

## ORIGINAL ARTICLE

# Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials

Yaa-Hui Dong,<sup>1</sup> Hsien-Ho Lin,<sup>1</sup> Wen-Yi Shau,<sup>2</sup> Yun-Chun Wu,<sup>1</sup> Chia-Hsui Chang,<sup>1,3</sup> Mei-Shu Lai<sup>1</sup>

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<sup>1</sup>Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

<sup>2</sup>Division of Health Technology Assessment, Center for Drug Evaluation, Taipei, Taiwan

<sup>3</sup>Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

## Correspondence to

Dr Mei-Shu Lai, Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17, Xuzhou Road, Taipei City 10055, Taiwan; [mslai@ntu.edu.tw](mailto:mslai@ntu.edu.tw)

Dr Chia-Hsui Chang, Department of Internal Medicine, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, 10002, Taiwan; [chiahsui123@yahoo.com.tw](mailto:chiahsui123@yahoo.com.tw)

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## ABSTRACT

**Background** The active-treatment comparative safety information for all inhaled medications in patients with chronic obstructive pulmonary disease (COPD) is limited. We aimed to compare the risk of overall and cardiovascular death for inhaled medications in patients with COPD.

**Methods** Through systematic database searching, we identified randomised controlled trials of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, long-acting  $\beta_2$  agonists (LABAs), inhaled corticosteroids (ICS), and LABA-ICS combination with at least a 6-month treatment duration. Direct comparison and mixed treatment comparison (MTC) meta-analyses were conducted to estimate the pooled ORs of death for each comparison.

**Results** 42 trials with 52 516 subjects were included. The MTC meta-analysis with the fixed effect model indicated tiotropium Soft Mist Inhaler was associated with an universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at a higher daily dose. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium HandiHaler or LABA. The results were similar for MTC and direct comparison meta-analyses, with less precision in the random effects model.

**Conclusion** Our study provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution.

## Key messages

### What is the key question?

- What is the difference in mortality for inhaled medications in patients with chronic obstructive pulmonary disease (COPD)?

### What is the bottom line?

- Our mixed treatment comparison meta-analysis indicated that tiotropium Soft Mist Inhaler had a significant risk of overall death compared with placebo and other inhaled medications. The risk was more evident for cardiovascular death, in patients with severe COPD and at a higher daily dose. In contrast, a long-acting  $\beta_2$  agonist (LABA)-inhaled corticosteroid (ICS) combination, tiotropium HandiHaler and LABAs had relatively safer profiles, and LABA-ICS seemed to have the lowest risk of overall death in patients with COPD.

### Why read on?

- In view of the safety spectrum for each inhaled medication, our results provided substantial implications for healthcare professionals. The findings remind physicians that they should take patients' conditions into account, prescribe tiotropium Soft Mist Inhaler with more caution and consider alternative treatments in high risk populations.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a substantial disease burden worldwide.<sup>1 2</sup> The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend inhaled long-acting anticholinergics and  $\beta_2$  agonists (LABAs) for maintenance therapy of COPD.<sup>2</sup> Add-on treatment with inhaled corticosteroids (ICS) is indicated for patients with repeated exacerbations.<sup>2</sup> However, an association of inhaled medications with cardiovascular complications has been noted, which is possibly related to their pharmacological effects.<sup>3 4</sup> Moreover, patients with COPD are susceptible to

overall and cardiovascular death.<sup>5 6</sup> Accordingly, it is important to examine the safety profiles of both outcomes for these medications.

Tiotropium, the only marketed long-acting anticholinergic, is approved as dry powder delivered via a HandiHaler device and solution delivered via a Respimat Soft Mist Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany). Based on the results of a large placebo-controlled trial,<sup>W1</sup> (please note, references with the prefix 'w' are listed in the online appendix), the US Food and Drug Administration (FDA) suggested that tiotropium HandiHaler has no excess risk of overall death and cardiovascular events.<sup>7–9</sup> However, a non-significant increased risk of overall death for



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tiotropium Soft Mist Inhaler was noted in placebo-controlled trials,<sup>10 W2 W3</sup> and a nearly 50% increased risk of overall death compared with placebo was reported in a meta-analysis.<sup>11</sup> For LABAs, the US FDA has continually highlighted the increased risk of death in patients with asthma.<sup>12 13</sup> However, safety concerns about LABAs remain inconclusive in patients with COPD in several trials and meta-analyses.<sup>14 15 W4–W7</sup> For LABA-ICS, a marginally non-significant benefit for overall survival was found in a placebo-controlled trial<sup>W8</sup> and a significantly decreased risk of death was observed in several meta-analyses.<sup>14 16</sup>

In view of the current evidence, it is necessary to address some limitations. First, none of the published trials simultaneously compared safety across various inhaled medications. Second, given the limited sample size, the risks of death for inhaled medications are generally undetermined by individual trials. Third, although traditional meta-analyses provide pooled risk estimates with better precision, the estimates are obtained only from direct comparison trials. Consequently, the information on comprehensive comparisons among different inhaled medications is insufficient.

The mixed treatment comparison (MTC) meta-analysis has a unique strength to integrate data from direct and indirect comparisons and facilitate multiple head-to-head comparisons across various treatments.<sup>17</sup> To comprehensively compare the risk of mortality for inhaled medications in patients with COPD, we conducted both direct comparison and MTC meta-analyses of randomised controlled trials.

## METHODS

### Data sources and searches

We searched MEDLINE, CINAHL, Cochrane Library and ClinicalTrials.gov from inception to July 2011 (see the online appendix for the detailed search strategy). We examined the bibliographies of eligible trials and systematic review articles for relevant trials. To identify unpublished trials, we searched the manufacturers' clinical trials registers.<sup>18–20</sup> If the outcomes of interest were not available from original articles or the above clinical trials registers, we contacted the authors or searched the US FDA website for additional information.

### Study selection

The inclusion criteria were randomised, double-blind, active or placebo-controlled trials; patients with COPD of any severity; patients receiving predefined treatments, including tiotropium Soft Mist Inhaler, tiotropium HandiHaler, LABA, LABA-ICS and ICS; trials providing data about overall or cardiovascular death; and trials lasting for 6 months or more. We excluded trials if they included patients with asthma, involved non-predefined treatment arms, and were published only in protocols, in abstracts, or in non-English languages.

### Outcome measures

The primary outcome was overall death. The secondary outcome was cardiovascular death based on the preferred terms defined by the Medical Dictionary for Regulatory Activities (see the online appendix).<sup>21</sup>

### Data extraction and assessment of risk of bias

Two investigators (YHD (pharmacist) and CHC (physician)) independently evaluated each identified reference and retrieved relevant characteristics from eligible trials. To assess the risk of bias of individual trials, we applied Cochrane's risk of bias tool. We also recorded how adverse events were monitored.<sup>22</sup> Any

disagreement was resolved by discussion and consensus (see the online appendix).

### Statistical analysis

We used the intention-to-treat analysis. A two-sided  $\alpha$  value of 0.05 was defined for statistical significance. The Peto method was applied for the direct comparison meta-analysis of rare events.<sup>23</sup> The Mantel-Haenszel method with the fixed effect model and different continuity correction factors was performed for the sensitivity analysis.<sup>24</sup> For each pairwise comparison, we estimated the risks of overall and cardiovascular death with the pooled OR and 95% CI. Statistical heterogeneity was evaluated by the  $I^2$  statistic, with a value of 50% or more illustrating a substantial level of heterogeneity. Publication bias was assessed by the funnel plot, the Begg's test and the Egger's test (see the online appendix).<sup>22</sup>

The Bayesian Markov chain Monte Carlo methods with fixed and random effects models were used for the MTC meta-analysis (see the online appendix).<sup>17</sup> Results were presented as the OR and 95% credible interval (CrI). For each treatment, we also estimated the probability of overall and cardiovascular death and the probability of being ranked as the riskiest intervention.

We performed subgroup analyses to address the risks of inhaled medications in trials with longer treatment durations (study duration  $\geq 1$  year) and trials enrolling patients with severe COPD (forced expiratory volume in 1 s (FEV<sub>1</sub>)  $< 50\%$  of predicted value).<sup>2</sup> A potential dose-response relation of tiotropium Soft Mist Inhaler was examined by stratification analyses by individually comparing 5  $\mu\text{g}/\text{day}$  and 10  $\mu\text{g}/\text{day}$  of tiotropium Soft Mist Inhaler with other treatments.

To address the possible trial heterogeneities and misclassification of cardiovascular death, we performed additional analyses. Meta-regression was conducted to adjust for related demographic characteristics (see the online appendix). Sensitivity analyses were performed by excluding trials with the ICS withdrawal design and by restricting the analyses to trials with objective adjudication of cause of death.<sup>25</sup>

STATA V9.0 (StataCorp) and WinBUGS V1.4.3 (MRC Biostatistics Unit, Cambridge, UK) was used for direct comparison and MTC meta-analyses, respectively. The WinBUGS code is shown in the online appendix. The predefined protocol is available from the authors on request.

## RESULTS

### Eligible trials

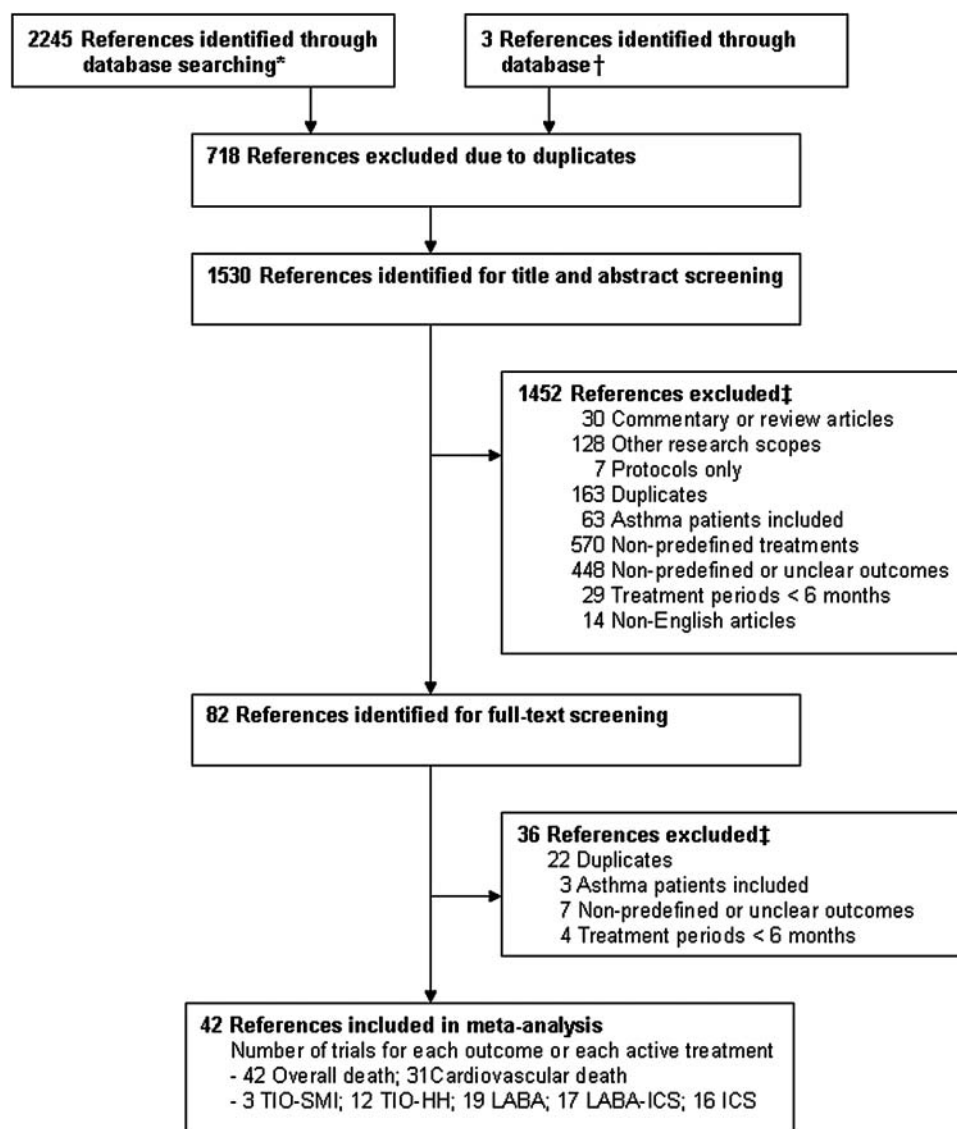
A total of 42 eligible trials reporting on overall death<sup>W1–W44</sup> and 31 trials reporting on cardiovascular death<sup>W1–W3 W5 W6 W8–W12 W15 W17–W23 W25 W27–W44</sup> were included in the meta-analysis (online appendix and figure 1).

These 42 trials enrolled 52 516 subjects, with similar characteristics across trials with different treatments (64 years of age, 73% men, 37% current smokers, 1 year study duration, and 44% of predicted value in FEV<sub>1</sub>). However, more subjects combined LABA or ICS use at baseline in tiotropium Soft Mist Inhaler and HandiHaler trials (table 1 and online tables S1 and S2).

### Assessment of risk of bias of included studies

All 42 trials were randomised, double-blind, with 24 trials addressing adequate randomisation procedures. Forty-one trials stated the withdrawal rate, which varied across trials and treatment groups (with the lowest value of 17% in the tiotropium Soft Mist Inhaler group and the highest values of 33% in the ICS and placebo groups). Twenty-eight trials described the

**Figure 1** Flow diagram of the search process. \*The number of references identified through each database was 731 (MEDLINE), 9 (CINAHL), 1464 (Cochrane) and 40 (ClinicalTrials.gov). †References were identified through bibliographies of eligible trials and systematic review articles and the clinical study registers of pharmaceutical companies. ‡References were usually excluded for more than one reason. ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium solution delivered via Resipmat Soft Mist Inhaler.



