Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

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ABSTRACT

Background

Long-acting bronchodilators comprising long-acting beta$_2$-agonists and the anticholinergic agent tiotropium are commonly used for managing persistent symptoms of chronic obstructive pulmonary disease. Combining these treatments, which have different mechanisms of action, may be more effective than the individual components. However, the benefits and risks of combining tiotropium and long-acting beta$_2$-agonists for the treatment of chronic obstructive pulmonary (COPD) disease are unclear.

Objectives

To assess the relative effects of treatment with tiotropium in addition to long-acting beta$_2$-agonist compared to tiotropium or long-acting beta$_2$-agonist alone in patients with chronic obstructive pulmonary disease.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials and clinicaltrials.gov up to January 2012.

Selection criteria

We included parallel group, randomised controlled trials of three months or longer comparing treatment with tiotropium in addition to long-acting beta$_2$-agonist against tiotropium or long-acting beta$_2$-agonist alone for patients with chronic obstructive pulmonary disease.

Data collection and analysis

Two review authors independently assessed trials for inclusion and then extracted data on trial quality and the outcome results. We contacted study authors for additional information. We collected information on adverse effects from the trials.

Main results

Five trials were included in this review, mostly recruiting participants with moderate or severe chronic obstructive pulmonary disease. All of them compared tiotropium in addition to long-acting beta$_2$-agonist to tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with long-acting beta$_2$-agonist (formoterol) alone. Two studies used the long-acting beta$_2$-agonist indacaterol, two used formoterol and one used salmeterol.

Compared to tiotropium alone (3263 patients), treatment with tiotropium plus long-acting beta$_2$-agonist resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). High withdrawal rates in the trials increased the uncertainty in this result, and the GRADE assessment for this outcome was therefore moderate. There were no significant differences in the other primary outcomes (hospital admission or mortality).

The secondary outcome of pre-bronchodilator FEV_1 showed a small mean increase with the addition of long-acting beta$_2$-agonist (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. There were wide confidence intervals around these outcomes and moderate heterogeneity for both exacerbations and withdrawals.

The results from the one trial comparing the combination of tiotropium and long-acting beta$_2$-agonist to long-acting beta$_2$-agonist alone (417 participants) were insufficient to draw firm conclusions for this comparison.

Authors' conclusions

The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and long-acting beta$_2$-agonist compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta$_2$-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus long-acting beta$_2$-agonist compared to long-acting beta$_2$-agonist alone. There were insufficient data to make comparisons between the different long-acting beta$_2$-agonists when used in addition to tiotropium.

PLAIN LANGUAGE SUMMARY

Is it better to take a combination of tiotropium and long-acting beta$_2$-agonists than either inhaler alone for the treatment of COPD?

Chronic obstructive pulmonary disease (COPD) is a lung disease which includes the conditions chronic bronchitis and emphysema. The symptoms include breathlessness and a chronic cough. COPD is an irreversible disease that is usually brought on by airway irritants, such as smoking or inhaled dust.

Long-acting beta$_2$-agonists and tiotropium are two types of inhaled medications that help widen the airways (bronchodilators) for up to 12 to 24 hours. These bronchodilators are commonly used to manage persistent symptoms of COPD. They can be used in combination or on their own. These bronchodilators work in different ways and therefore might be more beneficial if used together. The purpose of this review was to determine the benefits and risks of using a combination of both types of bronchodilator compared to the individual bronchodilators.

We found five studies involving 3263 patients comparing the long-term efficacy and side effects of combining tiotropium with a long-acting beta$_2$-agonist. The combination of tiotropium plus long-acting beta$_2$-agonist resulted, on average, in a slightly better quality of life and lung function for the patients compared to using only tiotropium, but did not show a difference in hospital admissions or mortality. There were not enough data to determine the risks and benefits of tiotropium plus long-acting beta$_2$-agonist treatment compared to long-acting beta$_2$-agonist alone.

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

LABA plus tiotropium versus tiotropium for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease
Settings:
Intervention: LABA plus tiotropium versus tiotropium

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Tiotropium	LABA plus tiotropium				
Change in quality of life St George's Respiratory Questionaire (SGRQ) . Scale from: 0 to 100. Follow-up: 6 to 12 months	The mean change in quality of life in the control group was **-4.5 units**[1]	The mean change in quality of life in the intervention group was **-6.3 units**[1] (-7.43 to -4.79)	**MD -1.61** (-2.93 to -0.29)	732 (2 studies)	⊕⊕⊕◯ **moderate**[2]	The mean treatment effect was statistically significant but it was smaller than what is regarded as a clinically important difference
Exacerbations leading to hospital admission Number of patients experiencing one or more events Follow-up: 6 to 12 months	**88 per 1000**	**93 per 1000** (57 to 148)	**OR 1.07** (0.63 to 1.81)	732 (2 studies)	⊕⊕◯◯ **low**[2,3]	
Hospital admission (all cause) Number of patients experiencing one or more events Follow-up: 6 to 12 months	**119 per 1000**	**120 per 1000** (79 to 179)	**OR 1.01** (0.63 to 1.61)	732 (2 studies)	⊕⊕◯◯ **low**[2,3]	

Mortality (all cause) Number of patients Follow-up: 3 to 12 months	**4 per 1000**	**6 per 1000** (2 to 16)	**OR 1.56** (0.56 to 4.33)	3263 (5 studies)	⊕⊕◯◯ **low**[4]

*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.

[1] The control group risk is based on Aaron 2007.
[2] One study was a year long with high and unbalanced dropouts.
[3] Wide confidence interval and few participants and events.
[4] There were two trials with no deaths and few deaths in the remaining three trials, leading to a wide confidence interval. Mortality was largely unknown in those who discontinued treatment.

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). The World Health Organization (WHO) has estimated that COPD is the fourth or fifth most common single cause of death worldwide and the treatment and management costs present a significant burden to public health. In the UK the annual cost of COPD to the National Health Service (NHS) is estimated to be £1.3 million per 100,000 people (NICE 2011). Furthermore, because of the slow onset and the under-recognition of the disease, it is heavily underdiagnosed (GOLD). 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, however air pollution and occupational dust and chemicals are also recognised risk factors. COPD is a progressive disease leading to decreased lung function over time, even with the best available care. There is currently no cure for COPD, though it is both a preventable and treatable disease. As yet, apart from smoking cessation and non-pharmacological treatments such as long term oxygen therapy in hypoxic patients, no intervention has been shown to reduce mortality (GOLD). Management of the disease is multi-faceted and includes interventions for smoking cessation (van der Meer 2001), pharmacological treatments (GOLD), education (Effing 2007), and pulmonary rehabilitation (Lacasse 2006). Pharmacological therapy is aimed at relieving symptoms, improving exercise tolerance and quality of life, slowing decline and even improving lung function, or preventing and treating exacerbations. COPD exacerbations impair patients' quality of life (GOLD). Furthermore, a large part of the economic burden of COPD is attributed to the cost of managing exacerbations, particularly those resulting in 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 to try to reduce and prevent exacerbations.

Description of the intervention

COPD pharmacological management tends to begin with one treatment and additional therapies are introduced, as necessary, to control symptoms (GOLD). The first step is often a short-acting bronchodilator for control of breathlessness when needed, either a short-acting beta$_2$-agonist or the short-acting anticholinergic agent ipratropium. For persistent or worsening breathlessness associated with lung function decline, long-acting bronchodilators may be introduced (GOLD). Long-acting bronchodilators include long-acting beta$_2$-agonists (LABA), such as salmeterol or formoterol; new ultra long-acting beta$_2$-agonist, such as indacaterol; and the long-acting anticholinergic agent tiotropium. For symptomatic patients with severe or very severe COPD (FEV_1 < 50% predicted) and repeated exacerbations, GOLD recommends the addition of inhaled corticosteroids (ICS) to bronchodilator treatment.

How the intervention might work

Tiotropium

Tiotropium is an anticholinergic agent which blocks the action of the neurotransmitter acetylcholine. It has an antagonistic effect on muscarinic acetylcholine receptors. Tiotropium has similar affinity for the five different subtypes of muscarinic receptors (M1 to M5), however airway smooth muscle expresses only the M2 and M3 subtypes (Proskocil 2005). Activation of the M3 receptor stimulates a number of intracellular signalling cascades leading to changes in intracellular Ca^{2+} homeostasis and contraction. Tiotropium dissociates slowly from M3 receptors giving a bronchodilator effect lasting over 24 hours, but dissociates rapidly from M2 receptors, which appear to be feedback inhibitory receptors (Barr 2005).

Tiotropium has gained widespread acceptance as a once daily maintenance therapy in stable COPD (Barr 2005; GOLD) for its effects on symptoms and exacerbations. In an early Cochrane review (Barr 2005) tiotropium was shown to reduce the primary endpoint of participants with COPD exacerbations compared to placebo (odds ratio (OR) 0.75; 95% CI 0.66 to 0.85). Within the same review, tiotropium was also associated with a significant benefit over placebo in breathlessness, quality of life, and a reduction in participants with exacerbations that required hospitalisation. Similar effects on symptoms and exacerbations were confirmed in a more recent, large randomised controlled trial of almost 6000 patients who were followed for over four years (Tashkin 2008). There was, however, no significant effect of tiotropium on lung function decline in this longer study. Anticholinergic side effects that may occur with tiotropium include dry mouth, constipation and tachycardia (Tashkin 2008). There has been concern expressed about cardiovascular adverse events on tiotropium (Singh 2009), but this was not shown in meta-analysis including the recent UPLIFT study (Celli 2010).

Long-acting beta$_2$-agonists

Inhaled beta$_2$-agonists activate beta$_2$-receptors in the smooth muscle of the airway leading to a cascade of reactions that result in bronchodilation. Beta$_2$-agonists may also act through other mechanisms such as respiratory muscle function or mucociliary clearance

because patients have shown improvements in symptoms whilst showing no improvement in lung function tests. Beta$_2$-agonists are particularly useful bronchodilators because they reverse bronchoconstriction regardless of the initial cause. The commonly used long-acting beta$_2$-agonists salmeterol and formoterol and the ultra long-acting beta$_2$-agonist indacaterol all have a higher selectivity for beta$_2$-receptors than beta$_1$-receptors (Moen 2010; Wallukat 2002). Beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, although 10% to 50% of the total beta-receptors in the heart are comprised of beta$_2$-receptors. The presence of beta$_2$-receptors in the heart raises the possibility that even highly selective beta$_2$-agonists may have cardiac effects. The duration of action for salmeterol and formoterol is approximately 12 hours, and they are therefore usually taken twice daily. Indacaterol has a duration of action of 24 hours and can, therefore, be taken once daily. The mechanism for activating beta$_2$-receptors differs between these long-acting beta$_2$-agonists. Formoterol is taken up into a membrane depot from where it gradually leaks out to interact with the receptor, whilst salmeterol binds near the receptor, allowing it to remain at the receptor site continually binding and releasing (Johnson 1998). Indacaterol has a higher affinity to lipid domains within the membrane than salmeterol, which may potentially explain its prolonged duration of action (Beier 2011). Independent of long-acting beta$_2$-agonist (LABA) type, stimulation of the beta$_2$-receptors leads to changes in intracellular Ca^{2+} homeostasis and bronchodilation (Tanaka 2005). As with tiotropium, LABAs are used as 'symptom controllers' in stable COPD. A prior Cochrane review found that salmeterol improves lung function compared to placebo (Appleton 2006). A more recent, large (3045 patients), long-term (three-year) randomised control trial also compared salmeterol to placebo (TORCH) (Calverley 2007). In this trial salmeterol use was associated with an increase in lung function and a significant reduction in the annual rate of moderate or severe exacerbations compared with placebo (rate ratio 0.85, $P < 0.001$). A systematic review, which included the TORCH study and another 13 trials looking at salmeterol or formoterol (6453 participants), showed that treatment with a LABA reduced the rate of exacerbations and improved lung function and quality of life compared to placebo, but had no significant effect on mortality (Rodrigo 2008). There have also been a few studies on indacaterol showing improvements in lung function, quality of life and exacerbations compared to placebo (Moen 2010). Possible side effects of LABAs include cardiac effects such as arrhythmia and palpitations, and muscle tremors, head ache, cough, and dry mouth (Beeh 2009; Berger 2008).

