

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis

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Background: A systematic review was undertaken to evaluate the efficacy of tiotropium, a long acting anticholinergic drug, on clinical events, symptom scales, pulmonary function, and adverse events in stable chronic obstructive pulmonary disease (COPD).

Methods: A systematic search was made of the Cochrane trials database, MEDLINE, EMBASE, CINAHL, and a hand search of 20 respiratory journals. Missing data were obtained from authors and the manufacturer. Randomised controlled trials of ≥ 12 weeks' duration comparing tiotropium with placebo, ipratropium bromide, or long acting β_2 agonists (LABA) were reviewed. Studies were pooled to yield odds ratios (OR) or weighted mean differences with 95% confidence intervals (CI).

Results: Nine trials (8002 patients) met the inclusion criteria. Tiotropium reduced the odds of a COPD exacerbation (OR 0.73; 95% CI 0.66 to 0.81) and related hospitalisation (OR 0.68; 95% CI 0.54 to 0.84) but not pulmonary (OR 0.50; 95% CI 0.19 to 1.29) or all-cause (OR 0.96; 95% CI 0.63 to 1.47) mortality compared with placebo and ipratropium. Reductions in exacerbations and hospitalisations compared with LABA were not statistically significant. Similar patterns were evident for quality of life and symptom scales. Tiotropium yielded greater increases in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) from baseline to 6-12 months than did placebo, ipratropium, and LABA. Decline in FEV₁ over 1 year was 30 ml (95% CI 7 to 53) slower with tiotropium than with placebo and ipratropium (data were not available for LABA). Reports of dry mouth and urinary tract infections were increased with tiotropium.

Conclusions: Tiotropium reduced COPD exacerbations and related hospitalisations, improved quality of life and symptoms, and may have slowed the decline in FEV₁. Long term trials are warranted to evaluate the effects of tiotropium on decline in FEV₁ and to clarify its role compared with LABA.

Chronic obstructive pulmonary disease (COPD) is currently the fourth or fifth leading cause of death in the most developed countries, and is projected to be the third cause of death worldwide by 2020.¹ Despite this burden, few pharmacological treatments for COPD have been proved to reduce clinical events, and none has been shown definitively to slow decline in forced expiratory volume in 1 second (FEV₁).

Tiotropium has a quaternary ammonium structure related to that of ipratropium bromide. It dissociates slowly from M₁ and M₃ receptors but rapidly from M₂ receptors,² which allows once daily dosing and has theoretical advantages since M₂ receptors are feedback inhibitory receptors.^{3,4}

A number of randomised clinical trials suggest that tiotropium might reduce clinical event rates and improve lung function, but these trials have been of borderline statistical power. We therefore undertook a meta-analysis of available randomised trials to evaluate the efficacy of tiotropium on clinical events, health related quality of life, symptoms, pulmonary function, and adverse events compared with placebo, ipratropium bromide, and long acting β_2 agonists (LABA). An earlier version of this meta-analysis was published electronically in the Cochrane Library.⁵

METHODS

Data sources

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 CENTRAL was performed. Searches were current as of May 2006.

Reference lists of all primary studies and review articles were reviewed for additional references. Authors of identified randomised trials were asked about published and unpublished studies. The manufacturer of tiotropium (Boehringer Ingelheim) was contacted regarding overlap between studies, unpublished studies, and supplemental data. Additional data were obtained from the Food and Drug Administration website.⁶

Study selection

The following criteria were used to select randomised controlled trials for inclusion in the meta-analysis:

- Target population: stable COPD consistent with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria,⁷ without evidence of an exacerbation for 1 month prior to study entry;
- Intervention: randomised clinical trials comparing tiotropium with placebo, ipratropium bromide, or LABA;
- Methodological criteria: studies that followed patients for 12 weeks or more after randomisation.

Two reviewers independently identified trials that appeared potentially relevant from titles and abstracts.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LABA, long acting β_2 agonist; SGRQ, St George's Respiratory Questionnaire; TDI, Transitional Dyspnoea Index

Using the abstract or the full text of each study, as necessary, two reviewers independently decided if trials fulfilled inclusion criteria for the review. Differences were resolved by discussion.

Data extraction and assessment of methodological quality

Two reviewers independently extracted data. Intention-to-treat results were used whenever available. Primary clinical outcomes were COPD exacerbations, related hospitalisations, and all-cause mortality. Secondary outcomes included disease specific mortality, health related quality of life scales (St George's Respiratory Questionnaire [SGRQ]⁸), symptom scores (Transitional Dyspnea Index [TDI], a multidimensional measure of breathlessness⁹), change in trough FEV₁ and forced ventilatory capacity (FVC) from baseline and from steady state 8–15 days after randomisation, and adverse events (dry mouth, constipation, urinary infection and obstruction, chest pain, myocardial infarction, arrhythmias and congestive heart failure). Methodological quality was assessed using the Cochrane approach and Jadad criteria.¹⁰

Statistical analysis

Trials were combined using RevMan (Version 4.2.8). Fixed effect odds ratios (OR) for dichotomous variables and weighted mean differences (WMD) for continuous variables with 95% confidence intervals (CI) were calculated for individual trials. Trials were pooled using fixed effect OR or WMD as appropriate. Heterogeneity was tested using the Breslow-Day test with a *p* value <0.1 considered statistically significant. A random effects model was used if heterogeneity was found. Weighted averages of cumulative incidences in the control

groups were calculated across all trials and for trials of 12 months' duration. Numbers needed to treat (NNT) were calculated from the pooled OR, 95% CI, and cumulative incidences in the control groups of the 12 month trials.¹¹

For each outcome, trials were pooled within categories of control group (placebo, ipratropium, or LABA). Since an earlier large randomised clinical trial showed that ipratropium does not reduce clinical events or slow the decline in FEV₁ relative to placebo,^{12, 13} summary estimates were calculated comparing tiotropium with placebo or ipratropium for these end points when there was statistical homogeneity across categories of control group. Adverse events were combined across all categories of control group when there was statistical homogeneity.

Publication bias was examined in funnel plots and tested with a modified Macaskill's test.¹⁴ The effects of tiotropium were examined across predefined subgroups by disease severity and concurrent LABA use.

RESULTS

Ninety nine articles were identified, of which 33 possibly fulfilled the inclusion criteria and 15 met the inclusion criteria (fig 1). Three of these articles reported the combined results of pairs of previously published and unpublished trials, and three others were secondary reports with overlapping participants. The net number of included trials was nine (8002 randomised patients). Table 1 shows the characteristics of the nine included trials.

Six of the included trials compared tiotropium with placebo, one compared tiotropium with ipratropium,¹⁵ one compared tiotropium with a LABA (salmeterol),¹⁶ and one compared tiotropium with placebo and with salmeterol.¹⁷ Six trials scored four out of five for methodological quality, two scored five out of five,^{15, 18} and one scored three out of five.¹⁹ Allocation concealment was described in only one trial.¹⁵ The protocols were extremely similar. All trials enrolled patients regardless of response to bronchodilators but excluded patients with a prior history of asthma; all but one¹⁸ excluded patients with a history of atopy or allergic rhinitis; and six excluded patients with a raised eosinophil count. All trials prohibited the use of non-study ipratropium and all but one¹⁸ prohibited the use of non-study LABA.

