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# Tiotropium versus placebo for inadequately controlled asthma: a meta-analysis

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# ABSTRACT

## Objective

This meta-analysis was performed to evaluate the efficacy and safety of addition of tiotropium to standard treatment regimens for inadequately controlled asthma.

## Methods

A systematic search was made of Pubmed, EMBASE, Medline, CENTRAL databases and Clinicaltrials.gov, and a hand search of leading respiratory journals. Randomized, double-blinding clinical trials on treatment of inadequately controlled asthma for 4 or more weeks with the addition of tiotropium, compared with placebo, were reviewed. Studies were pooled to odds ratio (OR) and weighted mean differences (WMD), with 95% confidence interval (CI).

## Results

Six trials met the inclusion criteria. Addition of tiotropium, compared with placebo, significantly improved all spirometric indices, including morning and evening PEF (WMD 20.59 L/min, 95% CI 15.36 to 25.81 L/min, P<.001 and WMD 24.95 L/min, 95% CI 19.22 to 30.69 L/min, P<.001, respectively), trough and peak $FEV_1$ (WMD 0.13 L, 95% CI 0.09 to 0.18 L, P<.001 and WMD 0.10 L, 95% CI 0.06 to 0.14 L, P<.001 respectively), $FEV_1AUC_{0\text{-}3h}$ (WMD 0.13 L, 95% CI 0.08 to 0.18 L, P<.001), trough and peak FVC (WMD 0.1 L, 95% CI 0.05 to 0.15 L, P<.001 and WMD 0.08 L,

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95% CI 0.04 to 0.13 L, P<.001 respectively), $FVCAUC_{0\text{-}3h}$ (WMD 0.11 L, 95% CI 0.06 to 0.15 L, P<.001). The mean change in ACQ-7 (WMD -0.12, 95% CI -0.21 to -0.03, P=.01) was markedly lower in tiotropium group, but not clinically significant. There were no significant differences in AQLQ score (WMD 0.09, 95% CI -0.01 to 0.20, P=.09), night awakenings (WMD 0.00, 95% CI -0.05 to 0.05, P=.99) or rescue medication use (WMD -0.18, 95% CI -0.36 to 0.00, P=.06). No significant increase was noticed in adverse events in tiotropium group (OR 0.80, 95% CI 0.62 to 1.03, p=.08).

## Conclusion

Addition of tiotropium to standard treatment regimens has significantly improved lung function without increasing adverse events in patients with inadequately controlled asthma. Long-term trials are required to assess the effects of addition of tiotropium on asthma exacerbations and mortality.

**Key words:** Asthma, inadequately controlled asthma, meta-analysis, anticholinergics, tiotropium

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# INTRODUCTION

Asthma is a chronic respiratory disease characterized by reversible airway obstruction that is secondary to airway inflammation and excessive smooth muscle contraction[1]. A great proportion of patients with asthma are suffering recurring symptoms and exacerbations, even after administration of high doses of inhaled corticosteroids (ICSs) combined with a long-acting β2 agonists(LABAs). The Global Initiative for Asthma (GINA) guidelines recommend addition of another medication to achieve optimal asthma control, such as anti-leukotrienes, theophyllines, anti-IgE, and immunosuppressants (e.g., systemic corticosteroids or cyclosporine)[2]. Nevertheless, many patients do not achieve symptom control with current options. Furthermore, there are also concerns about the safety of regular use of high-dose LABAs and ICSs in patients with asthma. Adding a second bronchodilator with a different mechanism of action into the treatment of inadequately controlled asthma might be a new available way to address the problem.

Parasympathetic nervous system is an important neural pathway controlling airway smooth muscle by muscarinic receptors. Stimulation of the parasympathetic nerve can result in broncho-constriction, bronchial vasodilatation and mucus secretion. Moreover, recent investigations revealed that non-neuronal cholinergic system was widely expressed in epithelial cells, eosinophils, submucosal glands, smooth muscle cells, and a variety of immune cells including lymphocytes, macrophages, and mast cells in the airway, suggesting that non-neuronal cholinergic signals played an important role in the pathophysiology of asthma[3]. Therefore, it seems favorable to

add an anti-cholinergic agent to block cholinergic signals in the treatment of asthma. Previous studies found no long-term benefits of short-acting anti-cholinergic agents in patient with persistent asthma[4,5]. Tiotropium bromide is an anti-cholinergic agent with long-lasting action which is characterized by a slow dissociation from acetylcholine M1 and M3 receptors[6,7]. Current COPD treatment guidelines recommend tiotropium as the first-choice long-acting bronchodilator for maintenance therapy in moderate or severe COPD because of its effectiveness, safety, and convenient once-daily dosing[8]. However, little has been known about its efficacy in asthma. In animal models of allergic asthma, it was shown that tiotropium inhibited airway inflammation and reduced airway remodeling[9,10]. Recently, beneficial effects of tiotropium maintenance dosing in patients with asthma have been reported in clinical study. Peters et al. demonstrated that addition of tiotropium improved symptoms and lung function in patients with mild-to-moderate asthma which had been poorly controlled with only low-dose ICS, and its effects were found to be non-inferior to those of salmeterol[11].In addition, Bateman et al. reported that tiotropium was not inferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma[12] and that addition of tiotropium to high-dose ICS plus LABA improved lung function in patients with poorly controlled severe asthma[16].

The aim of the present meta-analysis was to evaluate the efficacy and safety of tiotropium versus placebo in asthmatic patients whose symptoms were inadequately controlled with standard treatment regimens (i.e., ICS with or without LABAs).

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# METHODS

## Data Sources

We searched Pubmed, EMBASE, Medline and CENTRAL databases and Clinicaltrials.gov for trials published from January 1980 to December 2012 using the following search terms: "(tiotropium OR 'Ba 679 BR' OR Spiriva) AND asthma", and supplemented by hand searching of leading respiratory journals and conference abstracts. All publications and abstracts in English language were considered. Moreover, a further search in April 2013 did not identify additional trials that fulfilled our search criteria.

