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# Use of tiotropium Respimat® SMI vs. tiotropium Handihaler® and mortality in patients with COPD

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**Abstract**

**Background and research question:**

Tiotropium, a long-acting anticholinergic, is delivered via HandiHaler® or via Respimat®. RCTs suggest that use of Tiotropium Respimat® increases the risk of dying. We compared the risk of mortality between tiotropium Respimat® vs. HandiHaler®.

**Methods:**

Within the Integrated Primary Care Information database, we defined a source population of patients, ≥ 40 years, with at least 1 year of follow-up. Based on prescription data, we defined episodes of tiotropium use (Respimat® or Handihaler®). The risk of mortality, within these episodes, was calculated using a Cox proportional hazard regression analysis.

**Results:**

From the source population, 11287 patients provided 24522 episodes of tiotropium use. 496 patients died while being exposed to Handihaler® or Respimat®. Use of Respimat® was associated with almost 30% increased risk of dying ($HR_{adj}$ 1.27, 95% CI 1.03-1.57) with the highest risk for cardiovascular/cerebrovascular death ($HR_{adj}$ 1.56, 95% CI 1.08-2.25). The risk was higher in patients with co-existing cardiovascular disease ($HR_{adj}$ 1.36, 95% CI 1.07-1.73) than in patients without ($HR_{adj}$ 1.02, 95% CI 0.61-1.71).

**Conclusions:**

Use of tiotropium Respimat® was associated with an almost 30% increase of mortality compared to Handihaler® and the association was the strongest for cardiovascular/cerebrovascular death. It is unclear whether this association is causal or due to residual confounding by COPD severity.

**Key Words:**

COPD, Tiotropium Respimat® SMI, Tiotropium Handihaler®, mortality, cohort.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide, and it is known that the rate of COPD-related death is increasing [1]. COPD is characterized by a progressive decline in lung function which cannot be reversed by treatment. Bronchodilators are the mainstay of symptomatic management of COPD and include $\beta_2$ agonists, anticholinergics (AC), and methylxanthines, used alone or in combination. [2] Long-acting bronchodilators are more effective and convenient than the short-acting agents at producing maintained symptom relief.[2] Tiotropium is a long-acting inhaled AC bronchodilator developed for the long term, once daily, maintenance treatment of COPD. The efficacy and safety of tiotropium have been demonstrated in RCTs, with a significantly lower risk of COPD exacerbations and statistically non-significant reductions for mortality.[3] Tiotropium is delivered either by the HandiHaler® device, a single-dose dry powder inhaler (DPI) or via Respimat® Soft Mist Inhaler (SMI), a novel propellant-free inhaler.

Tiotropium HandiHaler® (Spiriva®) is a potent long-acting bronchodilator which clinical benefits have been established in several clinical studies [3-6]. The lung function improvements and the safety associated with tiotropium HandiHaler® have been reported in clinical trials of COPD patients [5, 7-11], including the UPLIFT (Understanding Potential Long term Impacts on Function with Tiotropium) study which is the largest long term RCT studying the efficacy and safety of Tiotropium HandiHaler® conducted so far.

Tiotropium Respimat® Soft Mist Inhaler (SMI), has been developed and proposed as an alternative device [12]. Based on its lower velocity, Respimat® SMI improves lung drug deposition, reduces oropharyngeal deposition, and may require a lower dose of drug than normally used with either dry powder inhalers or metered dose inhalers [13, 14].

In 2008, concerns were raised on the cardiovascular and cerebrovascular safety of tiotropium HandiHaler®. These concerns were based on 1) a report to the FDA, issued by Boehringer Ingelheim, the manufacturer of tiotropium, on pooled data from 29 placebo-controlled trials showing an increased risk of stroke in patients treated with tiotropium, and 2) a meta-analysis and a case-control study reporting an increased risk of mortality and/or cardiovascular events in patients who received inhaled anticholinergics (ipratropium or tiotropium). [15-17] In their initial report to the FDA, Boehringer Ingelheim also reported an increased risk of mortality with tiotropium Respimat® SMI device based on data from 3 one-year placebo controlled

trials. In January 2010, the FDA warning on the use of tiotropium Handihaler® was overruled, based on data from the UPLIFT study and updated meta-analysis (including the UPLIFT study), stating that the available data did no longer support an association between the use of tiotropium Handihaler® and an increased risk of stroke, heart attack or death from cardiovascular causes. [17] However, the concerns on the safety of tiotropium Respimat remained and Singh et al. published a meta-analysis in 2011 based on data from 5 RCTs showing a 50% increased risk of mortality of tiotropium Respimat® SMI compared to placebo. [18] Since the publication of the meta-analysis by Singh et al in 2011, new data were reported by Dong et al. These researchers conducted a meta-analysis to compare the safety of inhaled drugs (ICS, LABA and LAMA) in patients with COPD via mixed treatment comparison. They included 42 trials with 52 516 subjects enrolled, and reported an increased risk of mortality (OR 1.65, 95% CI 1.13-2.43) in patients treated with tiotropium Respimat® SMI vs. tiotropium HandiHaler®. [19]

The current available data do not allow drawing strong conclusions on the risk of mortality in patients treated with tiotropium Respimat® compared to tiotropium Handihaler® as no direct head to head comparisons have been done so far. Therefore, we conducted an observational cohort study to compare the risk of mortality in patients treated with tiotropium Respimat® using tiotropium HandiHaler® as reference category.