The weighted mean duration of the trials was 7.0 months (range 3–12). The severity of COPD was generally moderate to severe (ERS/ATS stage III–IV; range stage II–V); 38–80% of patients were taking ipratropium at enrolment, 32–50% were taking LABA, and 42–80% were taking inhaled corticosteroids.

Clinical events

COPD exacerbations

The cumulative incidence of COPD exacerbations among controls was 35% over the mean duration (7.0 months) of all trials, and 52% in the 1 year trials. Tiotropium reduced COPD exacerbations compared with placebo and compared with ipratropium (fig 2A). The cumulative incidence of exacerbations was lower with tiotropium than with salmeterol, but this difference was smaller and not statistically significant. The treatment effect of tiotropium was statistically homogeneous across the control groups (*p*=0.77) and the summary OR for tiotropium compared with placebo or ipratropium was 0.73 (95% CI 0.66 to 0.81). The corresponding NNT for tiotropium to prevent one exacerbation per year was 13 (95% CI 10 to 21).

Hospitalisations for COPD exacerbations

The cumulative incidence of exacerbation related hospitalisations among controls was 7% over the duration of all trials, and 9% in the 1 year trials. Tiotropium reduced the risk of hospitalisation for COPD exacerbations compared with placebo

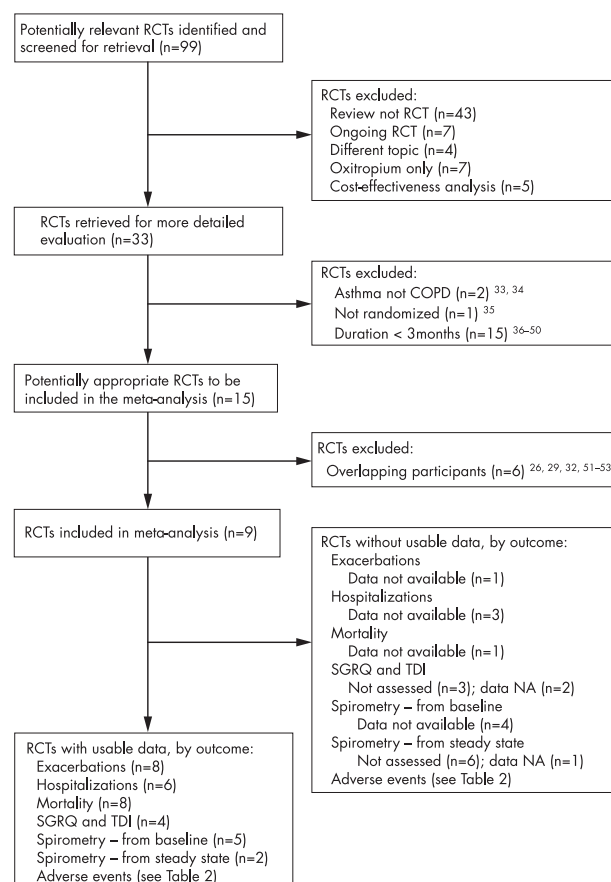


Figure 1 QUOROM flow diagram.

Table 1 Characteristics of the double blind randomised clinical trials included in the analysis

Study	Duration of trial/no randomised/ pre-randomisation run-in	Inclusion criteria/exclusion criteria/participant characteristics	Permitted co-therapies/discontinued co-therapies (% on co-therapy at baseline)	Control group intervention(s)
Beeh ²⁰	12 weeks N=1639 1 week washout period	Inclusion: COPD, FEV ₁ <70% predicted, ratio <70%, age >40 years, smoking history >10 py Exclusion: asthma, allergic rhinitis, atopy, oxygen use, arrhythmia, recent MI or CHF hospitalisation Characteristics: Mean age 62 years; 75% male; FEV ₁ : 1.3 (0.5) l; FVC 2.4 (0.7) l; ratio NA Inclusion: COPD, FEV ₁ <65% predicted, ratio <70%, age >40 years, smoking history >10 py Exclusion: asthma, allergic rhinitis, atopy, total eosinophil count ≥600/mm ³ , oxygen use, URI <6 weeks, other significant disease Characteristics: Mean age 64 years; 76% male; FEV ₁ 1.1 (0.4) l; FVC 2.6 (0.7) l; ratio 43 (10)% Inclusion: COPD, FEV ₁ <60% predicted, ratio <70%, age >40 years, smoking history >10 py Exclusion: asthma, allergic rhinitis, atopy, total eosinophil count ≥600/mm ³ , renal insufficiency, prostatic hypertrophy, glaucoma, other significant disease, COPD exacerbation <4 weeks, prednisone ≥10 mg/day, β blockers, oxygen use, recent pulmonary rehabilitation Characteristics: Mean age 64 years; 66% male; FEV ₁ 1.0 (0.4) l; FVC 2.4 (0.7) l; ratio 43 (10)% Inclusion: COPD, FEV ₁ <65% predicted, ratio <70%, age ≥40 years, smoking history >10 py Exclusion criteria: asthma, allergic rhinitis, atopy, total eosinophil count ≥600/mm ³ , oxygen use, prednisone ≥10 mg in prior month, MI <1 year, CHF <3 years, arrhythmia Characteristics: Mean age 65 years; 65% male; FEV ₁ 1.0 (0.4) l; FVC 2.3 (0.8) l; ratio 46 (12)% Inclusion: COPD, FEV ₁ <60% predicted, ratio <70%, age ≥40 years, smoking history >10 py, able to perform pulmonary rehabilitation Exclusion: asthma, allergic rhinitis, atopy, total eosinophil count ≥600/mm ³ , BMI <18 or >30 kg/m ² , other significant disease, recent URI, MI, CHF, arrhythmia Characteristics: Mean age 67 years; 56% male; FEV ₁ 0.9 (0.4) l; FVC 34 (12); ratio 43 (11)% Inclusion: COPD, pre-BD FEV ₁ 30-65% predicted, FEV ₁ /SVC <70%, age >40 years, smoking history >10 py, ≥1 exacerbation in prior year Exclusion: asthma, allergic rhinitis, atopy, renal insufficiency, oxygen use, COPD exacerbation <6 weeks, prednisone ≥10 mg/day, other significant medical illness Characteristics: Mean age: 65 years; 88% male; FEV ₁ 1.4 (0.4) l; FVC 2.6 (0.8) l; ratio 55 (12)% Inclusion: COPD, FEV ₁ <60% predicted, ratio <70%, age >40 years, smoking history >10 py Exclusion: asthma, renal insufficiency, prostatic hypertrophy, glaucoma, MI <6 months, arrhythmia, CHF hospitalisation <1 year, on cancer treatment, COPD exacerbation <4 weeks, prednisone ≥20 mg/day Characteristics: Mean age 68 years; 99% male; FEV ₁ 1.0 (0.4) l; ratio 48 (11)% Inclusion: COPD, FEV ₁ <50% predicted, FEV ₁ /SVC <70% predicted, RV ≤125% predicted, age >40 years, smoking history >10 py, ≥1 exacerbation in previous year Exclusion: asthma, allergic rhinitis, atopy, total eosinophil count ≥600/mm ³ , MI <1 year, arrhythmia, CHF <3 years, oxygen use, COPD exacerbation <6 weeks, prednisone ≥10 mg/day Characteristics: Mean age 59 years; 94% male; FEV ₁ 1.1 (0.3) l; FVC 2.4 (0.7) l; ratio 40 (7)% Inclusion: COPD, FEV ₁ <65% predicted, ratio <70%, age ≥40 years, smoking history >10 py Exclusion: asthma, allergic rhinitis, atopy, total eosinophil count ≥600/mm ³ , oxygen use, recent URI, other significant disease (van Noord ²¹ lists MI <1 year, CHF <3 years, arrhythmia, prostatic hypertrophy, glaucoma, anticholinergic drug allergy) Characteristics: Mean age 64 years; 85% male; FEV ₁ 1.2 (0.4) l; FVC 2.7 (0.8); ratio 46 (10)%	Permitted: SABA (76%), inhaled corticosteroid (57%), prednisone (16%), theophylline (52%) Discontinued: ipratropium (69%), LABA (50%) Permitted: NA (Donohue ³⁰ lists SABA (66%), inhaled corticosteroid (66%), prednisone (6%), theophylline (21%)) Discontinued: NA (Donohue ³⁰ lists ipratropium (53%), LABA (NA)) Permitted: SABA (58%), inhaled corticosteroid (50%), prednisone (2%) Discontinued: ipratropium (55%), LABA (47%), theophylline (12%) Permitted: SABA (99%), inhaled corticosteroid (42%), prednisone (7%), theophylline (23%) Discontinued: ipratropium (57%), LABA (NA) Permitted: SABA, inhaled and prednisone, theophylline (% NA) Discontinued: ipratropium, LABA (% NA) Permitted: SABA (94%), inhaled corticosteroid (63%), prednisone (2%) Discontinued: ipratropium (38%), LABA (32%), theophylline (7%) Permitted: SABA (94%), LABA (38%), inhaled corticosteroid (58%), prednisone (10%), theophylline (14%), oxygen (29%) Discontinued: ipratropium (80%) Permitted: SABA, inhaled and prednisone, theophylline (% NA) Discontinued: ipratropium, LABA (% NA) Permitted: SABA (76%), inhaled corticosteroid (80%), prednisone (9%), theophylline (16%) Discontinued: ipratropium (60%), LABA (NA)	Placebo (1) Salmeterol 50 µg bid by MDI (2) Placebo Salmeterol 50 µg bid by MDI Placebo Placebo Placebo Placebo Placebo Ipratropium 40 µg qid by MDI
Brusasco ¹⁷	6 months N=1207 2 week washout period			
Briggs ¹⁶	12 weeks N=653 2 week washout period			
Casaburi ¹⁹	12 months N=921 2 week washout period			
Casaburi ²⁰	25 weeks N=108 1 week training run-in			
Dusser ²¹	48 weeks N=1050 3 week run-in			
Newwohner ¹⁸	6 months N=1829 No run-in period			
Verkindre ²¹	12 weeks N=100 2 weeks run-in			
Vincken ¹⁵	12 months N=535 2 week washout period			

