

# Comorbidities of patients in tiotropium clinical trials: comparison with observational studies of patients with chronic obstructive pulmonary disease

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**Background:** There is an ongoing debate on whether patients with chronic obstructive pulmonary disease (COPD) seen in real-life clinical settings are represented in randomized controlled trials (RCTs) of COPD. It is thought that the stringent inclusion and exclusion criteria of RCTs may prevent the participation of patients with specific characteristics or risk factors.

**Methods:** We surveyed a database of patients recruited into 35 placebo-controlled tiotropium RCTs and also conducted a systematic literature review of large-scale observational studies conducted in patients with a documented diagnosis of COPD between 1990 and 2013. Patient demographics and comorbidities with a high prevalence in patients with COPD were compared between the two patient populations at baseline. Using the Medical Dictionary for Regulatory Activities (MedDRA; v 14.0), patient comorbidities in the pooled tiotropium RCTs were classified according to system organ class, pharmacovigilance (PV) endpoints, and Standardised MedDRA Queries to enable comparison with the observational studies.

**Results:** We identified 24,555 patients in the pooled tiotropium RCTs and 61,361 patients among the 13 observational studies that met our search criteria. The Global initiative for chronic Obstructive Lung Disease (GOLD) staging of patients in the RCTs differed from that in observational studies: the proportion of patients with GOLD stages I+II disease ranged from 40.0% to 51.5% in the RCTs but 24.5% to 44.1% in the observational studies; for GOLD stage III or IV disease these ranges were 7.2%–45.8% (RCTs) and 13.7–42.1% (observational studies). The comorbidities with the highest prevalence reported in the RCTs and observational studies were: hypertension (39.4%–40.0% vs 40.1%–60.6%), other ischemic heart disease (12.3%–14.2% vs 12.5%–41.0%), diabetes (10.3%–10.9% vs 4.0%–38.9%), depression (8.5%–9.5% vs 17.0%–20.6%), and cardiac arrhythmia (7.8%–11.4% vs 11.3%–15.8%).

**Conclusion:** The clinical profile of COPD patients treated in the tiotropium trial program appears to be largely in the range of clinical characteristics, including cardiovascular comorbidities, reported for “real-life patients.” The tiotropium RCTs tended to include patients with more severe disease than the observational studies.

**Keywords:** patient population, baseline characteristics, epidemiology, real-life patients, GOLD staging

## Introduction

Randomized controlled trials (RCTs) provide the best evidence to support the efficacy and safety of therapies and form the basis for regulatory approval of treatment for all diseases, including chronic obstructive pulmonary disease (COPD). A well-designed RCT has a high degree of internal validity and allows for data-driven determination of whether a cause–effect relationship exists between a study drug and its outcome. Patient populations in RCTs are subject to stringent inclusion and exclusion criteria,

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and thus could be perceived as having an inherent lack of external validity.<sup>1-4</sup> Furthermore, because patients entering RCTs are selected, their characteristics and concomitant treatment regimens may not reflect daily clinical practice.<sup>5</sup> Randomization and stringency in inclusion and exclusion criteria are nevertheless important for determining the comparative efficacy and safety of the study drug, limiting the potential for confounding and excluding patients at specific risks.

To bridge the gap between RCTs and how medications are used by clinicians in daily practice, noninterventional, or observational, studies or analyses of existing databases are conducted. Unlike RCTs, observational studies normally have less stringent inclusion and exclusion criteria and thus may provide a broader perspective on disease background, comorbid conditions, treatment patterns, and outcomes. Observational studies are also more representative of normal patterns of care.<sup>4</sup> Because they are more representative of daily clinical practice, observational studies have high external validity and can be generalized,<sup>4</sup> but can also be more prone to assessment bias<sup>1</sup> and outcomes may be confounded, in contrast to RCTs.<sup>6</sup>

According to published epidemiological and observational studies, some comorbid conditions with a high prevalence in patients with COPD include hypertension, ischemic heart disease, hypercholesterolemia, diabetes, arrhythmias, interstitial lung disease, lung cancer, anxiety, and depression.<sup>7-12</sup>

Based on the ongoing scientific discussion around the external validation of RCTs,<sup>13-15</sup> we sought to understand how representative the patients included in RCTs are to patients in a real-life clinical setting, and how the inclusion and exclusion criteria implemented for these trials may have influenced the recruited patient population. In particular, it is important to know whether patients with comorbidities are adequately represented in clinical trials of COPD, or whether they are deselected by exclusion criteria – or simply not recruited in sufficient numbers. To achieve this goal, we surveyed a database of patients recruited into tiotropium RCTs and also conducted a systematic literature review of large-scale observational studies in order to compare the demography and baseline characteristics of the RCT population with “real-life” patient populations.

## Methods

### Analysis of tiotropium RCTs

Data on patient baseline characteristics were taken from a database (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) of 28 placebo-controlled clinical trials conducted with a tiotropium HandiHaler® (SPIRIVA®, Boehringer

Ingelheim GmbH) and seven placebo-controlled trials using the tiotropium Respimat® Soft Mist™ Inhaler (SPIRIVA®, Boehringer Ingelheim GmbH). The 4-year Understanding the Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) trial (trial number 205.235) contributed the largest portion of patients to the placebo-controlled HandiHaler® database population (Table S1).

Statistical analysis was based on descriptive characterization of the pooled trials.

### Design of the RCTs in the analysis

Studies were randomized, placebo-controlled, double-blind, parallel-group trials of  $\geq 4$  weeks' duration, assessing either tiotropium HandiHaler® 18  $\mu\text{g}$  (once daily) or tiotropium Respimat® 5  $\mu\text{g}$  (two puffs of 2.5  $\mu\text{g}$  once daily) for the indication of COPD. Written informed consent was obtained from all patients and ethics committee approval was obtained for all protocols. As all trials were part of the tiotropium COPD development program, inclusion and exclusion criteria were similar across all trials. However, later trials were modified to have somewhat broader selection criteria (see inclusion and exclusion criteria). Principal patient characteristics like age, sex, anthropometrics, and ethnicity were recorded for all patients at baseline. Lung function (as measured by forced expiratory volume in 1 second [ $\text{FEV}_1$ ]) and smoking history were also captured for the entire population.

### Inclusion criteria of the RCTs in the analysis

The key inclusion criteria common to all tiotropium trials were: diagnosis of COPD,  $\text{FEV}_1$ /forced vital capacity ratio  $\leq 70\%$ , age  $\geq 40$  years, and  $\geq 10$  pack-years' smoking history. Other inclusion criteria such as  $\text{FEV}_1$  cutoffs and requirement for exacerbation history varied between studies.

