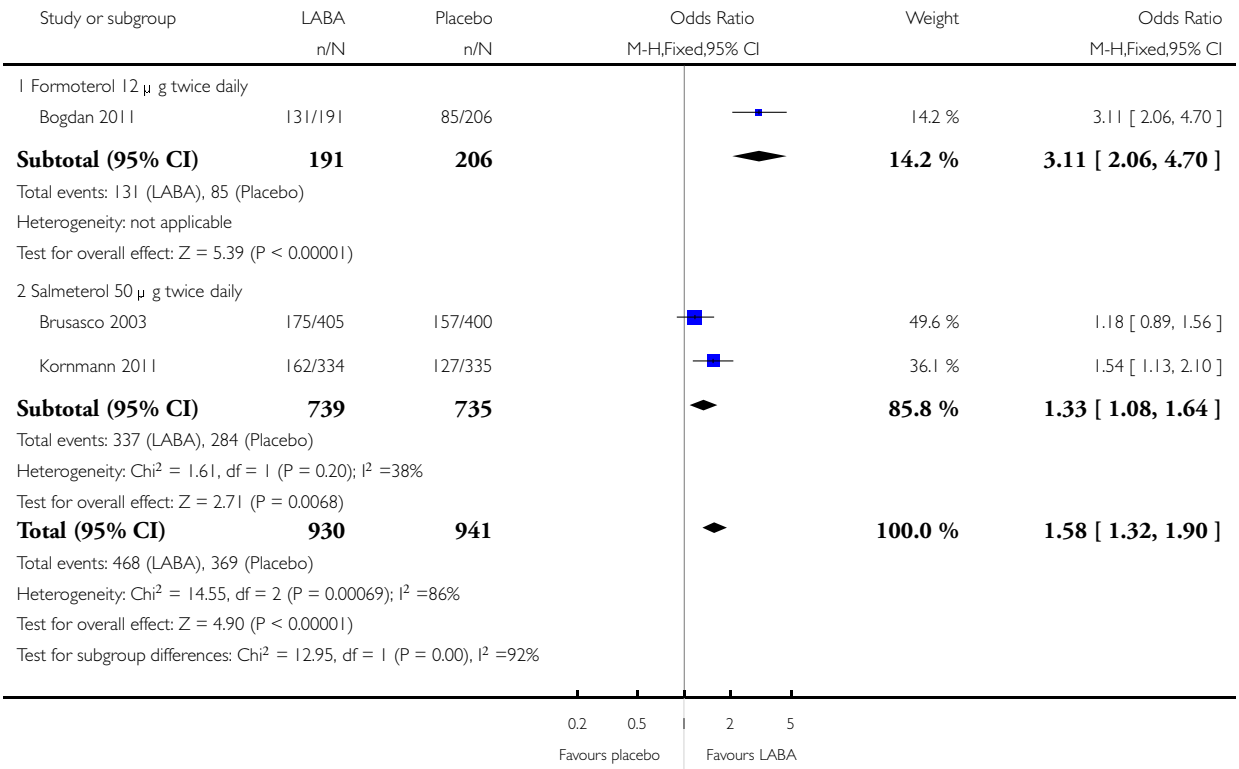
(4) Adjusted mean at endpoint

Analysis 1.2. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 2 Quality of life (number of people achieving the MCID on the SGRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 2 Quality of life (number of people achieving the MCID on the SGRQ)



Analysis 1.3. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 3 Quality of life (CRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 3 Quality of life (CRQ)

Study or subgroup	LABA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Salmeterol 50 μg twice daily							
Hanania 2003 (1)	177	6.4 (18)	185	5 (15)		30.3 %	1.40 [-2.02, 4.82]
Mahler 1999	135	7.1 (16.2665)	143	2.1 (15.5457)		25.3 %	5.00 [1.26, 8.74]
Mahler 2002 (2)	160	8 (18)	181	5 (15)		28.2 %	3.00 [-0.54, 6.54]
Rennard 2001	109	10.3 (19.7322)	103	6.8 (14.7159)		16.3 %	3.50 [-1.17, 8.17]
Total (95% CI)	**581**		**612**			**100.0 %**	**3.10 [1.22, 4.98]**

Heterogeneity: Chi^2 = 1.97, df = 3 (P = 0.58); I^2 =0.0%

Test for overall effect: Z = 3.23 (P = 0.0012)

Test for subgroup differences: Not applicable

(1) Standard deviations were not reported, and were imputed based on the SDs reported in Mahler 1999 and Rennard 2001

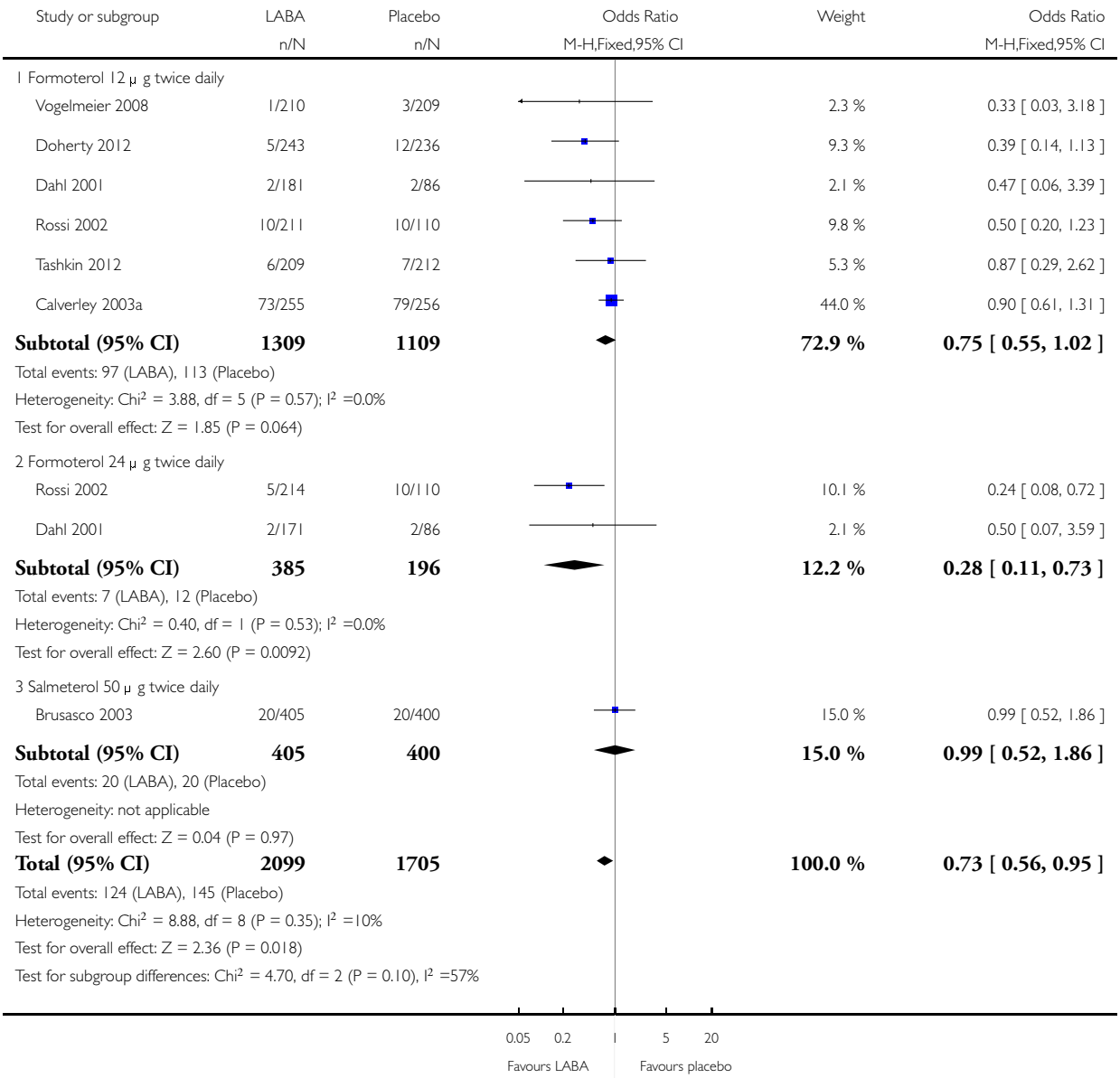
(2) Standard deviations were not reported, and were imputed based on the SDs reported in Mahler 1999 and Rennard 2001

Analysis 1.4. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 4 Severe exacerbations (hospitalisations).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 4 Severe exacerbations (hospitalisations)



Analysis 1.5. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 5 Severe/moderate exacerbations (hospitalisation or course of meds or ER visit.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 5 Severe/moderate exacerbations (hospitalisation ***or*** course of meds ***or*** ER visit

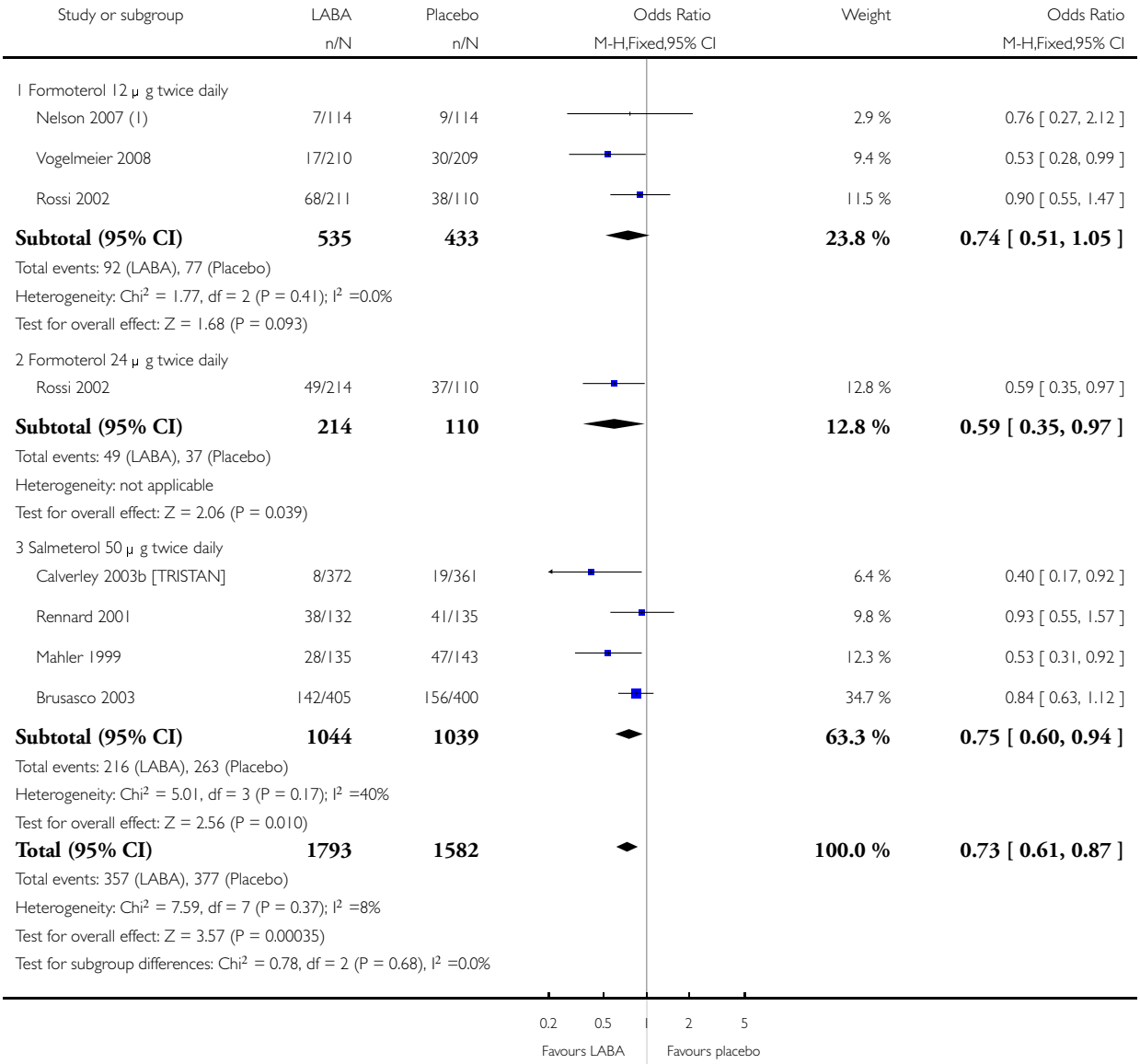
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Formoterol 12 µ g twice daily					
Bogdan 2011	8/199	17/208		4.1 %	0.47 [0.20, 1.12]
Campbell 2005	35/215	34/217		7.3 %	1.05 [0.63, 1.75]
Dahl 2010	126/435	145/432		26.8 %	0.81 [0.61, 1.08]
Rennard 2009	177/495	179/481		30.2 %	0.94 [0.72, 1.22]
Subtotal (95% CI)	**1344**	**1338**		**68.5 %**	**0.87 [0.73, 1.04]**
Total events: 346 (LABA), 375 (Placebo)					
Heterogeneity: Chi^2 = 3.03, df = 3 (P = 0.39); I^2 =1%					
Test for overall effect: Z = 1.54 (P = 0.12)					
2 Salmeterol 50 µ g twice daily					
Hanrahan 2008	41/290	44/293		9.7 %	0.93 [0.59, 1.48]
Mahler 2002	100/160	118/181		10.8 %	0.89 [0.57, 1.39]
Hanania 2003	55/177	63/185		11.0 %	0.87 [0.56, 1.36]
Subtotal (95% CI)	**627**	**659**		**31.5 %**	**0.90 [0.69, 1.16]**
Total events: 196 (LABA), 225 (Placebo)					
Heterogeneity: Chi^2 = 0.04, df = 2 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 0.83 (P = 0.41)					
Total (95% CI)	**1971**	**1997**		**100.0 %**	**0.88 [0.76, 1.02]**
Total events: 542 (LABA), 600 (Placebo)					
Heterogeneity: Chi^2 = 3.10, df = 6 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.85), I^2 =0.0%					

Analysis 1.6. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 6 Moderate exacerbations (course of antibiotics and/or steroids).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 6 Moderate exacerbations (course of antibiotics and/or steroids)



(1) Nelson 2007 and Mahler 1999 did not explicitly define exacerbations. Rates were more in keeping with 'moderate' than 'severe'.

