Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: Systematic review with meta-analysis

Gustavo J. Rodrigo a,*, José A. Castro-Rodriguez b,f, Luís J. Nannini c,g, Vicente Plaza Moral d,h, Eduardo A. Schiavi e,i

a Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Av. 8 de Octubre 3020, Montevideo 11600, Uruguay
b School of Medicine, Pontificia Universidad Católica de Chile, Lira 44, 1er. piso, Casilla 114-D, Santiago, Chile
c Sección Neumología, Hospital G. Baigorria, Universidad Nacional de Rosario, Ruta 11 y E. Perón, G. Baigorria 2152, Rosario, Santa Fe, Argentina
d Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, Universitat Autonoma de Barcelona, Avda. Sant Antoni M. Claret 167, Barcelona 08005, Spain
e Hospital de Rehabilitación Respiratoria María Ferrer, Dr. Enrique Finochietto 849 (1272), Buenos Aires, Argentina

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Summary

Background: There are safety concerns regarding the use of anticholinergics in the COPD patient population. The purpose of this review was to evaluate the cardiovascular risk of regular use of inhaled tiotropium bromide in patients with COPD of any severity.

Methods: Systematic searches were conducted in MEDLINE, EMBASE, the Cochrane Controlled Trials Register, manufacturers’ trial register, and FDA databases, without language restriction. Primary outcomes were a composite of major adverse cardiovascular events, cardiovascular mortality, and nonfatal myocardial infarction (MI) or stroke during the treatment period. Relative risks (RR) were estimated using fixed-effects models and statistical heterogeneity was estimated with the I² statistic.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; MI, myocardial infarction; RCTs, randomized controlled trials; RR, relative risk; SF, salmeterol/fluticasone.

* Corresponding author. Tel.: +5982 708 2354; fax: +5982 900 6313.
E-mail addresses: gurodrig@adinet.com.uy (G.J. Rodrigo), jacastro17@hotmail.com (J.A. Castro-Rodriguez), nanninilj@cimero.org.ar (L.J. Nannini), vplaza@santpau.es (V.P. Moral), eduardo.schiavi@gmail.com (E.A. Schiavi).

f Tel.: +562 354 8189; fax: +562 354 8122.
g Tel.: +54341 448 2068.
h Tel.: +3493 556 5972; fax: +3493 556 5601.
i Tel./fax: +54 4307 2567.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem. Current treatments may reduce symptoms, increase exercise capacity, reduce the number of exacerbations, and improve the health status of patients. Treatment guidelines indicate that bronchodilators are the standard of care in COPD patients. Specifically, anticholinergic agents are of particular value since vagal cholinergic tone appears to be a reversible component of airway narrowing. Tiotropium bromide, the most widely prescribed agent for the treatment of COPD in the world [Boehringer Ingelheim. Annual report 2007. http://www.boehringer-ingelheim.com/corporate/download/ar/AR2007.pdf (accessed 05.01.09)] has been available in Europe since 2002 and it was approved for use in the United States in early 2004. It is a synthetic quaternary anticholinergic agent with two important characteristics: it acts through prolonged M3 muscarinic receptor antagonism, and has a long duration of action, making it appropriate for once daily therapy. Substantial evidence from controlled studies in patients with COPD has shown greater benefits with tiotropium than with placebo, ipratropium or salmeterol.

Although a previous pooled analysis of 19 short-term placebo-controlled trials revealed no significant increase in the risk of cardiovascular (CV) adverse events with tiotropium bromide, two recent publications, a nested case-control study, and a systematic review with meta-analysis reported an increased risk for all-cause and CV mortality, myocardial infarction (MI) and stroke in COPD patients who received tiotropium or inhaled anticholinergics. Nevertheless, these studies have received criticism like inability to adjust for the duration of the treatment or double-counting of trials. On the contrary, a recent pool analysis which combines data from the tiotropium trials included in the Singh meta-analysis with published data from the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial concludes that tiotropium does not carry CV risks. However, this analysis did not include information on its methodology, and only assessed composite outcomes. Thus, accounting for these contradictory and limited messages regarding the security of inhaled anticholinergics, we performed an independent systematic review (according to the QUOROM statements) to evaluate the safety of regular use of inhaled tiotropium bromide in patients with any severity of COPD.

