Thorax Online First, published on July 14, 2006 as 10.1136/thx.2006.063271

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

R Graham Barr[1]
Jean Bourbeau[2]
Carlos A Camargo Jr[3]
Felix SF Ram[4]

1. Irving Assistant Professor of Medicine and Epidemiology, Columbia University Medical Centre, New York, NY
2. Associate Professor of Medicine, McGill University Health Centre, Montreal, Quebec, Canada
3. Associate Professor of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA
4. Senior Lecturer in Respiratory Medicine and Clinical Pharmacology, School of Health Sciences, Massey University, Auckland, New Zealand

Address reprint requests to: R Graham Barr, MD DrPH
Division of General Medicine, PH-9 East Room 105
Columbia University Medical Centre
630 West 168th Street
New York NY 10032 USA
E-mail: rgb9@columbia.edu

Word count: 2,754
Abstract word count: 290
Key words: Bronchodilator agents, cholinergic antagonists, chronic obstructive pulmonary disease, emphysema, chronic bronchitis

ABSTRACT

Objective: To evaluate the efficacy of tiotropium, a long-acting anticholinergic therapy, on clinical events, symptom scales, pulmonary function and adverse events in stable chronic obstructive pulmonary disease (COPD).

Data Sources: A compilation of systematic searches of the Cochrane Trials database, MEDLINE, EMBASE, CINAHL and hand-search of 20 respiratory journals. Missing data were obtained from authors and the manufacturer.

Design: A systematic review of high quality randomised controlled trials.

Review Methods: Randomised trials of ≥12 week's duration comparing tiotropium to placebo, ipratropium bromide, or long-acting $ß_2$-agonists (LABA). Studies were pooled to yield odds ratios (OR) or weighted mean differences with 95% confidence intervals (CI).

Results: Nine trials (8,002 patients) met 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 to placebo and ipratropium. Reductions in exacerbations and hospitalisations compared to LABA were not statistically significant. Similar patterns were evident for quality-of-life and symptom scales. Tiotropium yielded greater increases in FEV_1 and FVC from baseline to 6-12 months than did placebo, ipratropium and LABA. Decline in FEV_1 over one year was 30 ml (95% CI, 7 to 53 ml) 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. In addition, tiotropium improved quality-of-life and symptoms, and may have slowed decline in FEV_1. Long-term trials are warranted to evaluate the effects of tiotropium on decline in FEV_1 and to clarify its role compared to LABA.

BACKGROUND

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 therapies for COPD have been proven to reduce clinical events, and none has been shown definitively to slow decline in forced expiratory volume in one second (FEV_1).

Tiotropium has a quaternary ammonium structure related to that of ipratropium bromide. It dissociates slowly from M_1 and M_3 receptors but rapidly from M_2 receptors,[2] which allows once-daily dosing and has theoretically advantages since M_2 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 meta-analysed available randomised trials to evaluate the efficacy of tiotropium on clinical events, health-related quality-of-life, symptoms, pulmonary function, and adverse events compared to placebo, ipratropium bromide, and long-acting $ß_2$-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

We used the following criteria 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 one month prior to study entry;
- Intervention: randomised clinical trials comparing tiotropium to 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. 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 (the Transitional Dyspnea Index [TDI], a multidimensional measure of breathlessness [9]), change in trough FEV_1 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 decline in FEV_1 relative to placebo,[12, 13] summary estimates were calculated comparing tiotropium with placebo or ipratropium for these endpoints 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] Effects of tiotropium were examined across pre-defined subgroups by disease severity and concurrent LABA use.

RESULTS

Ninety-nine articles were identified, of which 33 possibly fulfilled inclusion criteria and 15 met inclusion criteria (Appendix 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 (8,002 randomised patients).

Table 1 shows the characteristics of the nine included trials.

Table 1. Characteristics of included double-blind randomised clinical trials.

Study	Duration of trial Number 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 2004 [20, 29]	3 months N=1,639 1-week wash-out 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	**Permitted**: SABA (76%), inhaled corticosteroid (57%), prednisone (16%), theophylline (52%) **Discontinued:** ipratropium (69%), LABA (50%)	Placebo
Brusasco 2003 [17]	6 months N=1,207 2 week wash-out period	**Inclusion:** COPD, FEV_1 <= 65% predicted, ratio <=70%, age >40 years, smoking history >10 py **Exclusion:** asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm³, 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 %	**Permitted:** NA (Donohue[30] lists SABA (66%), inhaled corticosteroid (66%), prednisone (6%), theophylline (21%)) **Discontinued:** NA (Donohue[30] lists ipratropium (53%), LABA (NA))	1. Salmeterol 50ug BID by metered dose inhaler 2. Placebo
Briggs 2005 [16]	12 weeks N=653 2 week wash-out period	**Inclusion:** COPD, FEV_1 <=60% predicted, ratio <=70%, age >40 years, smoking history >10 py **Exclusion:** asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm³, renal insufficiency, prostatic hypertrophy, glaucoma, other significant disease, COPD exacerbation <4 wks, prednisone >=10 mg/day, B-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 %	**Permitted:** SABA (58%), inhaled corticosteroid (50%), prednisone (2%) **Discontinued:** ipratropium (55%), LABA (47%), theophylline (12%)	Salmeterol 50 mcg BID by MDI
Casaburi 2002 [19]	12 months N=921 2 week wash-out period	**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/mm³, 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 %	**Permitted**: SABA (99%), inhaled corticosteroid (42%), prednisone (7%), theophylline (23%) **Discontinued:** ipratropium (57%), LABA (NA)	Placebo

Casaburi 2005 [31]	25 weeks N=108 1 week training run-in	**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/mm³, 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%	**Permitted**: SABA, inhaled and prednisone, theophylline (% NA) **Discontinued:** ipratropium, LABA (% NA)	Placebo
Dusser 2005 [21]	48 weeks N=1,050 3 week run-in	**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 wks, 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 %	**Permitted:** SABA (94%), inhaled corticosteroid (63%), prednisone (2%) **Discontinued:** ipratropium (38%), LABA (32%), theophylline (7%)	Placebo
Niewoehner 2005 [18]	6 months N=1,829 No run-in period	**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 hospitalization <1 year, on cancer treatment, COPD exacerbation <4 wks, prednisone >=20 mg/day **Characteristics:** Mean age: 68 years; 99% male; FEV_1: 1.0 L ± 0.4 L; ratio 48 ± 11 %	**Permitted:** SABA (94%), LABA (38%), inhaled corticosteroid (58%), prednisone (10%), theophylline (14%), oxygen (29%) **Discontinued:** ipratropium (80%)	Placebo
Verkindre 2005 [32]	12 weeks N=100 2 weeks run-in	**Inclusion:** COPD, FEV_1<=50% predicted, FEV_1/SVC<=70% predicted, RV<=125% predicted, age >40 years, smoking history > 10 py, >=1 exacerbation in prior year **Exclusion:** asthma, allergic rhinitis, atopy, total eosinophil count >= 600/mm³, MI <1 year, arrhythmia, CHF <3 years, oxygen use, COPD exacerbation <6 wks, 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 %.	**Permitted:** SABA, inhaled and prednisone, theophylline (% NA) **Discontinued:** ipratropium, LABA (% NA)	Placebo

Vincken 2002 [15]	12 months N=535 2 week wash-out period	**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[33] 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 (80%), prednisone (9%), theophylline (16%) **Discontinued:** ipratropium (60%), LABA (NA)	Ipratropium 40 ug QID by MDI

py = packyears; MI = myocardial infarction; CHF = congestive heart failure; NA = not available; URI = upper respiratory infection; SABA = short-acting bronchodilator; LABA = long-acting bronchodilator

Six of the included trials compared tiotropium to placebo, one compared tiotropium to ipratropium,[15] one compared tiotropium to a LABA (salmeterol),[16] and one compared tiotropium to placebo and to 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 one [18] excluded patients with a history of atopy or allergic rhinitis; and six excluded patients with an elevated eosinophil count. All trials prohibited the use of non-study ipratropium and all but one [18] prohibited the use of non-study LABA.

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

DATA SYNTHESIS

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 one-year trials. Tiotropium reduced COPD exacerbations compared to placebo and compared to ipratropium (Figure 1a). The cumulative incidence of exacerbations was lower with tiotropium than 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 to 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 one-year trials. Tiotropium reduced the risk of hospitalisation for COPD exacerbations compared to placebo (Figure 1b). Similar reductions in hospitalisations were observed compared to ipratropium and compared to 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 to 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 one-year trials. There were no statistically significant differences in all-cause mortality between tiotropium compared to placebo, ipratropium, or salmeterol (Figure 1c). The trials were statistically homogeneous across the control groups (P=0.57) and the summary estimate for tiotropium compared to 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 to placebo or ipratropium (OR 0.50; 95% CI, 0.19 to 1.29; Appendix 2). 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

The mean change in SGRQ over the course of the trials was larger with tiotropium compared to placebo (WMD -3.3; 95% CI, -4.6 to -2.0) and compared to 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=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).

Similar results were observed for the proportion with a clinically significant change in SGRQ (Figure 2a), although there was evidence of heterogeneity across the control groups (P=0.04).

Transitional Dyspnea Index

Data on mean change in TDI was inadequate for meta-analysis. Results for the proportion with a clinically significant change in TDI (Figure 2b) were similar to those for SGRQ. There was evidence of heterogeneity across the control groups (P=0.07).

Spirometric indices

Change in FEV_1 and FVC from baseline

The mean improvement in trough FEV_1 from baseline to the end of the trials was greater with tiotropium compared to placebo and compared to ipratropium (Figure 3a). A smaller but statistically significant difference was observed compared to salmeterol. There was evidence of statistical heterogeneity across the control groups (P<0.0001), which arose from the smaller mean difference compared to salmeterol. Similar results were seen for change in trough FVC from baseline (Figure 3b).