## Material and methods

*Setting*

The study was conducted in the Integrated Primary Care Information Project (IPCI) database. IPCI is a population-based longitudinal observational database that contains the complete computer-based medical records of more than 400 General Practitioners (GPs) throughout the Netherlands, who voluntarily chose to supply data to the database [20]. In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper of medical care and information from primary care visits, hospital admission and outpatient visits. At present, the ICPI database contains information on more than one million active patients. The IPCI database contains anonymized patient identification information (age, sex, patient identification number, and GP registration information), narratives, symptoms, signs, GP and specialist diagnoses, prescriptions, physical findings, laboratory values and summaries of specialist letters. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but they can also be entered as free text [21]. Therefore, the medical records do not only capture GP diagnosis and symptoms, but also the results and summaries of specialist care. Prescription data encompass product name, quantity dispensed, dosage regimens, formulation, strength and indication. The National Database of drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO. This system complies with European Union guidelines on the secondary use of health care data for medical research and has been proven valid for pharmaco-epidemiological research [22]. Guidelines on good pharmaco-epidemiological research are rigorously followed by all researchers working on the IPCI database [23].

*Source population*

The source population consisted of all patients registered in the IPCI database, 40 years or older and with at least one-year of valid database history. This meant that the practice had been contributing data to the IPCI database for at least one year and that the patient had been registered with the GP for at least one year. This one-year pre-enrollment period was required to characterize the patients in terms of co-existing co-morbidity. The study period lasted from 1$^{st}$ January, 2008 up to 1$^{st}$ June, 2011.

*Tiotropium cohort*

All patients who received a prescription for tiotropium during follow-up (split in an inception and prevalent user group), were included in the tiotropium cohort. Cohort entry was the date of first prescription (either Respimat® SMI or Handihaler® = inception cohort) or start of follow-up for prevalent users. Episodes of use were created based on repeat prescription of the same type.

A patient was considered as being a switcher when switching from Respimat® SMI to Handihaler® or vice-versa. Subjects were followed from episode start of tiotropium use (either Respimat® SMI or Handihaler®) until the stop date of the episode of use (+ 30 day to account for carry over), the end of follow-up or death whichever occurred first. Death was assigned to an exposure category if it occurred during use or with a maximum of 30 days after stopping use.

*Death*

To assess the cause of death, the complete medical file of the patients was reviewed and information on cause of death was retrieved from either the hospital discharge letters (when patients died in the hospital), from the death certificates or from the cause of death as recorded by the GP. Researchers reviewing the information were blinded to drug (device) exposure. The cause of death was classified into respiratory death (excluding lung cancer), cardio and cerebrovascular death, death related to cancer, other causes or causes unknown. Patients who died of a combination of cardio- and cerebrovascular death and respiratory death were classified into the former. Patients who died due to euthanasia were excluded from the analysis.

*Covariates*

As covariates we considered smoking history, underlying comorbidities (asthma, angina pectoris, ischemic heart disease, peripheral arterial disease, myocardial infarction, stroke or transient ischemic attack (TIA), heart failure, ventricular arrhythmia, hypertension, dyslipidemia, cancer, pneumonia, parkinsonism, depression, dementia, diabetes, and renal failure) and use of concomitant medications, all assessed at the

start date of the episode of tiotropium use. Smoking history was classified as “ever smoking” or “no smoking”. Smoking was defined through an extensive search of the patient’s electronic medical file including the use of drugs for smoking cessation. Concomitant drug use included central nervous system drugs, drugs affecting the cerebrovascular and cardiovascular system, and drugs affecting the respiratory system.

The presence of COPD was considered as a separate covariate in the analysis. A patient was considered to have COPD based on 1) either the presence of ICPC specific codes for COPD namely ICPC_R95 (chronic obstructive pulmonary disease) or ICPC_R91 (chronic bronchitis), or 2) free text searching including “COPD” OR “chronic bronchitis” OR “emphysema”.

As we did not have spirometry data on all patients and as spirometry is not systematically recorded in the IPCI database, COPD severity was based on algorithms validated and successfully used by other research groups.[24-26] COPD severity was assessed at the start date of each treatment episode based on 1) the number of systemic corticosteroids prescriptions, 2) the number of antibiotics for the treatment of lower respiratory tract infections, 3) previous hospitalizations for COPD exacerbations and 4) the number of GP visits in the one year prior to treatment episode. 5) In addition, we included visits to the respiratory physician in the one year prior to the episode start as a proxy for COPD severity.

*Statistical analysis*

To compare the baseline characteristics of the patients using tiotropium Respimat® SMI or HandiHaler®, at start of treatment episode, the non-parametric Mann-Whitney U test was applied for continuous variables, and the Chi-square test for categorical variables.

