Tiotropium formulations and safety: a network meta-analysis

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Abstract: Tiotropium is now delivered *via* two different inhaler devices: the original Handihaler 18 µg once daily, which uses a powder formulation; and the newer Respimat Soft Mist Inhaler (SMI) 5 µg once daily. It has been questioned whether the two devices can be assumed to have the same safety profile, although the TIOSPIR trial showed that tiotropium when administered *via* Respimat SMI 5 µg is not less safe than Handihaler 18 µg. Therefore, we have carried out a safety evaluation of tiotropium Handihaler 18 µg *versus* tiotropium Respimat SMI 5 µg and 2.5 µg, *via* systematic review and network meta-analysis of the currently available clinical evidence. The results of our meta-analysis with an extremely large number of patients analysed demonstrate that the safety profile of tiotropium HandiHaler is generally superior to that of tiotropium Respimat SMI, although no statistical difference was detected between these two devices. However, the SUCRA analysis favoured tiotropium Respimat SMI with regards to serious adverse events (AEs). We do not believe that using Respimat SMI rather that HandiHaler exposes patients to higher risks of real AEs. Rather, we believe that there may be a different cardiovascular (CV) response to muscarinic receptors blockage in individual patients. Therefore, it will be essential to make all possible efforts to proactively identify patients at increased risk of CV AEs when treated with tiotropium or another antimuscarinic drug.

Keywords: tiotropium, respimat SMI, handihaler, safety, COPD, meta-analysis

Introduction

There is well-built evidence indicating that tiotropium bromide is important in the maintenance treatment of chronic obstructive pulmonary disease (COPD) [Matera *et al.* 2014]. In fact, several large controlled trials have allowed documenting that this long-acting antimuscarinic agent not only improves lung function and reduces dyspnoea and rescue medication use in patients with COPD, but also impacts positively on health-related quality of life and reduces the risk of exacerbations, including those that require hospitalization [Keating, 2012; Karner *et al.* 2012].

However, concerns have been raised about the possible associations of tiotropium with cardiovascular (CV) morbidity and mortality [Singh *et al.* 2008], although a lot of data that have been generated since the publication of the first concerns were reassuring on the CV safety of tiotropium in COPD patients [Cazzola *et al.* 2010]. In particular, Celli and colleagues [Celli *et al.* 2010] revised 30 trials lasting at least 4 weeks, in which overall 10,846 patients received tiotropium, and documented a significant reduction in the risk of a major or even fatal CV event in the tiotropium group compared with the placebo group. Furthermore, a *post hoc* analysis of all-cause mortality and serious cardiac adverse events (AEs) in patients who suffered from cardiac arrhythmia, myocardial infarction (MI) or cardiac failure during the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study and completed the study, documented that tiotropium did not increase the risk of a major or even fatal CV event, following the occurrence of a cardiac event [Tashkin *et al.* 2015].

Tiotropium is now delivered *via* two different inhaler devices: the original Handihaler 18 µg once daily, which uses a powder formulation, and the newer Respimat Soft Mist Inhaler (SMI) 5 µg

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once daily. Respimat SMI delivers a higher fine-particle dose and allows higher drug deposition in the lung compared with aerosols produced by HandiHaler [Cazzola and Rogliani, 2015]. Remarkably, tiotropium HandiHaler 18 μg and Respimat SMI 5 μg have similar pharmacokinetic profiles. A recent extensive comparative pharmacokinetic and bronchodilator efficacy study in patients with COPD demonstrated a lower exposure but similar bronchodilator efficacy of once-daily tiotropium Respimat SMI 5 μg compared with tiotropium HandiHaler 18 μg [Hohlfeld *et al.* 2014].

Nonetheless, it has been questioned whether the two devices can be assumed to have the same safety profile [Cates, 2011]. In fact, Singh and colleagues [Singh *et al.* 2011] reported a 46% relative increase in risk of mortality from any cause in patients using the mist inhaler compared with placebo [relative risk 1.46, 95% confidence interval (CI) 1.01–2.10]. Furthermore, a Cochrane review, which used the Peto method for pooled estimation of odds ratio, suggested that tiotropium Respimat but not tiotropium HandiHaler significantly increases the risk of mortality [Karner *et al.* 2012]. Another direct treatment comparison meta-analysis of randomized controlled trials (RCTs) confirmed that tiotropium Respimat SMI increases the risk of death compared with tiotropium HandiHaler [Dong *et al.* 2013]. Although the massive Tiotropium Safety and Performance in Respimat (TIOSPIR) trial showed that tiotropium when administered *via* Respimat 5 μg is not less safe than Handihaler 18 μg [Wise *et al.* 2013], a large real-life study showed that use of tiotropium Respimat SMI was associated with an almost 30% increase of mortality compared with HandiHaler and the association was the strongest for CV/cerebrovascular death [Verhamme *et al.* 2013]. Therefore, it has been suggested that the administration of tiotropium *via* Respimat SMI should be avoided in patients with pre-existing CV comorbidities [Mathioudakis *et al.* 2014] and, more recently, also chronic kidney disease because of the renal excretion of tiotropium [Mathioudakis *et al.* 2015].

Therefore, in view of the patent dichotomy between what documented by the TIOSPIR study and the results of initial meta-analyses and the real-life study, we have carried out a safety evaluation of tiotropium Handihaler 18 μg *versus* tiotropium Respimat SMI 5 μg and 2.5 μg, *via* systematic review and network meta-analysis of the currently available clinical evidences.