Change in FEV_1 and FVC from steady state

The mean decline in trough FEV_1 from steady state was slower with tiotropium compared to placebo (Figure 4a). The treatment effect of tiotropium was similar compared to 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 FEV_1 for tiotropium compared to 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 significant differences were observed between tiotropium and either control group (Figure 4b).

Adverse events

Available data on adverse events are summarised in Table 2.

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

	Tiotropium compared to:				
	Placebo	**Ipratropium**	**Salmeterol**	**P-value for heterogeneity**	**Summary estimate**
Dry mouth					
Trials	4	1	2	P=0.24	7
Participants	2,835	535	1,460		4,830
Odds Ratio	4.6	2.1	4.7		3.9
(95% CI)	(3.0-7.1)	(1.05-4.2)	(2.4-9.2)		(2.8-5.5)
Constipation					
Trials	2	1	0	P=0.41	3
Participants	1,931	535			2,466
Odds Ratio	2.2	0.5			1.7
(95% CI)	(0.95-4.8)	(0.1-3.6)			(0.8-3.7)
Urinary retention					
Trials	3	0	1	P=0.85	4
Participants	2,733		807		3,540
Odds Ratio	2.5		3.0		2.6
(95% CI)	(0.5-14)		(0.1-75)		(0.6-12)
Urinary tract infection					
Trials	3	1	0	P=0.91	4
Participants	2,733	535			3,268
Odds Ratio	1.6	1.8			1.6
(95% CI)	(0.97-2.6)	(0.6-5.5)			(1.03-2.6)
Chest pain					
Trials	3	1	1	P=0.09	--
Participants	2,733	535	807		
Odds Ratio	0.9	2.5	1.2		
(95% CI)	(0.4-2.0)	(0.8-7.4)	(0.6-2.4)		
Myocardial infarction					
Trials	3	1	0	P=0.77	4
Participants	2,733	535			3,268
Odds Ratio	1.0	1.5			1.1
(95% CI)	(0.2-3.9)	(0.2-15)			(0.3-3.6)
Arrhythmia or atrial fibrillation					
Trials	4	1	0	P=0.05	--
Participants	4,561	535			
Odds Ratio	1.4	0.8			
(95% CI)	(0.4-5.7)	(0.3-1.8)			
Congestive heart failure					
Trials	3	1	0	P=0.86	4
Participants	2,837	535			3,372
Odds Ratio	0.8	0.5			0.8
(95% CI)	(0.4-1.6)	(0.1-8.1)			(0.4-1.5)

Dry mouth was significantly increased with tiotropium compared to placebo, ipratropium and salmeterol, and urinary tract infections were significantly increased compared to 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 to 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 compared to 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 FEV_1[20, 21] had a statistically similar estimate for exacerbations as the pooled estimate and as a trial in which 29% of patients were on oxygen [18] (Figure 1).

The effect of tiotropium on exacerbations in the one trial [18] 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 near-identical results. Funnel plots for the primary endpoints 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 demonstrated that tiotropium reduced COPD exacerbations and related hospitalisations compared to placebo or ipratropium. Increases in FEV_1 and FVC from baseline were significantly larger with tiotropium than with placebo, ipratropium and LABA. The decline in trough FEV_1 from steady state was slower with tiotropium compared to 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 to ipratropium in Europe.[22] The magnitude of the reduction in exacerbation-related hospitalisations with tiotropium was similar in comparison to 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 to placebo and ipratropium, the mean change in the SGRQ across all participants was close to the SGRQ's clinically significant change of 4 units, and 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 clinically significant compared to placebo and ipratropium at a threshold for FEV_1 of 100 mL [23] but not at a threshold of 225 mL.[24] Improvements in spirometric indices from baseline were statistically but not clinically significant compared to salmeterol.

The results of this systemic review are consistent with a prior review of therapies for COPD,[25] 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 FEV_1 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 COPD [26] and was consistent with a post-hoc analysis of one of the tiotropium trials.[27] However, this observation should be interpreted with caution considering that 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 one 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 to 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 to placebo and ipratropium. Heterogeneity would be introduced if ipratropium had an effect on the relevant outcomes, but ipratropium has been shown not to alter long-term decline in FEV_1,[13] hospitalisations or survival [12] compared to placebo. LABA, on the other hand, may reduce exacerbations compared to 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 endpoints 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 true 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 to 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 decline in FEV_1, although this finding requires confirmation in additional, long-term, randomised clinical trials.

ACKNOWLEDGEMENTS

We thank Maria Martinez-Torres for assistance with manuscript preparation and various individuals at Boehringer-Ingelheim who helped provide unpublished data to strengthen this systematic review. The assistance of Phillippa Poole (Cochrane Airways Review Group co-editor) was greatly appreciated.

COMPETING INTERESTS

Dr. Barr – none.

Dr Bourbeau has received honoraria for CME, membership on advisory boards and financial support from government agencies, contract and investigator-initiated research studies for a number of companies, including Altana, Astra Zeneca, Bayer, Boehringer-Ingelheim, GlaxoSmithKline, Novartis and Pfizer.

Dr Camargo has received investigator-initiated grants and consulting/lecture honoraria from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, and Novartis.

Dr. Ram – none.

FUNDING

Robert Wood Johnson Generalist Physician Faculty Scholar Award and National Institutes of Health (USA) HL075476, HL077612, HL063841.

LEGEND

Figure 1. Summary effects of tiotropium on COPD exacerbations (Panel A), hospitalisations (Panel B) and all-cause mortality (Panel C).

Figure 2. Summary effects of tiotropium on clinically significant changes in St. Georges Respiratory Questionnaire (Panel A) and Transitional Dyspnea Index (Panel B).

Figure 3. Summary effects of tiotropium on changes in trough FEV_1 (Panel A) and trough FVC (Panel B) from baseline prior to randomization until end of trials.

Figure 4. Summary effects of tiotropium on changes in trough FEV_1 (Panel A) and FVC (Panel B) from steady state 8 days after randomization until end of trials (one year).

REFERENCES

1. Murray, C.J.L. and A.D. Lopez, Alternative projections of mortality and disability by cause 1990-2020; Global Burden of Disease Study. Lancet 1997. **349**: p. 1498-504.
2. Haddad, E., J. Mak, and P. Barnes, Characterization of 3H Ba 679 BR, a slowly dissociation muscarinic antagonist, in human lung: radioligand binding and autoradiographic mapping. Mol Pharmacol 1994. **45**: p. 899-907.
3. Disse, B., et al., Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. Life Sci, 1999. **64**: p. 457-64.
4. Barnes, P.J., The pharmacological properties of tiotropium. Chest 2000. **117(2 Suppl)**: p. 63S-66S.
5. Barr, R.G., et al., Inhaled tiotropium for stable chronic obstructive pulmonary disease. The Cochrane Database of Systematic Reviews, 2005. **Issue 2**.
6. Report to the Food and Drug Administration, Pulmonary-Allergy Drugs Advisory Committee. NDA 21-395. Clinical briefing document. Integrated review of safety. 2002, Food and Drug Administration.
7. Celli, B.R. and W. MacNee, ATS/ERS Task force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J, 2004 **23**: p. 932-46.
8. Jones, P.W., et al., A self-complete measure of health status for chronic airflow limiation. The St. George's Respiratory Questionniare. Am Rev Resp Dis, 1990. **145**: p. 1321-27.
9. Mahler, D.A., et al., The measurement of dyspnea: contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984. **85** p. 751–58.
10. Jadad, A.R., et al., Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials, 1996. **17**(1): p. 1-12.
11. Cates, C., Visual Rx. www.nntonline.net 2006.
12. Anthonisen, N.R., et al., The Lung Health Study. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med, 2002. **166**: p. 333-39.
13. Anthonisen, N.R., et al., Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA., 1994. **272**(19): p. 1497-505.
14. Macaskill, P., S.D. Walter, and L. Irwig, A comparison of methods to detect publication bias in meta-analysis. Stat Med, 2001. **20**: p. 641-54.
15. Vincken, W., et al., Dutch/Belgium Tiotropium Study Group. Improved health outcomes in patients with COPD during one year's treatment with tiotropium. European Respiratory Journal, 2002. **19**: p. 209-16.
16. Briggs, D.D., Jr., et al., Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulmonary Pharmacology & Therapeutics, 2005. **18**(6): p. 397-404.
17. Brusasco, V., et al., Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003. **58**: p. 399-404.