**Table 1** Summary of trial characteristics and patient characteristics at baseline. Figures are means (ranges)

	Age (years)	Men (%)	Current smokers (%)	Study duration (years)	FEV <sub>1</sub> (% of predicted value)	Subjects with concomitant use of LABA (%)	Subjects with concomitant use of ICS (%)	Withdrawal rate (%)	Lost to follow-up (%)
Total (N=42)	64.0 (52.4–67.9)	73.2 (4.5–98.5)	37.1 (21.7–100)	1.2 (0.5–4)	44.4 (34.4–86.6)	33.3 (3.0–60.1)	47.3 (14.0–83.2)	27.9 (0.8–59.0)	1.5 (0.0–8.6)
Stratified by treatment*									
TIO-SMI (n=3)	64.9 (64.8–65.0)	76.4 (74.2–77.5)	36.0 (35.8–36.3)	1 (–)	45.5 (45.3–46.0)	41.5 (29.7–53.4)	54.9 (53.7–56.1)	17.1 (16.0–20.4)	1.3 (1.1–1.7)
TIO-HH (n=12)	64.4 (62.9–67.9)	77.0 (56.5–98.5)	33.2 (24.1–58.4)	1.2 (0.5–4)	45.3 (34.4–50.0)	42.5 (17.5–53.8)	59.1 (42.4–75.3)	24.3 (14.7–42.0)	1.1 (0.2–2.1)
LABA (n=19)	63.7 (60.0–65.7)	72.0 (54.0–80.6)	39.3 (34.5–55.0)	1 (0.5–3)	43.9 (36.0–53.8)	27.0 (3.0–54.5)	37.3 (14.0–57.0)	25.2 (10.0–43.5)	1.1 (0.4–3.0)
LABA-ICS (n=17)	64.3 (63.2–66.2)	72.2 (54.0–89.2)	36.5 (21.7–50.8)	1.2 (0.5–3)	40.5 (36.0–47.8)	26.8 (3.0–54.5)	34.6 (14.0–54.3)	26.8 (12.2–39.0)	1.8 (0.0–2.5)
ICS (n=16)	63.3 (52.4–67.4)	69.5 (4.5–84.5)	45.8 (27.5–100)	1.5 (0.5–4)	44.0 (36.0–86.6)	29.1 (8.5–56.0)	44.0 (19.8–83.2)	33.5 (0.8–43.8)	2.0 (0.0–8.6)
PL (n=34)	64.1 (52.4–67.9)	73.2 (4.5–98.5)	34.9 (21.7–100)	1.2 (0.5–4)	44.1 (34.4–86.6)	34.2 (8.5–60.1)	52.3 (19.8–83.2)	33.3 (0.8–59.0)	2.0 (0.0–6.8)

\*N' and 'n' represent the number of trials included in the meta-analysis and with each treatment, respectively.

\*The variables of age, proportion of men, percentage of current smokers, study duration, FEV<sub>1</sub>% of predicted value, and percentage of subjects with concomitant use of LABA or ICS were calculated by trials of individual treatments. The variables of withdrawal rate and lost to follow-up were calculated by treatment groups.

FEV<sub>1</sub>, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; PL, placebo; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium solution delivered via Resipmat Soft Mist Inhaler.

fraction of lost to follow-up, which was relatively low and less variant across different treatment groups (table 1 and online tables S2 and S3). Practice of adverse event monitoring was heterogeneous across trials, with six trials (25 533 subjects) describing objective adjudication of cause of death (online table S3).

### Direct comparison meta-analysis

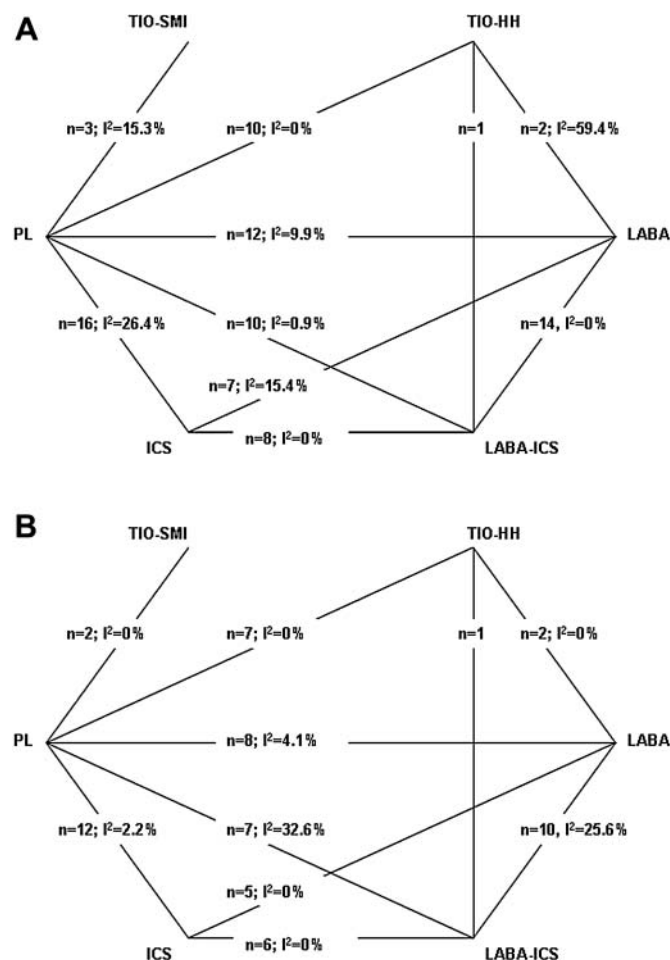
Figure 2 displays the network of each pairwise comparison. Statistical heterogeneity was minimal, with the exception of tiotropium HandiHaler versus LABA for overall death ( $I^2=59.4\%$ ).

The results of the direct comparison meta-analysis are summarised in table 2. For overall death and in comparison with placebo, tiotropium Soft Mist Inhaler was associated with a significantly increased risk (OR 1.49; 95% CI 1.05 to 2.11) whereas LABA-ICS showed a survival benefit (OR 0.81; 95% CI 0.67 to 0.98). Tiotropium HandiHaler, LABA and ICS had no excess risks. Among the active treatment comparisons, tiotropium HandiHaler posed a significantly higher risk than LABA-ICS (OR 1.81; 95% CI 1.07 to 3.05) based on one trial result while LABA-ICS showed a significantly decreased risk over ICS (OR 0.78; 95% CI 0.64 to 0.94). For cardiovascular death and in comparison with placebo, tiotropium Soft Mist Inhaler displayed a more pronounced risk (OR 1.96; 95% CI 1.07 to 3.60) while LABA was associated with a significantly decreased risk (OR 0.67; 95% CI 0.48 to 0.95). No significant

difference was observed among other comparisons. The results of the Peto method were similar to those of the Mantel-Haenszel method (online table S4). Publication bias was not detected by the funnel plot, the Begg's test or the Egger's test (online figure S1).

### MTC meta-analysis

The results of the MTC meta-analysis are listed in table 2. For overall death and in the fixed effect model, patients using tiotropium Soft Mist Inhaler had universally increased risks compared with those receiving placebo (OR 1.51; 95% CrI 1.06 to 2.19) or those using tiotropium HandiHaler (OR 1.65; 95% CrI 1.13 to 2.43), LABA (OR 1.63; 95% CrI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CrI 1.28 to 2.86). In contrast, LABA-ICS demonstrated a beneficial profile versus placebo (OR 0.80; 95% CrI 0.67 to 0.94) or ICS (OR 0.77; 95% CrI 0.64 to 0.93). For cardiovascular death, tiotropium Soft Mist Inhaler had a more apparent risk compared with placebo (OR 2.07; 95% CrI 1.09 to 4.16), tiotropium HandiHaler (OR 2.38; 95% CrI 1.20 to 4.99), LABA (OR 3.04; 95% CrI 1.48 to 6.55), LABA-ICS (OR 2.79; 95% CrI 1.37 to 6.02) and ICS (OR 2.39; 95% CrI 1.18 to 5.12). In contrast, LABA had a decreased risk versus placebo (OR 0.68; 95% CrI 0.50 to 0.93). In the random effects model, tiotropium Soft Mist Inhaler consistently demonstrated an increased risk of overall death versus any



**Figure 2** Network of comparisons included in meta-analysis. A. Overall death: N = 42. B. Cardiovascular death: N = 31. The denotation of 'N' and 'n' represented number of trials reporting on each outcome and with each direct pairwise comparison, respectively. Statistical heterogeneity was represented as the  $I^2$  value. ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; PL, placebo; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium dry powder delivered via HandiHaler.

**Table 2** Risk of overall death and cardiovascular death for each pairwise comparison from the direct comparison and MTC meta-analyses

Comparison	Overall death (N=42)			Cardiovascular death (N=31)		
	Direct comparison Peto OR (95% CI)	MTC fixed effect OR (95% CrI)	MTC random effects OR (95% CrI)	Direct comparison Peto OR (95% CI)	MTC fixed effect OR (95% CrI)	MTC random effects OR (95% CrI)
TIO-SMI vs						
TIO-HH	–	1.65 (1.13 to 2.43)	1.66 (1.04 to 2.75)	–	2.38 (1.20 to 4.99)	2.18 (0.73 to 6.48)
LABA	–	1.63 (1.10 to 2.44)	1.61 (1.002 to 2.66)	–	3.04 (1.48 to 6.55)	2.80 (0.91 to 8.52)
LABA-ICS	–	1.90 (1.28 to 2.86)	1.93 (1.20 to 3.24)	–	2.79 (1.37 to 6.02)	3.00 (1.08 to 9.95)
ICS	–	1.47 (0.99 to 2.21)	1.55 (0.96 to 2.65)	–	2.39 (1.18 to 5.12)	2.31 (0.76 to 7.15)
PL	1.49 (1.05 to 2.11)	1.51 (1.06 to 2.19)	1.54 (1.01 to 2.43)	1.96 (1.07 to 3.60)	2.07 (1.09 to 4.16)	2.18 (0.91 to 6.19)
TIO-HH vs						
LABA	0.76 (0.55 to 1.06)	0.99 (0.83 to 1.19)	0.97 (0.74 to 1.26)	1.24 (0.49 to 3.12)	1.27 (0.88 to 1.87)	1.29 (0.67 to 2.41)
	1.81 (1.07 to 3.05)	1.16 (0.95 to 1.41)	1.16 (0.88 to 1.55)	2.05 (0.97 to 4.34)	1.17 (0.81 to 1.69)	1.37 (0.77 to 2.92)
LABA-ICS*						
ICS	–	0.89 (0.73 to 1.09)	0.93 (0.71 to 1.31)	–	1.00 (0.69 to 1.46)	1.06 (0.52 to 2.20)
PL	0.93 (0.81 to 1.07)	0.92 (0.81 to 1.05)	0.93 (0.75 to 1.17)	0.81 (0.61 to 1.06)	0.87 (0.67 to 1.13)	1.00 (0.64 to 1.89)
LABA vs						
LABA-ICS	1.10 (0.91 to 1.32)	1.17 (0.98 to 1.39)	1.20 (0.95 to 1.54)	0.84 (0.59 to 1.20)	0.92 (0.65 to 1.29)	1.07 (0.64 to 2.16)
ICS	0.86 (0.71 to 1.04)	0.90 (0.76 to 1.07)	0.95 (0.75 to 1.32)	0.73 (0.50 to 1.07)	0.79 (0.56 to 1.11)	0.82 (0.44 to 1.64)
PL	0.90 (0.75 to 1.08)	0.93 (0.79 to 1.09)	0.95 (0.77 to 1.23)	0.67 (0.48 to 0.95)	0.68 (0.50 to 0.93)	0.78 (0.48 to 1.55)
LABA-ICS vs						
ICS	0.78 (0.64 to 0.94)	0.77 (0.64 to 0.93)	0.80 (0.62 to 1.03)	0.97 (0.68 to 1.39)	0.85 (0.61 to 1.20)	0.77 (0.36 to 1.38)
PL	0.81 (0.67 to 0.98)	0.80 (0.67 to 0.94)	0.80 (0.67 to 1.09)	0.81 (0.58 to 1.14)	0.74 (0.54 to 1.01)	0.73 (0.41 to 1.30)
ICS vs						
PL	1.01 (0.86 to 1.20)	1.03 (0.88 to 1.21)	1.00 (0.76 to 1.23)	0.88 (0.64 to 1.20)	0.87 (0.64 to 1.17)	0.94 (0.57 to 1.85)

\*N represents the number of trials reporting on each outcome.

\*Only one trial with the direct comparison of tiotropium HandiHaler and LABA-ICS for the analysis.

CrI, credible interval; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; MTC, mixed treatment comparison; PL, placebo; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium solution delivered via Resipmat Soft Mist Inhaler.

comparators, and showed an increased risk of cardiovascular death versus LABA-ICS. Between direct comparison and MTC meta-analyses, the direction in OR was identical for each comparison. The difference in OR was also minimal (within 10%), with the exception of tiotropium HandiHaler versus LABA or LABA-ICS (over 30%).

Among all the treatments, tiotropium Soft Mist Inhaler had the highest probability of overall and cardiovascular death (8% and 3.5%, respectively), with an approximate probability of 95% of being ranked as the riskiest treatment. In contrast, LABA-ICS had the lowest probability of overall death (4.5%), with a probability of 0% of being ranked as the riskiest treatment (table 3).

The analyses restricted to trials with longer treatment duration and trials enrolling patients with severe COPD showed similar results to the main analysis, although the risk of cardiovascular death associated with tiotropium Soft Mist Inhaler was slightly higher for patients with severe COPD using the fixed effect model (table 4). Three tiotropium Soft Mist Inhaler trials included a group treated with 5  $\mu$ g/day and two included a group treated with 10  $\mu$ g/day. Use of 10  $\mu$ g/day tiotropium Soft Mist Inhaler tended to be associated with a higher risk of overall death against all comparators, although the risks of cardiovascular death were irrespective of the dose of tiotropium (figure 3).

The MTC meta-regression adjusting for demographic characteristics did not substantially change the increased risk for tiotropium Soft Mist Inhaler versus other treatments (online tables S5 and S6). The sensitivity analyses which excluded trials with the ICS withdrawal design and restricted trials with objective adjudication of cause of death yielded similar results to the main analysis (online tables S7 and S8).