### Exclusion criteria of the RCTs in the analysis

The key exclusion criteria were: diagnosis of asthma, symptomatic prostatic hypertrophy or bladder neck obstruction, narrow-angle glaucoma, and known hypersensitivity to the study medication or components. For practical reasons, significant disease other than COPD that could significantly confound the study results or preclude study completion was also an exclusion criterion. Other exclusion criteria in earlier trial protocols were: heart failure resulting in hospitalization in the previous 3 years, cardiac arrhythmia requiring drug treatment, or myocardial infarction (MI) within the past year. Nevertheless, heart failure and ischemic heart disease were not necessarily exclusion criteria. Cardiac exclusion criteria were more liberal in more recent trials such as UPLIFT®

with HandiHaler® and trial number 205.372 with Respimat® (Table S1). Drug therapy for arrhythmias was permitted, provided the therapy was stable and the patient had no history of a life-threatening arrhythmia or pacemaker insertion. In addition, the criterion for recent MI was decreased to 6 months.

Use of theophylline, inhaled corticosteroids,  $\leq 10 \mu\text{g}$  daily doses of oral corticosteroids (provided the dosing was stable), and short-acting  $\beta_2$ -agonists was permitted in all trials. The 4-year UPLIFT® trial (5,992 patients),<sup>16</sup> as well as trial numbers 205.259,<sup>17</sup> 205.266 (1,829 patients),<sup>18</sup> 205.270,<sup>19</sup> 205.282,<sup>20</sup> 205.284,<sup>21</sup> 205.368,<sup>22</sup> and 205.372<sup>23</sup> also permitted use of long-acting  $\beta_2$ -agonists (LABAs) as prescribed. Nonstudy inhaled anticholinergics had to be withdrawn during the conduct of all studies.

### Definitions of comorbidities

The Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 was used to code relevant medical history/concomitant diagnoses (within the past 5 years) as reported by the investigator at baseline; preferred terms (PTs) were categorized under system organ classes (SOCs) within MedDRA. For conditions that are known to have a high prevalence in patients with COPD, MedDRA PTs denoting similar conditions were pooled as pharmacovigilance (PV) endpoints and Standardised MedDRA Queries (SMQs).

### Systematic literature review of observational studies

To identify suitable studies, a systematic literature search of studies reporting comorbidities among patients with COPD was conducted in the following databases: (1) MEDLINE® 1990, May 14, 2013; (2) BIOSIS Previews® 1993–2008, May 2013; (3) EMBASE Alert, May 14, 2013; (4) EMBASE 1993, May 15, 2013; and (5) SciSearch® 1990, May 2013.

The inclusion and exclusion criteria for the literature review are detailed in Figure 1. The inclusion criteria for the literature search did not specify how patient demography and comorbidity data were presented. It was only important that this information be reported. For this reason, the number of studies used for the individual analyses will vary.

### Results

In total, 17,990 and 6,565 patients were included in the HandiHaler® and Respimat® trials, respectively. For the systematic literature search, using the search parameters detailed in the “Methods” section, 806 study publications were returned. Following a secondary screen to exclude all studies reporting RCTs, hospitalized patient populations, age-restricted populations, or reported study populations of fewer than

900 patients, 793 studies were excluded and 13 epidemiological and observational studies<sup>12,24–38</sup> ( $n=61,361$  patients) were included for comparison with the anthropometrics of patients with COPD recruited in tiotropium RCTs (Table S2).

### Baseline demographics and clinical characteristics

The baseline demographics (Table 1) of the placebo and tiotropium groups were balanced between patient populations in the pooled HandiHaler® and Respimat® trials, with 34.1%–37.6% of patients enrolled in the tiotropium RCTs identified as current smokers, compared with 36.2%–43.0% in the observational studies. Patients enrolled in the tiotropium RCTs had a mean baseline post-bronchodilator FEV<sub>1</sub> of  $1.18 \pm 0.47$  L standard deviation (SD) and  $1.11 \pm 0.41$  L SD, for HandiHaler® and Respimat® trials, respectively, that were 41.5% and 40.2% of postbronchodilator FEV<sub>1</sub> predicted, for HandiHaler® and Respimat® trials, respectively. In the observational studies, the mean baseline post-bronchodilator FEV<sub>1</sub> ranged from 47.0%–56.7% of predicted. The distribution of patients with COPD enrolled in the tiotropium RCTs by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage was 51.5% and 40.0% (GOLD stages I–II), 39.8% and 45.8% (GOLD stage III), and 7.2% and 13.6% (GOLD stage IV) for HandiHaler® and Respimat® trials, respectively. In the comparison observational studies, there were more patients enrolled with mild to moderate disease (GOLD stage I+II; 24.5%–44.1%), compared with GOLD disease stages III or IV (13.7%–42.1%; Table 2).

Although all of the observational studies reported baseline comorbidities in the patient population, they differed in how this was reported. In some instances, these were reported either by SOC or PT. The observational studies also differed in the level of additional information reported, relating to patient baseline characteristics and baseline concomitant medications. For this reason, the numbers of studies included in the comparisons of these parameters differ in Tables 2–4.