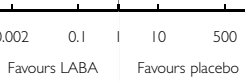
Analysis 1.7. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 7 Mortality (all-cause).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 7 Mortality (all-cause)

Study or subgroup	LABA n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol 12 µg twice daily				
Bogdan 2011	0/199	0/208		0.0 [0.0, 0.0]
Nelson 2007	0/114	0/114		0.0 [0.0, 0.0]
Dahl 2001	0/192	0/100		0.0 [0.0, 0.0]
Vogelmeier 2008	0/210	1/209		0.13 [0.00, 6.79]
Tashkin 2008 [SHINE]	1/284	1/300		1.06 [0.07, 16.95]
Campbell 2005	2/215	0/217		7.49 [0.47, 120.19]
Rossi 2002	3/211	0/110		4.62 [0.42, 50.53]
Tashkin 2012	3/209	1/212		2.78 [0.39, 19.86]
Doherty 2012	4/243	2/236		1.90 [0.38, 9.52]
Dahl 2010	3/435	4/432		0.74 [0.17, 3.29]
Rennard 2009	4/495	4/481		0.97 [0.24, 3.90]
Szafranski 2003	6/201	9/205		0.67 [0.24, 1.89]
Calverley 2003a	13/255	5/256		2.52 [0.98, 6.45]
Subtotal (95% CI)	**3263**	**3080**		**1.41 [0.87, 2.30]**
Total events: 39 (LABA), 27 (Placebo)				
Heterogeneity: Chi^2 = 8.77, df = 9 (P = 0.46); I^2 =0.0%				
Test for overall effect: Z = 1.38 (P = 0.17)				
2 Formoterol 24 µg twice daily				
Dahl 2001	0/191	0/100		0.0 [0.0, 0.0]
Rossi 2002	1/214	0/110		4.54 [0.07, 285.14]
Subtotal (95% CI)	**405**	**210**		**4.54 [0.07, 285.14]**
Total events: 1 (LABA), 0 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
3 Salmeterol 50 µg twice daily				
SLMF4010 2005	0/17	0/17		0.0 [0.0, 0.0]



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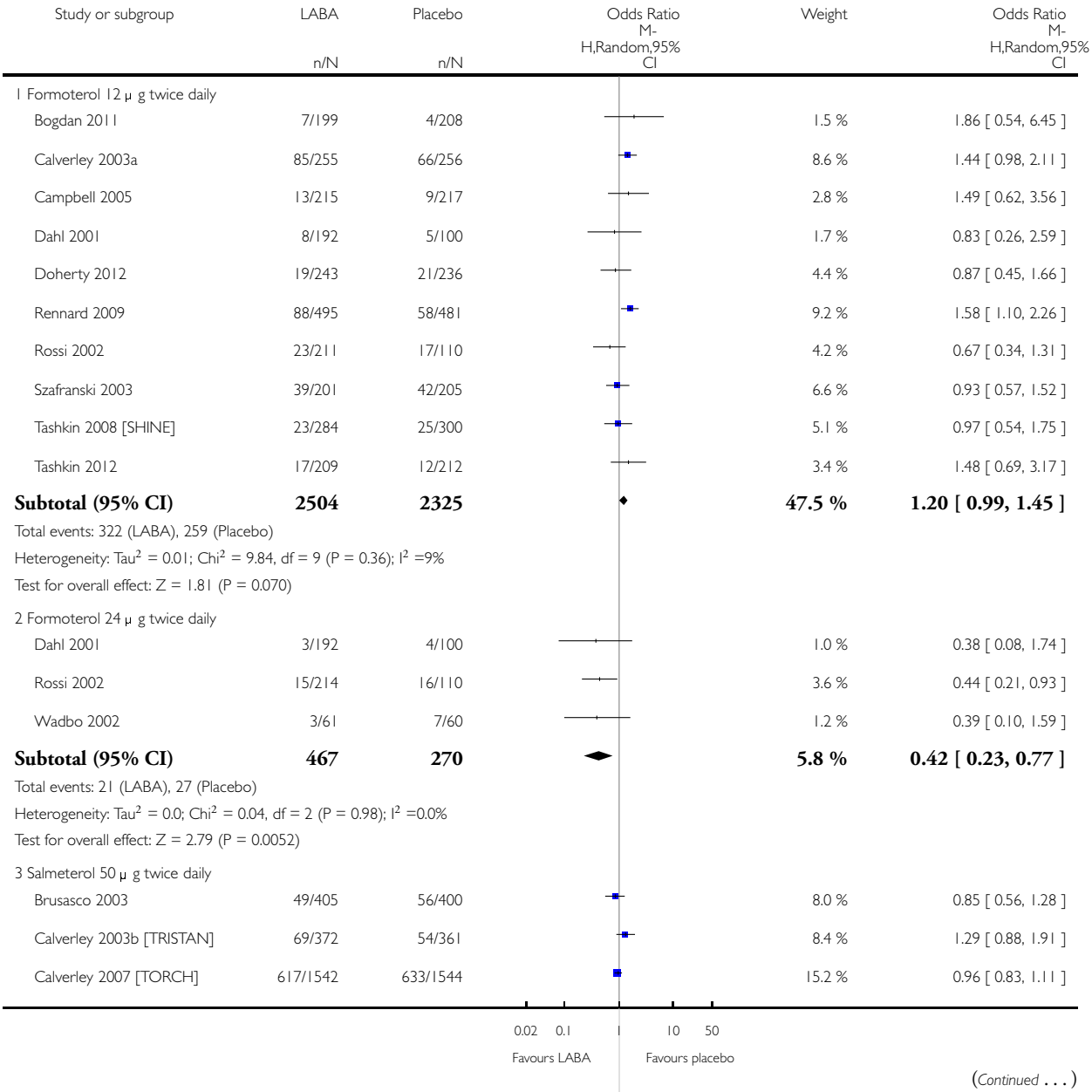
Study or subgroup	LABA n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Mahler 1999	0/135	0/143		0.0 [0.0, 0.0]
Hanania 2003	0/177	0/185		0.0 [0.0, 0.0]
Hanrahan 2008	0/293	0/294		0.0 [0.0, 0.0]
Rennard 2001	0/132	1/135		0.14 [0.00, 6.98]
Mahler 2002	0/160	3/181		0.15 [0.02, 1.46]
Kornmann 2011	0/334	3/335		0.13 [0.01, 1.30]
Calverley 2003b [TRISTAN]	3/372	7/361		0.43 [0.12, 1.50]
Brusasco 2003	6/405	5/400		1.19 [0.36, 3.90]
Calverley 2007 [TORCH]	205/1521	232/1524		0.87 [0.71, 1.06]
Subtotal (95% CI)	**3546**	**3575**		**0.83 [0.69, 1.01]**
Total events: 214 (LABA), 251 (Placebo)				
Heterogeneity: Chi^2 = 7.03, df = 5 (P = 0.22); I^2 =29%				
Test for overall effect: Z = 1.82 (P = 0.068)				
Total (95% CI)	**7214**	**6865**		**0.90 [0.75, 1.08]**
Total events: 254 (LABA), 278 (Placebo)				
Heterogeneity: Chi^2 = 20.23, df = 16 (P = 0.21); I^2 =21%				
Test for overall effect: Z = 1.15 (P = 0.25)				
Test for subgroup differences: Chi^2 = 4.44, df = 2 (P = 0.11), I^2 =55%				

Analysis 1.8. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 8 People with one or more non-fatal serious adverse event.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 8 People with one or more non-fatal serious adverse event



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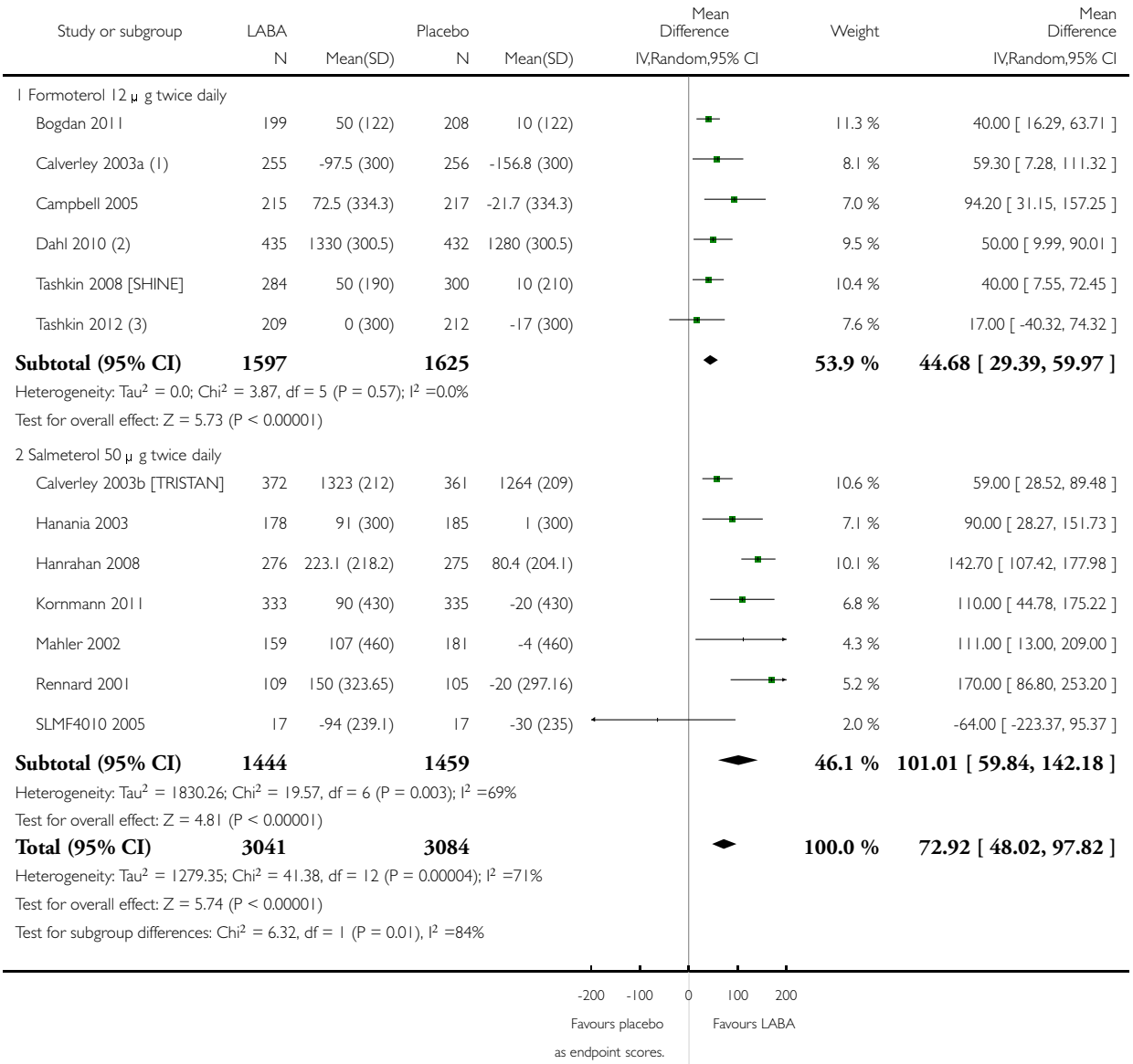
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Hanania 2003	5/177	11/185		1.9 %	0.46 [0.16, 1.35]
Hanrahan 2008	11/290	19/293		3.5 %	0.57 [0.27, 1.22]
Kornmann 2011	19/334	26/335		4.8 %	0.72 [0.39, 1.32]
Mahler 2002	7/160	11/181		2.3 %	0.71 [0.27, 1.87]
Rennard 2001	10/132	7/135		2.2 %	1.50 [0.55, 4.06]
SLMF4010 2005	1/17	3/17		0.4 %	0.29 [0.03, 3.13]
Subtotal (95% CI)	**3429**	**3451**		**46.7 %**	**0.93 [0.78, 1.10]**
Total events: 788 (LABA), 820 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 9.15, df = 8 (P = 0.33); I^2 =13%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Total (95% CI)	**6400**	**6046**		**100.0 %**	**0.97 [0.83, 1.14]**
Total events: 1131 (LABA), 1106 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 32.05, df = 21 (P = 0.06); I^2 =34%					
Test for overall effect: Z = 0.35 (P = 0.72)					
Test for subgroup differences: Chi^2 = 11.91, df = 2 (P = 0.00), I^2 =83%					

Analysis 1.9. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 9 Predose FEV1 (mL).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 9 Predose FEV$_1$ (mL)



(1) SD imputed by calculating the mean SD for change reported in the other included studies (mean SD for LABA and placebo were both 0.3))

(2) Change from baseline data and endpoint data were pooled in the analysis. Most studies reported change from baseline but data for Dahl 2010, and Calverley 2003b [TRISTAN] are entered