## DISCUSSION

This study demonstrated that tiotropium Soft Mist Inhaler was associated with higher risks of overall and cardiovascular death compared with placebo and other inhaled medications, with a potential dose-response effect on overall death. The risk of cardiovascular death associated with tiotropium Soft Mist Inhaler was also higher for patients with severe COPD, although this may simply be because more severe comorbidities impair cardiovascular systems. Instead, LABA-ICS was associated with the lowest risk of overall death. No excess risk was noted for tiotropium HandiHaler or LABA. In contrast with the Global Initiative for Chronic Obstructive Lung Disease guidelines recommending tiotropium or LABA as first-line maintenance therapy, our study highlighted the potential harm of tiotropium Soft Mist Inhaler. This finding should be weighed against other risks and benefits for individual treatments and allows a revision of the recommendations for management of COPD.

## Strengths of this study

This study compared different formulations of tiotropium and different categories of inhaled medications. Given that inhaled pharmacological treatment is the cornerstone of management of COPD, the question for physicians is not whether one drug should be prescribed but rather which one to choose. Our approach accordingly addressed the practical challenge and provided information for making treatment decisions. In addition, compared with previous meta-analyses,<sup>14–16 21 26–28 W45</sup> we included more trials, including a large comparative trial of inhaled long-acting bronchodilators.<sup>W20</sup> This amplified the sample size of the study and enabled us to make more precise

**Table 3** Probability of overall death and cardiovascular death and probability of being ranked as the riskiest intervention for each treatment from the MTC meta-analysis

Treatment	Overall death (N=42)				Cardiovascular death (N=31)			
	Probability of death, % (95% CrI)		Probability of being ranked as the riskiest intervention, %		Probability of death, % (95% CrI)		Probability of being ranked as the riskiest intervention, %	
	Fixed effect	Random effects	Fixed effect	Random effects	Fixed effect	Random effects	Fixed effect	Random effects
TIO-SMI	8.26 (2.55 to 23.61)	8.32 (2.51 to 24.46)	96.94	94.61	3.63 (0.98 to 12.82)	3.83 (0.90 to 15.63)	98.34	89.49
TIO-HH	5.19 (1.64 to 15.16)	5.18 (1.62 to 15.40)	0.08	0.79	1.56 (0.47 to 4.98)	1.79 (0.51 to 6.29)	0.27	4.74
LABA	5.26 (1.65 to 15.38)	5.34 (1.65 to 16.03)	0.15	1.30	1.22 (0.37 to 4.00)	1.40 (0.39 to 5.07)	0.01	1.04
LABA-ICS	4.52 (1.41 to 13.45)	4.50 (1.39 to 13.56)	0.00	0.06	1.33 (0.40 to 4.32)	1.29 (0.35 to 4.48)	0.04	0.31
ICS	5.78 (1.82 to 16.73)	5.52 (1.72 to 16.33)	2.50	2.57	1.55 (0.47 to 5.05)	1.70 (0.47 to 6.03)	0.45	3.60
PL	5.62 (1.79 to 16.23)	5.57 (1.77 to 16.26)	0.33	0.67	1.78 (0.56 to 5.56)	1.77 (0.55 to 5.49)	0.91	0.82

'N' represents the number of trials reporting on each outcome.

CrI, credible interval; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; MTC, mixed treatment comparison; PL, placebo; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium solution delivered via Resipmat Soft Mist Inhaler.

estimates. Furthermore, our subgroup and stratification analyses facilitated special populations or scenarios to be identified that require more caution when using tiotropium Soft Mist Inhaler.

### Safety of tiotropium Soft Mist Inhaler

A recent meta-analysis reported that tiotropium Soft Mist Inhaler had an increased risk of overall death (risk ratio 1.52; 95% CI 1.06 to 2.16) and cardiovascular death (risk ratio 2.05; 95% CI 1.06 to 3.99) versus placebo.<sup>11</sup> Our study further highlighted safety concerns of tiotropium Soft Mist Inhaler versus other active treatments. Some possible mechanisms have been proposed. One is that use of tiotropium Soft Mist Inhaler could yield higher systematic drug exposure compared with tiotropium HandiHaler,<sup>29</sup> although this was not observed in Japanese research.<sup>30</sup> Evidence also suggested that patients receiving a higher dose of tiotropium Soft Mist Inhaler had higher peak concentrations.<sup>29</sup> Another mechanism is the potential effect of underlying rhythm disorders on mortality. Data suggested that the elevated risks of tiotropium Soft Mist Inhaler compared with placebo were up to 3.2-fold for overall death and 8.6-fold for cardiovascular death in patients with cardiac rhythm disorders.<sup>7</sup> However, this substantial risk was not detected in patients without cardiac dysrhythmias.<sup>7–8</sup> Further studies, such as well designed randomised controlled trials with a head-to-head comparison of different formulations and doses of tiotropium<sup>31</sup> are warranted to clarify these hypotheses.

### Safety of tiotropium HandiHaler, LABA and LABA-ICS

Despite the potential harm of LABA among patients with asthma, we found no excess risk of LABA in patients with COPD. LABA tended to have a non-significant increased risk compared with LABA-ICS; however, the estimate was imprecise, with a likely inflated type I error due to multiple statistical tests. Meanwhile, we observed that tiotropium HandiHaler posed a nearly 80% increased risk of overall death when directly compared with LABA-ICS, although the result was based on one trial and became non-significant in the MTC analysis. A large population-based cohort study reported that tiotropium HandiHaler was associated with an excess risk of overall death versus LABA (HR 1.14; 95% CI 1.09 to 1.19).<sup>32</sup> However, it was noted that more patients in the LABA group combined ICS use during the study period. Considering all the evidence,

LABA-ICS may be associated with the lowest risk profile. Further studies are needed to identify optimal therapeutic combinations and regimes for treating patients with COPD.

### Limitations

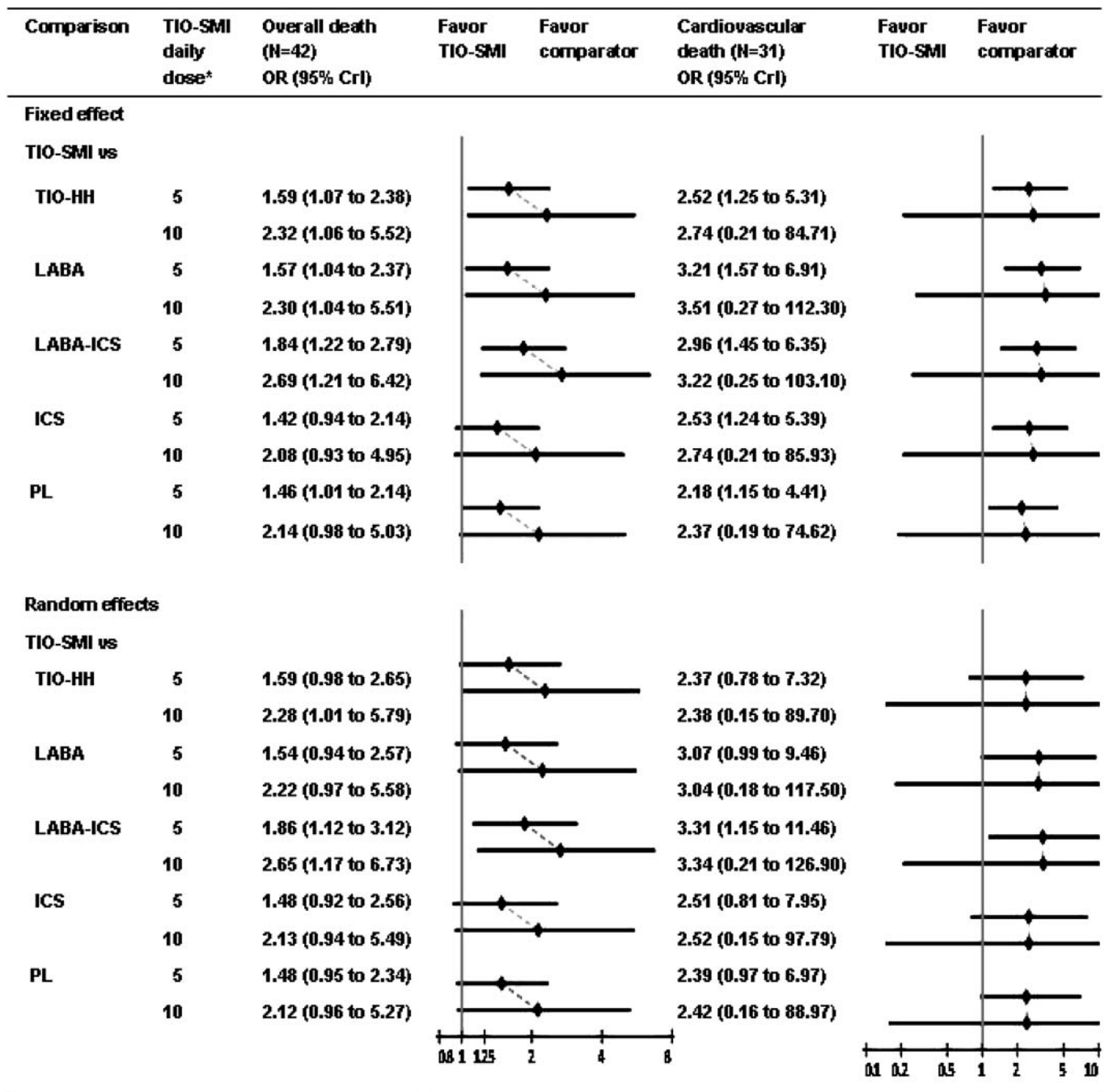
Our study has limitations. First, the validity of our MTC meta-analysis relies on the assumptions of similarity of demographic characteristics across trials and homogeneity of each relative treatment effect.<sup>33</sup> In our study, despite some variation, demographic characteristics were generally similar and the  $I^2$  statistic was minimal. To manage possible trial heterogeneities in the MTC meta-analysis, we used the random effects model and the meta-regression and yielded similar findings. Risk estimates were also consistent between direct comparison and MTC meta-analyses in terms of directions and magnitudes. All these approaches enhanced the validity of our study. However, we cannot rule out the influences from unmeasured covariates. Given rare events and few trials for some comparisons, statistical heterogeneity or publication bias is likely underpowered. We should also note that the difference in OR between direct comparison and MTC meta-analyses was particularly apparent in the comparisons of tiotropium HandiHaler versus LABA or LABA-ICS, which may be associated with the small number of trials involved in these comparisons.<sup>34</sup> Second, several trials were prevalent-user designs<sup>W8 W20</sup> or designed for investigating ICS withdrawal effects rather than treatment effects. Notably, a high percentage of subjects combined LABA or ICS use in tiotropium trials. Our sensitivity analysis and meta-regression adjustment for percentage of concomitant use of LABA or ICS did not change the main findings. However, further studies are necessary to clarify the standalone or add-on effects of these drugs taking into account these complicated elements. Third, all included trials excluded patients with significant diseases and half of them excluded patients with specific cardiovascular morbidities. This may limit the generalisability of our findings to frailer populations in real practice. Fourth, few tiotropium Soft Mist Inhaler trials were involved in our study and precluded further exploration, such as the dose-response effect. Fifth, cardiovascular death was a sparse, non-predefined outcome and without a homogeneous definition across trials. This may result in imprecise estimates and outcome misclassification is possible. However, we constructed this composite endpoint according to

**Table 4** Subgroup analysis for risk of overall death and cardiovascular death for each pairwise comparison from the MTC meta-analysis

Comparison	Overall death (N=42)				Cardiovascular death (N=31)			
	Study duration $\geq$ 1 year (N=27)		FEV <sub>1</sub> < 50% predicted value (N=30)		Study duration $\geq$ 1 year (N=18)		FEV <sub>1</sub> < 50% predicted value (N=22)	
	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)
TIO-SMI vs								
TIO-HH	1.65 (1.12 to 2.43)	1.65 (0.999 to 2.78)	1.64 (1.13 to 2.43)	1.67 (1.03 to 2.89)	2.39 (1.19 to 5.03)	2.04 (0.40 to 8.87)	2.42 (1.19 to 5.09)	2.25 (0.75 to 6.80)
LABA	1.66 (1.11 to 2.48)	1.66 (1.01 to 2.80)	1.63 (1.10 to 2.45)	1.65 (1.004 to 2.88)	3.14 (1.54 to 6.75)	2.82 (0.58 to 12.55)	3.19 (1.54 to 6.86)	3.07 (1.02 to 9.79)
LABA-ICS	1.94 (1.30 to 2.92)	2.02 (1.22 to 3.47)	1.90 (1.28 to 2.87)	1.98 (1.20 to 3.50)	2.78 (1.36 to 5.95)	3.11 (0.71 to 16.48)	2.86 (1.39 to 6.21)	3.19 (1.13 to 11.60)
ICS	1.49 (0.999 to 2.22)	1.58 (0.99 to 2.79)	1.45 (0.97 to 2.20)	1.57 (0.96 to 3.10)	2.43 (1.20 to 5.19)	2.33 (0.48 to 10.91)	2.53 (1.22 to 5.50)	2.63 (0.83 to 9.56)
PL	1.52 (1.06 to 2.19)	1.55 (1.02 to 2.47)	1.51 (1.06 to 2.20)	1.55 (1.01 to 2.52)	2.07 (1.09 to 4.14)	2.28 (0.71 to 9.28)	2.07 (1.09 to 4.21)	2.19 (0.90 to 6.29)
TIO-HH vs								
LABA	1.01 (0.84 to 1.21)	1.00 (0.75 to 1.35)	0.99 (0.83 to 1.19)	0.99 (0.74 to 1.33)	1.31 (0.89 to 1.94)	1.38 (0.53 to 3.80)	1.32 (0.90 to 1.93)	1.36 (0.72 to 2.69)
LABA-ICS	1.18 (0.97 to 1.44)	1.21 (0.90 to 1.70)	1.16 (0.95 to 1.42)	1.18 (0.87 to 1.64)	1.16 (0.80 to 1.69)	1.52 (0.64 to 4.98)	1.19 (0.82 to 1.72)	1.41 (0.79 to 3.25)
ICS	0.90 (0.74 to 1.10)	0.95 (0.71 to 1.42)	0.89 (0.72 to 1.09)	0.94 (0.68 to 1.50)	1.01 (0.69 to 1.50)	1.14 (0.40 to 3.72)	1.05 (0.71 to 1.56)	1.16 (0.54 to 2.91)
PL	0.92 (0.81 to 1.05)	0.93 (0.74 to 1.24)	0.92 (0.81 to 1.05)	0.93 (0.73 to 1.19)	0.86 (0.66 to 1.13)	1.10 (0.55 to 3.35)	0.86 (0.67 to 1.12)	0.97 (0.61 to 1.81)
LABA vs								
LABA-ICS	1.17 (0.98 to 1.40)	1.21 (0.94 to 1.61)	1.16 (0.98 to 1.39)	1.19 (0.92 to 1.58)	0.89 (0.62 to 1.26)	1.10 (0.53 to 3.08)	0.90 (0.64 to 1.27)	1.04 (0.61 to 2.12)
ICS	0.90 (0.75 to 1.07)	0.95 (0.74 to 1.35)	0.89 (0.74 to 1.07)	0.95 (0.72 to 1.44)	0.77 (0.54 to 1.11)	0.82 (0.31 to 2.33)	0.79 (0.56 to 1.14)	0.85 (0.44 to 1.90)
PL	0.92 (0.78 to 1.07)	0.93 (0.73 to 1.23)	0.93 (0.79 to 1.09)	0.94 (0.72 to 1.22)	0.66 (0.47 to 0.91)	0.80 (0.40 to 2.29)	0.65 (0.48 to 0.90)	0.71 (0.42 to 1.36)
LABA-ICS vs								
ICS	0.77 (0.64 to 0.92)	0.79 (0.60 to 1.10)	0.76 (0.63 to 0.92)	0.79 (0.60 to 1.20)	0.87 (0.62 to 1.23)	0.76 (0.24 to 1.87)	0.88 (0.62 to 1.25)	0.83 (0.37 to 1.64)
PL	0.78 (0.66 to 0.93)	0.77 (0.59 to 1.01)	0.80 (0.67 to 0.95)	0.79 (0.59 to 1.03)	0.74 (0.54 to 1.02)	0.73 (0.30 to 1.85)	0.73 (0.53 to 0.99)	0.69 (0.35 to 1.22)
ICS vs								
PL	1.02 (0.87 to 1.20)	0.98 (0.73 to 1.23)	1.04 (0.87 to 1.24)	0.99 (0.65 to 1.31)	0.85 (0.63 to 1.16)	0.97 (0.47 to 2.68)	0.82 (0.59 to 1.14)	0.83 (0.40 to 1.77)

