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Tiotropium for stable chronic obstructive pulmonary disease (Review)

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Tiotropium for stable chronic obstructive pulmonary disease.
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TABLE OF CONTENTS

[Intervention Review]

Tiotropium for stable chronic obstructive pulmonary disease

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ABSTRACT

Background

Tiotropium is a new anticholinergic therapy for chronic obstructive pulmonary disease (COPD) that differs from ipratropium by its functional relative selectivity for muscarinic receptor subtypes and which allows once-per-day dosing.

Objectives

To determine the efficacy of tiotropium on clinical endpoints such exacerbations and hospitalisations, symptom scales and pulmonary function compared to placebo and other bronchodilators used for stable COPD.

Search methods

Randomised controlled trials (RCTs) were identified from the Cochrane Airways Review Group Specialised Register, a compilation of systematic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and hand searching of 20 respiratory journals. Bibliographies from included studies and reviews were searched. The date of the last search was October 2004.

Selection criteria

Randomised clinical trials comparing tiotropium with placebo, ipratropium bromide, or long-acting ß2-agonists for greater than, or equal to, one month's duration.

Data collection and analysis

Two reviewers independently extracted data. Missing data were obtained from authors or the manufacturer of tiotropium. The data were analysed using the Cochrane Review Manager RevMan 4.2. Studies were pooled to yield weighted mean differences (WMD) or odds ratios (OR) and reported using 95% confidence intervals (CI).

Main results

From 69 identified references, nine RCTs (6,584 patients) met inclusion criteria. Tiotropium reduced the odds of a COPD exacerbation (OR 0.74; 95% CI 0.66 to 0.83) and related hospitalisations (OR 0.64; 95% CI 0.51 to 0.82) compared to placebo or ipratropium. When applied to an annual baseline risk of 45% for exacerbations and 10% for hospitalisation, the number of patients needed to treat with tiotropium for one year were 14 (95% CI 11 to 22) to prevent one exacerbation and 30 (95% CI 22 to 61) to prevent one hospitalisation compared to placebo and ipratropium. Reductions in these endpoints compared to long-acting ß2-agonists were not statistically significant. Similar patterns were evident for quality-of-life and symptom scales. Increases in FEV1 and FVC from baseline were significantly larger with tiotropium than with placebo, ipratropium and long-acting ß2-agonists over 6 to 12 months. The decline in trough FEV1 from steady state was 30 ml (95% CI

7 to 53 ml) less with tiotropium than with placebo or ipratropium over one year; no data on decline in FEV1 from steady state were available for long-acting ß2-agonists. Dry mouth was increased by tiotropium.

Authors' conclusions

Tiotropium reduced COPD exacerbations and related hospitalisations compared to placebo and ipratropium. It also improved health-related quality-of-life and symptom scores among patients with moderate and severe disease, and may have slowed decline in FEV1. Additional long-term studies are required to evaluate its effect on mortality and change in FEV1 to clarify its role in comparison to, or in combination with, long-acting ß2-agonists and to assess its effectiveness in mild and very severe COPD.

PLAIN LANGUAGE SUMMARY

Tiotropium for stable chronic obstructive pulmonary disease

Tiotropium (Spiriva) is a bronchodilator drug that has been developed to open the airways in the lungs effectively with once daily dosing. The main aims of therapy in COPD are to reduce exacerbations and related hospitalisations, improve quality of life, and reduce the rate of decline in lung function. The evidence from the trials in the review indicates that, compared with a placebo and ipratropium, tiotropium does reduce exacerbations and related hospitalisations and improves quality of life and symptoms in people with moderately severe COPD, although the evidence with regards to decline in lung function is less clear. Tiotropium caused dry mouth. Compared with other commonly used drugs in COPD, such as long-acting beta agonists (including salmeterol), there is not enough evidence for us to draw reliable conclusions. In order to better understand the effects of this drug we need long-term studies (over several years), studies conducted in mild and severe COPD, and additional studies that measure outcomes in relation to other agents used in the treatment of this condition.

BACKGROUND

Current recommendations for the therapy of patients with chronic obstructive pulmonary disease (COPD) suggest that anticholinergic drugs should play a prominent role (Ferguson 1993). The development of safe, effective, quaternary anticholinergic compounds that have functional relative selectivity for muscarinic receptor subtypes has generated renewed interest in anticholinergic bronchodilator therapy.

Tiotropium has a quaternary ammonium structure related to that of ipratropium bromide. Similar to ipratropium, tiotropium binds M1, M2 and M3 muscarinic receptors. Unlike ipratropium, tiotropium has kinetic selectivity for these receptors, dissociating slowly from M1 and M3 receptors but rapidly from M2 receptors (Haddad 1994). The slow dissociation of tiotropium from M1 and M3 receptors produces a bronchodilating effect which lasts over 24 hours, allowing once-daily dosing (Disse 1999). The rapid dissociation from M2 receptors may also be advantageous since these are feedback inhibitory receptors. Blocking M2 receptors, therefore, paradoxically increases acetylcholine release whereas unblocking them decreases acetylcholine release (Barnes 2000). Tiotropium may, therefore, have clinical benefits over ipratropium, one of the current first-line therapies for stable COPD.

OBJECTIVES

The aim of this review is to evaluate the efficacy of tiotropium on clinical endpoints, quality-of-life and symptom scales and pulmonary function from available randomised trial data comparing tiotropium to placebo, ipratropium bromide and long-acting ß2-agonists.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials comparing tiotropium with placebo, ipratropium bromide, or long-acting ß2-agonists. Since the primary purpose of the review was to evaluate long-term clinical responses to tiotropium, we excluded studies that followed patients for less than one month after randomisation.

Types of participants

Adult patients aged greater than 35 years with known stable COPD fulfilling American Thoracic Society (ATS), European Respiratory Society (ERS), or GOLD diagnostic criteria were included. COPD patients with partial reversibility on pulmonary function testing were included, consistent with these criteria. Patients had clinically stable disease without evidence of an exacerbation for one month prior to study entry. Patients with significant diseases other than COPD, a diagnosis of asthma, cystic fibrosis, bronchiectasis, or other lung diseases were excluded.

Types of interventions

Comparisons were made between the administration of:
1) tiotropium versus placebo;
2) tiotropium versus ipratropium bromide;
3) tiotropium versus long-acting ß2-agonists (salmeterol or formoterol).

Types of outcome measures

Primary outcomes

1) clinical outcomes - exacerbations, hospitalisations and mortality.

Secondary outcomes

1) health-related quality-of-life scales;
2) self-rated symptom score/symptoms of breathlessness;
3) change in forced expiratory volume in one second (FEV1) and change in forced ventilatory capacity (FVC): trough, peak and average; and other measures of pulmonary function, from baseline and from steady state (measured at 8 to 15 days after randomisation);
4) exercise performance - six-minute walk and other measures;
5) inhaled rescue medication used during the treatment period, and other concomitant medication usage including antibiotics and steroids;
6) adverse events - palpitations, dry mouth, blurred vision, urinary obstruction, and constipation.

Search methods for identification of studies

Searches were current as of October 2004.

Electronic searches

The Cochrane Airways Review Group Specialised Register of COPD trials is a compilation of references to reports of controlled clinical trials assembled from systematic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL and supplemented by hand searching of leading respiratory journals and conference abstracts. It is not limited by language of publication. The Register was searched using the following terms:

tiotropium OR "Ba 679 BR" OR Spiriva OR oxitropium.

In addition, a search of LILACS and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed.

Searching other resources

Reference lists of all primary studies and review articles were reviewed for additional references. Authors of identified randomised trials were asked about knowledge of other published and unpublished studies. The manufacturer of tiotropium (Boehringer Ingelheim) was contacted to clarify potential overlap between studies and to request results from unpublished studies and supplemental data from published studies.

Data collection and analysis

Selection of studies

Trials which appeared potentially relevant were identified independently by two reviewers. Using the full text of each study, two reviewers independently selected trials for inclusion in the review. Agreement was measured using simple agreement and kappa; third-party adjudication was used to resolve differences.

Data extraction and management

Two reviewers independently extracted data from included trials according to intention-to-treat principles and entered results into the Cochrane Collaboration software program (RevMan). In some

cases information regarding outcomes was estimated from graphs. This was performed independently by the two reviewers. Data extraction included the following items:

Population: age, gender, smoking status, study setting (country, practice setting), inclusion and exclusion criteria.
Intervention: dose, duration.
Control comparisons: placebo, ipratropium, long-acting ß2-agonists.
Concurrent treatments: ipratropium, short and long-acting ß2-agonists, theophylline, inhaled and systemic corticosteroids.
Outcomes: exacerbations (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 three days and usually associated with a therapeutic intervention), related hospitalisations, self-rated symptom score/symptoms, quality-of-life instruments, pulmonary function measures (change in FEV1 and FVC), timing of pulmonary function measures, 6-minute walk, adverse events (palpitations, dry mouth, blurred vision, urinary obstruction and constipation), assessors, adjudicator of clinical endpoints
Design: method of randomisation, presence and type of run-in period, study design (parallel, cross-over).

Assessment of risk of bias in included studies

After a preliminary review of all studies to confirm the basic requirements, two reviewers assessed the methodological quality of the included trials with particular emphasis on the concealment of allocation, which was ranked using Cochrane criteria (grade A: adequate concealment; grade B: uncertain; grade C: clearly inadequate concealment).

In addition, each study was assessed using the 0 to 5 scale described by Jadad, as summarised below.
1) Was the study randomised? (1=yes; 0=no)
2) Was the study double-blind? (1=yes; 0=no)
3) Were withdrawals and dropouts described? (1=yes; 0=no)
4) Was the method of randomisation well described and appropriate? (1=yes; 0=no)
5) Was the double blinding well described and appropriate? (1=yes; 0=no)
6) Deduct one point if methods for randomisation or blinding were inappropriate
Inter-rater reliability was measured for both quality scales by using kappa (weighted or unweighted) statistics.

Assessment of reporting biases

Funnel plots were constructed to check for the presence of publication bias.

Data synthesis

Trials were combined using RevMan (Version 4.2) and analyses were intention-to-treat whenever possible. When follow-up data was known to be missing (e.g., for change analyses), all available data were included and the number of persons included in the trial was considered to be the number of persons who completed the trial for that particular measure. For continuous variables, a fixed-effect weighted mean difference (WMD) and 95% confidence interval (CI) was calculated for each study. Studies were pooled using fixed-effect WMD and 95% CIs. For dichotomous variables, a fixed-effect odds ratio (OR) with 95% confidence intervals (95% CI) was calculated for individual studies. Heterogeneity was tested using the Breslow-Day test; a P value less than 0.1 was considered statistically significant. If heterogeneity was found, a random-effects model was used. Numbers needed to treat (NNT) were calculated from the pooled OR and its 95% CI applied to the risk in the placebo group using an online calculator (Visual Rx at www.nntonline.net). This calculator converts the risk in the placebo group to the corresponding odds, applies the OR to estimate the odds in the tiotropium group, converts that odds to the corresponding risk and calculates the risk difference, the inverse of which is the NNT.

For each outcome, trials were pooled within categories of control group (placebo, ipratropium or long-acting ß2-agonists). Results of the one study that had two control groups (placebo and salmeterol) were entered into the two corresponding categories. Heterogeneity was tested both within and across categories of control group, so defined. Since an earlier large randomised clinical trial showed that ipratropium does not reduce health outcomes or slow decline in FEV1 relative to placebo (Anthonisen 1994; Anthonisen 2002), summary estimates were calculated comparing tiotropium with placebo or ipratropium for each these endpoints, as long as there was statistical homogeneity across categories of control group. This summary estimate was calculated by pooling trials across categories of placebo and ipratropium control groups; it was not specified in the original protocol.

Subgroup analysis and investigation of heterogeneity

Subgroup and sensitivity analyses:
Heterogeneity was to be examined using the following subgroups, which were established a priori:
1) disease severity (related to baseline FEV1 and placebo-group exacerbation rate);
2) prior ipratropium use (dichotomised as yes or no);
3) concurrent therapy with routine beta-agonist use (short or long-acting) and corticosteroid (systemic or inhaled) use (both dichotomised as yes or no);
4) reversibility of airflow obstruction with ß2-agonist therapy (dichotomised as partial or none);
5) dose, duration and delivery method of therapy;
6) clinical description of COPD (dichotomised as emphysema or chronic bronchitis).

Sensitivity analysis

Quality weighting was also used to test the robustness of the results, and additional sensitivity analyses were performed comparing random-effects and fixed-effect models.

RESULTS

Description of studies

Results of the search

A total of 69 articles were identified in the Cochrane Collaboration Airways COPD Registry and from other sources. The review of titles and abstracts yielded 20 articles that possibly fulfilled inclusion criteria. Among these, 12 met inclusion criteria and were included in the analysis. Some of the included articles overlapped, such that three of these articles reported the combined results of pairs of separate trials: Casaburi (Casaburi 2002) reported results for participants enrolled in his previously reported trial (Casaburi

2000) and a previously unpublished trial; Vincken (Vincken 2002) reported results for participants enrolled in the trial reported by van Noord (van Noord 2000) and a previously unpublished trial; and Brasasco (Brusasco 2003) reported results for participants enrolled in the trial reported by Donohue (Donohue 2002) and a previously unpublished trial. The net number of included trials was therefore nine, with total number of patients who were randomised of 6,584.

Included studies

Details of individual trials are given in Characteristics of included studies.

Seven of the studies included in the overview were published in the peer-reviewed literature and two were published in abstract form. The characteristics of the studies are described in the Table of included studies. The protocols of all of these studies were extremely similar. All studies enrolled patients with COPD that met standardised criteria, that was moderately severe (GOLD Stage IIb, on average), and that was clinically stable. All studies enrolled patients regardless of response to bronchodilators but excluded patients with a prior history of asthma, atopy, allergic rhinitis and elevated eosinophil count.

Of the nine included studies, seven compared tiotropium to placebo, one compared tiotropium to ipratropium, and one compared tiotropium to placebo and to salmeterol. All studies prohibited the use of ipratropium and allowed the use of short-acting ß2-agonists and inhaled corticosteroids as co-therapies in the intervention group. Eight of nine studies prohibited the use of long-acting ß2-agonists (the exception being Niewoehner 2005 where long-acting ß2-agonists were permitted). Thirty-nine to 60% of randomised patients were taking ipratropium at enrolment. Of permitted co-therapies, 66 to 99% of patients were taking ß2-agonists at enrolment and 42 to 80% were taking inhaled corticosteroids. Use of long-acting ß2-agonists at enrolment was generally not reported separately from use of short-acting ß2-agonists.

Excluded studies

Eight studies were excluded from the review for the reasons listed in Characteristics of excluded studies.

Risk of bias in included studies

Overall, the methodological quality of the studies was good although not excellent (Table 1). Concealment of allocation was not described (Grade B) in nine and adequately described (Grade A) in three studies. Using the criteria of Jadad, two studies scored 5 out of a possible 5, seven studies scored 4 out of 5, and three studies scored 3 out of 5 for reporting of blinding, allocation and follow up.