py, pack years; MI, myocardial infarction; CHF, congestive heart failure; NA, not available; URI, upper respiratory infection; SABA, short acting bronchodilator; LABA, long acting bronchodilator; MDI, metered dose inhaler.

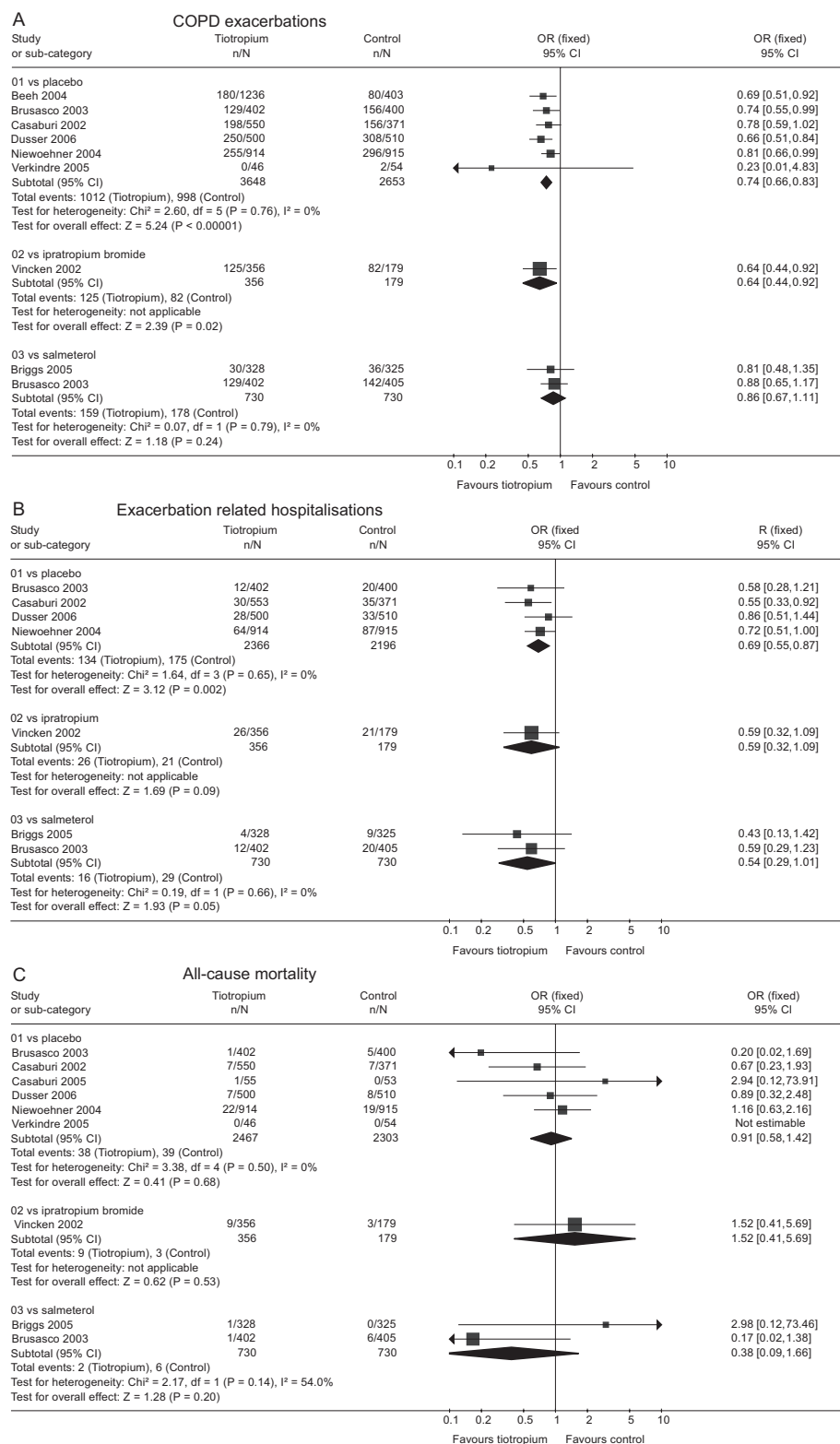


Figure 2 Summary effects of tiotropium on (A) COPD exacerbations, (B) hospitalisations, and (C) all-cause mortality.