Cox proportional hazards regression analyses were conducted to calculate crude (unadjusted) and adjusted hazard ratios (HR) and their 95% CI for the risk of all cause death associated with the use of tiotropium Respimat® SMI or HandiHaler®. The final model was built upon adjustment for smoking, COPD severity (see above), COPD duration (time from first prescription of bronchodilating drug until start of treatment episode), previous use of tiotropium and adjusting on all factors that changed the crude HR by more than 5%.

Sensitivity analyses were conducted by stratifying on cause of death, underlying co-morbidity of cardiovascular disease (arrhythmia, ischemic heart disease, heart failure, hypertension, peripheral artery disease and stroke), first episode of tiotropium use (either Respimat® SMI or HandiHaler®) during follow-up and excluding episodes of switching. In addition, we repeated the analysis first by not considering a 30 day carry over and second by extending the episodes up to the next prescription (= no untreated episodes between prescriptions). [27]

Finally, to control for differential prescribing of tiotropium Respimat® SMI (channeling bias where patients with more severe COPD or more underlying comorbidity are preferably prescribed Respimat® SMI), we repeated the analysis adjusting for the propensity score to be prescribed tiotropium Respimat® SMI. First a logistic regression model with all control variables was built to estimate propensity scores to be treated with tiotropium Respimat® SMI. Cox models were stratified across 10ths of the propensity score. [28] All statistical analyses were conducted with the statistical software packages SPSS/PC 20.0 (SPSS Inc, Chicago, III).

## Results

*Cohort of tiotropium users*

Within the total source population of 409,680 patients we defined a cohort of 11,287 tiotropium users. From the prescription records of these patients, 24,522 episodes of tiotropium use (either HandiHaler® or Respimat® SMI) were delineated. The mean (SD) age of the patients at the start of the first treatment episode was 68.1 (11.6) years and 51.9% of patients were male. 6560 out of the 11,287 patients (58.1 %) were already prescribed a treatment with tiotropium (either HandiHaler® or Respimat® SMI) at cohort entry and were thus considered as prevalent users. Of the incident users of tiotropium, 70% was prescribed HandiHaler® as first treatment and 30% Respimat® SMI. The mean duration of tiotropium use was 155 days per treatment episode (SD 232 days).

Baseline characteristics of patients at start of first prescription of either tiotropium HandiHaler® or Respimat® SMI are described in table 1. COPD severity and cardiovascular co-morbidity (angina pectoris, peripheral artery disease, myocardial infarction, stroke or transient ischemic attack (TIA), heart failure, dyslipidemia), cancer, diabetes mellitus, renal failure and pneumonia (in the one year prior to episode start), differed significantly between users of tiotropium HandiHaler® or tiotropium Respimat® SMI (table 1). The use of concomitant medication such as opioids, systemic corticosteroids, antibiotics, lipid lowering drugs, antiplatelet drugs, diuretics, ACE inhibitors, mucolytics, short-acting anticholinergics (SAAC) and short-acting β-agonists (SABA) also differed significantly between persons prescribed tiotropium HandiHaler® versus patients being prescribed tiotropium Respimat® SMI (table 1). When considering all treatment episodes, similar differences in baseline characteristics' between users of tiotropium HandiHaler® and tiotropium Respimat® SMI were observed (table 2).

*All cause mortality*

During a total tiotropium exposure of 11973 treatment years, 496 patients died. Of the 496 patients who died, 372 (75.0 %) were receiving tiotropium HandiHaler® while 124 were receiving tiotropium Respimat® SMI (25.0 %). The death rate was 60.7 per 1000 person-years during Respimat® exposure and 37.6 per 1000 person-years during HandiHaler® exposure. In the crude analysis, use of tiotropium Respimat®, compared to use of HandiHaler®, was associated with a 50% increased risk of dying (crude HR 1.57, 95%

CI 1.28 – 1.92). (Table 3) This increased risk remained upon adjustment for confounding factors (age, gender, smoking, COPD severity (including visit to the specialist), duration of COPD, previous episodes of tiotropium use and calendar time) ($HR_{adj}$ 1.27, 95% CI 1.03 – 1.58). (Table 3) No dose response relationship was observed.

*Cause specific mortality*

Cause of death was cardiovascular or cerebrovascular in 158 patients (31.6 %), respiratory in 95 patients (19.1 %), cancer in 139 patients (27.6 %), other causes in 51 patients (10.2%) or cause of death unknown in 53 patients (10.7%). The association between the use of tiotropium Respimat® and risk of death was the highest for cardio-and cerebrovascular death as cause ($HR_{adj}$ 1.56, 95% CI 1.08 – 2.25), followed by respiratory death ($HR_{adj}$ 1.34, 95% CI 0.80 – 2.22) (Table 4), although the 95% CI are wide and overlapping.

When repeating the analysis, excluding patients who died of both a cardiovascular and respiratory cause of death (n=29), the association remained. ($HR_{adj}$ 1.60, 95% CI 1.06-2.40) (data not shown).