Effects of interventions

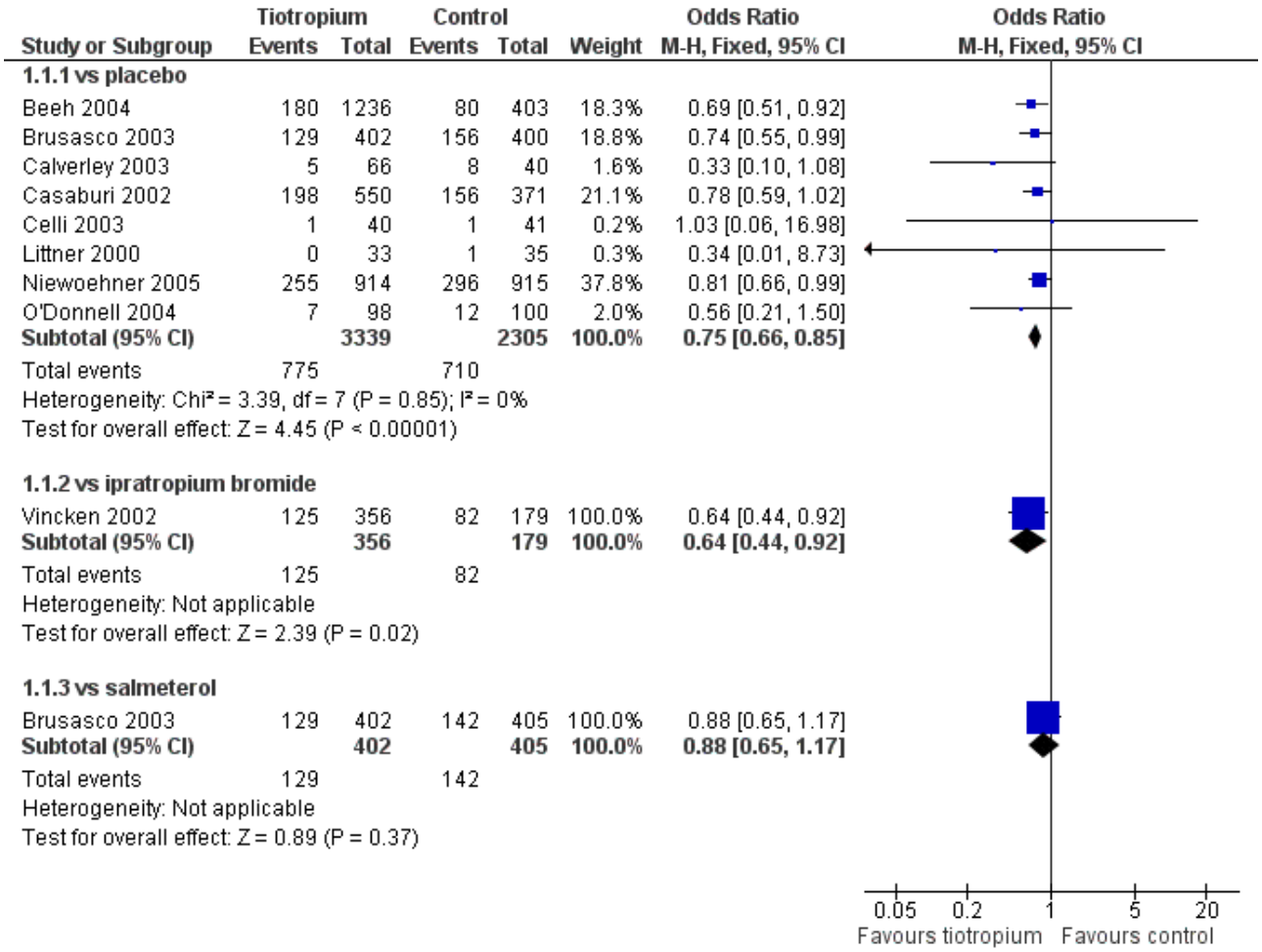
Clinical outcomes

We extracted and analysed results for cumulative incidence of COPD exacerbations, related hospitalisations, and all-cause mortality over the duration of the trials, which ranged from one to twelve months (weighted mean duration 6.3 months).

Exacerbations

The overall cumulative incidence of COPD exacerbations was 32% in the control groups (those not receiving tiotropium) over the duration of the trials. Tiotropium reduced the primary endpoint of COPD exacerbations compared to placebo (OR 0.75; 95% CI 0.66 to 0.85) and compared to ipratropium (OR 0.64; 95% CI 0.44 to 0.92). The cumulative incidence of exacerbations was lower in the tiotropium group than the salmeterol group but the difference was somewhat smaller and not statistically significant (OR 0.88; 95% CI 0.65 to 1.17). The treatment effect of tiotropium was statistically homogeneous across the control groups (P value 0.85) and the summary OR for tiotropium compared to placebo or ipratropium was 0.74 (95% CI 0.66 to 0.83), Figure 1.

Figure 1. Forest plot of comparison: 1 Health outcomes, outcome: 1.1 Exacerbations.



This summary OR was applied to a risk of exacerbation of 45% over one year (the weighted average of the risk in the placebo and ipratropium arms of two trials of 12 months duration (Casaburi 2002; Vincken 2002) to yield a NNT for tiotropium over 12 months of 14 (95% CI: 11 to 22; Figure 2).

Figure 2. Patients suffering COPD exacerbation when given Tiotropium for one year in comparison to placebo or Ipratropium

Hospitalisations

The overall cumulative incidence of exacerbation-related hospitalisations was 8% in the control groups over the duration of the trials. As shown in Detail 1:3, tiotropium reduced the proportion hospitalised for COPD exacerbations compared to placebo (OR 0.65; 95% CI 0.50 to 0.85). Similar reductions in hospitalisations were observed for tiotropium compared to ipratropium (OR 0.59; 95% CI 0.32 to 1.09) and compared to salmeterol (OR 0.59; 95% CI 0.29 to 1.23) but neither of these estimates were statistically significant, which may be due the smaller sample sizes. The treatment effect of tiotropium was statistically homogeneous across the control groups (P value 0.83) and the summary estimate for tiotropium compared to placebo or ipratropium was OR 0.64 (95% CI 0.51 to 0.82), Figure 3. When this OR was applied to a one year risk of hospitalisation of 10% in the two 12 month trials (Casaburi 2002; Vincken 2002), the NNT for tiotropium was 30 (95% CI 22 to 61; Figure 4).

Figure 3. Forest plot of comparison: 1 Health outcomes, outcome: 1.3 Hospitalisations for COPD.

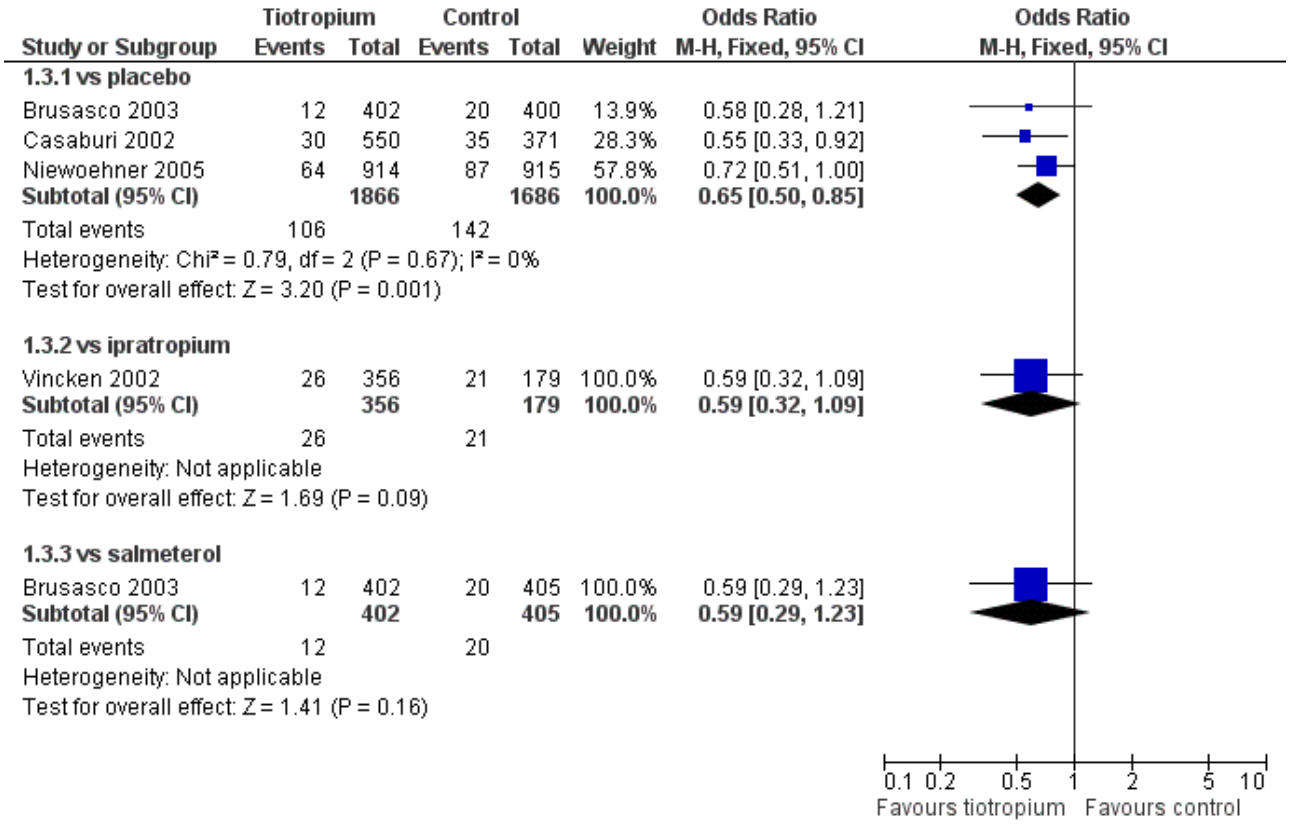
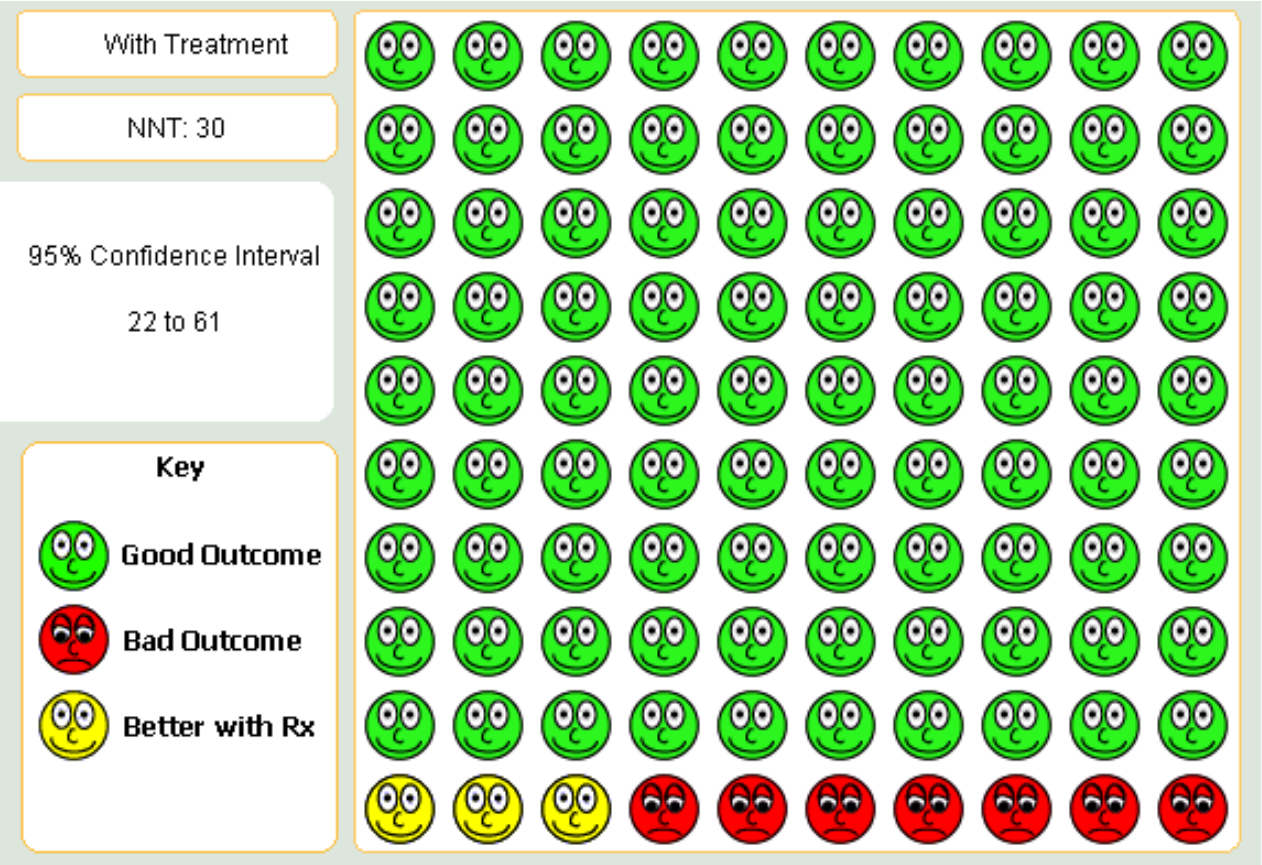


Figure 4. Patients with hospitalisation over one year on Tiotropium compared to placebo or Ipratropium



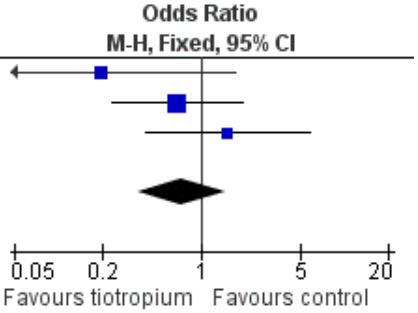
All-cause mortality

Cumulative all-cause mortality was 1.5% in the control groups over the duration of the trials. There were no statistically significant differences between tiotropium and placebo, ipratropium, or salmeterol (Detail 1:5). The trials were statistically homogeneous across the control groups (P value 0.22) and the summary estimate for tiotropium compared to other treatments was not significant; with a wide confidence interval due to small numbers (OR 0.73; 95% CI 0.35 to 1.49), Figure 5.

Figure 5. Forest plot of comparison: 1 Health outcomes, outcome: 1.6 All-cause mortality -- summary estimate.

Study or Subgroup	Tiotropium Events	Tiotropium Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Brusasco 2003	1	402	5	402	29.1%	0.20 [0.02, 1.70]
Casaburi 2002	7	550	7	371	48.2%	0.67 [0.23, 1.93]
Vincken 2002	9	356	3	179	22.7%	1.52 [0.41, 5.69]
Total (95% CI)		**1308**		**952**	**100.0%**	**0.73 [0.35, 1.49]**
Total events	17		15			

Heterogeneity: Chi² = 2.63, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.87 (P = 0.38)



Health-related quality of life and symptom scales

We extracted and analysed the mean change in health-related quality of life, measured by the St George's Respiratory Questionnaire (SGRQ), and the proportion with a clinically significant improvement in the SGRQ and Transitional Dyspnea Index (TDI) over the duration of the trials. We were not able to obtain adequate reports of mean change in TDI to allow its combination.

St George's Respiratory Questionnaire

As shown in Detail 2:1, the mean change in SGRQ over the course of the trials was larger with tiotropium than with placebo (WMD -3.3; 95% CI -4.6 to -0.8) and ipratropium (WMD -3.3; 95% CI -5.6 to -1.0). A smaller and non-significant difference was observed compared to salmeterol (WMD -1.4; 95% CI -3.2 to 0.4). The trials were statistically homogeneous across the control groups (P value 0.31) and the summary estimate for tiotropium compared to placebo or ipratropium was an improvement of WMD -3.3 (95% CI -4.7 to -2.2). The results for the proportion with a clinically significant change in SGRQ were similar to results for mean change in SGRQ. Statistically significant differences were observed for tiotropium compared to placebo and compared to ipratropium but not for tiotropium compared to salmeterol (Detail 2:3). There was evidence of statistical heterogeneity across the control groups (P value 0.03).

Transitional Dyspnea Index

As shown in Detail 2:4, the proportion with a clinically significant change in TDI over the course of the trials was greater with tiotropium than with placebo (OR 1.96; 95% CI 1.58 to 2.44) and ipratropium (OR 2.01; 95% CI 1.26 to 3.20) but was not significantly different from salmeterol (OR 1.08; 95% CI 0.80 to 1.46). There was evidence of statistical heterogeneity across the control groups (P value 0.07).

Spirometric indices

We extracted and analysed change in spirometric indices from baseline (prior to first drug dose) to the end of the trials, and change in spirometric indices from steady state (8 to 15 days after first drug dose) to the end of the trials for all available data.

Change in spirometric indices from baseline

As shown in Detail 3:1, the mean change in trough FEV1 from baseline was greater with tiotropium than with placebo (WMD 140 ml; 95% CI 118 to 162 ml) and ipratropium (WMD 150 ml; 95% CI 106 to 193 ml). A smaller but statistically significant difference was observed compared to salmeterol (WMD 40 ml; 95% CI 12 to 68 ml). There was evidence of statistical heterogeneity across the control groups (P value less than 0.0001), which arose from the smaller mean difference when tiotropium was compared to salmeterol. Similar results were observed for change in mean FEV1 and change in peak FEV1 (Details 3:2 and 3:3).

As shown in Detail 3:4, the mean change in trough FVC from baseline was greater with tiotropium than with placebo (WMD 278 ml; 95% CI 208 to 348) and ipratropium (WMD 210 ml; 95% CI 112 to 308 ml). A smaller but statistically significant difference was observed compared to salmeterol (WMD 90 ml; 95% CI 35 to 145 ml). There was evidence of statistical heterogeneity across the control groups (P value less than 0.0001). Similar results were observed for change in mean FEV1 and change in peak FVC except that the difference between tiotropium and ipratropium did not attain statistical significance (Details 3:5 and 3:6).

As shown in Detail 3:7, the mean change in morning peak flow from baseline was greater with tiotropium than with placebo (WMD 21 ml; 95% CI 15 to 28 ml) and ipratropium (WMD 16 ml; 95% CI 7 to 25 ml). No difference was observed compared to salmeterol (WMD 0 ml; 95% CI -8 to 9 ml). There was evidence of statistical heterogeneity across the control groups (P value 0.005). Similar results were observed for change in evening peak flow except that the difference between tiotropium and salmeterol was statistically significant (Detail 3:8).