Meta-analysis

Methods

A network meta-analysis was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Figure 1) [Moher *et al.* 2009].

Data sources and searches. Published and unpublished RCTs were searched in PubMed and Google Scholar (there is now agreement that for quick clinical searches, Google Scholar returns twice as many relevant articles as PubMed and provides greater access to free full-text articles [Shariff *et al.* 2013]) through June 2016, and citations of a previous published pooled-analyses was examined to identify further pertinent studies, if any [Halpin *et al.* 2015]. The terms "tiotropium" AND "Handihaler" AND/OR "Respimat" were searched.

Study selection. RCTs lasting at least 2 weeks and reporting the safety of tiotropium administered in COPD patients *via* Handihaler 18 μg or Respimat 5 μg and 2.5 μg, compared with inhaler containing matching placebo, were selected. Studies that have directly compared Handihaler 18 μg *versus* Respimat 5 μg and 2.5 μg have been also selected.

Data extraction and quality assessment. Two reviewers independently checked the relevant RCTs found from literature, and any difference in opinion about eligibility was resolved by consensus.

Data from included studies were extracted and checked for study characteristics and duration, number of enrolled patients, doses of tiotropium, disease characteristics, and AEs. The Jadad score, with a scale of 1–5 (score of 5 being the highest), was used to assess the quality of the RCTs concerning the likelihood of bias related with randomization, double blinding, withdrawals and dropouts [Calzetta *et al.* 2016a and 2016b].

The effect of study quality was examined by excluding trials with a Jadad score <3. The risk of publication bias was assessed by Egger's test [Rogliani *et al.* 2016].

Data synthesis and analysis. The endpoint of this network meta-analysis was to compare the safety

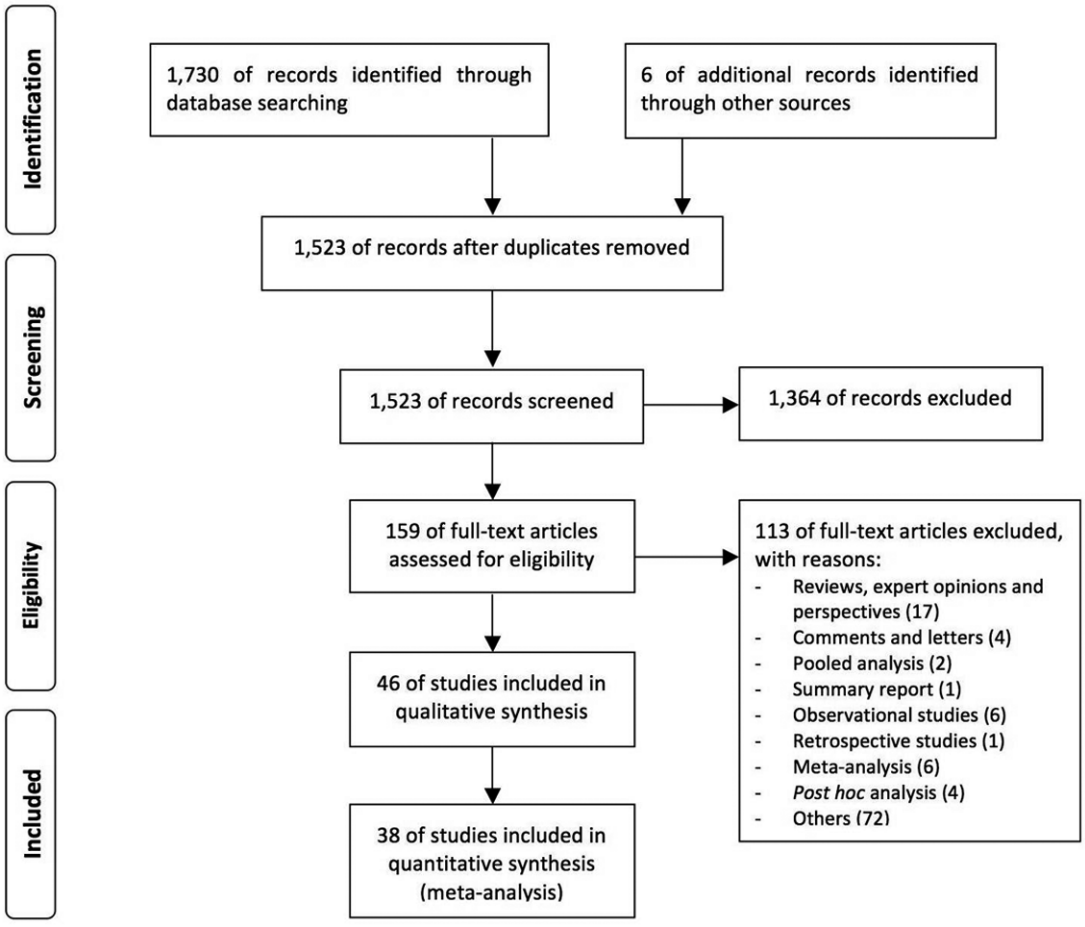

Figure 1. PRISMA flow diagram for the identification of studies included in the network meta-analysis concerning the safety profile of tiotropium Handihaler 18 µg *versus* tiotropium Respimat SMI 5 µg and 2.5 µg in COPD patients.

profile of tiotropium with regard of HandiHaler and Respimat inhalers by analysing the occurrence of AEs, serious adverse events (SAEs) and risk of death in COPD patients.