Methods

Search strategy and eligibility criteria

The search was conducted using different strategies. First, we searched MEDLINE (1966–May 2009), EMBASE (1980–May 2009) and Cochrane Controlled Trials Register (CENTRAL) (second quarter 2009) databases using the following MeSH, full text and keyword terms: tiotropium bromide OR Spiriva AND COPD OR chronic obstructive pulmonary disease. Second, a search of relevant files from Boehringer Ingelheim (http://trials.boehringer-ingelheim.com/com/Home/TrialResults/index.jsp) and FDA (www.fda.gov) clinical trials databases was performed. Third, reviews and texts were searched for citations. Finally, we contacted the manufacturer of tiotropium and obtained data from an updated integrated tiotropium clinical trial database. Trials published solely in abstract form were excluded because methods and results could not be fully analyzed. The search was without language restriction and unpublished studies were included.

The specific inclusion criteria were: 1) adult patients aged greater than 35 years with stable COPD satisfying American Thoracic Society/European Respiratory Society, or GOLD diagnostic criteria; 2) intervention: inhaled tiotropium bromide as the intervention drug compared with placebo or long-acting beta agonists (LABA) or LABA plus inhaled corticosteroid (ICS); 3) length of treatment: studies with more than 4 weeks of duration; 4) design: randomized (parallel group or cross-over) controlled trials (RCT); 5) primary outcomes: major adverse CV outcome composite (composite of nonfatal MI, stroke and CV death), CV mortality (including sudden death), nonfatal MI, and nonfatal stroke (including transient ischemic attack) during treatment period. All-cause mortality was determined as a secondary outcome.

Data extraction and validity assessment

Titles, abstracts, and citations were independently analyzed by all reviewers. From full text, they independently assessed studies for inclusion based on the criteria for population, intervention, study design and outcomes. Any disagreement over study inclusion was resolved by consensus. Two reviewers (GJR and LJN) extracted data from the selected studies and assessed each study for the

Results: Nineteen randomized controlled trials (18,111 participants) were selected. There was no difference in the incidence of adverse cardiovascular events (RR = 0.96; 95% CI, 0.82–1.12, I² = 6%). Among individual components of the composite outcome, tiotropium did not significantly increase the risk of cardiovascular death (RR = 0.93; 95% CI, 0.73–1.20, I² = 1%), nonfatal MI (RR = 0.84; 95% CI, 0.64–1.09, I² = 0%), and nonfatal stroke (RR = 1.04; 95% CI, 0.78–1.39, I² = 0%). A smoking history of ≥55 pack-years presented a trend to a higher rate of cardiovascular adverse events in patients receiving tiotropium.

Conclusions: Compared with control (placebo or salmeterol), tiotropium did not significantly increase the risk of adverse major cardiovascular events among COPD patients. Subgroup analysis suggested that smoking history can modify the risk of cardiovascular adverse events.
sequence generation, allocation sequence concealment, blinding, incomplete outcome data, and selective outcome reporting and other potential sources of bias. In the case of multiple published or unpublished reports for a particular study, data from the most recent version were extracted.

Data analysis

All outcomes were pooled using common relative risk (RR) and 95% confidence interval (CI). If pooled effect estimates for dichotomous outcomes were significantly different between groups, we calculated the number needed to harm (NNH) to cause an event. Heterogeneity was tested by means of the DerSimonian and Laird Q statistic. Heterogeneity was further measured by using the I² test. Values of 50% or more indicate a substantial level of heterogeneity. Without substantial heterogeneity, data were combined by mean of a fixed-effects model; otherwise, a random-effects model was used. A predefine sensitivity analysis was conducted to explore the influence of the following factors: the effect size for concealment allocation (adequate vs. unclear), trial duration (long-term >6 months to 4 years vs. short-term 6 weeks to 6 months), concomitant use of inhaled corticosteroids (≥55% of patients vs. <55% of patients) and smoking history (≥55 pack-years vs. <55 pack-years). Subgroups were compared using the interaction test. A p value <0.05 using a two-tailed test was considered to indicate significance. This meta-analysis was performed with the Review Manager 5.0.20 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results

A total of 19 RCT including 18,111 patients met the inclusion criteria and were selected for analysis (Fig. 1). Of them, fifteen studies compared tiotropium vs. placebo, two studies compared tiotropium vs. salmeterol/fluticasone (SF), one study compared tiotropium vs. salmeterol vs. placebo, and one compared tiotropium vs. salmeterol. Two trials were unpublished. There was a total agreement between the reviewers on inclusion of studies. Some of the selected studies reported results for patients enrolled in previous trials. Thus, Casaburi et al. reported combined results from Casaburi et al. and a similar unpublished trial. Likewise, Brusasco et al. presented combined results of Donohue et al. and a similar unpublished trial. Therefore, only Casaburi et al. and Brusasco et al. were included in the analysis.