'N' represents the number of trials reporting on each outcome, with a study duration  $\geq$  1 year, or enrolling patients with mean FEV<sub>1</sub> < 50% of predicted value at baseline.

CrI, credible interval; FEV<sub>1</sub>, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; MTC, mixed treatment comparison; PL, placebo; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium solution delivered via Resipmat Soft Mist Inhaler.



**Figure 3** Stratification analysis for risk of overall death and cardiovascular death for each pairwise comparison from the MTC meta-analysis, stratified by the daily dose of tiotropium Soft Mist Inhaler. \*The unit of daily dose is micrograms. CrI, credible interval; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; MTC, mixed treatment comparison; PL, placebo; TIO-HH, tiotropium dry powder delivered via HandiHaler; TIO-SMI, tiotropium solution delivered via Resipmat Soft Mist Inhaler.

the international recognised *Medical Dictionary for Regulatory Activities* definition. The analysis restricted to trials with objective adjudication of cause of death also provided similar results to the main analysis. Finally, in our included trials, the withdrawal rates were variable across treatment groups, with the lowest value in the tiotropium Soft Mist Inhaler group. This may raise concerns of overestimating the relative risk of tiotropium Soft Mist Inhaler due to underestimating the mortality of placebo and other active treatments.<sup>35</sup> However, the proportions of lost to follow-up were low across treatment groups. Moreover, vital status information was ascertained in all placebo-controlled trials of tiotropium Soft Mist Inhaler, even

for patients who withdrew early. Therefore, the unfavourable bias for tiotropium Soft Mist Inhaler should be limited.

### Clinical implications and conclusions

In view of the safety spectrum for each inhaled medication, our results provide substantial implications for physicians. Tiotropium Soft Mist Inhaler was associated with a 50–90% increased risk of overall death and a twofold to threefold increased risk of cardiovascular death versus placebo and other inhaled medications. Until more evidence is available, physicians should use Tiotropium Soft Mist Inhaler with caution and the dose should not exceed the recommended daily dose.

Alternative treatments may be considered in patients with severe COPD or with cardiac dysrhythmias.

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**Contributors** Conception and design: YHD, HHL, WYS, CHC, MSL. Analysis of the data: YHD, YCW. Interpretation of the data: YHD, HHL, WYS, CHC, MSL. Drafting of the article: YHD, HHL, WYS, CHC, MSL. Statistical expertise: HHL, WYS, CHC, MSL. Obtaining funding: MSL. All the authors have read the manuscript, revised it critically for important intellectual content, and approved the final version.

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1    **Online appendix**

2    **Comparative safety of inhaled medications in patients with chronic obstructive**  
3    **pulmonary disease: systematic review and mixed treatment comparison**  
4    **meta-analysis of randomized controlled trials**

5

6    **Authors** Yaa-Hui Dong,<sup>1</sup> Hsien-Ho Lin,<sup>1</sup> Wen-Yi Shau,<sup>2</sup> Yun-Chun Wu,<sup>1</sup> Chia-Hsuin  
7    Chang,<sup>1,3,\*</sup> Mei-Shu Lai<sup>1,\*</sup>

8

9    <sup>1</sup>Graduate Institute of Epidemiology and Preventive Medicine, College of Public

10    Health, National Taiwan University, Taipei, Taiwan

11    <sup>2</sup>Division of Health Technology Assessment, Center for Drug Evaluation, Taipei,

12    Taiwan

13    <sup>3</sup>Department of Internal Medicine, National Taiwan University Hospital, Taipei,

14    Taiwan

15

16    **\*Correspondence to**

17    **Dr. Mei-Shu Lai and Dr. Chia-Hsuin Chang**

# 1    **METHODS**

## 2    **Search strategy**

3    Full-text terms and Medical Subject Headings terms used for systematic database  
4    searching included chronic obstructive pulmonary disease (COPD), long-acting  
5    anticholinergics, long-acting beta-2 agonists (LABA), and inhaled corticosteroids  
6    (ICS).

7        The MEDLINE search strategy through the PubMed filter was as the following:

8    ("chronic obstructive pulmonary disease"[All Fields] OR "chronic obstructive lung  
9    disease"[All Fields] OR "chronic obstructive airway disease"[All Fields] OR  
10    "pulmonary disease, chronic obstructive"[MeSH Terms] OR "COPD"[All Fields])  
11    AND  
12    (("long acting anticholinergic"[All Fields] OR "cholinergic antagonists"[MeSH  
13    Terms] OR "tiotropium"[All Fields]) OR ("long acting beta 2 agonist"[All Fields]  
14    OR "long acting beta agonist"[All Fields] OR "LABA"[All Fields] OR "adrenergic  
15    beta 2 receptor agonists"[MeSH Terms] OR "adrenergic beta agonists"[MeSH Terms]  
16    OR "bronchodilator agents"[MeSH Terms] OR "salmeterol"[All Fields] OR  
17    "formoterol"[All Fields]) OR ("inhaled corticosteroid"[All Fields] OR  
18    "glucocorticoids"[MeSH Terms] OR "anti-inflammatory agents"[MeSH Terms] OR  
19    "budesonide"[All Fields] OR "fluticasone"[All Fields] OR "beclomethasone"[All

1 Fields] OR "triamcinolone"[All Fields]))

2 For the databases of MEDLINE, CINAHL, and Cochrane Library, the search  
3 results were further restricted to randomized controlled trials. For the databases of  
4 ClinicalTrials.gov, the search results were restricted to trials with results announced.

5 All the search strategies were discussed between two investigators, a pharmacist  
6 (YHD) and a physician (CHC), and the full consensus was achieved. The  
7 investigators also pre-tested whether the search strategies can involve relevant trials  
8 according the bibliographies of systematic review articles.

9

## 10 **Outcome measures**

11 The primary outcome was overall death. The secondary outcome was cardiovascular  
12 death. Most trials did not include cardiovascular death as a predefined outcome and  
13 there was no homogeneous definition of this endpoint across the trials. Therefore, for  
14 trials without reporting data on the specific endpoint of cardiovascular death, we  
15 constructed the composite endpoint of cardiovascular death by retrieving trial data  
16 from the serious adverse event reporting and summed the fatal events on the  
17 individual cardiovascular endpoints, which include sudden death, cardiac death,  
18 sudden cardiac death, and the preferred terms under the cardiac and vascular system  
19 organ classes defined by the Medical Dictionary for Regulatory Activities (MedDRA)

1 version 11.0.[21]

2 The preferred terms under the cardiac and vascular system organ classes defined  
3 by the MedDRA include atrial fibrillation/flutter, supraventricular tachycardia,  
4 tachycardia, ventricular tachycardia/fibrillation, palpitations, cardiac arrest, cardiac  
5 failure, ischemic heart disease, myocardial infarction, aneurysm, hypertension, and  
6 stroke.

7

#### 8 **Data extraction and assessment of risk of bias**

9 Two investigators (YHD and CHC) independently screened all articles identified  
10 based on titles and abstracts. The eligibilities of potentially relevant trials were  
11 independently evaluated based on the full-text articles. If trials produced multiple  
12 publications, we included the most recent publication or the publication with most  
13 complete information. A standardized data extraction form was used to extract the  
14 relevant characteristics for each eligible trial, including (a) trial characteristics (author,  
15 publication year, design of randomization and blinding, study location and duration,  
16 inclusion and exclusion criteria, inhaled medication used, and number of subjects  
17 included), (b) patient characteristics at baseline (mean age, proportion of male,  
18 percentage of current smokers, mean forced expiratory volume in 1 second (FEV1) %  
19 of predicted value, and percentage of subjects with concomitant use of LABA or ICS)

1 (c) withdrawal rate and the fraction of lost to follow-up, and (d) number of subjects  
2 with overall death or with cardiovascular death.

3 To assess the risk of bias, we applied Cochrane's risk of bias tool to evaluate  
4 each trial in terms of sequence generation, allocation concealment, binding of  
5 personnel and participants, incomplete outcome addressed (reporting of withdrawal  
6 rates and loss to follow-up), and free of selective reporting (reporting of primary and  
7 secondary endpoints). We also recorded how adverse events were monitored,  
8 including duration, intensity, other measures, and objective adjudication of cause of  
9 death.[22] Any disagreement was resolved by discussion and consensus.

10

## 11 **Statistical analysis**

12 Direct comparison meta-analysis

13 We mainly used the Peto method for the direct comparison meta-analysis. The Peto  
14 method does not require a continuity correction and has the advantage of providing  
15 the best confidence interval coverage when events are rare.[23] To account for the  
16 potential imbalance of sample size between treatment groups within trials, we  
17 conducted the sensitivity analysis by the Mantel-Haenszel method with different  
18 continuity correction factors (0.5, 0.1, 0.01, and without any continuity correction) for  
19 trials with zero events in active-treatment or placebo groups.[24] For each pairwise

1 comparison, the risks of overall and cardiovascular death were estimated with the  
2 pooled odds ratio (OR) and 95% confidence interval (CI). If one treatment was given  
3 at different doses within a trial, we collapsed the data to obtain an overall estimate.  
4 For pairwise comparisons including more than 10 trials, publication bias was assessed  
5 by visual inspection of the funnel plot and by the Begg's test and the Egger's test.[22]

6

#### 7 MTC meta-analysis

8 The MTC meta-analysis was conducted using the Bayesian Markov chain Monte  
9 Carlo (MCMC) methods.[17] Given the challenge of the homogeneity assumption in  
10 the MTC analysis, both fixed effect and random effects models were applied. To  
11 address the possible difference of demographic characteristics across trials, we  
12 performed meta-regression to adjust for variables of age, proportion of male,  
13 percentage of current smoker, study duration, FEV1, and percentage of subjects with  
14 concomitant use of LABA or ICS. We applied a vague prior distribution, ran 50,000  
15 MCMC iterations with a thin parameter of 5, and undertook the posterior inference  
16 after discarding the initial results of 9,999 iterations. The WinBUGS code for the main  
17 analysis was shown as follows, which was based on the code on the website of the  
18 Department of Community Based Medicine, University of Bristol, UK  
19 ([www.bris.ac.uk/cobm/research/mpes/mtc.html](http://www.bris.ac.uk/cobm/research/mpes/mtc.html)) except for the value of absolute log

```

1 odds of placebo, which was driven from our trial data.

2

3 Fixed effect:
4 model {
5   # Model and binomial likelihood
6   for(i in 1:N) { logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
7                   r[i]~dbin(p[i],n[i]) }
8   # Vague priors for trial baselines
9   for(j in 1:NS) { mu[j]~dnorm(0,.0001) }
10  # Vague priors for basic parameters
11  d[1]<-0
12  for (k in 2:NT) { d[k] ~ dnorm(0,.0001) }
13  # Absolute log odds(overall death) of placebo, based on the crude overall death probability of
14  placebo from trial data (5.580%)
15  mA ~ dnorm(-2.829,2.763)
16  # Absolute log odds(overall death) of tiotropium Soft Mist™ Inhaler, tiotropium HandiHaler®,
17  LABA, LABA-ICS and ICS
18  for (k in 1:NT) { logit(T[k])<- mA +d[k] }
19  # Ranking
20  for (k in 1:NT) { rk[k]<- NT+1 - rank(T[,k])
21                  best[k]<-equals(rk[k],1) }
22  # Pairwise ORs
23  for (c in 1:(NT-1))
24    { for (k in (c+1):NT)
25      { lor[c,k] <- d[k] - d[c]
26        log(or[c,k]) <- lor[c,k]
27      }
28    }
29  }
30
31 Random effects:
32 model {
33   for(i in 1:NS){
34     w[i,1] <-0
35     delta[i,t[i,1]]<-0
36   # Vague priors for trial baselines