## Study selection

The inclusion criteria of trials were as follows: a) double-blinding randomized controlled trials (RCT) on tiotropium compared with placebo; b) duration of at least 4 weeks; c) more than 12 years of age; d) patients with symptomatic asthma even after treatment with ICS or ICS plus LABAs; e) a history of asthma without other lung diseases, and f) the modified Jadad score of 4 points or above.

## Quality assessment

The methodological quality of each study was assessed by the Modified Jadad Scale (7 points)[13], which scores trials according to randomization, concealment of allocation, double blinding, withdrawals and dropouts. Studies with a score of 4 points or above were included.

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## Data extraction

Data extraction was based on reported statistics (means, SD and SE) for the intention to treat population. Two reviewers (TIAN Jing-wei and CHEN Jing-wu) independently extracted data from the selected studies. If disagreement arose, all the authors conferred till a consensus was arrived at. Authors of a publication were contacted if only its abstract was available or data were missing. Primary outcomes were changes from baseline in morning and evening peak expiratory flow (PEF). Secondary outcomes included changes from baseline in peak and trough forced expiratory volume in 1 second ($FEV_1$), peak and trough forced vital capacity (FVC), the area under the curve (AUC) of the first 3 hours of $FEV_1$ ($FEV_1AUC_{0-3h}$) and FVC($FVCAUC_{0-3h}$), night-time awakenings, rescue-bronchodilator use, Asthma Control Questionnaire (ACQ) score, Asthma Quality of Life Questionnaire (AQLQ) and adverse events.

## Statistical analysis

RevMan (Review Manager. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to analyze all collected data. Fixed effect odds ratios (OR) for dichotomous outcomes, and weighted mean difference (WMD) for continuous outcomes, with corresponding 95% confidence intervals (CI), were calculated for individual trials. Trials were pooled using fixed effect OR or WMD as appropriate. Heterogeneity was tested with a p value < .1

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considered statistically significant. The $I^2$ test was also calculated to efficiently test heterogeneity, with values of 25%, 50% and 75% considered to represent low, moderate and high heterogeneity, respectively. The differences between patients receiving tiotropium and those receiving placebo were pooled using a fixed effects model when there was no evidence of significant heterogeneity in the analysis; if significant heterogeneity was found, a random-effects model was used[14]. Publication bias was examined using funnel plots[15].

# RESULTS

## Search results

The progress of searching and selecting trials is presented in **Figure 1**. Of the 42 English articles were screened, we excluded 37 that were either not relevant or incomplete in data. To reduce heterogeneity across different trials, we only selected those comparing tiotropium (5 microgram qd, with Respimat® inhaler ) with placebo at both baseline and end of treatment period. Five articles involving 1648 participants, including six RCTs—three parallel RCTs and three crossover RCTs that met our inclusion criteria were selected for the present meta-analysis. Characteristics of the trials we included were shown in **Table 1** and **Table 2.** All data adopted in the present study had been published openly at either the website Clinicaltrial.gov or journals.

## Primary outcome

### Change in morning and evening PEF

Six trials included took morning and evening PEF as endpoints. The results of

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each study showed significant improvements in morning and evening PEF in patients treated with tiotropium. The overall analysis showed statistically significant improvements in morning PEF (WMD 20.25 L/min; 95% CI 15.36 to 25.81 L/min; P<.001) and in evening PEF (WMD 24.95 L/min; 95% CI 19.22 to 30.69 L/min; P<.001) in tiotropium group. (**Fig. 2**)

**Secondary outcome**

**Change in $FEV_1$**

Five trials reported peak and trough $FEV_1$ and four reported $FEV_1AUC_{0\text{-}3h}$. The results of each study showed significant greater improvements in peak and trough $FEV_1$ in patients treated with tiotropium than in those with placebo. The pooled analysis (1260 participants) showed statistically significant improvements in peak $FEV_1$ (WMD 0.13L; 95% CI 0.09 to 0.18 L; P<.001) and in trough $FEV_1$ (WMD 0.10L; 95% CI 0.06 to 0.14 L; P<.001)in tiotropium group. Three trials showed obvious improvements in $FEV_1AUC_{0\text{-}3h}$ in tiotropium group, though one study showed no significant differences between the two groups. The pooled analysis showed a statistically significant improvement in $FEV_1AUC_{0\text{-}3h}$ (WMD0.13 L;95% CI 0.08 to 0.18 L;P<.001)in tiotropium group. Nevertheless, improvement in $FEV_1$ was not nearly the minimum clinical important difference of 230 ml in asthma[20]. (**Fig. 3**).

**Change in FVC**

Five included trials reported FVC. Although no obvious improvements in peak FVC, trough FVC and $FVCAUC_{0\text{-}3h}$ were observed in one study, the cumulative analysis showed a statistically significant improvement respectively in peak FVC

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(WMD 0.10L; 95% CI 0.06 to 0.14 L; P<.001), trough FVC (WMD 0.08L; 95% CI 0.04 to 0.13 L; P<.001) and $FVCAUC_{0\text{-}3h}$(WMD 0.11L; 95% CI 0.06 to 0.15 L; P<.001)in tiotropium group. (**Fig. 4**).

**Asthma control**

Of the trials included, three reported score of ACQ-7 (Asthma Control Questionnaire). ACQ is a questionnaire consisting of a seven point scale ranging from 0(no impairment) to 6(maximum impairment), with a minimal clinically important difference of 0.5 units. The score was statistically lower with tiotropium than with placebo (WMD -0.12; 95% CI -0.21 to -0.03; p=.01).However, the improvement in ACQ-7 did not achieve the minimum clinical important difference of 0.5 units in asthma.

**Night awakenings**

Three trials showed data of mean number of night awakenings during the last week of treatment. The cumulative analysis showed no statistical differences between patients receiving tiotropium and placebo (WMD 0.00; 95% CI -0.05 to 0.05; $I^2$=0%; P=.99). (**Fig. 5**).