*Sensitivity analyses*

The risk was higher in patients with co-existing cardiovascular disease ($HR_{adj}$ 1.36, 95% CI 1.07-1.73) than in patients without ($HR_{adj}$ 1.02, 95% CI 0.61-1.71). (table 5) Exclusion of episodes in which the formulation of tiotropium was changed did not alter the association between use of Respimat® and death ($HR_{adj}$ 1.23, 95% CI 0.98 – 1.55). Further sensitivity analyses showed little impact of other assumptions, but lost statistical significance due to low numbers. The associations remained when a) excluding prevalent users, b) not considering a 30 day carry over effect or c) extending treatment episodes up to the next episode. (table 5) The association was the lowest when considering only the first episode of drug use ($HR_{adj}$ 1.17, 95% CI 0.85-1.60). Finally, the association between use of Respimat® and death remained upon propensity score adjustment. ($HR_{adj}$ 1.32, 95% CI 1.05-1.67).

## Discussion

In this observational cohort study in the general Dutch population of patients being 40 years or older, we found an almost 30% increased risk of death in patients using tiotropium Respimat® SMI compared to tiotropium HandiHaler®. Cause specific analysis showed that the risk was highest for cardiovascular death. Importantly, the risk of death in patients using tiotropium Respimat® SMI was higher in patients with co-existing cardiovascular disease than in patients without. Since COPD is associated with multiple comorbidities, including cardiovascular disease, and since COPD patients with cardiovascular disease are often excluded from randomized controlled trials, our observational cohort study provides novel and important data concerning the safety of tiotropium Respimat® SMI.

So far, few data are available on the head to head comparison between tiotropium HandiHaler® and Respimat® SMI. In a pooled analysis of two 30-week, double blind double-dummy, crossover studies, 207 patients were randomized to receive once daily tiotropium Respimat® SMI, tiotropium HandiHaler® or placebo [12]. Although this study showed non-inferiority of tiotropium Respimat® SMI in comparison to tiotropium HandiHaler® in terms of improvement of lung function (FEV1) and no significant differences in terms of mortality, there was a significantly higher systemic exposure in patients treated with tiotropium Respimat® SMI 10 µg daily. A more recent study in Japanese COPD patients, but with shorter duration of follow-up, compared the safety and efficacy of tiotropium 5 µg via Respimat® SMI to 18 µg tiotropium HandiHaler® and did not observe a difference in safety and efficacy of both formulations. [29].

To our knowledge, our study is the first to compare the safety of the 2 devices of tiotropium on a large scale during a long period of follow-up. We did observe a small increased risk of dying in patients treated with tiotropium Respimat® SMI. It is unclear whether this is a true association or whether this association could be explained by residual confounding. It is believed that the improved delivery of the tiotropium Respimat® results in higher plasma concentrations of tiotropium increasing the risk of anticholinergic cardiovascular effects (arrhythmia).[18] We mainly observed an increased risk for cardiovascular and cerebrovascular death, and in patients with underlying cardiovascular disease which is in favor of this hypothesis; however, we did not identify an obvious dose-response relationship, although it should be noted that tiotropium Respimat® SMI in the Netherlands is registered for 5 µg once daily and doses above are considered off-label.

As for all observational studies, our study has strengths, but also limitations. The main strength of this study is the study design, its large cohort size and the detailed information that is available on underlying co-morbidity. In addition, as we used data from a primary care database, where patient data is prospectively collected in view of patient care and irrespective of any research question, selection bias is unlikely. Moreover, the source population being used is representative of the general population, and thereby facilitates generalizability of our results.

Being observational, the study is sensitive to bias and confounding. Indeed, when looking at the baseline characteristics of patients treated with tiotropium Respimat® SMI vs. tiotropium Handihaler® it was noticed that patients treated with tiotropium Respimat® SMI had more severe COPD, more often consulted a respiratory physician and had more underling (cardiovascular) comorbidity. As these factors could be important confounders in the association between the use of Respimat® SMI and mortality, it was thus important to conduct adjusted analyses. To adjust for COPD severity, we used an algorithm already successfully used by other research groups [24-26]. To control for confounding by indication, we conducted a sensitivity analysis in which we adjusted for the propensity scores for the likelihood of being prescribed tiotropium Respimat® SMI and the association remained. Despite these measures, remaining confounding, including confounding of COPD severity might still be an issue. Ideally COPD severity should be assessed by pulmonary function, preferably post-bronchodilation. In primary care however, pulmonary function is not routinely assessed and not systematically recorded in the database. Finally, due to the nature of the database, exposure was based on prescription data rather than on actual drug intake.

Boehringer Ingelheim is currently conducting the TIOSPIR trial, a large international safety study to elucidate the risk of mortality in patients treated with tiotropium Respimat® SMI, using tiotropium HandiHaler® as reference category. This study enrolled up to 17000 patients who are followed up over 2 years and results of the trial are expected in 2014. [30] In addition, as the TIOSPIR trial excluded patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia or patients hospitalized for cardiac failure (NYHA class III or IV) during the past year, our data should be considered as added value as we did not exclude these patients. We recommend that, until further data becomes available, physicians should be aware that COPD patients with arrhythmia or a history of cardiovascular disease might be particularly at risk.