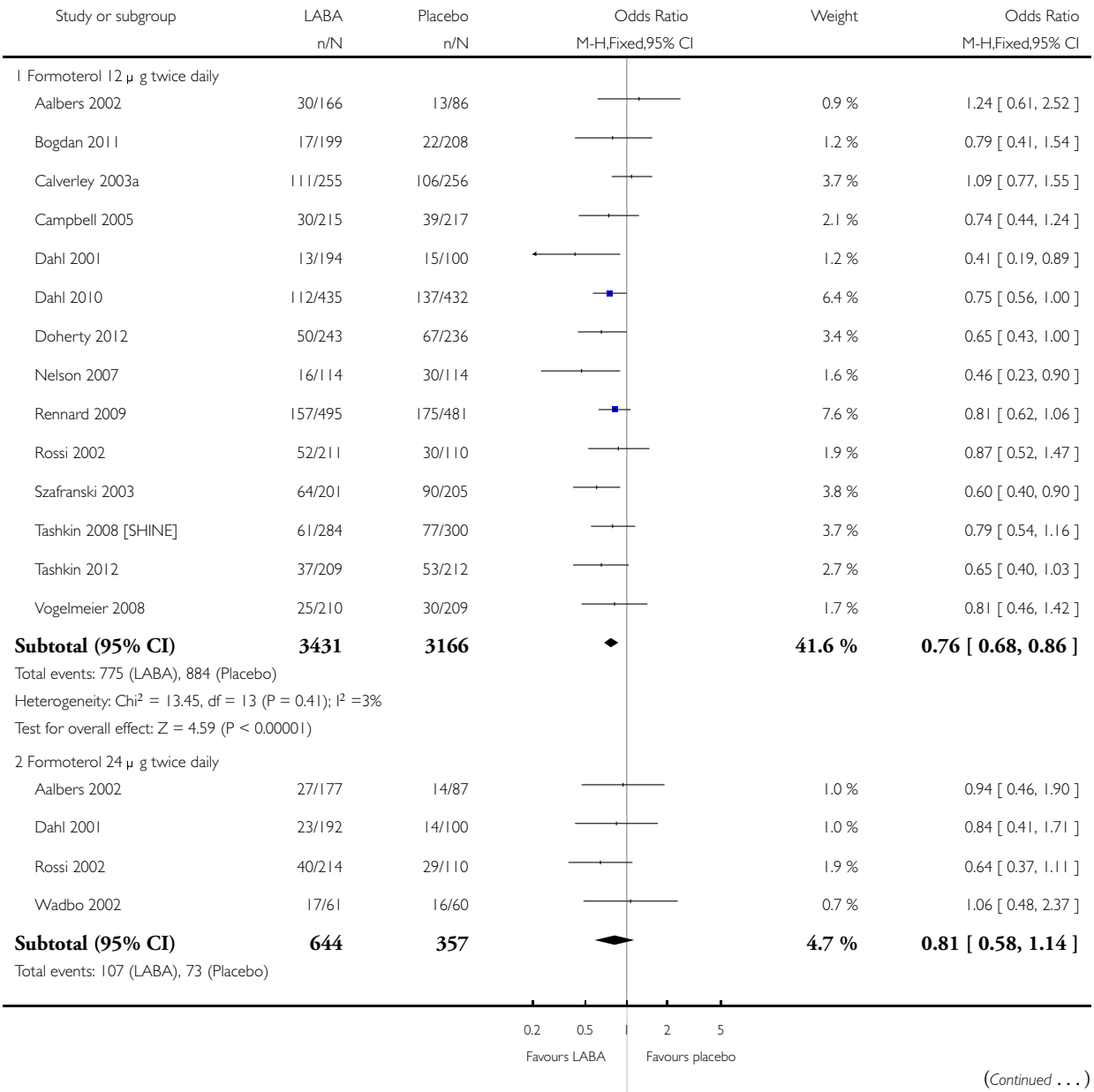
(3) SD imputed as for Calverley 2003a

Analysis 1.10. Comparison 1 All LABA versus placebo [subgrouped by drug], Outcome 10 Withdrawal.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 1 All LABA versus placebo [subgrouped by drug]

Outcome: 10 Withdrawal



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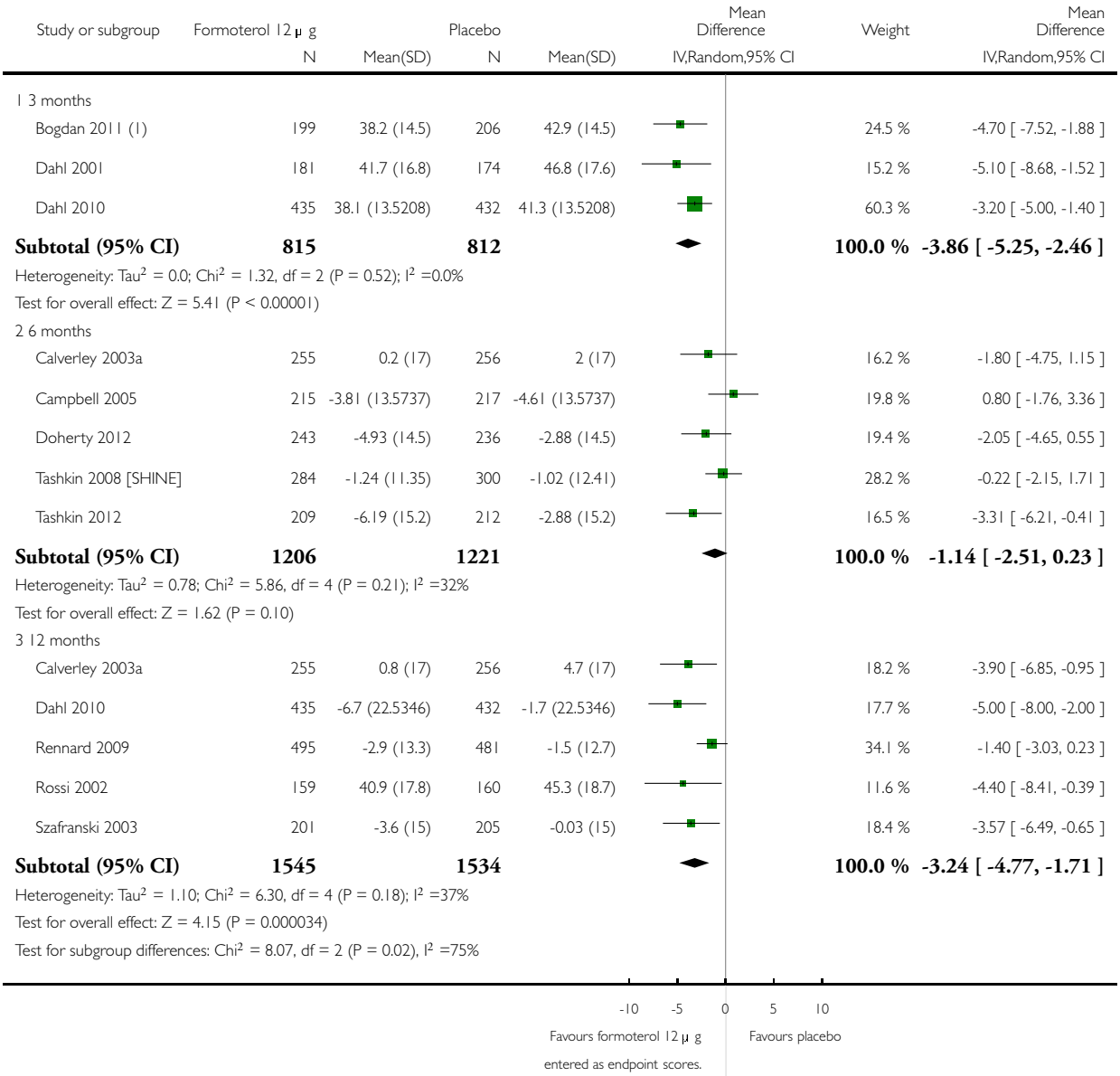
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 1.31, df = 3 (P = 0.73); I² =0.0%					
Test for overall effect: Z = 1.22 (P = 0.22)					
3 Salmeterol 50 µ g twice daily					
Brusasco 2003	76/405	103/400		5.2 %	0.67 [0.48, 0.93]
Calverley 2003b [TRISTAN]	119/372	140/361		6.0 %	0.74 [0.55, 1.01]
Calverley 2007 [TORCH]	582/1544	694/1545		27.0 %	0.74 [0.64, 0.86]
Hanania 2003	57/177	59/185		2.4 %	1.01 [0.65, 1.58]
Hanrahan 2008	44/293	64/294		3.4 %	0.64 [0.42, 0.97]
Kornmann 2011	50/334	70/335		3.7 %	0.67 [0.45, 0.99]
Mahler 1999	9/135	23/143		1.3 %	0.37 [0.17, 0.84]
Mahler 2002	45/160	69/181		2.9 %	0.64 [0.40, 1.00]
Rennard 2001	22/132	29/135		1.5 %	0.73 [0.40, 1.35]
SLMF4010 2005	7/17	7/17		0.3 %	1.00 [0.26, 3.92]
Subtotal (95% CI)	**3569**	**3596**		**53.7 %**	**0.72 [0.65, 0.80]**
Total events: 1011 (LABA), 1258 (Placebo)					
Heterogeneity: Chi² = 6.26, df = 9 (P = 0.71); I² =0.0%					
Test for overall effect: Z = 6.24 (P < 0.00001)					
Total (95% CI)	**7644**	**7119**		**100.0 %**	**0.74 [0.69, 0.80]**
Total events: 1893 (LABA), 2215 (Placebo)					
Heterogeneity: Chi² = 21.80, df = 27 (P = 0.75); I² =0.0%					
Test for overall effect: Z = 7.80 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.83, df = 2 (P = 0.66), I² =0.0%					

Analysis 2.1. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 1 Quality of life (SGRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 μ g versus placebo [subgrouped by trial duration]

Outcome: 1 Quality of life (SGRQ)



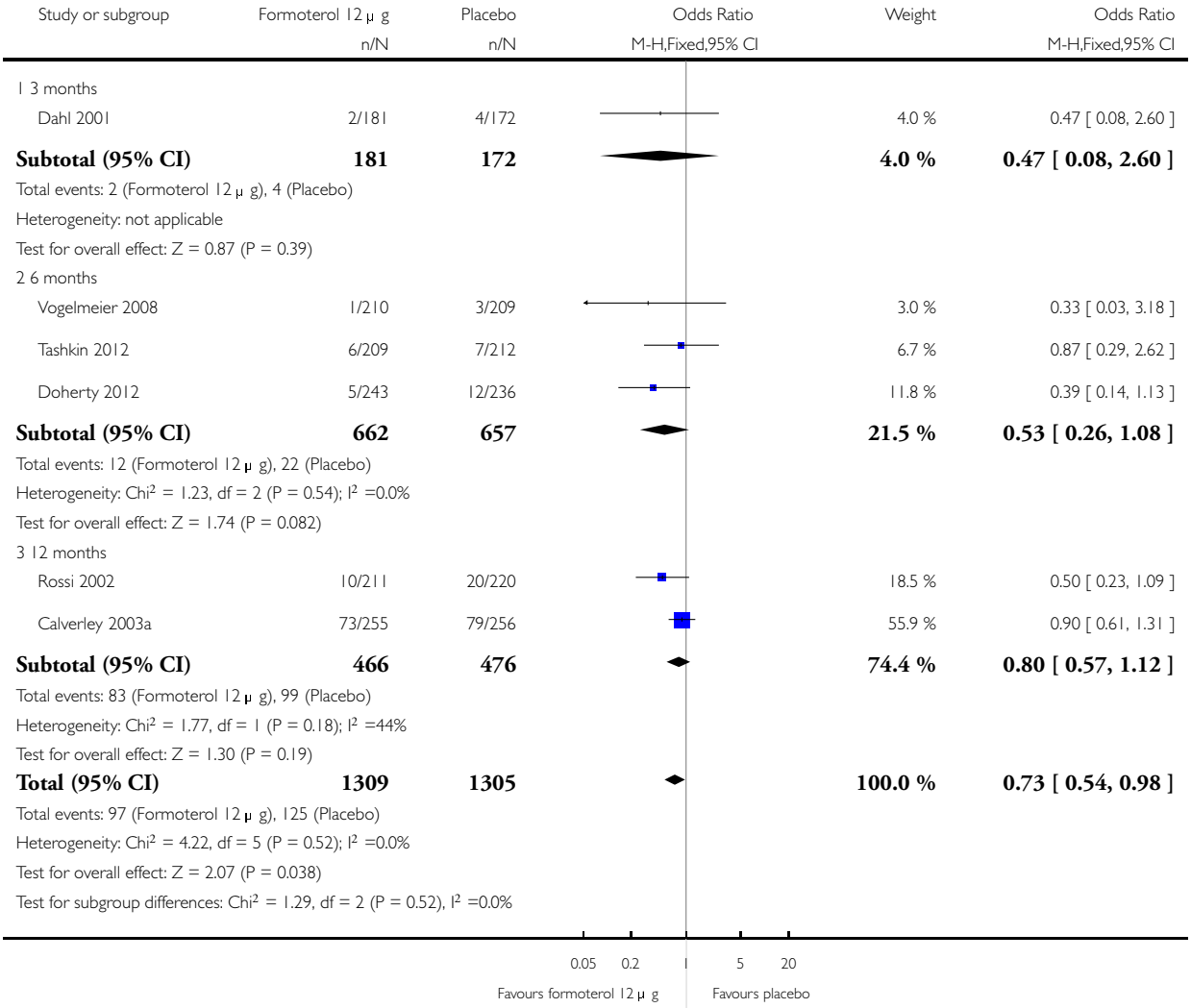
(1) Change from baseline data and endpoint data were pooled in the analysis. Most studies reported change from baseline but data for Bogdan 2011, Dahl 2001, Dahl 2010, and Rossi 2002 are

Analysis 2.2. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 2 Severe exacerbations (hospitalisations).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 μ g versus placebo [subgrouped by trial duration]

Outcome: 2 Severe exacerbations (hospitalisations)

