

Long-acting anticholinergic agents in patients with uncontrolled asthma: a systematic review and meta-analysis

S. W. Lee,* H. J. Kim,[†] K. H. Yoo,[‡] Y. B. Park,[§] J.-Y. Park,[¶] J. Y. Jung,[#] J.-Y. Moon,^{**} M. K. Byun,^{††}
S. W. Kim,^{‡‡} Y. H. Kim^{§§}

*Department of Pulmonary and Critical Care Medicine, and Clinical Research Center for Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [†]Institute for Evidence-based Medicine, Department of Preventive Medicine, College of Medicine, Korea University, Seoul, [‡]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, [§]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, [¶]Department of Pulmonology and Critical Care Medicine, Won Kwang University Sanbon Hospital, Sanbon, [#]Division of Pulmonology, Department of Internal Medicine, Severance Hospital, Yonsei University, College of Medicine, Seoul, ^{**}Department of Internal Medicine, Hanyang University College of Medicine, Seoul, ^{††}Division of Pulmonology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, ^{‡‡}Division of Pulmonary and Critical Care Medicine, Department of Medicine, Ewha Medical Center and Ewha Medical Research Institute, Ewha Womans University, School of Medicine, Mokdong Hospital, Seoul, ^{§§}Department of Pulmonary and Critical Care Medicine, Kyung Hee University Hospital at Gangdong, School of Medicine, Kyung Hee University, Seoul, Korea

SUMMARY

SETTING: A novel effective treatment is necessary for severe asthma.

OBJECTIVE: To review clinical trials examining the role of tiotropium in patients with poorly controlled asthma despite inhaled corticosteroid use with or without long-acting β_2 -agonists.

DESIGN: A computerised search of electronic databases (Medline, EMBASE and Cochrane Central Register) was performed. Randomised controlled trials of at least a 4-week treatment duration with findings published in English were included.

RESULTS: Five studies involving 1635 patients were analysed. Compared with a placebo or a double dose of inhaled corticosteroids, the addition of tiotropium

increased mean trough and peak forced expiratory volume in 1 second by 97 ml (95%CI 71–122) and 103 ml (95%CI 42–163), respectively. The mean differences in morning peak expiratory flow were 19.2 l/min (95%CI 11.8–26.6). Tiotropium also reduced the risk of severe acute exacerbation (OR 0.73, 95%CI 0.56–0.96) and improved Asthma Quality-of-Life Questionnaire score significantly by 0.10 (95%CI 0.04–0.16). There were no differences in serious adverse events.

CONCLUSION: The addition of tiotropium may be beneficial for patients with poorly controlled asthma, although exacerbation or safety issues should be clarified in long-term trials before its wide use in asthma.

KEY WORDS: asthma; tiotropium; anticholinergics

THE OBJECTIVE of asthma treatment is to achieve control of asthma symptoms. Inhaled corticosteroids (ICSs) are the mainstay of treatment and can effectively reduce asthma symptoms.¹ Leukotriene modifiers and long-acting β_2 -agonists (LABAs) are recommended for asthma that is not controlled with ICS. However, a substantial proportion of asthma patients do not achieve control, even after step-up therapy with high-dose ICSs, LABAs and other controllers.^{2,3} There are also safety concerns regarding the regular use of LABAs in patients with asthma,^{4,5} and the systemic side effects of ICSs should

not be underestimated.^{6,7} An alternative controller option is therefore both necessary and urgent.

Asthma is a chronic inflammatory disease characterised by airway hyperresponsiveness, which can be assessed by challenge with inhaled cholinergic drugs such as methacholine or acetylcholine.^{8,9} The cholinergic system is therefore considered to have a relevant role in asthma pathogenesis. Combined with β_2 -agonist, ipratropium shows good bronchodilation¹⁰ and reduced asthma exacerbation and hospitalisation.¹¹ However, current asthma guidelines merely state that ipratropium is a less effective asthma

Correspondence to: Yee Hyung Kim, Department of Pulmonary and Critical Care Medicine, Kyung Hee University Hospital at Gangdong, 149 Seoul 134–727, Republic of Korea. Tel: (+82) 2 440 6281. Fax: (+82) 2 440 8150. e-mail: yeehyung@gmail.com

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symptom reliever than rapid-acting inhaled β_2 -agonists, with unclear long-term benefits.³ Tiotropium is the bronchodilator of choice in symptomatic patients with chronic obstructive pulmonary disease (COPD). Tiotropium, a long-acting muscarinic antagonist (LAMA), has also shown potential as a controller of asthma,¹² but it remains to be recommended or approved for asthma treatment.

We performed a systematic review and meta-analysis of tiotropium in asthma treatment. We assessed whether this drug can improve pulmonary function, quality of life and acute exacerbation in asthma patients and thus function to control this disease.

METHODS

Data sources and search strategy

To identify potentially relevant articles, a comprehensive search was performed through electronic databases (Medline, EMBASE and Cochrane Central Register). The cut-off date for publication was 30 June 2013. Searches were limited to human studies in English. The highly sensitive search strategy for randomised trials was adopted using the following words and Medical Subject Headings terms: 'asthma', 'respiratory hypersensitivity', 'bronchial asthma', 'allergic asthma', 'cholinergic antagonists', 'anti-cholinergics', 'anti-cholinergic agents', 'cholinergic blocking agents', 'spiriva' and 'tiotropium bromide'. We also performed a manual search of the references listed in relevant review articles. As this study was a systematic review and meta-analysis, neither informed consent nor ethics approval was required.