Change in spirometric indices from steady state

Data on decline in FEV1 and FVC from steady state to the end of the trial were available for two 12-month trials, one comparing tiotropium with placebo and the other comparing tiotropium with ipratropium. As shown in Detail 3:9, the mean decline in trough FEV1 from steady state was statistically significantly slower with tiotropium than placebo (WMD 30 ml; 95% CI 2 to 56 ml) and statistically insignificantly slower with tiotropium than ipratropium (WMD 30 ml; 95% CI -14 to 74 ml). The trials were statistically homogeneous across the control groups (Pvalue greater than 0.99) and the summary estimate showed a WMD of 30 ml (95% CI 7 to 53 ml) slower decline in FEV1 for tiotropium compared to placebo or ipratropium. Results for decline in mean FEV1 and peak FEV1 were variable and showed non-significant differences for tiotropium compared to placebo or ipratropium (Details 3:10 and 3:11).
No statistically significant differences were observed between tiotropium and either control group for decline in trough, mean and peak FVC (Details 3:12, 3:13 and 3:14).

Adverse events

We attempted to extract data on all available adverse events, including palpitations, dry mouth, blurred vision, urinary obstruction, constipation, and cardiovascular events. The only adverse event which was reported with sufficient consistency to allow combination was dry mouth. As shown in Detail 7:1, dry mouth was significantly increased with tiotropium compared to placebo (OR 5.4; 95% CI 3.3 to 8.8), ipratropium (OR 2.1; 95% CI, 1.05 to 4.2), and salmeterol (OR 5.1; 95% CI 2.2 to 12). The statistical homogeneity of the effect of tiotropium across the control groups was borderline (P value 0.11).

Sensitivity analyses

We attempted to perform sensitivity analyses as specified in the methods but found that the trials were very similar with respect to disease severity, prior ipratropium use, concurrent therapies, reversibility of airflow obstruction, dose and method of delivery, and clinical description of COPD. In an attempt to characterise the effect of tiotropium on exacerbations in milder COPD, we restricted the analysis to the three trials with the highest mean baseline FEV1 (Beeh 2004; O'Donnell 2004; Vincken 2002), which produced a similar summary estimate (OR 0.66; 95% CI 0.53 to 0.83) to the overall estimate.

The effect of tiotropium on exacerbations in the one trial that permitted concurrent use of long-acting ß2-agonists (Niewoehner 2005: OR 0.81; 95% CI 0.66 to 0.99) was statistically similar to the eight others that withheld long-acting ß2-agonists (OR 0.71; 95% CI 0.61 to 0.82). A similar pattern was evident for hospitalisations:

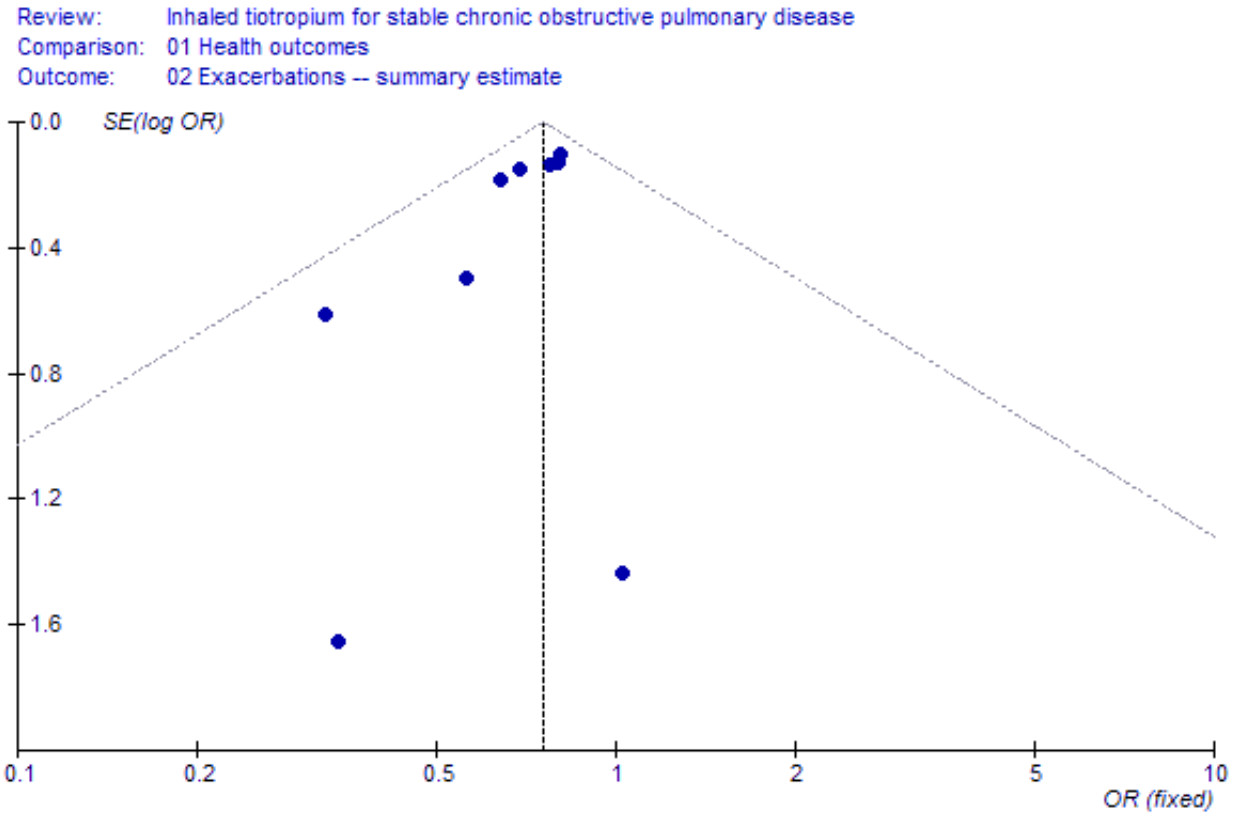
the OR for hospitalisations was 0.72 (95% CI 0.51 to 1.00) with concurrent use of long-acting ß2-agonists permitted and 0.57 (95% CI 0.41 to 0.81) with concurrent use of long-acting ß2-agonists prohibited.

Analyses restricted to trials of long-term duration (six months or more) yielded either identical or highly consistent results. The above-reported results for hospitalisation, mortality, SGRQ, TDI and change in spirometric indices from steady state were all based on long-term trials. The OR for exacerbations in the long-term trials was 0.78 (95% CI 0.69 to 0.88) and results for change in spirometric indices from baseline were also similar.

Additional sensitivity analyses by random-effects instead of fixed-effect models generally produced identical results since in the setting of homogeneity the random-effects model reduces to a fixed-effect model.

Funnel plots were checked for primary endpoints. The funnel plot for exacerbations showed asymmetry and a relative absence of small studies with results that did not favour tiotropium, suggesting the possibility of some publication bias (Figure 6). Funnel plots for other outcomes showed no clear evidence of publication bias, although the ability to detect such a bias was limited by the small number of included studies.

Figure 6. Funnel plot of included studies for COPD exacerbations



DISCUSSION

This systematic review of the currently available randomised trials of tiotropium for stable COPD demonstrated that tiotropium reduced COPD exacerbations and related hospitalisations compared to placebo or ipratropium. Similar improvements were evident for quality-of-life and symptom scales. Increases in FEV1 and FVC from baseline were significantly larger with tiotropium than with placebo, ipratropium and long-acting ß2-agonists. Although the total number of patients contributing data at one-year follow up in these trials was modest, there was a statistically significant difference in the decline in trough FEV1 from steady state with tiotropium compared to placebo or ipratropium.

The benefits observed with tiotropium for exacerbations and related hospitalisations were large and clinically important. COPD exacerbations were responsible for 8 million outpatient visits, 1.5 million emergency room visits, and 726,000 hospitalisations in the US in 2000 (Mannino 2002). A one-third reduction in hospitalisations could potentially yield significant reductions in morbidity and cost. Consistent with this expectation, tiotropium has been shown to be cost-effective, although not cost-saving, compared to ipratropium, in Europe (Oostenbrink 2004). The magnitude of the reduction in exacerbation-related hospitalisations with tiotropium was similar in comparison to placebo and ipratropium and was similar in the large placebo-controlled trials that did, and did not, permit continuation of long-acting ß2-agonists during the trial.

Changes in quality of life, symptom scales and spirometric indices also appeared clinically significant. Compared to placebo and to ipratropium, the mean change in the SGRQ across all participants was close to the SGRQ's clinically significant change of 4 units, and

substantially more participants on tiotropium achieved a clinically significant change in SQRQ and TDI compared to placebo and ipratropium. Improvements in spirometric indices from baseline were large and clinically significant compared to placebo and to ipratropium, and smaller but statistically significant compared to salmeterol.

The results of this meta-analysis were consistent with a prior overview (Sin 2003) with respect to exacerbations and quality of life. They extend that review with more than twice as many patients and additional outcomes of hospitalisations, mortality, symptom scales, spirometric indices and adverse events. Most striking of these is the observation that the decline in trough FEV1 from steady state was slower with tiotropium than with placebo or ipratropium. This difference was large relative to the differences observed in a meta-analysis of inhaled corticosteroids in COPD (Sutherland 2003). However, this observation should be interpreted with caution considering that it might also be due to: 1) incomplete attainment of steady state of tiotropium at 8 days; 2) chance, given that multiple spirometric indices were measured and that the duration of the relevant trials were only one year; and 3) bias, given that not all trial results for this index were available for inclusion in this summary estimate. Larger, longer-term trials are necessary to assess the validity of this result, which would be of major clinical relevance if replicated.

The trials included in this review were of good to excellent quality and used almost identical designs with regard to inclusion and exclusion criteria. The clinical characteristics of the patients recruited into the trials was, therefore, fairly homogeneous, and disease severity as measured by baseline spirometry and event rates in the control groups was also similar between trials. The clinical homogeneity of the trials resulted in statistical homogeneity for many outcome measures across the trials. Meta-analysis of these trials was, therefore, justified on clinical and statistical grounds.

We calculated summary estimates of the effects of tiotropium on clinical outcomes compared to placebo and ipratropium. Although on the face of it this approach may introduce some heterogeneity, we believe that it was justified on two grounds. First, heterogeneity would be introduced only if the control therapy (ipratropium) had an effect on the outcome. Ipratropium has been shown to not alter long-term decline in FEV1 (Anthonisen 1994), hospitalisations or survival (Anthonisen 2002) compared to placebo; long-acting ß2-agonists, on the other hand, have been shown to reduce exacerbations and hospitalisations compared to placebo. Second, there was very little statistical evidence of heterogeneity across trials with varying control groups. The effect of tiotropium on hospitalisations, for example, was the same for comparison groups of placebo and ipratropium.

Potential limitations of meta-analyses include double-counting of patients from overlapping publications, publication bias, and selection bias. A recent overview of therapies for COPD (Sin 2003), which meta-analysed SGRQ and COPD exacerbation results for tiotropium, erroneously included two pairs of trials as separate trials. The consequent double-counting of patients yielded an analysis based on 3,574 patients instead of the 2,663 patients that were actually randomised in the trials cited in that review. We avoided such double-counting by discussing trial overlap with the primary authors and with the manufacturer of tiotropium.

We evaluated for publication bias by checking funnel plots and found evidence of publication bias for exacerbations. Given the relatively small weight of the smaller studies for this outcome (less than 5%), it is unlikely that any small unpublished studies severely biased our results. Large unpublished studies would pose a bigger threat to the pooled results. In order to attempt to minimise such publication bias, we contacted the manufacturer of tiotropium to obtain a list of the published, unpublished, and ongoing trials of tiotropium. The manufacturer was very helpful in providing additional information on completed published trials but did not provide information on completed but unpublished trials. Publication bias, therefore, remains a potential concern. Two completed trials that compared tiotropium to salmeterol were published in a combined form (Brusasco 2003) that showed no difference between tiotropium and salmeterol. One of these trials showed that tiotropium was superior to salmeterol for exacerbations. It was published a year earlier (Donohue 2002) than the combined version; the other, which presumably showed that tiotropium was not superior to salmeterol for exacerbations is, as of this writing, yet to be published as a unique publication. We will continue to update this review in an attempt to minimise potential publication bias.

An additional possible concern with meta-analyses is selection bias, which refers to bias from non-differential selection of available trials for inclusion into the meta-analysis. To avoid selection bias a systematic and comprehensive search was conducted and two reviewers independently evaluated trials for inclusion into the meta-analysis using standardised pre-specified inclusion and exclusion criteria.

AUTHORS' CONCLUSIONS

Implications for practice

Tiotropium reduced COPD exacerbations and exacerbation-related hospitalisations compared to placebo or ipratropium. It improved health-related quality-of-life and symptom scores among patients with moderate and severe disease compared to placebo and ipratropium and can be recommended for the treatment of stable COPD. There was a suggestion from this review that tiotropium may slow decline in FEV1, although this finding requires confirmation.

Implications for research

Additional long-term studies are required to establish the effect of tiotropium on mortality and decline in FEV1, to evaluate its effectiveness in comparison to, and combination with, long-acting ß2-agonists, and to establish its role in mild and very severe COPD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Beeh 2004

Methods	Type: Parallel group. Duration: 3 months. Pre-randomization run-in period: 1 week wash-out period. Randomisation method: Not stated. Blinding: Double-blind. Co-interventions allowed during trial: short-acting B-agonist, inhaled corticosteroid, prednisone <= 10 mg/day, theophylline. Co-interventions NOT allowed during trial: ipratropium, long-acting B-agonist. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients, referral source not stated. Inclusion criteria: Prior diagnosis of COPD, FEV1 <= 70% predicted, ratio <=70%, age >40 years, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, use of daytime oxygen, recent history of myocardial infarction, drug treatment for arrhythmia, or recent hospitalisation for congestive heart failure Number recruited: 1,639 Mean age: 62 years Gender: 75% male Baseline FEV1: 1.3 +/- 0.5 L; FVC 2.4 +/- 0.7 L; Ratio NA Baseline co-interventions allowed during trial: short-acting B-agonist 76%, inhaled corticosteroid 57%, prednisone 16%,

Beeh 2004 *(Continued)*

	theophylline 52%. Baseline co-interventions NOT allowed during trial: ipratropium 69%, long-acting B-agonist 50%.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: Placebo.
Outcomes	Analysed: Cumulative incidence of exacerbations; Reported: Difference in FEV1 and FVC between intervention and control groups.
Notes	Analysed: Cumulative incidence of exacerbations; Reported: Difference in FEV1 and FVC between intervention and control groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Brusasco 2003

Methods	Type: Parallel group. Duration: 6 months. Pre-randomisation run-in period: 2 week wash-out period. Randomization method: Not stated. Blinding: Double-blind. Co-interventions allowed during trial: Not stated, but ?same as Donohue (2002): short-acting B-agonist, inhaled corticosteroid, prednisone <= 10 mg/day, theophylline. Co-interventions NOT allowed during trial: Not stated, but ?same as Donohue (2002): ipratropium, long-acting B-agonist. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients (18 countries), referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 <= 65% predicted, ratio <=70%, age >40 years, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, use of supplemental oxygen or upper respiratory infection within 6 weeks, significant disease other than COPD. Number recruited: 1,207 Mean age: 64 years Gender: 76% male Baseline FEV1: 1.1 +/- 0.4 L; FVC 2.6 +/- 0.7 L; Ratio 43 +/- 10 % Baseline co-interventions allowed during trial: Not reported. Baseline co-interventions NOT allowed during trial: Not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control1: Salmeterol 50ug BID by metered-dose inhaler. Control2: Placebo.
Outcomes	Analysed: Cumulative incidence of exacerbations, hospitalisations, and all-cause mortality; change in St. George's Respiratory Questionnaire and Transitional Dyspnea Index; change in trough FEV1 and FVC; adverse events Reported: rescue B-agonist use.
Notes	Reported combined results of Donohue (2002) and a similar unpublished trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Calverley 2003

Methods	Type: Parallel group. Duration: 6 weeks. Pre-randomisation run-in period: 1 week. Randomisation method: Not stated. Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, oral cor-

Calverley 2003 *(Continued)*

	ticosteroid (doses fixed throughout study period), short-acting B-agonist PRN. Co-interventions NOT allowed: ipratropium, long-acting B-agonist, oral B-agonist, theophylline. Confounders: None noted. Assessment score: 3
Participants	Setting: Outpatients in UK+Netherlands, referral population. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 25-65% predicted, ratio <=70%, age >40 years, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, COPD exacerbation in prior 4 weeks, significant disease other than COPD. Number recruited: 121 Mean age: 66 years Gender: 75% male Baseline FEV1: 1.1 +/- 0.4 L; FVC 2.2 +/- 0.7 L; Ratio 41 +/- 12 %. Baseline co-interventions allowed during trial: short-acting B-agonist 85%; inhaled corticosteroid 78%; oral corticosteroid 2%. Baseline co-interventions NOT allowed during trial: ipratropium 39%; long-acting B-agonist -- not reported; oral B-agonist 9%; theophylline 4%.
Interventions	Experimental1: tiotropium 18 ug qAM by handihaler. Experimental2: tiotropium 18 ug qPM by handihaler. Control: Placebo.
Outcomes	Analysed: Cumulative incidence of exacerbations, hospitalisations; change in FEV1 and FVC for groups.
Notes	The original report showed no difference in clinical outcomes between intervention groups receiving morning and evening tiotropium; these groups were therefore combined for analyses of clinical outcomes. For analyses of spirometric indices, data were included for morning tiotropium and placebo groups only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Casaburi 2000

Methods	Type: Parallel group. Duration: 3 months. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: By order of entry within each study centre. Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, prednisone <= 10 mg/day, theophylline (doses fixed throughout study period), short-acting B-agonist PRN. Co-interventions NOT allowed: ipratropium, long-acting B-agonist. Confounders: None noted. Assessment score: 3
Participants	Setting: Outpatients in US, referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 <= 65% predicted, ratio <=70%, age >=40 years old, smoking history > 10 pack years, 'clinically stable airway obstruction'. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, regular use of daytime supplemental oxygen, >=10 mg prednisone/day for COPD symptoms in prior month, MI within prior year, CHF within 3 years, use of anti-arrhythmic drug. Number recruited: 470 Mean age: 65 years Gender: 65% male Baseline FEV1: 1.0 +/- 0.4 L; FVC not stated; Ratio 46 +/- 12 %. Baseline co-interventions allowed during trial: Not reported. Baseline co-interventions NOT allowed during trial: Not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: Placebo.
Outcomes	Analysed: Change in trough, peak and average FEV1 and FVC. Adverse Events: deaths: 1.
Notes	Redundant with Casaburi (2002).