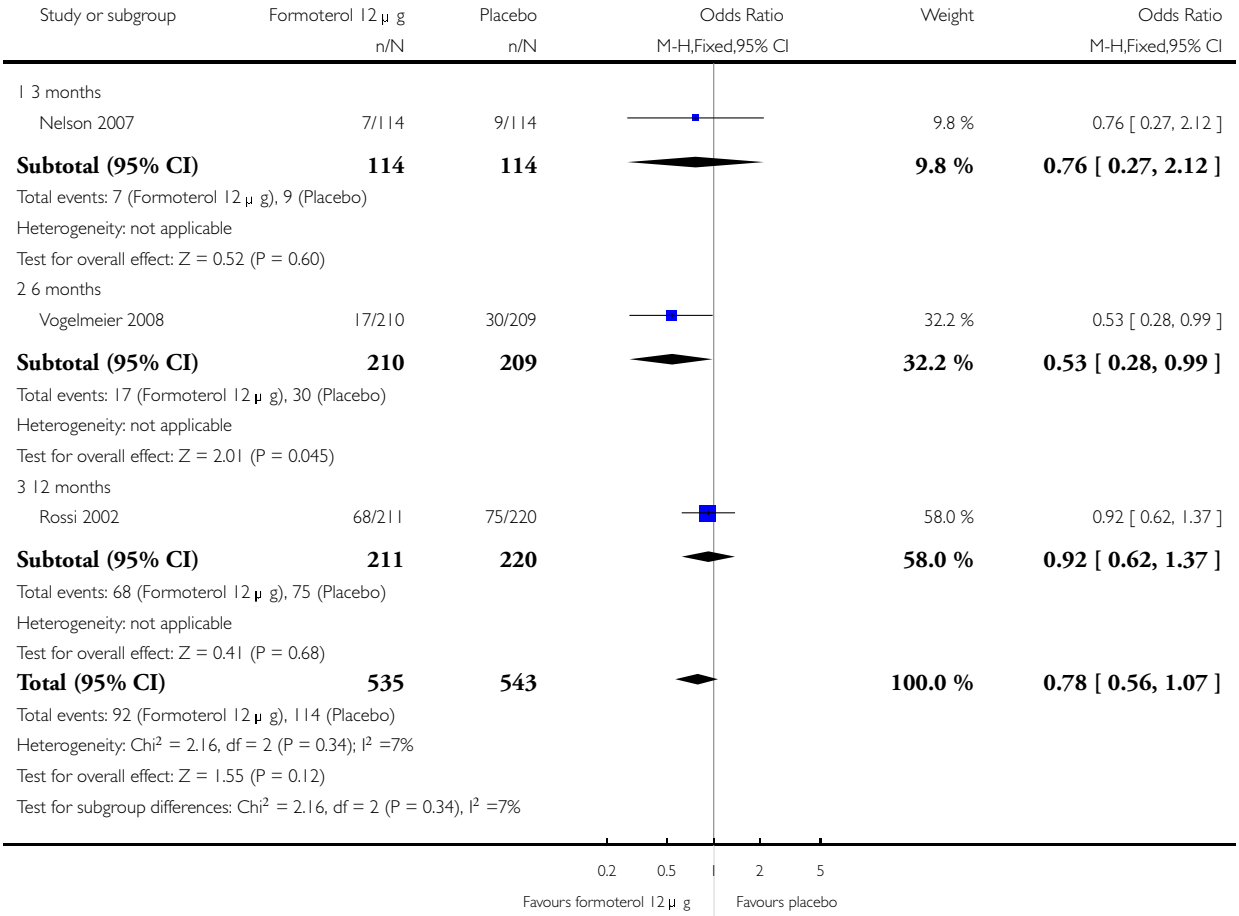


Analysis 2.3. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 3 Moderate exacerbations (course of antibiotics and/or steroids).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 μ g versus placebo [subgrouped by trial duration]

Outcome: 3 Moderate exacerbations (course of antibiotics and/or steroids)

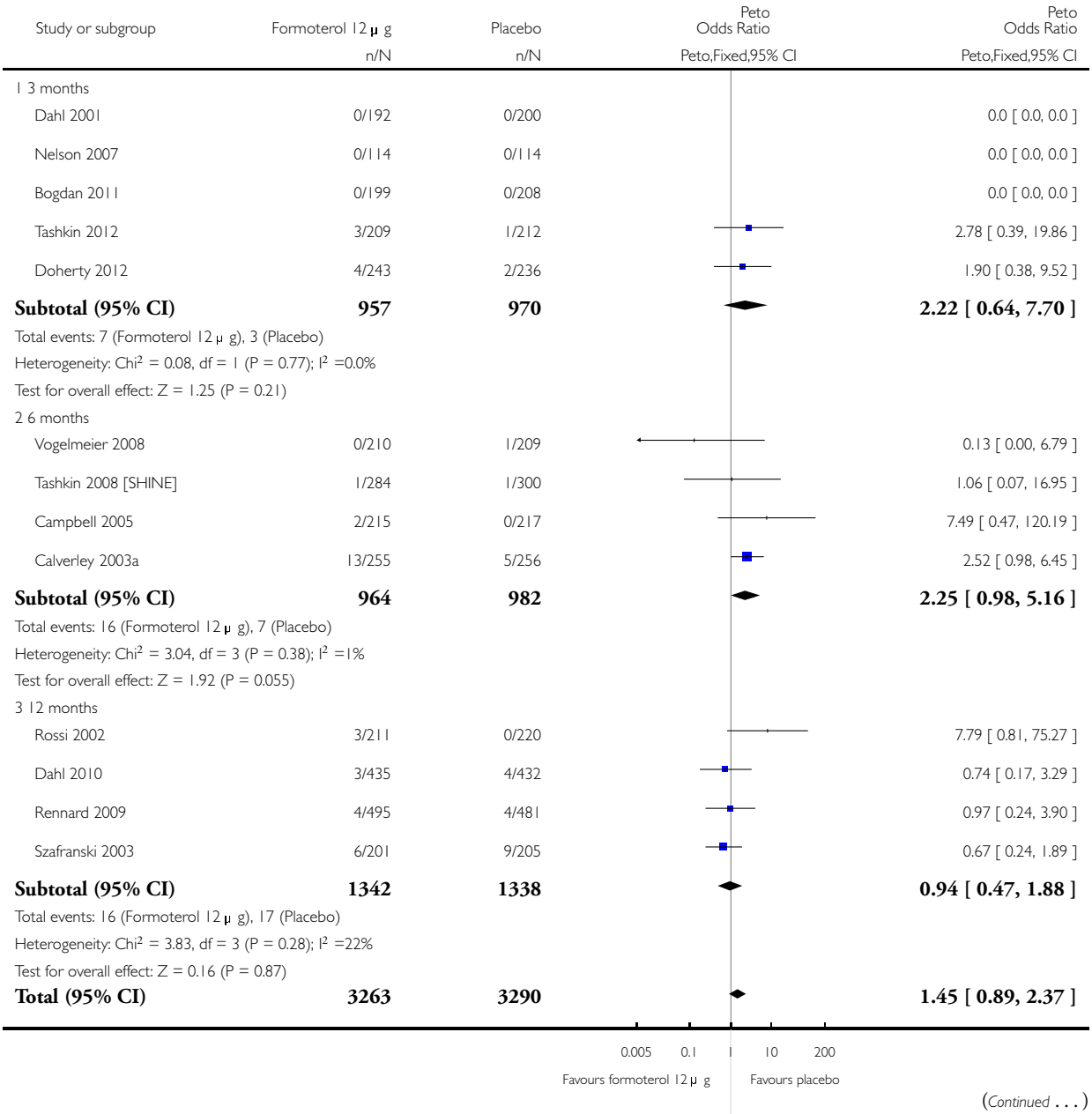


Analysis 2.4. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 4 Mortality (all-cause).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 μ g versus placebo [subgrouped by trial duration]

Outcome: 4 Mortality (all-cause)



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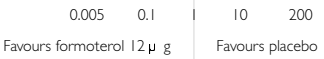
Study or subgroup	Formoterol 12 µ g n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 39 (Formoterol 12 µ g), 27 (Placebo)				
Heterogeneity: Chi^2 = 9.98, df = 9 (P = 0.35); I^2 =10%				
Test for overall effect: Z = 1.51 (P = 0.13)				
Test for subgroup differences: Chi^2 = 3.02, df = 2 (P = 0.22), I^2 =34%				



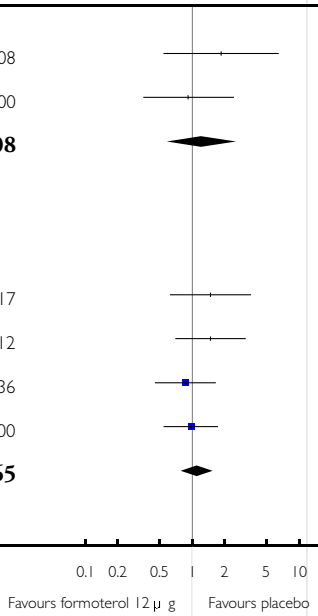
Analysis 2.5. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 5 Patients with one or more serious adverse event.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 µ g versus placebo [subgrouped by trial duration]

Outcome: 5 Patients with one or more serious adverse event

Study or subgroup	Formoterol 12 µ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 3 months					
Bogdan 2011	7/199	4/208		1.7 %	1.86 [0.54, 6.45]
Dahl 2001	8/192	9/200		3.7 %	0.92 [0.35, 2.44]
Subtotal (95% CI)	**391**	**408**		**5.4 %**	**1.21 [0.57, 2.58]**
Total events: 15 (Formoterol 12 µ g), 13 (Placebo)					
Heterogeneity: Chi^2 = 0.76, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.50 (P = 0.62)					
2 6 months					
Campbell 2005	13/215	9/217		3.7 %	1.49 [0.62, 3.56]
Tashkin 2012	17/209	12/212		4.8 %	1.48 [0.69, 3.17]
Doherty 2012	19/243	21/236		8.6 %	0.87 [0.45, 1.66]
Tashkin 2008 [SHINE]	23/284	25/300		9.8 %	0.97 [0.54, 1.75]
Subtotal (95% CI)	**951**	**965**		**26.9 %**	**1.10 [0.78, 1.55]**
Total events: 72 (Formoterol 12 µ g), 67 (Placebo)					



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Study or subgroup	Formoterol 12 µg n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 1.71, df = 3 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 0.53 (P = 0.59)					
3 12 months					
Rossi 2002	23/211	33/220		12.6 %	0.69 [0.39, 1.23]
Szafranski 2003	39/201	42/205		14.7 %	0.93 [0.57, 1.52]
Calverley 2003a	85/255	66/256		19.2 %	1.44 [0.98, 2.11]
Rennard 2009	88/495	58/481		21.2 %	1.58 [1.10, 2.26]
Subtotal (95% CI)	**1162**	**1162**		**67.8 %**	**1.23 [1.00, 1.52]**
Total events: 235 (Formoterol 12 µg), 199 (Placebo)					
Heterogeneity: Chi² = 7.61, df = 3 (P = 0.05); I² =61%					
Test for overall effect: Z = 1.95 (P = 0.052)					
Total (95% CI)	**2504**	**2535**		**100.0 %**	**1.20 [1.00, 1.43]**
Total events: 322 (Formoterol 12 µg), 279 (Placebo)					
Heterogeneity: Chi² = 10.41, df = 9 (P = 0.32); I² =14%					
Test for overall effect: Z = 2.00 (P = 0.045)					
Test for subgroup differences: Chi² = 0.32, df = 2 (P = 0.85), I² =0.0%					

Analysis 2.6. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 6 Predose FEV1 (mL).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 μ g versus placebo [subgrouped by trial duration]

Outcome: 6 Predose FEV_1 (mL)

Study or subgroup	Formoterol 12 μ g N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 3 months							
Bogdan 2011	199	50 (122)	208	10 (122)		41.6 %	40.00 [16.29, 63.71]
Subtotal (95% CI)	**199**		**208**			**41.6 %**	**40.00 [16.29, 63.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.31 (P = 0.00094)							
2 6 months							
Campbell 2005	215	72.5 (334.3)	217	-21.7 (334.3)		5.9 %	94.20 [31.15, 157.25]
Tashkin 2008 [SHINE]	284	50 (190)	300	10 (210)		22.2 %	40.00 [7.55, 72.45]
Tashkin 2012	209	0 (300)	212	-17 (300)		7.1 %	17.00 [-40.32, 74.32]
Subtotal (95% CI)	**708**		**729**			**35.2 %**	**44.41 [18.63, 70.18]**
Heterogeneity: Chi^2 = 3.35, df = 2 (P = 0.19); I^2 =40%							
Test for overall effect: Z = 3.38 (P = 0.00073)							
3 12 months							
Calverley 2003a	255	-97.5 (300)	256	-156.8 (300)		8.6 %	59.30 [7.28, 111.32]
Dahl 2010 (1)	435	1330 (300.5)	432	1280 (300.5)		14.6 %	50.00 [9.99, 90.01]
Subtotal (95% CI)	**690**		**688**			**23.2 %**	**53.46 [21.74, 85.17]**
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%							
Test for overall effect: Z = 3.30 (P = 0.00095)							
Total (95% CI)	**1597**		**1625**			**100.0 %**	**44.68 [29.39, 59.97]**
Heterogeneity: Chi^2 = 3.87, df = 5 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 5.73 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.44, df = 2 (P = 0.80), I^2 =0.0%							

Change from baseline data and endpoint data were pooled in the analysis. Only Dahl 2010 were entered as endpoint scores.