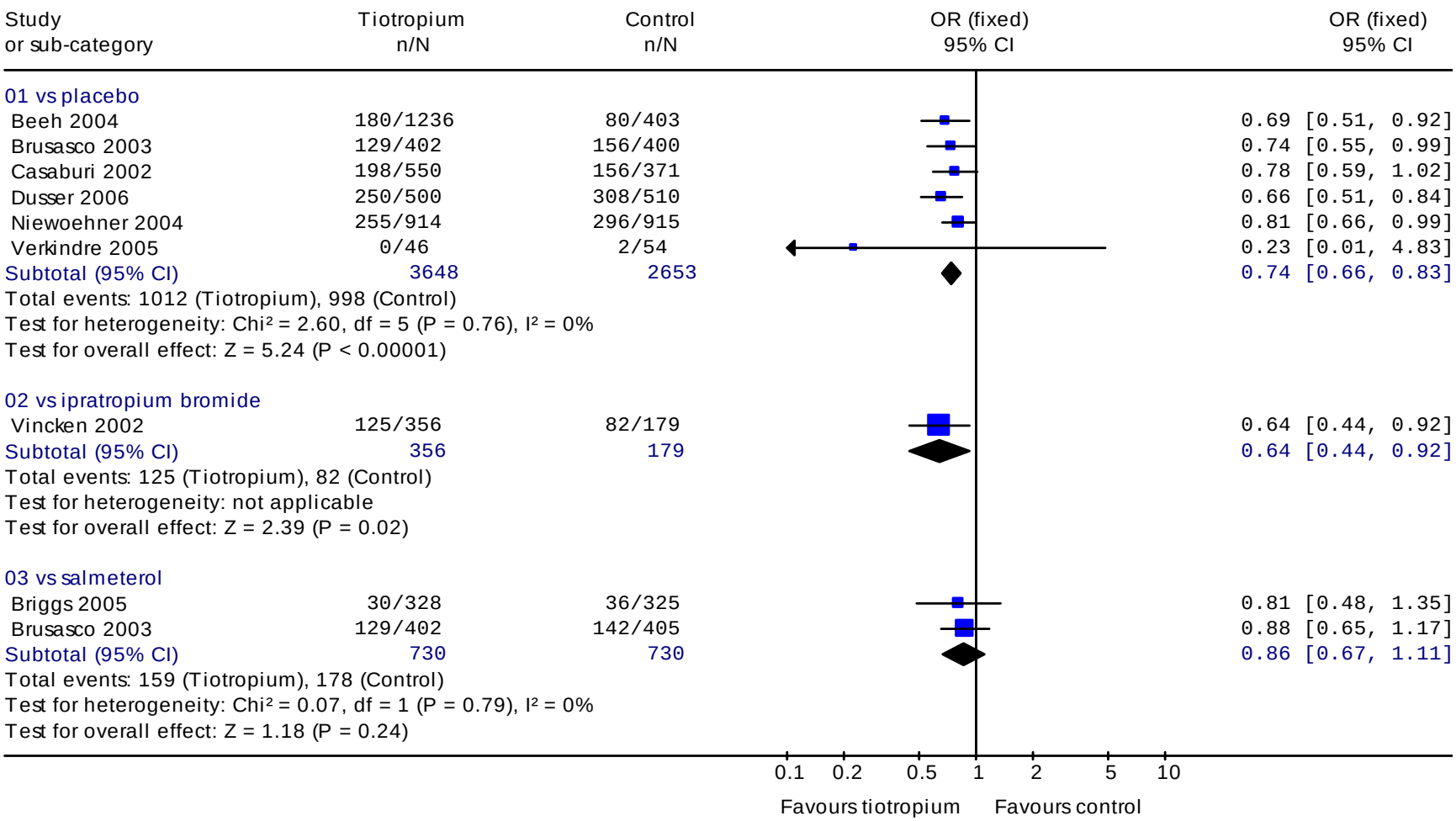
18. Niewoehner, D., et al., Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. A randomized trial. Ann Intern Med, 2005. **143**: p. 317-26.
19. Casaburi, R., et al., A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. European Respiratory Journal, 2002. **19**: p. 217-24.
20. Beeh, K.M., et al., Efficacy of tiotropium in patients with mild-to-moderate COPD (abstract). Amercian Journal of Respiratory and Critical Care Medicine, 2004. **169**: p. A519.
21. Dusser, D., M.-L. Bravo, and P. Iacono, on behalf of the MISTRAL study group. The effect of tiotropium on exacerbations and airflow in patients with COPD. Eur Respir J, 2006. **27**: p. 547-55.
22. Oostenbrink, J.B., et al., One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. European Respiratory Journal, 2004. **23**(2): p. 241-9.
23. Redelmeier, D.A., et al., Spirometry and dyspnea in patients with COPD. When small differences mean little. Chest, 1996. **109**: p. 1163-68.
24. Herpel, L.B., et al., Variability of spirometry in chronic obstructive pulmonary disease: results from two clinical trials. Am J Respir Crit Care Med, 2006. **173**: p. 1106-13.
25. Sin, D.D., et al., Contemporary Management of Chronic Obstructive Pulmonary Disease: Scientific Review. JAMA, 2003. **290**(17): p. 2301-2312.
26. Sutherland, E.R., et al., Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. Thorax 2003. **58**: p. 937-41.
27. Anzueto, A., et al., One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. Pulmonary Pharmacology & Therapeutics, 2005. **18**(2): p. 75-81.
28. Mahler, D.A., et al., Efficacy of salmeterol xinafoate in the treatment of COPD. Chest, 1999 **115**: p. 957-65.
29. Beeh, K.M., et al., Efficacy of tiotropium (Spiriva) in COPD of different severities [Wirksamkeit von Tiotropium (Spiriva) bei verschiedenen Schweregraden der COPD] (abstract). Pneumologie 2004. **58**: p. S43.
30. Donohue, J.F., et al., A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002. **122**: p. 47-55.
31. Casaburi, R., et al., Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest, 2005. **127**(3): p. 809-17.
32. Verkindre, C., et al., The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. Respiration, 2005. **482**: p. 1-8 (online ahead of print. DOI: 10.1159/000089655).
33. van Noord, J.A., et al., A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. The Dutch Tiotropium Study Group. Thorax 2000. **55** p. 289-94.

34. O'Connor, B.J., L.J. Towse, and P.J. Barnes, Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med, 1996. **154**: p. 876-80.
35. Terzano, C., et al., Early protective effects of tiotropium bromide in patients with airways hyperresponsiveness. European Review for Medical & Pharmacological Sciences, 2004. **8**(6): p. 259-64.
36. Maesen, F.P., et al., Ba 679 Br, a new long-acting antimuscarinic bronchodilator: a pilot dose-escalation study in COPD. Eur Respir J, 1993. **6**: p. 1031-36.
37. Maesen, F.P.V., et al., Tiotropium bromide, a new long-acting anti-muscarinic bronchodilator: a pharmacodynamic study in patients with chronic obstructive pulmonary disease(COPD). Dutch Study Group. Eur Respir J, 1995. **8**: p. 1506-13.
38. Littner, M.R., et al., Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2000. **161**: p. 1136-42.
39. van Noord, J.A., et al., Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease. Eur Respir J, 2002. **19**: p. 639-44.
40. Celli, B., et al., Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 2003. **124**: p. 1743-48.
41. Calverley, P.M., et al., Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax., 2003. **58**(10): p. 855-60.
42. Cazzola, M., et al., The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. Pulm Pharm Ther, 2004. **17**: p. 35-39.
43. Cazzola, M., et al., The functional impact of adding salmeterol and tiotropium in patients with stable COPD. Respiratory Medicine, 2004. **98**(12): p. 1214-21.
44. O'Donnell, D.E., et al., Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. European Respiratory Journal 2004. **23**: p. 832-40.
45. Hasani, A., et al., The effect of inhaled tiotropium bromide on lung mucociliary clearance in patients with COPD. Chest, 2004. **125**(5): p. 1726-34.
46. McNicholas, W.T., et al., Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. European Respiratory Journal, 2004. **23**(6): p. 825-31.
47. Cazzola, M., et al., Bronchodilator response to formoterol after regular tiotropium or to tiotropium after regular formoterol in COPD patients. Respiratory Medicine, 2005. **99**(5): p. 524-8.
48. Baloira Villar, A. and C. Vilarino Pombo, [Bronchodilator efficacy of combined salmeterol and tiotropium in patients with chronic obstructive pulmonary disease]. Archivos de Bronconeumologia, 2005. **41**(3): p. 130-4.
49. Maltais, F., et al., Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest, 2005. **128**(3): p. 1168-78.
50. Kim, S.J., et al., A comparison of tiotropium 18ug, once daily and ipratropium 40 ug, 4 times daily, in a double-blind, double-dummy, efficacy and safety study in