The network meta-analysis was performed by using a full Bayesian evidence network (chains: 4; initial values scaling: 2.5; tuning iterations: 20,000; simulation iterations: 50,000; tuning interval: 10), the convergence diagnostics for consistency and inconsistency was assessed by using the Brooks–Gelman–Rubin method [Calzetta *et al.* 2016 a and 2016b]. Results of network meta-analysis have been expressed as relative effect and 95% credible level (CrI). Due to the complex evidence network, the inconsistency of evidence has been assessed by inconsistency factor (IF), indicating whether one of the treatment has a different effect when it is compared with the others [Mavridis *et al.* 2015]. The probability that each intervention arm was the most effective was calculated by counting the proportion of iterations of the chain in which each intervention arm had the highest mean difference, and the surface under the cumulative ranking curve (SUCRA), representing the summary of these probabilities, was also calculated [Calzetta *et al.* 2016a and 2016b]. The SUCRA is 100% when a treatment is certain to be the best, and 0% when a treatment is certain to be the worst [Calzetta *et al.* 2016a and 2016b].

The optimal information size (OIS) was calculated as previously reported [Rogliani *et al.* 2016], and the statistical significance was assessed for $p < 0.05$. Evidence of asymmetry from Egger's test was considered to be significant for $p < 0.1$, and the graphical representation of 90% confidence bands have been presented [Calzetta *et al.*

2016a and 2016b]. GeMTC [Van Valkenhoef *et al.* 2012] was used for performing the network meta-analysis, and GraphPad Prism (CA, USA) software to graph the data.

Results

Study characteristics and OIS

Results obtained from 43,286 COPD patients (tiotropium HandiHaler 18 µg n = 16,016, tiotropium Respimat 5 µg n = 9,750, tiotropium Respimat 2.5 µg n = 5,889, matching placebo n = 11,631) were selected from 38 published and unpublished studies including 44 RCTs [Casaburi *et al.* 2002, 2005; Donohue *et al.* 2002; Brusasco *et al.* 2003; Calverley *et al.* 2003; Celli *et al.* 2003; Mcnicholas *et al.* 2004; O'Donnell *et al.* 2004; Covelli *et al.* 2005; Maltais *et al.* 2005; Niewoehner *et al.* 2005; Beeh *et al.* 2006; Dusser *et al.* 2006; Verkindre *et al.* 2006; Caillaud *et al.* 2007; Chan *et al.* 2007, Freeman *et al.* 2007; Garcia, 2007; Powrie *et al.* 2007; Ambrosino *et al.* 2008; Criner *et al.* 2008; Johansson *et al.* 2008; Magnussen *et al.* 2008; Moita *et al.* 2008; Tashkin *et al.* 2008; Tonnel *et al.* 2008; Voshaar *et al.* 2008; Bateman *et al.* 2010a, b; Ichinose *et al.* 2010; Sciurba *et al.* 2011; Fuhr *et al.* 2012; Abrahams *et al.* 2013; Cooper *et al.* 2013; Wise *et al.* 2013; Troosters *et al.* 2014; Beeh *et al.* 2015; Singh *et al.* 2015; Bouloukaki *et al.* 2016], between 2002 and 2016 (Figure 2).

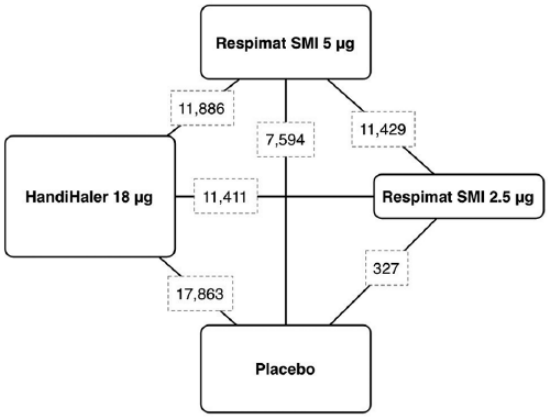

Figure 2. Diagram displaying the network of four arms involved in the Bayesian analysis. The links between nodes indicate the direct comparisons between pairs of treatments. The numbers shown along the link lines indicate the number of COPD patients comparing pairs of treatments head-to-head.

The relevant patient demographics, study characteristics, and Jadad score have been summarized in Table 1. The period of treatment ranged from 2 to 208 weeks, and two studies were assessed as having a Jadad score <3 [Garcia, 2007; Bouloukaki *et al.* 2016].

The number of COPD patients from the selected RCTs permitted to carry out a meta-analysis with a reasonable OIS to ensure a very good (probability of observing 20% overestimation for $\tau^2 = 0.25$: <5% at true relative risk reduction 10%) low risk of observing an overestimated intervention effect due to random errors in scenarios where the control group risk was low (1–5%).