Inclusion criteria

A systematic review and meta-analysis was performed in studies that met the following criteria: 1) randomised controlled trial that targeted adults aged ≥ 18 years and compared tiotropium with placebo or a double dose of ICSs; 2) treatment duration ≥ 4 weeks; 3) poorly controlled asthma despite ICS or ICS + LABA use; and 4) smoking history < 10 pack-years. Studies targeting patients with chronic obstructive pulmonary disease (COPD), overlap syndrome, bronchiectasis or acute exacerbation were excluded.

Study selection and data extraction

Two pulmonologists (SWL and YHK) independently retrieved potentially relevant studies, reviewed them according to the predefined criteria for eligibility, and extracted data. Any disagreement in the process of study selection or data extraction was resolved by consensus. A predefined form was used to extract data from each study. The primary outcomes were changes in trough/peak forced expiratory volume in 1 s (FEV₁) and forced volume capacity (FVC) as absolute values and morning/evening peak expiratory

flow (PEF) rates. We assessed quality of life, change in asthma-free days, frequency of rescue medicine use, Asthma Control Questionnaire (ACQ) score, number of severe acute exacerbations during follow-up, and frequency of serious adverse events. Quality of life was evaluated using the Asthma Quality-of-Life Questionnaire (AQLQ) or mini-AQLQ. Trough/peak FEV₁ and FVC, asthma-free days, and serious adverse events were used as defined by the authors of each study. Severe exacerbation was defined as a sudden worsening in respiratory symptoms, leading to the use of systemic corticosteroids or the increased use of ICSs or other asthma medications.

Quality assessment

The quality of the included studies was evaluated according to the Cochrane Handbook for Systematic Reviews of Interventions 'risk of bias' tool. A score of 'high', 'low' or 'unclear' was assigned to the following items: 1) sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other sources of bias.

Statistical analysis

Review Manager version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analyses. Statistical significance was evaluated using a raw mean difference for continuous variables and odds ratios with 95% confidence intervals (CIs) for dichotomous variables. Heterogeneity was assessed using I^2 statistics on a scale of 0–100%. We also investigated the influence of an individual study on the overall effect estimates by removing each study in turn to explore the robustness of the pooled effect. Subgroup analysis was also considered as needed. As the number of the trials included was low, we could not estimate potential publication bias with a funnel plot for all outcomes. $P < 0.05$ was considered statistically significant.

RESULTS

Identification of eligible trials

A total of 652 published articles were initially identified through database searches. After removing duplicated articles, 581 articles were screened. Of these, 13 articles underwent a full-text review. Five articles were considered appropriate for qualitative and quantitative synthesis (Figure 1).^{12–16} As a 2012 study published by Kerstjen et al. included two replicate trials,¹⁵ it was regarded as two independent trials. Six trials from five studies were thus included in the final analysis and a total of 1635 asthma patients (tiotropium vs. control: 894 vs. 899), whose mean age ranged from 42.2 to 54.8 years, were noted. Two

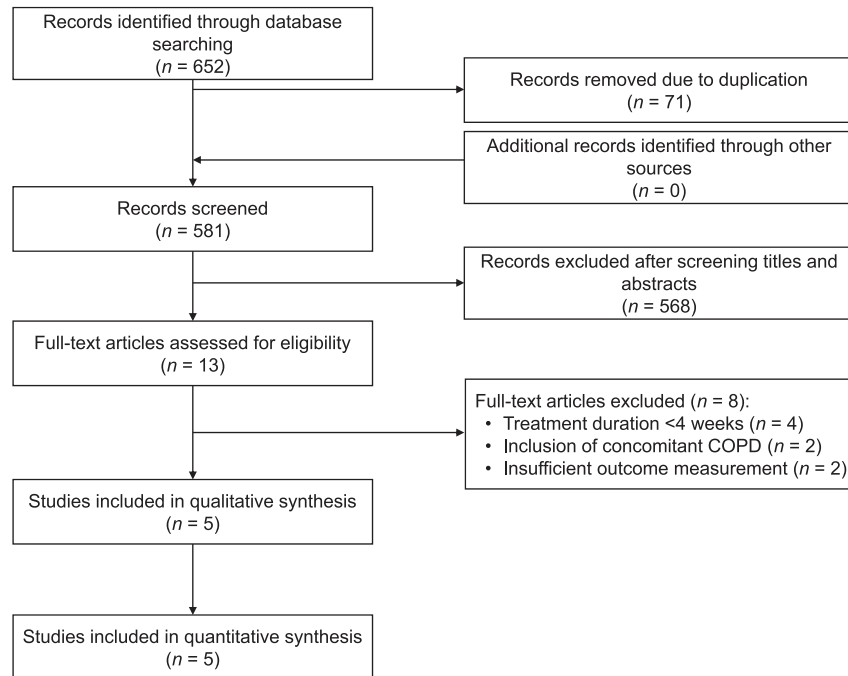


Figure 1 Study flow diagram. COPD = chronic obstructive pulmonary disease.

studies presented the number of patients screened; the proportions of included patients among those screened were 81.1% (107/132)¹⁴ and 68.3% (912/1335).¹⁵ The characteristics and quality of the trials included are shown in Table 1 and Figure 2.

Bronchodilator effect

Five trials, including two replicate trials published by Kerstjen et al., presented trough FEV₁ and FVC, respectively.^{12–15} Briefly, trough FEV₁ improved by 97 ml (95%CI 71–122, $P < 0.001$, $I^2 = 0\%$) (Figure 3A). Trough FVC also improved by 125 ml (95%CI 89–160, $P < 0.001$, $I^2 = 0\%$). Assessing the additional effect of tiotropium on ICS/LABAs, trough FEV₁ and FVC increased by 89 ml (95%CI 60–118, $P < 0.001$, $I^2 = 0\%$) and 123 ml (95%CI 84–161, $P < 0.001$, $I^2 = 0\%$), respectively.