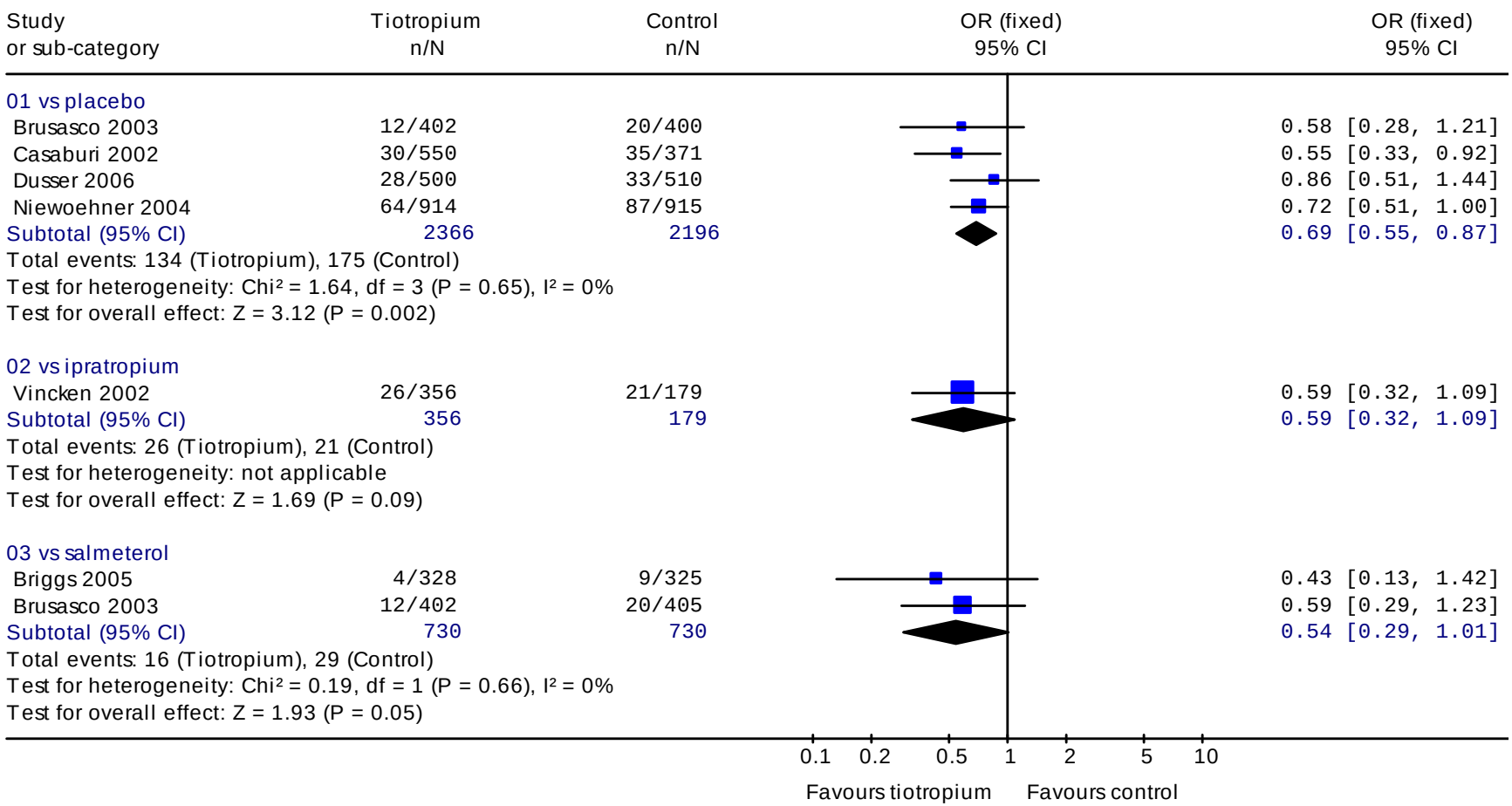
adults with chronic obstructive pulmonary disease [Korean]. Korean Tubercul Respir Dis, 2005. **58**: p. 498-506.
51. van Noord, J.A., et al., Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J, 2005. **26**: p. 214-22.
52. Casaburi, R., et al., The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. Chest, 2000. **118**: p. 1294-302.
53. Donohue, J.F., S. Menjoge, and S. Kesten, Tolerance to bronchodilating effects of salmeterol in COPD. Respiratory Medicine, 2003. **97**: p. 1014-20.
54. Tashkin, D. and S. Kesten, Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. Chest 2003. **123**: p. 1441-49.

Figure 1.

Panel A. COPD exacerbations



Panel B. Exacerbation-related hospitalisations



Panel C. All-cause mortality

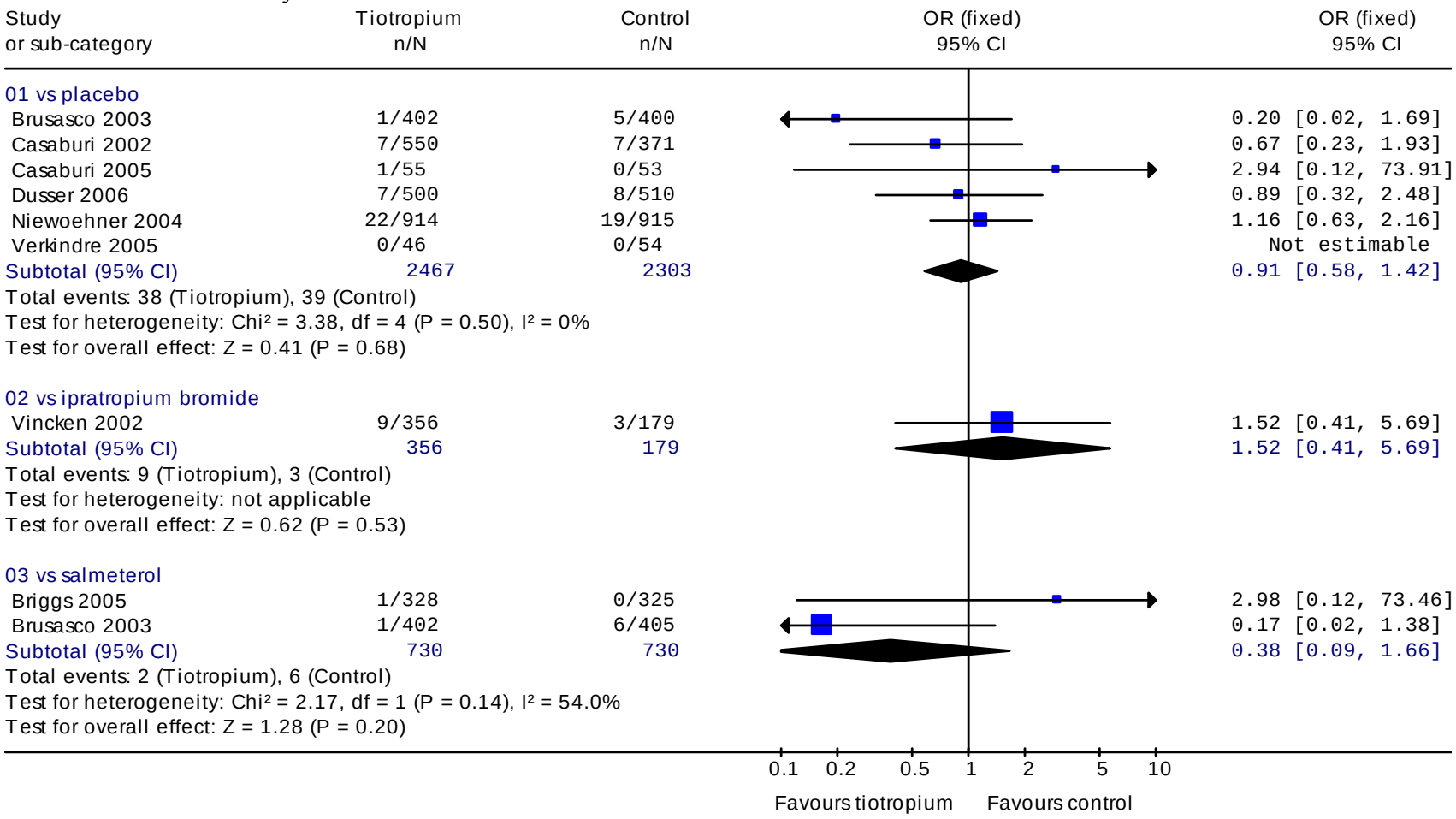
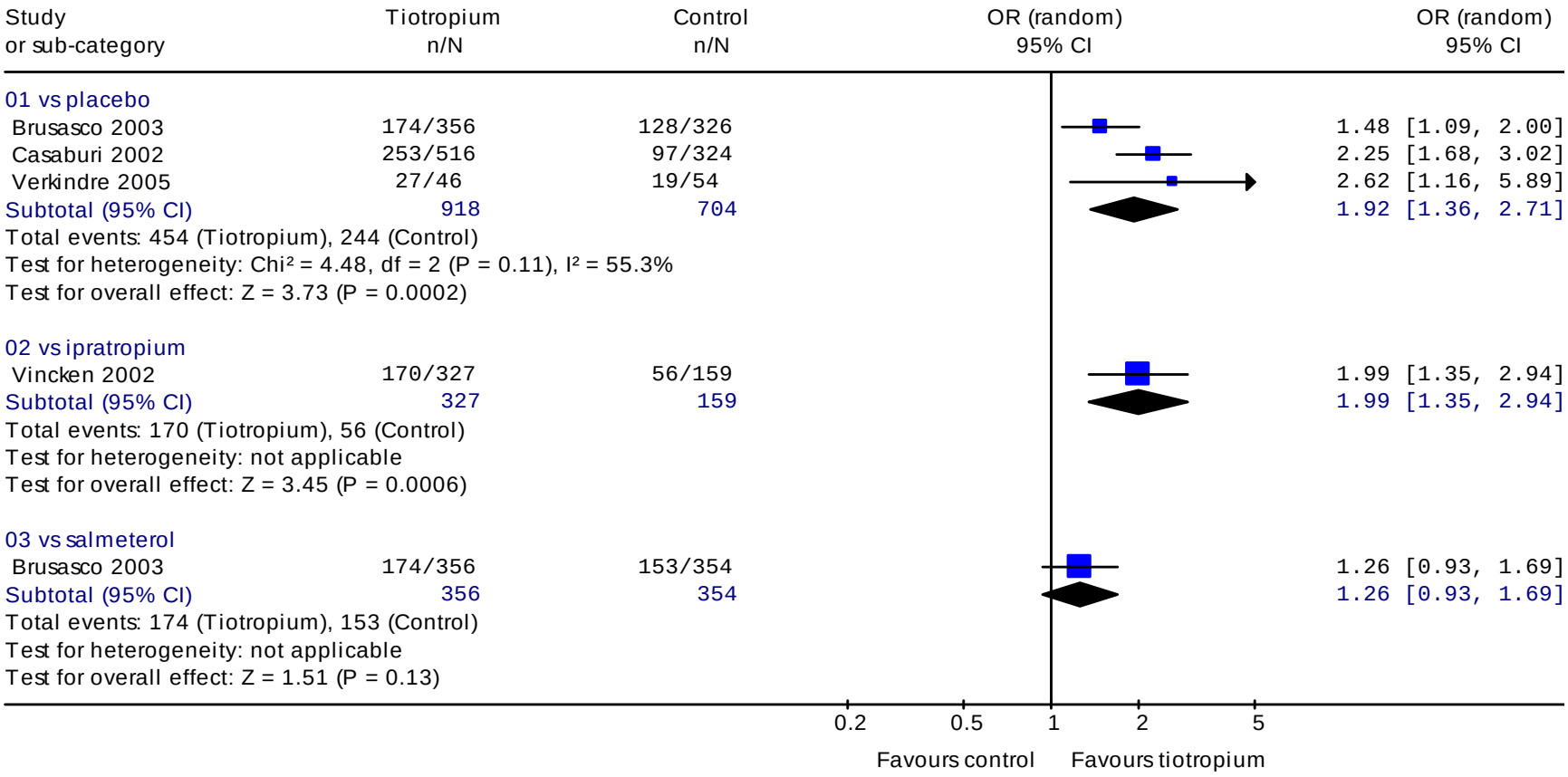


Figure 2.