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**Table 1. Patient characteristics at start of first treatment episode during follow-up**

| Characteristics | Tiotropium Handihaler Nº.(%) | Tiotropium Respimat* Nº.(%) |
|---|---|---|
| **Number of patients** | 9226 | 2827 |
| Age (mean, SD) | 68.09 (11.6) | 68.15 (11.8) |
| Gender | | |
| ♂ | 4776 (51.8) | 1468 (51.9) |
| ♀ | 4450 (48.2) | 1359 (48.1) |
| Smoking history | 7132 (77.3) | 2180 (77.1) |
| COPD diagnosis | 8459 (91.7) | 2567 (90.8) |
| Duration COPD (years) (mean, SD) | 5.29 (4.8) | 5.23 (5.0) |
| **COPD severity** | | |
| Number of antibiotics in 1 year prior (mean, SD) | **0.47 (1.0)** | **0.64 (1.2)** |
| Number of systemic corticosteroids in 1 year prior (mean, SD) | **0.61 (1.5)** | **0.96 (2.2)** |
| Number of GP visits in the 1 year prior (mean, SD) | **7.84 (6.5)** | **9.41 (7.7)** |
| Hospitalization for COPD exacerbation in 1 year prior | **196 (2.1)** | **124 (4.4)** |
| Consultation with respiratory physician in 1 year prior | **2791 (30.3)** | **1285 (45.5)** |
| **Co-morbidity (medical history of any of the conditions)** | | |
| Asthma | 2874 (31.1) | 872 (30.8) |
| Angina pectoris | 1218 (13.2) | 373 (13.2) |
| Ischemic heart disease | **725 (7.9)** | **257 (9.1)** |
| Peripheral arterial disease | **1252 (13.6)** | **430 (15.2)** |
| Myocardial infarction | **650 (7.0)** | **245 (8.7)** |
| Stroke or TIA | **1572 (15.3)** | **382 (18.5)** |
| Heart failure | **952 (10.3)** | **357 (12.6)** |
| Arrhythmia | 878 (9.5) | 294 (10.4) |
| Hypertension | 3711 (40.2) | 1195 (42.3) |
| Dyslipidemia (lipid disorders) | **1560 (16.9)** | **572 (20.2)** |
| Cancer | **1491 (16.2)** | **529 (18.7)** |
| Pneumonia (1 year before) | **650 (7.0)** | **245 (8.7)** |
| Parkinsonism | 79 (0.9) | 29 (1.0) |
| Depression | 1201 (13.0) | 379 (13.4) |
| Dementia | 155 (1.7) | 51 (1.8) |
| Diabetes mellitus | **1630 (17.7)** | **547 (19.3)** |
| Renal failure | **723 (7.8)** | **266 (9.4)** |
| **Use of concomitant medication at start of prescription** | | |
| **Central nervous system drugs** | | |
| Opioids | **500 (5.4)** | **194 (6.9)** |
| Hypnotic and sedatives | 898 (9.7) | 286 (10.1) |
| Anxiolytics | 945 (10.2) | 272 (9.6) |
| Antidepressants (SSRI) | 434 (4.7) | 149 (5.3) |
| Antipsychotics | 140 (1.5) | 34 (1.2) |
| Anti-Parkins drugs | 61 (0.6) | 18 (0.9) |
| Anticholinergics | 335 (3.6) | 124 (4.4) |
| Antihistaminics | 480 (5.2) | 158 (5.6) |
| **Drugs affecting cerebrovascular and cardiovascular disease** | | |
| Nitrates | 545 (5.9) | 193 (6.8) |
| Vitamin K antagonists | 803 (7.9) | 255 (9.0) |
| Lipid lowering drugs | **2450 (26.6)** | **805 (28.5)** |
| Antiplatelets | **2180 (23.6)** | **727 (25.7)** |

| Characteristics | Tiotropium Handihaler Nº.(%) | Tiotropium Respimat* Nº.(%) |
|---|---|---|
| Diuretics | **1981 (21.5)** | **666 (23.6)** |
| ß-blockers | 2015 (21.8) | 637 (22.5) |
| CCB | 1219 (13.2) | 396 (14.0) |
| ACE inhibitors | **2686 (29.1)** | **881 (31.2)** |
| Anti-arrhythmic drugs | 147 (1.6) | 41 (1.5) |
| **Other drugs** | | |
| Corticosteroids | **932 (10.1)** | **435 (15.4)** |
| Antibiotics | **1914 (20.7)** | **703 (24.9)** |
| NSAIDs | 734 (8.7) | 223 (7.9) |
| **Respiratory drugs** | | |
| Mucolytics | **447 (4.8)** | **173 (6.1)** |
| LTRA | 180 (1.9) | 69 (2.4) |
| SAAC (Ipratropium) | **579 (6.3)** | **320 (11.3)** |
| SABA | **1597 (17.3)** | **600 (21.2)** |
| LABA | 3556 (38.5) | 1066 (37.7) |
| ICS | 3925 (42.5) | 1174 (41.5) |
| Xanthines | 101 (1.1) | 34 (1.2) |

The bold values are statistically significant different between tiotropium Respimat® SMI against tiotropium Handihaler®.