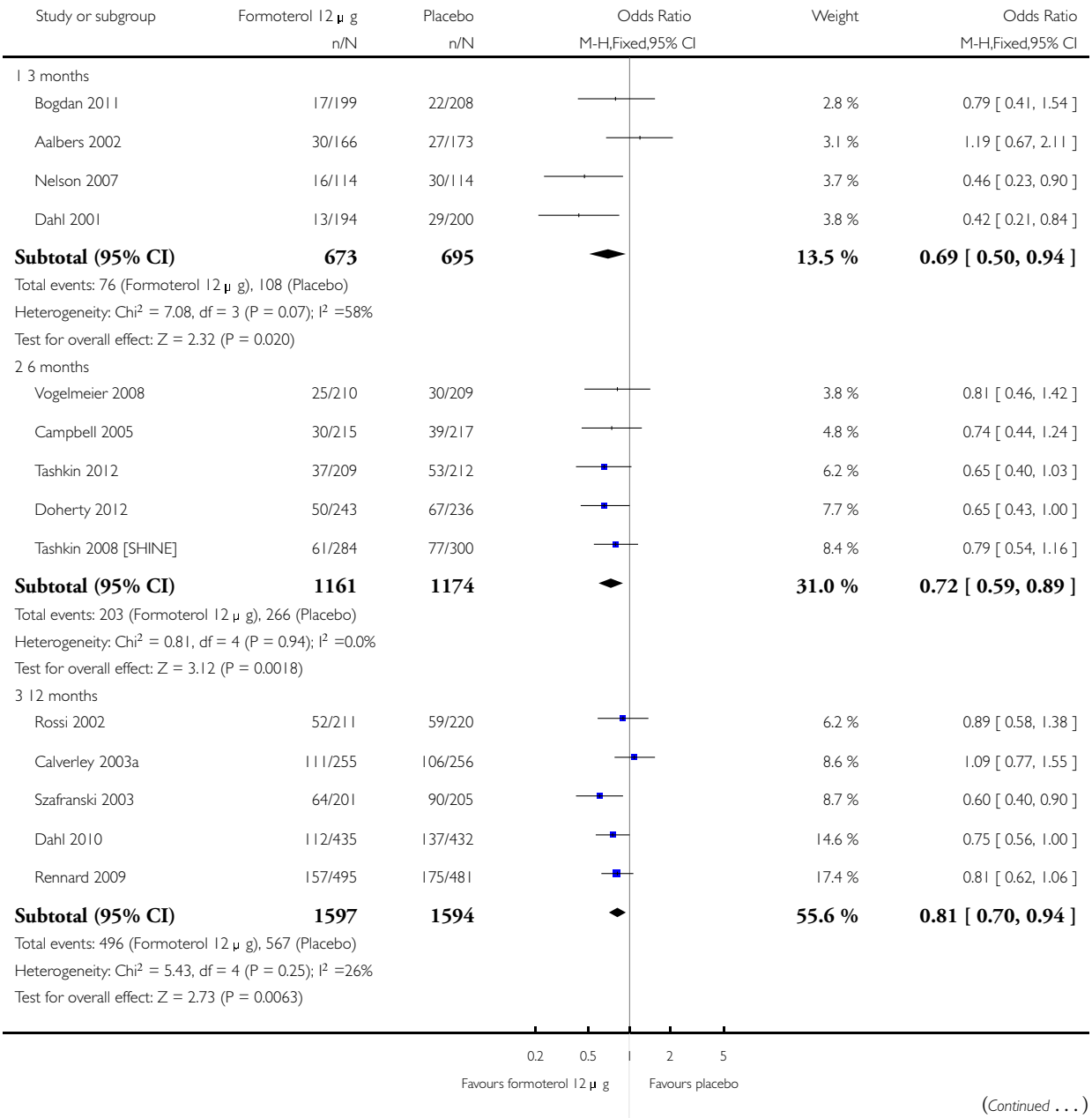
(1) Data was also presented for 3 months but omitted in this analysis to avoid double counting. Sensitivity analyses with the study included in both time-points did not change conclusions.

Analysis 2.7. Comparison 2 Formoterol 12 μg versus placebo [subgrouped by trial duration], Outcome 7 Withdrawal.

Review: Long-acting beta2-agonists for chronic obstructive pulmonary disease

Comparison: 2 Formoterol 12 μ g versus placebo [subgrouped by trial duration]

Outcome: 7 Withdrawal



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Study or subgroup	Formoterol 12 µg n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total (95% CI)	**3431**	**3463**	◆	**100.0 %**	**0.77 [0.69, 0.86]**
Total events: 775 (Formoterol 12 µg), 941 (Placebo)					
Heterogeneity: Chi^2 = 14.62, df = 13 (P = 0.33); I^2 =11%					
Test for overall effect: Z = 4.61 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.40, df = 2 (P = 0.50), I^2 =0.0%					

0.2 0.5 1 2 5

Favours formoterol 12 µg Favours placebo

Analysis 3.1. Comparison 3 Formoterol 24 µg versus placebo [subgrouped by trial duration], Outcome 1 Quality of life (SGRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 3 Formoterol 24 µg versus placebo [subgrouped by trial duration]

Outcome: 1 Quality of life (SGRQ)

Study or subgroup	Formoterol 24 µg N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 3 months							
Dahl 2001 (1)	169	43.5 (19.4)	86	46.8 (17.6)		21.5 %	-3.30 [-8.03, 1.43]
Wadbo 2002	61	0 (8.59)	60	1.5 (8.9034)		49.4 %	-1.50 [-4.62, 1.62]
Subtotal (95% CI)	**230**		**146**		◆	**70.9 %**	**-2.04 [-4.65, 0.56]**
Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 1.54 (P = 0.12)							
2 12 months							
Rossi 2002	171	42.3 (19)	160	45.3 (18.7)		29.1 %	-3.00 [-7.06, 1.06]
Subtotal (95% CI)	**171**		**160**		◆	**29.1 %**	**-3.00 [-7.06, 1.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							
Total (95% CI)	**401**		**306**		◆	**100.0 %**	**-2.32 [-4.52, -0.13]**
Heterogeneity: Chi^2 = 0.54, df = 2 (P = 0.76); I^2 =0.0%							
Test for overall effect: Z = 2.08 (P = 0.038)							
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%							

-10 -5 0 5 10

Favours formoterol 24 µg Favours placebo

(1) Dahl 2001 and Rossi 2002 data are endpoint scores, and Wadbo 2002 was presented as change from baseline

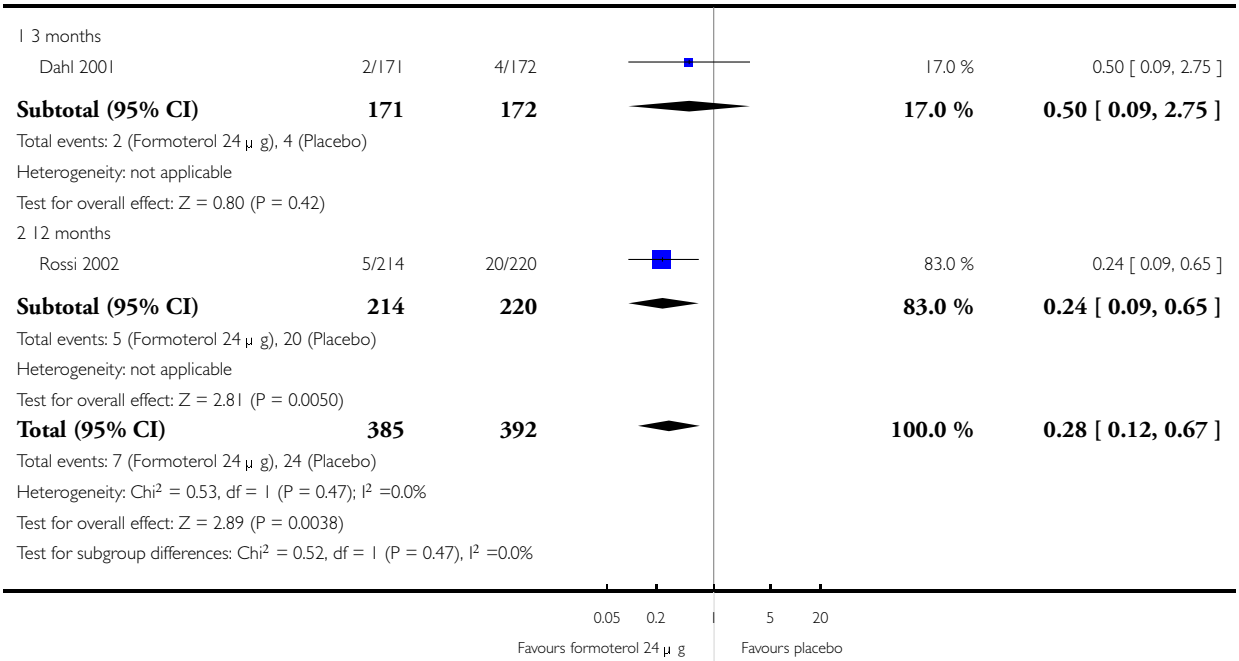
Analysis 3.2. Comparison 3 Formoterol 24 μg versus placebo [subgrouped by trial duration], Outcome 2 Severe exacerbations (hospitalisations).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 3 Formoterol 24 μ g versus placebo [subgrouped by trial duration]

Outcome: 2 Severe exacerbations (hospitalisations)

Study or subgroup	Formoterol 24 μ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 3 months					
Dahl 2001	2/171	4/172		17.0 %	0.50 [0.09, 2.75]
Subtotal (95% CI)	**171**	**172**		**17.0 %**	**0.50 [0.09, 2.75]**
Total events: 2 (Formoterol 24 μ g), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 12 months					
Rossi 2002	5/214	20/220		83.0 %	0.24 [0.09, 0.65]
Subtotal (95% CI)	**214**	**220**		**83.0 %**	**0.24 [0.09, 0.65]**
Total events: 5 (Formoterol 24 μ g), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.81 (P = 0.0050)					
Total (95% CI)	**385**	**392**		**100.0 %**	**0.28 [0.12, 0.67]**
Total events: 7 (Formoterol 24 μ g), 24 (Placebo)					
Heterogeneity: Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.89 (P = 0.0038)					
Test for subgroup differences: Chi^2 = 0.52, df = 1 (P = 0.47), I^2 =0.0%					



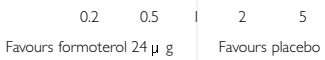
Analysis 3.3. Comparison 3 Formoterol 24 μg versus placebo [subgrouped by trial duration], Outcome 3 Moderate exacerbations (course of antibiotics and/or steroids).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 3 Formoterol 24 μ g versus placebo [subgrouped by trial duration]

Outcome: 3 Moderate exacerbations (course of antibiotics and/or steroids)

Study or subgroup	Formoterol 24 μ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 12 months				
Rossi 2002	49/214	75/220		0.57 [0.38, 0.88]



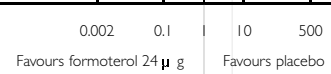
Analysis 3.4. Comparison 3 Formoterol 24 μg versus placebo [subgrouped by trial duration], Outcome 4 Mortality (all-cause).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 3 Formoterol 24 μ g versus placebo [subgrouped by trial duration]

Outcome: 4 Mortality (all-cause)

Study or subgroup	Formoterol 24 μ g n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 3 months				
Dahl 2001	0/191	0/200		0.0 [0.0, 0.0]
Subtotal (95% CI)	**191**	**200**		**0.0 [0.0, 0.0]**
Total events: 0 (Formoterol 24 μ g), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 12 months				
Rossi 2002	1/214	0/220		7.60 [0.15, 383.12]
Subtotal (95% CI)	**214**	**220**		**7.60 [0.15, 383.12]**
Total events: 1 (Formoterol 24 μ g), 0 (Placebo)				



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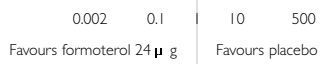
Study or subgroup	Formoterol 24 µ g n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 1.01 (P = 0.31)				
Total (95% CI)	**405**	**420**		**7.60 [0.15, 383.12]**
Total events: 1 (Formoterol 24 µ g), 0 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.01 (P = 0.31)				
Test for subgroup differences: Not applicable				



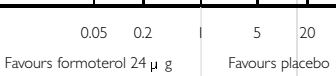
Analysis 3.5. Comparison 3 Formoterol 24 μg versus placebo [subgrouped by trial duration], Outcome 5 People with one or more non-fatal serious adverse events.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 3 Formoterol 24 µ g versus placebo [subgrouped by trial duration]

Outcome: 5 People with one or more non-fatal serious adverse events

Study or subgroup	Formoterol 24 µ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 3 months					
Wadbo 2002	3/61	7/60		9.4 %	0.39 [0.10, 1.59]
Dahl 2001	3/192	9/200		12.2 %	0.34 [0.09, 1.26]
Subtotal (95% CI)	**253**	**260**		**21.6 %**	**0.36 [0.14, 0.94]**
Total events: 6 (Formoterol 24 µ g), 16 (Placebo)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 2.08 (P = 0.038)					
2 12 months					
Rossi 2002	48/214	73/220		78.4 %	0.58 [0.38, 0.89]
Subtotal (95% CI)	**214**	**220**		**78.4 %**	**0.58 [0.38, 0.89]**
Total events: 48 (Formoterol 24 µ g), 73 (Placebo)					
Heterogeneity: not applicable					