Respectively four and three trials stated the values of peak FEV₁ and FVC.^{14–16} Overall, peak FEV₁ and FVC increased by 103 ml (95%CI 42–163, $P < 0.001$, $I^2 = 85\%$) and 112 ml (95%CI 79–145; $P < 0.001$; $I^2 = 0\%$), respectively (Figure 3B). The addition of tiotropium to ICSs/LABAs increased peak FEV₁ by 130 ml (95%CI 95–165; $P < 0.001$; $I^2 = 18\%$).

We analysed data on the PEF rate from all five available trials.^{13–16} Overall, morning and evening PEF rates improved by 19.2 l/min (95%CI 11.8–26.6, $P < 0.001$, $I^2 = 68\%$) and 23.0 l/min (95%CI 16.8–29.1, $P < 0.001$, $I^2 = 58\%$), respectively (Figure 4). Because significant heterogeneity was noted, a sensitivity analysis for morning PEF rate was conducted in four of the trials, excluding one trial published by Kerstjen et al. in 2011.¹⁴ This analysis

showed a pooled estimate of the morning PEF rate of 22.8 l/min (95%CI 17.8–27.8, $P < 0.005$, $I^2 = 0\%$). Furthermore, on excluding Peters et al.'s study from the analysis of the evening PEF rate,¹⁶ the sensitivity analysis showed that this trial might be a source of heterogeneity (pooled estimate 20.1; 95%CI 15.8–24.4, $P < 0.001$, $I^2 = 0\%$). Tiotropium increased the morning PEF rate by 17.2 l/min (95%CI 7.0–27.5, $P = 0.008$, $I^2 = 79\%$) in ICS+LABA users and by 23.5 l/min (95%CI 15.1–31.9, $P < 0.001$, $I^2 = 0\%$) in ICS-alone users. The evening PEF rate in each group also improved by 19.1 l/min (95%CI 14.2–24.1, $P < 0.001$, $I^2 = 2\%$) in ICS+LABA users and by 29.1 l/min (95%CI 17.6–40.6, $P < 0.001$, $I^2 = 63\%$) in ICS-alone users.

The effect on symptoms or quality of life

Five trials assessed quality of life using the AQLQ ($n = 3$) or mini-AQLQ ($n = 2$).^{12,13,15,16} The quality of life score assessed by the AQLQ increased by 0.1 (95%CI 0.04–0.16, $P = 0.001$, $I^2 = 0\%$) (Figure 5A), although the effect of tiotropium on the AQLQ score was not significant in ICS/LABA users (0.11, 95%CI –0.03–0.25, $P = 0.12$, $I^2 = 43\%$). The mini-AQLQ score did not improve significantly (0.06, 95%CI –0.08–0.2, $P = 0.41$, $I^2 = 0\%$).

The mean difference in terms of rescue medicine use (puffs/day) did not decrease; however, there was a declining trend (–0.21, 95%CI –0.43 to 0.02, $P = 0.07$, $I^2 = 0\%$, Figure 5B)^{13,15} A trend toward an increase in asthma-free days per week was also seen, although it was not significant (0.08, 95%CI –0.03 to 0.19, $P = 0.13$, $I^2 = 0\%$, Figure 5C).^{12,15,16} The

Table 1 Main characteristics of the RCTs included in the meta-analysis

Study, year	Design, duration	Patients, (characteristics) n	Sponsor	Baseline FEV ₁ (%)	AQLQ or mini-AQLQ	Intervention protocol	Primary end-point	Main conclusions
Fardon, 2007 ¹²	Single centre double-blind, crossover RCT, 4 weeks	18	Neolab (Manchester UK) and Cipla Ltd (Mumbai India)	51.0 ± 2.44	No remark	Salmeterol (100 µg/day) + placebo vs. salmeterol + tiotropium (18 µg/day) in patients who were on treatment with fluticasone (500 µg/day)	No remark	Tiotropium can offer small benefit when added to salmeterol + ICS No difference in mini-AQLQ score
Peters, 2010 ¹⁶	Multicentre, double-blind, triple-dummy crossover RCT, 14 weeks	210	National Heart, Lung, and Blood Institute	71.5 ± 14.9	5.43 ± 1.05	Tiotropium (18 µg/day) + beclomethasone (80 µg/day) vs. salmeterol (100 µg/day) + beclomethasone vs. double-dose beclomethasone	Morning PEF	Tiotropium was superior to double-dose ICS and not inferior to salmeterol in terms of lung function and symptom score
Bateman, 2011 ¹³	Multicentre, double-blind, double-dummy, parallel RCT, 16 weeks	388 (B16-Arg/Arg homozygotes)	Boehringer and Pfizer	75.3 ± 19.03	No remark	Addition of tiotropium (5 µg/day) was compared with addition of placebo or salmeterol (100 µg/day) in patients who were treated with ICS (budesonide)	Morning PEF	Tiotropium was superior to placebo and non-inferior to salmeterol in lung function No difference in symptom score
Kerstjens, 2011 ¹⁴	Multicentre, double-blind crossover RCT, 8 weeks	107	Boehringer and Pfizer	58.0 ± 11.6	4.8 ± 1.1	Two doses of tiotropium (5 and 10 µg/day) were compared with placebo as add-on therapy to ICS/LABA	Peak FEV ₁	Tiotropium improved lung function No difference in symptom score
Kerstjens, 2012 ¹⁵	Two replicate, multicentre, double-blind, parallel RCT, 48 weeks	912	Boehringer and Pfizer	54.8 ± 12.4	4.6 ± 1.1	Tiotropium (5 µg/day) was compared with placebo as add-on therapy to ICS/LABA	Peak/trough FEV ₁ , time to first severe acute exacerbation	Tiotropium reduced exacerbation and improved lung function added to ICS/LABA

RCT = randomized controlled trial; FEV₁ = forced expiratory volume in 1 second; AQLQ = Asthma Quality-of-Life Questionnaire; ICS = inhaled corticosteroid; PEF = peak expiratory flow; LABA = long-acting β₂-agonist.