**Rescue medication use**

Mean number of puffs of rescue medication during the whole day in the last week of treatment was reported in five trials. Although the pooled analysis showed a dropping trend in patients receiving tiotropium compared with those receiving placebo (WMD -0.18; 95% CI -0.36 to 0.00; $I^2$=0%; P=.06), the difference was not statistically significant. (**Fig. 6**).

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**Quality of Life**

Three trials reported AQLQ (Asthma Quality of Life Questionnaire). Although the cumulative analysis showed a little decrease in patients receiving tiotropium compared with those receiving placebo (WMD 0.09; 95% CI -0.01 to 0.20; $I^2$=0%; P=.09), no significant difference between the two groups was observed.

**Adverse events**

Incidence of adverse events was evaluated in 6 studies. The overall cumulative incidence of adverse events was 44.0% in tiotropium group and 47.4% in placebo group. All the adverse events reported in at least two trials were shown in **Table 3**. The overall analysis showed no statistically significant increase in total adverse events in tiotropium group (OR 0.80; 95% CI 0.62 to 1.03; p=0.08). Among adverse events, asthma exacerbation (OR 0.69; 95% CI 0.54 to 0.89; p=0.004） and peak expiratory flow rate decline decreased (OR0.70; 95% CI 0.52 to 0.96; p=0.02) markedly in tiotropium group. There was no statistical significant difference in serious adverse events between the two groups (OR 1.15; 95% CI 0.74 to 1.79; p=0.54) (**Fig. 7**).

## DISCUSSION

Asthma is a commom airway obstructive diseases and bronchodilators are very important to the management of symptoms of asthma[21]. The added benefits of combining two long-acting bronchodilators with different modes of action have been observed in patients with COPD [22]. Titropium will be approved by FDA in next months for asthma. However, guidelines do not specifically recommend addition of an

inhaled long-acting anticholinergic drug to current treatment of asthma [23]. This meta-analysis incorporates 6 RCT and includes data from 1648 patients with inadequately controlled asthma. To our knowledge, to date this is the first meta-analysis of the efficacy and safety of tiotropium versus placebo regarding clinically relevant outcomes in inadequately controlled asthma patients who are receiving ICSs or ICSs plus LABAs. The efficacy of tiotropium is evaluated by its impact on lung function and other clinical outcomes, including asthma control, quality of life, night awakenings, and rescue medication use.

This meta-analysis clearly shows the beneficial effects of the addition of tiotropium on lung function in inadequately controlled asthma patients who are receiving ICSs or ICSs plus LABAs. When compared with placebo, patients treated with tiotropium showed statistically significant improvements from baseline in all spirometric indices, including trough and peak $FEV_1$, $FEV_1AUC_{0\text{-}3h}$, trough and peak FVC, $FVCAUC_{0\text{-}3h}$ and morning and evening PEF. Although the improvement in $FEV_1$ was not nearly the minimum clinical important difference of 230 ml in asthma[20], it should be noted that the increases were in patients who were receiving ICSs or ICSs plus LABAs. There were no significant differences between tiotropium and placebo groups in AQLQ, night awakenings or rescue medication use. Although a statistically significant difference was reported for ACQ-7, it was not clinically significant. This suggests that despite good effects of tiotropium on lung function, no significant effect on other clinical parameters was demonstrated. Only two studies by Kerstjens et al reported data about exacerbations. Because the data currently available

on exacerbations are insufficient for a meta-analysis, further researches to investigate the effects of tiotropium on exacerbations are required. Kerstjens et al reported that addition of tiotropium prolonged the time to the first severe exacerbation (282 days vs. 226 days) with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; P=.03). The results are inconsistent with previous study. Peters et al[11] found that addition of tiotropium had no significant effect on asthma exacerbations though a trend was observed towards a better effect of tiotropium compared with a higher dose of ICS. The difference may be attributed to the treatment course in the study by Peters et al, which was too short to examine the rate of asthma exacerbations. Moreover, the study by Peters et al compared tiotropium with salmeterol and a higher dose of ICS while that by Kerstjens et al compared tiotropium with placebo in patients with poorly controlled asthma. Hospitalization and severe asthma exacerbations will affect the quality of life in subjects with asthma. Although Kerstjens et al. found a significant longer time to first exacerbation, our results showed no significant differences between tiotropium and placebo groups in AQLQ. The AQLQ was developed to measure patients' functional experiences over a 2-week period, and it asks patients to recall their experiences during the previous days. Therefore, it is not suitable for capturing the rapidly changing experiences that occur during an acute asthma exacerbation[30]. Furthermore, although the difference was not statistically significant, it was noticeable that there were trends towards the improvement of AQLQ (P=.09) and a reduction in the number of rescue medication use(P=.06) among patients treated with tiotropium. It indicated that the increase in

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sample size might get a positive result.

It was so surprising for us to find in this meta-analysis a decreasing trend, but statistically insignificant, in total adverse events among patients treated with tiotropium. Among total adverse events, asthma exacerbation and peak expiratory flow rate decline decreased obviously in tiotropium group, which might account for the decreasing trend in total adverse events among patients treated with tiotropium. In addition, no significant increase in serious adverse events was observed. Dry mouth, urinary retention and cardiovascular events are most concerning adverse event of anticholinergic agents. This analysis showed that these adverse events were reported in a very small part of the included patients, which were of mild to moderate severity according to the statements in the relevant articles. It should be noticed that the low incidence of cardiovascular events might have resulted from the exclusion of patients with serious cardiovascular diseases in the trials included for this meta-analysis. Excess cardiovascular events might have been anticipated in such patients.