```

```

1      mu[i] ~ dnorm(0,.0001)
2  # Model and binomial likelihood
3      for (k in 1:na[i]) { r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
4          logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]] }
5      for (k in 2:na[i]) {
6  # Trial-specific LOR distributions
7          delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
8  # Mean of LOR distributions
9          md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
10 # Precision of LOR distributions
11          taud[i,t[i,k]] <- tau *2*(k-1)/k
12 # Adjustment, multi-arm RCTs
13          w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])
14 # Cumulative adjustment for multi-arm trials
15          sw[i,k] <-sum(w[i,1:k-1])/(k-1) }
16      }
17 # Vague priors for basic parameters
18      d[1]<-0
19      for (k in 2:NT){ d[k] ~ dnorm(0,.0001) }
20 # Vague prior for random effects standard deviation
21      sd~dunif(0,2)
22      tau<-1/pow(sd,2)
23 # Absolute log odds(overall death) of placebo, based on the crude overall death probability of
24 placebo from trial data (5.580%)
25      mA ~ dnorm(-2.829,2.763)
26 # Absolute log odds(overall death) on tiotropium Soft Mist™ Inhaler, tiotropium HandiHaler®,
27 LABA, LABA-ICS and ICS
28      for (k in 1:NT) { logit(T[k])<- mA +d[k] }
29 # Ranking
30      for (k in 1:NT) { rk[k]<-NT+1 - rank(T[,k])
31          best[k]<-equals(rk[k],1)}
32 # Pairwise ORs
33      for (c in 1:(NT-1))
34          { for (k in (c+1):NT)
35              { lor[c,k] <- d[k] - d[c]
36                  log(or[c,k]) <- lor[c,k]
37              }
38          }

```

1 }

2

3

## 4 **RESULTS**

### 5 **Eligible trials**

6 We identified 2248 references through database searching and associated sources.

7 After screening and evaluating these references, 42 eligible trials reporting on overall

8 death[W1-W44] and 31 trials reporting on cardiovascular death[W1-W3, W5, W6,

9 W8 -W12, W15, W17-W23, W25, W27-W44] were included for the meta-analysis

10 (figure 1). Of these trials, three trials assessed tiotropium Soft Mist™ Inhaler and 12

11 trials assessed tiotropium HandiHaler®. 19, 17, and 16 trials evaluated LABA,

12 LABA-ICS, and ICS, separately. 34 trials were placebo-controlled trials. Based on the

13 predefined treatment arms, 32 trials were two-arm trials, three trials were three-arm

14 trials, and seven trials were four-arm trials.

15 All these trials excluded patients with significant diseases that might impact the

16 patients' capacity to finish the trials, and 21 trials clearly addressed specific

17 cardiovascular exclusion criteria (table S1). For most of the trials, inhaled short-acting

18 beta-2 agonists, oral corticosteroids, and antibiotics were allowed for as-needed

19 symptom relief and short-course treatment of exacerbations during the study period.

**Table S1** Characteristics of included trials

Author, Year	Comparison	No of subjects	Study location	Study duration	Specific CV exclusion criteria
Bateman, 2010 <sup>W2 W9</sup>	TIO-SMI vs PL	3991	336 centers in 31 countries	48 weeks	Recent history of MI, life-threatening cardiac arrhythmia, or hospitalization for cardiac failure
Bateman, 2010 <sup>*W3 W10</sup>	TIO-SMI vs PL	983	73 centers in 14 countries	48 weeks	NA
Bateman, 2010 <sup>*W3 W11</sup>	TIO-SMI vs PL	1007	78 centers in 14 countries	48 weeks	NA
Tashkin, 2008 <sup>W1</sup>	TIO-HH vs PL	5992	490 centers in 37 countries	4 years	Recent history of MI, life-threatening cardiac arrhythmia, or hospitalization for cardiac failure
Tonnel, 2008 <sup>W12</sup>	TIO-HH vs PL	554	123 centers in France	9 months	Recent history of MI, cardiac arrhythmia requiring drug therapy, or hospitalization for either heart failure or pulmonary edema
Ambrosino, 2008 <sup>W13</sup>	TIO-HH vs PL	234	12 centers in Italy	25 weeks	Recent history of MI, cardiac arrhythmia requiring drug therapy, or hospitalization for cardiac failure
Chan, 2007 <sup>W14</sup>	TIO-HH vs PL	913	101 centers in Canada	48 weeks	Recent history of MI or cardiac arrhythmia requiring drug therapy
Powrie, 2007 <sup>W15</sup>	TIO-HH vs PL	142	Single center in UK	1 year	NA
Dusser, 2005 <sup>W16</sup>	TIO-HH vs PL	1010	177 centers in France	48 weeks	NA
Casaburi, 2005 <sup>W17</sup>	TIO-HH vs PL	108	17 centers in US	25 weeks	Recent history of MI, cardiac arrhythmia requiring drug therapy, or hospitalization for cardiac failure
Niewoehner, 2005 <sup>W18</sup>	TIO-HH vs PL	1829	26 VA centers in US	6 months	Recent history of MI, serious cardiac arrhythmia, or hospitalization for heart failure

**Table S1** (Continued)

Author, Year	Comparison	No of subjects	Study location	Study duration	Specific CV exclusion criteria
Casaburi, 2002 <sup>W19</sup>	TIO-HH vs PL	921	50 centers	1 year	Recent history of MI, cardiac arrhythmia requiring drug therapy, or heart failure
Vogelmeier, 2011 <sup>W20</sup>	TIO-HH vs LABA	7376	725 centers in 25 countries	1 year	Severe CV disorders or recent history of MI, cardiac arrhythmia requiring medical or surgical treatment, or hospital admission for heart failure
Brusasco, 2003 <sup>W21</sup>	TIO-HH vs LABA vs PL	1207	18 countries	6 months	NA
Wedzicha, 2008 <sup>W22</sup>	TIO-HH vs LABA-ICS	1323	179 centers in 20 countries	104 weeks	Use of beta blockers
Stockley, 2006 <sup>W23</sup>	LABA vs PL	634	84 centers in 19 countries	12 months	NA
Campbell, 2005 <sup>W24</sup>	LABA vs PL	657	73 centers in 8 countries	6 months	Significant or unstable cardiovascular disorder
Chapman, 2002 <sup>W25</sup>	LABA vs PL	408	52 centers in 6 countries	24 weeks	NA
Shaker, 2009 <sup>W26</sup>	ICS vs PL	254	Single center in Denmark	4year	NA
Choudhury, 2007 <sup>W27</sup>	ICS vs PL	260	31 centers in UK	1 year	NA
van der Valk, 2002 <sup>W28</sup>	ICS vs PL	244	Single center in Netherlands	6 months	Cardiac insufficiency
Burge, 2000 <sup>W29</sup>	ICS vs PL	751	18 centers in UK	3 years	Use of beta blockers
Pauwels, 1999 <sup>W30</sup>	ICS vs PL	1277	39 centers in 9 countries	3 years	NA
Vestbo, 1999 <sup>W31</sup>	ICS vs PL	290	Single center in Denmark	3 years	NA
Paggiaro, 1998 <sup>W32</sup>	ICS vs PL	281	Europe, New Zealand, South Africa	6 months	NA
FLTA3025 <sup>W33</sup>	ICS vs PL	640	55 centers in US	24 weeks	NA
Calverley, 2010 <sup>W34</sup>	LABA-ICS vs LABA	718	76 centers in 8 countries	48 weeks	NA

**Table S1 (Continued)**

Author, Year	Comparison	No of subjects	Study location	Study duration	Specific CV exclusion criteria
Anzueto, 2009 <sup>W35</sup>	LABA-ICS vs LABA	797	98 centers in US and Canada	52 weeks	NA
Ferguson, 2008 <sup>W36</sup>	LABA-ICS vs LABA	782	94 centers in US and Canada	52 weeks	Clinically significant and uncontrolled CV disorders
Kardos, 2007 <sup>W37</sup>	LABA-ICS vs LABA	994	95 centers in Germany	44 weeks	NA
Wouters, 2005 <sup>W38</sup>	LABA-ICS vs LABA	373	39 centers in Netherlands	1 year	Recent history of MI, acute heart failure, or angina pectoris
SCO40041 <sup>W39</sup>	LABA-ICS vs LABA	186	31 centers in US	156 weeks	NA
Rennard, 2009 <sup>W4</sup>	LABA-ICS vs LABA vs PL	1964	237 centers in US, Europe, Mexico	12 months	Significant or unstable cardiovascular disorder
SFCT01/SCO30002 <sup>W40</sup>	LABA-ICS vs ICS vs PL	387	49 centers in Italy and Poland	52 weeks	NA
Zheng, 2007 <sup>W41</sup>	LABA-ICS vs PL	445	12 centers in China	24 weeks	NA
Tashkin, 2008 <sup>W5</sup>	LABA-ICS vs LABA vs ICS vs PL	1704	194 centers in 5 countries	26 weeks	Significant or unstable cardiovascular disorder
Calverley, 2007 <sup>W8</sup>	LABA-ICS vs LABA vs ICS vs PL	6184	444 centers in 42 countries	3 years	NA
Hanania, 2003 <sup>W42</sup>	LABA-ICS vs LABA vs ICS vs PL	723	76 centers in US	24 weeks	Abnormal clinically significant electrocardiogram
Calverley, 2003 <sup>W6</sup>	LABA-ICS vs LABA vs ICS vs PL	1465	196 centers in 25 countries	12 months	NA
Calverley, 2003 <sup>W7</sup>	LABA-ICS vs LABA vs ICS vs PL	1022	109 centers in 15 countries	12 months	Any relevant cardiovascular disorders or use of beta blockers
Szafranski, 2003 <sup>W43</sup>	LABA-ICS vs LABA vs ICS vs PL	812	89 centers in 11 countries	12 months	Any relevant cardiovascular disorders or use of beta blockers
Mahler, 2002 <sup>W44</sup>	LABA-ICS vs LABA vs ICS vs PL	674	65 centers in US	24 weeks	Abnormal clinically significant electrocardiogram

\*Data from trials NCT00168844<sup>W10</sup> and NCT00168831<sup>W11</sup> were reported together in Bateman and colleagues' article.<sup>W3</sup> Individual information for each trial was retrieved from the U.S. FDA and ClinicalTrials.gov. websites.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; CV, cardiovascular; MI, myocardial infarction; UK, United Kingdom; US, United States; VA, Veterans Affairs; NA, not available.

**Table S2** Baseline characteristics of patients and number of events for each outcome in included trials

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Bateman, 2010 <sup>W2 W9</sup>	TIO-SMI5 qd	1989 (78.1)	64.8 (9.1)	35.7	45.2 (13.5)	54.2	56.0	16.0	1.1	52	22
	PL	2002 (77.0)	64.8 (9.0)	35.9	45.4 (13.6)	52.6	56.1	18.6	1.4	38	12
Bateman, 2010 <sup>†W3 W10 W11</sup>	TIO- SMI5 qd	670 (73.3)	64.7 (8.6)	37.9	46.6 (NA)	30.0	49.0	17.2	1.3	16	6
	TIO- SMI10 qd	667 (74.7)	65.1 (8.5)	34.8	45.3 (NA)	30.0	57.0	20.4	1.7	19	2
	PL	653 (74.6)	65.2 (8.7)	36.1	46.2 (NA)	29.0	55.0	31.4	2.2	9	1
Tashkin, 2008 <sup>‡W1</sup>	TIO-HH18 qd	2986 (75.4)	64.5 (8.4)	29.3	47.7 (12.7)	60.1	61.6	36.8	2.1	381	76
	PL	3006 (73.9)	64.5 (8.5)	29.9	47.4 (12.6)	60.1	61.9	45.2	2.5	411	101
Tonnel, 2008 <sup>W12</sup>	TIO- HH18 qd	266 (86.8)	64.9 (9.7)	23.7	47.5 (13.3)	NA	NA	14.7	1.1	3	1
	PL	288 (85.4)	63.5 (10.1)	30.2	46.2 (12.4)	NA	NA	25.7	2.1	6	1
Ambrosino, 2008 <sup>§W13</sup>	TIO- HH18 qd	117 (82.9)	67.8 (7.8)	NA	42.5 (13.3)	11.1	NA	25.6	1.7	0	NA
	PL	117 (84.6)	66.9 (7.3)	NA	40.3 (12.6)	23.9	NA	23.1	4.3	0	NA
Chan, 2007 <sup>W14</sup>	TIO- HH18 qd	608 (59.0)	66.8 (8.7)	32.0	39.4 (13.4)	54.3	65.8	22.2	NA	15	NA
	PL	305 (61.0)	66.9 (9.1)	30.0	39.3 (13.6)	52.8	71.1	27.5	NA	4	NA
Powrie, 2007 <sup>W15</sup>	TIO- HH18 qd	69 (69.6)	66.3 (8.1)	59.4	50.9 (14.8)	42.0	73.9	30.4	NA	1	1
	PL	73 (56.2)	66.4 (9.8)	57.5	49.2 (15.6)	43.8	76.7	28.8	NA	2	1
Dusser, 2005 <sup>  W16</sup>	TIO- HH18 qd	500 (89.0)	64.5 (9.1)	27.0	48.2 (12.8)	31.0	65.0	23.4	NA	7	NA
	PL	510 (87.0)	65.0 (9.5)	24.0	47.6 (12.5)	32.5	61.6	28.8	NA	8	NA
Casaburi, 2005 <sup>W17</sup>	TIO- HH18 qd	55 (54.5)	65.9 (8.8)	29.1	32.6 (12.4)	NA	NA	NA	NA	1	0
	PL	53 (58.5)	67.3 (6.9)	18.9	36.2 (12.2)	NA	NA	NA	NA	0	0
Niewoehner, 2005 <sup>W18</sup>	TIO- HH18 qd	914 (98.0)	67.6 (8.7)	29.0	35.6 (12.6)	38.0	61.0	16.7	0.4	22	7
	PL	915 (99.0)	68.1 (8.5)	30.0	35.6 (12.6)	38.0	58.0	26.8	0.8	19	7