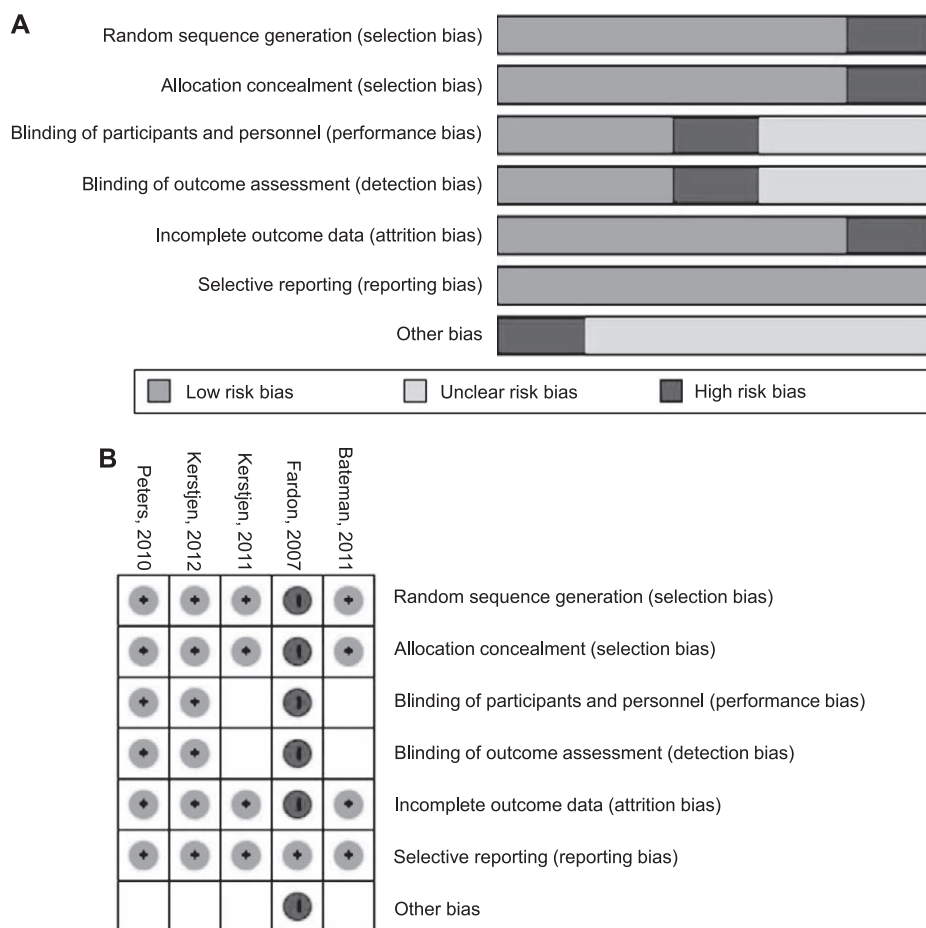


Figure 2 **A)** Risk of bias summary and **B)** risk of bias graph. Risk of bias summary reviews authors' judgments concerning risk of bias for included studies. Risk of bias graph presents authors' judgments concerning each risk of bias item presented as percentages across all included studies.

change in ACQ score decreased statistically (-0.18 , 95%CI -0.25 to -0.11 , $P < 0.001$, $I^2 = 0\%$), although it did not reach a minimally clinical important difference (Figure 5D).

Two trials evaluated the number of severe acute exacerbations of asthma.^{15,16} Although each trial failed to show statistical significance, the positive effect on the reduction in severe acute exacerbations was noted when data were pooled from these trials (OR 0.73, 95%CI 0.56–0.96, $P = 0.02$; $I^2 = 0\%$, Figure 6A).

Safety

We were able to pool data from four trials to assess serious adverse events.^{13–16} When tiotropium was added to baseline treatment, serious adverse events did not occur more frequently (OR 0.88, 95%CI 0.57–1.34, $P = 0.54$, $I^2 = 0\%$, Figure 6B).

DISCUSSION

Our study results show that tiotropium, an LAMA, can improve pulmonary function and quality of life

and reduce the number of severe exacerbations without increasing severe adverse events in short-term follow-up (≤ 48 weeks) in relatively young patients (mean age range 42.2–54.8) with uncontrolled asthma despite ICS or ICS+LABA use. Tiotropium also showed a tendency to increase the number of asthma-free days and reduce rescue medication use, although this was not statistically significant.

Bronchodilation is the most definite and consistent benefit of tiotropium in clinical trials. On the whole, tiotropium improved lung function by increasing the FEV₁, FVC, and PEF by respectively 97–103 ml, 112–125 ml and 19.2–23.0 l/min. These ranges are almost the same as those of patients with COPD.¹⁷ The improvement in lung function elicited by tiotropium was also largely similar, even when LABAs were included in the control medications. This result means that the ceiling for bronchodilation is not reached by LABAs alone,¹² giving room for LAMAs to obtain further therapeutic benefit.