Why it is important to do this review

Both tiotropium and long-acting beta$_2$-agonists are recommended for treatment of stable COPD (GOLD). However, patients whose COPD is not adequately managed by either LABA or tiotropium treatment alone could potentially benefit from treatment with a combination of the two. It has been suggested that combination therapies directed at both adrenergic and muscarinic receptors could provide greater, and potentially additive, bronchodilation compared with a beta$_2$-agonist or a muscarinic antagonist alone (Proskocil 2005). A number of trials have been published looking at the effect of adding tiotropium to LABA for treatment of COPD, and the clinical evidence to date suggests there may be benefits in combining the treatments without increasing side effects (Cazzola 2010). This review is necessary to specify and quantify the potential benefits from the combination treatment with LABA and tiotropium compared to the individual components alone.

This review will form part of a suite of reviews on the various combinations of tiotropium, long-acting beta$_2$-agonists and inhaled corticosteroids for the treatment of COPD. These reviews will ultimately be summarised in an overview. The first two of these reviews compared a combination of inhaled corticosteroids and long-acting beta$_2$-agonists with tiotropium (Welsh 2010) and triple therapy (inhaled corticosteroids, long-acting beta$_2$-agonist and tiotropium) with either tiotropium alone or inhaled corticosteroid (ICS) and LABA combination therapy (Karner 2011). Further reviews are in preparation comparing alternate permutations of these three drugs.

OBJECTIVES

To compare the relative effects on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in patients with chronic obstructive pulmonary disease randomised to the following therapies:

- long-acting beta$_2$-agonists and tiotropium versus long-acting beta$_2$-agonists alone; or
- long-acting beta$_2$-agonists and tiotropium versus tiotropium alone.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised trials (RCTs) with a parallel group design of at least 12 weeks duration. We did not exclude studies on the basis of blinding.

Types of participants

We included populations with a diagnosis of chronic obstructive pulmonary disease. We only included studies where an external set of criteria had been used to screen participants for this condition (for example the Global initiative for chronic Obstructive Lung Disease (GOLD), American Thoracic Society (ATS), British Thoracic Society (BTS), Thoracic Society of Australia and New Zealand (TSANZ)).

Types of interventions

We included participants who were randomised to receive inhaled long-acting beta$_2$-agonist in addition to tiotropium bromide compared to those on either inhaled tiotropium bromide alone or inhaled long-acting beta$_2$-agonist alone. We allowed any formulation of long-acting beta$_2$-agonists and tiotropium bromide. Participants were allowed inhaled steroids and other co-medications provided they were not part of the randomised treatment.

Types of outcome measures

Primary outcomes

1. Quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire, Chronic Respiratory Disease Questionnaire)
2. Hospital admissions; all cause and due to exacerbations
3. Mortality; all-cause
4. Disease specific mortality, if independently adjudicated

Secondary outcomes

1. Exacerbations; requiring short burst oral corticosteroids or antibiotics, or both
2. Forced expiratory volume in one second (FEV_1)
3. Symptoms
4. All-cause non-fatal serious adverse events
5. Disease specific serious adverse events, if independently adjudicated
6. Withdrawals

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 handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). All records in the CAGR coded as 'COPD' were searched in January 2012 using the following terms:
(tiotropium or spiriva) AND (*formoterol or salmeterol or bambuterol or indacaterol or clenbuterol or Serevent or Foradil or Oxis or (beta* and agonist*))
Clinicaltrials.gov was also searched in September 2011. The search terms are in Appendix 2. All databases were searched from their inception to the present and there was no restriction on language of publication.

Searching other resources

We searched the following manufacturer websites in September 2011: Boehringer Ingelheim (Spiriva, Spiriva Respimat); Pfizer (Spiriva); Novartis (indacaterol, formoterol); GlaxoSmithKline (salmeterol); AstraZeneca (formoterol). We reviewed reference lists of all primary studies and review articles for additional references.

Data collection and analysis

Selection of studies

Two review authors screened the titles and abstracts of citations retrieved through literature searches and obtained those deemed to be potentially relevant. We assigned each reference to a study identifier and independently assessed them against the inclusion criteria of this review.

Data extraction and management

We extracted information from each study for the following characteristics.

1. Design (design, total study duration and run-in, number of study centres and location, withdrawals, date of study).
2. Participants (N, mean age, age range, gender, COPD severity, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria).
3. Interventions (run-in, intervention treatment and inhaler type, control treatment and inhaler type).
4. Outcomes (primary and secondary outcomes specified and collected, time points reported).

Two authors extracted data from the studies into data collection forms. We discussed and resolved any discrepancies in the data, or consulted a third party where necessary. We transferred data from the data collection forms into Review Manager 5.

Assessment of risk of bias in included studies

We assessed the risk of bias according to recommendations outlined in the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2008) for the following items.

1. Allocation sequence generation.

2. Concealment of allocation.
3. Blinding of participants and investigators.
4. Incomplete outcome data.
5. Selective outcome reporting.

We noted other sources of bias. We graded each potential source of bias as low, high or unclear risk of bias.

Measures of treatment effect

Dichotomous data

We analysed dichotomous data variables (such as mortality and withdrawals) using odds ratios (OR). If count data were not available as the number of participants experiencing an event, we analysed the data as continuous, time-to-event or rate ratios, depending on how they were reported. This includes the outcomes: hospital admissions, exacerbations, and serious adverse events.

Continuous data

We analysed continuous outcome data (such as FEV_1 and quality of life) as fixed-effect model mean differences (MD) when the same scale was used, and standardised mean differences when different scales were employed in different studies. Mean difference based on the change from baseline was preferred over mean difference based on absolute values.

If data were not available for the same time point in all studies, we used the closest time points. Alternatively, end of study was used as a time of analysis for all studies. We used intention-to-treat (ITT) analysis on outcomes from all randomised participants, where possible, for primary analyses.

Unit of analysis issues

We analysed dichotomous data using participants as the unit of analysis (rather than events) to avoid counting the same participant more than once.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data, where possible. We also considered the impact of the unknown status of participants who withdrew from the trials as part of the sensitivity analysis.

Assessment of heterogeneity

We assessed the amount of statistical variation between the study results with the I^2 statistic measurement.

Assessment of reporting biases

We minimised reporting bias from non-publication of studies or selective outcome reporting by using a broad search strategy, contacting study authors directly and checking references of included studies. If we had found sufficient numbers of trials, we planned to visually inspect funnel plots.

Data synthesis

We combined dichotomous data using Mantel-Haenzsel odds ratios with 95% confidence intervals, with a fixed-effect model. Where events were rare, we employed the Peto odds ratio (OR) (since this does not require a continuity correction for zero cells). Where treatment effects were reported as a mean difference with 95% confidence interval or exact P value, we calculated the standard error, entered it with the mean difference (MD) and combined the results using a fixed effect Generic Inverse Variance (GIV) model in Review Manager 5.

Rate ratios and hazard ratios were combined using a fixed-effect GIV model.

Numbers needed to treat would have been calculated from the pooled odds ratio and its confidence interval (CI), and applied to appropriate levels of baseline risk.

We presented the findings of our primary outcomes in a summary of findings table using GradePro software and recommendations in the *Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Subgroup analysis and investigation of heterogeneity

Studies were subgrouped, where possible, according to:

1. type of long-acting beta-agonist;
2. severity of disease at baseline; and
3. tiotropium formulation.

Sensitivity analysis

We assessed the sensitivity of our primary outcomes to degree of bias by comparing the overall results with those exclusively from trials assessed as being at low risk of bias. We also compared the results from the fixed-effect models with results from random-effects models.

RESULTS

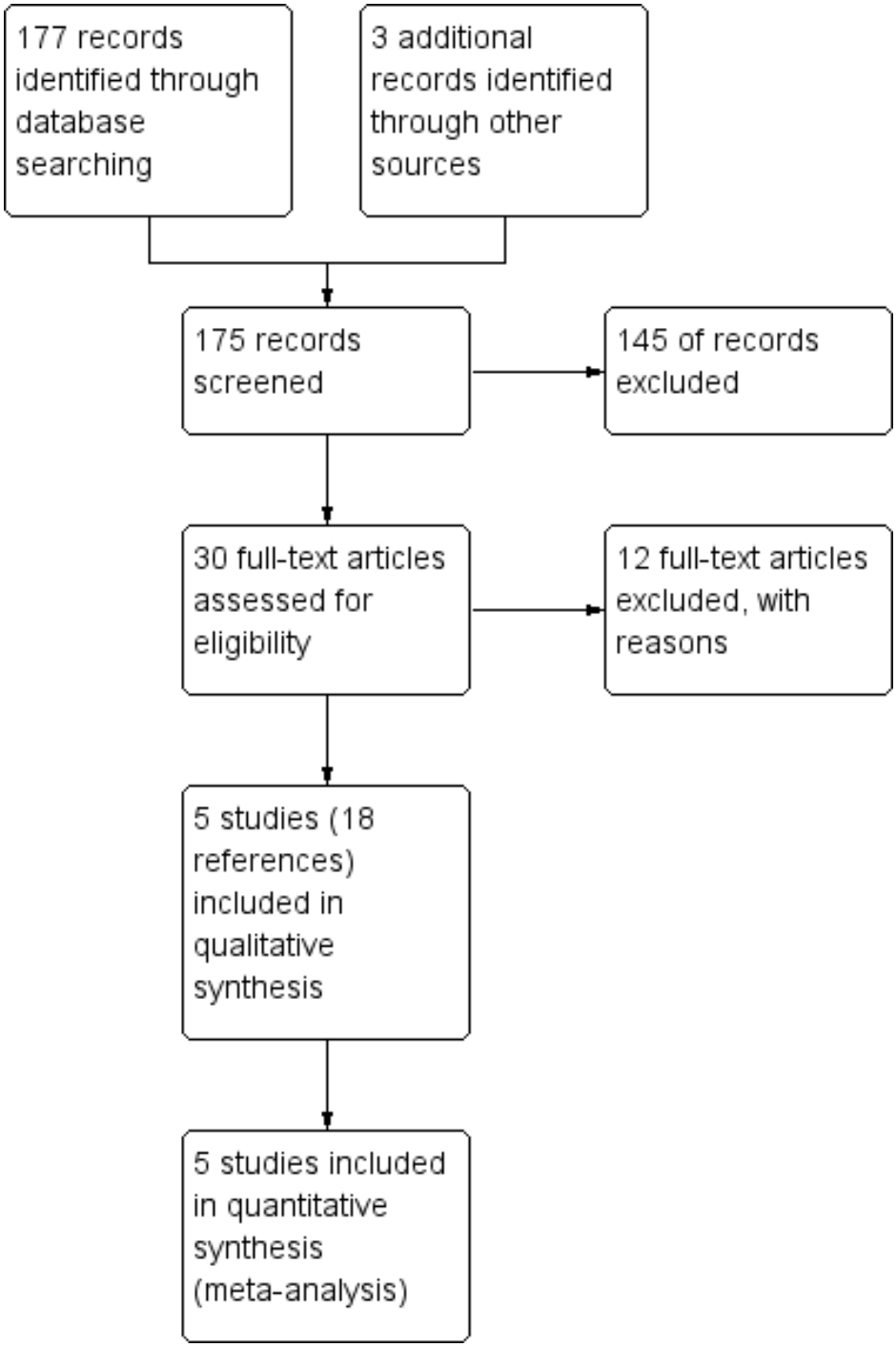
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The database search identified 172 references in September 2011 and an additional five references in January 2012. Of these we identified 27 as potentially relevant, which we obtained in full text for further assessment. Fifteen of these were eligible and belonged to five studies (Aaron 2007; Mahler 2010a; Mahler 2010b; Tashkin 2009; Vogelmeier 2008) (see Characteristics of included studies). Searching the manufacturers' websites we found study reports for three of the included studies (Mahler 2010a; Mahler 2010b; Vogelmeier 2008). Searching clinicaltrials.gov in September 2011 did not generate any additional eligible trials. For the study flow diagram see Figure 1.