We are very interested in the studies on tiotropium that used the DPI in asthma, because Handihaler is the only device available for tiotropium in China now. We found 6 RCTs on tiotropium that used the DPI in asthma population. Of the 6 RCTs, one evaluated the addition of tiotropium to an inhaled glucocorticoid, as compared with a doubling of the inhaled glucocorticoid or the addition of salmeterol[11]. The results showed that tiotropium improved symptoms and lung function in patients with inadequately controlled asthma when added to an inhaled glucocorticoid. Its effects appeared to be equivalent to those with the addition of salmeterol. To reduce

heterogeneity of different trials, we only selected the data comparing tiotropium with placebo. Another RCT was designed to determine the spirometric effects of tiotropium in COPD patients with concomitant asthma[24]. The results showed that the patients with COPD and concomitant asthma achieved spirometric improvements with tiotropium along with symptomatic benefits as seen by reduced need for rescue medication. To reduce heterogeneity of different trials, we also only selected data of asthma patients without other lung diseases. A RCT by Fardon T compared tiotropium with placebo, but the data it provided were not suitable for our meta-analysis[25]. Three RCTs investigated the protection of tiotropium with DPI device versus placebo or other anticholinergic drugs against methacholine-induced bronchoconstriction in asthma [26,27,28], but they were not relevant to this meta-analysis. Hence, we excluded the 6 RCTs on tiotropium that used DPI before ultimate analysis.

The main strength of our study was inclusion of a large pool of patients with inadequately controlled asthma, allowing us to perform robust analysis of clinically relevant outcomes following addition of tiotropium versus placebo to standard treatment strategy. The trials included in this analysis were of good quality and used almost identical designs with regard to inclusion and exclusion criteria. And the clinical characteristics of study populations were quite homogeneous. However, the results should be interpreted with caution because they might have been influenced by other factors. Firstly, there were differences in trial duration. The duration of treatment in the most trials here was too short to allow adequate evaluation of long-term efficacy and safety of tiotropium. Although a meta-analysis showed a 46%

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relative risk increase in death in COPD trials that used 5ug tiotropium Respimat® inhaler[29], it has not been elucidated whether the increase in death in asthma was brought about by the use of Respimat® inhaler. Further long-term studies are anticipated to answer this question. Secondly, the patients with inadequately controlled asthma included in this meta-analysis were over 12 years old, free from other pulmonary diseases and in non-smoking status. Therefore, it is inappropriate to generalize the results of this meta-analysis to all asthma patients. Thirdly, the trials included had different criteria for use of co-medications. In current trials, tiotropium is an additional medicine to standard treatment regimens rather than a first-choice medicine.

Clinical homogeneity of the trials resulted in statistical homogeneity for all outcome measures across the trials. Selection bias was avoided using a systematic search strategy, and we specified the inclusion and exclusion criteria. Furthermore, two reviewers independently evaluated the selected studies and a third reviewer was consulted to reach consensus if necessary. Double-counting of patients from overlapping publications was avoided. Funnel plots for the primary endpoint showed no clear evidence of publication bias. Selective reporting of secondary end points and non-intention to treat reports in published manuscripts may bias results. We minimized this bias by obtaining supplemental data for included studies.

## CONCLUSIONS

This meta-analysis indicates that addition of tiotropium to the treatment of

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inadequately controlled asthma, compared with placebo, may improve lung function and increase no adverse events. Because of the limitations of this meta-analysis, we suggest that further work should be required to compare addition of tiotropium with that of placebo. Larger, longer, multi-center, double-blind, parallel, randomized controlled trials are expected to validate the efficacy and safety of addition of tiotropium to standard treatment regimens for inadequately controlled asthma..

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## Conflict of interest

All authors have read and approved of the manuscript. The authors declare that they have no conflict of interest.

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| Reference | Number of Participants | Age (mean±SD) | Gender (Female/ Male) | Treatment duration (weeks) | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|---|
| Bateman[12] | 388 | 43.3 ± 12.6 | 240/148 | 16 | Age from 18 to 67 years old;homozygous for arginine at the 16th amino acid position of the beta2 adrenergic receptor (B16 Arg/Arg); have a documented history of asthma; moderate persistent asthma. | significant diseases other than asthma; myocardial infarction ≤ 6 months; hospitalisation for cardiac failure ≤ 1 year; life threatening cardiac arrhythmia; resection, radiation therapy or chemotherapy <5 years; COPD; active tuberculosis; pulmonary rehabilitation program ≤ 6 weeks. |
| Kerstjens-2[16] | 453 | 52.5 ± 12.1 | 262/191 | 48 | Age from 18 to 75 years old; at least a 5-year history of asthma; treated severe persistent asthma. | abnormal haematology; myocardial infarction ≤ 6 months; hospitalisation for cardiac failure; life threatening cardiac arrhythmia; active tuberculosis; resection, radiation therapy or chemotherapy <5 years; lung diseases other than asthma (e.g. COPD); asthma exacerbation or respiratory tract infection < 4 weeks. |
| Kerstjens-1[16] | 459 | 53.4 ± 12.6 | 289/170 | 48 | Age from 18 to 75 years old; at least a 5-year history of asthma; treated severe persistent asthma. | abnormal haematology; myocardial infarction ≤ 6 months; hospitalisation for cardiac failure; life threatening cardiac arrhythmia; active tuberculosis; resection, radiation therapy or chemotherapy <5 years; lung diseases other than asthma (e.g. COPD); asthma exacerbation or respiratory tract infection < 4 weeks. |
| NCT01122680[17] | 105 | 14.0 ± 1.5 | 38/67 | 4 | Age from 12 to 17 years old; at least a 3-month history of asthma; moderate persistent asthma; FEV1 ≥ 60% and ≤ 90% of predicted normal; bronchodilator reversibility*. | congenital or acquired heart disease; life-threatening cardiac arrhythmia; resection, radiation therapy or chemotherapy <5 years; lung diseases other than asthma; narrow-angle glaucoma; renal impairment. |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT01233284[18] | 149 | 49.3 ± 13.3 | 82/67 | 4 | Age from 18 to 75 years old; at least a 3-month history of asthma; bronchodilator reversibility*. | abnormal haematology; myocardial infarction ≤ 6 months; hospitalisation for cardiac failure; life threatening cardiac arrhythmia; active tuberculosis; resection, radiation therapy or chemotherapy <5 years; lung diseases other than asthma; moderate to severe renal impairment; narrow angle glaucoma. |
| NCT01152450[19] | 94 | 44.3 ± 13.2 | 55/39 | 4 | Age from 18 to 75 years old; At least a 3-month history of asthma; moderate persistent asthma; FEV1 ≥ 60% and ≤ 90% of predicted normal; bronchodilator reversibility*. | abnormal haematology; myocardial infarction ≤ 6 months; hospitalisation for cardiac failure; life threatening cardiac arrhythmia; active tuberculosis; resection, radiation therapy or chemotherapy <5 years; lung diseases other than asthma (e.g. COPD); pregnant or nursing women. |