Safety profile of tiotropium Handihaler versus tiotropium Respimat

The network meta-analysis did not indicate any significant difference ($p > 0.05$) between the safety profile of tiotropium HandiHaler 18 µg and tiotropium Respimat 5 µg or 2.5 µg. However, the resulting relative effects were overall in favour of tiotropium HandiHaler than Respimat, with regard of AEs, SAEs and risk of death (Figure 3A). These results have been also confirmed by the subset analysis carried out by excluding the RTCs with Jadad score <3 ($p > 0.05$ *versus* network meta-analysis including all of the RCTs).

The analysis of inconsistency indicated that no discrepancy exists between direct and indirect evidences (AEs IF 0.01, 95% CrI −0.93 to 0.87; $p > 0.05$; SAEs IF 0.01, 95% CrI −0.38 to 0.81, $p > 0.05$; risk of death IF 0.03, 95% CrI −2.65 to 1.94. $p > 0.05$). The Egger's test did not find any asymmetry ($p > 0.1$), suggesting that no publication bias was present in this network meta-analysis (Figure 3B).

Tiotropium HandiHaler 18 µg showed highest probability of being the best therapy with regard of AEs and risk of death (66% and 30%, respectively), as confirmed by SUCRA (87% and 61%, respectively), whereas tiotropium Respimat SMI 5 µg had the highest probability of being the best therapy with regard of SAEs (Table 2). In fact, the incidence of the most frequently reported CV SAEs such as cardiac failure, MI, and fibrillation was greater in patients receiving tiotropium HandiHaler (Table 3).

Table 1. Patient demographics, baseline and study characteristics.

Study and year	Study identifier	Study characteristics	Duration of study (weeks)	Number of analysed patients	Treatments and devices	Patients characteristics	Jadad score
Casaburi *et al.* [2002]	205.114-115-117-128	Randomized, double blind, placebo controlled	52	921	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽65% predicted; FEV_1/FVC <70%	5
Freeman *et al.* [2007]	NCT00274079	Multicentre, randomized, double blind, placebo controlled, parallel group	12	374	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾30% and ⩽65% predicted; FEV_1/FVC <70%	5
Ichinose *et al.* [2010]	NCT02331940	Randomized, double blind, double dummy, two-way crossover	4	294	Tiotropium Respimat SMI 5 µg; tiotropium HandiHaler 18 µg	COPD patients ⩾40 years; FEV_1 ⩽80% predicted; FEV_1/FVC ⩽70%	5
Niewoehner *et al.* [2005]	NCT00274547	Parallel group, randomized, double blind, placebo controlled	24	929	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC ⩽70%	5
Abrahams *et al.* [2013]	NCT00528996	Multiple dose, multicentre, multinational, randomized, double blind, parallel group	24	856	Tiotropium Respimat SMI 5 µg; placebo Respimat SMI	COPD patients ⩾40 years; FEV_1 <80% predicted; FEV_1/FVC <70%	4
Ambrosino *et al.* [2008]	NCT00157235	Multicentre, randomized, double blind, placebo controlled, parallel group	25	234	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC ⩽70%	4
Bateman *et al.* [2010a]	NCT00387088	Randomized, double blind, parallel group	48	3,917	Tiotropium Respimat SMI 5 µg; placebo Respimat SMI	COPD patients ⩾40 years; FEV_1 ⩽80% predicted; FEV_1/FVC <70%	4
Beeh *et al.* [2006]	NCT00274573	Randomized, double blind, placebo controlled	12	1,643	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽70% predicted; FEV_1/FVC ⩽70%	4
Brusasco *et al.* [2003]	205.130	Randomized, double blind, double dummy, parallel group	24	802	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽65% predicted; FEV_1/FVC <70%	4
Calverley *et al.* [2003]	205.123	Multicentre, randomized, double blind, double dummy, parallel group	6	121	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾25% and ⩽65% predicted; FEV_1/FVC <70%	4
Casaburi *et al.* [2005]	NCT00274521	Multicentre, single country, randomized, double blind, parallel group	25	108	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC ⩽70%	4
Chan *et al.* [2007]	NCT00277264	Multicentre, randomized, double blind, placebo controlled, parallel group	48	913	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽65% predicted; FEV_1/FVC ⩽70%	4
Cooper *et al.* [2013]	NCT00525512	Randomized, placebo controlled, double blind, parallel group	96	519	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽65% predicted; FEV_1/FVC ⩽70%	4

(Continued)

Table 1. (Continued)