There were seven long-term trials (28 weeks to 48 months) and twelve short-term trials (8 weeks to 6 months) (Table 1). The mean age of patients was 64.8 years (74% of males), with an average baseline FEV₁ of 41% of predicted normal values. Regarding allocation concealment, it was adequate in only 4 studies and unclear in the remaining fifteen. Withdrawal rate was available for all trials and ranged from 0% to 45.1%. The withdrawal rate was lower with tiotropium than with placebo (25.4% vs. 31.1%, p = 0.0001) or salmeterol (12.4% vs. 16.0%, p = 0.05). Contrary, the withdrawal rate was significantly higher with tiotropium compared with SF (38.6% vs. 33.0%, p = 0.03). Tiotropium was administered once a day via a HandiHaler device (Boehringer Ingelheim, Ingelheim am Rhein, Germany, 18 mcg) in 18 studies, and via the Respimat device (Boehringer Ingelheim, Ingelheim am Rhein, Germany, 5 or 10 mcg) in one study.

Primary outcomes

Data from fifteen studies with 15,695 patients (thirteen comparing tiotropium vs. placebo) showed no significant difference in the incidence of major composite adverse CV events between the tiotropium and control groups (3.6% vs. 4.0% respectively) (Fig. 2). The post-hoc subgroup analysis (based in thirteen trials that compared tiotropium with placebo) did not show significant differences regarding the duration of treatment, allocation concealment, and concomitant use of ICS. On the contrary, studies with COPD patients with a smoking history ≥55 pack-years presented a trend to a higher rate of composite CV events. It is to emphasize that the analysis of the two studies that compared tiotropium with SF showed an opposite effect with a significant higher incidence of adverse events in the tiotropium group.

Among individual components of the composite outcome, ten studies involving 13,356 patients (nine studies comparing tiotropium vs. placebo) showed that inhaled tiotropium did not significantly increase the risk of CV death (1.7% vs. 1.9% respectively).
On the other hand, inhaled tiotropium did not significantly increase the risk of nonfatal MI compared with placebo, or salmeterol or SF (1.6% vs. 2.0% respectively) (Fig. 4). Finally, the incidence of nonfatal stroke was equivalent with tiotropium than with controls (1.8% vs. 1.8% respectively) (Fig. 5). There was no evidence of statistical heterogeneity among the included trials for any of these end points. Because one study contributed with the largest weight in the fixed-effects model, we excluded it in a new analysis limited to the remained trials. However, this exclusion did not change the primary conclusions on adverse CV composite (RR = 1.31; 95% CI, 0.94–1.81, \( I^2 = 0\% \), \( p = 0.57 \)), CV mortality (RR = 1.68; 95% CI, 0.98–2.78; \( I^2 = 0\% \), \( p = 0.08 \)), MI (RR = 0.94; 95% CI, 0.59–1.52; \( I^2 = 0\% \), \( p = 0.81 \), and stroke (RR = 1.12; 95% CI, 0.43–2.90; \( I^2 = 0\% \), \( p = 0.81 \)) respectively.

### Secondary outcome

Tiotropium did not significantly increase the risk of all-cause mortality (RR = 0.97; 95% CI, 0.86–1.09; \( I^2 = 20\% \), \( p = 0.61 \)) in meta-analysis of sixteen studies involving 17,051 patients. Once more, a study comparing tiotropium with SF showed a significant higher incidence of all-cause deaths in the tiotropium group (RR = 1.87; 95% CI, 1.07–3.28, \( p = 0.03 \)). Finally, the exclusion of the study