(fig 2B). Similar reductions in hospitalisations were observed compared with ipratropium and compared with salmeterol, but neither of these differences was statistically significant. The treatment effect of tiotropium was statistically homogeneous across the control groups ($p = 0.76$) and the summary estimate for tiotropium compared with placebo or ipratropium was OR 0.68 (95% CI 0.54 to 0.84). The corresponding NNT for

tiotropium to prevent one exacerbation related hospitalisation per year was 38 (95% CI 26 to 76).

Mortality

Cumulative all-cause mortality among controls was 1.5% over the duration of all trials and 1.7% in the 1 year trials. There were no statistically significant differences in all-cause

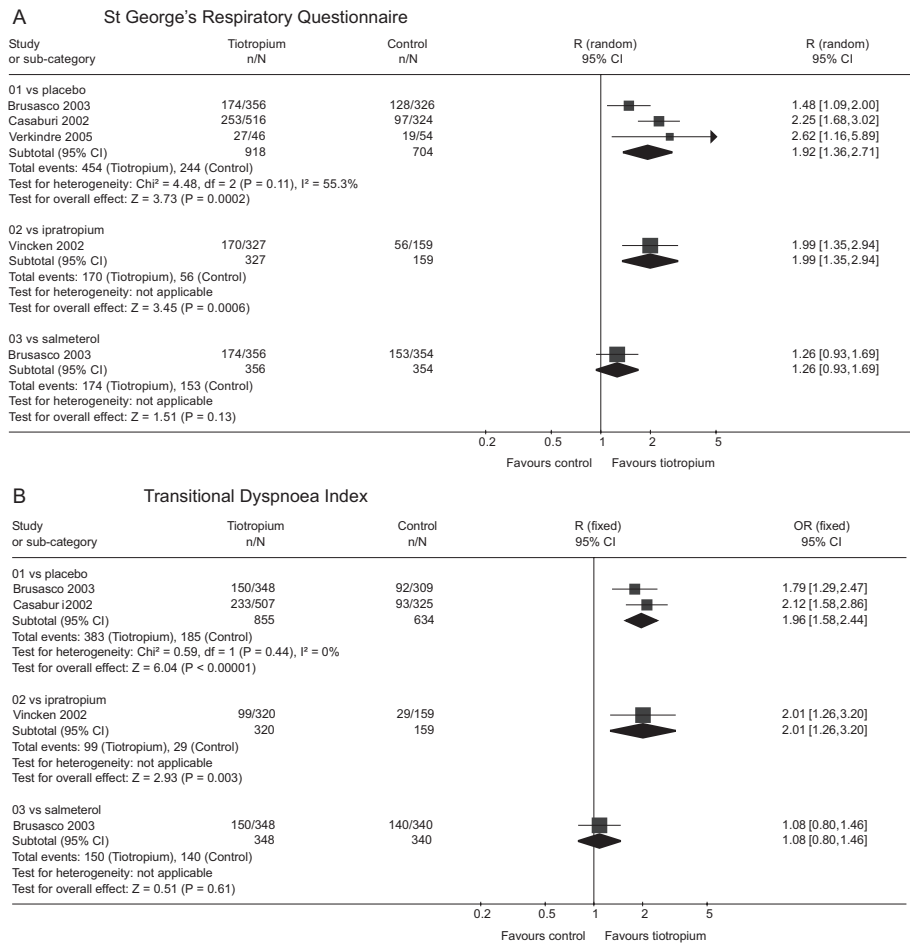


Figure 3 Summary effects of tiotropium on clinically significant changes in (A) St George's Respiratory Questionnaire and (B) Transitional Dyspnoea Index.

mortality between tiotropium and placebo, ipratropium, or salmeterol (fig 2C). The trials were statistically homogeneous across the control groups ($p = 0.57$) and the summary estimate for tiotropium compared with placebo or ipratropium was not significant (OR 0.96; 95% CI 0.63 to 1.47).

Mortality from pulmonary causes was non-significantly lower with tiotropium compared with placebo or ipratropium (OR 0.50; 95% CI 0.19 to 1.29; fig S1 available online only at <http://www.thoraxjnl.com/supplemental>). Heterogeneity was not evident. There were no statistically significant differences for cardiovascular mortality (OR 1.17; 95% CI 0.54 to 2.51), cancer mortality (0.77; 95% CI 0.28 to 2.12), and mortality from other causes (OR 2.77; 95% CI 0.81 to 9.45).

Health related quality of life and symptom scales
St George's Respiratory Questionnaire (SGRQ)

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 -2.0) or with ipratropium (WMD -3.3 ; 95% CI -5.6 to -1.0). A smaller and non-significant difference was observed compared with salmeterol (WMD -1.4 ; 95% CI -3.2 to 0.4). The trials were statistically homogeneous across the control groups ($p = 0.31$) and the summary estimate for tiotropium compared with placebo or ipratropium was an improvement of WMD -3.3 (95% CI -4.7 to -2.2).

Similar results were observed for the proportion with a clinically significant change in SGRQ (fig 3A), although there was evidence of heterogeneity across the control groups ($p = 0.04$).

Transitional Dyspnoea Index (TDI)

Data on mean change in TDI was inadequate for meta-analysis. The results for the proportion with a clinically significant change in TDI (fig 3B) were similar to those for SGRQ. There was evidence of heterogeneity across the control groups ($p = 0.07$).

Spirometric indices

Change in FEV₁ and FVC from baseline

The mean improvement in trough FEV₁ from baseline to the end of the trials was greater with tiotropium than with placebo or ipratropium (fig 4A). A smaller but statistically significant difference was observed compared with salmeterol. There was evidence of statistical heterogeneity across the control groups ($p < 0.0001$) which arose from the smaller mean difference compared with salmeterol. Similar results were seen for change in trough FVC from baseline (fig 4B).

Change in FEV₁ and FVC from steady state

The mean decline in trough FEV₁ from steady state was slower with tiotropium than with placebo (fig 5A). The treatment effect of tiotropium was similar to that of ipratropium, although the latter result was not statistically significant. The trials were statistically homogeneous across the control groups ($p > 0.99$) and the summary estimate showed a WMD of 30 ml (95% CI 7 to 53 ml) slower decline in FEV₁ for tiotropium compared with placebo or ipratropium.