Study and year	Study identifier	Study characteristics	Duration of study (weeks)	Number of analysed patients	Treatments and devices	Patients characteristics	Jadad score
Criner *et al.* [2008]	NCT00106821	Randomized, double blind, placebo controlled, parallel group	8	166	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽65% predicted; FEV_1/FVC ⩽70%	4
Donohue *et al.* [2002]	NA	Placebo controlled, multicentre, multinational, randomized, parallel group	24	410	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC <70%	4
Dusser *et al.* [2006]	NCT00274014	Randomized, double blind, parallel group	52	1,010	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾30% and ⩽65% predicted; FEV_1/FVC ⩽70%	4
Fuhr *et al.* [2012]	NCT00868231	Two centre, double blind, placebo and active controlled crossover	2	54	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾30% and <80% predicted; FEV_1/FVC <70%	4
Sciurba *et al.* [2011]	NCT00523991	Randomized, double blind, placebo controlled, multicentre	24	456	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients 40–80 years; FEV_1 ⩾50% and <80% predicted; FEV_1/FVC ⩽70%	4
Tashkin *et al.* [2008]	NCT00144339	Randomized, double blind, placebo controlled, parallel group	208	5,992	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽70% predicted; FEV_1/FVC ⩽70%	4
Tonnel *et al.* [2008]	NCT00274053	Randomized, double blind, placebo controlled, multicentre, parallel group	36	554	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾20% and ⩽70% predicted; FEV_1/FVC ⩽70%	4
Troosters *et al.* [2014]	NCT00523991	Randomised, parallel group, double blind placebo controlled, multicentre	24	457	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients 40-80 years; FEV_1 ⩾50% and <80% predicted; FEV_1/FVC <70%	4
Verkindre *et al.* [2005]	205.215	Multicentre, randomized, double blind, parallel group	12	100	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1⩽50% predicted; FEV_1/FVC ⩽70%	4
Voshaar *et al.* [2008]	NCT00239473; NCT00240435	Two identical, randomized, double blind, double dummy, placebo and activecontrolled, parallel group	12	361	Tiotropium Respimat SMI 5 µg; placebo Respimat SMI	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC <70%	4
Wise *et al.* [2013]	NCT01126437	Randomized, double blind, parallel group study	119	17,116	Tiotropium Respimat SMI 5 µg and 2.5 µg; tiotropium HandiHaler 18 µg HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽70% predicted; FEV_1/FVC ⩽70%	4
Bateman *et al.* [2010b]	NCT00168844; NCT00168831	Two identical, multicentre, multinational, randomized, double blind, parallel group	48	1,323	Tiotropium Respimat SMI 5 µg; placebo Respimat SMI	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC <70%	3
Beeh *et al.* [2015]	NCT01559116	Double blind, placebo controlled, multicentre, incomplete crossover study	6	413	Tiotropium Respimat SMI 5 µg and 2.5 µg; placebo Respimat SMI	COPD patients ⩾40 years; FEV_1 <80% predicted; FEV_1/FVC <70%	3

Table 1. (Continued)

Study and year	Study identifier	Study characteristics	Duration of study (weeks)	Number of analysed patients	Treatments and devices	Patients characteristics	Jadad score
Caillaud *et al.* [2007]	205.127	Multicentre, randomised, double blind within device, parallel group, active and placebo controlled, dose ranging	3	125	Tiotropium Respimat SMI 5 µg and 2.5 µg; tiotropium HandiHaler 18 µg; placebo Respimat SMI; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾30% and ⩽65% predicted; FEV_1/FVC <70%	3
Celli *et al.* [2003]	205.218	Randomized, double blind, placebo controlled, parallel group	4	81	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾30% and ⩽65% predicted; FRC ⩾120%	3
Covelli *et al.* [2005]	NCT00239460	Randomized, double blind, placebo controlled, parallel group	12	178	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC <70%	3
Johansson *et al.* [2008]	NCT00144196	Randomized, double blind, parallel group, multicentre	12	224	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩾60% predicted; FEV_1/FVC ⩽70%	3
Magnussen *et al.* [2008]	NCT00152984	Multicentre, multinational, prospective, randomized, placebo controlled, double blind	12	472	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽80% predicted; FEV_1/FVC ⩽70%	3
Maltais *et al.* [2005]	NCT00274508	Randomized, double blind, placebo controlled, parallel group	6	261	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients 40–75 years; FEV_1 ⩽65% predicted; FRC ⩾120%	3
Moita *et al.* [2008]	NCT00239408	Randomized, double blind, parallel group, placebo controlled	12	311	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽70% predicted; FEV_1/FVC ⩽70%	3
O'Donnell *et al.* [2004]	205.131	Multicentre, randomized, placebo controlled, parallel group	6	187	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients 40–70 years; FEV_1 ⩽65% predicted; FRC ⩾120%	3
Powrie *et al.* [2007]	NCT00405236	Single centre, double blind, randomized, placebo controlled	52	142	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 <80% predicted; FEV_1/FVC ⩽70%	3
Singh *et al.* [2015]	NCT01964352; NCT02006732	Two replicate, multinational, double-blind, parallel group, placebo controlled	12	812	Tiotropium Respimat SMI 5 µg; placebo Respimat SMI	COPD patients ⩾40 years; FEV_1 ⩾30% and <80% predicted; FEV_1/FVC <70%	3
Bouloukaki *et al.* [2016]	NCT02331940	Prospective, randomized, open label, parallel group	24	200	Tiotropium Respimat SMI 5 µg; tiotropium HandiHaler 18 µg	COPD patients ⩾40 years; FEV_1 ⩾50% and <80% predicted; FEV_1/FVC ⩽70%	2
Garcia [2007]	NCT00144326	Randomized, double blind, placebo controlled	12	250	Tiotropium HandiHaler 18 µg; placebo HandiHaler	COPD patients ⩾40 years; FEV_1 ⩽60% predicted; FEV_1/FVC ⩽70%	2

COPD, chronic obstructive pulmonary disease; FEV_1, force expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity.