### Baseline comorbidities

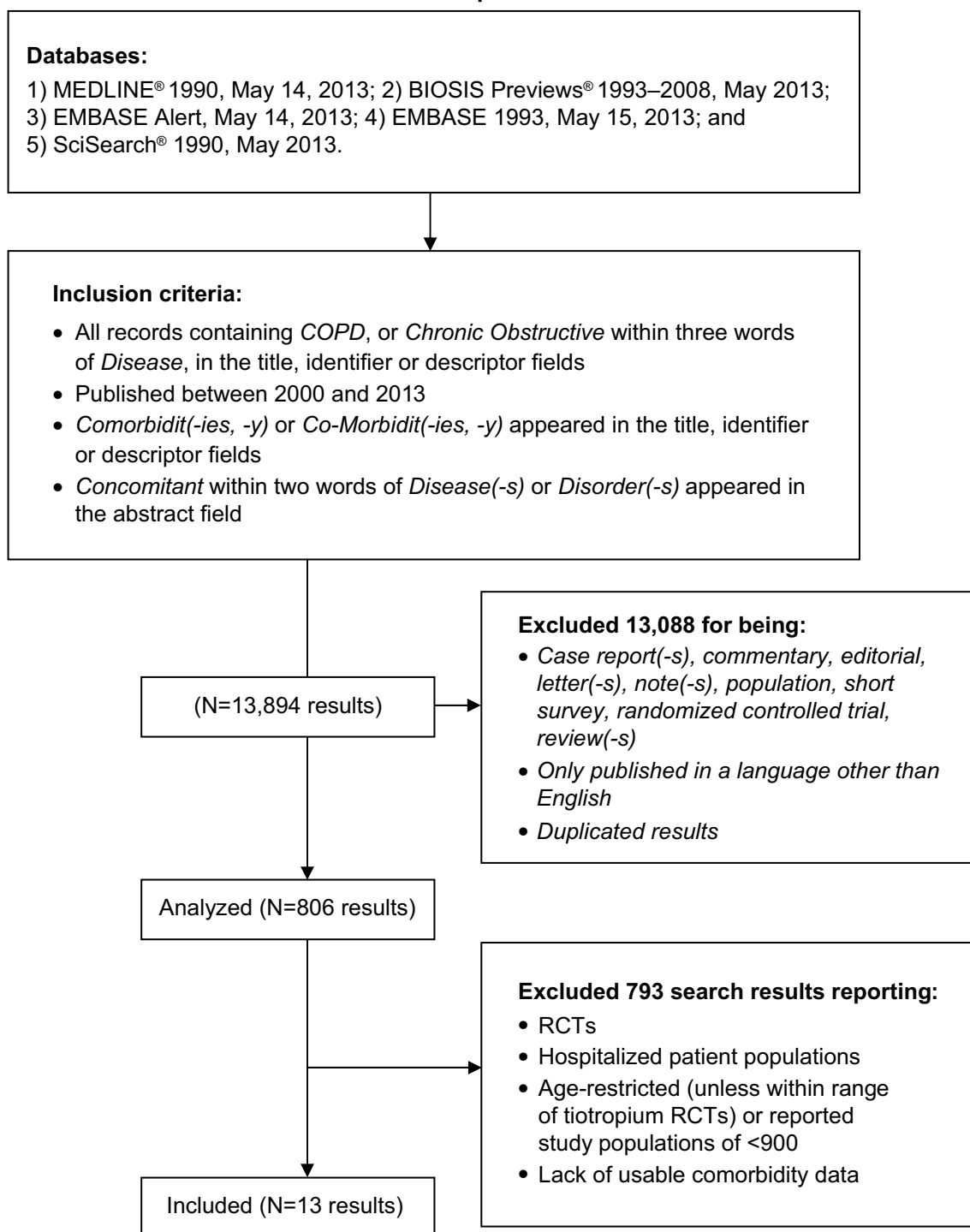
The majority of patients in the HandiHaler® and Respimat® trials were diagnosed with comorbidities at baseline (79.4% and 74.2%, respectively), with vascular and cardiac disorders being the most frequent (39.3% and 24.6% in the HandiHaler® trials, respectively, and 40.1% and 24.3% in the Respimat® trials, respectively) (Table 3). The incidence of comorbidities was similar between the placebo and tiotropium treatment groups in both sets of trials. In four observational studies that enrolled a total of 17,048 patients with COPD, associated comorbidities grouped by SOC

included cardiac (9.4%–32.3%), vascular (11.4%–45.0%), metabolic and nutritional (9.9%–22.2%), and psychiatric (11.9%) disorders (Table 3).

For comorbidities that are known to have a high prevalence in patients with COPD (hypertension, ischemic heart

disease, dyslipidemia, diabetes, anxiety, and depression), SMQs or PV endpoints were used for the RCTs and applicable PTs were grouped to combine endpoints for observational studies in order to evaluate their prevalence in study populations at baseline (Table 4 and Table S3).

### Observational studies of COPD that report comorbidities: 2000–2013



**Figure 1** Systematic literature review of observational studies.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; RCTs, randomized controlled trials.

**Table 1** Baseline characteristics of patients in the 28 pooled tiotropium HandiHaler® and seven pooled tiotropium Respimat® trials

Characteristic	Tiotropium HandiHaler® trials		Total (N=17,990)	Tiotropium Respimat® trials		Total (N=6,565)
	Placebo (n=8,343)	Tiotropium (n=9,647)		Placebo (n=3,283)	Tiotropium (n=3,282)	
Drug exposure, patient years	11,680	13,222	24,902	2,577	2,706	5,282
Age, years (mean, SD)	64.63 (8.9)	64.38 (8.8)	64.50 (8.8)	64.73 (8.9)	64.64 (8.9)	64.69 (8.9)
Age, n (%)						
<60 years	2,329 (27.9)	2,773 (28.7)	5,102 (28.4)	911 (27.7)	926 (28.2)	1,837 (28.0)
≥60 to <70 years	3,333 (39.9)	3,974 (41.2)	7,307 (40.6)	1,358 (41.4)	1,348 (41.1)	2,706 (41.2)
≥70 years	2,681 (32.1)	2,900 (30.1)	5,581 (31.0)	1,014 (30.9)	1,008 (30.7)	2,022 (30.8)
Race, n (%)						
White	6,941 (83.2)	8,321 (86.3)	15,262 (84.8)	2,552 (77.7)	2,561 (78.0)	5,113 (77.9)
Black	280 (3.4)	240 (2.5)	520 (2.9)	67 (2.0)	54 (1.6)	121 (1.8)
Asian	220 (2.6)	229 (2.4)	449 (2.5)	616 (18.8)	621 (18.9)	1,237 (18.8)
Other	2 (0.0)	2 (0.0)	4 (0.0)	3 (0.1)	0 (0.0)	3 (0.0)
Missing data	900 (10.8)	855 (8.9)	1,755 (9.8)	45 (1.4)	46 (1.4)	91 (1.4)
Sex, n (%)						
Male	6,327 (75.8)	7,315 (75.8)	13,642 (75.8)	2,429 (74.0)	2,451 (74.7)	4,880 (74.3)
Female	2,016 (24.2)	2,332 (24.2)	4,348 (24.2)	854 (26.0)	831 (25.3)	1,685 (25.7)
Smoking history, n (%)						
Never smoked	2 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Ex-smoker	5,527 (66.2)	6,314 (65.5)	11,841 (65.8)	2,045 (62.3)	2,048 (62.4)	4,093 (62.3)
Current smoker	2,809 (33.7)	3,329 (34.5)	6,138 (34.1)	1,238 (37.7)	1,233 (37.6)	2,471 (37.6)
Missing data	5 (0.1)	4 (0.0)	9 (0.1)	—	—	—
GOLD stage, n (%) <sup>a</sup>	n=4,514	n=5,300	n=9,814	n=3,283	n=3,282	n=6,565
I-II	2,291 (50.8)	2,763 (52.1)	5,054 (51.5)	1,332 (40.6)	1,291 (39.3)	2,623 (40.0)
II	1,823 (40.4)	2,086 (39.4)	3,909 (39.8)	1,493 (45.5)	1,513 (46.1)	3,006 (45.8)
IV	334 (7.4)	371 (7.0)	705 (7.2)	441 (13.4)	453 (13.8)	894 (13.6)
Missing data	66 (1.5)	80 (1.5)	146 (1.5)	17 (0.5)	25 (0.8)	42 (0.6)
Mean FEV <sub>1</sub> , L (SD)	1.17 (0.5)	1.18 (0.5)	1.18 (0.5)	1.11 (0.4)	1.11 (0.4)	1.11 (0.4)
Mean FEV <sub>1</sub> , % predicted (SD)	41.22 (14.2)	41.66 (14.4)	41.46 (14.3)	40.30 (12.5)	40.11 (12.3)	40.21 (12.4)
Mean FVC, L (SD)	2.51 (0.8)	2.49 (0.8)	2.50 (0.8)	2.45 (0.8)	2.45 (0.8)	2.45 (0.8)
Mean FVC, % predicted (SD)	70.24 (19.2)	69.39 (19.0)	69.79 (19.1)	70.32 (17.9)	70.05 (17.9)	70.18 (17.9)
Mean FEV <sub>1</sub> /FVC ratio (SD)	0.47 (0.1)	0.48 (0.1)	0.48 (0.1)	0.46 (0.1)	0.46 (0.1)	0.46 (0.1)