**Table 1 Characteristics of participants of included studies.**

***bronchodilator reversibility is defined as an increase in FEV1 of equal above 12% and equal above 200 mL 15 minutes after 400 µg salbutamol.**

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| Reference | Control design | End point | Treatment groups | Basic drugs |
|---|---|---|---|---|
| Bateman[12] | **parallel** | **Primary outcome measures:**morning PEF. **Secondary outcome measures:**morning and evening PEF, morning and evening $FEV_1$, asthma symptom, Mini-AQLQ, blood pressure, pulse rate. | **tiotropium 5 μg qd; Salmeterol 50 μg bid** | **ICS** |
| Kerstjens-2[16] | **Parallel** | **Primary outcome measures:** peak $FEV_1$, trough $FEV_1$ and time to first severe asthma exacerbation. **Secondary outcome measures:** AUC 0~3h $FEV_1$, FVC, PEF, asthma exacerbations, hospitalizations for exacerbations, AQLQ, ACQ, asthma symptom free days, rescue medication use. | **tiotropium 5 μg qd** | **ICS and LABA** |
| Kerstjens-1[16] | **Parallel** | **Primary outcome measures:** peak $FEV_1$, trough $FEV_1$ and time to first severe asthma exacerbation. **Secondary outcome measures:** AUC 0~3h $FEV_1$, FVC, PEF, asthma exacerbations, hospitalizations for exacerbations, AQLQ, ACQ, asthma symptom free days, rescue medication use. | **tiotropium 5 μg qd** | **ICS and LABA** |
| NCT01122680[17] | **Cross-over** | **Primary outcome measures:** peak $FEV_1$. **Secondary outcome measures:** trough and AUC 0~3h $FEV_1$, FVC, PEF, rescue medication use, ACQ, nighttime awakenings. | **tiotropium 1.25 μg qd; tiotropium 2.5 μg qd; tiotropium 5 μg qd** | **ICS** |
| NCT01233284[18] | **Cross-over** | **Primary outcome measures:** peak $FEV_1$. **Secondary outcome measures:** trough and AUC 0~3h $FEV_1$, FVC, PEF, rescue medication use, nighttime awakenings. | **tiotropium 1.25 μg qd; tiotropium 2.5 μg qd; tiotropium 5 μg qd** | **ICS alone or with LAB SABA.** |
| NCT01152450[19] | **Cross-over** | **Primary outcome measures:** AUC 0~3h $FEV_1$. **Secondary outcome measures:** PEF, $FEV_1$, FVC, rescue medication use, nighttime awakenings. | **tiotropium 2.5 μg bid; tiotropium 5 μg qd.** | **ICS alone or with LAB SABA.** |

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**Table 2** Studies Included in the Present Analysis.

* qd, once daily; bid, twice daily; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; SABA, short-acting $\beta_2$-agonist.

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| | | Trials | Participants | Tiotropium (%) | Placebo (%) | Odds ratio | 95% CI | P value |
|---|---|---|---|---|---|---|---|---|
| serious adverse events | gastrointestinal disorders | 4 | 1456 | 0.685 | 0.551 | 1.19 | 0.36 to 3.90 | 0.78 |
| | general disorders | 2 | 912 | 0.219 | 0.219 | 1 | 0.14 to 7.24 | 1 |
| | infections and infestations | 3 | 1166 | 1.370 | 1.031 | 1.35 | 0.48 to 3.78 | 0.57 |
| | injury | 3 | 1094 | 0.733 | 0.548 | 1.29 | 0.32 to 5.20 | 0.72 |
| | musculoskeletal and connective tissue disorders | 2 | 912 | 0.658 | 1.096 | 0.67 | 0.18 to 2.41 | 0.54 |
| | neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 | 912 | 0.877 | 0.439 | 1.87 | 0.39 to 8.86 | 0.43 |
| | nervous system disorders | 3 | 1067 | 0.560 | 0.377 | 1.33 | 0.29 to 6.03 | 0.71 |
| | psychiatric disorders | 2 | 743 | 1.096 | 0 | 5.19 | 0.60 to 44.67 | 0.13 |
| | respiratory, thoracic and mediastinal disorders | 2 | 912 | 4.825 | 4.825 | 1 | 0.55 to 1.83 | 1 |
| | vascular disorders | 2 | 635 | 1.294 | 0.613 | 2.11 | 0.38 to 11.61 | 0.39 |
| other adverse events | infections and infestations | 3 | 1166 | 18.322 | 17.698 | 1.06 | 0.78 to 1.44 | 0.69 |
| | peak expiratory flow rate decreased | 2 | 912 | 20.395 | 26.754 | 0.7 | 0.52 to 0.96 | 0.02 |
| | nervous system disorders | 3 | 1094 | 5.495 | 6.022 | 0.92 | 0.55 to 1.53 | 0.74 |
| | asthma | 3 | 1166 | 30.993 | 39.003 | 0.69 | 0.54 to 0.89 | 0.004 |