<table>
<thead>
<tr>
<th>First author [Reference]</th>
<th>Location and duration</th>
<th>Patients, n (% male)</th>
<th>Mean age, y</th>
<th>Mean baseline FEV1, % predicted</th>
<th>Smoking history</th>
<th>Withdrawal rate (%)</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman20 12 centers; 6 wk</td>
<td>T: 56 (67.9)</td>
<td>62.4</td>
<td>45.9</td>
<td>57.1%</td>
<td>0</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Briggs21 50 centers; 12 wk</td>
<td>S: 325 (68.0)</td>
<td>64.6</td>
<td>37.7</td>
<td>56.1 pack-yrs</td>
<td>3.9</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Brusasco22 18 countries; 24 wk</td>
<td>S: 405 (75.1)</td>
<td>64.1</td>
<td>37.7</td>
<td>44.8 pack-yrs</td>
<td>18.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casaburi23 50 centers; 52 wk</td>
<td>T: 550 (66.5)</td>
<td>65.0</td>
<td>39.1</td>
<td>63.0 pack-yrs</td>
<td>18.7</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Casaburi24 17 centers; 25 wk</td>
<td>T: 55 (54.5)</td>
<td>65.9</td>
<td>32.6</td>
<td>58.7 pack-yrs</td>
<td>14.5</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Chan25 101 centers; 48 wk</td>
<td>T: 608 (59.0)</td>
<td>66.8</td>
<td>39.4</td>
<td>50.2 pack-yrs</td>
<td>27.5</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Covelli26 12 centers; 12 wk</td>
<td>T: 100 (66.0)</td>
<td>65.8</td>
<td>40.2</td>
<td>66.0 pack-yrs</td>
<td>10.0</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Criner27 20 centers; 8 wk</td>
<td>T: 80 (75.0)</td>
<td>61.8</td>
<td>41.9</td>
<td>45.6 pack-yrs</td>
<td>5.0</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Dusser28 177 centers; 54 wk</td>
<td>T: 500 (89.0)</td>
<td>64.5</td>
<td>48.2</td>
<td>27%</td>
<td>23.4</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Moita29 31 centers; 12 wk</td>
<td>T: 144 (95.0)</td>
<td>63.6</td>
<td>41.4</td>
<td>57.1 pack-yrs</td>
<td>7.5</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Niewoehner30 26 centers; 26 wk</td>
<td>T: 915 (99.0)</td>
<td>68.1</td>
<td>35.6</td>
<td>69.4 pack-yrs</td>
<td>26.7</td>
<td>Adequate</td>
<td></td>
</tr>
<tr>
<td>Powrie11 Single centre; 52 wk</td>
<td>T: 69 (69.6)</td>
<td>66.3</td>
<td>50.9</td>
<td>54.6 pack-yrs</td>
<td>30.4</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Spiriva 205–25032 2 centers; 28 wk</td>
<td>T: 76 (82.8)</td>
<td>64.6</td>
<td>39.6</td>
<td>33.0 pack-yrs</td>
<td>15.7</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Spiriva 205–25733 294 centers; 12 wk</td>
<td>T: 1236 (76.0)</td>
<td>62.2</td>
<td>46.4</td>
<td>NS</td>
<td>18.1</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Tashkin13 490 centers; 48 mo</td>
<td>T: 2986 (75.4)</td>
<td>64.5</td>
<td>39.5</td>
<td>49.0 pack-yrs</td>
<td>36.8</td>
<td>Adequate</td>
<td></td>
</tr>
<tr>
<td>Tonnel34 123 centers; 40 wk</td>
<td>T: 3006 (73.9)</td>
<td>64.5</td>
<td>39.3</td>
<td>48.4 pack-yrs</td>
<td>45.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogelmeier35 86 centers; 24 wk</td>
<td>T: 76 (82.8)</td>
<td>64.6</td>
<td>39.6</td>
<td>33.0 pack-yrs</td>
<td>15.7</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Voshaar36 64 centers; 12 wk</td>
<td>T: 360 (70.5)</td>
<td>64.0</td>
<td>39.5</td>
<td>52.5 pack-yrs</td>
<td>9.4</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Wedzicha37 20 countries; 24 mo</td>
<td>T: 665 (84)</td>
<td>65.0</td>
<td>39.4</td>
<td>39.5 pack-yrs</td>
<td>41.9</td>
<td>Adequate</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) Pl = placebo; mo = months; NS = Not stated; S = salmeterol; SF = salmeterol/fluticasone; T = tiotropium; wk = weeks; yrs = years.
by Tashkin et al.\textsuperscript{13} did not modify the conclusion (RR = 1.15; 95% CI, 0.85–1.57; $I^2 = 18\%$, $p = 0.33$).