Declines in trough FVC from steady state to the end of the two trials were heterogeneous ($p = 0.08$) and no statistically

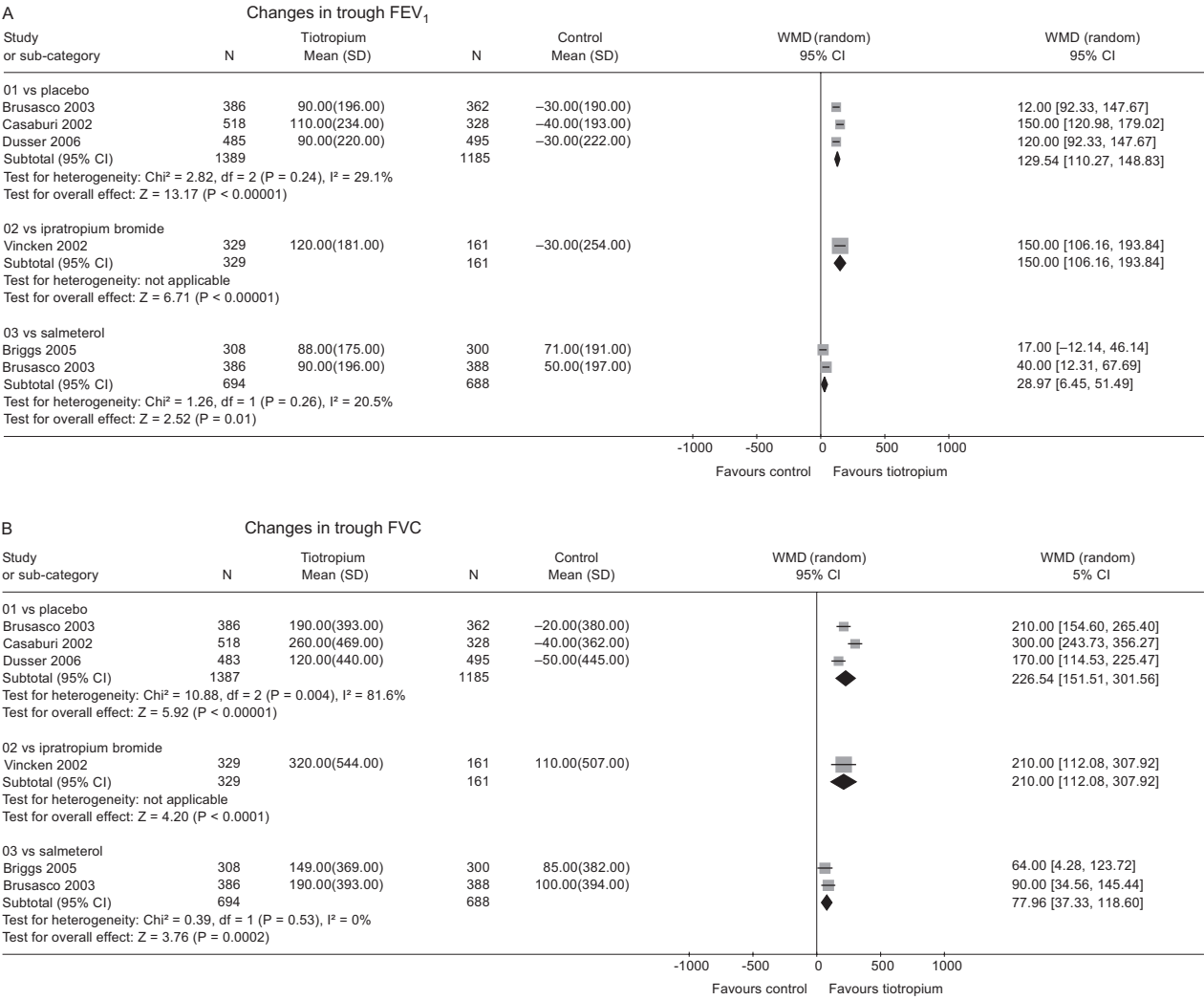


Figure 4 Summary effects of tiotropium on changes in (A) trough FEV₁ and (B) trough FVC from baseline before randomisation until end of trials.

significant differences were observed between tiotropium and either control group (fig 5B).

Adverse events

Available data on adverse events are summarised in table 2. Dry mouth was significantly increased with tiotropium compared with placebo, ipratropium and salmeterol, and urinary tract infections were significantly increased compared with placebo and ipratropium (data were not available for salmeterol). Consistent but not statistically significant increases were observed for systemic anticholinergic adverse events (constipation and urinary retention). Heterogeneity was evident for arrhythmias or atrial fibrillation overall and in comparison with placebo (p = 0.05). This heterogeneity resulted from one trial that reported atrial fibrillation results only. When this trial was excluded, heterogeneity was not evident (p = 0.71) and the frequency of arrhythmias was significantly higher with tiotropium than with placebo (OR 2.33; 95% CI 1.11 to 4.88).

Subgroup and sensitivity analyses

The trials were very similar with respect to disease severity and concurrent LABA use. The two trials with the highest baseline mean FEV₁^{20 21} had a statistically similar estimate for exacerbations as the pooled estimate and as a trial in which 29% of patients were on oxygen¹⁸ (fig 2).

The effect of tiotropium on exacerbations in the one trial¹⁸ that permitted concurrent use of LABA (OR 0.81; 95% CI 0.66 to 0.99) was statistically similar to the others that withheld LABA (OR 0.70; 95% CI 0.62 to 0.80).

Sensitivity analyses by quality weighting and random effects models yielded nearly identical results. Funnel plots for the primary end points showed no clear evidence of publication bias and the modified Macaskill test did not suggest publication bias for exacerbations (p = 0.65).

DISCUSSION

This systemic review of the currently available randomised trials of tiotropium for stable COPD showed that tiotropium reduced COPD exacerbations and related hospitalisations compared with placebo or ipratropium. Increases in FEV₁ and FVC from baseline were significantly larger with tiotropium than with placebo, ipratropium, and LABA. The decline in trough FEV₁ from steady state was slower with tiotropium than with placebo or ipratropium, and pulmonary mortality was non-significantly lower with tiotropium.