**Notes:** <sup>a</sup>GOLD stage I, ≥80% predicted; stage II, <80% to ≥50% predicted; stage III, <50% to ≥30% predicted; stage IV, <30% predicted. Only eight HandiHaler® trials where post-bronchodilator values have been collected contribute to the denominator of the percentages.

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; L, liters; SD, standard deviation.



**Table 2** Baseline demographics and clinical characteristics of patients with COPD in the pooled tiotropium HandiHaler®, pooled tiotropium Respimat® trials, and comparison observational studies

Characteristic/ demographic	Pooled tiotropium HandiHaler® (n=17,990)	Pooled tiotropium Respimat® trials (n=6,565)	de Lucas-Ramos et al <sup>26</sup> (n=970)	Agusti et al <sup>24</sup> (n=2,164)	Jones et al <sup>31</sup> (n=1,817)	Divo et al <sup>12</sup> (n=1,659)	Schnell et al <sup>36</sup> (n=995)	Mannino et al <sup>32</sup> (n=20,296) <sup>†</sup>
Age, years (mean, SD)	64.5 (8.8)	64.7 (8.9)	64.1 (8.8)	63.4 (7.1)	64.9 (9.6)	66.0 (9.0)	62.7 <sup>a</sup> (61.7–63.8)	–
Sex, n (%)								
Male	13,642 (75.8)	4,880 (74.3)	681 (70.4)	1,411 (65.2)	1,305 (71.8)	1,477 (89.0)	397 (39.9)	9,038 (44.5)
Female	4,348 (24.2)	1,685 (25.7)	286 (29.6)	750 (34.8)	512 (28.2)	182 (11.0)	598 (60.1)	11,258 (55.5)
Smoking history								
Current smoker, n (%)	6,138 (34.1)	2,471 (37.6)	–	784 (36.2)	781 (43)	–	–	8,260 (40.9)
Pack-years (mean, SD)	49.0 (28.4)	46.5 (26.3)	65.8 (34.8)	48.6 (27.1)	40.4 (24.4)	–	–	–
GOLD stage, n (%) <sup>b</sup>								
I–II	5,054 (51.5)*	2,623 (40.0)	383 (39.5)	954 (44.1)	–	728 (44.0)	–	4,968 (24.5)
III	3,909 (39.8)*	3,006 (45.8)	325 (33.5)	911 (42.1)	–	639 (39.0)	–	530 (2.6)
IV	705 (7.2)*	894 (13.6)	260 (27.0)	296 (13.7)	–	292 (17.0)	–	–
Mean FEV <sub>1</sub> , % predicted (SD)	41.46 (14.3)	40.21 (12.4)	47 (13.9)	48.3 (15.8)	56.7 (20.1)	49.0 (20.0)	–	–
Mean FVC, % predicted (SD)	69.79 (19.1)	70.18 (17.9)	66.1 (16.5)	–	–	–	–	–
Mean FEV <sub>1</sub> /FVC ratio (SD)	0.48 (0.1)	0.46 (0.1)	0.58 <sup>c</sup> (0.9)	0.45 (0.1)	–	–	–	–

**Notes:** \*95% confidence intervals presented; <sup>a</sup>GOLD stage I, ≥80% predicted; stage II, <80% to ≥50% predicted; stage III, <50% to ≥30% predicted; stage IV, <30% predicted; <sup>b</sup>FEV<sub>1</sub>/FVC ratio <0.7 was an inclusion criterion. <sup>c</sup>n=9814 for the pooled tiotropium HandiHaler® RCTs. <sup>†</sup>The number of patients in GOLD stages I–IV only makes up 27.1% of patients that either had lung function of FEV<sub>1</sub>/FVC <0.70 and FEV<sub>1</sub> ≥80% predicted; presence of respiratory symptoms in the absence of any lung function abnormality; or FEV<sub>1</sub>/FVC ≥0.70 and FVC <80% predicted.

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; SD, standard deviation; COPD, chronic obstructive pulmonary disease.

**Table 3** Prevalence of comorbidities of interest by Medical Dictionary for Regulatory Activities (MedDRA) system organ class at baseline in patients with COPD

Comorbidities	28 SPIRIVA® HandiHaler® trials	Seven Respimat® trials	Rodríguez et al <sup>34</sup>	Huiart et al <sup>29</sup>	Sundh et al <sup>38</sup>	Pasquale et al <sup>33</sup>
COPD patient population, N	16,351	6,565	1,927	5,648	919	8,554
Baseline comorbidities, N (%)						
Vascular disorders						
Cardiac disorders	6,525 (39.9)	2,634 (40.1)	–	2,539 (45.0)	–	972 (11.4)
Respiratory, thoracic, and mediastinal disorders	4,020 (24.6)	1,597 (24.3)	153 <sup>a</sup> (9.4)	1,826 (32.3)	208 (22.6)	1,568 (18.3)
Gastrointestinal disorders	2,631 (16.1)	862 (13.1)	–	–	–	–
Psychiatric disorders	3,175 (19.4)	1,143 (17.4)	–	–	–	–
Neoplasms benign, malignant, and unspecified	2,275 (13.9)	863 (13.1)	–	–	109 (11.9)	–
Metabolism and nutrition disorders	188 (1.2)	54 (0.8)	48 <sup>b</sup> (2.5)	–	–	–
	1,682 (10.3)	709 (10.8)	–	678 (12.0)	91 (9.9)	1,900 (22.2)

**Notes:** <sup>a</sup>A total of 1,627 patients eligible for this analysis; <sup>b</sup>1,924 eligible patients for this analysis. Concomitant diagnoses of comorbidities were not collected in HandiHaler® trial number 205.257; comorbidities of interest include those most frequently reported in COPD trials. MedDRA v 14.0 was used for analysis of the 28 SPIRIVA® HandiHaler® trials and the seven Respimat® trials.