**Discussion**

This is the largest systematic review with meta-analysis designed to evaluate the safety of regular use of tiotropium bromide in patients with COPD of any severity. Our analysis included 19 RCT (comparing tiotropium with placebo, or with salmeterol or with SF), with more than 18,000 patients, and found that tiotropium did not increase the risk of CV mortality, nonfatal CV events (MI and stroke), and all-cause mortality compared with controls. However, because most of included studies compared tiotropium with placebo, these conclusions are based mainly in this comparison. However, when we included in the analysis data from four studies\textsuperscript{20–22,37} that compare tiotropium with salmeterol or SF, the summary effect estimate did not change, without evidence of clinical and statistical heterogeneity between trials. A more detailed analysis showed that contrary to the tiotropium vs. salmeterol comparisons\textsuperscript{20,37} displayed an opposite tendency. Thus, the use of SF was associated with a non-significant lower incidence in CV mortality\textsuperscript{37} and MI incidence.\textsuperscript{20–37} In a similar way, the Wedzicha et al. trial\textsuperscript{37} showed a significant decrease in the all-cause mortality rate compared with tiotropium, suggesting a protective effect of ICS. Although the withdrawal rate was similar between tiotropium and SF in a 6-week trial,\textsuperscript{20} in the 2-year Wedzicha study\textsuperscript{37} the withdrawal rate was significantly higher with tiotropium compared with SF (due to COPD exacerbations, perceived lack of efficacy, or unwillingness to remain in the study). Conversely, there was a small but significant increase in reported pneumonia in the SF-treated group.

The influence on the results was explored through sensitivity analysis (Table 2). Although limited by its post-hoc nature, the subgroup analysis suggests that some factors could modify the risk of CV adverse events. Thus, while there were no significant differences between short and long-term trials, adequate or unclear allocation concealment, and concomitant use of ICS, data suggested that the risk could be modified according the CV risk profile of patients. Thus, patients with a smoking history of $\geq 55$ pack-years presented a trend to a higher incidence of major CV adverse events.

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**Figure 2** Pooled relative risk for major adverse composite cardiovascular events (with 95% confidence interval) of eligible studies comparing inhaled tiotropium with control.
The results of our review contradict a recent meta-analysis that focused on the CV safety of anticholinergics in COPD. Specifically, Singh et al. performed a systematic review on the basis of 17 selected RCT, and concluded that anticholinergics (tiotropium and ipratropium) are associated with a significantly increased risk of CV death, MI or stroke. However, there were several important differences between the Singh et al. study and our current analysis. 1) Singh et al. performed a pool analysis of a mix of studies that compared tiotropium vs. placebo (eight studies), tiotropium vs. salmeterol (one study), tiotropium vs. SF (one study), tiotropium vs. salmeterol vs. placebo (two studies), ipratropium vs. placebo (one study), ipratropium vs. salmeterol (one study), and ipratropium vs. albuterol vs. placebo (three studies). So, placebo-controlled trials were pooled together with active controlled trials, assuming that the comparator drug is interchangeable with a placebo. 2) On the contrary, we focus our analysis exclusively to tiotropium comparisons (vs. placebo, salmeterol or SF). 3) The meta-analysis by Singh et al. showed a significant increase in the nonfatal or fatal cardiovascular risk based in the ipratropium vs. control comparison (RR = 1.70; 95% CI, 1.19 to 2.42; I² = 0%, p = 0.003). Contrary, in the same analysis, twelve studies that compared tiotropium vs. control (placebo or salmeterol or SF) did not show a significant higher incidence of adverse severe cardiovascular events (RR = 1.43; 95% CI, 0.95 to 2.16; p = 0.08; I² = 0%, p = 0.08). The difference in the CV events was primary derived from four (three comparing tiotropium with placebo and one with SF) long-term studies (duration of study > 6 months). Furthermore, the difference in CV events could be due to bias. Thus, Oba et al. found evidence of possible publication bias when long-term studies were analyzed statistically and graphically. 4) Two of the twelve included studies represented redundant data and should have been excluded. 5) Our review added nine new RCT studies with more than 10,000 COPD patients; additionally, we excluded two redundant studies selected in a previous review. 6) The Singh et al. study assessed as a primary outcome measure a composite of nonfatal major adverse CV events and CV death; additionally, the risk of all-cause mortality was determined as a secondary outcome. Our review not only includes these two outcomes but also adds to the analysis the incidence of MI, stroke and CV deaths. 7) In the Singh et al. review, the number of the control group in the study by Chan et al. was 305 instead 350.