The benefits observed with tiotropium for exacerbations and related hospitalisations were large and clinically important. Consistent with these findings, tiotropium has been shown to be cost effective although not cost saving compared with ipratropium in Europe.²² The magnitude of the reduction

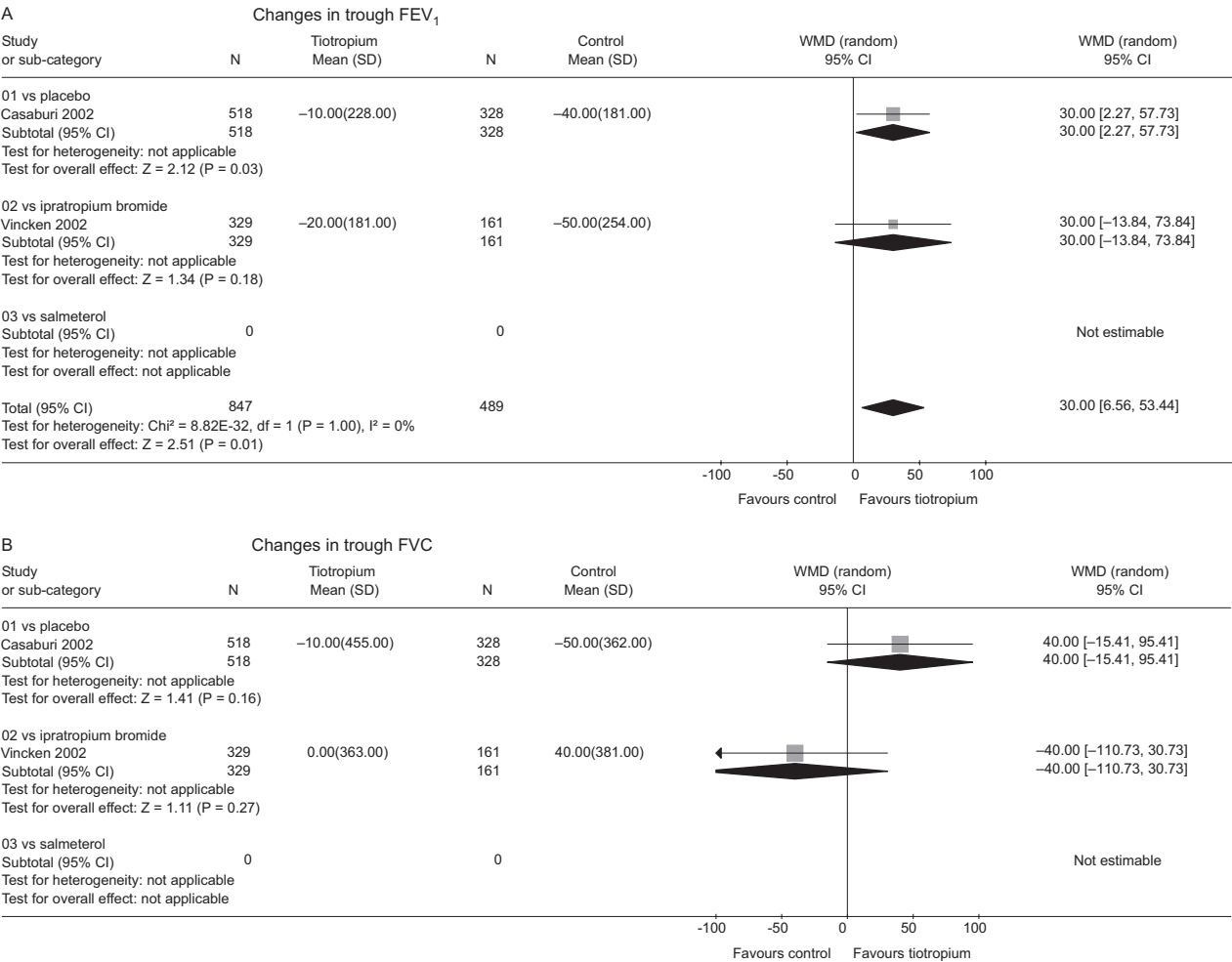


Figure 5 Summary effects of tiotropium on changes in (A) trough FEV₁ and (B) trough FVC from steady state 8 days after randomisation until end of trials (1 year).

in exacerbation related hospitalisations with tiotropium was similar in comparison with placebo, ipratropium and salmeterol, and was similar in large placebo controlled trials that did and did not permit use of LABA.

Changes in health related quality of life, symptom scales, and spirometric indices also appeared clinically significant. Compared with placebo and ipratropium, the mean change in the SGRQ across all participants was close to the clinically significant change in SGRQ of 4 units, and more participants on tiotropium achieved a clinically significant change in SQRQ and TDI compared with placebo and ipratropium. Improvements in spirometric indices from baseline were clinically significant compared with placebo and ipratropium at a threshold for FEV₁ of 100 ml²³ but not at a threshold of 225 ml.²⁴ Improvements in spirometric indices from baseline were statistically but not clinically significant compared with salmeterol.

The results of this systemic review are consistent with a previous review of treatments for COPD²⁵ which reported on exacerbations and quality of life but which was limited by double counting of patients randomised to tiotropium. Our results correct and extend that review with more than twice the number of randomised patients and additional outcomes of hospitalisations, mortality, symptom scales, spirometric indices, and adverse events.

We found 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 difference observed in a meta-analysis of inhaled corticosteroids in COPD²⁶ and was

consistent with a post hoc analysis of one of the tiotropium trials.²⁷ However, this observation should be interpreted with caution as it might 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 was only 1 year; and (3) bias, given that most but possibly not all trial results for this measure were available for meta-analysis. Larger longer term trials are necessary to assess the validity of this result, which would be of major clinical relevance if replicated.

Mortality from pulmonary causes was non-significantly lower among those randomised to tiotropium compared with placebo or ipratropium. This finding suggests that observed benefits on exacerbations and hospitalisations might translate into reductions in pulmonary mortality, but requires evaluation in long term randomised trials designed specifically to examine pulmonary mortality. Estimates for disease-specific mortality can be subject to more biases than all-cause mortality, and we note that all-cause mortality did not differ appreciably between tiotropium and placebo.

The trials included in this review were of good quality and used almost identical designs with regard to inclusion and exclusion criteria. The clinical homogeneity of the trials resulted in statistical homogeneity for most outcome measures across the trials. We calculated summary estimates of the effects of tiotropium compared with placebo and ipratropium. Heterogeneity would be introduced if ipratropium had an effect on the relevant outcomes, but ipratropium has been shown not

Table 2 Adverse events with tiotropium compared with placebo, ipratropium, and salmeterol, with summary estimates across all available data

	Tiotropium compared with			p value for heterogeneity	Summary estimate
	Placebo	Ipratropium	Salmeterol		
Dry mouth					
Trials	4	1	2	0.24	7
Participants	2835	535	1460		4830
Odds ratio (95% CI)	4.6 (3.0 to 7.1)	2.1 (1.05 to 4.2)	4.7 (2.4 to 9.2)		3.9 (2.8 to 5.5)
Constipation					
Trials	2	1	0	0.41	3
Participants	1931	535			2466
Odds ratio (95% CI)	2.2 (0.95 to 4.8)	0.5 (0.1 to 3.6)			1.7 (0.8 to 3.7)
Urinary retention					
Trials	3	0	1	0.85	4
Participants	2733		807		3540
Odds ratio (95% CI)	2.5 (0.5 to 14)		3.0 (0.1 to 75)		2.6 (0.6 to 12)
Urinary tract infection					
Trials	3	1	0	0.91	4
Participants	2733	535			3268
Odds ratio (95% CI)	1.6 (0.97 to 2.6)	1.8 (0.6 to 5.5)			1.6 (1.03 to 2.6)
Chest pain					
Trials	3	1	1	0.09	–
Participants	2733	535	807		
Odds ratio (95% CI)	0.9 (0.4 to 2.0)	2.5 (0.8 to 7.4)	1.2 (0.6 to 2.4)		
Myocardial infarction					
Trials	3	1	0	0.77	4
Participants	2733	535			3268
Odds ratio (95% CI)	1.0 (0.2 to 3.9)	1.5 (0.2 to 15)			1.1 (0.3 to 3.6)
Arrhythmia or atrial fibrillation					
Trials	4	1	0	0.05	–
Participants	4561	535			
Odds ratio (95% CI)	1.4 (0.4 to 5.7)	0.8 (0.3 to 1.8)			
Congestive heart failure					
Trials	3	1	0	0.86	4
Participants	2837	535			3372
Odds ratio (95% CI)	0.8 (0.4 to 1.6)	0.5 (0.1 to 8.1)			0.8 (0.4 to 1.5)

to alter the long term decline in FEV₁,¹³ hospitalisations or survival¹² compared with placebo. LABA, on the other hand, may reduce exacerbations compared with placebo.^{25, 28}