**Table S2 (Continued)**

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Casaburi, 2002 <sup>‡W19</sup>	TIO- HH18 qd	550 (66.5)	65.0 (9.0)	NA	39.1 (13.7)	NA	44.0	18.7	NA	7	6
	PL	371 (62.8)	65.0 (9.0)	NA	38.1 (14.1)	NA	40.0	27.8	NA	7	1
Vogelmeier, 2011 <sup>W20</sup>	TIO- HH18 qd	3707 (74.4)	62.9 (9.0)	48.0	49.2 (13.3)	51.5	53.6	15.8	0.2	64	9
	SAL50 bid	3669 (74.9)	62.8 (9.0)	48.3	49.4 (13.1)	51.5	53.3	17.7	0.4	78	7
Brusasco, 2003 <sup>‡W21</sup>	TIO- HH18 qd	402 (77.4)	63.8 (8.0)	NA	39.2 (11.6)	NA	NA	15.4	NA	1	1
	SAL50 bid	405 (75.1)	64.1 (8.5)	NA	37.7 (11.7)	NA	NA	18.8	NA	6	1
	PL	400 (76.3)	64.6 (8.6)	NA	38.7 (12.1)	NA	NA	25.8	NA	5	2
Wedzicha, 2008 <sup>W22</sup>	TIO-D 18 qd	665 (84.0)	65.0 (NA)	38.0	39.4 (NA)	46.0	51.0	42.0	2.0	38	19
	SAL50/FLU500 bid	658 (81.0)	64.0 (NA)	38.0	39.1 (NA)	43.0	48.0	35.3	2.3	21	9
Stockley, 2006 <sup>W23</sup>	SAL50 bid	316 (77.0)	62.4 (9.2)	47.0	46.1 (14.5)	22.0	54.0	24.0	1.6	6	6
	PL	318 (76.0)	62.3 (9.1)	46.0	45.8 (14.1)	22.0	60.0	18.0	2.8	5	2
Campbell, 2005 <sup>W24</sup>	FOR9 bid	215 (61.0)	60.0 (NA)	54.0	53.0 (NA)	NA	47.0	14.0	0.5	2	NA
	FOR9 bid and prn	225 (71.0)	60.0 (NA)	56.0	54.4 (NA)	NA	45.0	12.9	0.5	1	NA
	PL	217 (73.0)	60.1 (NA)	55.0	54.1 (NA)	NA	44.0	18.0	0.5	0	NA
Chapman, 2002 <sup>W25</sup>	SAL50 bid	201 (64.0)	65.0 (9.0)	44.0	44.0 (NA)	NA	NA	10.0	NA	1	1
	PL	207 (64.0)	64.0 (10.0)	43.0	46.0 (NA)	NA	NA	13.5	NA	2	1
Shaker, 2009 <sup>W26</sup>	BUD400 bid	127 (62.0)	63.6 (7.5)	100.0	51.0 (11.0)	NA	NA	43.0	1.6	5	NA
	PL	127 (54.0)	63.6 (7.2)	100.0	53.0 (11.0)	NA	NA	49.0	3.1	5	NA
Choudhury, 2007 <sup>W27</sup>	FLU500 bid	128 (48.0)	67.6 (8.9)	40.6	53.2 (18.2)	35.1	NA	43.8	8.6	3	0
	PL	132 (56.0)	67.3 (9.0)	35.6	55.0 (17.1)	31.8	NA	59.0	6.8	0	0

**Table S2 (Continued)**

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
van der Valk, 2002 <sup>W28</sup>	FLU500 bid	123 (85.4)	64.1 (6.8)	22.0	57.5 (14.1)	59.0	86.2	0.8	0.0	4	1
	PL	121 (83.5)	64.0 (7.7)	33.0	56.1 (14.8)	53.0	80.2	0.8	0.0	0	0
Burge, 2000 <sup>W29</sup>	FLU500 bid	376 (6.0)	63.7 (7.1)	36.3	50.3 (14.9)	NA	NA	43.6	4.3	32	10
	PL	375 (3.0)	63.8 (7.1)	39.4	50.0 (14.9)	NA	NA	53.3	4.8	36	12
Pauwels, 1999 <sup>W30</sup>	BUD400 bid	634 (73.5)	52.5 (7.5)	100.0	76.8 (12.4)	NA	NA			8	NA
	PL	643 (72.2)	52.4 (7.7)	100.0	76.9 (13.2)	NA	NA	30.0	2.7	10	NA
Vestbo, 1999* <sup>W31</sup>	BUD bid	145 (58.6)	59.0 (8.3)	75.9	86.2 (20.6)	NA	NA	24.8	NA	4	3
	PL	145 (62.1)	59.1 (9.7)	77.2	86.9 (21.1)	NA	NA	35.2	NA	5	0
Paggiaro, 1998 <sup>W32</sup>	FLU500 bid	142 (70.0)	62.0 (NA)	49.0	59.0 (18.0)	11.0	NA	13.0	0.0	0	0
	PL	139 (78.0)	64.0 (NA)	49.0	55.0 (17.0)	16.0	NA	19.0	1.4	2	0
FLTA3025 <sup>W33</sup>	FLU500 bid	218 (66.1)	63.3 (10.0)	NA	NA	NA	NA	33.0	NA	0	0
	FLU250 bid	216 (72.2)	65.2 (8.7)	NA	NA	NA	NA	35.0	NA	0	0
	PL	206 (68.0)	64.8 (9.5)	NA	NA	NA	NA	38.0	NA	0	0
Calverley, 2010 <sup>W34</sup>	FOR12/BECLO200 bid	237 (79.3)	63.0 (9.0)	38.8	41.9 (5.6)	44.4	43.5	13.1	1.3	2	NA
	FOR12/BUD400 bid	242 (81.5)	64.1 (9.1)	36.1	42.3 (6.0)	43.2	36.6	12.4	2.1	4	NA
	FOR bid	239 (81.1)	63.7 (8.8)	37.3	42.5 (5.9)	42.9	36.1	14.2	1.3	0	NA
Anzueto, 2009 <sup>W35</sup>	SAL50/FLU250 bid	394 (51.0)	65.4 (9.1)	42.0	41.2 (14.3)	8.0	14.0	32.0	1.3	4	0
	SAL50 bid	403 (57.0)	65.3 (8.8)	43.0	40.0 (12.6)	9.0	14.0	39.0	3.0	6	0
Ferguson, 2008 <sup>W36</sup>	SAL50/FLU250 bid	394 (58.0)	64.9 (9.0)	40.0	39.8 (13.9)	12.0	15.0	30.0	2.5	6	4
	SAL50 bid	388 (52.0)	65.0 (9.1)	38.0	40.6 (15.4)	11.0	18.0	38.0	2.6	3	1

**Table S2 (Continued)**

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Kardos, 2007 <sup>W37</sup>	SAL50/FLU500 bid	507 (74.0)	63.8 (8.3)	40.6	40.4 (8.9)	53.6	49.7	21.1	0.8	7	1
	SAL50 bid	487 (77.6)	64.0 (8.2)	44.4	40.3 (8.5)	55.4	49.9	19.5	0.6	9	3
Wouters, 2005 <sup>W38</sup>	SAL50/FLU500 bid	189 (73.0)	63.0 (7.9)	39.0	47.4 (13.9)	3.0	21.0	18.0	NA	2	1
	SAL50 bid	184 (75.0)	64.0 (7.7)	35.0	48.2 (12.9)	3.0	24.0	25.0	NA	4	3
SCO40041 <sup>W39</sup>	SAL50/FLU250 bid	92 (59.8)	65.4 (8.4)	NA	NA	NA	NA	39.0	NA	5	0
	SAL50 bid	94 (62.8)	65.9 (9.5)	NA	NA	NA	NA	41.0	NA	7	2
Rennard, 2009 <sup>W4</sup>	FM9/BUD320 bid	494 (62.3)	63.2 (8.9)	NA	38.6 (11.4)	NA	NA	27.1	1.8	5	NA
	FM9/BUD160 bid	494 (62.8)	63.6 (9.2)	NA	39.6 (10.9)	NA	NA	29.0	2.4	2	NA
	FM9 bid	495 (65.3)	62.9 (9.1)	NA	39.3 (11.9)	NA	NA	31.7	2.4	4	NA
	PL	481 (65.3)	62.9 (9.2)	NA	40.8 (11.5)	NA	NA	36.4	2.7	4	NA
SFCT01/SCO30002 <sup>W40</sup>	SAL50/FLU500 bid	131 (84.0)	63.9 (10.1)	NA	NA	NA	NA	34.4	NA	1	1
	FLU500 bid	131 (83.2)	64.6 (8.7)	NA	NA	NA	NA	26.0	NA	0	0
	PL	125 (80.0)	65.7 (9.0)	NA	NA	NA	NA	32.0	NA	0	0
Zheng, 2007 <sup>W41</sup>	SAL50/FLU500 bid	297 (90.6)	66.0 (8.2)	21.0	47.0 (NA)	NA	NA	12.0	2.0	2	0
	PL	148 (86.5)	66.6 (7.7)	23.0	47.0 (NA)	NA	NA	11.0	0.7	0	0

**Table S2 (Continued)**

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Tashkin, 2008 <sup>W5</sup>	FM9/BUD320 bid	277 (67.9)	63.1 (9.0)	44.4	39.1 (11.8)	35.4	54.2	14.1	1.4	3	1
	FM9/BUD160 bid	281 (64.4)	63.6 (9.0)	44.8	39.9 (11.2)	36.7	52.7	13.5	1.1	4	2
	FM9 bid + Bud320 bid	287 (74.2)	63.7 (9.0)	41.5	39.2 (11.4)	33.1	55.1	16.7	2.1	0	0
	FM9 bid	284 (65.5)	63.5 (9.5)	41.9	39.6 (12.8)	33.1	55.3	21.5	1.4	1	1
	BUD320 bid	275 (67.6)	63.4 (8.8)	42.9	39.7 (12.0)	34.5	52.0	22.9	0.4	2	1
	PL	300 (69.0)	63.2 (9.6)	39.7	41.3 (12.1)	32.7	56.3	25.7	2.3	1	1
Calverley, 2007 <sup>W8</sup>	SAL50/FLU500 bid	1546 (75.0)	65.0 (8.3)	43.0	44.3 (12.3)	9.0	19.0	34.6	1.9	193	60
	SAL50 bid	1542 (76.0)	65.1 (8.2)	43.0	43.6 (12.6)	9.0	18.0	37.7	1.0	205	45
	FLU500 bid	1552 (75.0)	65.0 (8.4)	43.0	44.1 (12.3)	8.0	20.0	39.0	1.5	246	61
	PL	1544 (76.0)	65.0 (8.2)	43.0	44.1 (12.3)	8.0	22.0	44.9	1.4	231	71
Hanania, 2003 <sup>W42</sup>	SAL50/FLU250 bid	178 (61.0)	63.0 (NA)	43.0	41.0 (11.0)	NA	23.0	30.0	1.8	0	0
	SAL50 bid	177 (58.0)	64.0 (NA)	51.0	42.0 (12.0)	NA	20.0	32.0	1.8	0	0
	FLU250 bid	183 (66.0)	63.0 (NA)	48.0	42.0 (11.0)	NA	28.0	27.0	1.8	0	0
	PL	185 (68.0)	65.0 (NA)	47.0	42.0 (12.0)	NA	30.0	32.0	1.8	0	0
Calverley, 2003 <sup>W6</sup>	SAL50/FLU500 bid	358 (75.0)	62.7 (8.7)	52.0	44.8 (14.7)	42.0	50.0	25.0	2.2	2	0
	SAL50 bid	372 (70.0)	63.2 (8.6)	51.0	44.3 (13.8)	42.0	49.0	32.0	2.2	3	1
	FLU500 bid	374 (70.0)	63.5 (8.5)	53.0	45.0 (13.6)	40.0	54.0	29.0	2.1	3	2
	PL	361 (75.0)	63.4 (8.6)	47.0	44.2 (13.7)	38.0	52.0	39.0	1.7	7	4

**Table S2 (Continued)**

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Calverley, 2003 <sup>W7</sup>	FOR9/BUD320 bid	254 (78.0)	64.0 (NA)	33.0	36.0 (10.0)	31.0	47.0	29.1	0.0	5	NA
	FOR9 bid	255 (75.0)	63.0 (NA)	36.0	36.0 (10.0)	30.0	48.0	43.5	1.2	13	NA
	BUD400 bid	257 (74.0)	64.0 (NA)	39.0	36.0 (10.0)	30.0	51.0	39.7	0.8	6	NA
	PL	256 (75.0)	65.0 (NA)	30.0	36.0 (10.0)	25.0	46.0	41.4	1.2	5	NA
Szafranski, 2003 <sup>W43</sup>	FM9/BUD320 bid	208 (76.0)	64.0 (NA)	30.0	36.0 (NA)	17.0	26.0	28.0	NA	6	NA
	FM9 bid	201 (76.0)	63.0 (NA)	38.0	36.0 (NA)	16.0	28.0	32.0	NA	6	NA
	BUD400 bid	198 (80.0)	64.0 (NA)	36.0	37.0 (NA)	17.0	24.0	31.0	NA	5	NA
	PL	205 (83.0)	65.0 (NA)	34.0	36.0 (NA)	20.0	26.0	44.0	NA	9	NA
Mahler, 2002 <sup>W44</sup>	SAL50/FLU500 bid	165 (62.0)	61.9 (NA)	46.0	41.0 (NA)	NA	NA	32.0	NA	0	0
	SAL50 bid	160 (64.0)	63.5 (NA)	46.0	40.0 (NA)	NA	NA	28.0	NA	0	0
	FLU500 bid	168 (61.0)	64.4 (NA)	46.0	41.0 (NA)	NA	NA	40.0	NA	0	0
	PL	181 (75.0)	64.0 (NA)	54.0	41.0 (NA)	NA	NA	38.0	NA	3	0

\*The unit of dose is mcg. Budesonide was given as 800 mcg in the morning and 400 mcg in the evening for 6 months and 400 mcg bid for 30 months.