Risk of bias

Bias	Authors' judgement	Support for judgement

Casaburi 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Casaburi 2002

Methods	Type: Parallel group. Duration: 12 months. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: Not stated but ?same as Casaburi (2000): by order of entry within each study centre. Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, prednisone <= 10 mg/day, theophylline (doses fixed throughout study period), short-acting B-agonist PRN. Co-interventions NOT allowed: ipratropium, long-acting B-agonist. Confounders: None noted. Assessment score: 3
Participants	Setting: Outpatients in US, referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 <= 65% predicted, ratio <=70%, age >=40 years old, smoking history > 10 pack years, 'clinically stable airway obstruction'. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, regular use of daytime supplemental oxygen, >=10 mg prednisone/day for COPD symptoms in prior month, MI within prior year, CHF within 3 years, use of anti-arrhythmic drug. Number recruited: 921 Mean age: 65 years Gender: 65% male Baseline FEV1: 1.0 +/- 0.4 L; FVC 2.3 +/- 0.8 L; Ratio 46 +/- 12 %. Co-interventions at baseline allowed during trial: short-acting B-agonist 99%; inhaled corticosteroid 42%; oral corticosteroid 7%; theophylline 23%. Co-interventions at baseline NOT allowed during trial: ipratropium 57%; long-acting B-agonist -- not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: Placebo.
Outcomes	Analysed: Change in FEV1, FVC and PEFR; cumulative incidence of COPD exacerbations, increase B- agonist use. Adverse Events: Deaths: 7.
Notes	Reported combined results of Casaburi (2000) and a similar unpublished trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Celli 2003

Methods	Type: Parallel group. Duration: 1 month. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: Not stated. Blinding: Double-blind. Co-interventions allowed: Not stated. Co-interventions NOT allowed: ipratropium, long-acting B-agonist. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients in US, referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 30-65% predicted, ratio <=70%, TGV >= 120%, age >40 years, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, recent upper respiratory infection. Number recruited: 81 Mean age: 64 years Gender: 61% male Baseline FEV1: 1.1 +/- 0.4 L; FVC 2.5 +/- 0.8 L; Ratio 47 +/- 10 %, TGV 5.5 +/- 1.4 L. Baseline co-interventions allowed during trial: Not reported. Baseline co-interventions NOT allowed during trial: Not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: Placebo.
Outcomes	

Celli 2003 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Donohue 2002

Methods	Type: Parallel group. Duration: 6 months. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: Not stated. Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, prednisone <= 10 mg/day, theophylline, short-acting B-agonist PRN Co-interventions NOT allowed: ipratropium, long-acting B-agonist. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients (12 countries), referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 <= 60% predicted, ratio <=70%, age >40 years, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, use of daytime supplemental oxygen, recent upper respiratory infection, significant disease other than COPD. Number recruited: 623 Mean age: 65 years Gender: 75% male Baseline FEV1: 1.1 +/- 0.4 L; FVC 2.6 +/- 0.7 L; Ratio 42 +/- 9 %. Co-interventions at baseline allowed during trial: Short-acting B-agonist 66%; inhaled corticosteroid 66%; oral corticosteroid 6%; theophylline 21%. Co-interventions at baseline NOT allowed during trial: Ipratropium 53%; long-acting B-agonist -- not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control1: salmeterol 50ug BID by metered-dose inhaler. Control2: Placebo.
Outcomes	Analysed: Cumulative incidence of exacerbations, hospitalisations, and all-cause mortality; change in St. George's Respiratory Questionnaire and Transitional Dyspnea Index; change in trough FEV1 and FVC; adverse events Others: None Mortality: None Morbidity: None.
Notes	Redundant with Brasasco (2003).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Littner 2000

Methods	Type: Parallel group. Duration: 1 month. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: Not stated. Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, theophylline (doses fixed throughout study period), short-acting B-agonist PRN. Co-interventions NOT allowed: ipratropium, long-acting B-agonist, oral corticosteroid, cromolyn. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients in US, referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 30-65% predicted, ratio <=70%, age >=40 years old, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, use of supplemental oxygen or upper respiratory infection within 6 weeks or during run-in period, significant disease other than COPD. Number recruited: 169 Mean age: 66 years Gender: 57% male Baseline FEV1: 1.1 +/- 0.3 L; FVC not

Littner 2000 *(Continued)*

	stated; Ratio not stated. Baseline co-interventions allowed during trial: Not reported. Baseline co-interventions NOT allowed during trial: Not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler (n=33). Control: Placebo (n=35).
Outcomes	Analysed: Change in trough FEV1 and FVC. Adverse Events:
Notes	Data were extracted from this dose-ranging study for patients randomised to the clinical dose of tiotropium (18ug) and placebo only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Niewoehner 2005

Methods	Type: Parallel group. Duration: 6 months. Pre-randomisation run-in period: No. Randomisation method: Block. Blinding: Double-blind. Co-interventions allowed during trial: Inhaled corticosteroid, theophylline (doses fixed throughout study period), long-acting B-agonist, short-acting B-agonist PRN. Co-interventions NOT allowed during trial: ipratropium. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients at 26 US Veterans' Administration medical centers. Inclusion criteria: Prior diagnosis of COPD, FEV1 <= 60% predicted, ratio <=70%, age >40 years, smoking history > 10 pack years. Exclusion criteria: Prior diagnosis of asthma, significant disease other than COPD Number recruited: 1,829 Mean age: 68 years Gender: 99% male Baseline FEV1: 1.0 L Baseline co-interventions allowed during trial: Not reported. Baseline co-interventions NOT allowed during trial: Not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control1: Placebo.
Outcomes	Analysed: Cumulative incidence of exacerbations, hospitalisations.
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

O'Donnell 2004

Methods	Type: Parallel group. Duration: 6 weeks. Pre-randomisation run-in period: 2 week wash-out period and to "familiarise [participants] with all testing procedures and to establish a standardised training history" Randomisation method: Not stated. Blinding: Double-blind. Co-interventions allowed: short-acting B-agonist (rescue), inhaled corticosteroid, prednisone, theophylline, mycolytic agents Co-interventions NOT allowed: ipratropium, oral and long-acting B-agonists. Confounders: None noted. Assessment score: 4
Participants	Setting: Outpatients, referral source not stated. Inclusion criteria: Prior diagnosis of stable COPD, FEV1 <= 65% predicted, FRC >=120% predicted, age 40-70 years, smoking history > 10 pack years. Exclusion

O'Donnell 2004 *(Continued)*

	criteria: asthma, allergic rhinitis, or atopy, significant disease other than COPD, important contraindications to exercise testing, exercise limitation not related to fatigue or exertional dyspnoea, participation in pulmonary rehabilitation program within 6 weeks Number recruited: 198 Mean age: 61 years Gender: 69% male Baseline FEV1: 1.3 +/- 0.5 L; FVC 2.8 +/- 0.8 L; Ratio 45 +/- 10 % Baseline co-interventions allowed during trial: Not reported. Baseline co-interventions NOT allowed during trial: Not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: Placebo.
Outcomes	Analysed: Cumulative incidence of exacerbations; change in St. George's Respiratory Questionnaire and Transitional Dyspnea Index; change in trough FEV1 and FVC; adverse events Reported: Difference between tiotropium and placebo in other pulmonary function (FEV1/FVC, SG, IC, RV, FRV, RV/TLC, FRC/TLC, TLC) and exercise capacity (Borg, IC, VT, fR, VE, IRV at rest, isotime and peak exercise).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

van Noord 2000

Methods	Type: Parallel group. Duration: 3 months. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: Block (2:1) Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, prednisone <= 10 mg/day, theophylline (doses fixed throughout study period), short-acting B-agonist (PRN). Co-interventions NOT allowed: ipratropium, long-acting B-agonists, oral B-agonists, cromolyn. Confounders: None noted. Assessment score: 5
Participants	Setting: Outpatients at 14 centres in the Netherlands, referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 <= 65% predicted, ratio <=70%, age >=40 years old, smoking history > 10 pack years, 'stable airway obstruction'. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, supplemental oxygen, upper respiratory tract infection in prior 6 weeks, MI in prior year, CHF within 3 years, use of anti-arrhythmic drug, known hypersensitivity to anticholinergic drugs, known symptomatic prostatic hypertrophy, narrow angle glaucoma. Number recruited: 228 Mean age: 64 years Gender: 84% male Baseline FEV1: 1.2 +/- 0.4 L; FVC 2.8 +/- 0.8 L; Ratio 45 +/- 11 %. Baseline co-interventions allowed during trial: short-acting B-agonist 69%; inhaled corticosteroid 76%; oral corticosteroid 9%; theophylline 13%. Baseline co-interventions NOT allowed during trial: ipratropium 56%; long-acting B-agonist -- not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: ipratropium 40 ug QID by MDI.
Outcomes	Analysed: Change in trough FEV1 and FVC. Reported: Rescue B-agonist use. Others: None Mortality: None Morbidity: None.
Notes	Redundant with Vincken (2002).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Vincken 2002

Methods	Type: Parallel group. Duration: 12 months. Pre-randomisation run-in period: 2 week wash-out period. Randomisation method: Block (2:1) Blinding: Double-blind. Co-interventions allowed: Inhaled corticosteroid, prednisone <= 10 mg/day, theophylline (doses fixed throughout study period), short-acting B-agonist (PRN). Co-interventions NOT allowed: ipratropium, long-acting B-agonists, oral B-agonists, cromolyn. Confounders: None noted. Assessment score: 5
Participants	Setting: Outpatients in Netherlands and Belgium, referral source not stated. Inclusion criteria: Prior diagnosis of COPD (ATS), FEV1 <= 65% predicted, ratio <=70%, age >=40 years old, smoking history > 10 pack years. Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm^3, regular use of supplemental oxygen, recent upper respiratory tract infection, 'significant disease other than COPD.' Number recruited: 535 Mean age: 64 years Gender: 85% male Baseline FEV1: 1.2 +/- 0.4 L; FVC 2.7 +/- 0.8; Ratio 46 +/- 10 %. Baseline co-interventions allowed during trial: short-acting B-agonist 76%; inhaled corticosteroid 80%; oral corticosteroid 9%; theophylline 16%. Baseline co-interventions NOT allowed during trial: ipratropium 60%; long-acting B-agonist -- not reported.
Interventions	Experimental: tiotropium 18ug qD by handihaler. Control: ipratropium 40 ug QID by MDI.
Outcomes	Analysed: Cumulative incidence of exacerbations, hospitalisations; change in Dyspnea Index; change in trough FEV1 and FVC; change in PEFR, QOL. Adverse Events:
Notes	Reported combined results of van Noord (2000) and a similar unpublished trial. Some patients received 9 months of treatment instead of 12 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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

Study	Reason for exclusion
Cazzola 2004	Duration less than one month
Donohue 2003	Same participants as Donohue 2002
Maesen 1993	Not randomised
Maesen 1995	Duration less than one month
O'Connor 1996	Asthma not COPD
Tashkin 2003	Same participants as Casaburi 2002
van Noord 2002	Duration less than one month
Witek 2003	Same participants as Brasasco 2003

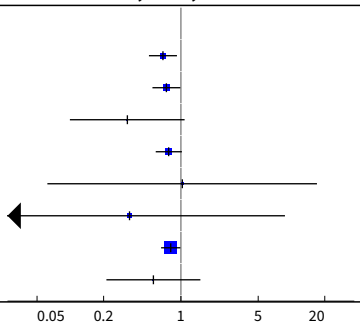
DATA AND ANALYSES

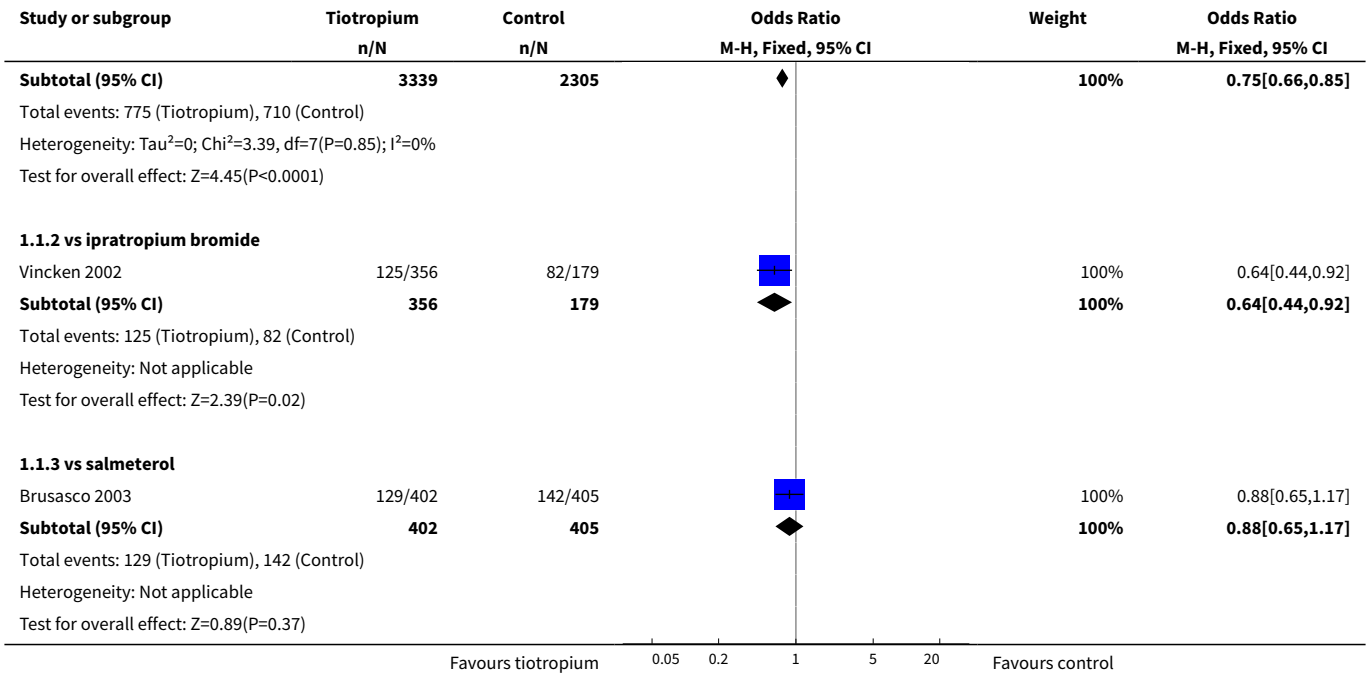
Comparison 1. Health outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 vs placebo	8	5644	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.66, 0.85]
1.2 vs ipratropium bromide	1	535	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.92]
1.3 vs salmeterol	1	807	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.17]
2 Exacerbations -- summary estimate	9	6179	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.66, 0.83]
3 Hospitalisations for COPD	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 vs placebo	3	3552	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.50, 0.85]
3.2 vs ipratropium	1	535	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.09]
3.3 vs salmeterol	1	807	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.23]
4 Hospitalisations for COPD -- summary estimate	4	4087	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.51, 0.82]
5 All-cause mortality	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 vs placebo	2	1723	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.20, 1.23]
5.2 vs ipratropium bromide	1	535	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.41, 5.69]
5.3 vs salmeterol	1	807	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.38]
6 All-cause mortality -- summary estimate	3	2260	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.35, 1.49]

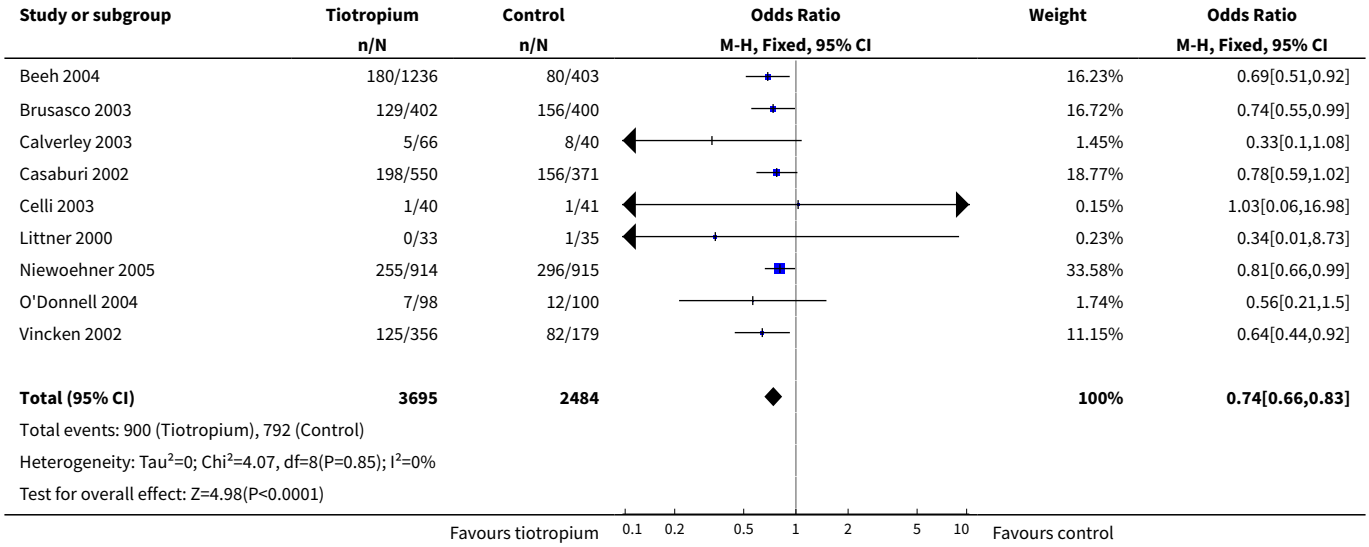
Analysis 1.1. Comparison 1 Health outcomes, Outcome 1 Exacerbations.