**Table 3** Adverse events with tiotropium compared with placebo.

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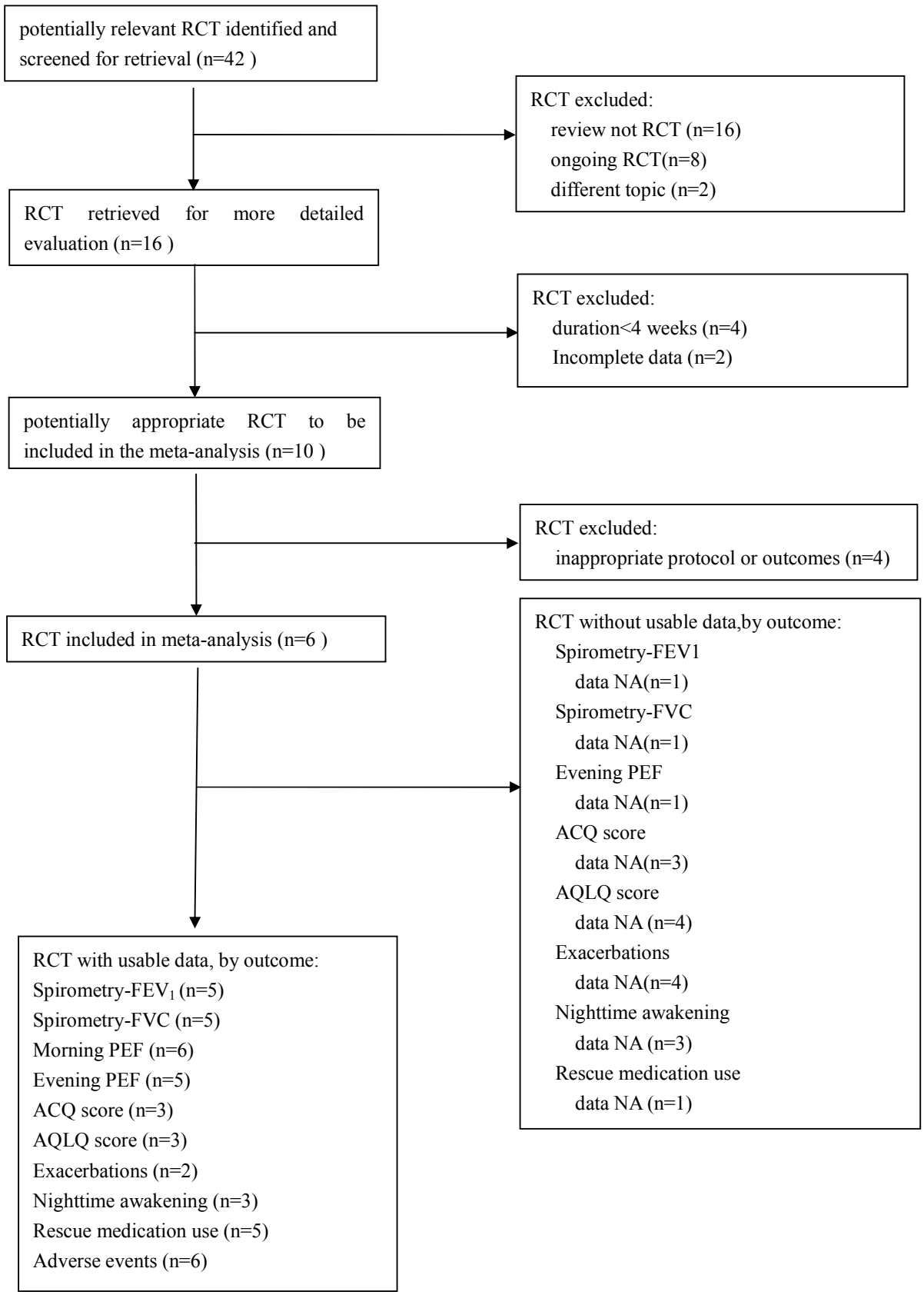
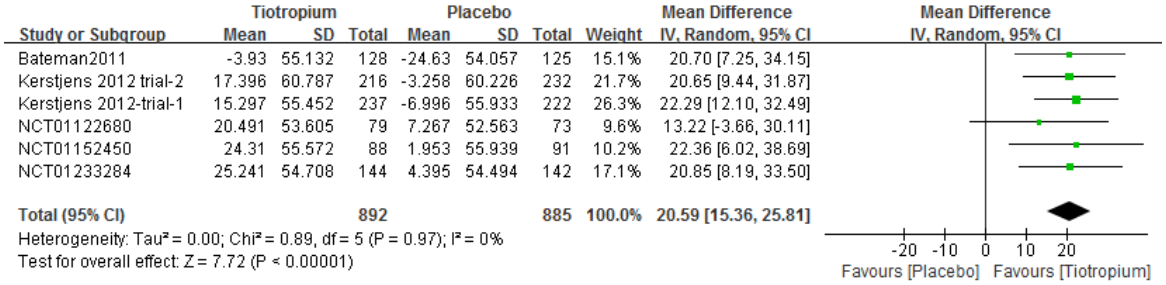



**Figure 1** Flow chart showing strategy for identification of relevant studies.
NA, not available; RCT, randomized controlled trials.