†Data from trials NCT00168844<sup>W10</sup> and NCT00168831<sup>W11</sup> were reported together in Bateman and colleagues' article.<sup>W3</sup> Individual information on overall death for each trial was retrieved from the U.S. FDA website. For the trial NCT00168844, number of subjects with overall death was 9 (TIO-SMI5), 8 (TIO-SMI10), and 7 (PL). For the trial NCT00168831, the figure was 7 (TIO-SMI5), 11 (TIO-SMI10), and 2 (PL). Pooled information on cardiovascular death for trials NCT00168844 and NCT00168831 were available in the U.S. FDA website.

‡Information on cardiovascular death was available in the the U.S. FDA website.

§Information on overall death was available in the the U.S. FDA website.

||Information on overall death was from the material provided by the manufacturer.<sup>W45</sup>

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; SAL, salmeterol; FOR, formoterol; BUD, budesonide; FLU, fluticasone; BECLO, beclomethasone; PL, placebo; qd, once a day; bid, twice a day; prn, as-needed treatment; FEV1, forced expiratory volume in 1 second; CV, cardiovascular; NA, not available.

**Table S3** Risk of bias in included trials

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Bateman, 2010 <sup>W2 W9</sup>	Yes	Yes	Yes	AEs monitored at baseline, weeks 4, 24, and 48 and up to 30 days after the last dose of medication; vital signs, PE, laboratory test, and ECG; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Bateman, 2010 <sup>*W3 W10</sup>	Unclear	Unclear	Yes	AEs and fatal AEs monitored throughout the treatment period and up to 30 days after the last dose of medication; vital signs, PE, laboratory test, ECG, and Holter monitoring; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Bateman, 2010 <sup>*W3 W11</sup>	Unclear	Unclear	Yes	AEs and fatal AEs monitored throughout the treatment period and up to 30 days after the last dose of medication; vital signs, PE, laboratory test, ECG, and Holter monitoring; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Tashkin, 2008 <sup>W1</sup>	Yes	Yes	Yes	AEs, SAEs, and fatal events monitored throughout the treatment period and up to 30 days after the last dose of medication; PE and laboratory test; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes

**Table S3 (Continued)**

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Tonnel, 2008 <sup>W12</sup>	Yes	Yes	Yes	AEs monitored throughout the treatment period; vital signs and PE	Unclear	Yes	Yes	Yes
Ambrosino, 2008 <sup>W13</sup>	Unclear	Unclear	Yes	AEs, vital signs, and PE	Unclear	Yes	Yes	Yes
Chan, 2007 <sup>W14</sup>	Unclear	Unclear	Yes	AEs monitored throughout the treatment period; vital signs	Unclear	Yes	No	Yes
Powrie, 2007 <sup>W15</sup>	Unclear	Unclear	Yes	AEs monitored throughout the treatment period and up to 30 days after the last dose of medication; vital signs, PE, and laboratory test	Unclear	Yes	No	Yes
Dusser, 2005 <sup>W16</sup>	Unclear	Unclear	Yes	AEs monitored throughout the treatment period; PE	Unclear	Yes	No	Yes
Casaburi, 2005 <sup>W17</sup>	Unclear	Unclear	Yes	AEs, vital signs, and PE	Unclear	No	No	Yes
Niewoehner, 2005 <sup>W18</sup>	Yes	Yes	Yes	SAEs monitored within 30 days of the last dose of medication	Unclear	Yes	Yes	Yes
Casaburi, 2002 <sup>W19</sup>	Unclear	Unclear	Yes	AEs collected at baseline, week 1, every 3 weeks throughout the first 13 weeks, and every 6 weeks for the next 36 weeks; PE, laboratory test, and ECG	Unclear	Yes	No	Yes

**Table S3 (Continued)**

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Vogelmeier, 2011 <sup>W20</sup>	Yes	Yes	Yes	SAEs monitored at baseline, months 2, 4, 8, and 12 and up to 30 days after the last dose of medication; vital signs and PE; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Brusasco, 2003 <sup>W21</sup>	Unclear	Unclear	Yes	AEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Wedzicha, 2008 <sup>W22</sup>	Yes	Yes	Yes	AEs monitored at weeks 2, 8, and every 12 weeks and up to 1 day after the last dose of medication; SAEs monitored up to 30 days after the last dose of medication; PE and ECG	Unclear	Yes	Yes	Yes
Stockley, 2006 <sup>W23</sup>	Yes	Yes	Yes	AEs and SAEs monitored up to 1 day after the last dose of medication	Unclear	Yes	Yes	Yes
Campbell, 2005 <sup>W24</sup>	Yes	Yes	Yes	AEs monitored at baseline, months 2, 4, and 6; vital signs, laboratory test, and ECG	Unclear	Yes	Yes	Yes
Chapman, 2002 <sup>W25</sup>	Yes	Yes	Yes	AEs and SAE individually monitored up to 1 day and 30 days after the last dose of medication	Unclear	Yes	No	Yes
Shaker, 2009 <sup>W26</sup>	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Choudhury, 2007 <sup>W27</sup>	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
van der Valk, 2002 <sup>W28</sup>	Yes	Yes	Yes	AEs monitored at 3 and 6 months	Unclear	Yes	Yes	Yes

**Table S3 (Continued)**

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Burge, 2000 <sup>W29</sup>	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period; laboratory test	Unclear	Yes	Yes	Yes
Pauwels, 1999 <sup>W30</sup>	Unclear	Unclear	Yes	AEs monitored every 3 months; laboratory test	Unclear	Yes	Yes	Yes
Vestbo, 1999 <sup>W31</sup>	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
Paggiaro, 1998 <sup>W32</sup>	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
FLTA3025 <sup>W33</sup>	Unclear	Unclear	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Calverley, 2010 <sup>W34</sup>	Yes	Yes	Yes	AEs monitored at baseline, weeks 4, 12, 24, 36, and 48; vital signs, laboratory test, ECG, and Holter monitoring	Unclear	Yes	Yes	Yes
Anzueto, 2009 <sup>W35</sup>	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
Ferguson, 2008 <sup>W36</sup>	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
Kardos, 2007 <sup>W37</sup>	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
Wouters, 2005 <sup>W38</sup>	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes

**Table S3** (Continued)

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
SCO40041 <sup>W39</sup>	Unclear	Unclear	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Rennard, 2009 <sup>W4</sup>	Yes	Yes	Yes	AEs monitored at baseline, months 1, 2, 4, 6, 9, and 12 and up to 30 days after the last study visit; vital signs, laboratory test, ECG, and Holter monitoring	Unclear	Yes	Yes	Yes
SFCT01/SCO30002 <sup>W40</sup>	Unclear	Unclear	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Zheng, 2007 <sup>W41</sup>	Unclear	Unclear	Yes	AEs monitored at baseline, weeks 2, 4, 8, 12, 16, 20, and 24 and up to a 2 weeks post-treatment; vital signs, PE, laboratory test, ECG, and Holter monitoring	Unclear	Yes	Yes	Yes
Tashkin, 2008 <sup>W5</sup>	Yes	Yes	Yes	AEs monitored at baseline, months 1, 2, 4, and 6 and up to 30 days after the last study visit; vital signs, laboratory test, and ECG	Unclear	Yes	Yes	Yes
Calverley, 2007 <sup>W8</sup>	Yes	Yes	Yes	AEs monitored every 12 weeks; PE and laboratory; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Hanania, 2003 <sup>W42</sup>	Unclear	Unclear	Yes	AEs and SAEs monitored up to 1 day after the last dose of medication; vital sign, PE, laboratory test, ECG	Unclear	Yes	Yes	Yes

**Table S3 (Continued)**

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Calverley, 2003 <sup>W6</sup>	Yes	Yes	Yes	AEs and SAEs monitored at baseline, weeks 2, 4, 8, 16, 24, 32, 40, and 52; PE and laboratory test	Unclear	Yes	Yes	Yes
Calverley, 2003 <sup>W7</sup>	Unclear	Unclear	Yes	AEs monitored at month 1, 2, 3, and every 3 months	Unclear	Yes	Yes	Yes
Szafranski, 2003 <sup>W43</sup>	Unclear	Unclear	Yes	AEs monitored at baseline, months 1, 2, 3, and every 3 months; laboratory and ECG	Unclear	Yes	No	Yes
Mahler, 2002 <sup>W44</sup>	Unclear	Unclear	Yes	AEs and SAE monitored up to 1 day after the last dose of medication; vital signs, PE, laboratory test, ECG and Holter monitoring	Unclear	Yes	No	Yes

\*Data from trials NCT00168844<sup>W10</sup> and NCT00168831<sup>W11</sup> were reported together in Bateman and colleagues' article.<sup>W3</sup> Individual information for each trial was retrieved from the U.S. FDA and ClinicalTrials.gov websites.

AE, adverse event; SAE, serious adverse event; PE, physical examination; Electrocardiography, ECG.

**Table S4** Risk of overall death and cardiovascular death for each pairwise comparison from the direct comparison meta-analysis using the Mantel-Haenszel method with the fixed effect model and different continuity correction factors

Comparison	Overall death (N=42), fixed effect Mantel-Haenszel OR (95% CI)				Cardiovascular death (N=31), fixed effect Mantel-Haenszel OR (95% CI)			
	Continuity correction	Continuity correction	Continuity correction	Without continuity	Continuity correction	Continuity correction	Continuity correction	Without continuity
	factor of 0.5	factor of 0.1	factor of 0.01	correction	factor of 0.5	factor of 0.1	factor of 0.01	correction
TIO-SMI vs								
PL	1.52 (1.05 to 2.18)	1.52 (1.05 to 2.18)	1.52 (1.05 to 2.18)	1.52 (1.05 to 2.18)	2.07 (1.06 to 4.01)	2.07 (1.06 to 4.01)	2.07 (1.06 to 4.01)	2.07 (1.06 to 4.01)
TIO-HH vs								
LABA	0.76 (0.55 to 1.06)	0.76 (0.55 to 1.06)	0.76 (0.55 to 1.06)	0.76 (0.55 to 1.06)	1.24 (0.49 to 3.15)	1.24 (0.49 to 3.15)	1.24 (0.49 to 3.15)	1.24 (0.49 to 3.15)
LABA-ICS*	1.84 (1.07 to 3.17)	1.84 (1.07 to 3.17)	1.84 (1.07 to 3.17)	1.84 (1.07 to 3.17)	2.12 (0.95 to 4.72)	2.12 (0.95 to 4.72)	2.12 (0.95 to 4.72)	2.12 (0.95 to 4.72)
PL	0.93 (0.81 to 1.07)	0.93 (0.81 to 1.07)	0.93 (0.81 to 1.07)	0.93 (0.80 to 1.06)	0.80 (0.61 to 1.06)	0.80 (0.61 to 1.06)	0.80 (0.61 to 1.06)	0.80 (0.61 to 1.06)
LABA vs								
LABA-ICS	1.10 (0.92 to 1.32)	1.10 (0.91 to 1.32)	1.10 (0.91 to 1.32)	1.12 (0.93 to 1.35)	0.84 (0.59 to 1.20)	0.84 (0.59 to 1.20)	0.84 (0.58 to 1.20)	0.79 (0.55 to 1.14)
ICS	0.86 (0.71 to 1.04)	0.86 (0.71 to 1.04)	0.86 (0.71 to 1.04)	0.86 (0.71 to 1.04)	0.74 (0.50 to 1.08)	0.73 (0.50 to 1.07)	0.73 (0.50 to 1.07)	0.73 (0.50 to 1.07)
PL	0.90 (0.75 to 1.08)	0.90 (0.75 to 1.08)	0.90 (0.75 to 1.08)	0.90 (0.75 to 1.08)	0.68 (0.48 to 0.96)	0.67 (0.48 to 0.95)	0.67 (0.47 to 0.95)	0.67 (0.47 to 0.95)
LABA-ICS vs								
ICS	0.78 (0.64 to 0.94)	0.78 (0.64 to 0.94)	0.78 (0.64 to 0.94)	0.77 (0.64 to 0.94)	0.97 (0.69 to 1.38)	0.97 (0.68 to 1.38)	0.97 (0.69 to 1.39)	0.99 (0.69 to 1.41)
PL	0.81 (0.67 to 0.98)	0.81 (0.66 to 0.98)	0.81 (0.66 to 0.98)	0.80 (0.66 to 0.98)	0.81 (0.58 to 1.14)	0.81 (0.58 to 1.14)	0.81 (0.58 to 1.14)	0.84 (0.60 to 1.19)
ICS vs								
PL	1.01 (0.86 to 1.19)	1.01 (0.86 to 1.20)	1.01 (0.86 to 1.20)	1.004 (0.85 to 1.19)	0.88 (0.65 to 1.19)	0.88 (0.65 to 1.20)	0.88 (0.64 to 1.20)	0.83 (0.61 to 1.14)

The denotation of ‘N’ represented number of trials reporting on each outcome.

\*Only 1 trial with the direct comparison of tiotropium HandHaler® and LABA-ICS for the analysis.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; OR, odds ratio; CI, confidence interval.