Exacerbation and mortality are important issues in asthma treatment. Previous studies failed to show a

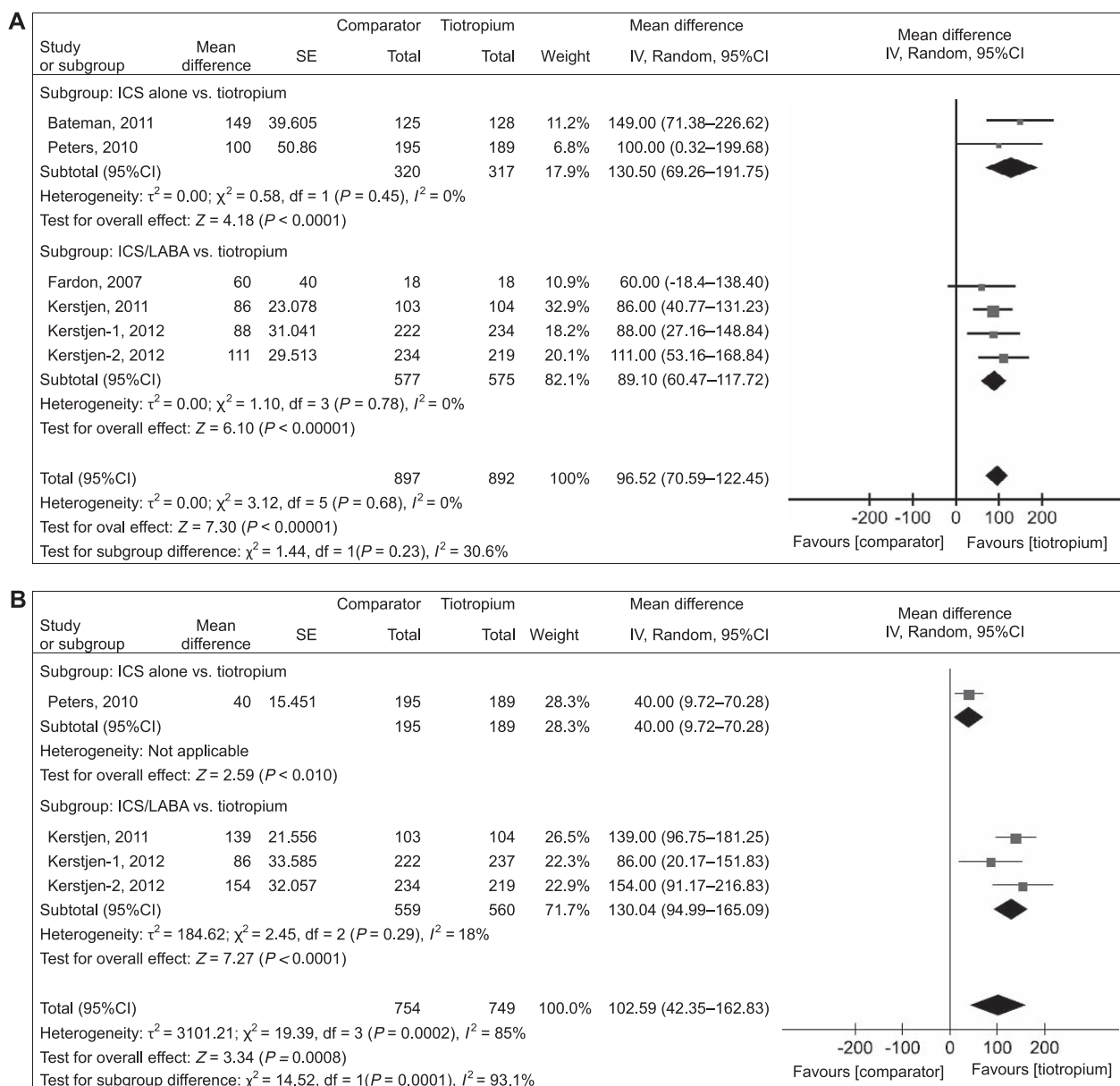


Figure 3 The differences of **A**) trough and **B**) peak forced expiratory volume in 1 second (ml) for tiotropium vs. comparators. Comparators include placebo or double dose of ICS. SE = standard error; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonists.

significant reduction in the number of exacerbation events.^{15,16} However, our meta-analysis showed that the number of events could also be reduced by tiotropium therapy. Evaluation of mortality is important, but it is not easy, as long-term follow-up and a large number of patients are required. Drugs that reduce severe exacerbations can therefore usually be expected to reduce the risk of death due to asthma. In this context, tiotropium can be introduced into asthma treatment if combined with ICSs, given that tiotropium may reduce exacerbation.

Meta-analysis for quality of life showed a significant improvement in the AQLQ. The improvement in this parameter was somewhat small, and three of the

five trials that evaluated quality of life failed to show a significant improvement. In the light of the improvement in lung function, this modest symptomatic benefit was somewhat surprising and hard to explain. One possible explanation is that there is little clinical benefit from additional bronchodilation from LAMAs in patients who already use a β_2 agonist. In addition, the AQLQ includes four domains, and although respiratory symptoms could be improved in accordance with bronchodilation, the parameters in other domains could be more resistant to improvement.

However, despite the above beneficial effects on asthma, several issues should be considered before