Study or subgroup	Tiotropium n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 vs placebo					
Beeh 2004	180/1236	80/403		18.26%	0.69[0.51,0.92]
Brusasco 2003	129/402	156/400		18.81%	0.74[0.55,0.99]
Calverley 2003	5/66	8/40		1.63%	0.33[0.1,1.08]
Casaburi 2002	198/550	156/371		21.12%	0.78[0.59,1.02]
Celli 2003	1/40	1/41		0.17%	1.03[0.06,16.98]
Littner 2000	0/33	1/35		0.25%	0.34[0.01,8.73]
Niewoehner 2005	255/914	296/915		37.79%	0.81[0.66,0.99]
O'Donnell 2004	7/98	12/100		1.95%	0.56[0.21,1.5]

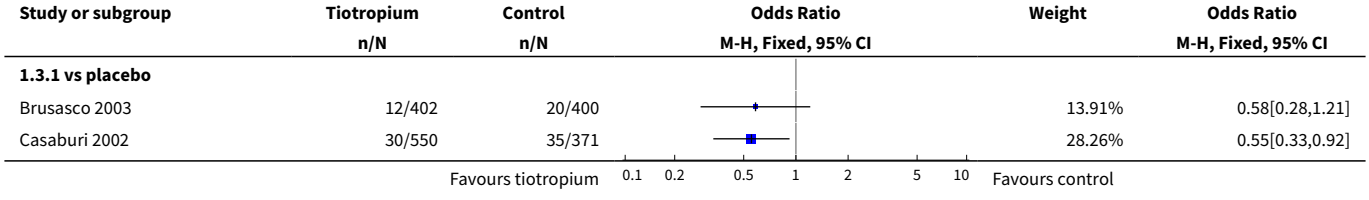


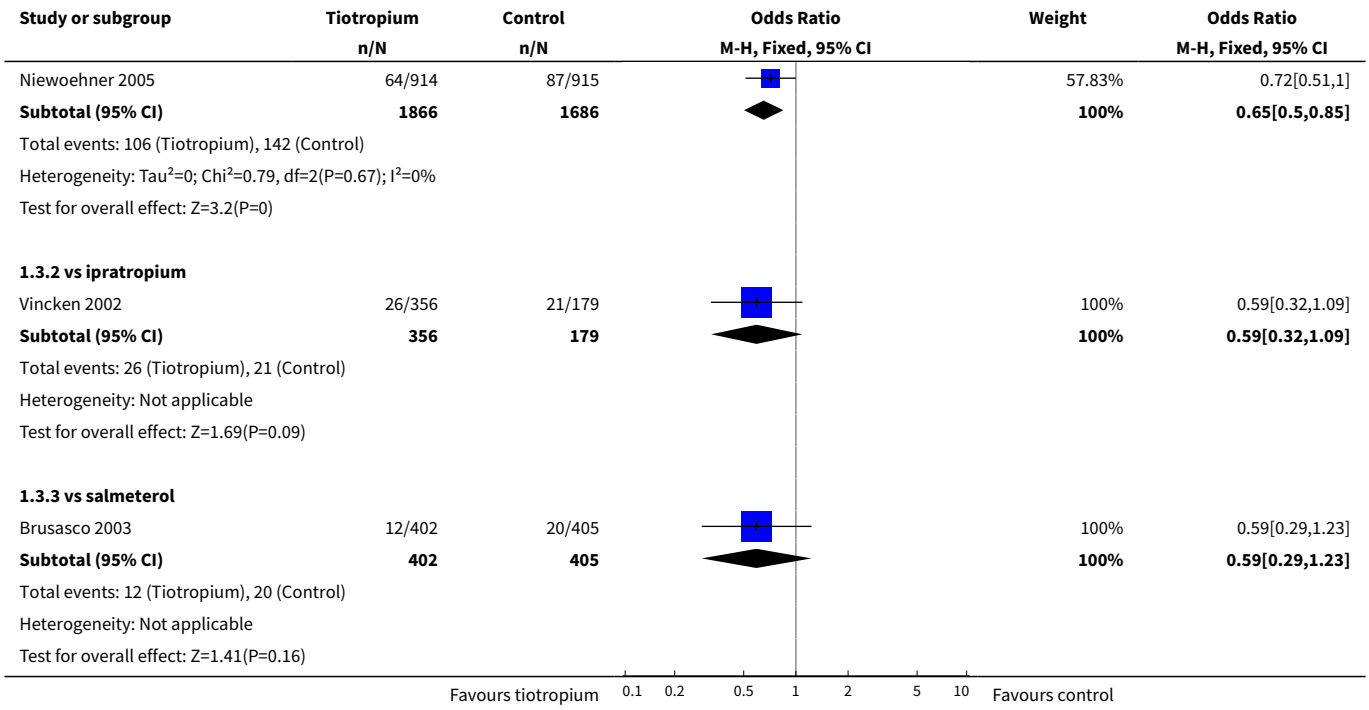


Analysis 1.2. Comparison 1 Health outcomes, Outcome 2 Exacerbations -- summary estimate.

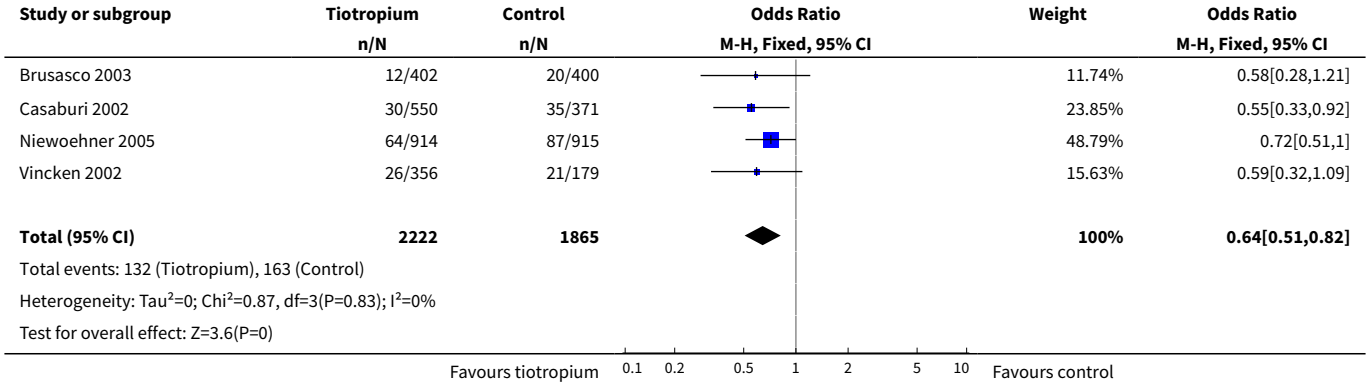


Analysis 1.3. Comparison 1 Health outcomes, Outcome 3 Hospitalisations for COPD.

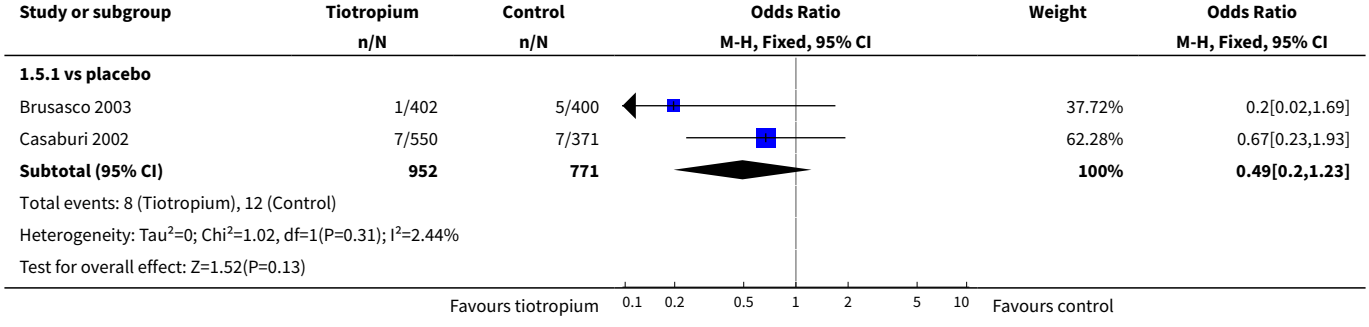


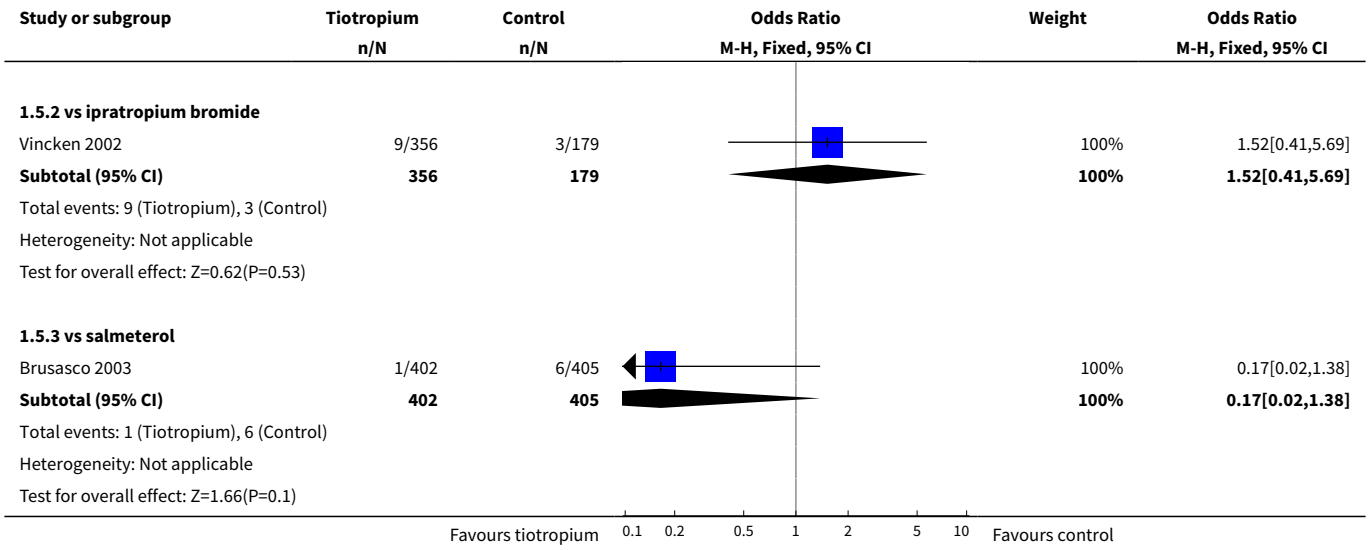


Analysis 1.4. Comparison 1 Health outcomes, Outcome 4 Hospitalisations for COPD -- summary estimate.

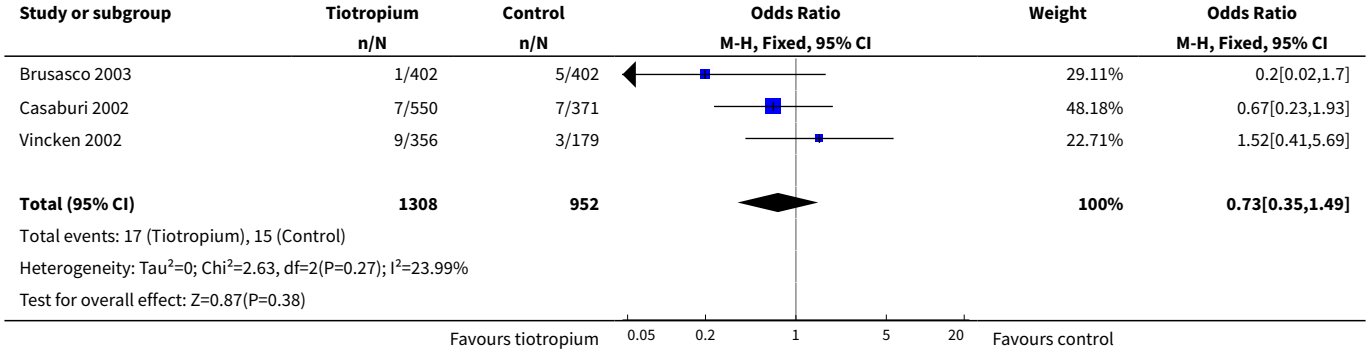


Analysis 1.5. Comparison 1 Health outcomes, Outcome 5 All-cause mortality.





Analysis 1.6. Comparison 1 Health outcomes, Outcome 6 All-cause mortality -- summary estimate.



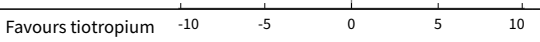
Comparison 2. Quality of life and symptom scales

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in SGRQ	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 vs placebo	2	1522	Mean Difference (IV, Random, 95% CI)	-3.27 [-4.50, -2.04]
1.2 vs ipratropium bromide	1	486	Mean Difference (IV, Random, 95% CI)	-3.3 [-5.63, -0.97]
1.3 vs salmeterol	1	710	Mean Difference (IV, Random, 95% CI)	-1.40 [-3.24, 0.44]
2 Mean change in SGRQ -- summary estimate	3	2008	Mean Difference (IV, Fixed, 95% CI)	-3.28 [-4.37, -2.19]
3 Clinically significant change in SGRQ	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 vs placebo	2	1522	Odds Ratio (M-H, Random, 95% CI)	1.83 [1.21, 2.76]
3.2 vs ipratropium	1	486	Odds Ratio (M-H, Random, 95% CI)	1.99 [1.35, 2.94]
3.3 vs salmeterol	1	710	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.93, 1.69]
5 Clinically significant change in TDI focal score	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 vs placebo	2	1489	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [1.58, 2.44]
5.2 vs ipratropium	1	479	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [1.26, 3.20]
5.3 vs salmeterol	1	688	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.80, 1.46]

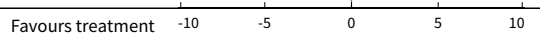
Analysis 2.1. Comparison 2 Quality of life and symptom scales, Outcome 1 Mean change in SGRQ.