**Table S5** Meta-regression for risk of overall death and cardiovascular death from the MTC meta-analysis, adjusted for age, proportion of male, and percentage of current smokers

Comparison	Overall death (N=42), OR (95% CrI)			Cardiovascular death (N=31) , OR (95% CrI)		
	Adjusted for age	Adjusted for proportion of male	Adjusted for percentage of current smokers	Adjusted for age	Adjusted for proportion of male	Adjusted for percentage of current smokers
Fixed effect						
TIO-SMI vs						
TIO-HH	1.65 (1.13 to 2.45)	1.65 (1.13 to 2.44)	1.62 (1.11 to 2.41)	2.39 (1.21 to 4.97)	2.40 (1.19 to 5.03)	2.47 (1.23 to 5.16)
LABA	1.63 (1.11 to 2.44)	1.63 (1.11 to 2.43)	1.65 (1.12 to 2.47)	3.06 (1.50 to 6.51)	3.07 (1.50 to 6.55)	3.12 (1.53 to 6.67)
LABA-ICS	1.91 (1.29 to 2.86)	1.91 (1.29 to 2.88)	1.92 (1.29 to 2.89)	2.81 (1.39 to 6.00)	2.82 (1.38 to 6.02)	2.82 (1.38 to 6.00)
ICS	1.48 (0.995 to 2.20)	1.47 (0.997 to 2.20)	1.48 (0.998 to 2.20)	2.40 (1.19 to 5.10)	2.41 (1.19 to 5.17)	2.41 (1.18 to 5.11)
PL	1.52 (1.06 to 2.20)	1.52 (1.06 to 2.19)	1.52 (1.06 to 2.20)	2.08 (1.10 to 4.13)	2.09 (1.10 to 4.19)	2.08 (1.10 to 4.14)
Random effects						
TIO-SMI vs						
TIO-HH	1.67 (1.05 to 2.75)	1.66 (1.04 to 2.79)	1.63 (0.98 to 2.71)	2.14 (0.65 to 6.56)	2.16 (0.67 to 6.92)	2.23 (0.83 to 6.39)
LABA	1.59 (0.97 to 2.59)	1.60 (0.998 to 2.65)	1.60 (0.96 to 2.75)	2.93 (0.90 to 9.42)	2.76 (0.83 to 8.81)	3.55 (1.20 to 9.95)
LABA-ICS	1.93 (1.19 to 3.18)	1.93 (1.18 to 3.25)	1.92 (1.14 to 3.31)	3.15 (1.06 to 11.62)	3.04 (0.995 to 10.99)	3.67 (1.35 to 11.52)
ICS	1.50 (0.93 to 2.51)	1.52 (0.94 to 2.68)	1.49 (0.90 to 2.64)	2.46 (0.76 to 8.64)	2.25 (0.64 to 7.66)	2.88 (0.94 to 8.19)
PL	1.50 (0.995 to 2.37)	1.53 (1.002 to 2.44)	1.49 (0.96 to 2.41)	2.31 (0.91 to 6.95)	2.18 (0.85 to 6.78)	2.50 (1.06 to 6.54)

The denotation of 'N' represented number of trials reporting on each outcome.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; MTC, mixed treatment comparison; OR, odds ratio; CrI, credible interval.

**Table S6** Meta-regression for risk of overall death and cardiovascular death from the MTC meta-analysis, adjusted for study duration, FEV1, percentage of subjects with concomitant use of LABA or ICS

Comparison	Overall death (N=42), OR (95% CrI)				Cardiovascular death (N=31) , OR (95% CrI)			
	Adjusted for study duration	Adjusted for FEV1	Adjusted for percentage of subjects with concomitant use of LABA	Adjusted for percentage of subjects with concomitant use of ICS	Adjusted for study duration	Adjusted for FEV1	Adjusted for percentage of subjects with concomitant use of LABA	Adjusted for percentage of subjects with concomitant use of ICS
Fixed effect								
TIO-SMI vs								
TIO-HH	1.65 (1.13 to 2.44)	1.65 (1.13 to 2.45)	1.61 (1.10 to 2.38)	1.62 (1.10 to 2.40)	2.39 (1.20 to 5.04)	2.39 (1.21 to 5.04)	2.49 (1.23 to 5.23)	2.38 (1.20 to 5.02)
LABA	1.63 (1.10 to 2.43)	1.63 (1.10 to 2.44)	1.62 (1.09 to 2.43)	1.61 (1.08 to 2.42)	3.05 (1.50 to 6.54)	3.12 (1.53 to 6.73)	3.20 (1.54 to 6.87)	3.16 (1.55 to 6.81)
LABA-ICS	1.91 (1.29 to 2.87)	1.91 (1.28 to 2.88)	1.88 (1.26 to 2.83)	1.89 (1.26 to 2.83)	2.81 (1.38 to 6.05)	2.81 (1.39 to 6.06)	2.86 (1.40 to 6.15)	2.84 (1.40 to 6.07)
ICS	1.47 (0.99 to 2.20)	1.47 (0.99 to 2.21)	1.41 (0.95 to 2.14)	1.42 (0.95 to 2.14)	2.40 (1.18 to 5.12)	2.40 (1.19 to 5.15)	2.51 (1.21 to 5.39)	2.48 (1.22 to 5.36)
PL	1.52 (1.06 to 2.19)	1.52 (1.06 to 2.20)	1.51 (1.06 to 2.19)	1.51 (1.06 to 2.19)	2.07 (1.09 to 4.19)	2.08 (1.10 to 4.20)	2.08 (1.09 to 4.18)	2.07 (1.09 to 4.15)
Random effects								
TIO-SMI vs								
TIO-HH	1.70 (1.001 to 2.90)	1.66 (1.03 to 2.76)	1.57 (0.85 to 2.91)	1.59 (0.87 to 2.90)	1.98 (0.61 to 6.70)	2.17 (0.60 to 7.02)	2.52 (0.83 to 8.68)	2.23 (0.61 to 7.66)
LABA	1.65 (0.96 to 2.78)	1.62 (0.999 to 2.68)	1.59 (0.82 to 3.10)	1.53 (0.80 to 2.85)	2.61 (0.79 to 8.45)	2.03 (0.57 to 8.17)	4.06 (1.16 to 13.93)	3.34 (0.83 to 11.90)
LABA-ICS	1.98 (1.14 to 3.51)	1.96 (1.20 to 3.29)	1.90 (0.93 to 3.82)	1.79 (0.89 to 3.52)	2.72 (0.83 to 10.95)	1.70 (0.51 to 5.90)	4.67 (1.34 to 18.82)	3.80 (0.95 to 15.62)
ICS	1.59 (0.93 to 2.83)	1.55 (0.97 to 2.70)	1.48 (0.74 to 3.13)	1.41 (0.71 to 2.92)	2.07 (0.61 to 7.35)	1.71 (0.46 to 6.37)	3.68 (0.94 to 14.39)	2.94 (0.61 to 11.59)
PL	1.57 (1.02 to 2.49)	1.54 (1.01 to 2.43)	1.57 (0.95 to 2.81)	1.55 (0.94 to 2.69)	2.17 (0.86 to 6.37)	2.16 (0.86 to 6.44)	2.53 (1.002 to 7.82)	2.34 (0.83 to 7.68)

The denotation of 'N' represented number of trials reporting on each outcome.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; MTC, mixed treatment comparison; OR, odds ratio; CrI, credible interval; FEV1, forced expiratory volume in 1 second.

**Table S7** Sensitivity analysis for risk of overall death and cardiovascular death from the MTC meta-analysis, excluded trials with the ICS withdrawal design<sup>W27, W28, W38</sup>

Comparison	Overall death (N=39)		Cardiovascular death (N=28)	
	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)
TIO-SMI vs				
TIO-HH	1.65 (1.13 to 2.44)	1.68 (1.06 to 2.79)	2.39 (1.20 to 5.05)	2.22 (0.74 to 6.39)
LABA	1.65 (1.12 to 2.47)	1.65 (1.03 to 2.76)	3.11 (1.53 to 6.73)	2.97 (0.98 to 8.61)
LABA-ICS	1.92 (1.29 to 2.88)	1.97 (1.20 to 3.29)	2.77 (1.37 to 5.91)	2.97 (1.05 to 9.63)
ICS	1.51 (1.02 to 2.26)	1.63 (1.02 to 2.88)	2.42 (1.20 to 5.20)	2.41 (0.81 to 7.30)
PL	1.52 (1.06 to 2.19)	1.55 (1.03 to 2.44)	2.07 (1.10 to 4.21)	2.19 (0.92to 6.02)
TIO-HH vs				
LABA	0.998 (0.83 to 1.20)	0.98 (0.74 to 1.29)	1.30 (0.90 to 1.91)	1.33 (0.71 to 2.52)
LABA-ICS	1.16 (0.95 to 1.41)	1.17 (0.87 to 1.58)	1.16 (0.81 to 1.67)	1.34 (0.75 to 2.88)
ICS	0.91 (0.75 to 1.11)	0.96 (0.73 to 1.43)	1.02 (0.69 to 1.49)	1.08 (0.54 to 2.32)
PL	0.92 (0.81 to 1.04)	0.92 (0.74 to 1.17)	0.87 (0.67 to 1.12)	0.98 (0.64 to 1.84)
LABA vs				
LABA-ICS	1.16 (0.98 to 1.39)	1.19 (0.93 to 1.55)	0.89 (0.63 to 1.26)	1.001 (0.59 to 2.02)
ICS	0.91 (0.77 to 1.09)	0.98 (0.77 to 1.41)	0.78 (0.55 to 1.10)	0.81 (0.44 to 1.62)
PL	0.92 (0.78 to 1.08)	0.94 (0.74 to 1.21)	0.67 (0.49 to 0.91)	0.74 (0.46 to 1.42)
LABA-ICS vs				
ICS	0.79 (0.65 to 0.94)	0.83 (0.64 to 1.18)	0.87 (0.62 to 1.23)	0.81 (0.39 to 1.48)
PL	0.79 (0.67 to 0.94)	0.79 (0.61 to 1.02)	0.75 (0.55 to 1.02)	0.74 (0.41 to 1.32)
ICS vs				
PL	1.01 (0.86 to 1.18)	0.96 (0.70 to 1.19)	0.86 (0.63 to 1.16)	0.91 (0.54 to 1.75)

The denotation of ‘N’ represented number of trials reporting on each outcome.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS,

inhaled corticosteroids; PL, placebo; MTC, mixed treatment comparison; OR, odds ratio; CrI, credible interval.

**Table S8** Sensitivity analysis for risk of cardiovascular death from the Bucher's indirect comparison analysis, based on data of five placebo controlled trials with objective adjudication of cause of death\* <sup>W1-W3, W8</sup>

Comparison	Cardiovascular death (N=5), OR (95% CI)
TIO-SMI vs	
TIO-HH	2.60 (1.32 to 5.13)
LABA	3.12 (1.53 to 6.35)
LABA-ICS	2.34 (1.16 to 4.72)
ICS	2.31 (1.15 to 4.65)

\* Six trials (with 25 533 subjects) were designed to adjudicate causes of death by an expert committee, <sup>W1-W3, W8, W20</sup> five of which (with 17 341 subjects) were placebo controlled trials. <sup>W1-W3, W8</sup> Given that number of this type of trials was not enough for the MTC meta-analysis, we used the Bucher's approach<sup>25</sup> to indirectly compare the risk of cardiovascular death for each inhaled medication relative to each active control using placebo as a common comparator.

The denotation of 'N' represented number of trials reporting on cardiovascular death.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; OR, odds ratio; CI, confidence interval.

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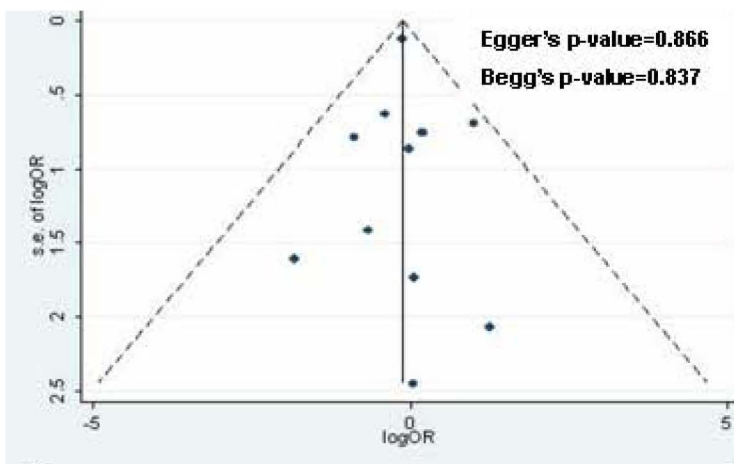
**Figure S1** Funnel plot comparing logOR and s.e. of logOR for the test comparisons\* and outcomes

\*Publication bias was only assessed for pairwise comparisons including more than 10 trials.<sup>22</sup>

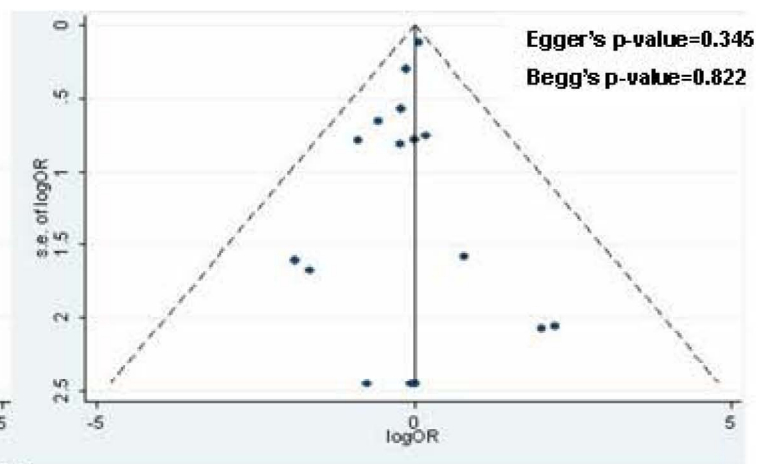
A. LABA vs PL (Overall death). B. LABA vs LABA-ICS (Overall death). C. ICS vs PL (Overall death). D. ICS vs PL (Cardiovascular death). LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; OR, odds ratio; s.e., standard error.

Figure S1

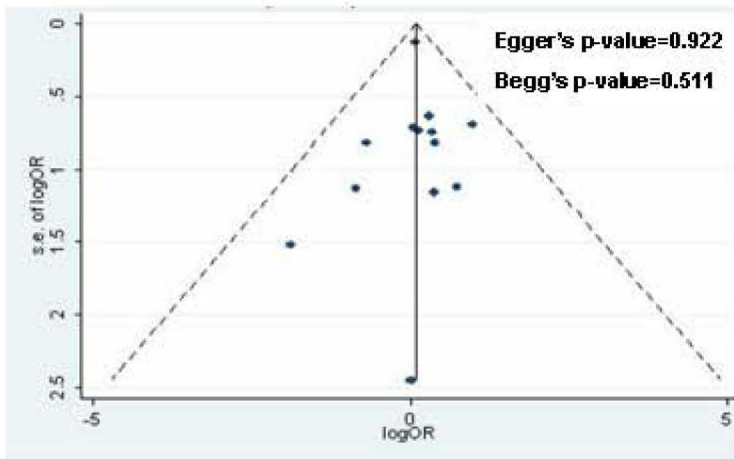
A



C



B



D