Panel A. Clinically significant change in St. Georges Respiratory Questionnaire



Panel B. Clinically significant change in Transitional Dyspnea Index.

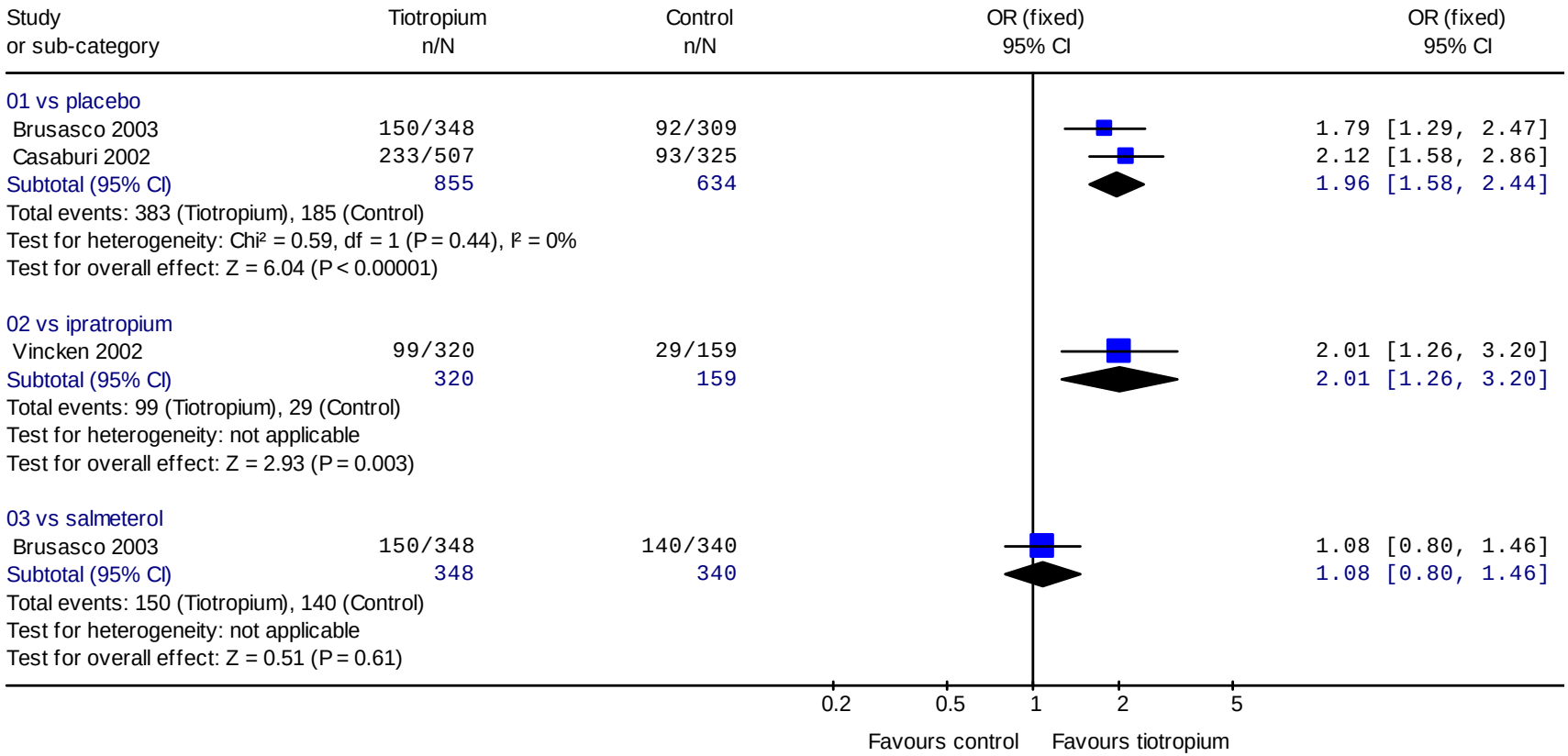
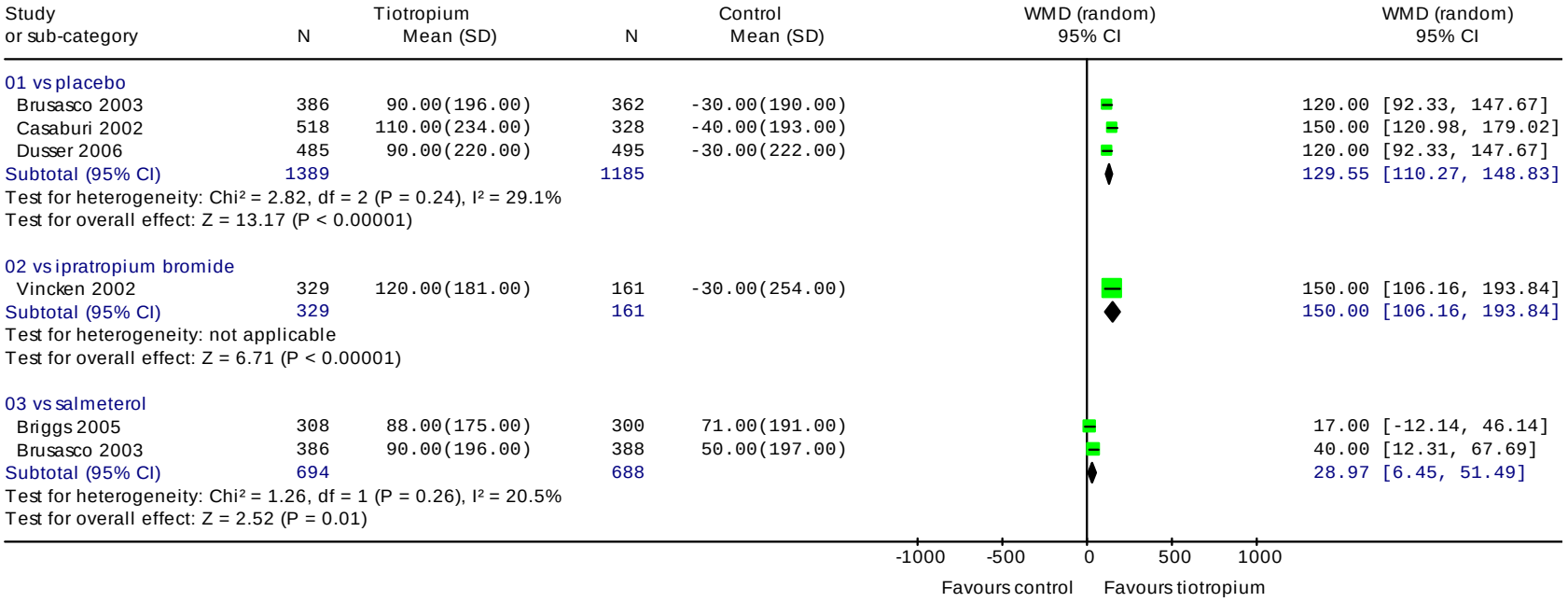


Figure 3.

Panel A. Change in trough FEV_1 from baseline prior to randomization until end of trials.



Panel B. Change in trough FVC from baseline prior to randomization until end of trials