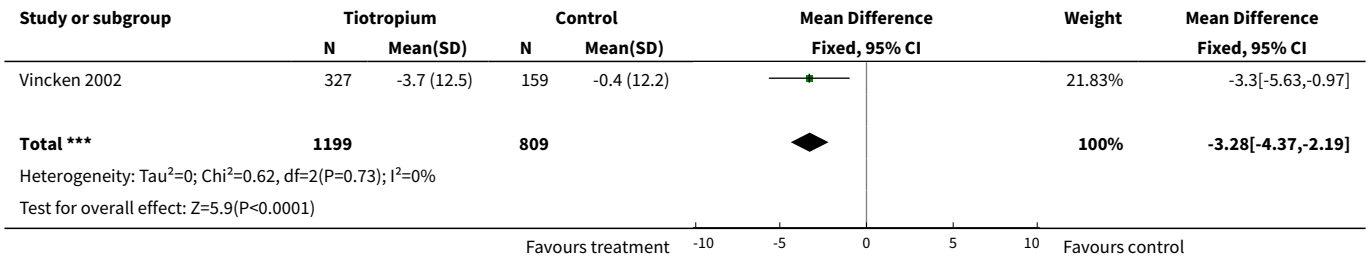
Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.1.1 vs placebo							
Brusasco 2003	356	-4.2 (12.4)	326	-1.5 (12.6)		42.97%	-2.7[-4.58,-0.82]
Casaburi 2002	516	-3.2 (11.8)	324	0.5 (11.7)		57.03%	-3.7[-5.33,-2.07]
Subtotal ***	**872**		**650**			**100%**	**-3.27[-4.5,-2.04]**
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=5.2(P<0.0001)							
2.1.2 vs ipratropium bromide							
Vincken 2002	327	-3.7 (12.5)	159	-0.4 (12.2)		100%	-3.3[-5.63,-0.97]
Subtotal ***	**327**		**159**			**100%**	**-3.3[-5.63,-0.97]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=2.78(P=0.01)							
2.1.3 vs salmeterol							
Brusasco 2003	356	-4.2 (12.4)	354	-2.8 (12.6)		100%	-1.4[-3.24,0.44]
Subtotal ***	**356**		**354**			**100%**	**-1.4[-3.24,0.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.49(P=0.14)							



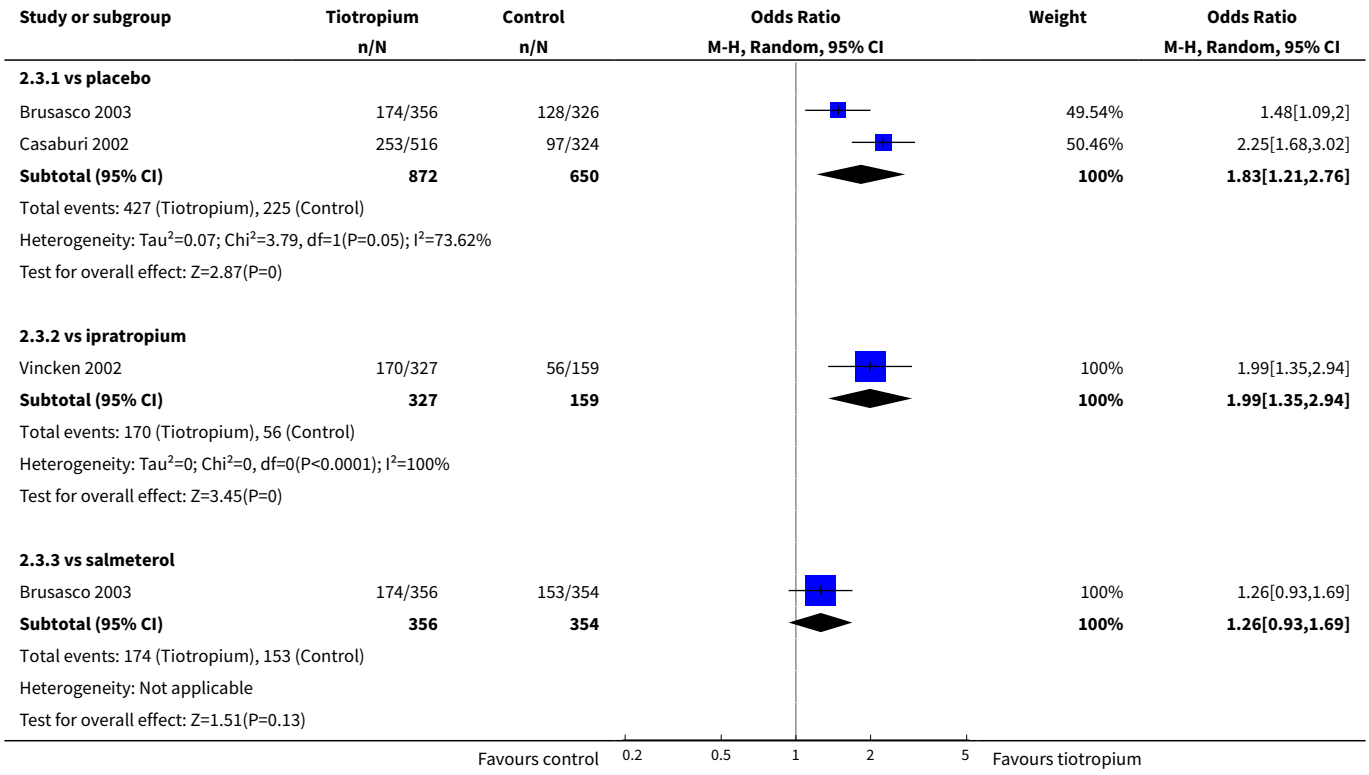
Analysis 2.2. Comparison 2 Quality of life and symptom scales, Outcome 2 Mean change in SGRQ -- summary estimate.

Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Brusasco 2003	356	-4.2 (12.4)	326	-1.5 (12.6)		33.59%	-2.7[-4.58,-0.82]
Casaburi 2002	516	-3.2 (11.8)	324	0.5 (11.7)		44.58%	-3.7[-5.33,-2.07]

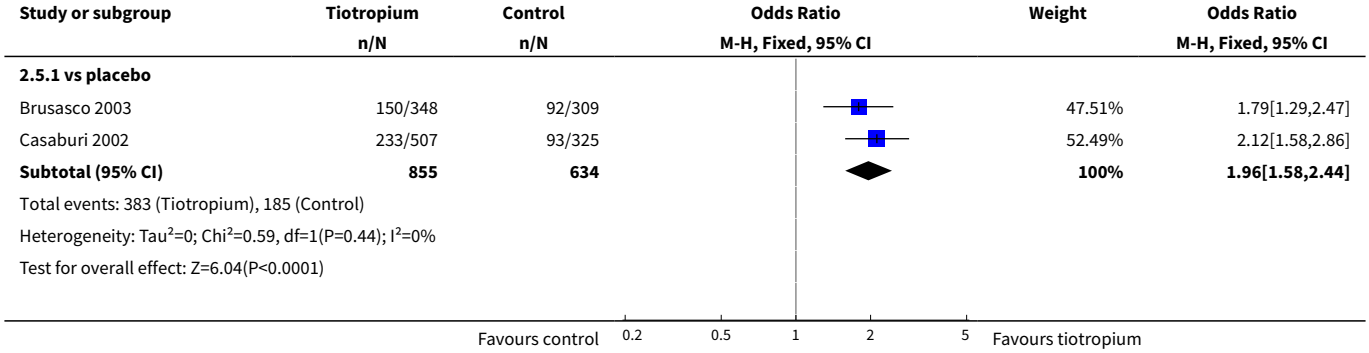


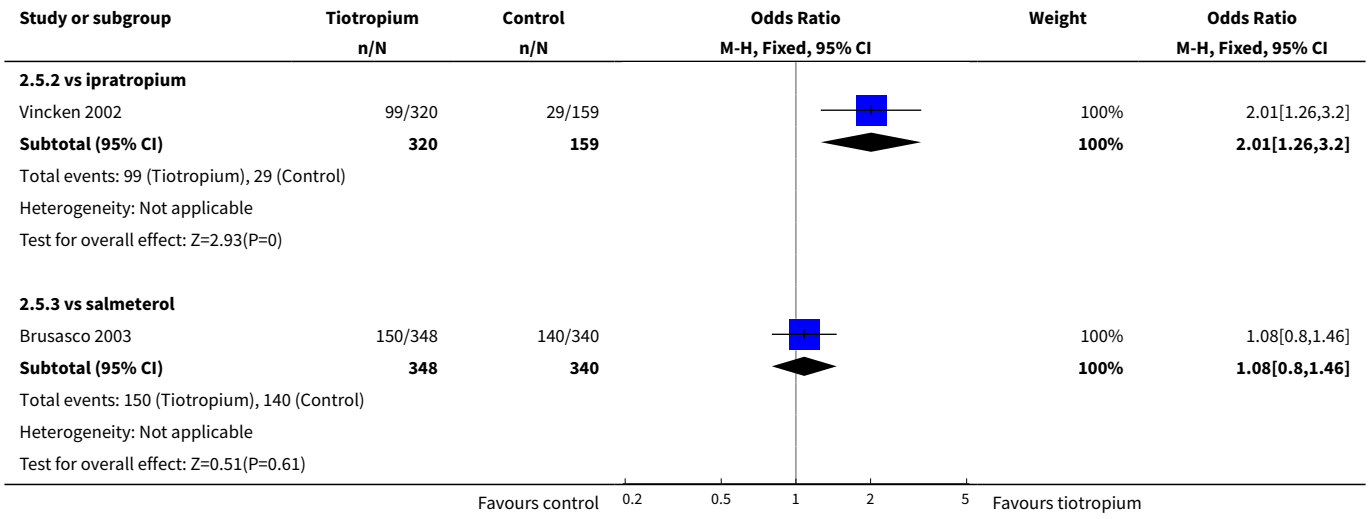


Analysis 2.3. Comparison 2 Quality of life and symptom scales, Outcome 3 Clinically significant change in SGRQ.



Analysis 2.5. Comparison 2 Quality of life and symptom scales, Outcome 5 Clinically significant change in TDI focal score.





Comparison 3. Spirometry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in trough FEV1 from baseline	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 vs placebo	4	1735	Mean Difference (IV, Random, 95% CI)	139.96 [118.28, 161.64]
1.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	150.0 [106.16, 193.84]
1.3 vs salmeterol	1	774	Mean Difference (IV, Random, 95% CI)	40.0 [12.31, 67.69]
2 Change in mean FEV1 from baseline	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 vs placebo	4	1735	Mean Difference (IV, Random, 95% CI)	203.94 [184.76, 223.11]
2.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	100.0 [56.16, 143.84]
2.3 vs salmeterol	1	774	Mean Difference (IV, Random, 95% CI)	70.0 [42.31, 97.69]
3 Change in peak FEV1 from baseline	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 vs placebo	3	1669	Mean Difference (IV, Fixed, 95% CI)	220.55 [201.08, 240.02]
3.2 vs ipratropium bromide	1	490	Mean Difference (IV, Fixed, 95% CI)	100.0 [56.16, 143.84]
3.3 vs salmeterol	1	774	Mean Difference (IV, Fixed, 95% CI)	80.0 [52.31, 107.69]

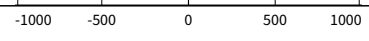
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Change in trough FVC from baseline	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 vs placebo	4	1735	Mean Difference (IV, Random, 95% CI)	278.10 [208.37, 347.84]
4.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	210.0 [112.08, 307.92]
4.3 vs salmeterol	1	774	Mean Difference (IV, Random, 95% CI)	90.0 [34.56, 145.44]
5 Change in mean FVC from baseline	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 vs placebo	4	1735	Mean Difference (IV, Random, 95% CI)	387.20 [343.45, 430.94]
5.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	80.0 [-17.92, 177.92]
5.3 vs salmeterol	1	774	Mean Difference (IV, Random, 95% CI)	140.0 [84.56, 195.44]
6 Change in peak FVC from baseline	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 vs placebo	3	1669	Mean Difference (IV, Random, 95% CI)	405.08 [337.12, 473.03]
6.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	90.0 [-7.92, 187.92]
6.3 vs salmeterol	1	774	Mean Difference (IV, Random, 95% CI)	150.0 [94.56, 205.44]
7 Change in morning PEFR from baseline	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 vs placebo	4	1723	Mean Difference (IV, Random, 95% CI)	21.42 [14.83, 28.02]
7.2 vs ipratropium bromide	1	504	Mean Difference (IV, Random, 95% CI)	15.6 [6.53, 24.67]
7.3 vs salmeterol	1	772	Mean Difference (IV, Random, 95% CI)	0.30 [-8.31, 8.91]
8 Change in evening PEFR from baseline	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 vs placebo	3	1542	Mean Difference (IV, Random, 95% CI)	30.34 [23.19, 37.49]
8.2 vs ipratropium bromide	1	503	Mean Difference (IV, Random, 95% CI)	13.40 [3.95, 22.85]
8.3 vs salmeterol	1	765	Mean Difference (IV, Random, 95% CI)	11.0 [2.35, 19.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Change in trough FEV1 from day 8, with summary estimate	2	1336	Mean Difference (IV, Random, 95% CI)	30.00 [6.56, 53.44]
9.1 vs placebo	1	846	Mean Difference (IV, Random, 95% CI)	30.0 [2.27, 57.73]
9.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	30.0 [-13.84, 73.84]
9.3 vs salmeterol	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Change in mean FEV1 from day 8, with summary estimate	2	1336	Mean Difference (IV, Random, 95% CI)	15.72 [-7.72, 39.15]
10.1 vs placebo	1	846	Mean Difference (IV, Random, 95% CI)	10.0 [-17.73, 37.73]
10.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	30.0 [-13.84, 73.84]
10.3 vs salmeterol	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Change in peak FEV1 from day 8, with summary estimate	2	1336	Mean Difference (IV, Random, 95% CI)	10.00 [-17.72, 37.72]
11.1 vs placebo	1	846	Mean Difference (IV, Random, 95% CI)	0.0 [-27.73, 27.73]
11.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	30.0 [-13.84, 73.84]
11.3 vs salmeterol	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Change in trough FVC from day 8	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 vs placebo	1	846	Mean Difference (IV, Random, 95% CI)	40.0 [-15.41, 95.41]
12.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	-40.0 [-110.73, 30.73]
12.3 vs salmeterol	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change in mean FVC from day 8, with summary estimate	2	1336	Mean Difference (IV, Random, 95% CI)	-3.80 [-47.42, 39.81]
13.1 vs placebo	1	846	Mean Difference (IV, Random, 95% CI)	0.0 [-55.41, 55.41]
13.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	-10.0 [-80.73, 60.73]
13.3 vs salmeterol	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Change in peak FVC from day 8, with summary estimate	2	1336	Mean Difference (IV, Random, 95% CI)	24.99 [-24.98, 74.97]
14.1 vs placebo	1	846	Mean Difference (IV, Random, 95% CI)	20.0 [-50.63, 90.63]
14.2 vs ipratropium bromide	1	490	Mean Difference (IV, Random, 95% CI)	30.0 [-40.73, 100.73]
14.3 vs salmeterol	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Spirometry, Outcome 1 Change in trough FEV1 from baseline.

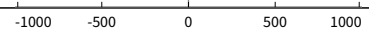
Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 vs placebo							
Brusasco 2003	386	90 (196)	362	-30 (190)		42.65%	120[92.33,147.67]
Casaburi 2002	518	110 (234)	328	-40 (193)		39.86%	150[120.98,179.02]
Celli 2003	37	110 (122)	38	-60 (123)		13.78%	170[114.55,225.45]
Littner 2000	33	130 (230)	33	-20 (230)		3.71%	150[39.02,260.98]
Subtotal ***	**974**		**761**			**100%**	**139.96[118.28,161.64]**
Heterogeneity: Tau^2=87.59; Chi^2=3.6, df=3(P=0.31); I^2=16.69%							
Test for overall effect: Z=12.65(P<0.0001)							
3.1.2 vs ipratropium bromide							
Vincken 2002	329	120 (181)	161	-30 (254)		100%	150[106.16,193.84]
Subtotal ***	**329**		**161**			**100%**	**150[106.16,193.84]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.71(P<0.0001)							
3.1.3 vs salmeterol							
Brusasco 2003	386	90 (196)	388	50 (197)		100%	40[12.31,67.69]
Subtotal ***	**386**		**388**			**100%**	**40[12.31,67.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.83(P=0)							



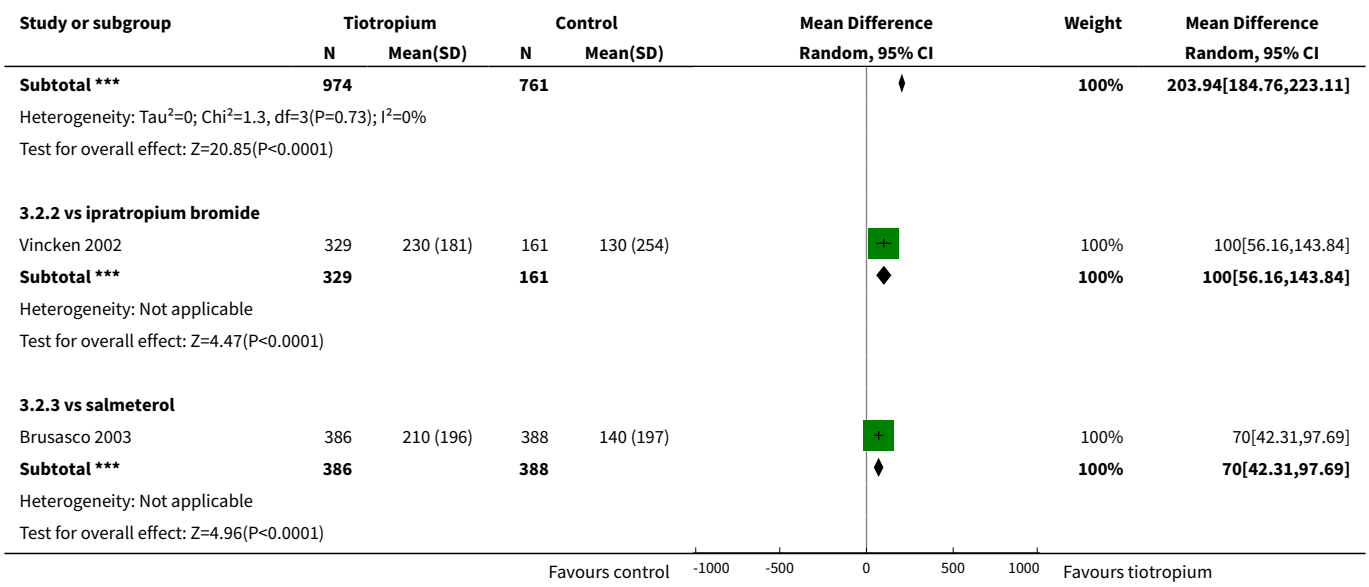
Favours control — Favours tiotropium

Analysis 3.2. Comparison 3 Spirometry, Outcome 2 Change in mean FEV1 from baseline.