Figure 1. Study flow diagram.



Included studies

Study design

The longest study was Aaron 2007 with a duration of one year, then Vogelmeier 2008 with 24 weeks and Mahler 2010a, Mahler 2010b and Tashkin 2009 with 12 weeks of treatment. They were all multi-centre studies. The Aaron 2007 study was conducted at 27 Canadian medical centres, Tashkin 2009 in 35 centres across the United States, and three studies were conducted in a large number of study centre in several different countries (Mahler 2010a; Mahler 2010b; Vogelmeier 2008).

Sample size

There were 3473 participants randomised to the relevant treatment arms in the included studies: LABA + tiotropium (1621), tiotropium (1642), and LABA (210).

Participants

The mean age of participants varied from 63 to 68 years. The gender distribution varied from 54% to 79% males. All studies included participants with moderate to severe COPD, although Aaron 2007 and Vogelmeier 2008 also included patients with very severe COPD (FEV_1 less than 30% predicted) according to GOLD guideline definitions of COPD. The mean baseline lung function varied between 38% and 52% predicted across the studies.

Interventions

All included studies used 18 µg of tiotropium (Handihaler), one inhalation daily. In Aaron 2007 the LABA used was salmeterol 25 µg/puff, two puffs twice daily using a pressurized metered-dose inhaler and a spacer device. Both Mahler 2010a and Mahler 2010b used indacaterol single-dose dry powder inhaler (SDDPI) at 150 μg once daily. Tashkin 2009 and Vogelmeier 2008 both used formoterol. In Tashkin 2009 the dose used was 12 µg twice daily (Foradil Aerolizer) and in Vogelmeier 2008 the concentration was 10 µg twice daily (multi-dose dry powder inhaler).

Permitted co-treatment

In all five studies participants were allowed to use inhaled salbutamol, when necessary, to relieve symptoms. Mahler 2010a, Mahler 2010b, Tashkin 2009 and Vogelmeier 2008 permitted continued use of regimens of inhaled corticosteroid that were stable prior to entry throughout the study. In Aaron 2007 respiratory medications such as oxygen, antileukotrienes, and methylxanthines were continued in all patient groups.

Outcomes

The primary outcome for Aaron 2007 was the proportion of patients suffering one or more COPD exacerbations. The primary outcome for Vogelmeier 2008 was FEV_1 measured two hours post-dose at the end of the study. In Tashkin 2009 the primary outcome was also post-dose FEV_1, but the normalised area under the curve for FEV_1 measured from zero to four hours post-morning dose at the last visit.

Funding

The Aaron 2007 study was funded by the Canadian Institutes of Health Research and the Ontario Thoracic Society. The Tashkin 2009 study was funded by Schering-Plough (markets formoterol) and Mahler 2010a, Mahler 2010b and Vogelmeier 2008 by Novartis (markets formoterol and indacaterol).

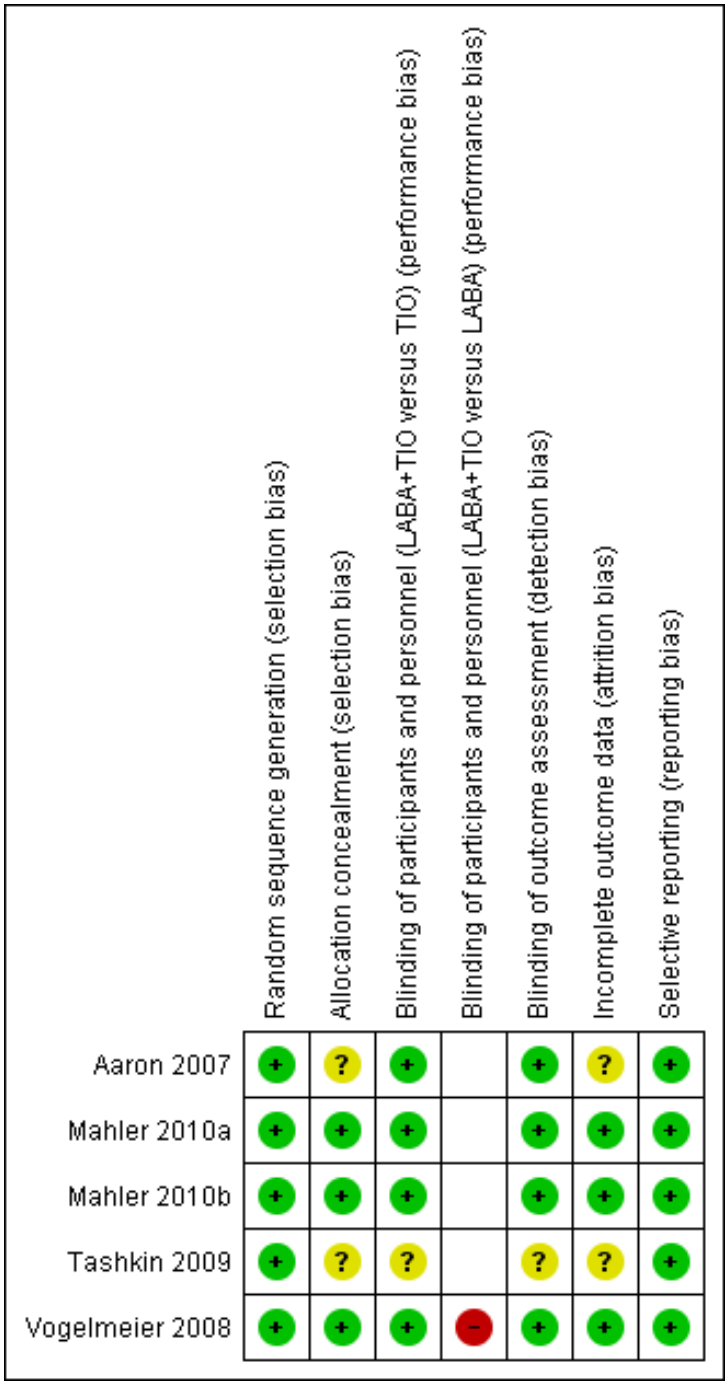
Excluded studies

Eleven studies failed to meet the eligibility criteria for the review (see Characteristics of excluded studies). Seven of these compared tiotropium alone with a long-acting $beta_2$-agonist but had no treatment arm with a combination of the two (Bateman 2001; Brusasco 2003; Di Marco 2003; Fujimoto 2007; Gross 2003; Meyer 2008; ten Hacken 2007). Six studies were of crossover design (Gross 2003; Jones 2010; Meyer 2008; ten Hacken 2007; van Noord 2003; van Noord 2005) and seven had a treatment period shorter than 12 weeks (Fujimoto 2007; Gross 2003; Meyer 2008; New 2009; ten Hacken 2007; van Noord 2003; van Noord 2005).

Risk of bias in included studies

An assessment of the risk of bias is presented in the Characteristics of included studies table, and an overview of the findings is shown in (Figure 2).

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



Allocation

All three studies reported adequate sequence generation, through a computer generated system, and allocation concealment. Information from Vogelmeier 2008 was kindly supplied on request. In Aaron 2007 and Vogelmeier 2008 randomisation data were kept strictly confidential until the time of unblinding, and was not accessible by anyone involved in the study before or after randomisation. In Tashkin 2009 the randomisation code was labelled on the medication kit.

Blinding

The blinding in Aaron 2007 was adequate. In Aaron 2007 both research staff and patients were blinded to the treatment assignment until the end of the study. The different inhalers were identical and they were enclosed in tamper-proof blinding devices. Clinical data for suspected exacerbations were reviewed by a blinded committee and the statistician who performed the analysis was initially blinded to patient group assignments. The Vogelmeier 2008 study was partially blinded with tiotropium being administered open-label, but double-blind for the long-acting beta$_2$-agonist treatment. The risk of performance bias was therefore high for the comparison LABA + tiotropium versus LABA, and low for LABA + tiotropium versus tiotropium. The risk of detection bias was also low as outcome assessors and data analysts were blinded to patient group assignments. Information from Vogelmeier 2008 was kindly supplied on request. Tashkin 2009 did not fully describe in the study report who was blinded.

Incomplete outcome data

Aaron 2007 suffered from high withdrawal rates in the different study groups (74 patients (47%) withdrew from the tiotropium + placebo group and 64 patients (43%) on LABA + tiotropium). For most patients, data were recorded throughout the one-year trial period regardless of whether patients discontinued treatment with study medications. The rates of patients who stopped therapy and did not complete the trial were 30 patients (19%) on tiotropium + placebo and 20 patients (14%) on LABA + tiotropium. Mortality data were obtained for all participants with the exception of two out of 148 participants (1.4%) on LABA + tiotropium and four out of 156 participants (2.6%) on tiotropium + placebo, who withdrew and declined further study. In Tashkin 2009 the number of withdrawals was also uneven but was relatively low (LABA + tiotropium (14.5%), and tiotropium + placebo (6.1%)). In the other three studies the number of withdrawals in the different groups were relatively low and even (Mahler 2010a: LABA + tiotropium (6.8%) and tiotropium + placebo (6.2%); Mahler 2010b: LABA + tiotropium (5.1%) and tiotropium + placebo (6.5%); Vogelmeier 2008: LABA + tiotropium (12%), LABA (12%) and tiotropium + placebo (13%)).

Selective reporting

All the included studies adequately reported outcome data for the primary and secondary outcomes that they had pre-specified in the study records, but we did not compare reported outcomes to the trial protocols.

Effects of interventions

See: **Summary of findings for the main comparison** LABA plus tiotropium versus tiotropium for chronic obstructive pulmonary disease

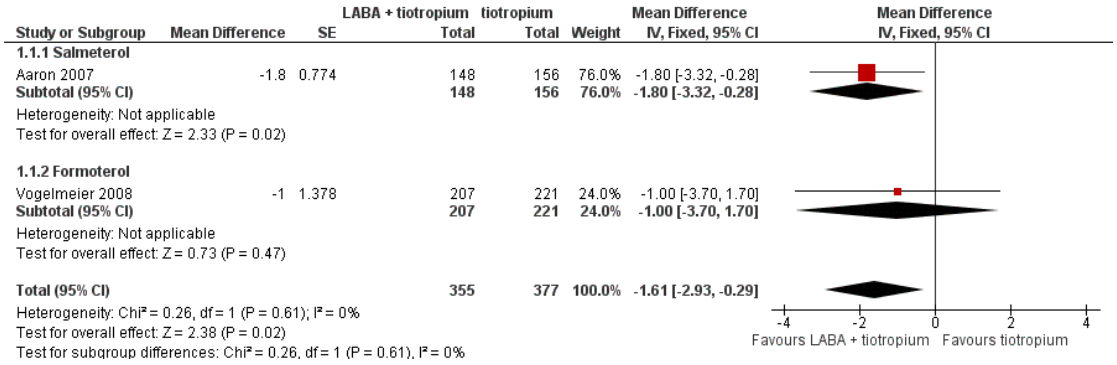
LABA plus tiotropium versus tiotropium

We planned to analyse the data using subgroups for disease severity, type of long-acting beta$_2$-agonist, and tiotropium formulation. We subgrouped the data in the forest plots according to type of long-acting beta$_2$-agonist. However, these need to be interpreted with caution because of the small number of trials and the many significant differences between them, including length of study.

Primary outcome: quality of life

Two studies (729 participants) looked at changes in quality of life using the St George's Respiratory Questionnaire (SGRQ); Aaron 2007 added salmeterol to tiotropium and Vogelmeier 2008 added formoterol to tiotropium. A decrease in SGRQ score denotes an improvement in quality of life and a difference of at least four units is regarded as clinically significant (SGRQ-C manual 2008). Aaron 2007 showed an improvement in quality of life in the control arm, tiotropium alone, of -4.5 units after one year. The pooled result of the treatment difference between LABA + tiotropium and tiotropium alone showed that the combination treatment led to -6.1 unit improvement in quality of life. This difference was significantly larger (statistically) than with tiotropium alone (MD -1.61; 95% CI -2.93 to -0.29), see Figure 3. The confidence interval of this mean difference excludes the minimal clinically important difference of four units but there is additional uncertainty in relation to the quality of life in those patients who withdrew from the study.