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

**Table 4** Prevalence of comorbidities of interest by pharmacovigilance (PV) endpoint/Standardized MedDRA Query (SMQ) at baseline in subjects with COPD

Study		28 SPIRIVA® HandiHaler® trials†	Seven Respimat® trials†	García-Olmos et al <sup>28</sup>	de Lucas-Ramos et al <sup>26</sup>	Agusti et al <sup>24</sup>	Schane et al <sup>35</sup>	Curkendall et al <sup>25</sup>	Divo et al <sup>12</sup>	Schnell et al <sup>36</sup>	Mannino et al <sup>32</sup>	Pasquale et al <sup>33</sup>
COPD patient population (N)		16,351	6,565	3,183	970	2,164	1,736	11,493	1,659	995	20,296	8,554
Baseline comorbidities (N, %)												
SMQ cardiac arrhythmias, sub-SMQ cardiac arrhythmia terms		1,277 (7.8)	750 (11.4)	503 (15.8)	153 (15.8)	260 (12.0)	–	1,299 (11.3)	216 (13.0)	–	–	–
SMQ depression and self-injury (excluding suicide and self-injury) (narrow)		1,554 (9.5)	556 (8.5)	643 (20.2)	–	368 (17.0)	–	–	–	205 (20.6)	–	–
SMQ hyperglycemia/new-onset diabetes mellitus (narrow)		1,677 (10.3)	715 (10.9)	661 (20.8)	377 (38.9)	216 (10.0)	375 (21.6)	–	66 (4.0)	162 (16.3)	2,578 (12.7)	1,900 (22.2)
SMQ cardiac failure (narrow)		769 (4.7)	217 (3.3)	256 (8.0)	238 (24.5)	151 (7.0)	850 (49.0)	2,184 (19.0)	260 (15.7)	120 (12.1)	–	1,568 (18.3)
SMQ hypertension (narrow)		6,448 (39.4)	2,627 (40.0)	1,655 (52.0)	499 (51.4)	–	1,052 (60.6)	–	–	601 (60.4)	8,139 (40.1)	–
Stroke PV		441 (2.7)	162 (2.5)	–	96 (9.9)	87 (4.0)	248 (14.3)	552 (4.8)	–	89 (8.9)	–	–
SMQ ischemic heart disease, sub-SMQ MI (broad)		664 (4.1)	226 (3.4)	–	–	195 (9.0)	–	264 (2.3)	–	–	–	–
SMQ ischemic heart disease sub-SMQ, other ischemic heart disease (broad)		2,326 (14.2)	809 (12.3)	–	121 (12.5)	562 (26.0)	711 (41.0)	–	501 (30.2)	126 (12.7)	–	–

**Notes:** †Data are SMQs. MedDRA v 14.0 was used for analysis of the 28 SPIRIVA® HandiHaler® trials and the seven Respimat® trials; however concomitant diagnoses of comorbidities were not collected in HandiHaler® trial number 205.257. Comorbidities of interest include those most frequently reported in COPD trials.

**Abbreviations:** MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease.

Hypertension was diagnosed in 39.4% of patients in the HandiHaler® and 40.0% of patients in the Respimat® trials. Diagnoses of ischemic heart disease (14.2% and 12.3%) cardiac arrhythmias (7.8% vs 11.4%), depression (9.5% vs 8.5%), and diabetes (10.3% vs 10.9%) were similar in the pooled HandiHaler® and Respimat® trials, respectively (Table 4).

When reported by applicable PTs, the comorbidities with the highest prevalence in epidemiological and observational studies were hypertension (40.1%–60.6%), cardiac arrhythmia (11.3%–15.8%), depressed mood (17.0%–20.6%), cardiac failure (7.0%–49.0%), and ischemic heart disease (12.5%–41.0%, Table 4). In UPLIFT®, increases in comorbid conditions from baseline to year 4 were observed (Table S4).

## Discussion

We have analyzed the demographic data of patients in randomized, placebo-controlled clinical studies with tiotropium HandiHaler® and Respimat® of at least 4 weeks' duration and compared these with data from epidemiological and observational studies. The background for this comparison was that, recently, several authors questioned the validity of RCTs for the evaluation of the safety of drugs in the treatment of COPD in clinical practice.<sup>13,14</sup> The pivotal argument for these concerns was that the inclusion and exclusion criteria of RCTs prevent patients at greater risk (notably of cardiovascular [CV] risk) from participating in these studies. This could then potentially lead to a more positive safety evaluation of the drugs in question compared with clinical practice in a real-life setting.

This study of the characteristics of the 24,555 patients included in the randomized trials of tiotropium showed that the clinical profile, including age, sex, smoking history, and anthropometrics of these patients, is similar to that observed in large epidemiological and observational studies of patients with COPD. However, the proportions of patients with mild to moderate disease (GOLD stages I+II) ranged from 24.5% to 44.1% in the observational studies but from 40.0% to 51.5% in the tiotropium trials, while patients with severe disease (GOLD stage III or IV) were represented in similar numbers in the tiotropium RCTs (7.2%–45.8%) as in the observational studies (13.7%–42.1%).