Abbreviations: ACE (angiotensin-converting enzyme), CCB (calcium channel blockers), COPD (chronic obstructive pulmonary disease), ICS (inhaled corticosteroids), LAAC (long-acting anticholinergics), LABA (long-acting ß-agonists), LTRA (leukotriene receptor antagonists), GP (general practitioner), NSAIDs (non-steroidal anti-inflammatory drugs), SABA (short-acting ß-agonists), SD (standard deviation), SSRI (selective serotonin reuptake inhibitors), TIA (transient ischemic attack)

**Table 2. Patient characteristics at start of treatment episodes during follow-up**

| Characteristics | Tiotropium Handihaler Nº.(%) | Tiotropium Respimat* Nº.(%) |
|---|---|---|
| **Number of patients** | **19341** | **5181** |
| Age (mean, SD) | | |
| Gender | | |
| ♂ | 9955 (51.5) | 2727 (52.6) |
| ♀ | 9386 (48.5) | 2454 (47.4) |
| Smoking history | 15053 (77.8) | 4024 (77.7) |
| COPD diagnosis | 17909 (92.6) | 4755 (91.8) |
| Duration COPD (years) (mean, SD) | 5.53 (5.00) | 5.96 (4.84) |
| **COPD severity** | | |
| Number of antibiotics in 1 year prior (mean, SD) | **0.48 (1.1)** | **0.67 (1.2)** |
| Number of systemic corticosteroids in 1 year prior (mean, SD) | **0.64 (1.6)** | **1.06 (2.9)** |
| Number of GP visits in the 1 year prior (mean, SD) | **8.07 (6.7)** | **9.60 (7.7)** |
| Hospitalization for COPD exacerbation in 1 year prior | **476 (2.5)** | **231 (4.5)** |
| Consultation with respiratory physician in 1 year prior | **6145 (31.8)** | **2479 (47.8)** |
| **Co-morbidity (medical history of any of the conditions)** | | |
| Asthma | 6091 (31.5) | 1653 (31.9) |
| Angina pectoris | **2716 (14.0)** | **787 (15.2)** |
| Ischemic heart disease | 1632 (8.4) | 473 (9.1) |
| Peripheral arterial disease | **2752 (14.2)** | **807 (15.6)** |
| Myocardial infarction | **1413 (7.3)** | **471 (9.1)** |
| Stroke or TIA | **1618 (8.4)** | **537 (10.4)** |
| Heart failure | **2062 (10.7)** | **693 (13.3)** |
| Arrhythmia | **1831 (9.5)** | **567 (10.9)** |
| Hypertension | 7799 (40.3) | 2153 (41.6) |
| Dyslipidemia (lipid disorders) | **3268 (16.9)** | **1080 (20.8)** |
| Cancer | **3142 (16.2)** | **914 (17.6)** |
| Pneumonia (1 year before) | **1177 (6.1)** | **458 (8.8)** |
| Parkinsonism | 169 (0.9) | 43 (0.8) |
| Depression | 2619 (13.5) | 748 (14.4) |
| Dementia | 379 (1.9) | 95 (1.8) |
| Diabetes mellitus | **3585 (18.5)** | **1040 (20.1)** |
| Renal failure | **1650 (8.5)** | **518 (10.0)** |
| **Use of concomitant medication at start of prescription** | | |
| **Central nervous system drugs** | | |
| Opioids | **1131 (5.8)** | **364 (7.0)** |
| Hypnotic and sedatives | 1916 (9.9) | 535 (10.3) |
| Anxiolytics | 1995 (10.3) | 508 (9.8) |
| Antidepressants (SSRI) | 918 (4.7) | 274 (5.3) |
| Antipsychotics | **314 (1.6)** | **62 (1.2)** |
| Anti-Parkins drugs | 132 (0.7) | 40 (0.8) |
| Anticholinergics | 771 (4.0) | 234 (4.5) |
| Antihistaminics | 1018 (5.3) | 285 (5.5) |
| **Drugs affecting cerebrovascular and cardiovascular disease** | | |
| Nitrates | **1137 (5.9)** | **383 (7.4)** |
| Vitamin K antagonists | 1723 (8.9) | 465 (9.0) |
| Lipid lowering drugs | **5095 (26.3)** | **1509 (29.1)** |
| Antiplatelets | **4519 (23.4)** | **1394 (26.9)** |

| Characteristics | Tiotropium Handihaler Nº.(%) | Tiotropium Respimat* Nº.(%) |
|---|---|---|
| Diuretics | **4006 (20.7)** | **1209 (23.3)** |
| ß-blockers | **4189 (21.7)** | **1199 (23.1)** |
| CCB | **2494 (12.9)** | **739 (14.3)** |
| ACE inhibitors | **5591 (28.9)** | **1602 (30.9)** |
| Anti-arrhythmic drugs | 312 (1.6) | 104 (2.0) |
| **Other drugs** | | |
| Corticosteroids | **1839 (9.5)** | **728 (14.1)** |
| Antibiotics | **3663 (18.9)** | **1135 (21.9)** |
| NSAIDs | 1495 (7.7) | 386 (7.5) |
| **Respiratory drugs** | | |
| Mucolytics | **903 (4.7)** | **304 (5.9)** |
| LTRA | **376 (4.7)** | **126 (2.4)** |
| SAAC (Ipratropium) | **997 (5.2)** | **481 (9.3)** |
| SABA | **3231 (16.7)** | **1092 (21.1)** |
| LABA | 7333 (37.9) | 1653 (37.9) |
| ICS | 7961 (41.2) | 2137 (41.2) |
| Xanthines | 196 (1.0) | 67 (1.3) |

The bold values are statistically significant different between tiotropium Respimat® SMI against tiotropium Handihaler®.