Figure 3. Forest plot of comparison: 1 LABA plus tiotropium versus tiotropium, outcome: 1.1 Change in quality of life.



Primary outcome: hospital admissions

Aaron 2007 and Vogelmeier 2008 (729 participants) also reported the number of patients who were admitted to hospital for any cause and due to exacerbations. Data for Aaron 2007 and Vogelmeier 2008 were kindly supplied on request. The number of hospitalised patients were similar and there was no statistically significant difference between the treatment groups for hospitalisations for any cause (OR 1.01; 95% CI 0.63 to 1.61) or due to exacerbation (OR 1.07; 95% CI 0.63 to 1.81). There was a wide confidence interval for the result as the total number of participants with an event was low, and there was additional uncertainty arising from the potential additional admissions that were not known in the patients who withdrew. See Figure 4 and Figure 5 respectively.

Figure 4. Forest plot of comparison: 1 LABA plus tiotropium versus tiotropium, outcome: 1.2 Hospital admission (all cause).

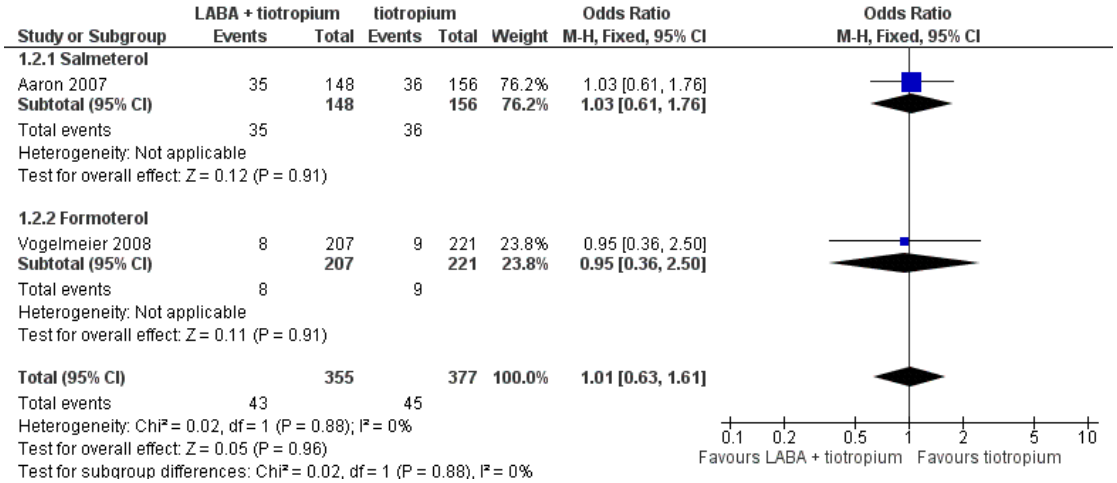
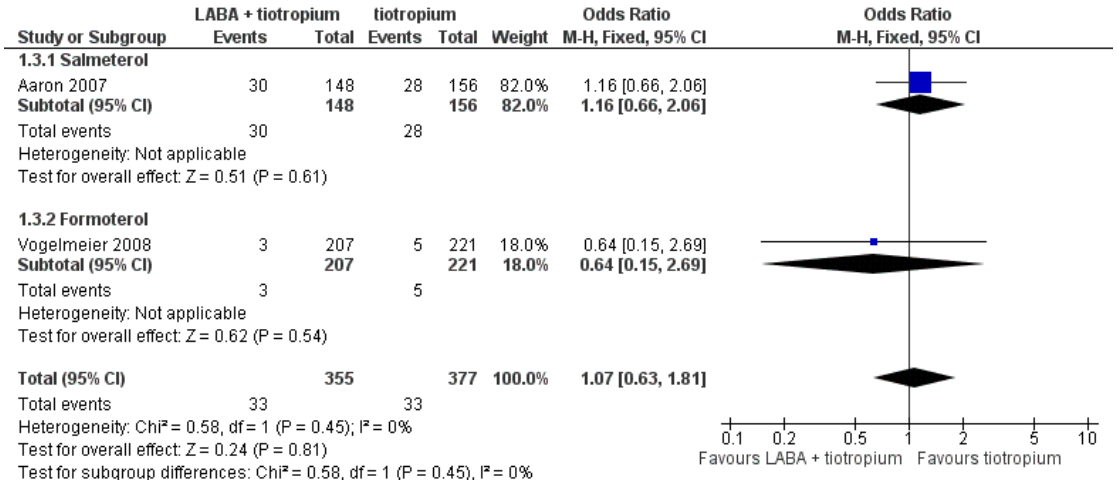


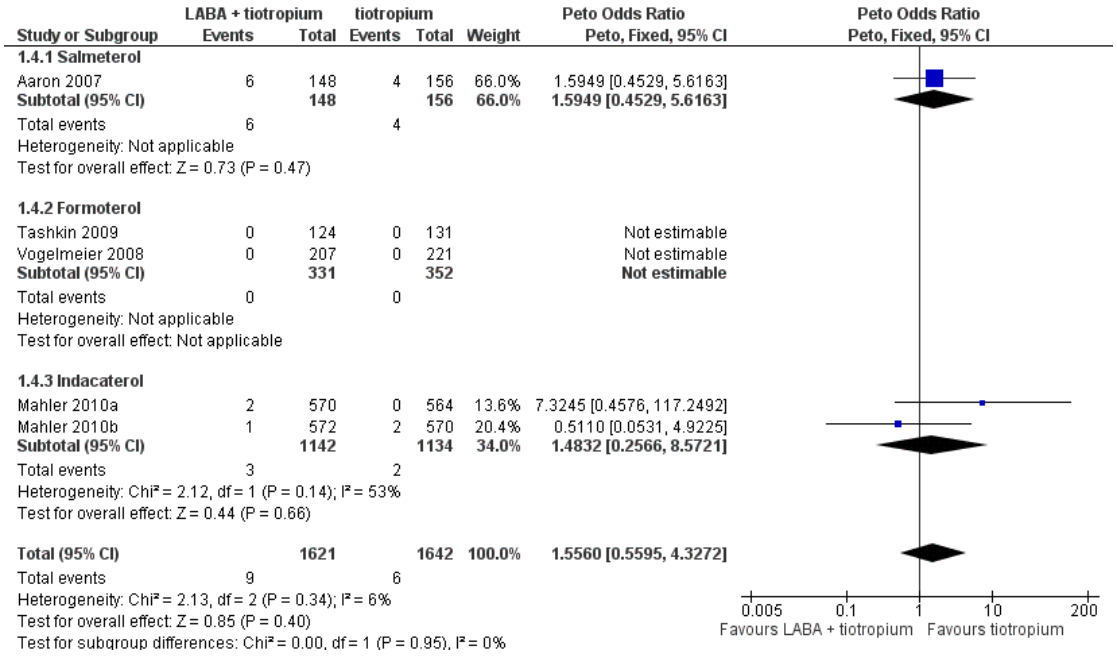
Figure 5. Forest plot of comparison: 1 LABA plus tiotropium versus tiotropium, outcome: 1.3 Hospital admission (exacerbation).



Primary outcome: mortality (all causes)

All five studies (3263 participants) reported mortality for formoterol, salmeterol and indacaterol, however, there were no deaths during the study periods in Tashkin 2009 and Vogelmeier 2008. In the remaining three studies there was no statistically significant difference between the treatment groups as the number of events was low, leading to wide confidence intervals for the difference between the groups (Peto OR 1.56; 95% CI 0.56 to 4.33), see Figure 6. Moreover, there were considerably more participants who discontinued treatment than the numbers who died, adding further uncertainty to the true impact on mortality.

Figure 6. Forest plot of comparison: 1 LABA plus tiotropium versus tiotropium, outcome: 1.4 Mortality (all cause).



Secondary outcome: exacerbations

Three studies (987 participants), on formoterol and salmeterol, reported the number of patients suffering one or more exacerbation during the study period (Aaron 2007; Tashkin 2009; Vogelmeier 2008). Aaron 2007 defined exacerbations as a sustained worsening of the patient's respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD. Vogelmeier 2008 reported the number of patients suffering COPD exacerbations who required additional therapy, defined as COPD-related adverse events (AEs) requiring additional therapy, where COPD-related AEs were defined as AEs coding to the preferred terms: COPD, COPD exacerbated, cough, any term containing 'dyspnoea', lower respiratory tract infection, chronic bronchitis, bronchospasm, bronchial obstruction and respiratory failure; and additional therapy was any COPD therapy reported as being used to treat a COPD exacerbation, other than rescue bronchodilator. In Tashkin 2009 the definition of exacerbation was not described, but it was stated that most patients who needed treatment for their exacerbations received antibiotics alone or a course of antibiotics and systemic steroids. The baseline risk also varied greatly between the studies. In the one-year study (Aaron 2007) 62.8% of patients on tiotropium alone experienced one or more exacerbations, whereas in Tashkin 2009 and Vogelmeier 2008 the number was 10.7% and 10.4%, respectively. There was also substantial heterogeneity between the studies (I^2 = 55%) and the exacerbation status of the patients who withdrew from each study was unknown. In Tashkin 2009 there were more patients experiencing exacerbations in the LABA + tiotropium group (OR 1.70; 95% CI 0.82 to 3.52); Vogelmeier 2008 showed the opposite result (OR 0.58; 95% CI 0.28 to 1.17); and in Aaron 2007 there was almost no difference between the groups (OR 1.09; 95% CI 0.68 to 1.75). In a sensitivity analysis Aaron 2007 reported a similar result when assuming that all patients who were lost to follow up had an exacerbation (OR 0.87; 95% CI 0.52 to 1.45). We did not pool the results for this outcome due to the clinical heterogeneity between the studies.

Secondary outcome: lung function (pre-dose FEV_1)

All five studies (3263 participants) looked at lung function. Four of the studies looked at different measures of post-bronchodilator FEV_1 as their primary outcome, but all five also reported pre-bronchodilator FEV_1 values. The improvement in pre-bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the LABA + tiotropium group compared to the tiotropium group (MD 0.07 L; 95% CI 0.05 to 0.09). The improvement in FEV_1 in the control arm, tiotropium alone, after six months of treatment was 0.13 L in Vogelmeier 2008 and 0.03

L after one year in Aaron 2007. Data for both Aaron 2007 and Vogelmeier 2008 were kindly supplied on request.

Secondary outcome: symptom score

Both Tashkin 2009 and Vogelmeier 2008 looked at changes in symptom scores. However, we were not able to obtain standard deviations for the data from Tashkin 2009. Vogelmeier 2008 used a total daily symptom score which was the sum of the scores for breathlessness, cough, wheeze, amount and colour of sputum. Each were scored on a scale from zero to three where zero was equal to no symptoms. Vogelmeier 2008 kindly supplied data on request which showed a large uncertainty and no statistically significant difference between the treatment groups in total symptom score (MD 0.21; 95% CI -0.30 to 0.72).

Secondary outcome: serious adverse events (non-fatal)

All five studies (3263 participants) reported the number of patients suffering from serious, but non-fatal, adverse events during the study period, for which there was no statistically significant difference (OR 1.09; 95% CI 0.76 to 1.55). However, the confidence interval was wide. Data for Vogelmeier 2008 were kindly supplied on request. It appears that Tashkin 2009 and Vogelmeier 2008 included COPD primary outcome data in the serious adverse events but Aaron 2007 did not.

Secondary outcome: withdrawal

All five studies (3263 participants) reported the number of withdrawals from study medication in each treatment group. Most of the studies had relatively even withdrawal rates and there was no statistically significant difference between the treatment groups (OR 1.00; 95% CI 0.74 to 1.37). The exception was Tashkin 2009 (LABA + tiotropium 12%, tiotropium alone 6%), which introduced moderate heterogeneity in the pooled result (I^2 = 38%).