Potential limitations of meta-analyses include double counting of patients from overlapping publications, publication bias, reporting bias, and selection bias from differential inclusion of available trials. We avoided double counting by discussing trial overlap with the primary authors and the manufacturer of tiotropium, and evaluated for publication bias with funnel plots and statistical tests. Selective reporting of secondary end points and of non-intention to treat reports in published manuscripts may bias results; we minimised this bias by obtaining supplemental data for five of the nine included studies, although complete intention to treat analyses were missing for most studies due to missing data. We avoided selection bias by pre-specified inclusion and exclusion criteria, a systematic search, and independent evaluation of trial inclusion by two reviewers.

In conclusion, tiotropium reduced COPD exacerbations and exacerbation related hospitalisations compared with placebo or ipratropium. It also improved health related quality of life and symptom scores and can be recommended for the

treatment of stable COPD. The results of this systematic review suggest that tiotropium may slow the decline in FEV₁, although this finding requires confirmation in additional long term randomised clinical trials.

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Figure S1 showing mortality from pulmonary causes, cardiovascular causes, cancer and other causes is available online at <http://www.thoraxjnl.com/supplemental>.

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systematic sampling, but is avoided in trials with patients prospectively randomised and analysed on an intention-to-treat basis. We emphasise that we did not perform any stage-based subanalyses, but compared the whole CMLND population with the systematic sampling group.

The exclusions after randomisation clearly should not have occurred, but were adequately reported. In all, 25 patients had small-cell cancer or a non-malignant pathology, 48 had incomplete primary resection, 5 turned out to have metastatic deposits from other sites and 15 were excluded because of upstaging to IIIB or IV only. The exclusions were well matched, with 52 occurring in the CMLND group and 41 in the systematic sampling group. We therefore believe this had little effect on the overall analysis.

It should also be mentioned that in one of the trials, only patients with cT1N0 adenocarcinoma of ≤ 2 cm diameter were randomised. Mechanistically, the authors hypothesised that this is the group least likely to benefit from CMLND; however, their inclusion in the pooled analysis still resulted in a clear benefit in favour of CMLND. In fact, the pooled hazard ratio of 0.78 is superior to that of adjuvant chemotherapy meta-analyses⁴ that have created such enthusiasm in lung cancer circles of late. Therefore, we are concerned that as a result of this editorial, groups treating lung cancer may not demand from their surgeons that which they are demanding from their medical oncologists—an evidence-based improvement in survival with an adjuvant intervention.

We also await the results of the ACOSOG Z30 trial,⁵ which will address this question for patients in clinical stage I. This will also allow a pooled analysis of 1959 patients, which should be able to put this question to rest after 50 years of controversy. Until then, the level I evidence is that CMLND should be performed as part of the surgical treatment of patients with stage I–IIIA non-small-cell lung cancer.

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Authors' reply

We thank Dr Wright for his comments, but respectfully disagree. Although it is certainly possible that complete mediastinal lymph node dissection (CMLD) might improve survival in non-small-cell lung cancer (NSCLC), all three of the studies performed to date were limited by stage migration and other biases. Although overall exclusions were matched, we do not know whether exclusions due to upstaging were necessarily matched between study arms. In fact, limited data from the studies suggest that they were not. In the study by Wu *et al*,¹ after post-randomisation exclusions, there were more patients with stage I (42% *v* 24%) and fewer with stage IIIa (28% *v* 48%) in the lymph node sampling group than in the CMLD group. Furthermore, the authors of one of the other three included studies concluded that stage migration might have resulted in an observed survival benefit for patients undergoing CMLD,² and a previous systematic review on CMLD in NSCLC also concluded that stage migration existed for two of the three included studies.³

In addition, there are other limitations. For example, because the study by Sugi *et al*⁴ included only patients with peripheral NSCLC < 2 cm, the results are not generalisable to all patients with early-stage disease. The study by Wu *et al* had unequal follow-up between study arms.^{1,3} The study by Izbicki *et al*² had significantly more patients with squamous cell carcinoma in the lymph node sampling group (53%) than in the CMLD group (32%, $p = 0.03$). Finally, two of the three studies were unblinded during follow-up.^{1,4} Even if a small survival benefit exists, this must be weighed against the substantially higher morbidity for patients undergoing CMLD reported in two of the three included studies.^{2,4} The results of the ACOSOG Z30 trial should help address these trade-offs.⁵

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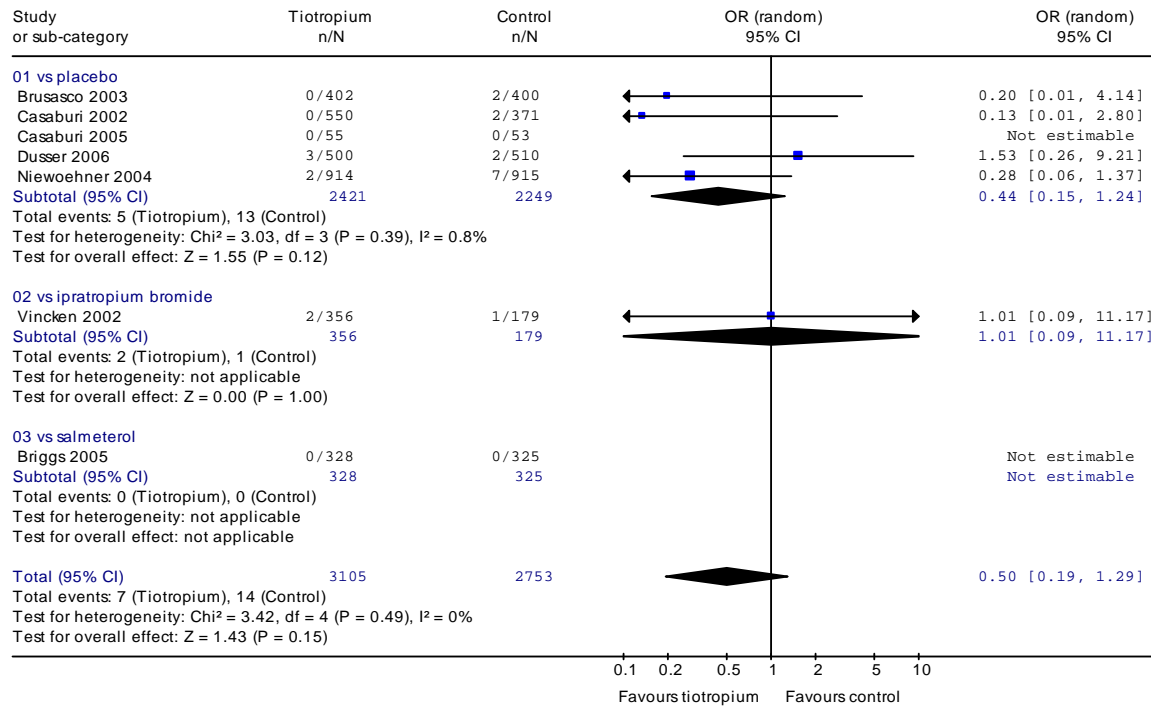
CORRECTION