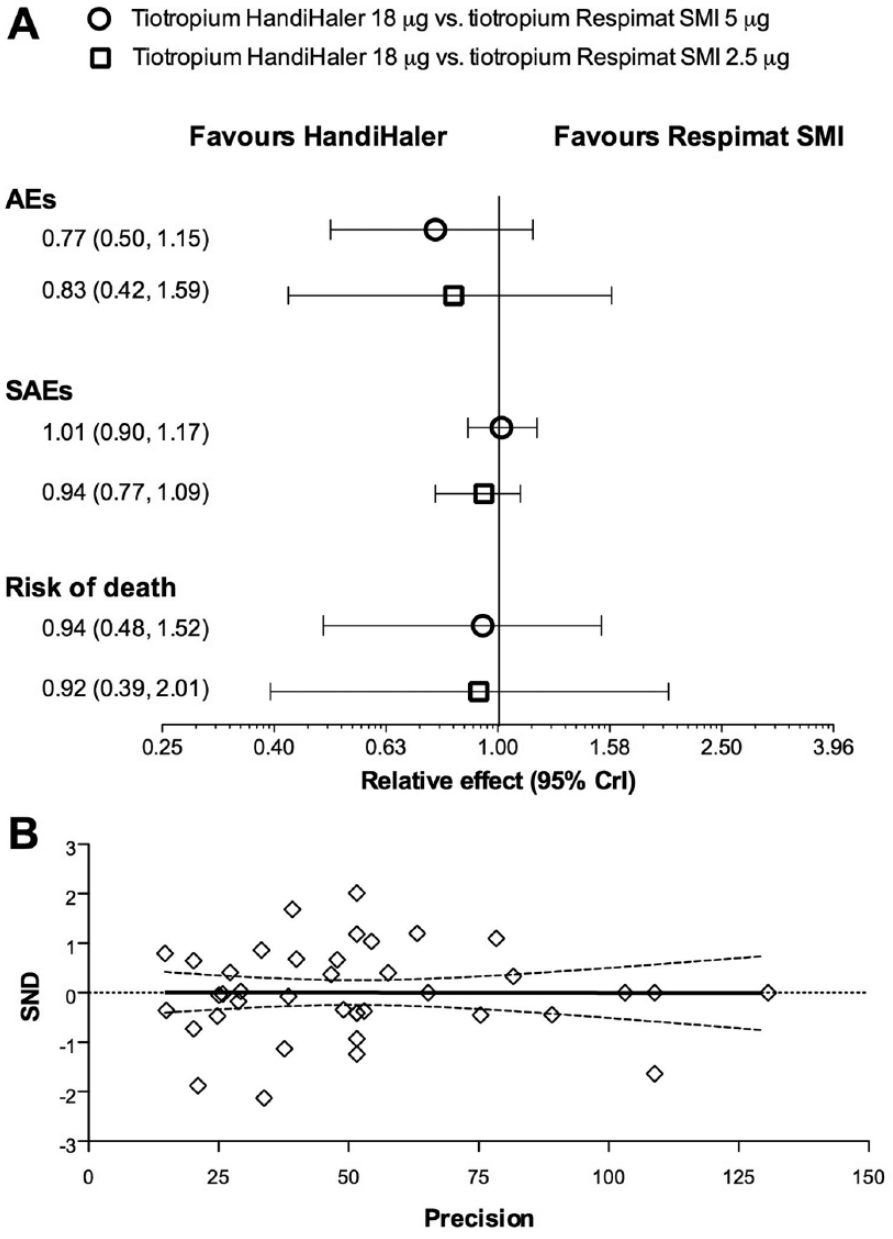

Figure 3. Overall Forest plot of the impact of tiotropium Handihaler 18 μg *versus* tiotropium Respimat SMI 5 μg and 2.5 μg on AEs, SAEs and risk of death (A, data expressed as relative effect and 95% CrI). Publication bias assessment via Egger's test (B). AEs, adverse events; SAEs, serious AEs; SND, standard normal deviate.

Discussion

In recent years, several reviews and pooled safety analysis, probably not entirely independent because they include authors who are employees of the drug company that manufactures and markets tiotropium Respimat SMI and HandiHaler and therefore with a potential conflict of interest, indicate that tiotropium, given *via* either HandiHaler or Respimat SMI, does not increase the overall risks of AEs, SAEs, fatal AEs, or CV events [Halpin *et al*. 2015]. Furthermore, two *post hoc* analyses of TIOSPIR study have respectively demonstrated that tiotropium Respimat SMI and HandiHaler have similar safety and efficacy profiles in patients who are naïve to anticholinergic therapy [Wise *et al*. 2015] and it is safe to switch patients from tiotropium HandiHaler to tiotropium Respimat SMI also because the efficacy is maintained over the switch [Dahl *et al*. 2015].

The results of this independent network meta-analysis demonstrate that the safety profile of

Table 2. Probability of best therapy and SUCRA values.

Treatment	Probability of being the best therapy (%)	SUCRA value (%)
AEs		
Tiotropium HandiHaler 18 μg	66	87
Tiotropium Respimat SMI 5 μg	6	45
Tiotropium Respimat SMI 2.5 μg	28	56
SAEs		
Tiotropium HandiHaler 18 μg	14	55
Tiotropium Respimat SMI 5 μg	38	65
Tiotropium Respimat SMI 2.5 μg	4	11
Risk of death		
Tiotropium HandiHaler 18 μg	30	61
Tiotropium Respimat SMI 5 μg	21	45
Tiotropium Respimat SMI 2.5 μg	23	40

AE, adverse event; SAE, serious adverse event; SUCRA, surface under the cumulative ranking curve.

tiotropium HandiHaler is generally superior to that of tiotropium Respimat SMI, although no statistical difference was detected between these two devices.