## Comorbidities

The most prevalent comorbidities reported by SOC observed in the COPD patient population at baseline in the pooled tiotropium trials were: cardiac, vascular, respiratory,

gastrointestinal, psychiatric, and metabolic disorders. These were represented in the observational studies in similar proportions (Table 3). In particular, the prevalence of cardiac disorders in the 22,916 evaluable patients in the tiotropium RCT population was 24.3%–24.6%. Of the 17,048 patients with COPD in the epidemiologic/observational studies,<sup>21,25,26,30</sup> the prevalence of cardiac disorders was in the range of 9.4%–32.3%. In a recent letter to the editor,<sup>39</sup> the authors conducted an audit of patients discharged from hospital in New Zealand after an exacerbation of COPD and found that 38% patients prescribed tiotropium had comorbidities that would have made them ineligible for participation in UPLIFT®. Based on this observation, the authors concluded that the findings from UPLIFT® had limited generalizability to clinical practice in New Zealand. However, this New Zealand patient population is a very severe population of patients that required hospital admission, whereas patients included in UPLIFT®, as in all major clinical trials of COPD, consisted of ambulatory patients. The pattern of comorbidities of very severe admitted patients may differ, but this New Zealand patient population represents a minority of patients with COPD of special severity with increased risks of side effects secondary to all drugs and that require a personalized approach with careful evaluation of the expected benefits and risks of any given treatment.

Although it was excluded from our systematic literature review because it is a pooled analysis of epidemiological studies, validation of the current analysis is provided by a study conducted by Patel and Hurst.<sup>40</sup> Using data from two large, population-based epidemiological studies (the Atherosclerosis Risk in Communities [ARIC] Study and the Cardiovascular Health Study [CHS], 20,296 adults aged >44 years),<sup>40</sup> they reported that the prevalence of CV disease (defined as a composite of ischemic heart disease, heart failure, stroke, and/or transient ischemic attack) in patients with COPD was 20.0%–22.0%. This is similar to the 24.6% and 24.3% prevalence of cardiac disorders that we determined in the tiotropium trials. This contradicts the concerns that the inclusion and exclusion criteria of tiotropium RCTs prevent patients at greater risk (notably of CV risk) from participating in these studies.

Comorbidities of interest were selected on the basis of being the most frequently reported in COPD trials and also to maximize the degree of comparisons with the observational studies identified in our systematic literature review. For eight selected comorbidities of interest (Table 4), our analysis revealed that hypertension had the highest prevalence in patients enrolled in tiotropium RCTs (39.4%–40.0%).



This was lower than the range (51.4%–60.6%) reported in four out of nine observational studies<sup>26,28,32,35,36</sup> (total: 6,884 patients) used in our comparison. However, in a population-based National Institutes of Health cohort of 20,296 patients with COPD aged  $\geq 45$  years, the prevalence of hypertension was 40.1%,<sup>32</sup> similar to that reported for patients in tiotropium RCTs.

Although not included in our current analysis because it is not among the most frequently reported comorbidities among patients with COPD, two reports, by Verhamme et al<sup>41</sup> and Mathioudakis et al,<sup>42</sup> have suggested an association between mortality and renal impairment in patients with COPD treated with tiotropium via HandiHaler<sup>®</sup> or Respimat<sup>®</sup>. A pooled safety analysis of tiotropium delivered via the HandiHaler<sup>®</sup> or the Respimat<sup>®</sup> Soft Mist<sup>™</sup> Inhaler that encompasses 22 Phase III and IV tiotropium clinical trials and evaluated 10,805 patients showed that there was no trend for increased incidence rate ratios of adverse events with worsening renal function for either tiotropium HandiHaler<sup>®</sup> or Respimat<sup>®</sup>. (Table S5).<sup>43</sup>

## Limitations of the study

A major limitation of this study is the difference in the reporting of baseline characteristics and comorbidities in the observational studies identified in our systematic literature review. Only six of the observational studies reported the GOLD staging of patients. Although included in this comparison, Mannino et al's study<sup>32</sup> reports GOLD staging for only 27.1% of the patients enrolled, which complicates interpretation of these results. Furthermore, four studies reported baseline comorbidities by SOC, and none of these allowed for a full comparison with the tiotropium RCTs. This means that for comorbidities such as respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, psychiatric disorders, and neoplasms, the patient population against which the tiotropium RCT population is compared is limited (only 2,846 from two of the four observational studies as compared with 22,916 in the tiotropium RCTs combined). This variability complicates interpretation of these results due to the limited sample size. Although this situation is repeated for comparison of baseline comorbidities in Table 4, it is mitigated to some extent by the inclusion of 51,050 patients from nine out of 13 observational studies for comparison to the 22,916 patients identified in the included tiotropium RCTs.

Another limitation of this study is that it does not take into account the various factors that add to the complexity of studying comorbidities in patients with COPD. These include: smoking status, which has been shown to be a

risk factor for diabetes mellitus and dyslipidemia; age; polypharmacy; lack of treatment of comorbidities; and lack of specific case definitions for comorbidities.<sup>7</sup> However, with regard to smoking status, the percentage of current smokers enrolled in the tiotropium RCTs is similar to the percentage identified as current smokers in the observational studies included in our analysis.

Lastly, patients with recent unstable cardiac diseases (MI within 6 months and new unstable arrhythmia or severe heart failure within 1 year) were excluded from the tiotropium RCTs. Therefore, the findings in the tiotropium studies cannot be extended to these patients.

## Conclusion

The clinical profile (defined by SOC) of patients with COPD treated in the tiotropium trial program appears to be largely in the range of clinical characteristics, including CV comorbidities reported for “real-life patients.” Overall, patients in the tiotropium studies were comparable to those patients enrolled in the observational studies with regard to the severity of disease (GOLD stages III and IV).

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Marc Miravittles has received speaker fees from Almirall, Boehringer Ingelheim, Pfizer, AstraZeneca, Chiesi, Esteve, GlaxoSmithKline, Menarini, Novartis, Talecris-Grifols, Takeda-Nycomed, and Novartis, and consulting fees from Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Gebro Pharma, MediImmune, Novartis, Talecris-Grifols, and Takeda-Nycomed.