LABA plus tiotropium versus LABA

Vogelmeier 2008 was the only eligible study identified that compared LABA + tiotropium versus LABA (417 patients). The study was not blinded for this comparison for any of the outcomes as tiotropium was administered open-label. The LABA used in Vogelmeier 2008 was formoterol. The study reported the following results for outcomes of interest for this review.

Primary outcomes

For the primary outcomes there were no significant differences between the treatments for quality of life (SGRQ, MD 0.00; 95% CI -2.70 to 2.70) and the number of patients admitted to hospital for any cause (OR 1.02; 95% CI 0.37 to 2.76) (data kindly supplied by Vogelmeier 2008). There were, however, fewer patients admitted to hospital for an exacerbation in the formoterol + tiotropium group (3 people out of 207) compared to the formoterol group (9 people out of 221), but the number of events was low and the confidence intervals were wide (OR 0.35; 95% CI 0.09 to 1.30). There were no deaths reported in either of the treatment groups.

Secondary outcomes

For all of the secondary outcomes, there were wide confidence intervals and no statistically significant difference between formoterol + tiotropium and formoterol alone: number of patients suffering exacerbations (OR 0.76; 95% CI 0.36 to 1.61), lung function (pre-dose FEV_1 at the end of study, MD 0.00 L; 95% CI -0.10 to 0.10), total symptom score (MD 0.09; 95% CI -0.46 to 0.64) (data kindly supplied by Vogelmeier 2008), number of patients suffering serious non-fatal adverse events (OR 1.07; 95% CI 0.44 to 2.63) (data kindly supplied by Vogelmeier 2008), and withdrawals (OR 1.02; 95% CI 0.56 to 1.84).

DISCUSSION

Summary of main results

This systematic review set out to investigate the long-term (three months or longer) effects of tiotropium in combination with LABA compared to either LABA alone or tiotropium alone, for the treatment of COPD. Five randomised, parallel group, placebo-controlled trials with 3473 participants were identified. All five studied the effects of tiotropium in combination with LABA compared to tiotropium alone, whereas only one of these studies (Vogelmeier 2008, 417 participants) also looked at tiotropium in combination with LABA compared to LABA alone.

LABA plus tiotropium versus tiotropium

This review found that compared to tiotropium alone, treatment with tiotropium plus long-acting $beta_2$-agonist resulted in a slightly larger improvement in the mean health-related quality of life (SGRQ, MD -1.61; 95% CI -2.93 to -0.29). This represented a change from baseline of -6.1 units with both treatments compared to tiotropium alone, which improved by -4.5 units from baseline. This mean improvement was small in relation to the threshold of four units for a clinically significant difference. No significant differences were found in the other primary outcomes (hospital admissions and mortality). Pre-bronchodilator FEV_1 also showed a statistically significant improvement with LABA + tiotropium compared to tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant difference between the groups. There were, however, wide

confidence intervals regarding the results for all outcomes and moderate heterogeneity for both exacerbations and withdrawals.

LABA plus tiotropium versus LABA

The study looking at the effect of formoterol + tiotropium versus formoterol (Vogelmeier 2008, 417 participants) showed very wide confidence intervals and no statistically significant difference between the treatment groups for any of the relevant outcomes reported: health-related quality of life, hospitalisations (all-cause and due to exacerbations), mortality (there were no deaths during the study period in either group), exacerbations, FEV_1, symptom scores, serious adverse events or withdrawals. The fact that only one study, with a relatively small total number of participants, was included in this review makes the result for outcomes with few events or small differences less reliable.

Overall completeness and applicability of evidence

The lack of clear differences in effect between the treatment groups for many of the outcomes may be due to the relatively short treatment duration, with four out of five studies being shorter than one year. This led to few events, wide confidence intervals and low power to detect any differences. For continuous outcomes such as lung function, quality of life and symptom scores, studies with a duration of less than six months may not provide enough time to reach a steady state, which may also influence the result in a conservative way.

The results from this review indicate a small improvement in the mean health-related quality of life and lung function for patients on a combination of LABA and tiotropium compared to tiotropium alone. The mean improvement for both outcomes was statistically significant but relatively small in relation to the minimum clinically important difference for each outcome. However, there may still be a significant number of patients who have a clinically relevant improvement compared to the number with a clinically relevant deterioration. This kind of responder analysis may be a useful additional way of measuring health-related quality of life.

Quality of the evidence

We encountered heterogeneity in the outcomes COPD exacerbations and the number of patients withdrawing from the studies. This could be from one or more of several sources, such as the differences in definition of exacerbation and the length of the studies. The smallest study (Tashkin 2009, 255 participants) had more uneven withdrawal rates compared with the other studies.

Agreements and disagreements with other studies or reviews

In addition to the long-term (three months or longer duration) studies presented in this review there have been several studies looking at acute and short-term (up to six weeks) effects of tiotropium + LABA compared to tiotropium or LABA alone (Cazzola 2010). One short-term, parallel group study also looked at health-related quality of life using the SGRQ (Tashkin 2008a). After six weeks treatment they found no difference between tiotropium + LABA compared to tiotropium alone. However, at least for LABA it may take up to six months of treatment to reach a steady state and to see the full effect on quality of life (Calverley 2007).

Cost effectiveness

The cost effectiveness of tiotropium + LABA treatment compared to both tiotropium alone and triple therapy consisting of ICS and LABA combination inhaler + tiotropium has been assessed for the Aaron 2007 study (Najafzadeh 2008). The setting for this one-year study was within the Canadian healthcare system and the cost effectiveness evaluation was based on 2006 prices. In this study, treatment with tiotropium + LABA resulted in both higher costs and a higher rate of exacerbations than treatment with tiotropium alone. However, when focusing on patients with severe COPD tiotropium + LABA resulted in equal exacerbation rates and slightly lower costs compared to tiotropium alone, although there was considerable uncertainty around this result. Therefore, based on Aaron 2007, tiotropium on its own is the most cost effective treatment compared to tiotropium + LABA when looking at the incremental cost for exacerbations avoided and per additional quality adjusted life year. However, for a chronic illness like COPD a cost effectiveness study of one year is unlikely to capture all relevant costs and benefits.

AUTHORS' CONCLUSIONS

Implications for practice

The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and long-acting $beta_2$-agonist compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting $beta_2$-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus long-acting $beta_2$-agonist compared to long-acting $beta_2$-agonist alone. There were insufficient data to make comparisons between the different long-acting $beta_2$-agonists when used in addition to tiotropium.

Implications for research

Additional long-term (12 months or longer) larger studies are needed to clarify the risks and benefits of tiotropium + LABA treatment compared to the individual drugs. If the number of participants is large enough this will enable analysis to assess the suitability of this combination of therapies for patients with different severities of COPD. For quality of life measurements in future studies, it may be beneficial to use both mean changes with 95% confidence intervals and responders analysis. However, the responders analysis would preferably include both the number of people who have a clinically meaningful improvement as well as the number of people who have a clinically meaningful worsening. Presenting just one side of the data distribution, as in the percentage of patients with a clinically meaningful improvement, is becoming more common but is of limited value.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aaron 2007

Methods	**Design:** A randomised, double-blind, placebo-controlled, parallel group trial from October 2003 to January 2006. The trial included 27 Canadian medical centres; 20 centres were academic hospital-based pulmonary clinics, 5 were community-based pulmonary clinics, and 2 were community-based primary care clinics
Participants	**Population**: 304 adults, with a clinical history of moderate or severe COPD as defined by ATS and GOLD guidelines, were randomised to tiotropium + salmeterol (148) and tiotropium (156) **Baseline Characteristics**: Mean age 68 years. COPD severity moderate to severe with mean FEV_1 predicted of 38%. 57% men. **Inclusion Criteria**: At least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomisation; age older than 35 years; a history of 10 pack-years or more of cigarette smoking; documented chronic airflow obstruction, with an FEV_1/FVC ratio less than 0.70 and a post-bronchodilator FEV_1 less than 65% of the predicted value. **Exclusion Criteria**: History of physician-diagnosed asthma before 40 years of age; history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction; those receiving oral prednisone; those with a known hypersensitivity or intolerance to tiotropium, salmeterol, or fluticasone-salmeterol; history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery, or diffuse bilateral bronchiectasis; and those who were pregnant or were breastfeeding
Interventions	**1**. Tiotropium + salmeterol: tiotropium 18 μg once daily using a Handihaler plus salmeterol 25 μg/puff, 2 puffs twice daily using a pressurized metered-dose inhaler using a spacer device **2**. Tiotropium + placebo: tiotropium, 18 μg once daily, plus placebo inhaler, 2 puffs twice daily
Outcomes	**Primary**: Proportion of patients with one or more exacerbation of COPD **Secondary**: Mean number of COPD exacerbations per patient-year; the total number of exacerbations that resulted in urgent visits to a health care provider or emergency department; the number of hospitalizations for COPD; the total number of hospitalizations for all causes; changes in health-related quality of life, dyspnoea, lung function
Notes	**Co-medication**: All study patients were provided with inhaled albuterol and were instructed to use it when necessary to relieve symptoms. Any treatment with inhaled corticosteroids, long-acting 2-agonists, and anticholinergics that the patient may have been using before entry was discontinued on entry into the study. Therapy with other respiratory medications, such as oxygen, antileukotrienes, and methylxanthines, was continued in all patient groups
Risk of bias	

Aaron 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done through central allocation of a randomisation schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site
Allocation concealment (selection bias)	Unclear risk	Neither research staff nor patients were aware of the treatment assignment before or after randomisation
Blinding of participants and personnel (LABA+TIO versus TIO) (performance bias)	Low risk	Neither research staff nor patients were aware of the treatment assignment before or after randomisation. The metered-dose inhalers containing placebo, salmeterol, and fluticasone-salmeterol were identical in taste and appearance, and they were enclosed in identical tamper-proof blinding devices. The medication canisters within the blinding devices were stripped of any identifying labelling
Blinding of outcome assessment (detection bias) Exacerbations	Low risk	The assembled data from the visit for the suspected exacerbation were presented to a blinded adjudication committee for review, and the committee confirmed whether the encounter met the study definition of COPD exacerbation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of people who stopped drug therapy was high in both groups. 74 patients (47%) withdrew from the tiotropium + placebo group and 64 patients (43%) on LABA + tiotropium group. However, the number of people who did not complete the trial was lower (30 patients (19%) on tiotropium + placebo and 20 patients (14%) on LABA + tiotropium). The incomplete data were however addressed by sensitivity analyses of the data comprising alternative assumptions for patients who prematurely withdrew from treatment
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Mahler 2010a

Methods	**Design:** A multi-centre, multi-national, randomised, double-blind, parallel-group study from March 2009 to March 2010. The trial included 186 study centres in 14 countries: Argentina (10), Australia (6), Colombia (5), Denmark (5), Germany (25), Greece (4) , Guatemala (5), Mexico (5), Peru (6), Philippines (2), South Africa (6), Spain (13), Turkey (13), and USA (81)
Participants	**Population**: 1134 patients with a clinical history of moderate or severe COPD as defined by GOLD guidelines, were randomised to tiotropium + indacaterol (570) and tiotropium (564) **Baseline Characteristics**: Mean age 64 years, 67% male, mean FEV_1 1.3 L, mean FEV_1 predicted 49%, 47 pack-years smoking history. **Inclusion Criteria**: Men and women aged $\geq$40 years with moderate-to-severe COPD, with a smoking history $\geq$10 pack-years and post-bronchodilator $FEV_1 \leq 65\%$ and $\geq$ 30% predicted and $FEV_1/FVC < 70\%$. **Exclusion Criteria**: Patients who have received systematic corticosteroids and/or antibiotics and/or was hospitalised for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period or had a respiratory tract infection within 6 weeks prior to screening. Patients with concomitant pulmonary disease, a history of asthma, diabetes Type I or uncontrolled diabetes Type II, lung cancer or a history of lung cancer, a history of certain cardiovascular comorbid conditions
Interventions	**1**. Indacaterol 150 μg through single-dose dry powder inhaler (SDDPI), once daily + tiotropium 18 μg through SDDPI Handihaler, once daily **2**. Placebo to indacaterol + tiotropium 18 μg through SDDPI Handihaler, once daily
Outcomes	**Primary**: Standardised area under the curve (AUC) FEV_1 between 5min and 8h post-dose after 12 weeks of treatment. **Secondary**: Trough FEV_1 on day 1 and after 12 weeks treatment, FEV1 AUC (5min-8h) day 1, FEV_1 AUC (5min-4h) on day 1 and after 12 weeks of treatment, resting inspiratory capacity (IC), use of albuterol as rescue medication, safety (adverse events and serious adverse events)
Notes	**Co-medication**: Albuterol was available for rescue use. Patients receiving inhaled corticosteroids (ICS) at baseline continued treatment (or the ICS component alone if taken as a fixed combination with a bronchodilator) at equivalent dose and regimen throughout the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A patient randomisation list was produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomisation numbers
Allocation concealment (selection bias)	Low risk	The randomisation numbers were linked to the different treatment arms, which in