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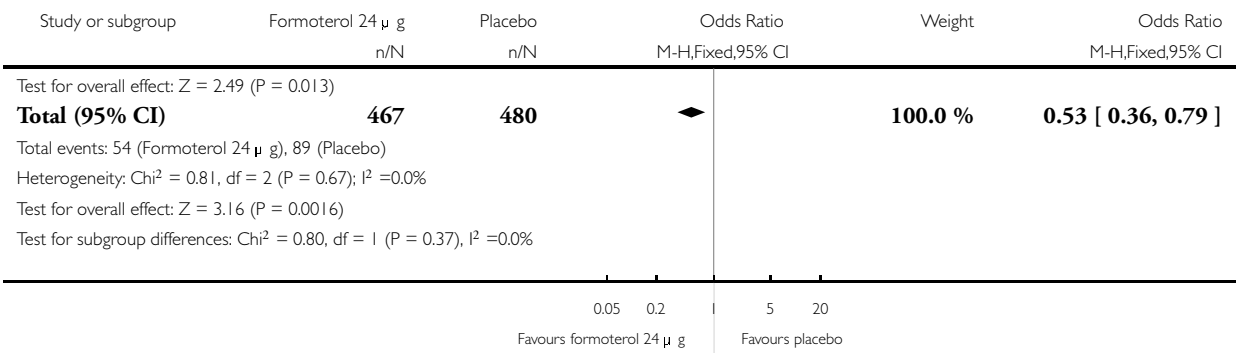
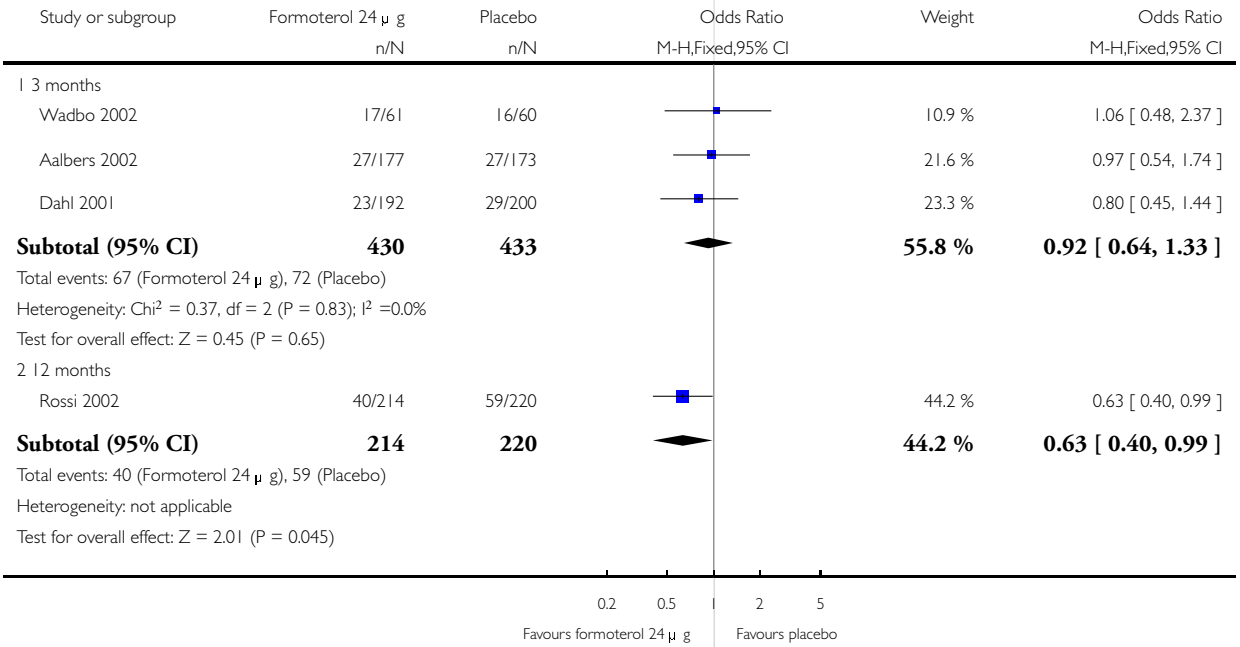


Analysis 3.6. Comparison 3 Formoterol 24 μg versus placebo [subgrouped by trial duration], Outcome 6 Withdrawal.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 3 Formoterol 24 µ g versus placebo [subgrouped by trial duration]

Outcome: 6 Withdrawal



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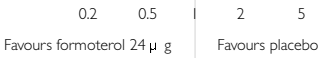
Study or subgroup	Formoterol 24 µg n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total (95% CI)	**644**	**653**		**100.0 %**	**0.79 [0.59, 1.05]**
Total events: 107 (Formoterol 24 µg), 131 (Placebo)					
Heterogeneity: Chi^2 = 2.01, df = 3 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.62 (P = 0.10)					
Test for subgroup differences: Chi^2 = 1.64, df = 1 (P = 0.20), I^2 =39%					



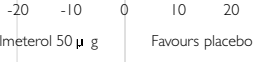
Analysis 4.1. Comparison 4 Salmeterol 50 µg versus placebo [subgrouped by trial duration], Outcome 1 Quality of life (SGRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 µg versus placebo [subgrouped by trial duration]

Outcome: 1 Quality of life (SGRQ)

Study or subgroup	Salmeterol 50 µg N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 6 months							
Brusasco 2003	405	-2.8 (14.087)	400	-1.5 (14)		19.9 %	-1.30 [-3.24, 0.64]
Kornmann 2011	292	-5.6 (15.4)	274	-1.5 (14.9)		14.5 %	-4.10 [-6.60, -1.60]
SLMF4010 2005	17	-7.1 (15.2555)	17	2.7 (16.0801)		1.1 %	-9.80 [-20.34, 0.74]
Subtotal (95% CI)	**714**		**691**			**35.6 %**	**-3.10 [-6.03, -0.17]**
Heterogeneity: Tau^2 = 3.52; Chi^2 = 4.89, df = 2 (P = 0.09); I^2 =59%							
Test for overall effect: Z = 2.07 (P = 0.038)							
2 12 months							
Calverley 2003b [TRISTAN] (1)	372	45.2 (7.7149)	361	46.3 (9.5)		29.9 %	-1.10 [-2.35, 0.15]
Subtotal (95% CI)	**372**		**361**			**29.9 %**	**-1.10 [-2.35, 0.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.72 (P = 0.086)							
3 36 months							
Calverley 2007 [TORCH]	1521	-0.8 (14.0772)	1524	0.2 (14.0772)		34.5 %	-1.00 [-2.00, 0.00]



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Study or subgroup	Salmeterol 50 µ g N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**1521**		**1524**		◆	**34.5 %**	**-1.00 [-2.00, 0.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.96 (P = 0.050)							
Total (95% CI)	**2607**		**2576**		◆	**100.0 %**	**-1.64 [-2.78, -0.50]**
Heterogeneity: Tau^2 = 0.73; Chi^2 = 7.76, df = 4 (P = 0.10); I^2 =48%							
Test for overall effect: Z = 2.81 (P = 0.0049)							
Test for subgroup differences: Chi^2 = 1.79, df = 2 (P = 0.41), I^2 =0.0%							

-20 -10 0 10 20

Favours salmeterol 50 µ g Favours placebo

(1) All data except Calverley 2003b [TRISTAN] (endpoint scores) are presented as change from baseline

Analysis 4.2. Comparison 4 Salmeterol 50 μg versus placebo [subgrouped by trial duration], Outcome 2 Severe exacerbations (hospitalisations).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 µ g versus placebo [subgrouped by trial duration]

Outcome: 2 Severe exacerbations (hospitalisations)

Study or subgroup	Salmeterol 50 µ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 6 months				
Brusasco 2003	20/405	20/400		0.99 [0.52, 1.86]

0.2 0.5 1 2 5

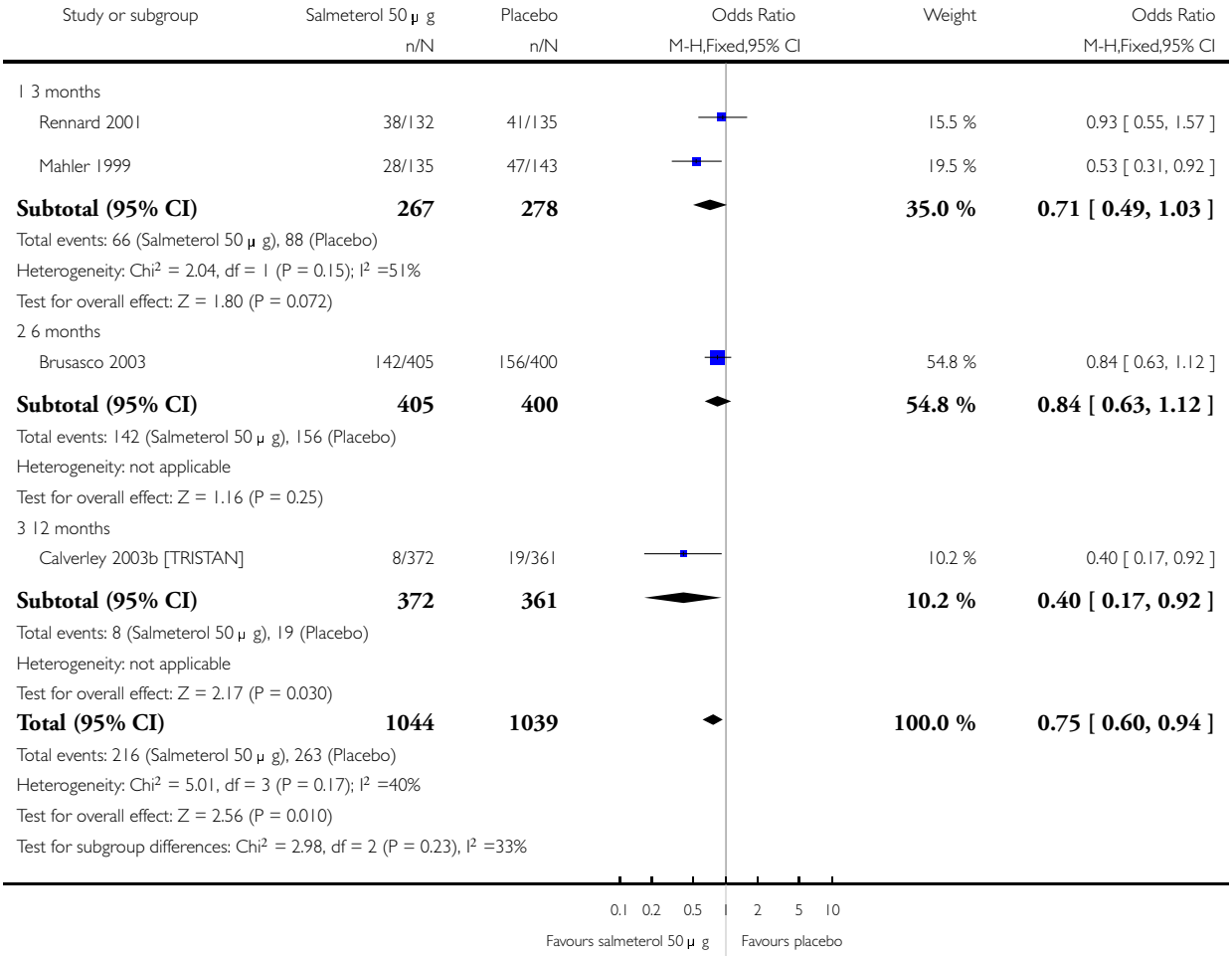
Favours salmeterol 50 µ g Favours placebo

Analysis 4.3. Comparison 4 Salmeterol 50 μg versus placebo [subgrouped by trial duration], Outcome 3 Moderate exacerbations (course of antibiotics and/or steroids).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 μ g versus placebo [subgrouped by trial duration]

Outcome: 3 Moderate exacerbations (course of antibiotics and/or steroids)

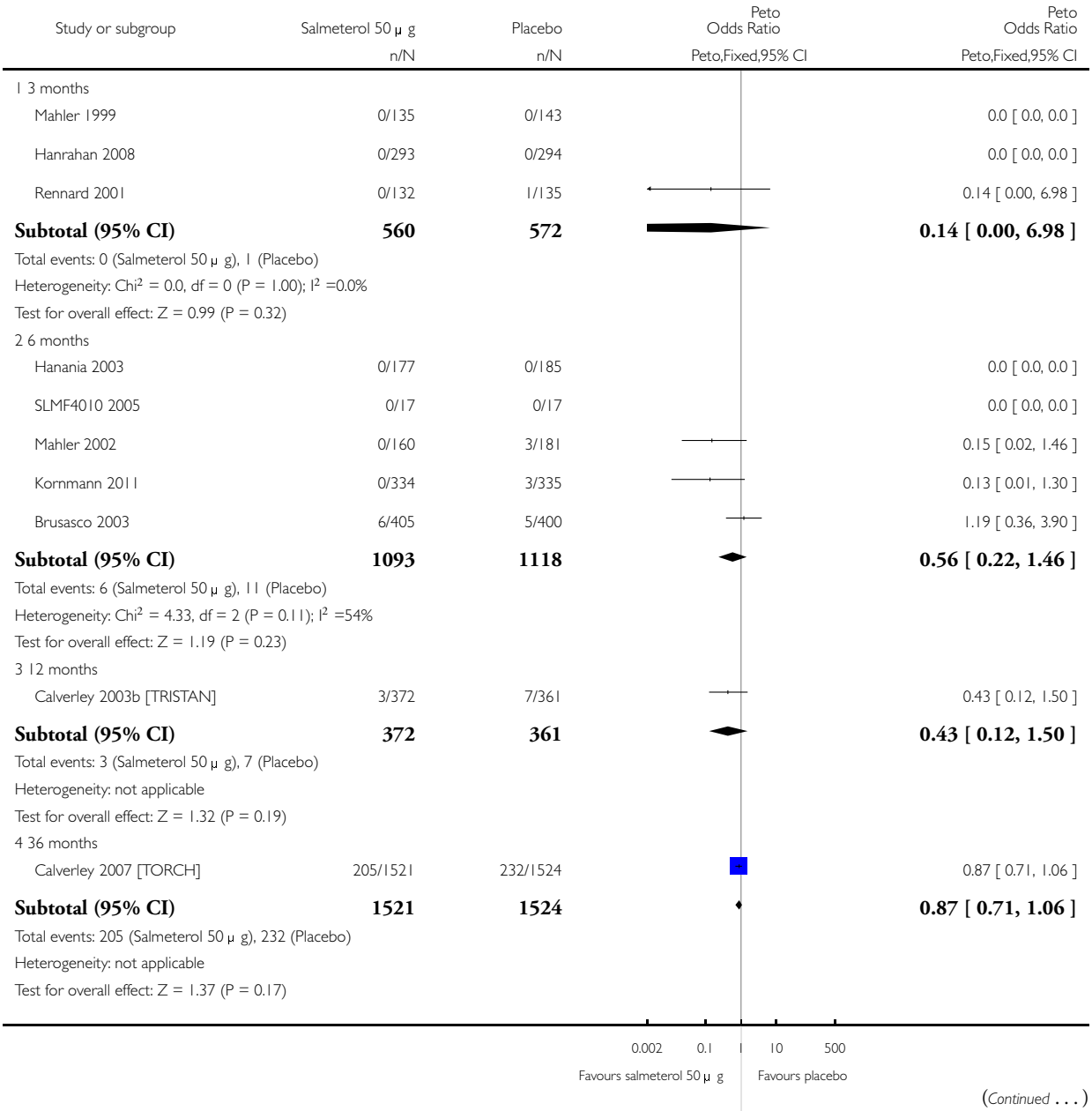


Analysis 4.4. Comparison 4 Salmeterol 50 μg versus placebo [subgrouped by trial duration], Outcome 4 Mortality (all-cause).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 μ g versus placebo [subgrouped by trial duration]