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## Supplementary materials

**Table S1** Clinical trials included in the pooled tiotropium HandiHaler® and Respimat® analysis

Boehringer Ingelheim trial number	Trial duration (weeks)	Placebo-treated patients (N)	Tiotropium-treated patients (N)	Reference
<b>HandiHaler® trials</b>				
205.114/117	48	191	279	Casaburi et al <sup>1</sup>
205.115/128	48	180	271	Casaburi et al <sup>1</sup>
205.123 (ECLIPSE®)	6	40	81	Agusti et al <sup>2</sup>
205.124	4	30	65	McNicholas et al <sup>3</sup>
205.130	24	201	209	Brusasco et al <sup>4</sup>
205.131	6	100	98	O'Donnell et al <sup>5</sup>
205.137	24	199	193	Brusasco et al <sup>4</sup>
205.214 (MISTRAL)	48	510	500	Dusser et al <sup>6</sup>
205.215	12	54	46	Verkindre et al <sup>7</sup>
205.218	4	41	40	Celli et al <sup>8</sup> and Maltais et al <sup>9</sup>
205.223	6	130	131	Maltais et al <sup>9</sup>
205.230	25	53	55	Casaburi et al <sup>10</sup>
205.235 (UPLIFT®)	210	3,006	2,986	Tashkin et al <sup>11</sup>
205.247	25	117	117	Kesten et al <sup>12</sup>
205.256 (TIPHON)	36	288	266	Tonnel et al <sup>12</sup>
205.257	12	403	1,236	Beeh et al <sup>13</sup>
205.259 (SAFE)	48	305	608	Chan et al <sup>14</sup>
205.266	24	915	914	Niewoehner et al <sup>15</sup>
205.269	16	127	123	Powrie et al <sup>16</sup>
205.270	52	73	69	Powrie et al <sup>16</sup>
205.276 (SPRUCE)	12	195	200	Freeman et al <sup>17</sup>
205.281	12	117	107	Johansson et al <sup>18</sup>
205.282 (SAFE Portugal)	12	164	147	Moita et al <sup>19</sup>
205.284	12	96	100	Covelli et al <sup>20</sup>
205.294	8	86	80	Criner et al <sup>21</sup>
205.301	12	244	228	Magnussen et al <sup>22</sup>
205.365	24	219	238	Sciurba et al <sup>23</sup>
205.368 (EXACTT)	96	259	260	Cooper et al <sup>24</sup>
<b>Respimat® trials</b>				
205.251/252	12	181	180	Voshaar et al <sup>25</sup>
205.254/255	52	653	670	Bateman et al <sup>26</sup>
205.372	52	1,965	1,952	Bateman et al <sup>27</sup>
I,205.4	4	55	53	Littner et al <sup>28</sup>
I,205.14	24	429	427	Abrahams et al <sup>29</sup>

**Note:** Trial numbers refer to the Boehringer Ingelheim trials database.

**Abbreviations:** ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; EXACTT, Exercise Endurance and COPD Treated With Tiotropium; MISTRAL, Mesure de l'Influence de SPIRIVA® sur les Troubles Respiratoires Aigus à Long terme [measuring the influence SPIRIVA® on acute respiratory disorders for the long term]; SAFE, SPIRIVA® Assessment of FEV<sub>1</sub>; SPRUCE, SPIRIVA® Usual Care; TIPHON, Tiotropium: Influence sur la Perception de l'amélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT®, Understanding the Potential Long-term Impacts on Function with Tiotropium; COPD, chronic obstructive pulmonary disease.

**Table S2** Observational studies meeting the inclusion criteria for the systematic literature review

Publication titles	Number of patients with COPD assessed	Cohort background	Citation
Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study	3,183	The study was conducted in a health area of the Madrid Autonomous Region (Comunidad Autónoma de Madrid). The practice population totalled 198,670 persons attended by 129 family physicians.	García-Olmos L et al <sup>30</sup>
Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly medicare population	8,554	This study involved patients who were aged 40–89 years, had been enrolled continuously for 24 months or more, had at least two separate insurance claims for COPD with chronic bronchitis and had pharmacy claims for COPD maintenance medications between 1 January 2007 and 31 March 2009.	Pasquale MK et al <sup>31</sup>
Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease	1,659	This study followed 1,664 patients (BODE cohort) from pulmonary clinics in the USA and Spain for a median duration of 51 months between 1997 and 2009.	Divo M et al <sup>32</sup>
Chronic obstructive pulmonary disease as a cardiovascular risk factor: Results of a case-control study (CONSISTE study)	970	The study cohort was recruited from primary and specialized care consultations in Spain. COPD patients were recruited when they attended the clinic for a routine check-up.	de Lucas-Ramos P et al <sup>33</sup>
The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008	995	This study draws from a multi-year analytic sample of 14,828 subjects aged 45+, including 995 with COPD, from NHANES, 1999–2008. COPD was defined by self-reported physician diagnosis of chronic bronchitis or emphysema	Schnell K et al <sup>34</sup>
Health-related quality of life in patients by COPD severity within primary care in Europe	1,817	This study enrolled subjects 40–80 years old, diagnosed with COPD at least 6 months before the start of the study. Patients were recruited from primary care setting in Belgium, France, Germany, Italy, the Netherlands, Spain and the UK.	Jones PW et al <sup>35</sup>
Co-morbidity, body mass index and quality of life in COPD using the Clinical COPD Questionnaire	919	This study recruited patients with COPD from both primary and secondary healthcare settings in Sweden.	Sundh J et al <sup>36</sup>
Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD	20,296	The study included patients enrolled in the Cardiovascular Health and the Atherosclerosis Risk in Communities Studies. Patients were >65 and 45–64 years old respectively.	Mannino DM et al <sup>37</sup>
Prevalence and risk factors for depressive symptoms in persons with chronic obstructive pulmonary disease	1,736	The study subjects were interviewed in the 2004 wave of the Health and Retirement Survey, a nationally representative population-based study of subjects aged 50 years and older in the United States with self-reported COPD.	Schane RE et al <sup>38</sup>
Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients	11,493	Subjects were persons aged ≥40 years from Saskatchewan, Canada, with a diagnosis of COPD between 1997 and 2000, and received two or more prescriptions for bronchodilators within 6 months of diagnosis.	Curkendall SM et al <sup>39</sup>
Characterization of COPD heterogeneity in the ECLIPSE cohort	2,164	The ECLIPSE cohort consisted of patients with clinically stable COPD.	Agusti A et al <sup>2</sup>
Cardiovascular morbidity and mortality in COPD	5,648	The population-based cohort included in this study were patients with COPD ≥55 years old receiving a first treatment for COPD between 1990 and 1997 in Saskatchewan, Canada, and were part of the Saskatchewan Health Databases.	Huiart L et al <sup>40</sup>
Heart failure, myocardial infarction, lung cancer and death in COPD patients: a UK primary care study	1,927	The GPRD was used to identify a cohort of 1927 patients with a first recorded diagnosis of COPD. Subjects were followed for up to 5 years to identify new diagnoses of lung cancer, MI and heart failure.	Rodríguez LA et al <sup>41</sup>

**Abbreviations:** BODE, Body mass index, airflow Obstruction, Dyspnea and Exercise capacity; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GPRD, General Practice Research Database; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey.