(a)Change in morning PEF




(b)Change in evening PEF

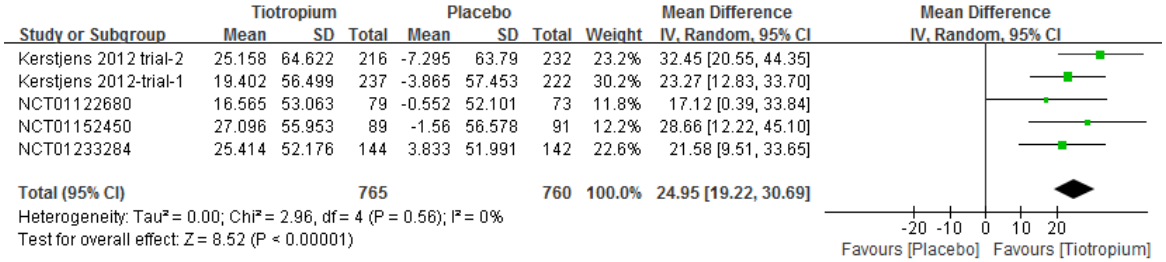
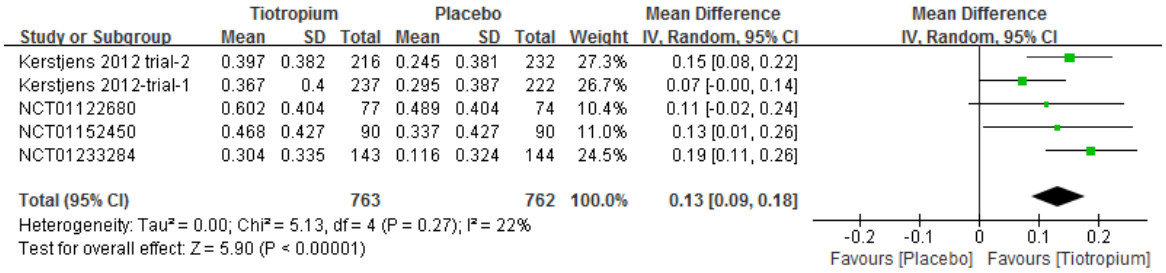
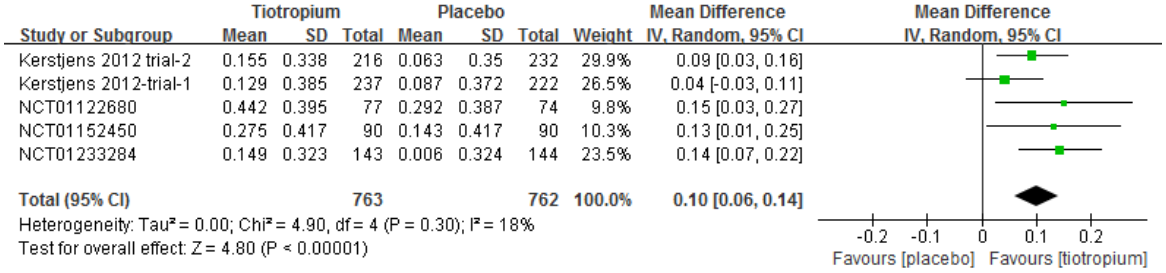



**Figure 2** Effects of tiotropium versus placebo on PEF.

(a)Change in peak $FEV_1$




(b)Change in trough $FEV_1$




(c)Change in $FEV_1$ $AUC_{0\sim3h}$

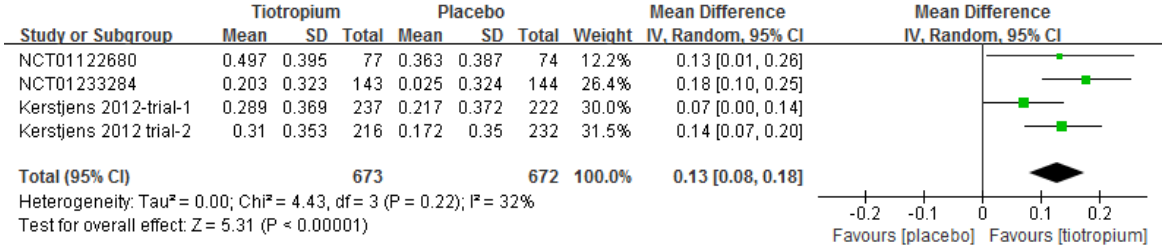
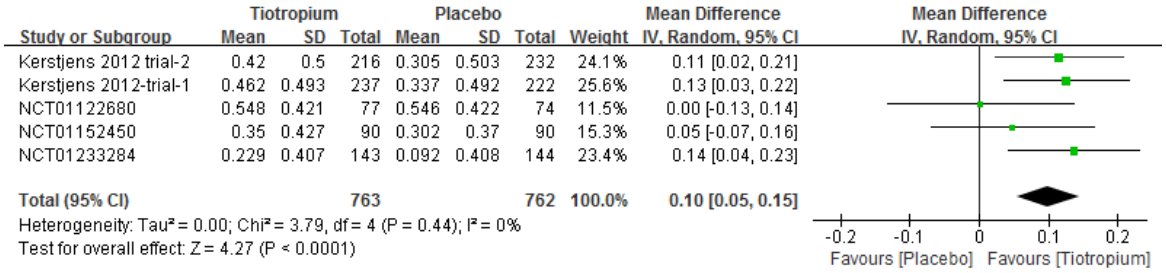
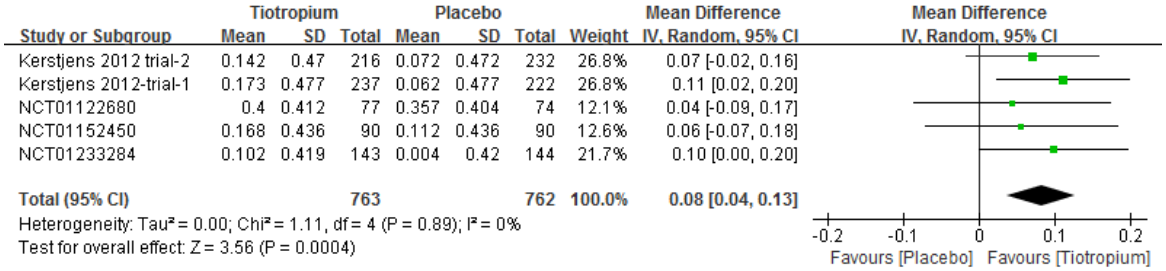