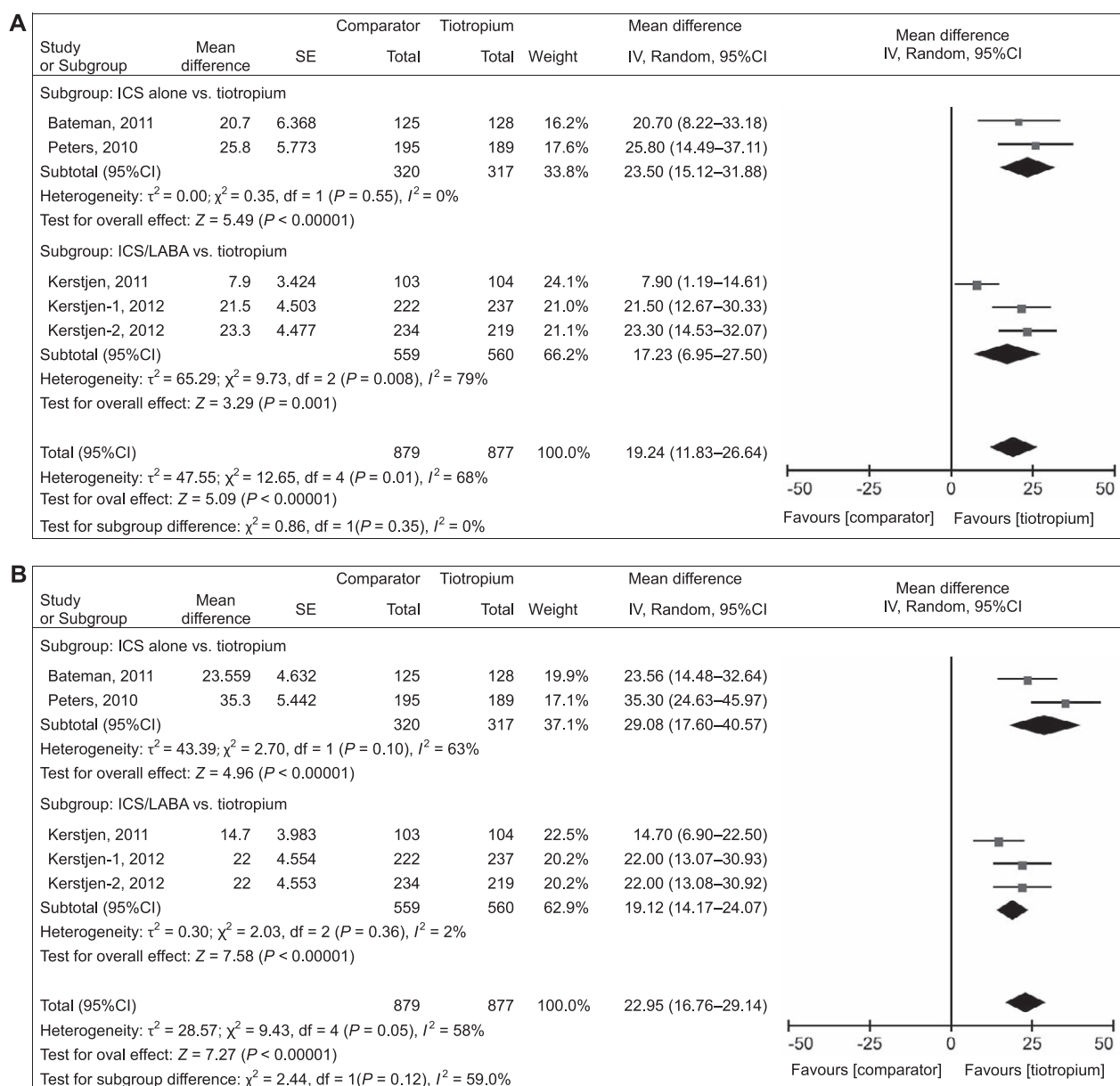


Figure 4 The differences of **A**) morning and **B**) evening peak expiratory flow rate (l/min) for tiotropium vs. comparators. Comparators include placebo or double dose of ICS. SE = standard error; ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonists.

recommending tiotropium in asthma guidelines. First, bronchodilation is the primary outcome in most studies and the main effect of tiotropium in asthma patients, but a simple improvement in lung function does not guarantee long-term effect and safety. In 1990, LABA, another major bronchodilator, was considered a major advance in asthma treatment, with evidence that LABAs improved lung function and quality of life.^{18,19} However, concerns about the possible risks associated with LABAs were raised soon after their introduction into clinical practice. Patients with asthma who discontinue ICS use after symptom control with LABAs may be at risk of severe exacerbations.²⁰ There have also been concerns about

LABAs causing a potential increase in the risk of mortality.^{20,21} The long-term usage of LABAs might also have similar issues. Safety should therefore be determined in further studies, and we should pay attention to unexpected adverse events after the introduction of tiotropium in actual clinical practice. Second, the main pathogenesis of asthma is chronic inflammation in the airway, but the anti-inflammatory effect of anticholinergics is still controversial. Although the potential anti-inflammatory effects of anticholinergic agents have been postulated in vitro,^{22,23} convincing evidence of their anti-inflammatory effect in humans is still scarce.²⁴ LABAs should be used with ICSs, as there is no evidence for their