Abbreviations: ACE (angiotensin-converting enzyme), CCB (calcium channel blockers), COPD (chronic obstructive pulmonary disease), ICS (inhaled corticosteroids), LAAC (long-acting anticholinergics), LABA (long-acting ß-agonists), LTRA (leukotriene receptor antagonists), GP (general practitioner), NSAIDs (non-steroidal anti-inflammatory drugs), SABA (short-acting ß-agonists), SD (standard deviation), SSRI (selective serotonin reuptake inhibitors), TIA (transient ischemic attack)

**Table 3. Crude and adjusted Hazard Ratios (HRs) for all-cause mortality in users of tiotropium Respimat® versus users of tiotropium Handihaler®**

| | **Tiotropium Respimat®** | **Tiotropium Respimat® 2.5 µg** | **Tiotropium Respimat® 5 µg** |
|---|---|---|---|
| | **Number of death = 124** | **Number of death = 27** | **Number of death = 97** |
| **Variable** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.57 (1.28-1.92)** | **1.67 (1.13-2.47)** | **1.54 (1.23-1.93)** |
| Covariates included in the Cox model to calculate adjusted HRs | | | |
| Age | **1.61 (1.31-1.98)** | **1.54 (1.04-2.29)** | **1.63 (1.30-2.03)** |
| + Gender | **1.60 (1.30-1.96)** | **1.57 (1.06-2.32)** | **1.60 (1.28-2.01)** |
| + smoking | **1.59 (1.30-1.95)** | **1.56 (1.06-2.31)** | **1.61 (1.28-2.01)** |
| + number of prescriptions of oral corticosteroids in 1 year prior to episode start* | **1.50 (1.22-1.85)** | **1.52 (1.03-2.25)** | **1.49 (1.19-1.88)** |
| + number of GP visits in 1 year prior to episode start | **1.36 (1.11-1.68)** | 1.31 (0.88-1.94) | **1.39 (1.10-1.75)** |
| + hospitalization for COPD in 1 year prior to episode start | **1.34 (1.09-1.66)** | 1.26 (0.85-1.87) | **1.37 (1.09-1.72)** |
| + number of prescriptions of antibiotics for treatment of LRTI in 1 year prior to episode start | **1.34 (1.09-1.65)** | 1.24 (0.83-1.84) | **1.37 (1.09-1.73)** |
| + consultation with respiratory physician in 1 year prior to episode start | **1.26 (1.02-1.57)** | 1.22 (0.82-1.82) | **1.28 (1.02-1.62)** |
| + number of previous episodes of tiotropium Respimat® and/or Handihaler® use | **1.28 (1.04-1.58)** | 1.21 (0.81-1.80) | **1.30 (1.03-1.64)** |
| + calendar time (year of start date treatment episode) | **1.31 (1.06-1.63)** | 1.23 (0.82-1.83) | **1.34 (1.06-1.69)** |
| + duration of COPD | **1.27 (1.03-1.58)** | 1.20 (0.82-1.79) | **1.28 (1.02-1.62)** |

*- variables that changed the crude HR with more than 5%
Bold results = statistically signficant

**Table 4. Crude and adjusted Hazard Ratios (HRs) for cause-specific mortality in users of tiotropium Respimat® versus users of tiotropium Handihaler®**

| **Cardiovascular and cerebrovascular mortality (Number of death=158)** | |
|---|---|
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.84 (1.30-2.61)** |
| Covariates included in the Cox model to calculate adjusted HRs | |
| Age | **1.89 (1.34-2.68)** |
| + Gender | **1.88 (1.33-2.67)** |
| + smoking | **1.88 (1.33-2.67)** |
| + use of corticosteroids in 1 year prior to episode start | **1.79 (1.26-2.56)** |
| + number of GP visits in 1 year prior to episode start | **1.64 (1.15-2.34)** |
| + hospitalization for COPD in 1 year prior to episode start | **1.58 (1.11-2.26)** |
| + use of Antibiotics for treatment of LRTI in 1 year prior to episode start | **1.58 (1.10-2.26)** |
| + consultation with respiratory physician in 1 year prior to episode start | **1.48 (1.04-2.12)** |
| + number of previous episodes of tiotropium Respimat® and/or Handihaler® use | **1.49 (1.04-2.12)** |
| + calendar time (year of start date treatment episode) | **1.58 (1.10-2.29)** |
| + duration of COPD | **1.54 (1.07-2.23)** |
| + cardiovascular comorbidity | **1.56 (1.08-2.25)** |
| **Respiratory mortality (Number of death=95)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | 1.55 (0.97-2.49) |
| Covariates included in the Cox model to calculate adjusted HRs | |
| Age | **1.61 (1.00-2.60)** |
| + Gender | 1.59 (0.99-2.56) |
| + smoking | 1.59 (0.99-2.56) |
| + use of corticosteroids in 1 year prior to episode start | 1.43 (0.87-2.33) |
| + number of GP visits in 1 year prior to episode start | 1.31 (0.80-2.13) |
| + hospitalization for COPD in 1 year prior to episode start | 1.27 (0.78-2.07) |
| + use of Antibiotics for treatment of LRTI in 1 year prior to episode start | 1.28 (0.78-2.09) |
| + consultation with respiratory physician in 1 year prior to episode start | 1.24 (0.76-2.03) |
| + number of previous episodes of tiotropium Respimat® and/or Handihaler® use | 1.24 (0.76-2.03) |
| + calendar time (year of start date treatment episode) | 1.33 (0.80-2.21) |
| + duration of COPD | 1.34 (0.80-2.22) |
| **Mortality due to cancer (Number of death=139)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | 1.47 (0.99-2.17) |
| Covariates included in the Cox model to calculate adjusted HRs | |
| Age | **1.51 (1.02-2.23)** |
| + Gender | **1.50 (1.01-2.21)** |