Remarkably, the SUCRA analysis favoured tiotropium Respimat SMI with regards to SAEs. In fact, the incidence of the most frequently reported CV SAEs such as cardiac failure, MI, and fibrillation was greater in patients receiving tiotropium *via* HandiHaler. However, the results obtained by the SUCRA analysis should be interpreted with caution, because the relative effect estimate for SAEs was mainly centred between tiotropium HandiHaler 18 μg and tiotropium Respimat SMI 5 μg.

In any case, despite the large CrI values, the risk of death was always smaller for tiotropium HandiHaler than tiotropium Respimat SMI.

As expected, the extremely large number of patients analysed in this network meta-analysis has completely abolished any publication bias, regardless of the quality of the RCTs included in the analysis.

To the best of the authors' knowledge, this is the first network meta-analysis aimed to investigate the safety profile of tiotropium Handihaler *versus* tiotropium Respimat SMI. Indeed, this study represents the natural step-forward from a recent pooled analysis [Halpin *et al.* 2015] that, inexplicably, did not include the data from RCTs in which the direct comparison between tiotropium Handihaler and tiotropium Respimat was performed, such as the studies of Bouloukaki and colleagues [Bouloukaki *et al.* 2016], Ichinose and colleagues [Ichinose *et al.* 2010], and Wise and colleagues [Wise *et al.* 2013], the latter being the largest RCT with >17,000 COPD patients treated with tiotropium for 2.3 years.

The trend towards a better safety profile of tiotropium HandiHaler compared with tiotropium Respimat SMI is difficult to be explained, given the repeated documentation of a systemic exposure for the two devices within the margins of equivalence [van Noord *et al.* 2009; Ichinose *et al.* 2010; Hohlfeld *et al.* 2014]. These pharmacokinetic data do not support the hypothesis proposed by Singh and colleagues [Singh *et al.* 2011] that the Respimat SMI results in earlier systemic exposure to, and higher plasma concentrations of, tiotropium after dosing increasing the risk of anticholinergic CV effects (arrhythmia). In any case, a study that analysed all data from the tiotropium clinical trial database involving Holter-ECG monitoring in patients with COPD did not show any clinically relevant differences between Respimat SMI and HandiHaler with respect to changes in heart rate or in the proportion of patients experiencing supraventricular or ventricular premature beats while on tiotropium [Hohlfeld *et al.* 2015].

The unexpected finding of our meta-analysis is the evidence that the incidence of the most frequently reported CV SAEs such as cardiac failure,

Table 3. Cardiovascular serious adverse events available by study results posted in the ClinicalTrials.gov repository database.

	Tiotropium HandiHaler 18 µg (*n* = 8,911)	Tiotropium Respimat SMI 5 µg (*n* = 8,871)	Tiotropium Respimat SMI 2.5 µg (*n* = 5,861)
	n (%)	*n* (%)	*n* (%)
Cardiac failure (including acute, chronic, congestive, tamponade)	171 (1.88)	83 (0.94)	72 (1.23)
Myocardial infarction (including acute)	118 (1.30)	77 (0.87)	74 (1.26)
Fibrillation (including atrial, flutter, ventricular)	110 (1.21)	49 (0.55)	54 (0.92)
Angina (including pectoris, unstable)	82 (0.90)	55 (0.62)	30 (0.51)
Tachycardia (including, atrial, sinus, supraventricular, ventricular)	54 (0.59)	37 (0.42)	29 (0.49)
Aneurysm (including aortic, peripheral, rupture)	40 (0.44)	28 (0.32)	22 (0.38)
Hypertension (including accelerated, crisis)	38 (0.42)	12 (0.14)	13 (0.22)
Cardiac arrest	38 (0.42)	18 (0.20)	12 (0.20)
Conduction disorders (including atrioventricular block, block complete, first degree block, bundle branch block left and right)	35 (0.38)	13 (0.5)	8 (0.14)
Acute coronary syndrome	34 (0.37)	23 (0.26)	12 (0.20)
Aortic disorders (including dissection, occlusion, rupture, stenosis, thrombosis)	29 (0.32)	8 (0.09)	8 (0.14)
Arteriosclerosis (including coronary, obliterans)	27 (0.30)	12 (0.14)	13 (0.22)
Cardiac disorders (including cardiomegaly, cardiomiopathy)	25 (0.27)	9 (0.10)	1 (0.02)
Bradycardia (including sinus)	23 (0.25)	15 (0.17)	9 (0.15)
Cardiovascular insufficiency	17 (0.19)	9 (0.10)	12 (0.20)
Adams-Stokes syndrome	16 (0.18)	3 (0.03)	5 (0.09)
Arteritis	16 (0.18)	7 (0.08)	5 (009)
Varicose vein (including bleeding)	15 (0.16)	4 (0.05)	4 (0.07)
Cardiac asthma	12 (0.13)	2 (0.02)	5 (0.09)
Circulatory collapse	12 (0.13)	6 (0.07)	3 (0.05)
Cor pulmonale (including acute, chronic)	10 (0.11)	5 (0.06)	6 (0.10)
Coronary artery diseases (including embolism, insufficiency, occlusion, stenosis)	10 (0.11)	8 (0.09)	7 (0.12)
Vein thrombosis	9 (0.10)	4 (0.05)	4 (0.07)
Diastolic dysfunction	8 (0.09)	7 (0.08)	5 (0.09)
Embolism	6 (0.07)	1 (0.01)	0 (0.00)
Extrasystoles (including supraventricular, ventricular)	4 (0.04)	4 (0.05)	5 (0.09)
Extremity necrosis	4 (0.04)	2 (0.02)	1 (0.02)
Arterial disorders (including haemorrhage, insufficiency, occlusive disease, stenosis, thrombosis)	4 (0.04)	0 (0.00)	0 (0.00)
Haematoma	4 (0.04)	5 (0.06)	3 (0.05)
Haemorrhage	4 (0.04)	2 (0.02)	5 (0.09)
Hypertensive cardiomyopathy	4 (0.04)	3 (0.03)	4 (0.07)
Hypotension (including orthostatic)	3 (0.03)	0 (0.00)	2 (0.03)
Shock (including cardiogenic, hypovolaemic, haemorragic)	2 (0.02)	0 (0.00)	0 (0.00)
Artery stenosis (including iliac, peripheral, subclavian)	2 (0.02)	2 (0.02)	4 (0.07)
Intermittent claudication	2 (0.02)	0 (0.00)	0 (0.00)
Ischaemia (including ischaemic cardiomyopathy, myocardial and peripheral ischaemia)	2 (0.02)	2 (0.02)	1 (0.02)
Ventricular disorders (including dysfunction, failure)	2 (0.02)	0 (0.00)	0 (0.00)
Leriche syndrome	1 (0.01)	0 (0.00)	0 (0.00)
Lymphoedema	1 (0.01)	1 (0.01)	0 (0.00)
Valve diseases (including mixed, incompetence, stenosis)	1 (0.01)	0 (0.00)	3 (0.05)