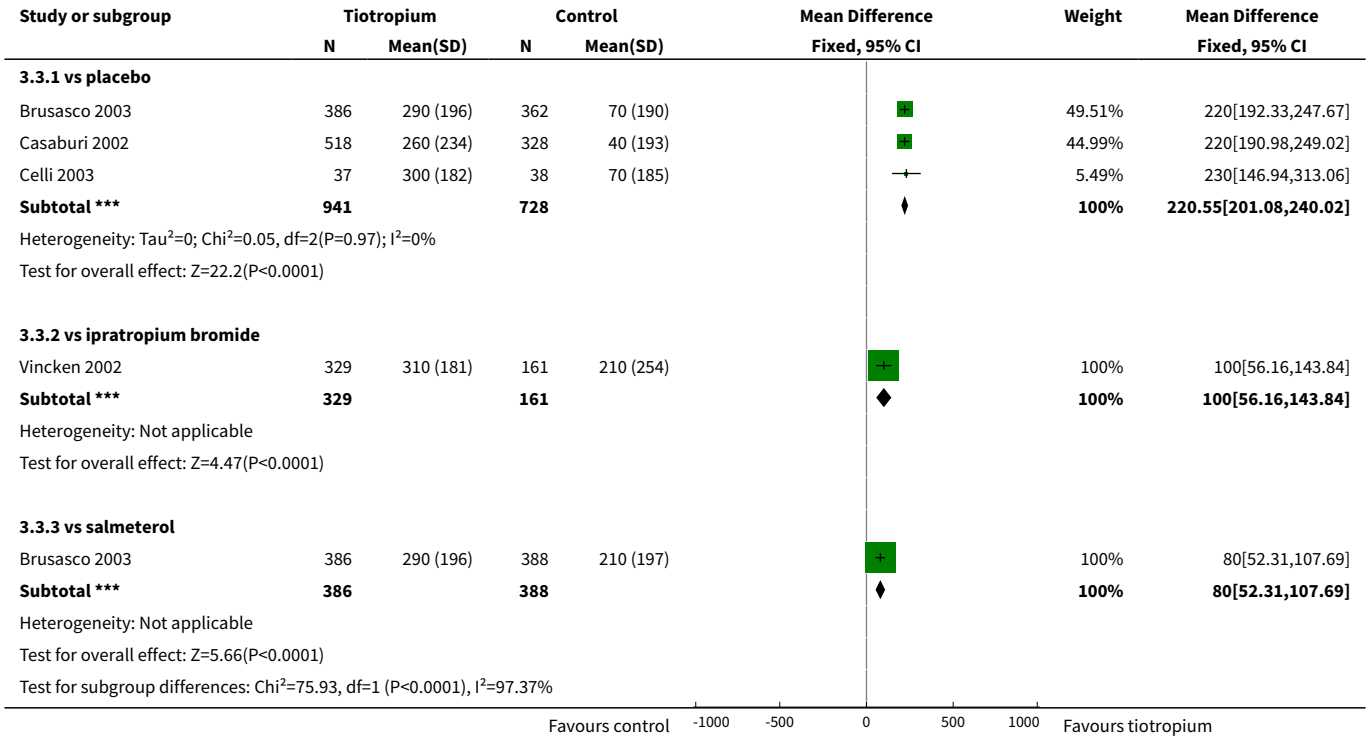
Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.2.1 vs placebo							
Brusasco 2003	386	210 (196)	362	10 (190)		48.04%	200[172.33,227.67]
Casaburi 2002	518	190 (234)	328	-20 (193)		43.65%	210[180.98,239.02]
Celli 2003	37	210 (182)	38	-10 (185)		5.33%	220[136.94,303.06]
Littner 2000	33	150 (230)	33	0 (230)		2.99%	150[39.02,260.98]



Favours control — Favours tiotropium

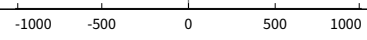


Analysis 3.3. Comparison 3 Spirometry, Outcome 3 Change in peak FEV1 from baseline.



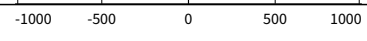
Analysis 3.4. Comparison 3 Spirometry, Outcome 4 Change in trough FVC from baseline.

Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.4.1 vs placebo							
Brusasco 2003	386	190 (393)	362	-20 (380)		37.23%	210[154.6,265.4]
Casaburi 2002	518	260 (469)	328	-40 (362)		36.96%	300[243.73,356.27]
Celli 2003	37	320 (365)	38	0 (370)		12.91%	320[153.65,486.35]
Littner 2000	33	340 (345)	33	-30 (345)		12.9%	370[203.53,536.47]
Subtotal ***	**974**		**761**			**100%**	**278.1[208.37,347.84]**
Heterogeneity: Tau^2=2600.89; Chi^2=7.21, df=3(P=0.07); I^2=58.42%							
Test for overall effect: Z=7.82(P<0.0001)							
3.4.2 vs ipratropium bromide							
Vincken 2002	329	320 (544)	161	110 (507)		100%	210[112.08,307.92]
Subtotal ***	**329**		**161**			**100%**	**210[112.08,307.92]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.2(P<0.0001)							
3.4.3 vs salmeterol							
Brusasco 2003	386	190 (393)	388	100 (394)		100%	90[34.56,145.44]
Subtotal ***	**386**		**388**			**100%**	**90[34.56,145.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.18(P=0)							



Analysis 3.5. Comparison 3 Spirometry, Outcome 5 Change in mean FVC from baseline.

Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.5.1 vs placebo							
Brusasco 2003	386	400 (393)	362	50 (380)		44.24%	350[294.6,405.4]
Casaburi 2002	518	420 (455)	328	0 (362)		44.24%	420[364.59,475.41]
Celli 2003	37	500 (426)	38	50 (432)		4.91%	450[255.82,644.18]
Littner 2000	33	400 (345)	33	30 (345)		6.61%	370[203.53,536.47]
Subtotal ***	**974**		**761**			**100%**	**387.2[343.45,430.94]**
Heterogeneity: Tau^2=326.91; Chi^2=3.52, df=3(P=0.32); I^2=14.77%							
Test for overall effect: Z=17.35(P<0.0001)							
3.5.2 vs ipratropium bromide							
Vincken 2002	329	500 (544)	161	420 (507)		100%	80[-17.92,177.92]
Subtotal ***	**329**		**161**			**100%**	**80[-17.92,177.92]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.6(P=0.11)							
3.5.3 vs salmeterol							
Brusasco 2003	386	400 (393)	388	260 (394)		100%	140[84.56,195.44]
Subtotal ***	**386**		**388**			**100%**	**140[84.56,195.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.95(P<0.0001)							



Analysis 3.6. Comparison 3 Spirometry, Outcome 6 Change in peak FVC from baseline.

Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.6.1 vs placebo							
Brusasco 2003	386	550 (393)	362	190 (380)		48.89%	360[304.6,415.4]
Casaburi 2002	518	580 (455)	328	140 (543)		40.63%	440[369.37,510.63]
Celli 2003	37	670 (426)	38	190 (432)		10.47%	480[285.82,674.18]
Subtotal ***	**941**		**728**			**100%**	**405.08[337.12,473.03]**
Heterogeneity: Tau^2=1659.66; Chi^2=3.83, df=2(P=0.15); I^2=47.76%							
Test for overall effect: Z=11.68(P<0.0001)							
3.6.2 vs ipratropium bromide							
Vincken 2002	329	660 (544)	161	570 (507)		100%	90[-7.92,187.92]
Subtotal ***	**329**		**161**			**100%**	**90[-7.92,187.92]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.8(P=0.07)							
3.6.3 vs salmeterol							
Brusasco 2003	386	550 (393)	388	400 (394)		100%	150[94.56,205.44]
Subtotal ***	**386**		**388**			**100%**	**150[94.56,205.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.3(P<0.0001)							

Analysis 3.7. Comparison 3 Spirometry, Outcome 7 Change in morning PEFR from baseline.

Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.7.1 vs placebo							
Brusasco 2003	384	24.6 (61)	363	3 (61)		56.82%	21.6[12.85,30.35]
Calverley 2003	37	16.1 (36)	34	-6.5 (36)		15.49%	22.6[5.84,39.36]
Casaburi 2002	507	34.2 (90)	332	13.8 (91)		27.69%	20.4[7.86,32.94]
Littner 2000	33	20 (0)	33	0 (0)			Not estimable
Subtotal ***	**961**		**762**			**100%**	**21.42[14.83,28.02]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=2(P=0.98); I^2=0%							
Test for overall effect: Z=6.36(P<0.0001)							
3.7.2 vs ipratropium bromide							
Vincken 2002	336	22.2 (49)	168	6.6 (49)		100%	15.6[6.53,24.67]
Subtotal ***	**336**		**168**			**100%**	**15.6[6.53,24.67]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.37(P=0)							
3.7.3 vs salmeterol							
Brusasco 2003	384	24.6 (61)	388	24.3 (61)		100%	0.3[-8.31,8.91]
Subtotal ***	**384**		**388**			**100%**	**0.3[-8.31,8.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.07(P=0.95)							

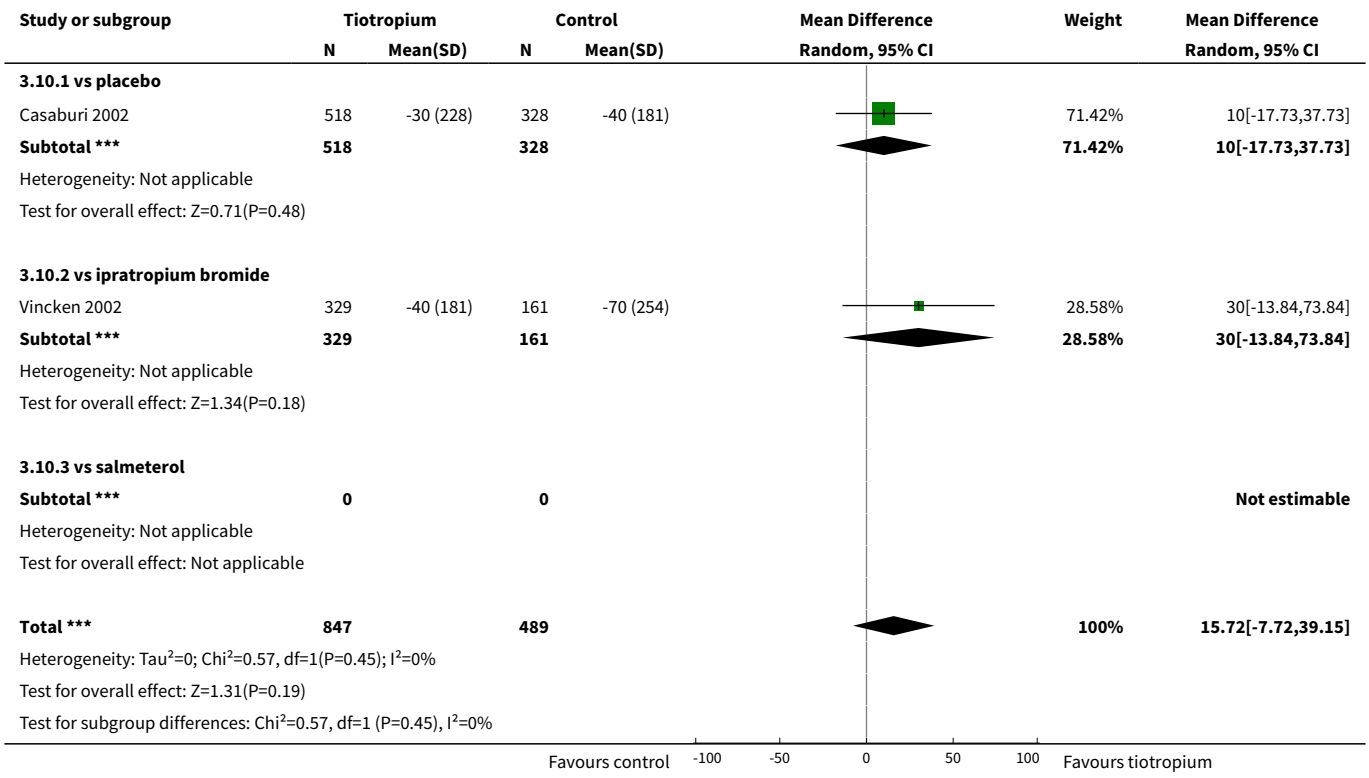
Analysis 3.8. Comparison 3 Spirometry, Outcome 8 Change in evening PEFR from baseline.

Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.8.1 vs placebo							
Brusasco 2003	380	29.7 (61)	361	-2.6 (61)		66.23%	32.3[23.51,41.09]
Casaburi 2002	479	32.3 (85)	311	5.8 (87)		33.77%	26.5[14.19,38.81]
Littner 2000	1	0 (0)	10	0 (0)			Not estimable
Subtotal ***	**860**		**682**			**100%**	**30.34[23.19,37.49]**
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%							
Test for overall effect: Z=8.32(P<0.0001)							
3.8.2 vs ipratropium bromide							
Vincken 2002	335	22.9 (51)	168	9.5 (51)		100%	13.4[3.95,22.85]
Subtotal ***	**335**		**168**			**100%**	**13.4[3.95,22.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.78(P=0.01)							
3.8.3 vs salmeterol							
Brusasco 2003	380	29.7 (61)	385	18.7 (61)		100%	11[2.35,19.65]
Subtotal ***	**380**		**385**			**100%**	**11[2.35,19.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.49(P=0.01)							

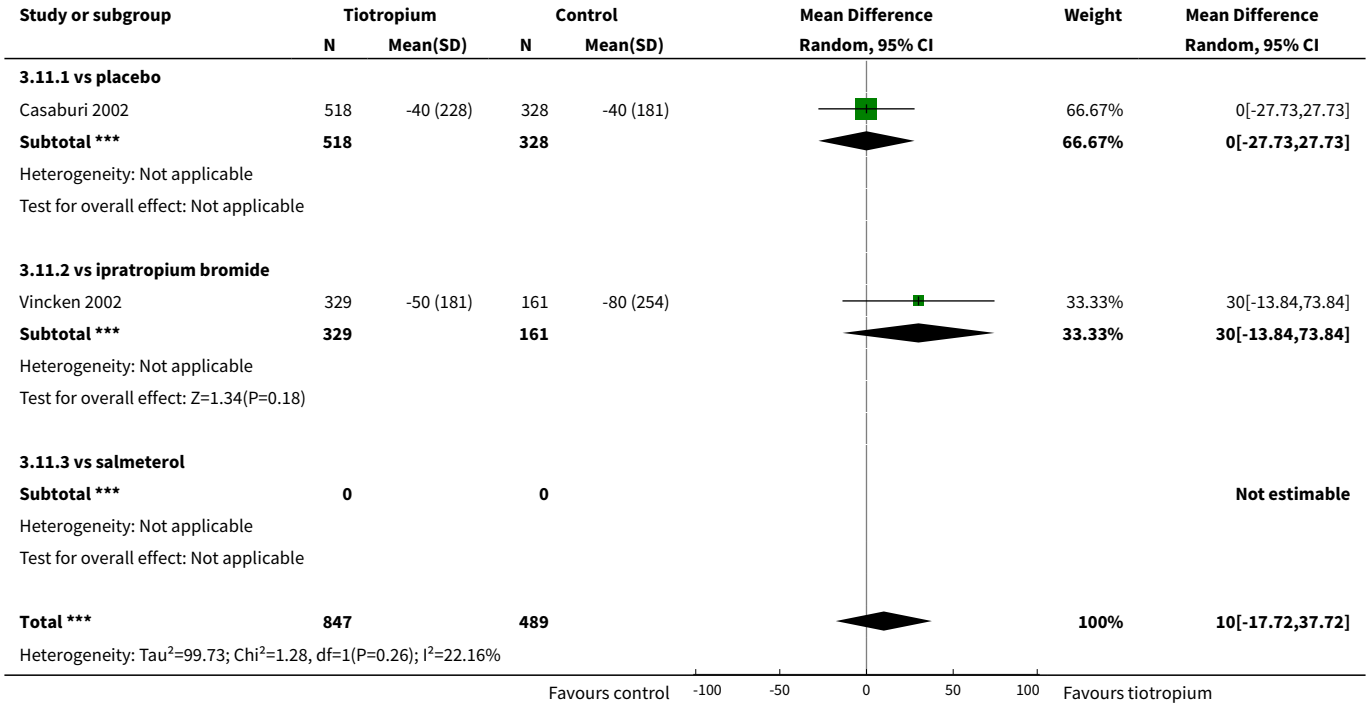
Analysis 3.9. Comparison 3 Spirometry, Outcome 9 Change in trough FEV1 from day 8, with summary estimate.