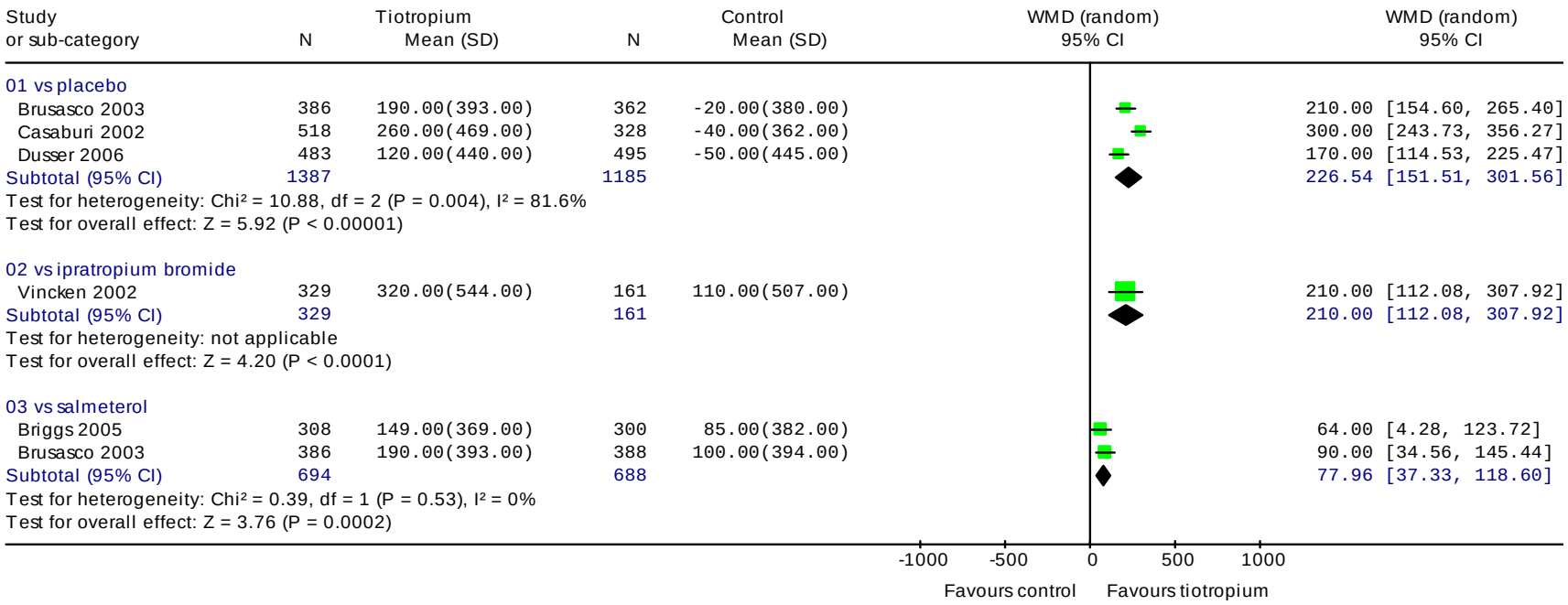
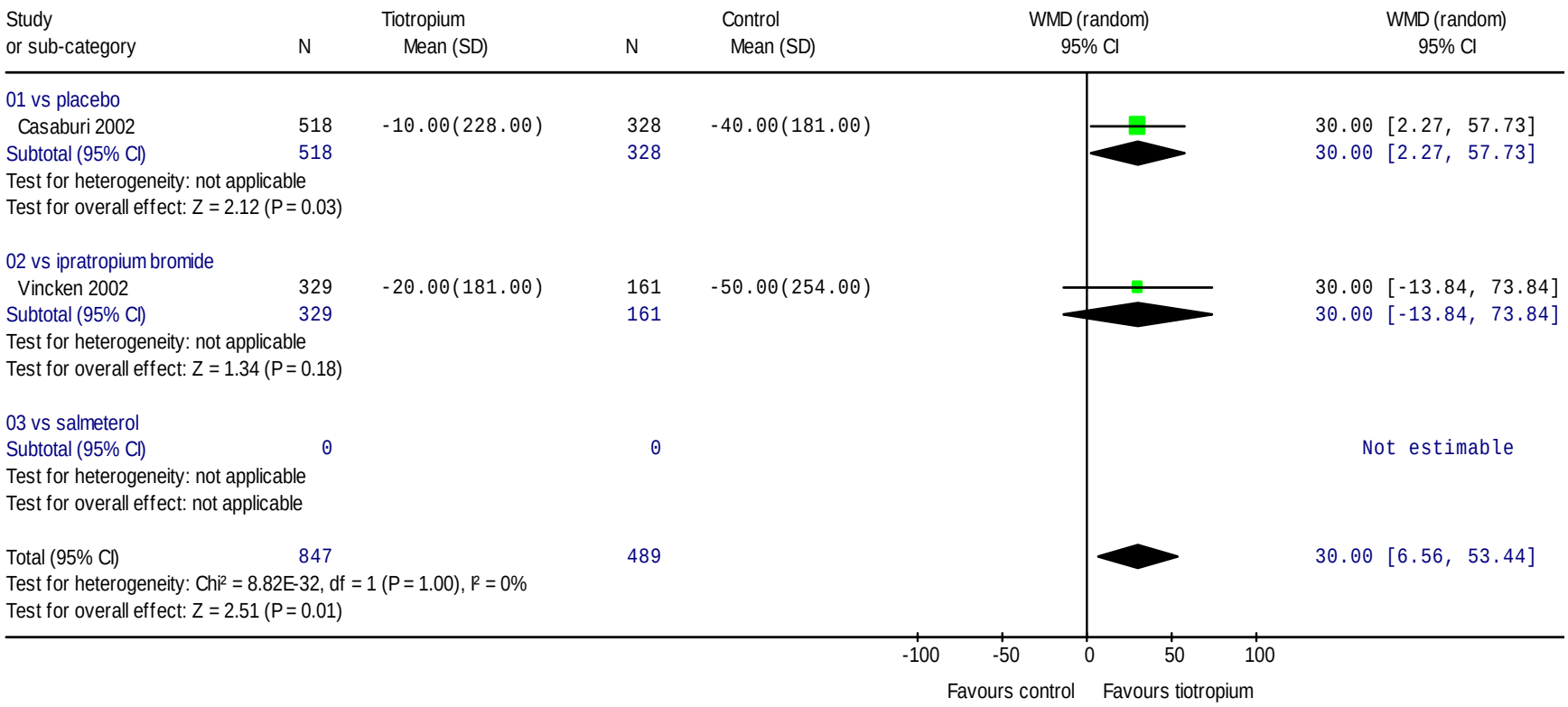
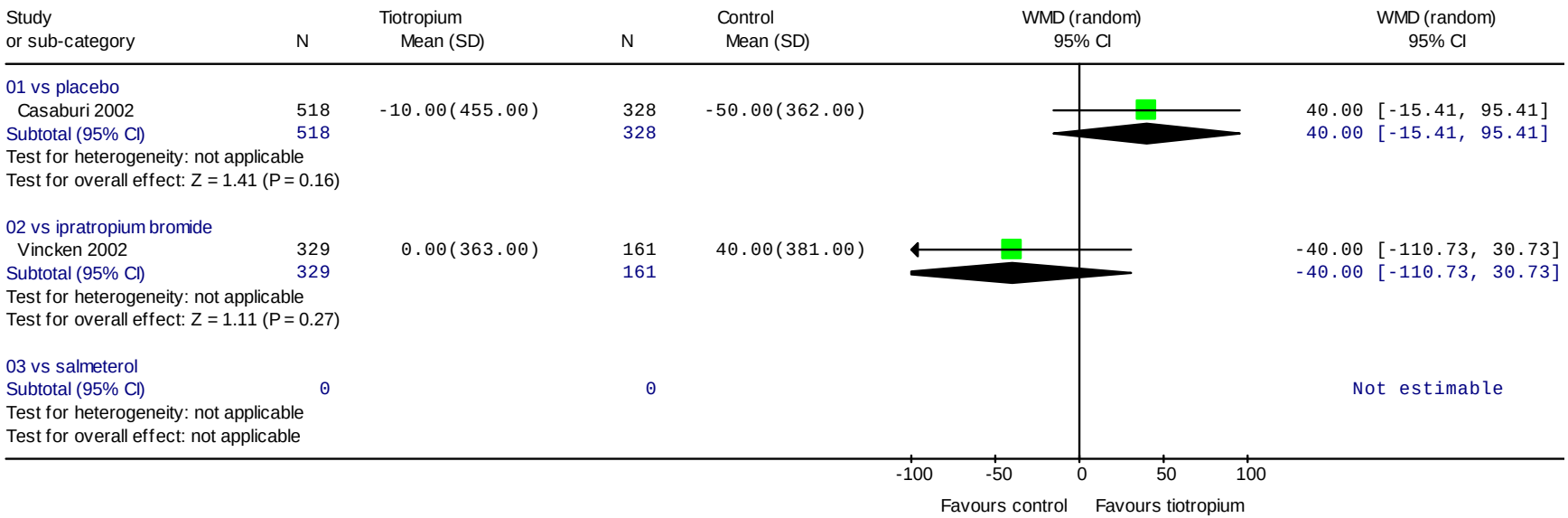


Figure 4.

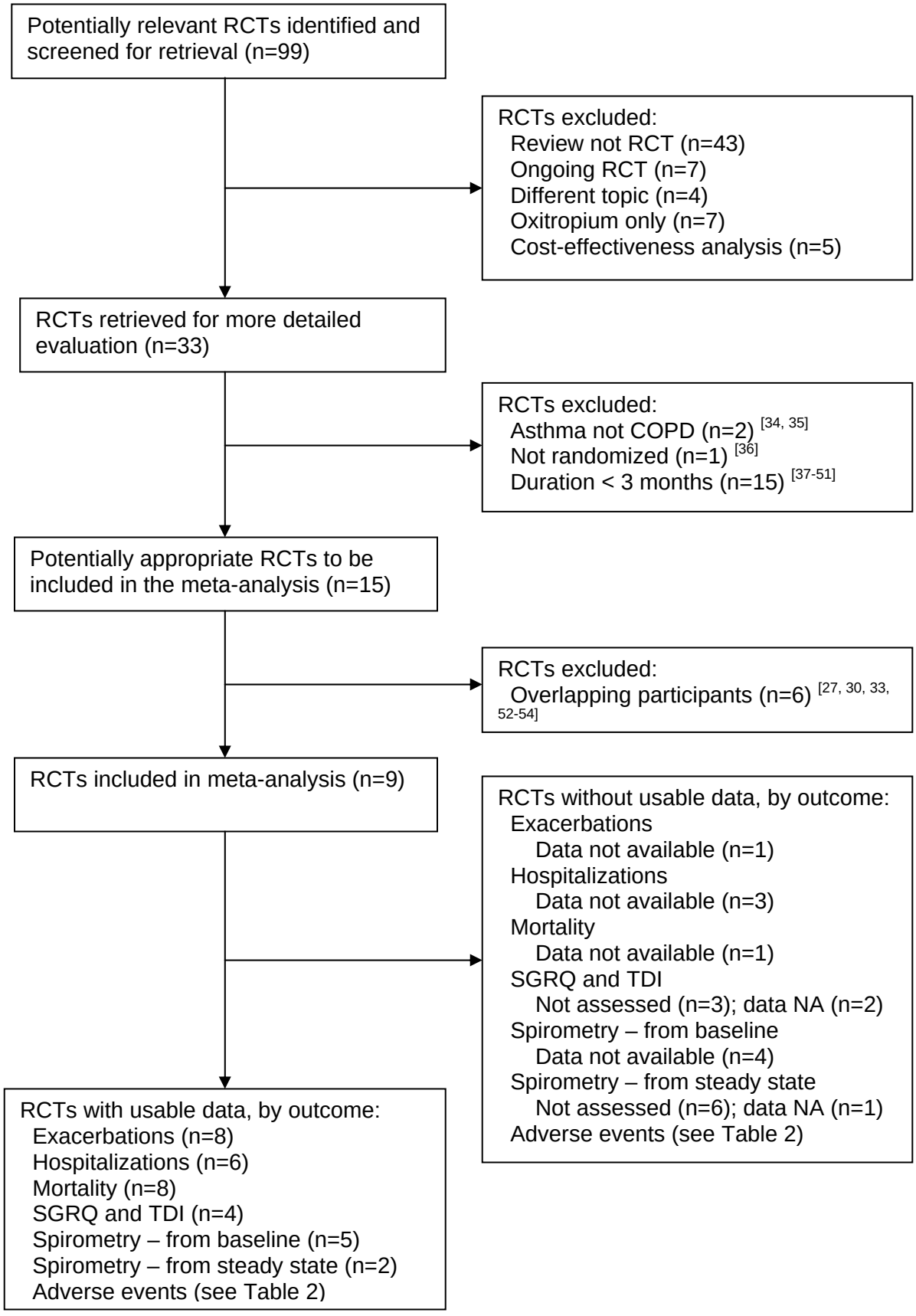
Panel A. Change in trough FEV_1 from steady state 8 days after randomization until one year.