doi: 10.1136/thx.2006.063271corr1

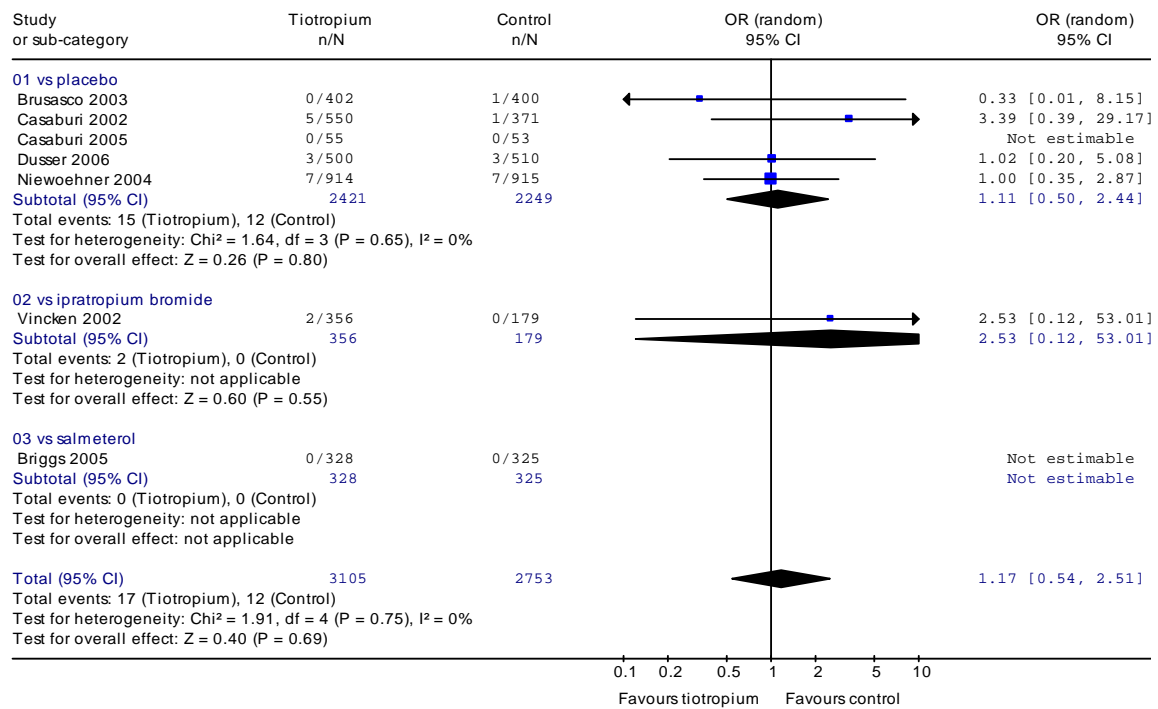
The authors of the article entitled "Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis" (Barr RG, Bourbeau J, Camargo CA, *et al*. *Thorax* 2006;**61**:854–62), published in the October issue, have noticed an error in figure 1. Reference 26 in figure 1 should refer to a paper not in the reference list: Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003;**21**:267–72. Where reference 26 is cited in the text this correctly refers to the paper listed in the reference list.

Figure S1

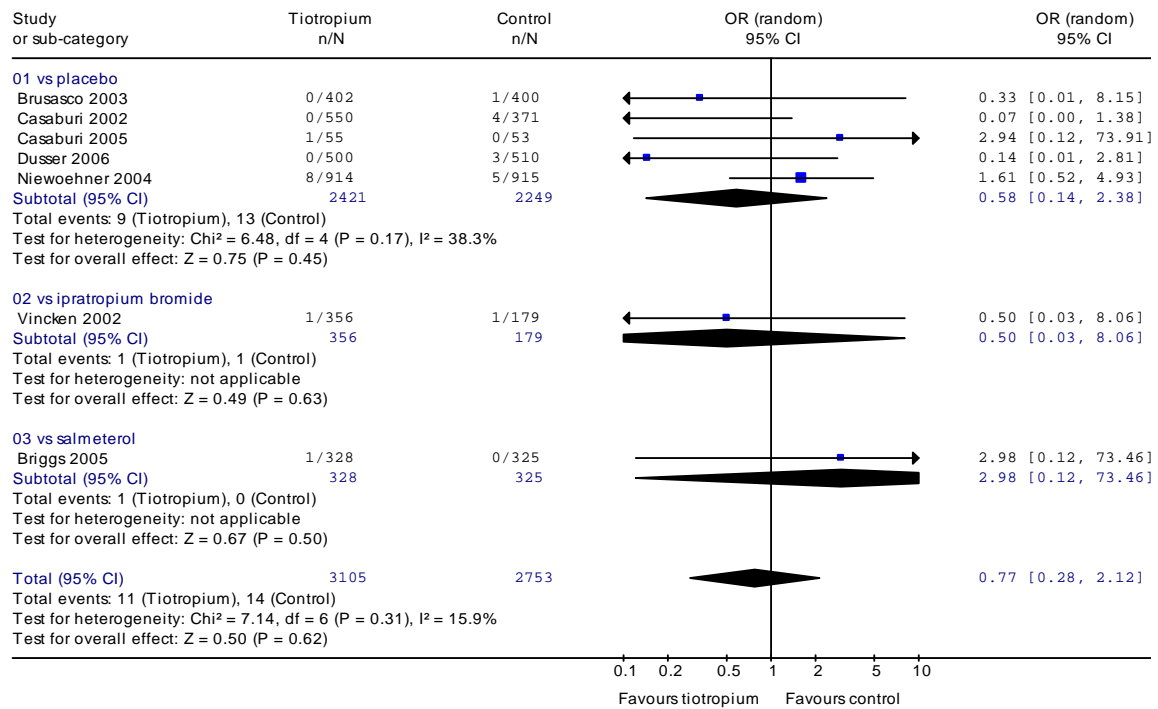
(A) Mortality from Pulmonary Causes



(B) Mortality from Cardiovascular Causes



(C) Mortality from Cancer Causes



(D) Mortality from Other Causes