Table 3. (Continued)

	Tiotropium HandiHaler 18 µg (*n* = 8,911)	Tiotropium Respimat SMI 5 µg (*n* = 8,871)	Tiotropium Respimat SMI 2.5 µg (*n* = 5,861)
	n (%)	*n* (%)	*n* (%)
Palpitations	1 (0.01)	0 (0.00)	1 (0.02)
Pericardial disorders (including effusion, pericarditis)	1 (0.01)	1 (0.01)	1 (0.02)
Peripheral vascular disorder	1 (0.01)	0 (0.00)	1 (0.02)
Post thrombotic syndrome	1 (0.01)	1 (0.01)	0 (0.00)
Arrhythmia (including supraventricular, sinus arrhythmia, sick sinus syndrome, supraventricular, tachyarrhythmia, ventricular)	1 (0.01)	0 (0.00)	0 (0.00)
Steal syndrome	1 (0.01)	0 (0.00)	0 (0.00)
Vascular shunt	1 (0.01)	1 (0.01)	0 (0.00)
Vasculitis	0 (0.00)	0 (0.00)	1 (0.02)
Vasodilatation	0 (0.00)	1 (0.01)	1 (0.02)
Venous insufficiency	0 (0.00)	0 (0.00)	1 (0.02)

See Bateman *et al*. [2010a, 2010b], Sciurba *et al*. [2011], Cooper *et al*. [2013], Wise *et al*. [2013], Troosters *et al*. [2014], Beeh *et al*. [2015] and Singh *et al*. [2015].

MI, and fibrillation was greater in patients receiving tiotropium HandiHaler. In any case, it is important to highlight that we found a low absolute risk of CV AEs with both devices (Table 3).

It is obvious, at this point, to wonder whether the possible occurrence of AEs is linked to a particular genetic predisposition never investigated until now (modification of Regulator of G-protein signalling 6 (RGS6) [Patanè, 2015]) rather than to a specific device, emphasizing the need for further studies in a real-world setting to identify high-risk patients that may benefit from ECG surveillance.

In any case, it is now documented that M3 muscarinic receptor overexpression reduces the incidence of arrhythmias and mortality after myocardial ischemia-reperfusion by protecting the myocardium from ischemia at least in mice [Liu *et al*. 2011]. The protective mechanism of this receptor is rather complex. It regulates heart rate and cardiac repolarization, modulates inotropic effects, elicits cytoprotection against ischaemic injuries of myocardium, and regulates cell-to-cell communication [Wang *et al*. 2007]. Intriguingly, the expression of M3 muscarinic receptors appears to be increased in patients with atrial fibrillation, atrial dilatation, congestive heart failure, ventricular myocardial ischemia, and cardiac hypertrophy [Patanè, 2014]. Is it possible that changes in this overexpression can induce different responses to the blockade of muscarinic receptors operated by antimuscarinic drugs? In fact, all of the antimuscarinic drugs can cause more or less serious CV AEs [Sing *et al*. 2008; Matera *et al*. 2014].

We do not believe that using Respimat SMI rather that HandiHaler exposes patients to higher risks of real AEs. Rather, we believe that there may be a different CV response to muscarinic receptors blockage in individual patients. Therefore, it will be essential to make all possible efforts to proactively identify patients at increased risk of CV AEs when treated with tiotropium or another antimuscarinic drug.

In any case, we cannot forget this is a potentially dangerous occurrence, and health care providers need to be advised before incorporating antimuscarinic drugs in the management of COPD.

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