Our review meets most of the methodological criteria suggested for scientific reviews. We selected seven new published and two unpublished RCT that reported at least one fatal or nonfatal CV event, with more than 10,000 new COPD patients; additionally, we excluded two redundant studies selected in a previous review. All of the selected studies were RCT and combined with no evidence of clinical and statistical heterogeneity between trials, increasing the confidence of our findings. Among the studies added, the UPLIFT trial is the longest (4-year) and largest study (almost 6000 patients with COPD) that

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**Figure 3** Pooled relative risk for cardiovascular mortality (with 95% confidence interval) of eligible studies comparing inhaled tiotropium with control.
Figure 4  Pooled relative risk for nonfatal myocardial infarction (with 95% confidence interval) of eligible studies comparing inhaled tiotropium with control.

Figure 5  Pooled relative risk for stroke (with 95% confidence interval) of eligible studies comparing inhaled tiotropium with control.
Table 2  Sensitivity analysis. Comparisons between Relative Risks (RR) in composite adverse cardiovascular events stratified by concealment allocation (adequate vs. unclear), trial duration (long-term >6 months to 4 years vs. short-term 6 weeks to 6 months), concomitant use of inhaled corticosteroids (>55% vs. <55% of patients), and smoking history (>55 pack-years vs. <55 pack-years).

<table>
<thead>
<tr>
<th>Subgroup comparisons</th>
<th>RR (95%CI)</th>
<th>Interactive test17 RR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate13,30,34 vs. unclear22–26,28,29,31,32,36</td>
<td>0.87 (0.74–1.04), I² = 0% vs. 1.15 (0.73–1.82), I² = 4%</td>
<td>1.32 (0.81–2.15)</td>
<td>0.26</td>
</tr>
<tr>
<td>Long-term13,23,25,28,31,32,34 vs. short-term12,24,26,27,29,30,33–36</td>
<td>0.90 (0.76–1.07), I² = 24% vs. 1.10 (0.54–2.28), I² = 0%</td>
<td>1.22 (0.58–2.56)</td>
<td>0.59</td>
</tr>
<tr>
<td>&gt;55 pack-years13,22,25,28,31,32,34,36 vs. &lt;55% of patients22–25,28,32,34,36</td>
<td>0.89 (0.75–1.06), I² = 0% vs. 2.91 (0.88–9.57), I² = 0%</td>
<td>1.20 (0.72–2.00)</td>
<td>0.47</td>
</tr>
<tr>
<td>&lt;55 pack-years23,24,26,29,30 vs. ≥55 pack-years23,24,26,29,30</td>
<td>0.87 (0.74–1.03), I² = 0% vs. 1.51 (0.79–2.81), I² = 0% vs. 1.73 (0.90–3.37)</td>
<td>0.09</td>
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</tbody>
</table>

Compared inhaled tiotropium with placebo. However, the UPLIFT study is different from previous tiotropium trials. Thus, because its protocol allowed the use of short acting anticholinergics for the treatment of COPD exacerbations, the potential cardiotoxic effect of these drugs administered in both arms, could potentially mask the CV adverse effects of tiotropium. However, after we excluded this study, the conclusions did not change through the different outcomes assessed.

In summary, the conclusions of this review were: 1) inhaled tiotropium did not increase the risk of major adverse CV events (MI, stroke, CV deaths) and all-cause mortality. 2) Unlike other comparisons (tiotropium vs. placebo or salmeterol), the use of SF was associated with a lower incidence in CV events and all-cause mortality compared with tiotropium, suggesting a protective effect of ICS. Conversely, there was a small but significant increase in reported pneumonia in the SF-treated group. Nevertheless, these conclusions are based mainly in data from one study. 3) Subgroup analysis suggests that the smoking history could modify the risk of CV adverse events. So, caution should be advised in patients at risk for CV disease. The same is true for SF in patients at high risk for pneumonia. 4) Because none of the trials were prospectively designed to assess the CV risk of inhaled anticholinergics in patients with COPD, CV outcomes may not have been prospectively defined in a uniform fashion across the trials. Adequately designed randomized trials prespecified on CV outcomes will allow to clarify completely this issue.

Conflict of interests

Dr. Rodrigo has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Dr. Esteve SA and Merck Sharp and Dome. Dr. Castro-Rodriguez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Merck Sharp and Dohme, GlaxoSmithKline and Grunenthal; and as member of advisory board for GlaxoSmithKline. Dr. Nannini has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca and Altana. Dr. Plaza has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline, Dr. Esteve SA and Merck Sharp and Dohme. Dr. Schiavi has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca and Boehringer Ingelheim. He has also participated as a member of advisory board for Boehringer Ingelheim.

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