Table S3 Reference listing – definition of pharmacovigilance endpoints

PV endpoint/SMQ	PT
Stroke PV	Amaurosis fugax, basal ganglia hemorrhage, basilar artery occlusion, basilar artery thrombosis, brachiocephalic artery occlusion, brain stem hemorrhage, brain stem infarction, brain stem ischemia, brain stem stroke, brain stem thrombosis, carotid aneurysm rupture, carotid arterial embolus, carotid artery occlusion, carotid artery thrombosis, cerebellar artery occlusion, cerebellar artery thrombosis, cerebellar embolism, cerebellar hematoma, cerebellar hemorrhage, cerebellar infarction, cerebellar ischemia, cerebellar arteriovenous malformation hemorrhagic, cerebellar artery embolism, cerebellar artery occlusion, cerebellar artery thrombosis, cerebellar hematoma, cerebellar hemorrhage, cerebellar hemorrhage fetal, cerebellar hemorrhage neonatal, cerebellar infarction, cerebellar infarction foetal, cerebellar ischemia, cerebellar thrombosis, cerebrovascular accident, embolic cerebellar infarction, embolic stroke, hemorrhage intracranial, hemorrhagic cerebellar infarction, hemorrhagic stroke, hemorrhagic transformation stroke, intracranial hematoma, intracranial tumour hemorrhage, intraoperative cerebellar, artery occlusion, intraventricular hemorrhage, intraventricular hemorrhage neonatal, ischemic cerebellar infarction, ischemic stroke, lacunar infarction, lateral medullary syndrome, pituitary hemorrhage, pituitary infarction, post procedural stroke, precerebral artery occlusion, putamen hemorrhage, reversible ischemic neurologic deficit, ruptured cerebellar aneurysm, stroke in evolution, subarachnoid hemorrhage, subarachnoid hemorrhage neonatal, subdural hemorrhage neonatal, thalamic infarction, thalamus hemorrhage, thrombotic cerebellar infarction, thrombotic stroke, transient ischemic attack, vertebral artery occlusion, vertebral artery thrombosis

Note: MedDRA v 14.0 used for reporting.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; PV, pharmacovigilance; SMQ, Standardised MedDRA Query.

Table S4 Distribution of patient comorbidities by pharmacovigilance endpoint/Standardised MedDRA Query (SMQ) in the UPLIFT® trial

Concomitant conditions	UPLIFT® baseline	UPLIFT® year 4
Patients with any concomitant conditions, N (%)	5,263 (87.8)	5,884 (98.2)
Cardiac diseases	1,555 (26.0)	2,216 (37.0)
SMQ ischemic heart disease sub-SMQ myocardial infarction (broad)	170 (2.8)	329 (5.5)
SMQ other ischemic heart disease (broad)	922 (15.4)	1,145 (19.1)
SMQ cardiac arrhythmias sub SMQ cardiac arrhythmia terms	386 (6.4)	710 (11.8)
SMQ cardiac arrhythmias sub-SMQ tachyarrhythmias	261 (4.4)	535 (8.9)
PT hypertension	2,373 (39.6)	2,793 (46.6)
Stroke PV	139 (2.3)	283 (4.7)
PT diabetes mellitus	334 (5.6)	467 (7.8)
SMQ depression and self-injury sub-SMQ depression (excluding suicide and self-injury) (narrow)	525 (8.8)	715 (11.9)

Note: MedDRA version 13.1 used for reporting.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; UPLIFT®, Understanding Potential Long-term Impacts on Function with Tiotropium; PV, pharmacovigilance.

**Table S5** Incidence rate ratios (IRRs) (95% confidence interval) of on-treatment adverse events (AEs) categorized by renal function at baseline (NICE cutoff)

On-treatment adverse events	HandiHaler® (15 studies)			Respimat® (seven studies)		
	Normal, 852/692	Mild, 1,104/821	Moderate, 451/349	Normal, 1,104/1,040	Mild, 1,479/1,539	Moderate, 662/660
Renal function or impairment, n in tiotropium/placebo group						
AEs (total)	0.95 (0.84, 1.08)	0.86 (0.77, 0.96)	0.78 (0.66, 0.93)	0.88 (0.80, 0.98)	0.98 (0.90, 1.07)	0.92 (0.81, 1.04)
SAEs (total)	0.99 (0.72, 1.37)	0.95 (0.73, 1.24)	0.74 (0.52, 1.05)	1.08 (0.85, 1.38)	0.84 (0.70, 1.02)	0.95 (0.75, 1.20)
SAEs (cardiac SOC)	0.92 (0.40, 2.12)	0.85 (0.45, 1.62)	1.32 (0.55, 3.19)	1.87 (0.99, 3.52)	0.78 (0.46, 1.34)	1.19 (0.68, 2.06)
FAEs	0.82 (0.21, 3.14)	1.23 (0.43, 3.50)	0.61 (0.22, 1.72)	2.54 (0.80, 8.13)	1.09 (0.61, 1.94)	1.28 (0.70, 2.36)
FAEs in cardiac SOC <sup>#</sup>	0.61/0.00*	0.35 (0.07, 1.70)	3.05 (0.49, 19.14)	2.80 (0.55, 14.33)	0.74 (0.17, 3.27)	2.40 (0.84, 6.87)
FAEs in general disorders SOC <sup>#</sup>	0.00/0.59*	0.14/0.00*	0.00/0.00*	0.94 (0.06, 14.97)	1.99 (0.50, 7.93)	0.36/0.00*
MACE <sup>#</sup>	1.07 (0.26, 4.44)	1.38 (0.65, 2.94)	1.10 (0.44, 2.76)	1.40 (0.55, 3.58)	0.51 (0.27, 0.96)	1.17 (0.57, 2.37)
Fatal MACE (including death unknown) <sup>#</sup>	1.89 (0.16, 22.49)	0.57 (0.16, 1.99)	3.05 (0.49, 19.14)	1.85 (0.45, 7.59)	0.99 (0.37, 2.62)	2.28 (0.88, 5.90)

**Notes:** Renal function classification: normal  $\geq 90$  mL/min, mild  $\geq 60$  to  $< 90$  mL/min, moderate  $\geq 30$  to  $< 60$  mL/min, severe  $< 30$  mL/min creatinine. The IRR could not be calculated for severe renal impairment due to low patient numbers. <sup>#</sup>The same patients may fulfill criteria for inclusion in different AE categories. Hence, numbers are not additive. \*If there are no events in the placebo or tiotropium group, IRRs cannot be calculated (division by zero) or are equal to zero, respectively; the incident rates for tiotropium/placebo are presented instead.

**Abbreviations:** FAE, fatal adverse event; MACE, major adverse cardiovascular event; NICE, National Institute for Health and Care Excellence; SAE, serious adverse event; SOC, system organ class.

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