**Figure 3** Effects of tiotropium versus placebo on $FEV_1$.

(a)Change in peak FVC




(b)Change in trough FVC




(c)Change in FVC AUC $_{0\sim3h}$

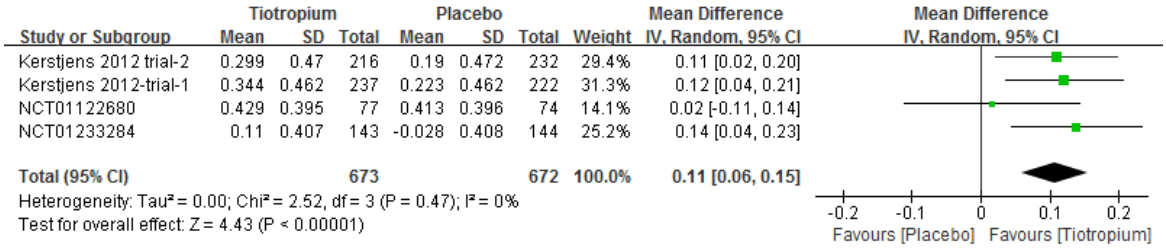



**Figure 4** Effects of tiotropium versus placebo on FVC.

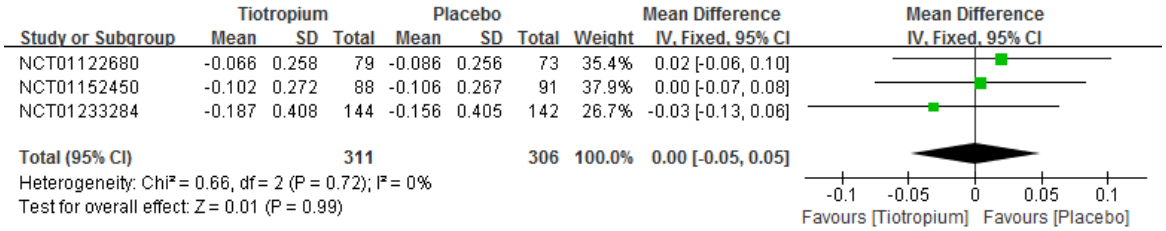



**Figure 5** Effects of tiotropium versus placebo on night awakenings.

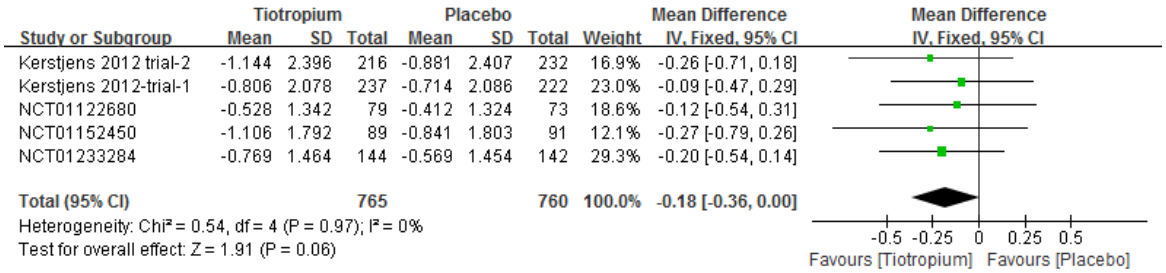
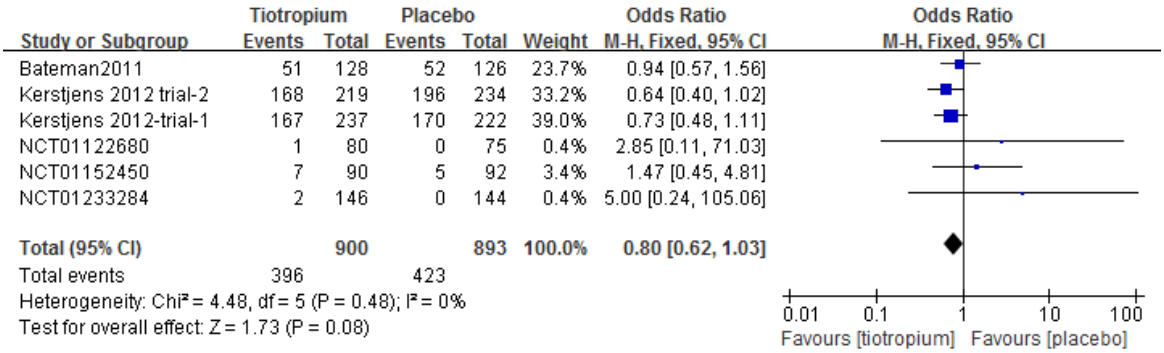



**Figure 6** Effects of tiotropium versus placebo on rescue medication use

(a)Total adverse events




(b)Serious adverse events

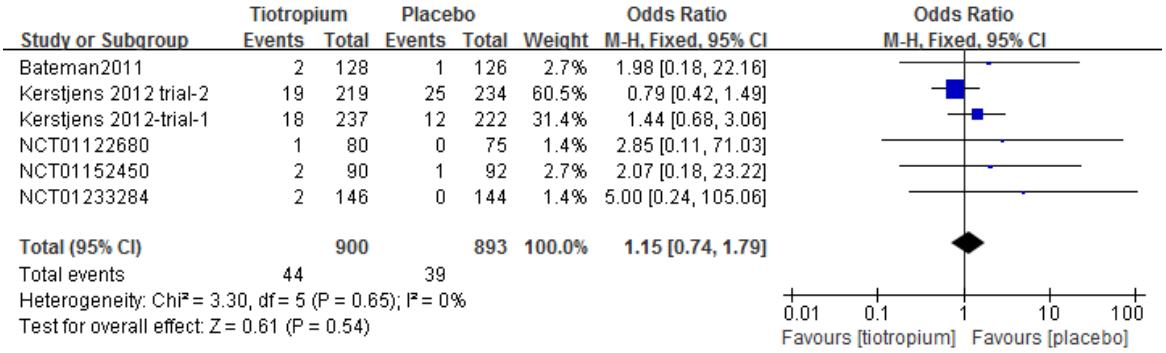



**Figure 7** Effects of tiotropium versus placebo on adverse events.