| | |
|---|---|
| + smoking | **1.49 (1.01-2.21)** |
| + use of corticosteroids in 1 year prior to episode start | 1.39 (0.94-2.07) |
| + number of GP visits in 1 year prior to episode start | 1.26 (0.84-1.87) |
| + hospitalization for COPD in 1 year prior to episode start | 1.27 (0.86-1.90) |
| + use of Antibiotics for treatment of LRTI in 1 year prior to episode start | 1.27 (0.85-1.89) |
| + consultation with respiratory physician in 1 year prior to episode start | 1.13 (0.76-1.68) |
| + number of previous episodes of tiotropium Respimat® and/or Handihaler® use | 1.16 (0.78-1.73) |
| + calendar time (year of start date treatment episode) | 1.12 (0.74-1.69) |
| + duration of COPD | 1.06 (0.70-1.59) |
| **Death related to other causes or cause of death unknown (Number of death=104)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | 1.33 (0.82-2.13) |
| Covariates included in the Cox model to calculate adjusted HRs | |
| Age | 1.38 (0.86-2.22) |
| + Gender | 1.37 (0.85-2.20) |
| + smoking | 1.37 (0.85-2.20) |
| + use of corticosteroids in 1 year prior to episode start | 1.32 (0.82-2.14) |
| + number of GP visits in 1 year prior to episode start | 1.23 (0.76-2.00) |
| + hospitalization for COPD in 1 year prior to episode start | 1.22 (0.76-1.98) |
| + use of Antibiotics for treatment of LRTI in 1 year prior to episode start | 1.22 (0.76-1.98) |
| + consultation with respiratory physician in 1 year prior to episode start | 1.24 (0.76-1.98) |
| + number of previous episodes of tiotropium Respimat® and/or Handihaler® use | 1.25 (0.77-2.03) |
| + calendar time (year of start date treatment episode) | 1.29 (0.78-2.11) |
| + duration of COPD | 1.26 (0.76-2.07) |

**Table 5. Sensitivity analyses: Crude and adjusted Hazard Ratios (HRs) for all-cause mortality in users of tiotropium Respimat® versus users of tiotropium Handihaler®**

| **Mortality in patients with cardiovascular comorbidity (Number of death=387)** | |
|---|---|
| **Variable** | |
| *Unadjusted (crude)* | **1.62 (1.29-2.04)** |
| Fully adjusted model* | **1.36 (1.07-1.73)** |
| **Mortality in patients without cardiovascular comorbidity (Number of death=109)** | |
| **Variable** | |
| *Unadjusted (crude)* | 1.25 (0.77-2.02) |
| Fully adjusted model* | 1.02 (0.61-1.71) |
| **Mortality in patients excluding switchers (Number of death=472)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.49 (1.20-1.86)** |
| Fully adjusted model* | 1.23 (0.98-1.55) |
| **Mortality only considering first episode of use (Number of death =258)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.39 (1.03-1.88)** |
| Fully adjusted model* | 1.17 (0.85-1.60) |
| **Mortality only considering incident users (Number of death=165)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.59 (1.17-2.16)** |
| Fully adjusted model* | 1.27 (0.93-1.75) |
| **Mortality not considering 30 day carry over effect (Number of death=387)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.51 (1.19-1.91)** |
| Fully adjusted model* | 1.21 (0.94-1.56) |
| **Mortality when treatment episodes are extended up to the next episode (Number of death=388)** | |
| **Variable** | **HR (95% CI)** |
| *Unadjusted (crude)* | **1.53 (1.21-1.94)** |
| Fully adjusted model* | 1.22 (0.95-1.57) |
| **Propensity score adjusted model – full cohort (Number of death=496)** | |
| **Variable** | |
| Propensity score adjusted model | **1.32 (1.05-1.67)** |
| **Propensity score adjusted model – incident users (Number of death=165)** | |
| **Variable** | |
| Propensity score adjusted model | 1.29 (0.90-1.84) |

*Adjusted for age, gender, smoking, use of systemic corticosteroids in 1 year prior to episode start, number of GP visits in 1 year prior to episode start, hospitalization for COPD exacerbation, use of antibiotics for treatment of LRTI in 1 year prior to episode start, consultation with respiratory physician in one year prior to episode start, previous episodes of tiotropium use, calendar time and duration COPD.