Mahler 2010a (*Continued*)

		turn were linked to medication numbers. A separate medication randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs
Blinding of participants and personnel (LABA+TIO versus TIO) (performance bias)	Low risk	Patients, investigator staff, persons performing the assessments, data analysts and the Novartis trial team were all blinded
Blinding of outcome assessment (detection bias) Exacerbations	Low risk	Persons performing the assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were low and even (tiotropium + indacaterol 6.8%, tiotropium 6.2%)
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Mahler 2010b

Methods	**Design:** A multi-centre, multi-national, randomised, double-blind, parallel-group study from April 2009 to February 2010. The trial included 182 study centres in 11 countries: Argentina (9), Canada (16), Colombia (3), Czech Republic (9), Hungary (4), India (9) , Netherlands (6), Philippines (3), Slovakia (10), Spain (11), and USA (102)
Participants	**Population**: 1142 patients with a clinical history of moderate or severe COPD as defined by GOLD guidelines, were randomised to tiotropium + indacaterol (572) and tiotropium (570) **Baseline Characteristics**: Mean age 63 years, 65% male, mean FEV_1 1.3 L, mean FEV_1 predicted 49%, 46 pack-years smoking history. **Inclusion Criteria**: Men and women aged $\geq$40 years with moderate-to-severe COPD, with a smoking history $\geq$10 pack-years and post-bronchodilator $FEV_1 \leq 65\%$ and $\geq$ 30% predicted and $FEV_1/FVC < 70\%$. **Exclusion Criteria**: Patients who have received systematic corticosteroids and/or antibiotics and/or was hospitalised for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period or had a respiratory tract infection within 6 weeks prior to screening. Patients with concomitant pulmonary disease, a history of asthma, diabetes Type I or uncontrolled diabetes Type II, lung cancer or a history of lung cancer, a history of certain cardiovascular comorbid conditions
Interventions	**1**. Indacaterol 150 μg through single-dose dry powder inhaler (SDDPI), once daily + tiotropium 18 μg through SDDPI Handihaler, once daily **2**. Placebo to indacaterol + tiotropium 18 μg through SDDPI Handihaler, once daily

Mahler 2010b (*Continued*)

Outcomes	**Primary**: Standardised area under the curve (AUC) FEV_1 between 5min and 8h post-dose after 12 weeks of treatment. **Secondary**: Trough FEV_1 on day 1 and after 12 weeks treatment, FEV1 AUC (5min-8h) day 1, FEV_1 AUC (5min-4h) on day 1 and after 12 weeks of treatment, resting inspiratory capacity (IC), use of albuterol as rescue medication, safety (adverse events and serious adverse events)
Notes	**Co-medication**: Albuterol was available for rescue use. Patients receiving inhaled corticosteroids (ICS) at baseline continued treatment (or the ICS component alone if taken as a fixed combination with a bronchodilator) at equivalent dose and regimen throughout the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A patient randomisation list was produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomisation numbers
Allocation concealment (selection bias)	Low risk	The randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs
Blinding of participants and personnel (LABA+TIO versus TIO) (performance bias)	Low risk	Patients, investigator staff, persons performing the assessments, data analysts and the Novartis trial team were all blinded
Blinding of outcome assessment (detection bias) Exacerbations	Low risk	Persons performing the assessments were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were low and even (tiotropium + indacaterol 5.1%, tiotropium 6.5%)
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Tashkin 2009

Methods	**Design:** A randomised, double-blind, active-control, parallel group trial. The trial included 35 centres across the United States, of which the majority were primary care centres
Participants	**Population**: 255 adults with a clinical history of COPD were randomised to tiotropium + formoterol (124) and tiotropium (131) **Baseline Characteristics**: Mean age 64 years. COPD severity mild to severe. 67% men. **Inclusion Criteria**: Male and non-pregnant female patients aged >40 years who had a clinical history of COPD were enrolled in this study. Each patient had a post-bronchodilator FEV1 < 70% and >30% predicted normal or >0.75 L, whichever was less, at run-in, and a FEV_1 to FVC ratio (FEV_1/FVC) of < 0.70 at screening and run-in. Daytime and/or nighttime symptoms of COPD, including dyspnoea, must have been present on ≥4 of the 7 days before the baseline visit **Exclusion Criteria**: A current or previous history of asthma or other significant medical condition that may have interfered with study treatment as assessed by the investigator, smoking cessation within the previous 3 months, ventilator support for respiratory failure within the previous year, the use of oxygen (≥2 L/min or for >2 h/d), initiation of pulmonary rehabilitation within the previous 3 months, the requirement for nasal continuous positive airway pressure or bilevel positive airway pressure, clinically significant lung disease other than COPD (i.e., bronchiectasis, sarcoidosis, pulmonary fibrosis, tuberculosis), sleep apnoea, chronic narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder neck obstruction, and the need for chronic or prophylactic antibiotic therapy
Interventions	**1**. Formoterol (Foradil Aerolizer) 12 μg twice daily and tiotropium (Handihaler) 18 μg once-daily in the morning delivered via 2 separate inhalers **2**. Formoterol-matched placebo twice-daily and tiotropium 18 μg once-daily delivered via 2 separate inhalers
Outcomes	**Primary**: The normalized area under the curve (AUC) for FEV_1 measured 0 to 4 hours post-morning dose (FEV_1 AUC0-4h) at the last visit. **Secondary**: Changes from baseline in trough (average of values obtained 10 and 30 min pre-dose) FEV_1 and FVC, weekly morning and evening peak expiratory flow (PEF), symptom severity scores, transition dyspnoea index (TDI), and health related quality of life (St. George's Respiratory Questionnaire, SGRQ) scores, number and severity of exacerbations, the global therapeutic response, discontinuations because of worsening COPD, and percentages of patients achieving targeted improvements in the SGRQ and TDI scores, use of rescue albuterol, nocturnal awakenings requiring rescue albuterol, changes in study or concomitant medications, and adverse events
Notes	**Co-medication**: Continued use of prior stable inhaled corticosteroid regimens and systemic corticosteroids for the treatment of exacerbations was permitted throughout the study. All patients were provided with albuterol for use as rescue medication **Run-in**: Following screening, prohibited medications (i.e., beta-agonists, beta-blockers, cromolyn sodium, ipratropium bromide, leukotriene antagonists, cytotoxic agent, and theophylline) were withdrawn. Patients previously using TIO or FORM discontinued the drugs at least 4 weeks or 48 hours before screening, respectively. Patients completed a 2-week run-in period using placebo and as-needed rescue albuterol

Tashkin 2009 (*Continued*)

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

Vogelmeier 2008

Methods	**Design:** A randomised, partly-blind , partly placebo-controlled, parallel group trial from October 2004 to November 2005. The trial included 86 centres in Germany (30), Italy (19), Netherlands (9), Russian federation (9), Poland (7), Czech Republic (4), Spain (4) and Hungary (4)
Participants	**Population**: 638 adults, with a clinical history of moderate to very severe COPD as defined by GOLD guidelines, were randomised to tiotropium + formoterol (207), formoterol (210), and tiotropium (221) **Baseline Characteristics**: Mean age 63 years. COPD severity moderate to very severe with mean FEV_1 predicted of 52%. 78% men. **Inclusion Criteria**: Males and females with stable COPD aged ≥40 years at COPD onset and with a smoking history of ≥10 pack-years, forced expiratory volume in 1 second (FEV_1) < 70% of patient's predicted normal value (and ≥1.00 L), and FEV_1/ forced vital capacity (FVC) < 70%. They were to be symptomatic on at least 4 of 7 days prior to randomisation (symptom score >0 on diary card) **Exclusion Criteria**: Patients who had a respiratory tract infection or had been hospitalised for an acute exacerbation of COPD within the month prior to screening. Patients with a clinically significant condition such as ischaemic heart disease that might com-

	promise patient safety or compliance were also excluded
Interventions	**1**. Formoterol 10 µg twice daily via multi-dose dry powder inhaler (MDDPI) **2**. Tiotropium 18 µg once daily via the HandiHaler + formoterol 10 µg via MDDPI
Outcomes	**Primary**: FEV_1 measured 2 hours post-dose after 24 weeks of treatment. **Secondary**: FEV_1 and FVC at other time points during the study (5 min, 2 and 3 hours post-dose following the first dose of treatment, and after 12 and 24 weeks of treatment) ; COPD exacerbations; symptom scores, rescue medication use and PEF; quality of life, and 6-minute walking distance
Notes	**Co-medication**: Salbutamol pMDI (2 × 100 µg/puff) was permitted as rescue medication. Patients were asked not to use salbutamol in the 8 hours before a study visit. Patients could receive inhaled corticosteroids (ICS) at a stable daily dose (any patients receiving fixed combinations of ICS and $beta_2$-agonists were switched to receive the same dose of ICS and on demand salbutamol) **Run-in**: A screening period of up to 4 weeks included 2 weeks for washout of disallowed medications and 2 weeks for eligibility assessment and baseline evaluations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomisation list was produced using a validated system that automates the random assignment of treatment groups to randomisation numbers in the specified ratio. The randomisation scheme was reviewed by a Biostatistics Quality Assurance Group and locked by them after approval
Allocation concealment (selection bias)	Low risk	Randomisation data were kept strictly confidential until the time of unblinding, and was not accessible by anyone else involved in the study
Blinding of participants and personnel (LABA+TIO versus TIO) (performance bias)	Low risk	The study was partially blinded. The study was double-blind for treatment comparison tiotropium + formoterol vs. tiotropium + placebo (MDDPI only), but not for other comparisons as tiotropium was administered open-label. Randomisation was not stratified. Certihaler active and placebo devices were identical in packaging, labelling, schedule of administration and appearance
Blinding of participants and personnel (LABA+TIO versus LABA) (performance bias)	High risk	The study was partially blinded. The study was double-blind for treatment compari-

		son tiotropium + formoterol vs. tiotropium + placebo (MDDPI only), but not for other comparisons as tiotropium was administered open-label. Randomisation was not stratified. Certihaler active and placebo devices were identical in packaging, labelling, schedule of administration and appearance
Blinding of outcome assessment (detection bias) Exacerbations	Low risk	Persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of withdrawals in the different groups were relatively low and even (LABA + tiotropium (12.1%), formoterol (11.9%) and tiotropium + placebo (13.1%))
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

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

Study	Reason for exclusion
Bateman 2001	No tiotropium plus long-acting beta$_2$-agonists combination treatment
Brusasco 2003	No tiotropium plus long-acting beta$_2$-agonists combination treatment
Di Marco 2003	No tiotropium plus long-acting beta$_2$-agonists combination treatment
Fujimoto 2007	8 weeks of treatment and no tiotropium plus long-acting beta$_2$-agonists combination treatment
Gross 2003	4 weeks of treatment, no tiotropium plus long-acting beta$_2$-agonists combination treatment, and crossover design
Jones 2010	crossover design
Meyer 2008	2 weeks of treatment, no tiotropium plus long-acting beta$_2$-agonists combination treatment, and crossover design
New 2009	6 weeks of treatment
ten Hacken 2007	6 weeks of treatment, no tiotropium plus long-acting beta$_2$-agonists combination treatment, and crossover design
van Noord 2003	6 weeks of treatment and crossover design