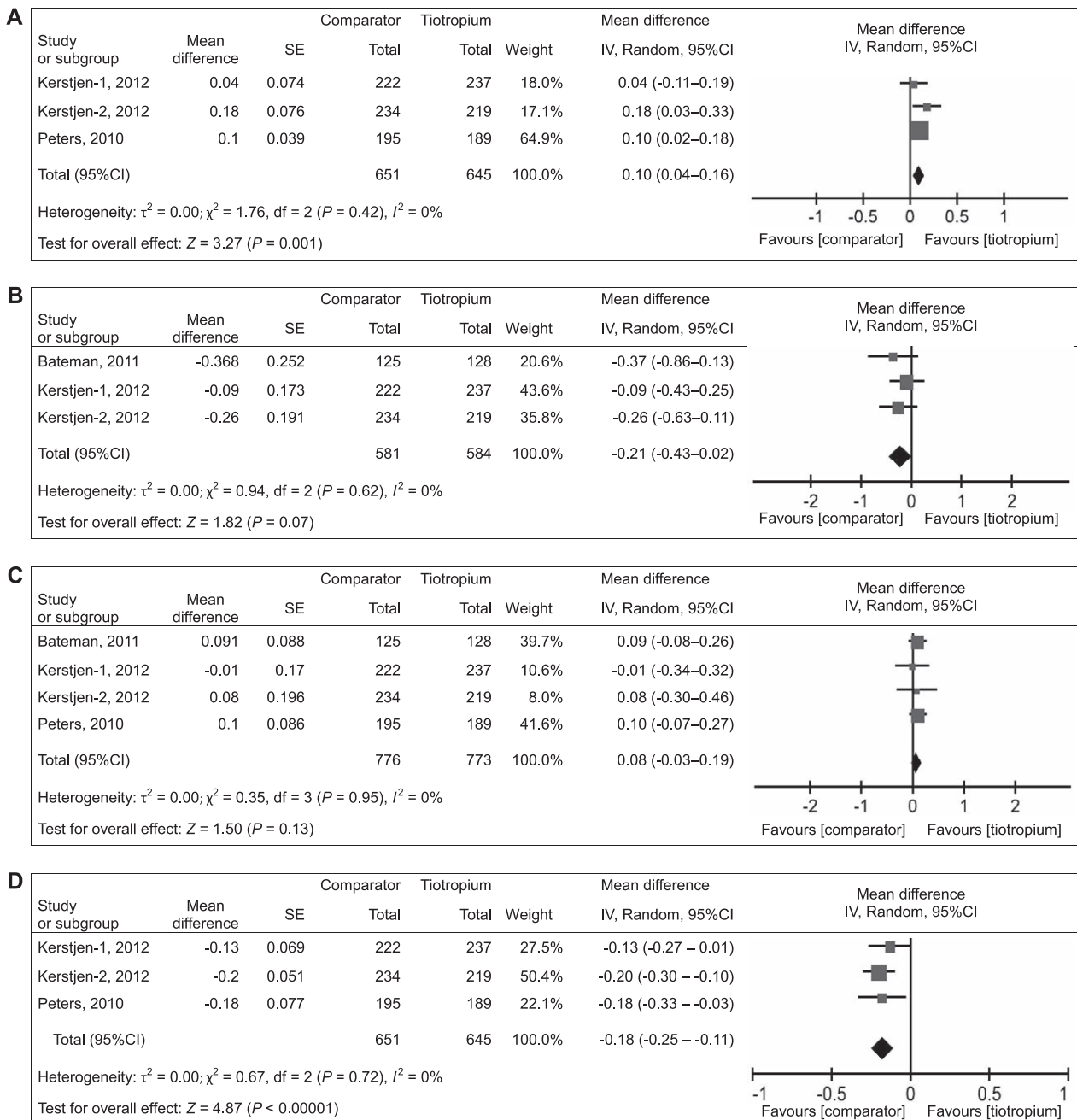


Figure 5 Changes in **A**) AQLQ, **B**) the number of days with rescue medicine use, **C**) change in asthma-free days and **D**) changes in ACQ. Comparators include placebo or double dose of ICS. SE = standard error; AQLQ = Asthma Quality-of-Life Questionnaire; ACQ = Asthma Control Questionnaire; ICS = inhaled corticosteroids.

single use in asthma. However, despite these concerns, this meta-analysis indicates that the effects of tiotropium in asthma patients are promising. Recent international guidelines on severe asthma have commented on the role of tiotropium based on several previous clinical studies.²⁵

Tiotropium is the first drug of choice in the treatment of symptomatic COPD.¹⁷ As it is sometimes very hard to distinguish asthma from COPD, the enrolment of some patients with characteristics of COPD in asthma trials may be inevitable. It is

therefore important to exclude COPD to determine the effects of tiotropium on asthma. The trials of our study used criteria including bronchodilator response,^{12,13,16} young age,¹³ smoking history (<10 pack years),^{13–16} high dose ICS users^{14,15} and long asthma history¹⁵ to enrol asthma dominant phenotype and exclude COPD. Although the potential for misclassification is still present, the trials included tried to exclude COPD using current available methods.