Outcome: 4 Mortality (all-cause)



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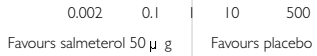
Study or subgroup	Salmeterol 50 µ g n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total (95% CI)	**3546**	**3575**	♦	**0.83 [0.69, 1.01]**
Total events: 214 (Salmeterol 50 µ g), 251 (Placebo)				
Heterogeneity: Chi^2 = 7.03, df = 5 (P = 0.22); I^2 =29%				
Test for overall effect: Z = 1.82 (P = 0.068)				
Test for subgroup differences: Chi^2 = 2.69, df = 3 (P = 0.44), I^2 =0.0%				



Analysis 4.5. Comparison 4 Salmeterol 50 μg versus placebo [subgrouped by trial duration], Outcome 5 People with one or more non-fatal serious adverse events.

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 µ g versus placebo [subgrouped by trial duration]

Outcome: 5 People with one or more non-fatal serious adverse events

Study or subgroup	Salmeterol 50 µ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 3 months					
Rennard 2001	10/132	7/135		1.2 %	1.50 [0.55, 4.06]
Hanrahan 2008	11/290	19/293		3.3 %	0.57 [0.27, 1.22]
Subtotal (95% CI)	**422**	**428**	◆	**4.5 %**	**0.81 [0.45, 1.46]**
Total events: 21 (Salmeterol 50 µ g), 26 (Placebo)					
Heterogeneity: Chi^2 = 2.29, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 0.70 (P = 0.49)					
2 6 months					
SLMF4010 2005	1/17	3/17		0.5 %	0.29 [0.03, 3.13]
Mahler 2002	7/160	11/181		1.8 %	0.71 [0.27, 1.87]
Hanania 2003	5/177	11/185		1.9 %	0.46 [0.16, 1.35]
Kornmann 2011	19/334	26/335		4.5 %	0.72 [0.39, 1.32]
Brusasco 2003	49/405	56/400		9.1 %	0.85 [0.56, 1.28]

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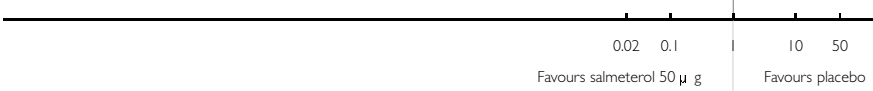
Study or subgroup	Salmeterol 50 µ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**1093**	**1118**		**17.8 %**	**0.74 [0.55, 1.01]**
Total events: 81 (Salmeterol 50 µ g), 107 (Placebo)					
Heterogeneity: Chi^2 = 1.76, df = 4 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.93 (P = 0.054)					
3 12 months					
Calverley 2003b [TRISTAN]	69/372	54/361		8.2 %	1.29 [0.88, 1.91]
Subtotal (95% CI)	**372**	**361**		**8.2 %**	**1.29 [0.88, 1.91]**
Total events: 69 (Salmeterol 50 µ g), 54 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
4 36 months					
Calverley 2007 [TORCH]	617/1542	633/1544		69.5 %	0.96 [0.83, 1.11]
Subtotal (95% CI)	**1542**	**1544**		**69.5 %**	**0.96 [0.83, 1.11]**
Total events: 617 (Salmeterol 50 µ g), 633 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					
Total (95% CI)	**3429**	**3451**		**100.0 %**	**0.94 [0.83, 1.06]**
Total events: 788 (Salmeterol 50 µ g), 820 (Placebo)					
Heterogeneity: Chi^2 = 9.15, df = 8 (P = 0.33); I^2 =13%					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Chi^2 = 5.25, df = 3 (P = 0.15), I^2 =43%					

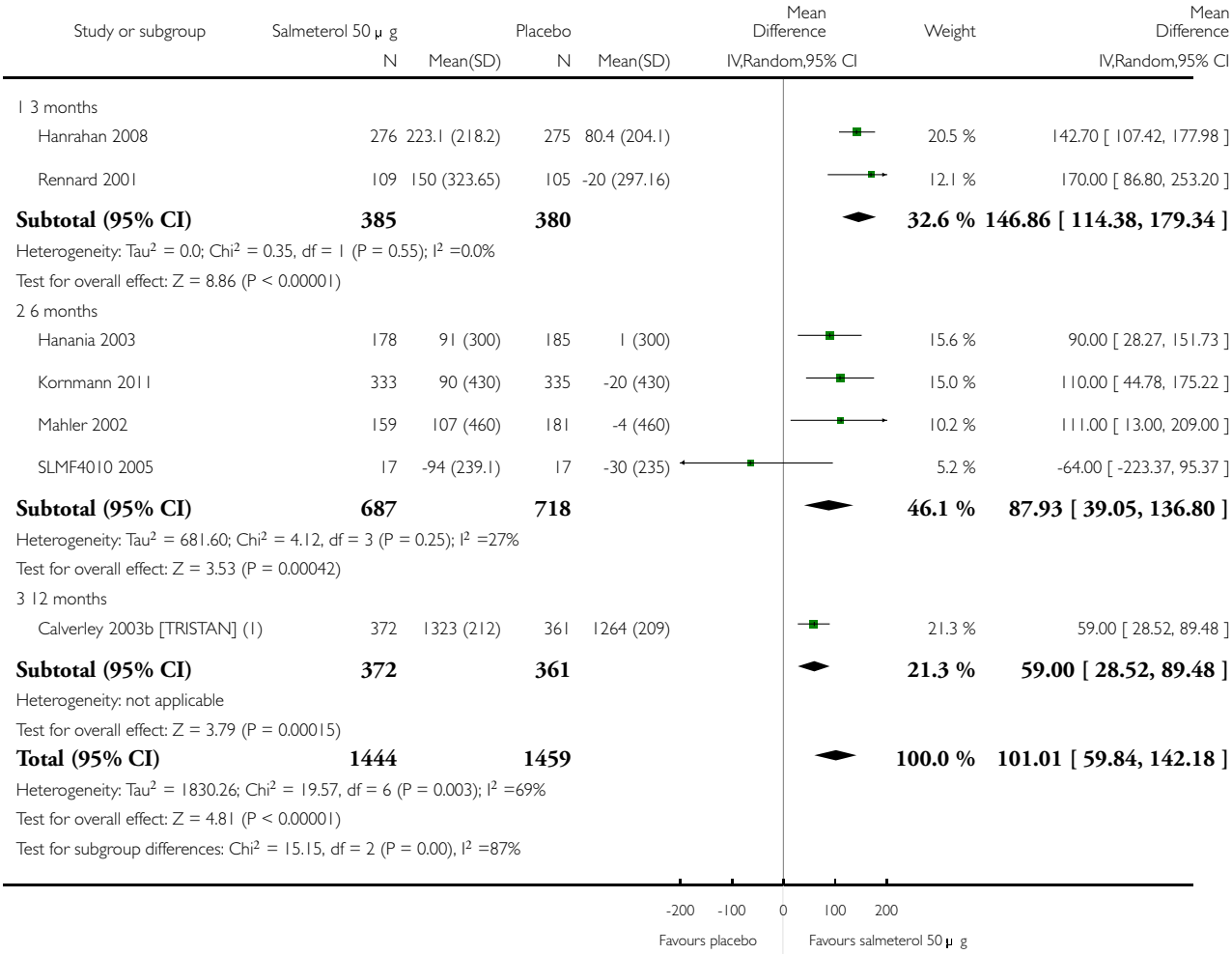


Analysis 4.6. Comparison 4 Salmeterol 50 μg versus placebo [subgrouped by trial duration], Outcome 6 Predose FEV1 (mL).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 μ g versus placebo [subgrouped by trial duration]

Outcome: 6 Predose FEV$_1$ (mL)



(1) All data except that from Calverley 2003b [TRISTAN] (endpoint scores) were entered as change from baseline

Analysis 4.7. Comparison 4 Salmeterol 50 μg versus placebo [subgrouped by trial duration], Outcome 7 Withdrawal.

Review: Long-acting beta2-agonists for chronic obstructive pulmonary disease

Comparison: 4 Salmeterol 50 μ g versus placebo [subgrouped by trial duration]

Outcome: 7 Withdrawal

Study or subgroup	Salmeterol 50 μ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 3 months					
Mahler 1999	9/135	23/143		2.4 %	0.37 [0.17, 0.84]
Rennard 2001	22/132	29/135		2.8 %	0.73 [0.40, 1.35]
Hanrahan 2008	44/293	64/294		6.3 %	0.64 [0.42, 0.97]
Subtotal (95% CI)	**560**	**572**		**11.5 %**	**0.60 [0.44, 0.83]**
Total events: 75 (Salmeterol 50 μ g), 116 (Placebo)					
Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² =0.0%					
Test for overall effect: Z = 3.11 (P = 0.0019)					
2 6 months					
SLMF4010 2005	7/17	7/17		0.5 %	1.00 [0.26, 3.92]
Hanania 2003	57/177	59/185		4.5 %	1.01 [0.65, 1.58]
Mahler 2002	45/160	69/181		5.4 %	0.64 [0.40, 1.00]
Kornmann 2011	50/334	70/335		6.9 %	0.67 [0.45, 0.99]
Brusasco 2003	76/405	103/400		9.8 %	0.67 [0.48, 0.93]
Subtotal (95% CI)	**1093**	**1118**		**27.1 %**	**0.72 [0.59, 0.88]**
Total events: 235 (Salmeterol 50 μ g), 308 (Placebo)					
Heterogeneity: Chi² = 3.17, df = 4 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 3.21 (P = 0.0013)					
3 12 months					
Calverley 2003b [TRISTAN]	119/372	140/361		11.2 %	0.74 [0.55, 1.01]
Subtotal (95% CI)	**372**	**361**		**11.2 %**	**0.74 [0.55, 1.01]**
Total events: 119 (Salmeterol 50 μ g), 140 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.92 (P = 0.055)					
4 36 months					
Calverley 2007 [TORCH]	582/1544	694/1545		50.2 %	0.74 [0.64, 0.86]
Subtotal (95% CI)	**1544**	**1545**		**50.2 %**	**0.74 [0.64, 0.86]**
Total events: 582 (Salmeterol 50 μ g), 694 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.07 (P = 0.000046)					
Total (95% CI)	**3569**	**3596**		**100.0 %**	**0.72 [0.65, 0.80]**

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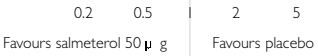
Study or subgroup	Salmeterol 50 µ g n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 1011 (Salmeterol 50 µ g), 1258 (Placebo)					
Heterogeneity: Chi² = 6.26, df = 9 (P = 0.71); I² =0.0%					
Test for overall effect: Z = 6.24 (P < 0.00001)					
Test for subgroup differences: Chi² = 1.40, df = 3 (P = 0.71), I² =0.0%					



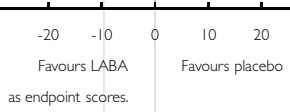
Analysis 5.1. Comparison 5 [Sensitivity analysis-ICS use] All LABA versus placebo, Outcome 1 Quality of life (SGRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 5 [Sensitivity analysis—ICS use] All LABA versus placebo

Outcome: 1 Quality of life (SGRQ)

Study or subgroup	LABA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Formoterol 12 µ g twice daily							
Bogdan 2011 (1)	199	38.2 (14.5)	206	42.9 (14.5)		3.8 %	-4.70 [-7.52, -1.88]
Calverley 2003a	255	0.8 (17)	256	4.7 (17)		3.5 %	-3.90 [-6.85, -0.95]
Doherty 2012 (2)	243	-4.93 (14.5)	236	-2.88 (14.5)		4.5 %	-2.05 [-4.65, 0.55]
Rennard 2009	495	-2.9 (13.3)	481	-1.5 (12.7)		11.5 %	-1.40 [-3.03, 0.23]
Szafranski 2003	201	-3.6 (15)	205	-0.03 (15)		3.6 %	-3.57 [-6.49, -0.65]
Tashkin 2008 [SHINE]	284	-1.24 (11.35)	300	-1.02 (12.41)		8.2 %	-0.22 [-2.15, 1.71]
Tashkin 2012	209	-6.19 (15.2)	212	-2.88 (15.2)		3.6 %	-3.31 [-6.21, -0.41]
Subtotal (95% CI)	**1886**		**1896**			**38.7 %**	**-2.16 [-3.04, -1.27]**
Heterogeneity: Chi² = 10.68, df = 6 (P = 0.10); I² =44%							
Test for overall effect: Z = 4.76 (P < 0.00001)							
2 Formoterol 24 µ g twice daily							