Panel B. Change in trough FVC from steady state 8 days after randomization until one year.

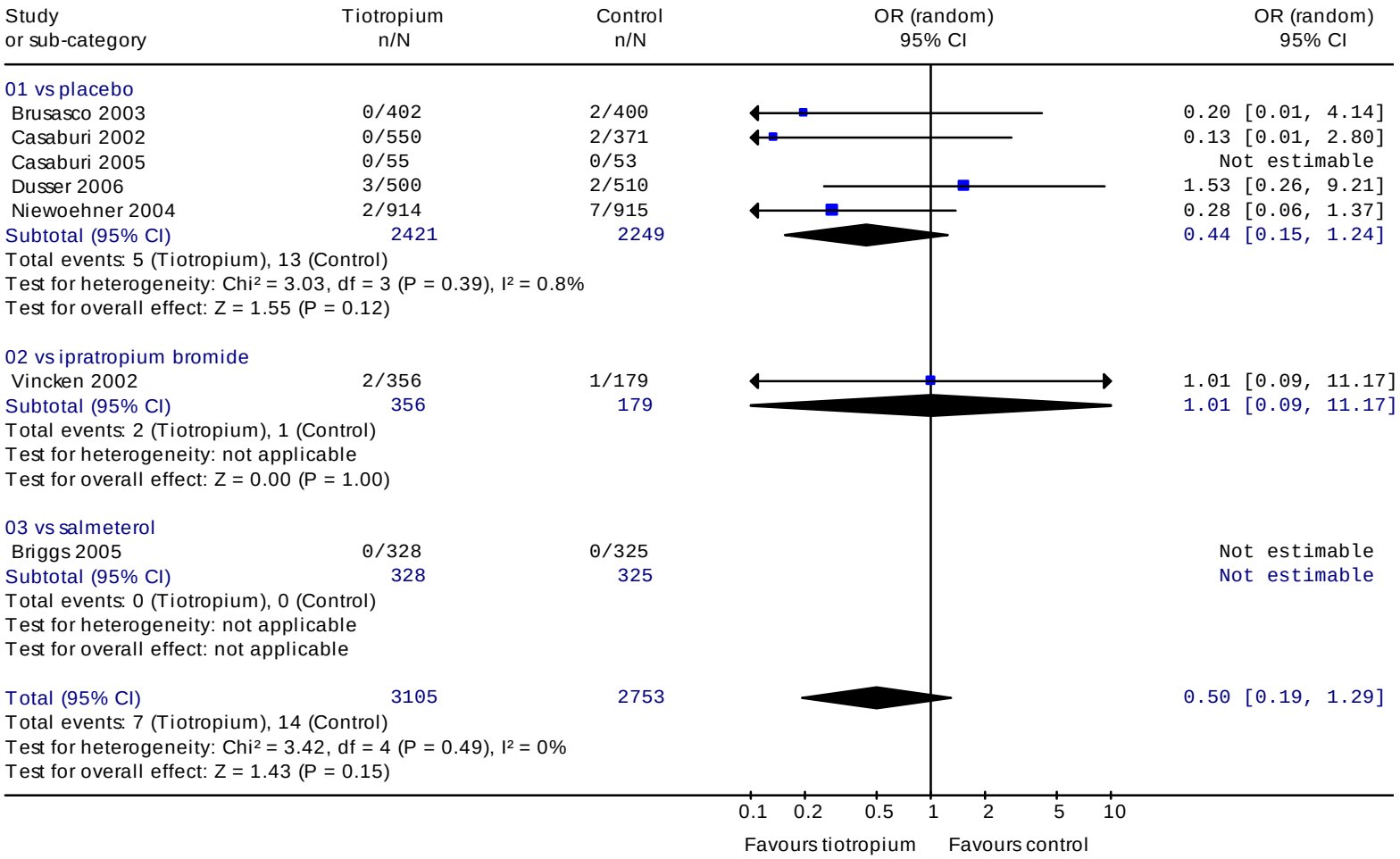


APPENDIX 1 -- QUOROM Flow Diagram

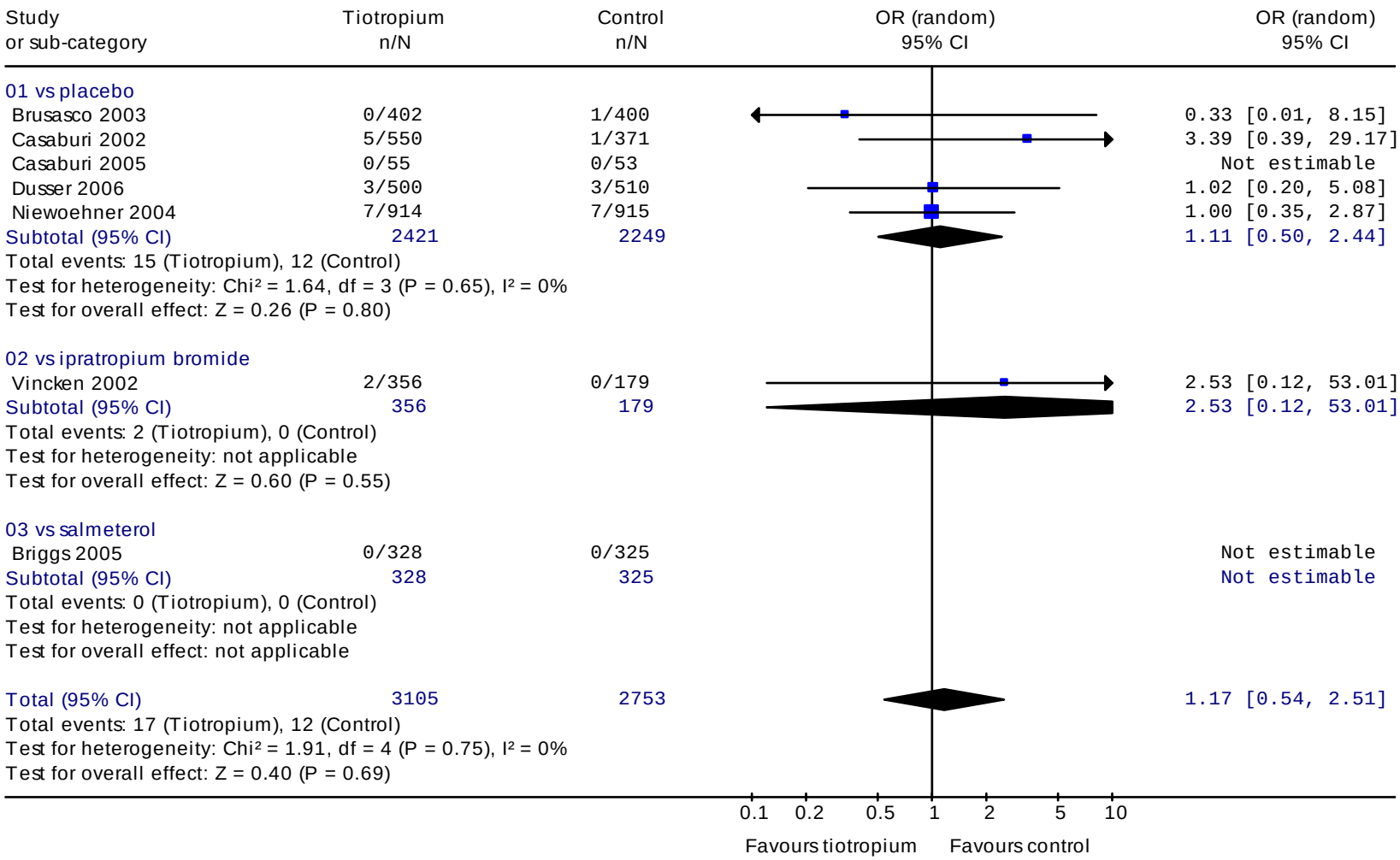


APPENDIX 2

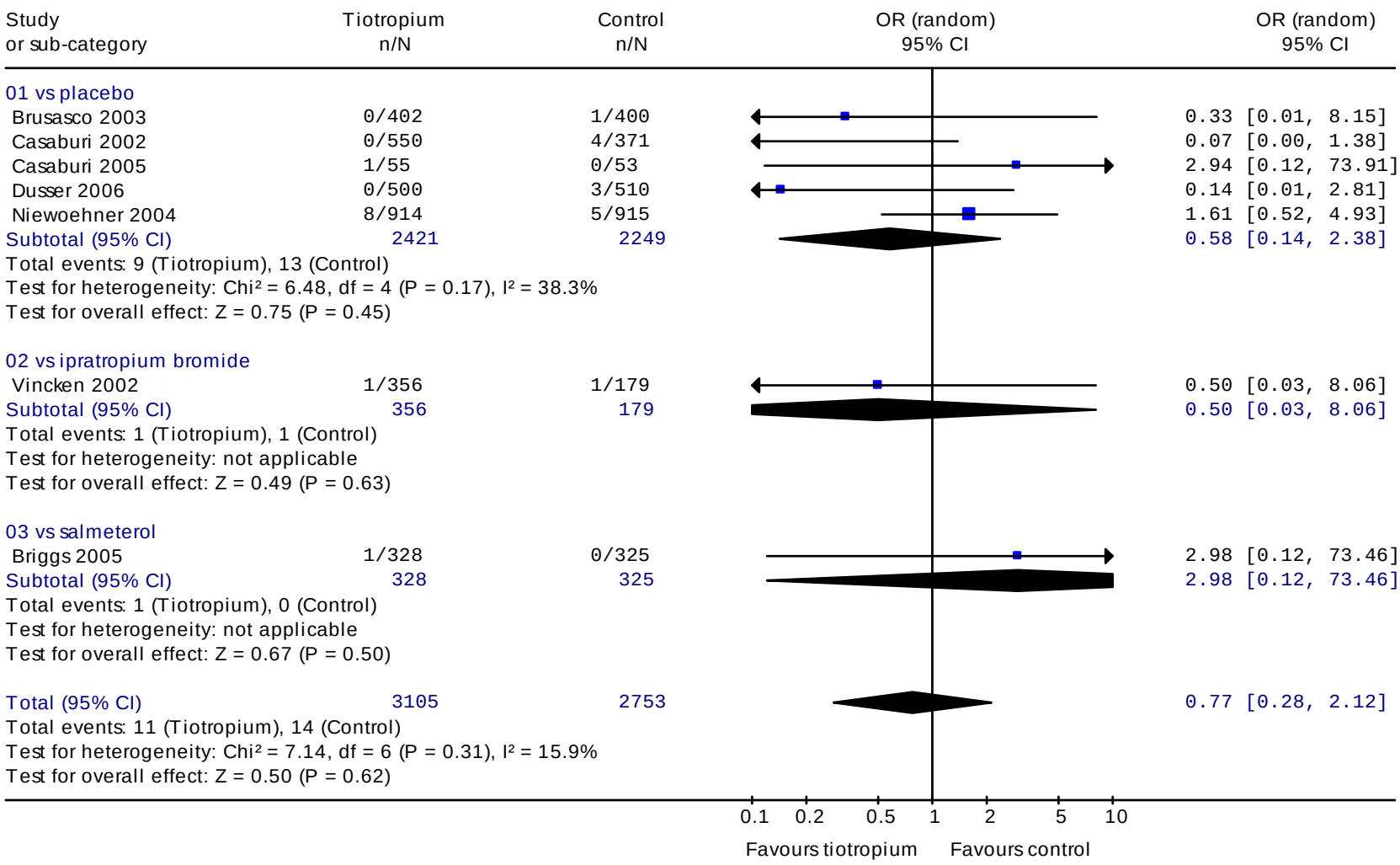
Panel A. Mortality from Pulmonary Causes



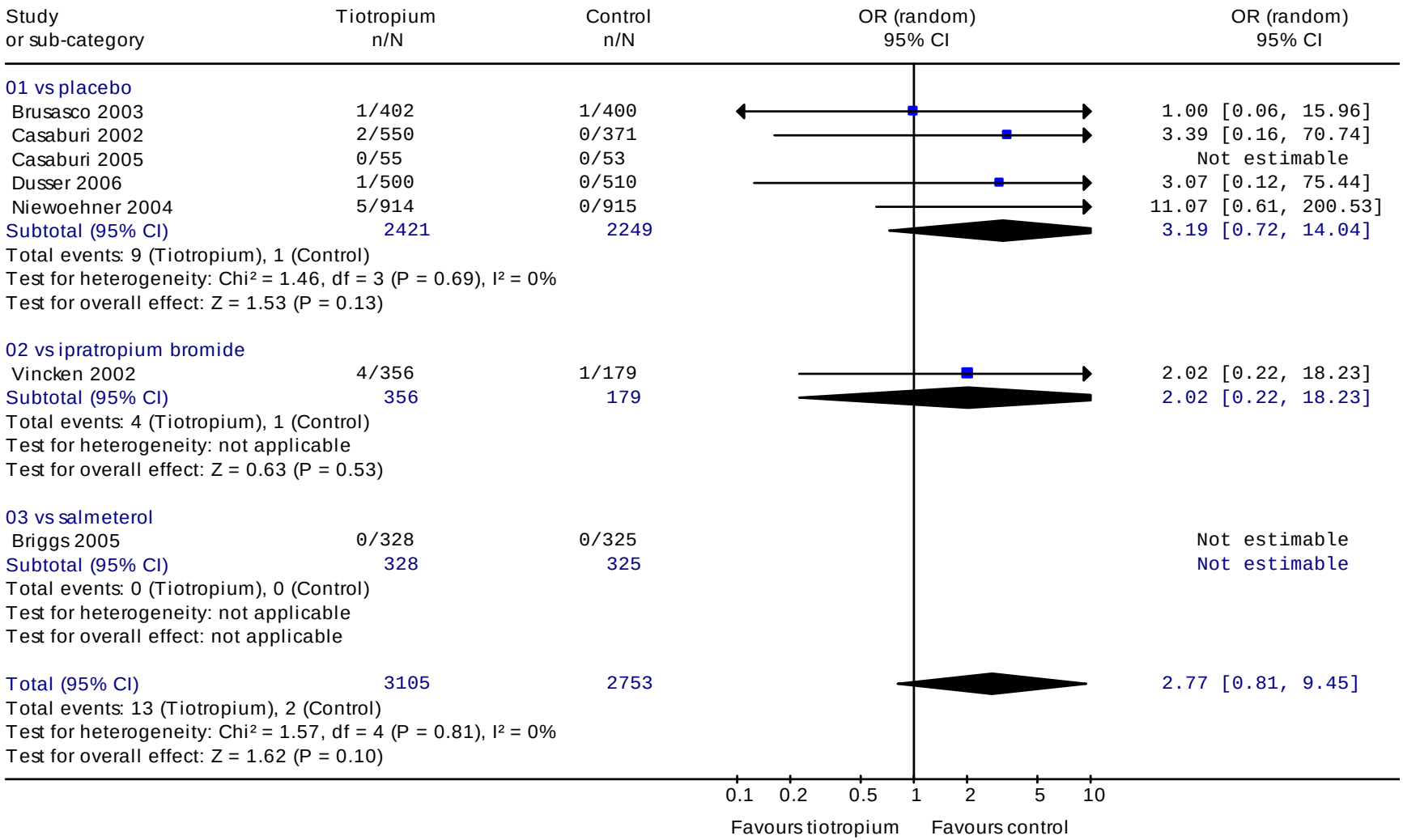
Panel B. Mortality from Cardiovascular Causes



Panel C. Mortality from Cancer Causes



Panel D. Mortality from Other Causes



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 $\leqslant 2$ 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-analyses[4] 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.

Gavin M Wright

Correspondence to: G M Wright, St Vincent's Hospital, 55 Victoria Parade Fitzroy, Melbourne 3065, Victoria, Australia; gavin.wright@svhm.org.au

Competing interests: None declared.

References

1 **Wright G**, Manser RL, Byrnes G, *et al.* Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. *Thorax* 2006;**61**:597–603.
2 **Holty J-EC**, Gould MK. When in doubt should we cut it out? The role of surgery in non-small cell lung cancer. *Thorax* 2006;**61**:554–6.
3 **Feinstein AR**, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985;**312**:1604–8.
4 **Pignon JP**, Tirbodet H, Scagliotti GV, *et al.* Lung Adjuvant Cisplatin Evaluation: a pooled analysis of five randomised clinical trials including 4,584 patients. *Proc Am Soc Clin Oncol* 2006;**24**(Part 1):No 188, 7008.