(*Continued*)

van Noord 2005	6 weeks of treatment and crossover design

DATA AND ANALYSES

Comparison 1. LABA plus tiotropium versus tiotropium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in quality of life	2	732	Mean Difference (Fixed, 95% CI)	-1.61 [-2.93, -0.29]
1.1 Salmeterol	1	304	Mean Difference (Fixed, 95% CI)	-1.8 [-3.32, -0.28]
1.2 Formoterol	1	428	Mean Difference (Fixed, 95% CI)	-1.0 [-3.70, 1.70]
2 Hospital admission (all cause)	2	732	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.63, 1.61]
2.1 Salmeterol	1	304	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.61, 1.76]
2.2 Formoterol	1	428	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.36, 2.50]
3 Hospital admission (exacerbation)	2	732	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.63, 1.81]
3.1 Salmeterol	1	304	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.66, 2.06]
3.2 Formoterol	1	428	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.15, 2.69]
4 Mortality (all cause)	5	3263	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [0.56, 4.33]
4.1 Salmeterol	1	304	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.45, 5.62]
4.2 Formoterol	2	683	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Indacaterol	2	2276	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.26, 8.57]
5 Exacerbation	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Salmeterol	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Formoterol	2		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Trough FEV1	5	3263	Mean Difference (Fixed, 95% CI)	0.07 [0.05, 0.09]
6.1 Salmeterol	1	304	Mean Difference (Fixed, 95% CI)	0.03 [-0.07, 0.13]
6.2 Formoterol	2	683	Mean Difference (Fixed, 95% CI)	0.06 [0.02, 0.11]
6.3 Indacaterol	2	2276	Mean Difference (Fixed, 95% CI)	0.07 [0.05, 0.10]
7 Symptom score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Formoterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Serious adverse event (non-fatal)	5	3263	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.76, 1.55]
8.1 Salmeterol	1	304	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.37, 2.40]
8.2 Formoterol	2	683	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.54, 2.13]
8.3 Indacaterol	2	2276	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.72, 1.81]
9 Withdrawal	5	3263	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.74, 1.37]
9.1 Salmeterol	1	304	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.33]
9.2 Formoterol	2	683	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.52, 4.09]
9.3 Indacaterol	2	2276	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.34]

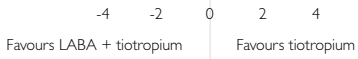
Analysis 1.1. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 1 Change in quality of life.

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 1 Change in quality of life

Study or subgroup	LABA + tiotropium N	tiotropium N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Salmeterol						
Aaron 2007	148	156	-1.8 (0.774)		76.0 %	-1.80 [-3.32, -0.28]
Subtotal (95% CI)					**76.0 %**	**-1.80 [-3.32, -0.28]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.33 (P = 0.020)						
2 Formoterol						
Vogelmeier 2008	207	221	-1 (1.378)		24.0 %	-1.00 [-3.70, 1.70]
Subtotal (95% CI)					**24.0 %**	**-1.00 [-3.70, 1.70]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)					**100.0 %**	**-1.61 [-2.93, -0.29]**
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%						
Test for overall effect: Z = 2.38 (P = 0.017)						
Test for subgroup differences: Chi^2 = 0.26, df = 1 (P = 0.61), I^2 =0.0%						



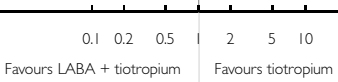
Analysis 1.2. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 2 Hospital admission (all cause).

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 2 Hospital admission (all cause)

Study or subgroup	LABA + tiotropium n/N	tiotropium n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Salmeterol					
Aaron 2007	35/148	36/156		76.2 %	1.03 [0.61, 1.76]
Subtotal (95% CI)	**148**	**156**		**76.2 %**	**1.03 [0.61, 1.76]**
Total events: 35 (LABA + tiotropium), 36 (tiotropium)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.91)					
2 Formoterol					
Vogelmeier 2008	8/207	9/221		23.8 %	0.95 [0.36, 2.50]
Subtotal (95% CI)	**207**	**221**		**23.8 %**	**0.95 [0.36, 2.50]**
Total events: 8 (LABA + tiotropium), 9 (tiotropium)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
Total (95% CI)	**355**	**377**		**100.0 %**	**1.01 [0.63, 1.61]**
Total events: 43 (LABA + tiotropium), 45 (tiotropium)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%					

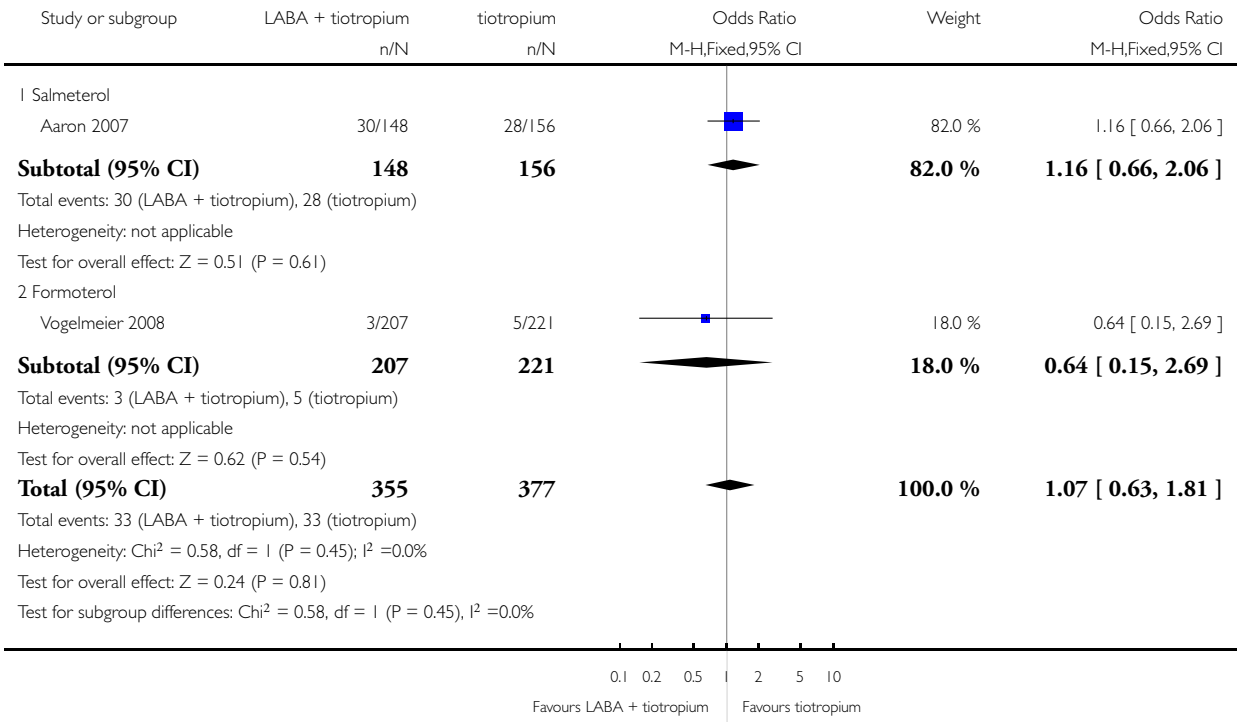


Analysis 1.3. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 3 Hospital admission (exacerbation).

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 3 Hospital admission (exacerbation)

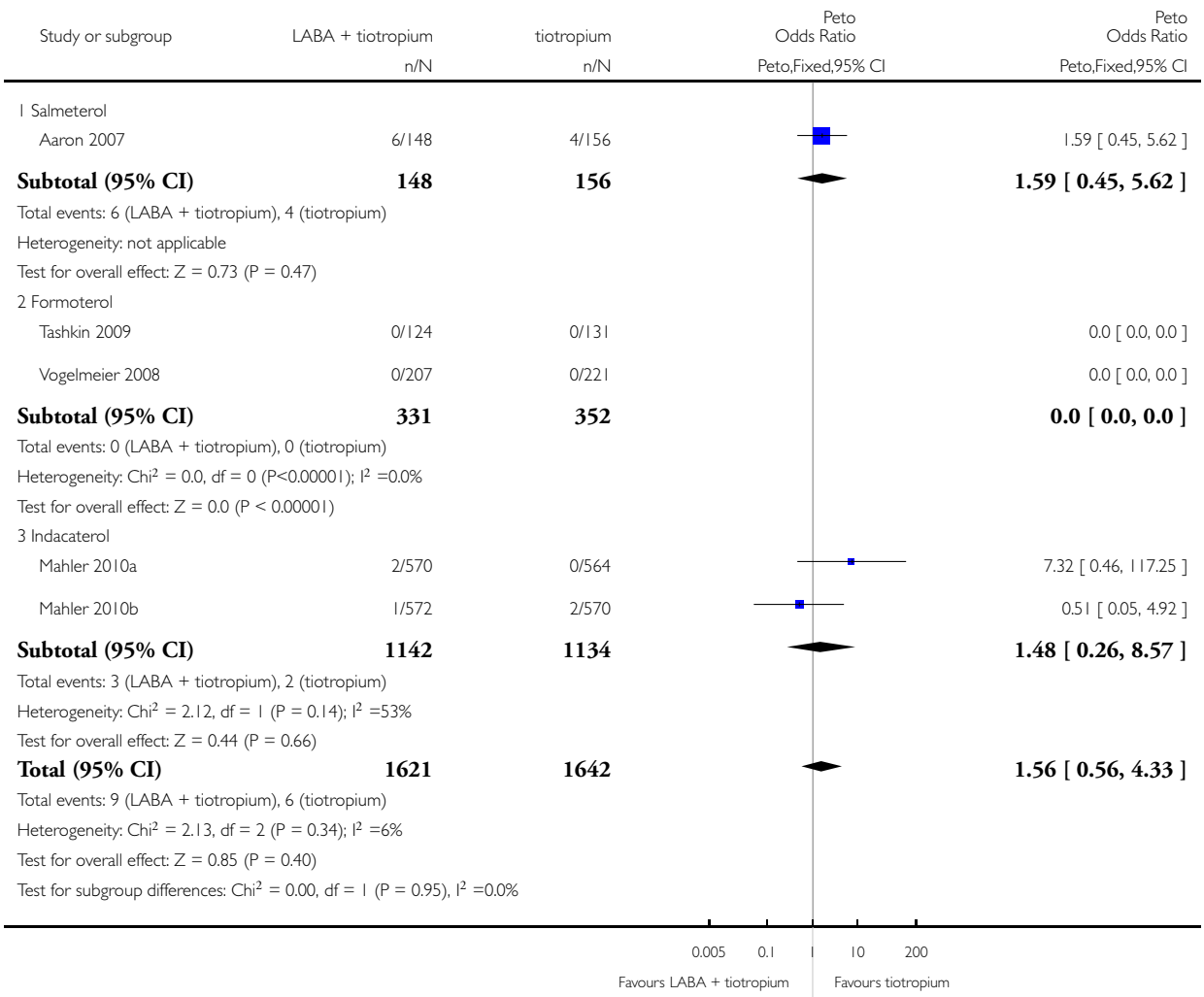


Analysis 1.4. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 4 Mortality (all cause).