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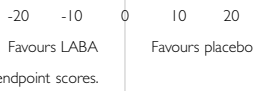
Study or subgroup	LABA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wadbo 2002	61	0 (8.59)	60	1.5 (8.9034)		3.1 %	-1.50 [-4.62, 1.62]
Subtotal (95% CI)	**61**		**60**			**3.1 %**	**-1.50 [-4.62, 1.62]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.94 (P = 0.35)							
3 Salmeterol 50 μ g twice daily							
Brusasco 2003	405	-2.8 (14.087)	400	-1.5 (14)		8.1 %	-1.30 [-3.24, 0.64]
Calverley 2003b [TRISTAN]	372	45.2 (7.7149)	361	46.3 (9.5)		19.3 %	-1.10 [-2.35, 0.15]
Calverley 2007 [TORCH]	1521	-0.8 (14.0772)	1524	0.2 (14.0772)		30.5 %	-1.00 [-2.00, 0.00]
SLMF4010 2005	17	-7.1 (15.2555)	17	2.7 (16.0801)		0.3 %	-9.80 [-20.34, 0.74]
Subtotal (95% CI)	**2315**		**2302**			**58.2 %**	**-1.12 [-1.84, -0.39]**
Heterogeneity: Chi^2 = 2.70, df = 3 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 3.02 (P = 0.0025)							
Total (95% CI)	**4262**		**4258**			**100.0 %**	**-1.53 [-2.08, -0.98]**
Heterogeneity: Chi^2 = 16.55, df = 11 (P = 0.12); I^2 =34%							
Test for overall effect: Z = 5.44 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.17, df = 2 (P = 0.20), I^2 =37%							



(1) Change from baseline data and endpoint data were pooled in the analysis. Most studies reported change from baseline but data for Bogdan 2011 and Calverley 2003b [TRISTAN] are entered

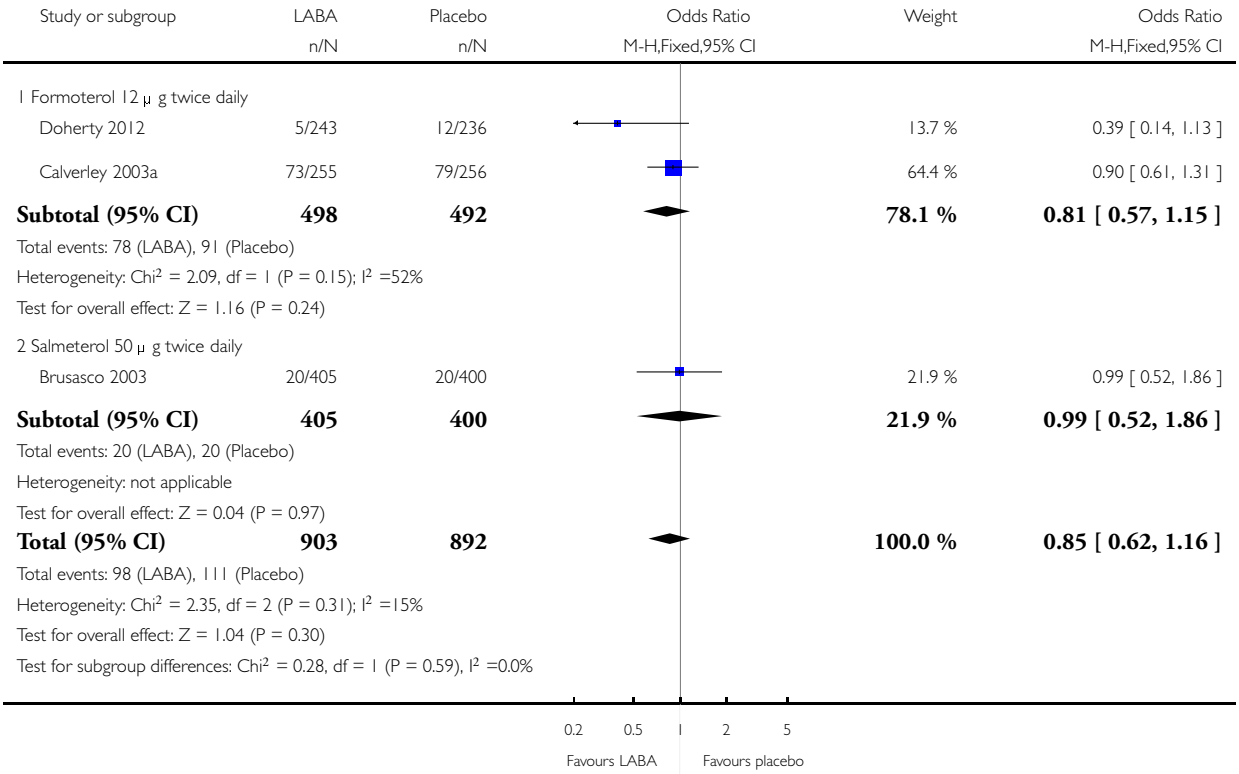
(2) SDs for Doherty 2012 and Szafranski 2003 were imputed based on population variance and that of other arms within the studies

Analysis 5.2. Comparison 5 [Sensitivity analysis-ICS use] All LABA versus placebo, Outcome 2 Severe exacerbations (hospitalisations).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 5 [Sensitivity analysis—ICS use] All LABA versus placebo

Outcome: 2 Severe exacerbations (hospitalisations)



Analysis 6.1. Comparison 6 [Sensitivity analysis-attrition] All LABA versus placebo, Outcome 1 Quality of life (SGRQ).

Review: Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Comparison: 6 [Sensitivity analysis—attrition] All LABA versus placebo

Outcome: 1 Quality of life (SGRQ)

Study or subgroup	LABA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Formoterol 12 µ g twice daily							
Bogdan 2011 (1)	199	38.2 (14.5)	206	42.9 (14.5)		3.8 %	-4.70 [-7.52, -1.88]
Calverley 2003a	255	0.8 (17)	256	4.7 (17)		3.5 %	-3.90 [-6.85, -0.95]
Campbell 2005	215	-3.81 (13.5737)	217	-4.61 (13.5737)		4.7 %	0.80 [-1.76, 3.36]
Dahl 2001	181	41.7 (16.8)	86	46.8 (17.6)		1.5 %	-5.10 [-9.55, -0.65]
Doherty 2012 (2)	243	-4.93 (14.5)	236	-2.88 (14.5)		4.5 %	-2.05 [-4.65, 0.55]
Rossi 2002	159	40.9 (17.8)	80	45.3 (18.7)		1.3 %	-4.40 [-9.34, 0.54]
Tashkin 2008 [SHINE]	284	-1.24 (11.35)	300	-1.02 (12.41)		8.2 %	-0.22 [-2.15, 1.71]
Tashkin 2012	209	-6.19 (15.2)	212	-2.88 (15.2)		3.6 %	-3.31 [-6.21, -0.41]
Subtotal (95% CI)	**1745**		**1593**			**31.2 %**	**-2.07 [-3.06, -1.08]**
Heterogeneity: Chi^2 = 16.51, df = 7 (P = 0.02); I^2 =58%							
Test for overall effect: Z = 4.09 (P = 0.000043)							
2 Formoterol 24 µ g twice daily							
Dahl 2001	169	43.5 (19.4)	86	46.8 (17.6)		1.4 %	-3.30 [-8.03, 1.43]
Rossi 2002	171	42.3 (19)	80	45.3 (18.7)		1.2 %	-3.00 [-7.99, 1.99]
Wadbo 2002	61	0 (8.59)	60	1.5 (8.9034)		3.1 %	-1.50 [-4.62, 1.62]
Subtotal (95% CI)	**401**		**226**			**5.7 %**	**-2.25 [-4.56, 0.06]**
Heterogeneity: Chi^2 = 0.50, df = 2 (P = 0.78); I^2 =0.0%							
Test for overall effect: Z = 1.91 (P = 0.056)							
3 Salmeterol 50 µ g twice daily							
Brusasco 2003	405	-2.8 (14.087)	400	-1.5 (14)		8.1 %	-1.30 [-3.24, 0.64]
Calverley 2003b [TRISTAN] (3)	372	45.2 (7.7149)	361	46.3 (9.5)		19.4 %	-1.10 [-2.35, 0.15]
Calverley 2007 [TORCH]	1521	-0.8 (14.0772)	1524	0.2 (14.0772)		30.6 %	-1.00 [-2.00, 0.00]
Kornmann 2011	292	-5.6 (15.4)	274	-1.5 (14.9)		4.9 %	-4.10 [-6.60, -1.60]
Subtotal (95% CI)	**2590**		**2559**			**63.0 %**	**-1.31 [-2.01, -0.61]**
Heterogeneity: Chi^2 = 5.27, df = 3 (P = 0.15); I^2 =43%							

data for Bogdan 2011, Dahl 2001, Rossi 2002, and Calverley 2003b [TRISTAN] are entered as endpoint scores.

(*Continued . . .*)

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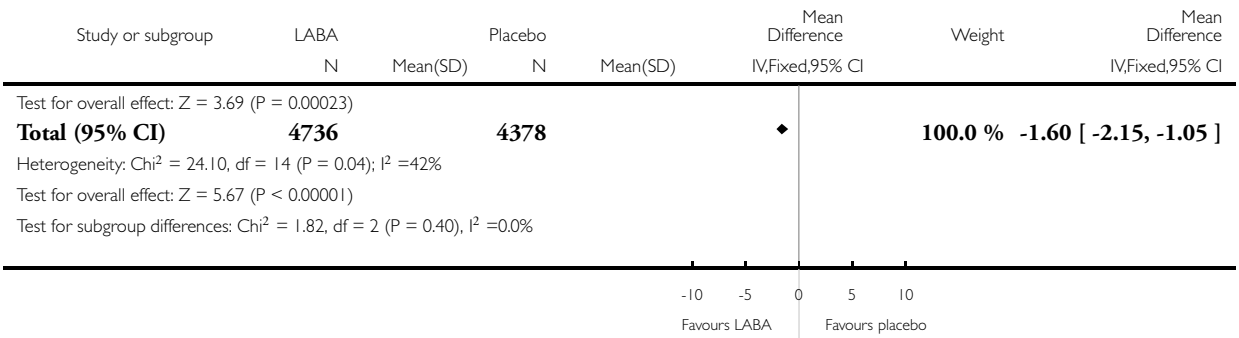

data for Bogdan 2011, Dahl 2001, Rossi 2002, and Calverley 2003b [TRISTAN] are entered as endpoint scores.

(1) Last available score with imputed SD (based on other studies). Change from baseline data and endpoint data were pooled in the analysis. Most studies reported change from baseline but

(2) SDs for Doherty 2012 and Szafranski 2003 were imputed based on population variance and that of other arms within the studies

(3) Adjusted mean at endpoint

ADDITIONAL TABLES

Table 1. Length of included studies with summary demographics

Trial length	Study IDs	Mean age, years, median (range)	Male, %, median (range)
3 months	Aalbers 2002; Bogdan 2011; Dahl 2001; Hanrahan 2008; Mahler 1999; Nelson 2007; Rennard 2001; Wadbo 2002; Watkins 2002	63.5 (62 to 67)	66.5 (52 to 87)
6 months	Brusasco 2003; Campbell 2005; Doherty 2012; Hanania 2003; Kornmann 2011; Mahler 2002; SLMF4010 2005; Tashkin 2008 [SHINE]; Tashkin 2012; Vogelmeier 2008	63 (59 to 65)	75 (63 to 88)
12 months	Calverley 2003a; Calverley 2003b [TRISTAN]; Dahl 2010; Rennard 2009; Rossi 2002; Szafranski 2003	63.5 (63 to 64)	77.5 (75 to 80)
36 months	Calverley 2007 [TORCH]	65 (N/A)	76

Table 2. Baseline severity within the included studies

FEV_1 % predicted at baseline	Study IDs	Mean baseline SGRQ, median (range)
30% ≤ mean < 40%	Brusasco 2003; Calverley 2003a; Doherty 2012; Szafranski 2003; Wadbo 2002	50 (47 to 53)
40% ≤ mean < 50%	Calverley 2003b [TRISTAN]; Calverley 2007 [TORCH]; Dahl 2010; Hanania 2003; Hanrahan 2008; Mahler 1999; Mahler 2002; Rennard 2009; Tashkin 2008 [SHINE]	50 (48 to 55)
50% ≤ mean < 60%	Aalbers 2002; Bogdan 2011; Campbell 2005; Dahl 2010; Kornmann 2011; Vogelmeier 2008	45 (44 to 49)

Five studies did not report mean % predicted FEV_1 at baseline; 10 of the studies presented here did not provide baseline SGRQ.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (Ebsco)	Monthly
AMED (Ebsco)	Monthly

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. (randomised 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

Appendix 2. Search strategy for Clinicaltrials.gov

search terms: formoterol OR salmeterol OR LABA OR long-acting OR "long acting"
condition: COPD
study type: interventional studies

CONTRIBUTIONS OF AUTHORS

Chris Mavergames and Kayleigh Kew assessed studies for inclusion. Chris, Julia Walters and Kayleigh extracted data from the papers and assessed studies for risk of bias. Kayleigh analysed the data and wrote the review, with input from Julia.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK.

Programme grant funding

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Studies were analysed in four trial duration subgroups rather than the two stated in the protocol (≤ one year or > one year). It was not deemed appropriate to organise subgroups according to severity at baseline because the study populations were similar, and so this was not performed. An additional sensitivity analysis related to the use of other medications during the trials was conducted to deal with several studies in which the proportion of participants taking inhaled steroids fell just above or just below the 50% cut-off for exclusion.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenergic beta-2 Receptor Agonists [*administration & dosage]; Drug Administration Schedule; Pulmonary Disease, Chronic Obstructive [drug therapy; mortality]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male