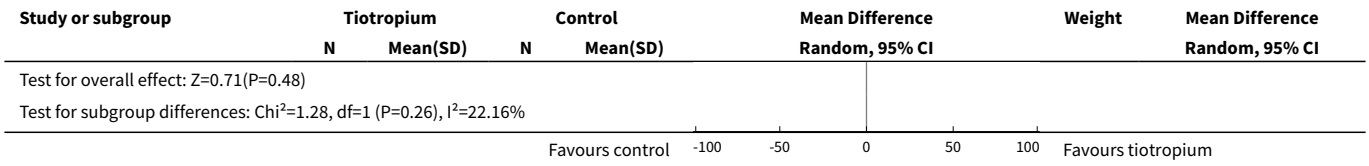
Study or subgroup	Tiotropium N	Tiotropium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.9.1 vs placebo							
Casaburi 2002	518	-10 (228)	328	-40 (181)		71.42%	30[2.27,57.73]
Subtotal ***	**518**		**328**			**71.42%**	**30[2.27,57.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.12(P=0.03)							
3.9.2 vs ipratropium bromide							
Vincken 2002	329	-20 (181)	161	-50 (254)		28.58%	30[-13.84,73.84]
Subtotal ***	**329**		**161**			**28.58%**	**30[-13.84,73.84]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.34(P=0.18)							
3.9.3 vs salmeterol							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**847**		**489**			**100%**	**30[6.56,53.44]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Z=2.51(P=0.01)							
Test for subgroup differences: Chi^2=0, df=1 (P=1), I^2=0%							

Analysis 3.10. Comparison 3 Spirometry, Outcome 10 Change in mean FEV1 from day 8, with summary estimate.

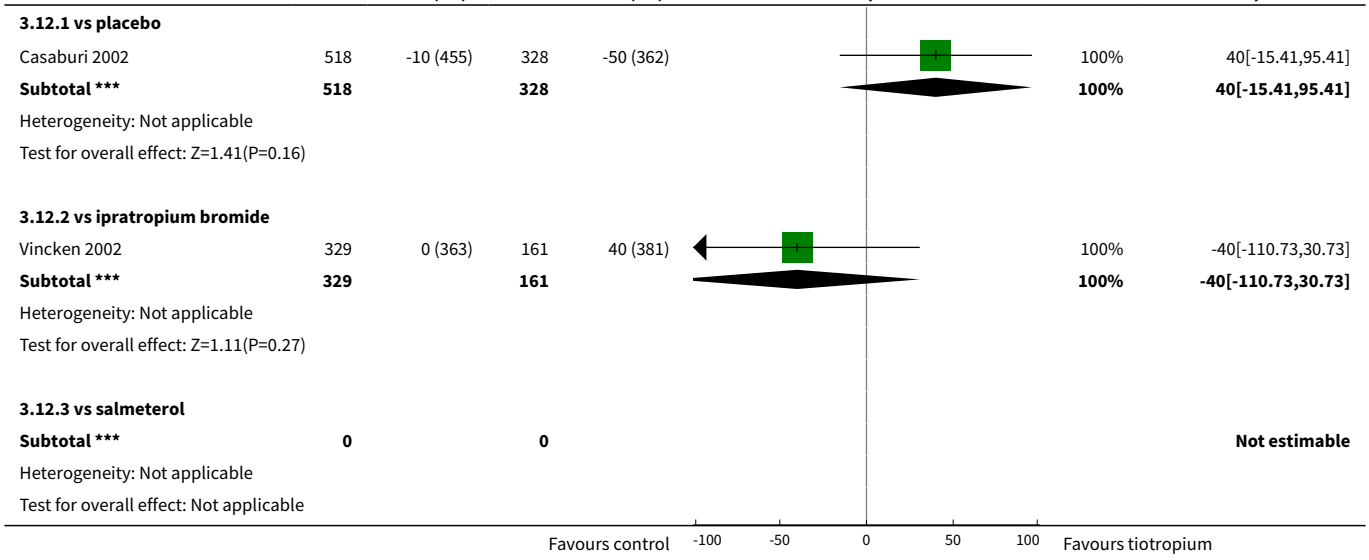


Analysis 3.11. Comparison 3 Spirometry, Outcome 11 Change in peak FEV1 from day 8, with summary estimate.

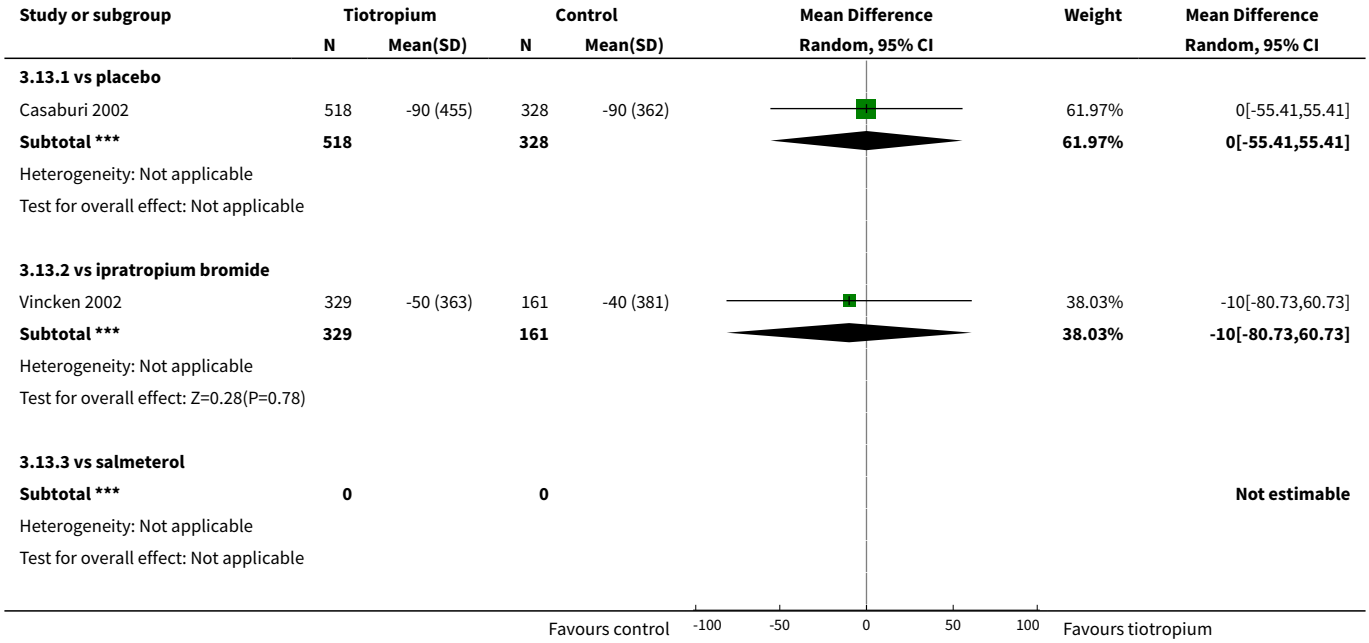


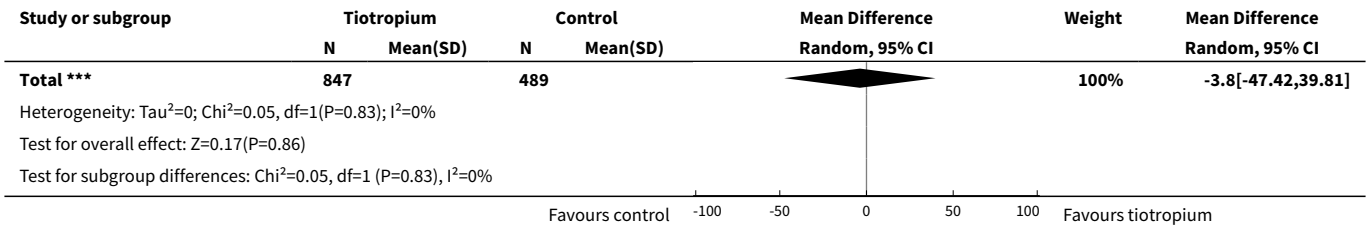


Analysis 3.12. Comparison 3 Spirometry, Outcome 12 Change in trough FVC from day 8.

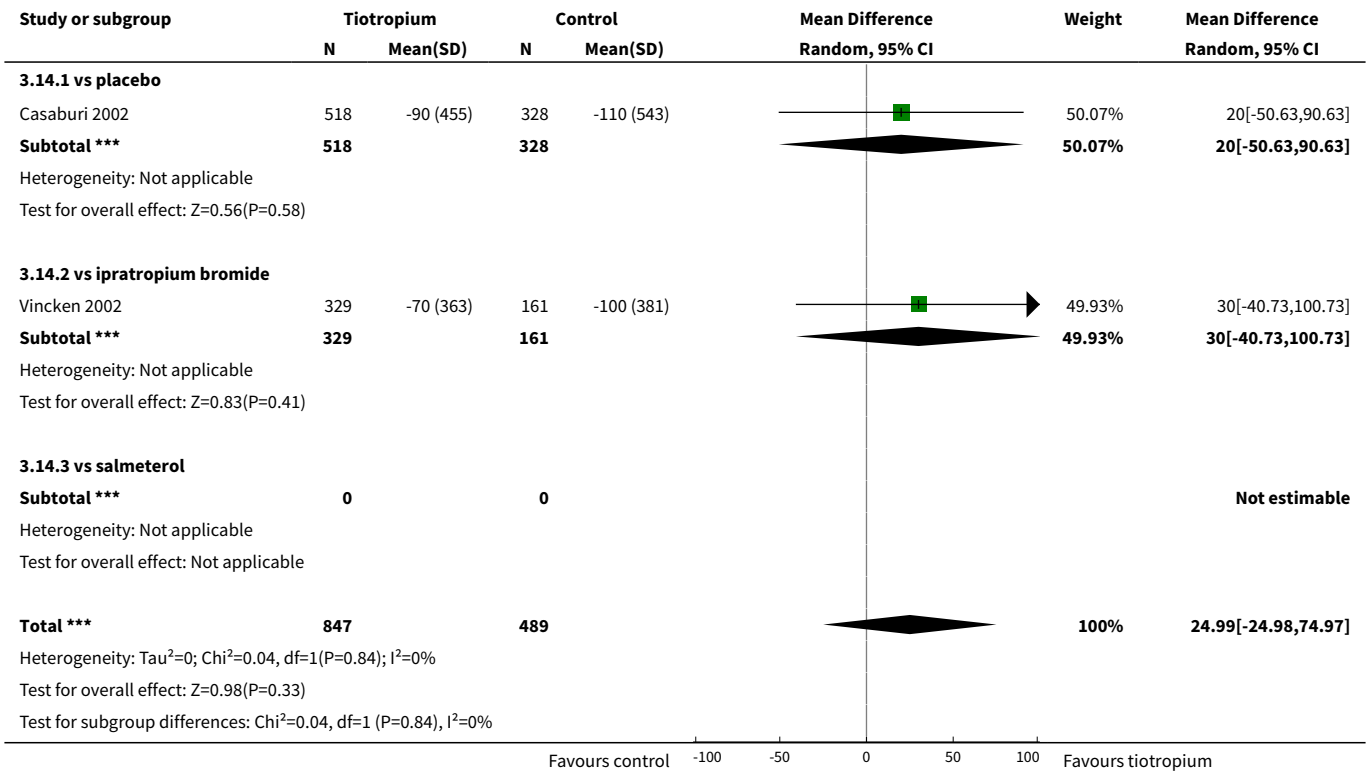


Analysis 3.13. Comparison 3 Spirometry, Outcome 13 Change in mean FVC from day 8, with summary estimate.





Analysis 3.14. Comparison 3 Spirometry, Outcome 14 Change in peak FVC from day 8, with summary estimate.

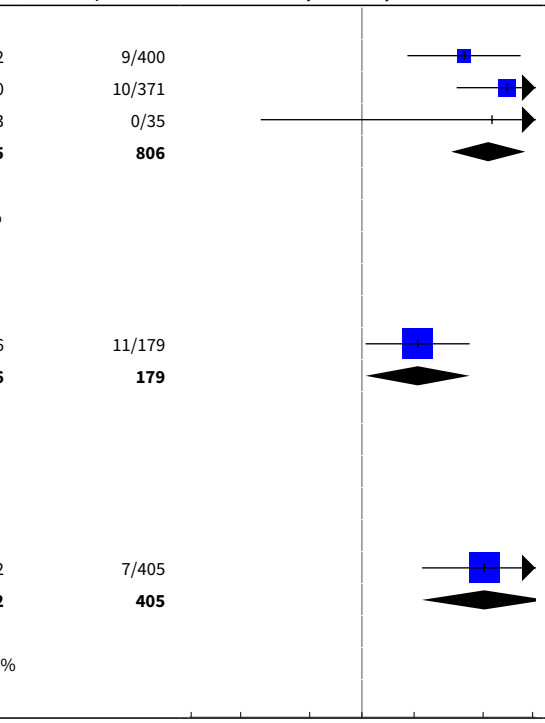


Comparison 7. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dry mouth	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 vs placebo	3	1791	Odds Ratio (M-H, Random, 95% CI)	5.35 [3.27, 8.76]
1.2 vs ipratropium bromide	1	535	Odds Ratio (M-H, Random, 95% CI)	2.10 [1.05, 4.18]
1.3 vs salmeterol	1	807	Odds Ratio (M-H, Random, 95% CI)	5.08 [2.22, 11.64]

Analysis 7.1. Comparison 7 Adverse events, Outcome 1 Dry mouth.

Study or subgroup	Tiotropium n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
7.1.1 vs placebo					
Brusasco 2003	33/402	9/400		43.09%	3.89[1.83,8.23]
Casaburi 2002	88/550	10/371		54.34%	6.88[3.52,13.42]
Littner 2000	2/33	0/35		2.57%	5.63[0.26,121.88]
Subtotal (95% CI)	**985**	**806**		**100%**	**5.35[3.27,8.76]**
Total events: 123 (Tiotropium), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.26, df=2(P=0.53); I^2=0%					
Test for overall effect: Z=6.67(P<0.0001)					
7.1.2 vs ipratropium bromide					
Vincken 2002	43/356	11/179		100%	2.1[1.05,4.18]
Subtotal (95% CI)	**356**	**179**		**100%**	**2.1[1.05,4.18]**
Total events: 43 (Tiotropium), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.11(P=0.03)					
7.1.3 vs salmeterol					
Brusasco 2003	33/402	7/405		100%	5.08[2.22,11.64]
Subtotal (95% CI)	**402**	**405**		**100%**	**5.08[2.22,11.64]**
Total events: 33 (Tiotropium), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=3.85(P=0)					



WHAT'S NEW

Date	Event	Description
21 November 2012	Review declared as stable	This review is no longer being updated. It has been replaced by three new Cochrane reviews (tiotropium versus placebo (Karner 2012); tiotropium versus LABA (Chong 2012) and tiotropium verus ipratropium bromide (Cheyne 2011)).

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 2, 2005

Date	Event	Description
3 July 2008	Amended	Converted to new review format.
31 January 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

RGB: trial identification and selection, quality scoring, data extraction, attainment of unpublished data, manuscript drafting and revision, statistical expertise
JB: trial identification and selection, quality scoring, data extraction, attainment of unpublished data, manuscript revision
CAC: quality scoring, data extraction, attainment of unpublished data, manuscript revision
(Previous aurthor: Felix Ram: trial identification and selection, quality scoring, data extraction, manuscript revision, statistical expertise)

DECLARATIONS OF INTEREST

Dr Bourbeau has received unrestricted educational grants for research from Boehringer-Ingelheim and GlaxoSmithKline. Dr Camargo has received financial support from government agencies, private foundations, professional organizations, and manufacturers of pharmaceuticals and medical devices including Boehringer-Ingelheim and GlaxoSmithKline.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Robert Wood Johnson Generalist Faculty Scholar Award (RG Barr), USA.
- HL-63841 NIH (CA Camargo Jr), USA.

NOTES

This review is no longer being updated. It has been replaced by three new Cochrane reviews (tiotropium versus placebo (Karner 2012); tiotropium versus LABA (Chong 2012) and tiotropium verus ipratropium bromide (Cheyne 2011)).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Cholinergic Antagonists [*administration & dosage]; Ipratropium [administration & dosage]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic; Scopolamine Derivatives [*administration & dosage]; Spirometry; Tiotropium Bromide

MeSH check words

Humans