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 4 Mortality (all cause)

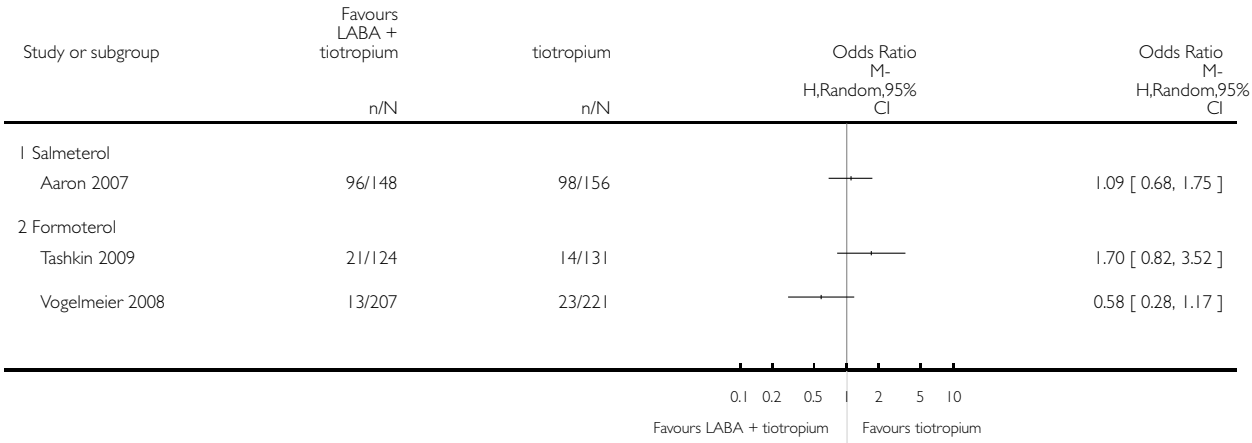


Analysis 1.5. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 5 Exacerbation.

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 5 Exacerbation

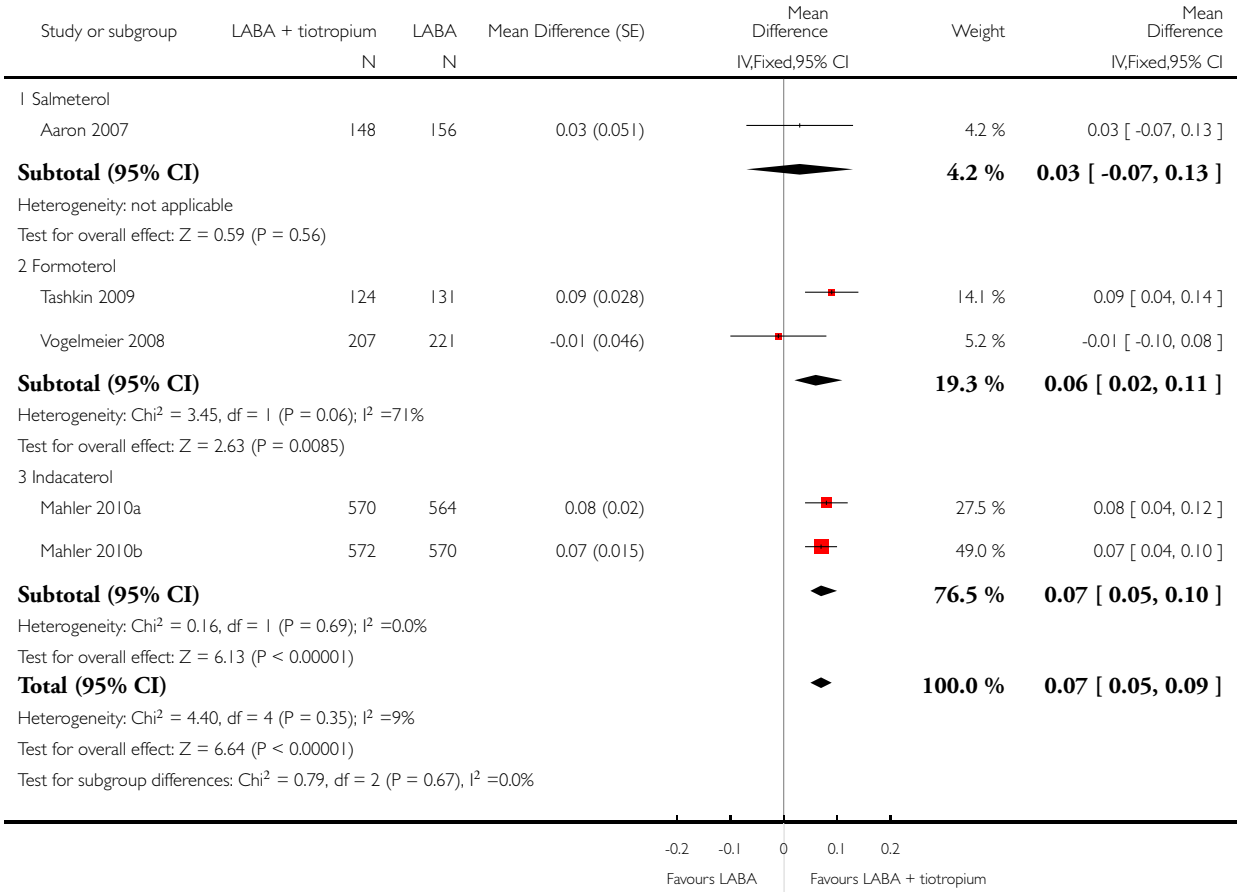


Analysis 1.6. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 6 Trough FEV1.

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 6 Trough FEV1



Analysis 1.7. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 7 Symptom score.

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 7 Symptom score

Study or subgroup	LABA + tiotropium N	Mean(SD)	tiotropium N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Formoterol						
Vogelmeier 2008	207	4.61 (2.81)	221	4.4 (2.59)		0.21 [-0.30, 0.72]

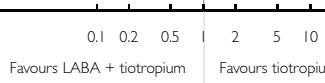
Analysis 1.8. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 8 Serious adverse event (non-fatal).

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 8 Serious adverse event (non-fatal)

Study or subgroup	LABA + tiotropium n/N	tiotropium n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Salmeterol					
Aaron 2007	9/148	10/156		15.6 %	0.95 [0.37, 2.40]
Subtotal (95% CI)	**148**	**156**		**15.6 %**	**0.95 [0.37, 2.40]**
Total events: 9 (LABA + tiotropium), 10 (tiotropium)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.91)					
2 Formoterol					
Tashkin 2009	7/124	7/131		10.9 %	1.06 [0.36, 3.11]
Vogelmeier 2008	10/207	10/221		15.7 %	1.07 [0.44, 2.63]
Subtotal (95% CI)	**331**	**352**		**26.6 %**	**1.07 [0.54, 2.13]**
Total events: 17 (LABA + tiotropium), 17 (tiotropium)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.85)					



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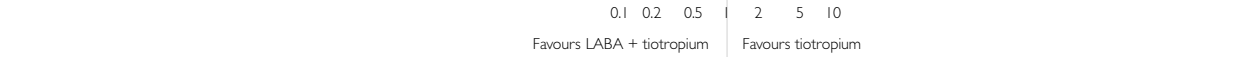
Study or subgroup	LABA + tiotropium n/N	tiotropium n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
3 Indacaterol					
Mahler 2010a	21/570	17/564		28.1 %	1.23 [0.64, 2.36]
Mahler 2010b	19/572	18/570		29.7 %	1.05 [0.55, 2.03]
Subtotal (95% CI)	**1142**	**1134**		**57.8 %**	**1.14 [0.72, 1.81]**
Total events: 40 (LABA + tiotropium), 35 (tiotropium)					
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 0.56 (P = 0.58)					
Total (95% CI)	**1621**	**1642**		**100.0 %**	**1.09 [0.76, 1.55]**
Total events: 66 (LABA + tiotropium), 62 (tiotropium)					
Heterogeneity: Chi² = 0.24, df = 4 (P = 0.99); I² =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Chi² = 0.13, df = 2 (P = 0.94), I² =0.0%					



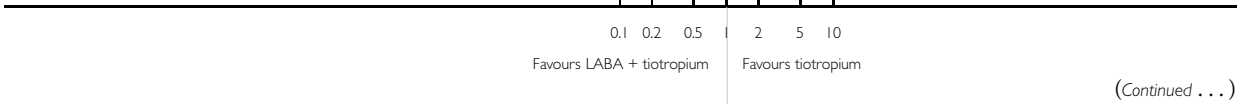
Analysis 1.9. Comparison 1 LABA plus tiotropium versus tiotropium, Outcome 9 Withdrawal.

Review: Long-acting beta$_2$-agonist in addition to tiotropium versus either tiotropium or long-acting beta$_2$-agonist alone for chronic obstructive pulmonary disease

Comparison: 1 LABA plus tiotropium versus tiotropium

Outcome: 9 Withdrawal

Study or subgroup	LABA + tiotropium n/N	tiotropium n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Salmeterol					
Aaron 2007	64/148	74/156		24.9 %	0.84 [0.54, 1.33]
Subtotal (95% CI)	**148**	**156**		**24.9 %**	**0.84 [0.54, 1.33]**
Total events: 64 (LABA + tiotropium), 74 (tiotropium)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.46)					
2 Formoterol					
Tashkin 2009	18/124	8/131		10.2 %	2.61 [1.09, 6.25]
Vogelmeier 2008	25/207	29/221		18.9 %	0.91 [0.51, 1.61]
Subtotal (95% CI)	**331**	**352**		**29.1 %**	**1.46 [0.52, 4.09]**



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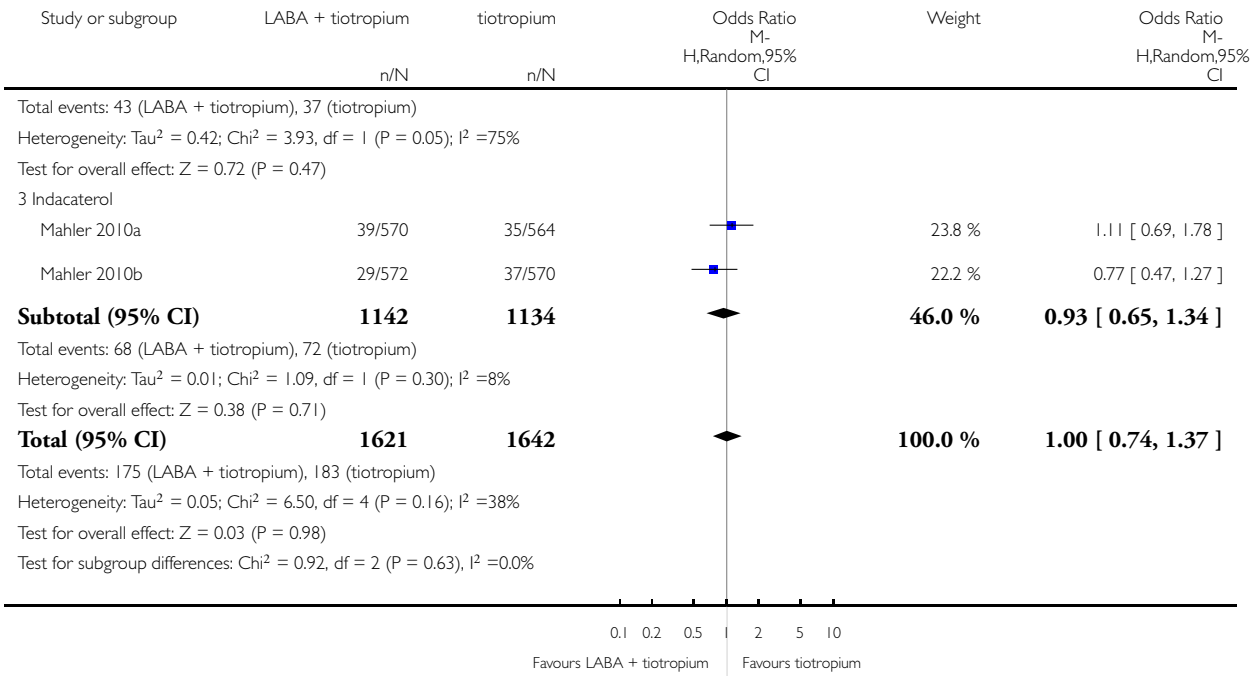

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*the Cochrane Library*)	Quarterly
PSYCHINFO (Ovid)	Monthly

(*Continued*)

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

COPD AND tiotropium AND salmeterol

COPD AND tiotropium AND formoterol

COPD AND tiotropium AND indacaterol

HISTORY

Protocol first published: Issue 2, 2011

Review first published: Issue 4, 2012

CONTRIBUTIONS OF AUTHORS

Charlotta Karner assessed studies for inclusion, extracted data, conducted the analysis and wrote the review with input from Chris Cates.

DECLARATIONS OF INTEREST

None known

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External sources

- No sources of support supplied