5 **Allen MS**, Darling GE, Pechet TT, *et al.* Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;**81**:1013–19.

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]

J-E C Holty
Center for Primary Care and Outcomes Research, Stanford, University, Stanford, California, USA

M K Gould
VA Palo Alto Health Care System, Palo Alto, California, USA; Stanford University Medical Center, Palo Alto, California, USA; Center for Primary Care and Outcomes Research, Stanford University, Stanford, California, USA

Correspondence to: Dr J-E C Holty, Division of Pulmonary and Critical Care Medicine, University School of Medicine, 300 Pasteur Drive, H3143, Stanford, CA 94305-5236, USA; jholty@stanford.edu

Competing interests: None declared.

References

1 **Wu YL**, Huang ZF, Wang SY, *et al.* A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002;**36**:1–6.
2 **Izbicki J**, Passlick B, Pantel K, *et al.* Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Ann Surg* 1998;**227**:138–44.
3 **Barnard J**, Dunning J, Musleh G, *et al.* Is there a role for the use of radical lymph node dissection in the surgical management of resectable non-small cell lung cancer? *Interact Cardiovasc Thorac Surg* 2004;**3**:294–9.
4 **Sugi K**, Nawata K, Fujita N, *et al.* Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. *World J Surg* 1998;**22**:290–5.
5 **Allen MS**, Darling GE, Pechet TTV, *et al.* Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;**81**:1013–20.

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.