One other meta-analysis has also shown some

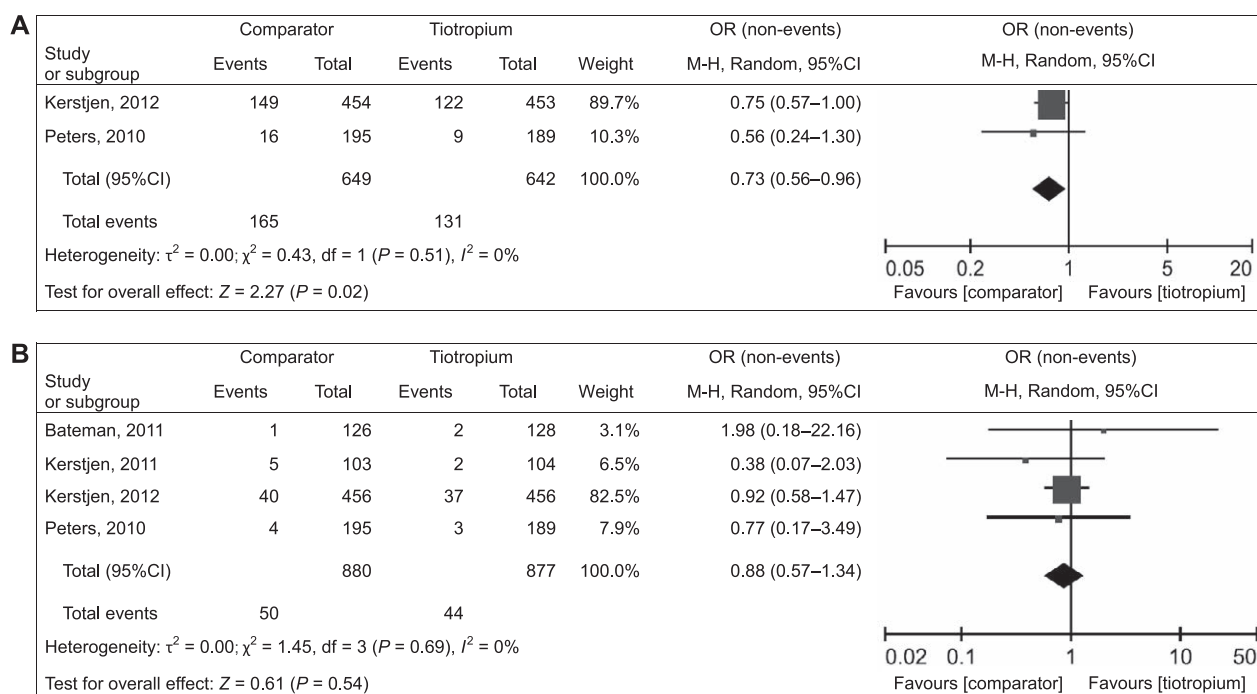


Figure 6 Relative risk of **A**) severe acute exacerbation and **B**) serious adverse events. Comparators include placebo or double dose of ICS. OR = odds ratio; ICS = inhaled corticosteroids.

benefits of tiotropium in asthma patients.²⁶ However, this study mainly focused on its bronchodilator effects and included data from non-peer-reviewed trials sponsored by pharmaceutical companies. We only included peer-reviewed studies to exclude funding biases as much as possible. Furthermore, our study showed that bronchodilation effects were preserved in patients who had already used LABAs, and exacerbation events could be reduced.

CONCLUSION

The currently available evidence indicates that tiotropium may have various beneficial effects on pulmonary function, acute exacerbation and quality of life in asthma patients. However, concerns remain about safety, and the parameters tested, with the exception of pulmonary function, only showed relatively small improvements. The small number of trials, large heterogeneity in sample size, and uncertainty of possible selection bias should also be considered before adopting tiotropium as a therapeutic agent in asthma. Further studies of long-term follow-up should be encouraged to observe actual clinical practice and select appropriate target patients.

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Conflict of interest: none declared.

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RESUME

CONTEXTE : Un traitement nouveau et efficace est nécessaire pour l'asthme grave.

OBJECTIF : Revoir les données cliniques relatives au rôle du tiotropium chez des patients atteints d'un asthme mal contrôlé malgré le recours aux corticostéroïdes inhalés avec ou sans β_2 -agonistes à libération prolongée.

SCHEMA : Une recherche informatisée a été réalisée grâce aux bases de données électroniques (Medline, EMBASE et Registre Central de Cochrane). Les essais randomisés contrôlés d'un traitement d'au moins 4 semaines et publiés en anglais ont été inclus.

RÉSULTATS : Cinq études impliquant 1635 patients ont finalement été analysées. Comparée au placebo ou à une dose double de corticostéroïdes inhalés, l'adjonction de tiotropium a accru le volume minimal moyen et le volume expiratoire maximal seconde de 97 ml (IC95%

71–122) et de 103 ml (IC95% 42–163), respectivement. Les différences moyennes du flux expiratoire maximal matinal étaient de 19,2 l/min (IC95% 11,8–26,6). Le tiotropium a également réduit le risque d'aggravation aiguë grave (OR 0,73 ; IC95% 0,56–0,96) et a amélioré significativement le score du questionnaire de qualité de vie dans l'asthme de 0,10 (IC95% 0,04–0,16). Il n'y a pas eu de différence en termes d'effets secondaires graves.

CONCLUSION : L'adjonction de tiotropium pourrait être bénéfique aux patients dont l'asthme est mal contrôlé ; cependant, les problèmes d'aggravation et de sécurité d'emploi devraient être clarifiés au cours d'essais à long terme avant son utilisation large dans l'asthme.

RESUMEN

MARCO DE REFERENCIA: Es preciso definir un nuevo tratamiento eficaz del asma grave.

OBJETIVO: Examinar los ensayos clínicos que han evaluado la eficacia del tiotropio en los pacientes aquejados de asma mal regulada pese al uso de corticoesteroides inhalados, asociados o no con agonistas β_2 de acción prolongada.

MÉTODO: Se llevó a cabo una búsqueda bibliográfica informatizada de los ensayos clínicos comparativos aleatorizados de tratamiento con una duración mínima de 4 semanas y publicados en inglés, en las bases de datos (Medline, EMBASE y el Registro Central Cochrane).

RESULTADOS: Al final, se escogieron para análisis cinco estudios que vinculaban a 1635 pacientes. La adición de tiotropio al placebo aumentó de 97 ml el promedio del punto más bajo del flujo espiratorio forzado en un segundo (IC95% 71–122) y al adicionarlo a una dosis

doble de corticoesteroides inhalados el incremento fue de 103 ml (IC95% 42–163). El promedio de las diferencias del flujo espiratorio forzado en la mañana fue 19,2 l/min (IC95% 11,8–26,6). El tiotropio también disminuyó el riesgo de aparición de exacerbaciones agudas graves (OR 0,73; IC95% 0,56–0,96) y mejoró de manera significativa en 0,10 puntos la calificación del cuestionario de calidad de vida en asma (IC95% 0,04–0,16). No se observaron diferencias en la frecuencia de reacciones adversas graves.

CONCLUSIÓN: La adición de tiotropio al tratamiento puede ser útil en los pacientes que presentan un asma mal regulada, pero se precisan ensayos a largo plazo que aclaren aspectos relacionados con las exacerbaciones y la seguridad farmacológica, antes de generalizar su uso en el tratamiento del asma.